The Stability of Pharmaceutical Powders:
Effect of Additives and Coating

by

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A thesis presented for the degree of

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The decomposition of drugs in the solid state has been studied using aspirin and salsalate as models. The feasibility of using suspension systems for predicting the stability of these drugs in the solid state has been investigated. It has been found that such systems are inappropriate in defining the effect of excipients on the decomposition of the active drug due to changes in the degradation pathway. Using a high performance liquid chromatographic method, magnesium stearate was shown to induce the formation of potentially immunogenic products in aspirin powders. These products which included salicylsalicylic acid and acetylsalicylsalicylic acid were not detected in aspirin suspensions which had undergone the same extent of decomposition.

By studying the effect of pH and of added excipients on the rate of decomposition of aspirin in suspension systems, it has been shown that excipients such as magnesium stearate containing magnesium oxide, most probably enhance the decomposition of both aspirin and salsalate by alkalinising the aqueous phase. In the solid state, pH effects produced by excipients appear to be relatively unimportant. Evidence is presented to suggest that the critical parameter is a depression in melting point induced by the added excipient. Microscopical examination in fact showed the formation of clear liquid layers in aspirin samples containing added magnesium stearate but not in control samples.

Kinetic equations which take into account both the diffusive barrier presented by the liquid films and the geometry of the aspirin crystals were developed. Fitting of the experimental data to these equations showed good agreement with the postulated theory.

Monitoring of weight losses during the decomposition of aspirin revealed that in the solid systems studied where the bulk of the decomposition product sublimes, it is possible to estimate the extent of degradation from the residual weight, provided the initial weight is known. The corollary is that in such open systems, monitoring of decomposition products is inadequate for assessing the extent of decomposition.

In addition to the magnesium stearate-aspirin system, mepyramine maleate-aspirin mixtures were used to model interactive systems. Work carried out in an attempt to stabilise such systems included microencapsulation and film coating. The protection obtained was dependent on the interactive species used. Gelatin for example appeared to stabilise aspirin against the adverse effects of magnesium stearate but increased its decomposition in the presence of mepyramine maleate.

Key Words:

Stability in the solid state. Kinetics. Aspirin.

Drug-drug reaction. Drug-excipient reaction.

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Memorandum

This dissertation, which is being submitted for the degree of Doctor of Philosophy in the University of Aston in Birmingham is an account of work carried out under the supervision of Dr. A. Li Wan Po in the Department of Pharmacy, the University of Aston in Birmingham from January 1979 to January 1982. Dr. W. J. Irwin acted as adviser.

Except where acknowledged by references in the text, the work described is claimed to be original and has not been submitted for any other award.

PMroso
Paul V. Mroso

February 1982

To My Wife, Dora,

My Daughter Heidi and My Son Anthony

CHAPTER 1

INTRODUCTION

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1. INTRODUCTION

1.1 The importance of stability studies

Drug formulations must possess adequate chemical and physical stability to ensure satisfactory therapeutic and toxicological performance. Stability studies therefore involve

(i) the monitoring of changes in drug potency that may occur with storage,

(ii) the prediction of the quality and general acceptability of a drug product under in-use conditions,

(iii) the investigation of the effects of additives on the quality, potency or efficacy of a formulation and

(iv) the detection of potentially toxic degradation products.

The detection of undesirable, pharmacologically active degradation products in pharmaceutical dosage forms, as exemplified by the potentially immunogenic substances in aspirin tablets (1-3), the nephrotoxic substance, 4-epianhydrotetracycline in degraded tetracycline tablets (4) and the formation of m-aminophenol in p-aminosalicylic acid tablets (5, 6), illustrate the importance of stability studies.

Defining and quantifying such undesirable changes in drug formulations are of paramount importance in any rational design and evaluation of drug dosage forms.

1.2 Stability Testing Techniques

The degradative route of any substance is either physical or chemical in nature (5, 7). In the solid state, chemical reactions may be preceded by a physical change such as melting, dissolution or recrystallisation (8). The choice of the method for stability testing depends on the nature of the chemical substance, its formulation and the probable storage conditions. In pharmaceutical stability studies both physical and chemical changes are observed. In such studies, tablets, capsules, powders or granules are stored at either normal or exaggerated conditions of heat, light, humidity or oxygen tension samples are removed at pre-determined intervals, and the degree of change determined. Likewise solutions or suspensions could be subjected to varying conditions of pH, temperature, ionic strength, light or oxygen tension.

Prediction of the stability of drugs and pharmaceutical preparations depends upon quantitative mathematical expressions (9). In order to use such mathematical expressions, adequate analytical methods must be developed so as to quantify the rates of degradations.

1.2.1 Stability Indicating Methods of Assay

Stability-indicating assays must be capable of monitoring the changes of the parent compound in the presence of its degradation products, or the estimation of the degradation product in the presence of the parent compound.

The complexity of decomposition pathways and the diversities in formulations and additives make it necessary to develop suitable stability-indicating assays.

Chromatography has found wide use in the analysis of formulated pharmaceutical products. Gas-liquid chromatography (10) and high performance liquid chromatography (HPLC) (11-16) stand out as the most widely used analytical techniques. The use of HPLC as an analytical tool is extended to clinical samples which may contain low levels of drugs and metabolites contaminated with various biochemicals as well as in the analysis of pharmaceuticals which may consist of several drugs and excipients. Theoretical and technological advances have now resulted in HPLC systems which can provide for accuracy, precision, selectivity, sensitivity and speed in analysis of drugs in clinical samples and in pharmaceutical dosage forms. In addition to the above advantages, HPLC complements rather than competes with other available methods. It is more suitable than gas chromatography (GC) for assays of many polar, ionic or thermolabile drugs which can be measured by HPLC with no derivatisation and minimal extraction procedures (16).

Spectrophotometric methods have been used and reported in the literature (17-19). In the study of hydrolysis of aspirin anhydride, the formation of aspirin and salicylic acid were monitored by ultra violet spectrophotometric methods. In the study of the kinetics of hydrolysis of acetylsalicylic acid in suspension both salicylic acid and acetylsalicylic acid were assayed by ultraviolet spectrophotometry. In this study, the effect of additives was investigated, and it was found that 50% w/v sorbitol exerted a significant stabilising effect of aspirin in suspension. Polyethylene glycol 6000 and polyvinylpyrrolidone exhibited apparent stabilising effects which were attributed to the formation of an insoluble gummy precipitate. The enhanced degradation of aspirin in suspension induced by glycerin was explained by the better solvent action of the glycerin-water solution which increased the solubility of aspirin (18).

Chemical methods including acid-base titration or reactions which result in colour complexes form the bulk of the official compendial methods of assay. Examples of such methods which have been used in the assay of aspirin and salicylic acid include the colour complex formation between salicylic acid and ferric ions (Fe^{+++}), or non-aqueous titration (19).

Physico-chemical methods such as differential thermal analysis (DTA) (20-25) and diffuse reflectance spectroscopy (DRS) (26-29) have also been used in stability studies.

Differential thermal analysis (DTA) is a thermal technique in which the heat effects associated with chemical or physical changes are measured as a function of time or temperature while a substance is being heated at a uniform rate. Physical changes such as crystalline transitions, fusion, evaporation or sublimation and some chemical changes such as oxidative decomposition and decarboxylation can be observed. The heat of absorption or liberation which occurs during the course of these changes can be measured by the differential thermal methods (25). The use of DTA has been extended to the determination of reaction kinetics (20, 24). Critical evaluation of the utility of thermal methods for the detection of possible interactions occurring between solid components of pharmaceuticals has been reported (25).

Diffuse reflectance spectroscopy (DRS) is a method of measuring the light reflecting power of a sample relative to a standard (29). Light reflection from a solid is said to be diffuse because solid surfaces consist of absorbing and light scattering particles, uniformly or randomly distributed with a layer sufficiently thick to make the surface opaque. The diffuse reflectance power of a solid has been utilised in detecting solid-solid interactions by measuring the changes in the reflectance with reaction time (29). The method is essentially qualitative (28) but correlation of change in reflectance with chemical degradation such as in the interaction between ascorbic acid and silicic acid have been reported (26).

Sestak et al. (30) has reviewed methods which have been reported in the literature for analysis and use in quantifying rates of reactions. In addition to the above methods, these techniques include thermogravimetry (TG), electrothermal analysis (ETA), high temperature microscopy (hot stage), emanation thermal analysis (ETA), thermomagnetic analysis (TMA) and photothermal analysis (PTA).

1.2.2 Kinetic Description of Systems

The underlying principle of chemical reaction kinetics is the law of mass action. The rate of any chemical reaction, for dilute solution approximation, is proportional to the products of the concentrations of the substances involved in the reaction. Despite some observed deviations in the rates of reactions as predicted from the application of the law and from the stoichiometry of the reaction, the kinetics of degradation of substances in solution is well documented (31).

1.2.2.1 Kinetics of Degradations in Solutions

Reaction rate is usually defined as the rate of change of concentration of a substance involved in the reaction. Frost and Pearson (31) have expressed the definition mathematically as

$$\frac{-dc}{dt} = kC_t^{\,n} \qquad \text{--- Eq. 1(a)}$$

where $\frac{dc}{dt}$ = the rate of change of the concentration (the minus sign means decreasing concentration)

k = the rate constant (Units $|\text{CONC}|^{1-n}\,|\text{TIME}|^{-1}$)

C_t = concentration of reactant at any time t

n = order of reaction

Integration of equation 1a with the limits taken as C = Co at t = 0 and C at t = t, first, second and third order equations as expressed below are obtained applicable to single component only (31):

First order: $\ln \frac{C_0}{C_t} = kt$ --- Eq. 1b

Second order: $\frac{1}{C_t} - \frac{1}{C_o} = kt$ --- Eq. 1c

Third order: $\frac{1}{{C_t}^2} - \frac{1}{{C_o}^2} = 2kt$ --- Eq. 1d

For all cases (except n = 1) the equations can be represented by a general form (31):

$$\left|\frac{1}{(n-1)}\right| \left|\frac{1}{C_t^{n-1}} - \frac{1}{C_o^{n-1}}\right| = kt \qquad \text{--- Eq. 2}$$

The order of a reaction is a dominant term in describing the reactions in homogeneous systems and in a few cases of reactions in the solid state. A number of pharmaceutical dosage forms have been shown to follow first order kinetics as described in Section 1.3.2.2. In the study of degradation of aspirin solutions, Edward (32) observed the reactions to follow first order kinetics at various temperatures and pH values. Garrett (33) studied the kinetics of solvolysis of acyl esters of salicylic acid and compared the stability of the esters by the use of first order rate constants.

1.2.2.2 Kinetics of Degradation of Solids and Solid Dosage Forms

The kinetics of reactions in the solid state are complex in nature and the velocity of such reactions cannot be defined in a similar manner to those in solution (34). Reaction rate in the solid state has been defined (34) as the change with time of the thickness of the layer of product formed, or the weight of the layer or the number of gram equivalents of the product formed. For interface advance the velocity, k, has units $cm^2\ sec^{-1}$. The probable reason for the difference in the definition of reaction rates for degradations in solution and those in the solid state is that solid state reactions neither take place in the volume nor in the bulk of the substance, but at the interface between reactant phases (35).

Pope and Judd (20) have presented an equation claimed to be a general one for decomposition of solids in which the reaction is described by the contracting geometry models:

For $n \neq 1$

$$1 - \left|1 - kt(1 - n)\right|^{\frac{1}{1 - n}} = \alpha \qquad \text{--- Eq. 3}$$

where α = a dimensionless parameter which represents the fraction decomposed

k = reaction rate constant ($time^{-1}$)

n = order of reaction

However, close examination of equation 3 reveals that it could be derived from equation 2 by substituting the concentration parameter of equation 2 by, α, the fraction decomposed. The validity of this general equation 3 is limited since n in equations 2 and 3 will not have a similar meaning. However when $n = \frac{1}{2}$ or $\frac{1}{3}$, equation 3 can be used to describe the reaction of a contracting cylinder or sphere respectively and in this case n describes the geometry of the system.

The order of reaction, therefore, is not used to classify reactions in the solid state instead, the shapes of the α versus t decomposition profiles coupled with the physico-chemical processes

Table 1

GENERAL CLASSIFICATION OF SOLID STATE REACTIONS

Curve Shape Description	Examples of Kinetic Equations
(a) Accelerator Rate Equations	
(i) The Power law: $\alpha^{\frac{1}{n}} = kt$	Eq. 4
(ii) Exponential law: $\log \alpha = kt$	Eq. 5
(b) Sigmoid rate Equations (Basic Nucleation Theories)	
(i) Avrami-Erofeev $\alpha = 1 - e^{-kt^n}$	Eq. 6
(ii) Prout-Tompkins $\log \frac{\alpha}{1 - \alpha} = kt$	Eq. 7
(c) Deceleratory Rate Equations	
(i) Diffusional Models (Jander Equation) $\left\|1 - (1 - \alpha)^{\frac{1}{3}}\right\|^2 = (2k/\gamma_0^2)t$	Eq. 8
(ii) Contracting Geometry Models $1 - (1 - \alpha)^n = (k/\alpha_0)t$	Eq. 9
(iii) Basic Homogeneous Kinetic Equation	
a) First order $\log(1 - \alpha) = k_1t$	Eq. 10
b) Second order $(1 - \alpha)^{-1} = k_2t$	Eq. 11
c) Third order $(1 - \alpha)^{-2} = k_3t$	Eq. 12

such as diffusion or nucleation, which are usually involved in such reactions.

Based on such shapes and kinetic equations, reactions in the solid state have been classified as shown in Table 1 (8, 36). From Table 1, the parameters in equations 4-12 (Table 1) can be defined by k = the rate constant. It may embrace complex functions such as diffusion or geometric factors like radius. Usually it has units $\underline{\text{time}^{-1}}$. α = dimensionless parameter that describes the fraction decomposed (usually expressed as a percentage of initial drug content).

$\alpha = \frac{C_o - C_t}{C_o}$ when C_o, the initial amount of intact drug is taken as 1 then $\alpha = (1 - C_t)$ then C_t = proportion of drug content at any time t.

$\underline{n}$ does not define the order of reaction as in homogenous systems. It is basically a constant that describes the geometry of the system. For example in contracting geometry models, $n = \frac{1}{2}$ or $\frac{1}{3}$ for a cylinder and sphere respectively. In nucleation theories $\underline{n}$ is defined as a sum of two parameters σ and a as shown by equation 13.

$$n = \sigma + a \qquad \text{--- Eq. 13}$$

where $\underline{\sigma}$ is the number of elementary steps in the transformation of a nucleus site to an actively growing nucleus. $\underline{a}$ depends on the number of directions in which the nuclei grow. These parameters have typical values as follows:

$\underline{a}$ has values of 1 to 3
$\underline{\sigma}$ " " of 1 to 3
n " " of 2 to 6 (3-5 are mostly quoted) (35, 36).

Detailed description of equations which enable the determination of n and eventually the rate constant, have been presented by Galwey (36).

The kinetic equations enable the quantitative definition of the rates of formation or disappearance of substances in a chemical reaction. The prediction of shelf-life of pharmaceutical products from accelerated stability studies are placed on a quantitative basis by the application of fundamental kinetic principles (37).

1.2.3 Accelerated Stability Testing

Accelerated stability studies at high temperatures have been used to estimate shelf-life under normal storage conditions. An obvious advantage of accelerated stability testing is the time saved particularly in assessing trial formulations. Frequently correlations from accelerated stability tests have been based on insufficient number of elevated temperatures or on empirical relations in supposedly similar preparations (37). The influence of temperature on the reaction rate was put on a sound mathematical basis by Arrhenius (38), and developed an equation currently expressed as:

$$k = Ae^{-E/RT} \qquad \text{--- Eq. 14(a)}$$

where k = reaction rate constant

A = frequency factor

E = energy of activation

R = gas constant

T = reaction temperature (Kelvin scale)

This equation has found wide application in both homogeneous and heterogeneous systems. In order to explain some of the differences in the reactions of solids from those of liquids, minor modifications to equation 14(a) were thought necessary and equation 14b was presented (39):

$$k = \gamma C e^{-E/RT} \qquad \text{--- Eq. 14(b)}$$

where γ = vibration frequency in a reaction co-ordinate

C = the reactant molecular concentration in a unit area of interface

In homogeneous solution systems, the activation energy (E) has values in the range of 50-100 KJ mole^{-1} (12-24 Kcal/mole) (40) while in the solid state reactions such as the decomposition of calcium carbonate and molybdenum oxide, values of 305.42 and 251.04 KJ mole^{-1} (73 and 60 Kcal/mole) respectively have been reported (41).

In addition to the calculation of activation energy, the Arrhenius equation enables the estimation of a rate constant at the expected normal storage conditions, a value usually used to derive the shelf life of a preparation. A good correlation between the shelf life obtained through accelerated stability studies and that obtained by long-term studies has been obtained (42). In such studies, the stability of Vitamins A, B and C in a multivitamin tablet formulation stored at 50^{o}, 60^{o} and 70^{o}C were studied. Formulations with moisture content at 3-4% levels, were observed to follow pseudo first-order thermodegradation rates. If the moisture level was maintained below 1% the first order thermodegradation rates were reduced by 78% for Vitamin A; 73% for thiamine and by 70% for ascorbic acid. Assays performed on samples whose moisture level was below 1%, stored at room temperature for

15, 24, 31, 35 and 38 months confirmed that the calculated thermodegradation curve of the vitamin preparation could be used safely as an estimate of potency over a 3-year period.

Slater et al. (43) showed that shelf-life prediction of Vitamin A stability in multivitamin tablets calculated by the classical Arrhenius treatment gave variations in predictions. When the data was treated by a "modified" Arrhenius method, the variation was reduced. It was further observed that the variation is particularly serious when the limiting ingredient for expiration dating is a pre-processed raw material and not a single entity chemical. It is important to say that in this study the Arrhenius equation was not altered. The modified application simply increases the degree of freedom by determining a greater number of rate constants from the available data, which decreases the range of the predicted rate constant values. In many stability studies involving pharmaceutical dosage forms, the Arrhenius equation was generally found to be applicable (44).

The predicted shelf life of a preparation will only be valid if the accelerated test is carried out on the final packaged product. Before valid conclusions can be drawn from such tests, it is necessary to determine that the elevated temperatures do not alter the order of the chemical reaction. When the decomposition process is complex involving a series of simultaneous and/or consecutive reactions, each having a characteristic energy of activation, storage of the product at elevated temperatures may produce a change in the relative contributions of the component reactions. It is also possible that elevated temperature may induce a decomposition process that is not normally significant at ambient temperatures. The shelf life prediction only applies to the product formulation investigated and that one cannot expect the prediction to be valid for different formulations of the same drug.

1.3 Solid State Reactions

In the review of reactions in the solid state, Cohn (45) observed that, although the reactions were first described in 1820, reports on solid state reactions were rare until the early 1900's that relatively ample reports became available (46-48). The author (45) attempted to define reactions in the solid state as chemical processes in which one or more solids participate. Reactants form a product reaction layer adjacent to their boundaries which increases with the progress of the chemical reaction. Chemical reactions were classified as structure sensitive properties of solids in contrast to the structure-insensitive properties of solids which included chemical formulae, lattice dimensions and true density (45).

Among the early studies of solid state reactions are the decompositions of silver permanganate and potassium permanganate (46 and 47 respectively). Sieverts and Theberath (46) observed that dry silver permanganate decomposed slowly even at 50°C, traces of water brought about a large increase in velocity of decomposition. On further addition of water, only little effect on the reaction rate is observed. At 50°C, the $\underline{\alpha}$ versus $\underline{t}$ curves were characterised by a long almost linear portion. The reaction velocity was described by an approximate autocatalytic equation (equation 15) when the reaction was carried out at 30°C.

$$\frac{d\alpha}{dt} = k\alpha(a - \alpha) \qquad \text{--- Eq. 15}$$

where k = rate constant

a = initial amount of reactant

α = amount decomposed

$\frac{d\alpha}{dt}$ = the rate of change of α with respect to time t

This equation was observed not to describe the same reaction at 50°C.

Hinshelwood and Bowen (47) reported on the rate of chemical reaction in the crystalline solid. Using potassium permanganate, potassium perchlorate, ammonium dichromate and tetranitroaniline, the authors studied the decompositions at various temperatures and concluded that changes appear to be confined to the molecules in the neighbourhood of the surface and further observed that when disintegration of the crystal structure takes place the reaction was strongly accelerated.

Hedvall (49) recognised and reported that reactions in the solid state occur frequently and represent indeed an important branch of chemistry. From the available early literature, it is noted that studies were carried out mostly in the fields of chemical engineering, metallurgy, ceramics and in inorganic chemistry. Through such studies, kinetics of reactions were developed and factors influencing reaction rates, mechanisms or pathways were documented.

1.3.1 Factors Influencing Reactions in the Solid State

Jander (50) studied the reaction between two kinds of crystals and proposed a theory involving the vibration of crystal molecules in the space lattice. The vibrations cause initial contact between two compounds forming a molecular layer of the reaction product at the contact surface. Diffusion of one or both compounds through the reaction layer then propagates the reaction. Higher temperatures favour the increase in reaction velocity because of increased amplitude of vibration.

Nucleation is the process by which the reaction interface is initially established at perhaps a limited number of points in the reactant, usually at a surface and possibly at an imperfection (8). Potential nucleus-forming sites are generally associated with some type of lattice imperfection such as lattice defects, dislocations and cracks. Reactions of solids often occur at the area of contact of two solid phases, thus before a chemical change takes place, it is necessary to generate this interface. This process is called nucleation (36). Factors which encourage the nucleation process have been reported extensively, the notable factor being crystal defects (51-55) which generally cause an increase in reaction rate.

Brislow and Rees (52) observed that in the thermal decomposition of cadmium iodide, the reaction occurred preferably along crystal dislocations and probably along dislocation lines as observed under a beam of an electron microscope. In another study, a cube was examined (55). The corner atoms were the most reactive and that the reaction would proceed along the direction exposing more of the plane. Microscopic imperfections were claimed to influence rates of reactions strongly. Any defect that leads to a decrease in lattice energy is said to enhance the reaction rate. In the decomposition of cadmium carbonate, samples with fewer defects had higher activation energy for decomposition and low reaction rates.

Physical adsorption (56, 57) is claimed to correlate with perturbations of solid bonds on the crystal surface and so become responsible for influencing reactions through contact among particles

(58). It was observed that reaction rate between solids, the temperature of polymorphic transitions and fusion, rates of recrystallization and the mechanical properties of solids vary when measured under different gaseous atmospheres. Mutual polarisation of surface atom and the physically adsorbed molecule may weaken the polarisation contribution to forces binding the solid atom to its neighbours and therefore allow an atom to be displaced more readily from its lattice position (56). Reactions taking place on a solid surface are said to occur because the stability of the adsorbed substance is modified by forces between it and the surface so that a smaller amount of energy suffices to bring it to a reactive condition (54, 57). Furthermore certain reactions which would not occur in homogeneous systems, for example the decomposition of ammonia, will be rendered possible by the presence of active surfaces (57). Initial contact of substances reacting in the solid state has been defined as the ratio of originally contacting molecules to stoichiometric molecules in the mixture (58). The reaction rate was found to be directly proportional to the magnitude of the initial extent of contact of reacting substances. In controlled conditions, the greater the difference in grain size of the components, the greater will a change in the ratio of components affect the magnitude of the initial extent of contact, and also the reaction rate in the solid state (58).

The effect of particle size on the reaction rate has been well documented (59-61). Using the equation of Carter (Table 14) which was a modification of Jander equation (Table 1, equation 8), Sasaki (59-60) introduced the concept of particle size distribution into the kinetics of solid state reactions; using the data for the reaction between zirconium oxide and lead oxide to give lead zirconate. Feitknecht (61) observed further that solid state reaction mechanisms could be influenced by particle size. Nicholson (62) observed the variation of surface area during the thermal decomposition of solids; and showed that surface area increases linearly with fraction decomposed and that sintering is proportional to surface area. Surface area changes are complicated by the fact that elevated temperatures encourage sintering so that the particles in contact weld together, leading to a reduction in surface area. Sintering can be distinguished according to T_S, which is the ratio of absolute temperature of reaction to the absolute melting temperature of the solid. When T_S is less or about 0.2 adhesion of particles occur, between 0.2-0.35 surface diffusion predominates and when the ratio is 0.5 bulk diffusion is possible (62).

A study was conducted by Petersen (63) to investigate whether the rate of diffusion within a porous structure influences the overall rate of a chemical reaction taking place at the surface. In studies of slow self propagating reactions in solids Hill et al. (64) concluded that propagation of heat for the reaction occurred only by thermal conduction. In addition, diffusion of hot gaseous products through the interstices may in some cases convey heat over and above that conducted by the solid.

In mixed powder systems, both the particle size (65) and the mixing ratio of the reactant constituents (41, 66, 67) have been shown to influence reaction velocity. Both the mixing and the mixing ratio are claimed to influence reaction through contact. Komatsu (66) derived an equation for the rate of reaction under the assumption that reaction starts from contact zones of solid particles. The reaction velocity being proportional to the number of contact zones, while diffusion and surface forces are the rate determining factors.

It has been observed and reported that water could increase the rate of reaction of solids, through adsorption or hydrate formation (68-70) or through catalysis (71). Forestier and Haasser (68) studied the effect of physical state on the rate of reaction between metal oxides and water. The studies revealed that the effect of water on the reaction between solids is greater for those solids having greater affinity for water either by adsorption or hydrate formation. By using magnetic detection for ferrites the authors studied the reaction between Fe_2O_3 and oxides of nickel, lead and magnesium. Even minute traces of water were observed to increase the reaction rates. The data was explained in terms of the number of contact points and the effect of adsorbed water vapour on the surface of the crystal lattice. Taradoire (69) observed that soluble compounds adsorb water to form a surface film, which, in the presence of other matter in contact, causes double decomposition. The author explained reactions such as corrosion which occurs as a result of water vapour and may lead to many solid reactions even at room temperatures. Perrin and Roubault (71) described the effects of water on reactions in the solid state as catalytic in nature. In the reaction of calcium carbonate and silicon dioxide, only compounds that contained water catalysed the reaction. Water was therefore claimed to mediate the catalytic effect. It was further claimed that the presence of low melting point substances such as alkali fluorides and chlorides might act similarly.

Geometric arrangements in crystalline reagents were proposed by Marawetz (72) to explain pronounced differences in reactivity of closely related compounds and the differences in the products in solution and in the solid state. The geometrical arrangement of the molecules in the crystal is of crucial importance in determining its reactivity. Whenever observed phenomena cannot be accounted for by the chemical properties of isolated molecules, but are clearly a consequence of their geometrical arrangement in the crystal structure, the process is said to be under "topochemical control". Evidence for the existence of such phenomena was outlined by the following examples:

(i) A reaction occurs in the solid state, when the liquid reagent is either totally unreactive or reacts at a much lower rate.

(ii) Pronounced differences, which cannot be accounted for by known chemical principles are found in the reactivity of crystals of closely related compounds.

(iii) Different reaction products are obtained when the reaction is carried out in the solid state and in the liquid state.

(iv) The same reagent in different crystal modifications has a different reactivity or leads to different reaction products.

(v) Reaction products are formed whose molecules have a preferred orientation, in a crystallographic direction of the present reagent ("topotaxy").

These observed phenomena were said to be demonstrated in free radical reactions in organic crystals, isomerization and dimerization reactions and solid state polymerization reactions involving chain growth. In the photochemical stability of tricyclic neuroleptic drugs, induction of cis-trans isomerization was rapid in solution (73) but believed to be very slow or insignificant in the solid state.

The importance of high pressure in gas solid reactions (74-76) has found wide use in many industrial processes and such reactions have been claimed to offer unique possibilities in organic chemistry (75). Kinetics of some solid state reactions at high pressure, were studied by Zeto (76) who observed the influence of both temperature and pressure on the polymorphic transformation reactions of silicates. Pressure was observed to increase the transformation rate. The reaction between organic crystals and gases appear to be greatly influenced by the crystal structure (75). The authors (75) further stress that crystal structure data for molecular crystals should lead to a rapid development of the principles governing the packing of such crystals and their reactivity. The resulting control of such reactions should provide a means of causing them when desired as for example for synthesis or the means of preventing them when they are to be avoided, such as in the stabilization of pharmaceuticals.

The factors that influence chemical reactions in the solid state, as outlined above, have shown that reaction rates and even pathways are influenced in a complex manner which can probably be understood best with detailed kinetic studies.

1.3.2 Development of Solid-State Reaction Kinetics

Solid-state reaction kinetics were originally developed from the use of double decomposition reactions involving gas evolution. The degree of decomposition was monitored by measuring gas volumes or changes in weight of the reactant. In most experiments, simple inorganic substances like the carbonates, silicates (50) and oxides (69, 71) were studied.

1.3.2.1 Reaction Kinetics for Inorganic Solid Substances

The first and probably the most detailed kinetic model for solid state reaction is that of Jander (50, 77-80). Jander presented a theory of reaction between two kinds of crystals. The reaction was dependent upon temperature and crystal size and the rates were dependent upon general diffusion laws. By studying the reaction of barium and calcium carbonates with silica at temperatures in the region of 800°C, Jander developed a mathematical expression (Table 1, Equation 8), which is popularly referred to as "Jander's Equation", to define the velocity of the observed reaction. Some gas-solid reactions (81) for the systems studied, were found to be influenced significantly by air and water vapour. Water vapour was shown to effect the extent of reaction profoundly. Jander's equation was used to quantify the reaction velocity. In order to measure accurately the velocity of reactions in the solid state in which gas is evolved Jander and Hoffmann (82) devised a system consisting of flow meters and manometers, to study the barium carbonate and silica reaction, at temperatures ranging from 624 to 748°C and observed that the reaction was independent of external pressure.

Several modifications have been done on the basic Jander Equation (83-89) and the most reported reason for modifying is the limitation of the applicability (83) and some error in the basic assumptions (87).

Ginstling and Fradkina (83), for example, studied the reaction of a mixture of calcium carbonate and molybdenum oxide. Initially

MoO_3 sublimes and forms a film of $CaMoO_3$ and as this complex thickens, the rate of diffusion of MoO_3 towards the centre as well as an outward diffusion of carbon dioxide becomes the rate controlling factors. An equation derived based on diffusion was applicable. For the same data, Jander's equation did not yield constant values for the rate constant during course of the reaction.

Kroger and Ziegler (84) observed that reactions between carbonates and silicates in glass manufacturing at temperatures in the range of 700-900°C are strongly dependent on the formation of the first polyeutectic melts. The mole ratios of the constituents determine the rate of reaction in the batch mixes. The reactions were found not to correspond well with the linear Jander model. The relationship between the change of thickness of the reaction product layer with time was found to be a better approximation when expressed in the form of equation 16(a),

$$Y^2 = K \ln t \qquad \text{--- Eq. 16(a)}$$

in contrast to that used by Jander

$$y^2 = 2Kt \qquad \text{--- Eq. 16(b)}$$

where Y = thickness of reaction product layer

K = the rate constant for the advance of reaction product interface (cm^2/sec)

t = time

The relationship (equation 16(a)) is claimed to be a better approximation because it embraces the structural changes occurring with time in the layers of the reaction product. The factor <u>ln t</u> corresponds to a continuous change of diffusion in the reaction layers.

Carter (87) discussed some over-simplifications in the basic assumptions of Jander's equation. The author claimed that the rate of advance of the interface as given by Jander (equation 16(b)) is for the reaction of a plane surface and that the volume of the product was assumed to be equal to that of the reactants. The author further concluded that the developed equation (Table 14) was shown to model the oxidation of nickel spheres to 100% reaction. The fit between earlier but simplified models and published rates for small amounts of reaction, results because any shape of particle approximates to a plane if only a thin layer of particle is reacted.

In studies with solid salts, the formation of nuclei or reactive centres have been reported (90, 91).

Cooper and Garner (91) studied the formation of dehydration nuclei on crystals of chrome alum. The authors observed that uniform growth of nuclei resulted in circular shaped nuclei and when there were marked differences between the rates of growth in different directions on the crystal surface, the nuclei possessed complex outline as observed for $CuSO_4.5H_2O$ to be star shaped. These shapes of nuclei were claimed to be linked with induction periods observed in solid state reactions.

In the decomposition of barium azide Bartlett et al. (92) observed that reaction proceeds at the interface between the anhydrous azide and discrete nuclei of metallic barium formed on the surface. The nuclei are formed at a rate proportional to the square of the time, and when such nuclei are large, they grow at a constant rate. Izmailov (93) reviewed the theory of topochemical reactions and reported that the velocity in the case of a decomposing single crystal is initially proportional to the third power of time, if it is assumed that the reaction centres appear continuously during the reaction period. The reaction of decomposing solids (94-98) as well as mixed powders (99-100) have been studied extensively on the basis of the nucleation theory, with the resultant development of kinetic equations.

Avrami (101-103) used, as a basis the empirically developed equation of Austin and Rickett (104) to develop an equation which describes reaction kinetics by the probability of formation of nuclei. The equation which has been described in the literature as the Avrami equation (105, 106) or the Avrami-Erofeer (36) or the Johanson-Mehl-Avrami-Erofeer-Koglomorov (30) equation is presented in the form:

$$\frac{\alpha_t}{1 - \alpha_t} = \beta t^n \qquad \text{--- Eq. 17}$$

where α_t = fraction decomposed at time t

β and n = constants

In a series of studies, Komatsu (105) used a modified form of the Avrami equation to study the decomposition of potassium permanganate. Okamura _et al._ (106) studied the thermal decomposition of 5-nitro-acetyl salicylic acid in a humid environment and applied successfully the Avrami equation.

Prout and Tompkins (107) attempted to explain the kinetics of decomposition of potassium permanganate in a form which when suitably modified could be applied to other similar reactions. An equation (Table 1, equation 7) which has the form of a modified auto-catalytic expression was found applicable and a theory was postulated, to lead to the correct relation. The theory postulated was based on the formation and growth of nuclei. Erofeev and Smirnova (108) confirmed the findings of Prout and Tompkins (107) and further showed that the reaction is applicable up to 82% decomposition and that reaction centres were whole crystal planes. Furthermore, the authors reported that no reaction nuclei could be observed under a microscope. Belkevich (109) reviewed the topokinetic equations and the application of such equations to thermal decomposition of solids, and found that several equations which were not based on nucleation theory as inapplicable for decomposition of lead, nickel and silver oxalates. The Prout-Tompkins and the Koglomorov-Erofeev (30) equations were found to model the data up to 10-15% only. An equation which was claimed to be a better model for the above reactions was presented:

$$\left(\frac{1}{1 - \alpha_t}\right)^u - 1 = kt^n \qquad \text{--- Eq. 18}$$

where $u = s - 1$ $(s > 1)$ it is a constant referring to the crystal structure and the number of intersections of nuclei

α_t = proportion reacted at any time t

k = rate constant

n = the number of stages in the formation of initial centres

In highly dispersed systems, where random nucleation forms only a single nucleus on an individual particle, the kinetics is then described by a unimolecular decay law for the final stages of decomposition as derived by Mampel (110) (Table 1, equation 10). The decomposition of cadmium carbonate (111) and the reaction between bromine and ozone (112) were shown to follow first order kinetics. The reduction of lead oxide by hydrogen was shown to follow equation 9 (Table 1) (113) which has been shown recently to approximate the unimolecular decay law (114).

Many of the kinetic equations describing reactions in the solid state which appear in the literature have been empirically developed, while only a few have been developed on the basis of sound mathematical foundations. Eyraud (115) observed the large number of equations that have been presented, together with the diversity of kinetics for similar compounds and attributed to possible inaccuracy of data, and so suggested the need to have rigidly controlled experimental conditions so as to attain reproducibility. In a study of the decomposition of calcium carbonate in vacuum and in the presence of carbon dioxide it was found that erratic results were obtained such that it was impossible to develop a mathematical correlation (116), while good results were obtained for the decomposition of calcium carbonate hexahydrate (117).

The problems regarding the correlation of experimental data and the developed equations were also noted by Hüttig (118) who suggested classifying solid state reactions into five groups. These were reactions dependent on polymorphism, fusibility, volatility, surface effects and degree of homogeity of mixtures. Posin and Ginstling (119) also classified the reactions in the solid state into three groups based on evaporation or sublimation, diffusion and true chemical reactions. Unfortunately, the equations which were developed to correlate with the above classification did not match the data, so modified equations which were again developed (120) found some applicability in specific reactions (83).

Another classification of solid state reactions (121), together with various communications on the kinetics of solid state reactions (122, 123) stresses further the complexity and problems inherent in the interpretation of the kinetics of solid state reactions.

1.3.2.2 Reaction Kinetics: Organic and Pharmaceutical Solid Compounds

The stability of pure chemicals is well covered in the chemical journals but the study of pharmaceutical solids has not yet been covered extensively (114). Leeson and Mattocks (124) were probably the first to recognise and report that the decomposition of aspirin in the solid state did not follow the known solution kinetics. An alternative equation (Table 14) based on sorbed moisture layer theory was presented. Lachman (125) demonstrated the applicability of solution kinetics to the degradation of tablet dosage forms. Nelson et al. (126) studied the decomposition of aspirin solids in admixture with alkaline additives and used the Jander model to evaluate the kinetics of decomposition at low temperatures and the geometrical kinetic model (the contracting cylinder model) at temperatures higher than 45^{o}C. Other studies in which pharmaceutical decompositions have been monitored kinetically include the work of Kornblum and Sciarrone (127) and that of Carstensen and Kothari (128). These authors used Bawn kinetics to study solid state decomposition which occurred with melting, for alkoxyfuroic acids.

In the kinetic studies of solid dosage forms, many authors have tried to answer fundamental questions about the actual physical phenomena involved in the overall undesirable changes observed as a result of chemical changes. In the study of degradation mechanisms for water soluble drugs in the solid state (129) it was proposed that dissolution of the drug in the sorbed moisture was followed by adsorption of the dissolved drug on the main excipient. Degradation is then confined to the first monolayer of the sorbed solution.

Many kinetic studies on pharmaceutical dosage forms that have been reported in the literature are based on equations that describe degradation in solutions or on the equations that have been developed and applied to inorganic crystals or mixtures of reactive inorganic substances.

Zero-order kinetics have been reported to be followed in the reaction between bromine and ozone (112) in which the reaction could revert to first order depending on the amount of oxide. The decarboxylation of p-aminosalicylic acid was found to follow a sigmoid type curve in dry atmosphere but in moist atmosphere, zero order kinetics appeared to be indicative of the degradation pattern (127). In the experiments in moist atmosphere (with aqueous tension of 181.0 mm Hg) the induction period was greatly diminished. The zero-order kinetics observed were attributed to the solubility of the p-aminosalicylic acid in the sorbed moisture layer which appeared to be a function of the aqueous tension over the sample. The degradation of folic acid powder (130) in the pure drug and as a mixture in microcrystalline cellulose was followed for 18 months at 3 temperatures (55-85^{0}C) and 3 relative humidities (30-70%). A zero-order relation was observed up to 35% degradation. The thermal degradation of fumagillin in the absence of air (138) and the degradation of vitamin A esters (132) were described by zero order kinetics.

The degradation of nitrazepam, formulated in microcrystalline cellulose, under the stress of temperature and humidity was found to adhere to no published kinetic model.

However, the degradation of vitamin A in vitamin (AB_1C) multivitamin tablets (42, 43), and the degradation of vitamin A in solid-dosage forms were found to adhere to pseudo first-order kinetics. The decarboxylation of p-amino-salicylic acid (135), the photodegradation of fumagillin in the presence or absence of air (131), the degradation of aspirin in microcrystalline cellulose (136) and the kinetics of fading of certified dyes in tablet formulae (137) have been described by first order kinetics.

Second-order kinetics were shown to be applicable in the thermal decomposition of fumagillin in the presence of air (138).

The Jander's Equation was demonstrated in the study of the effect of water on the degradation of probanthelin bromide mixed with dried aluminium hydroxide gel. The degree of dispersion was found to influence the rate of degradation (139). Nelson et al. (126) used the Jander equation to describe the kinetics of degradation of aspirin in the presence of alkaline additives in the solid state.

Rastogi and others (140, 141) used an equation based on the change in thickness of reaction interface with time, to monitor the reaction between picric acid and α-naphthol. By following the movement of the coloured interface, the authors expressed the advance of interface by the following expression:

$$y^2 = 2kte^{-py} \qquad \text{--- Eq. 19}$$

where y = thickness of product layer

p and k are constants.

Linear relationships were observed for plots of log y/t against y.

In the study of decomposition of mono- and di-nitrobenzenediazo-oxides in vacuum, Vaughan and Phillips (142) showed that their results were in agreement to the theory of solid phase decomposition put forward by Prout and Tompkins (107). Hirota et al. (143)

studied the air oxidation of ascorbic acid and used Lacey's theory (144) which was developed for non-catalytic gas-solid reactions to estimate the shelf life. Hasegawa et al. (145) studied the degradation of aspirin derivatives and found that the Avrami equation (101), the Prout-Tompkins equation (107, 146) and an equation developed by Kawakita (147) could not be used to describe the experimental data obtained. The authors found that only the power expression (Table 1, equation 4) could fit the decomposition fraction in the acceleratory period. As the decomposition mechanisms were very complex, the authors attempted to express the decomposition curves by an empirical formula (Table 14) in order to investigate the influence of decomposition conditions on the decomposition rate. The decomposition of 5-nitroacetylsalicylic acid crystals in humid conditions was found to adhere to Avrami equation (106).

The development of equations describing kinetics of decomposition of pharmaceutical solids and solid-dosage forms seem to suffer from the same lack of a unified approach similar to the reports appearing in the chemical journals on the stability of pure chemicals.

Carstensen and Musa (150) described the decomposition of benzoic acid derivatives on the basis of their melting points and that decomposition was first-order beyond the liquefaction point. In the decomposition of 5-(tetradecyloxy)-2-furoic acid, a novel hypolipidemic agent (128, 151), the overall reaction was considered to be controlled by the sum of the rate constants for the degradation of the intact solid and in the liquid decomposition product. This type of data analysis has been termed Bawn kinetics (128).

The pyrolysis of acetaldoxime (148, 149) has been shown to yield fifteen degradation products and a free radical mechanism was proposed. Kinetically the reaction was said to be first order. The effects of additives was studied and it was found that propylene acts as an inhibitor while nitric oxide causes considerable acceleration. The overall reaction was described to proceed through an initial slow first order reaction, followed by a faster one of about 1.2 order.

Many reports on the decomposition of pharmaceutical products have not included kinetic equations. Examples include the study on the stability of aspirin tablets at 20°C, 40% RH (152), the report on the state of aspirin after 34 years of storage under ambient conditions of temperature (153) the browning of spray dried lactose (154), the decomposition of ascorbic acid in dosage forms (155), thiamine mononitrate (156) and that of thiamine, riboflavin and niacinamide (157).

1.4 Drug-Drug and Drug-Excipient Reactions

Drug-drug and drug-excipient reactions have been grouped (7) as drug incompatibilities which fall into three major divisions, namely physical, chemical and therapeutic incompatibilities. Physical incompatibilities include precipitation, colour change, melting and polymorphic changes. Chemical incompatibilities involve reactions in which bond cleavage occurs with the resultant formation of new substances. Therapeutic incompatibilities cover the aspects of reactions experienced by a patient when taking two drugs simultaneously, and are referred to in the literature as adverse drug reactions or drug interactions. However, this classification is not perfect since some adverse reactions are known, the cause being a physical or chemical change of the drug. Such changes have been observed for p-aminosalicylic acid (6). The drug is normally used with streptomycin or isoniazid in the treatment of tuberculosis. Acute haemolytic anaemia with methemoglobinemia was observed in children treated with the drug after it had undergone decomposition (6).

In this thesis the emphasis is on chemical incompatibilities. The reactions between aspirin and codeine (158, 159), that of aspirin in admixture with quinine sulphate, codeine phosphate, luminal ^{R} and phenacetin (160), aspirin with aminophyline (161), aspirin with amphetamine (162), aspirin with acetaminophen (163), aspirin with homatropine (164) and aspirin with phenylephrine (165) serve as examples which stress the importance of studying chemical incompatibilities in pharmaceutical dosage forms. Although the reactions of aspirin are said to be due to acetylation of alcoholic, amino or phenolic groups (164) the observed degradation of aspirin in the presence of calcium succinate and calcium carbonate (166) suggest the role of other mechanisms. In this study (166) aspirin with calcium carbonate in the absence of moisture was observed to be stable but not with calcium succinate. The use of either calcium or sodium succinate when combined with aspirin could overcome the depressant effect on tissue metabolism and respiration shown by aspirin and salicylates when administered in large or protracted doses, such as in the treatment of rheumatoid arthritis.

When developing a dosage form, various types of excipients may be required to modify the properties of the dosage form or to facilitate processing. Such excipients, however, may be responsible for drug-excipient interactions or may interfere with assay procedures for drug substances (167).

Drug excipient reactions are known to occur (168, 169). These interactions include the benzoic acid-starch complexation (170), the enhanced degradation of aspirin in the presence of magnesium stearate (171-174), or calcium stearate (172, 175) and with magnesium oxide (176). In a comparative study (172) it was shown that the additives exerted great differences in their effect on the enhancement of aspirin degradation. In order of decreasing severity the additives were listed in the following order: calcium stearate > magnesium stearate > stearic acid > talc. Addition of mineral oil in talc makes it less suitable as a lubricant for aspirin. The washing of USP talc with acid was shown to enhance aspirin stability (177). The presence of basic impurities in magnesium stearate (174) was claimed to induce the observed high rate of aspirin degradation in suspension systems containing added magnesium stearate. Precirol ^{R} which is glyceryl palmitostearate, was shown to enhance the stability of aspirin, when it was incorporated in an aspirin tablet made from starch and magnesium stearate (173). The presence of water in aspirin-ascorbic acid matrices has been claimed to be responsible for the observed degradation of the components (178). The method of granulation of APC tablets (179) and the incorporation of fatty acid lubricants (180) in aspirin solid-dosage forms, have been shown to influence the stability of the formulations. The type of container (181) was shown to influence the rate of pyrolytic degradation of aspirin anhydride. This was claimed to be accelerated by surface irregularities and by contact with alkalis, even those contained by "soft" glass. The presence of solvates, moisture, excipients and products diminished the induction period and increased the slope of the acceleratory phase of the sigmoid type decomposition curve. Micronisation and subsequent drying were found to favour stabilization since entrapped solvent and any of the contaminants were said to be sufficiently volatile to be removed by such procedures. The major route of decomposition with temperature was the formation of a liquid melt at the surfaces which serves as solvent for the decomposition.

A cautionary warning on the possible reaction of drugs with new steel utensils (182) has been reported. The reaction between vitamin C powder and metallic ions of copper, cobalt, manganese, zinc and iron has been reported (183). The influence of solid vehicle matrices and additives like mannitol and lactose on the stability of vitamin A, B_1 and C tablets has been investigated (184).

The abundance of reports on incompatibility studies have prompted suggestions for techniques such as the factorial design of experiments for detecting such interactions (167, 185).

1.4.1 Possible Mechanisms of Reactions in the Solid State

Carstensen and others (129) noted that there have been few reports on the actual physical phenomena, apart from purely chemical reactions which are involved in the degradation of solid dosage forms. In their discussion on possible mechanisms involved in the degradation of water soluble drugs, the authors stressed that for dry non-interacting solids or for sorbed moisture layers saturated with drug (similar to a concentrated "suspension") the degradation should be of zero order type. Observations however, reveal the adherence of first order reaction kinetics in such systems, implying that the degradations are much more complex than those which can be expected from reactions in saturated solutions.

Jander (77) proposed the mechanism of interface advance in reactions involving two kinds of crystals. The reaction mechanism which is based on diffusion controlled processes, has been used to explain and develop many kinetic equations applicable to mixtures of solids (84-88, 119, 126). These equations appear to be useful in explaining drug-drug or drug-excipient interactions in the solid state.

The nucleation theories as developed by Prout and Tompkins (107, 146) and Avrami (101-103) have been used to rationalise observed decomposition patterns in pure substances (95, 142) and in mixtures (105).

The unimolecular decay law, as developed by Mampel (110) was based on nucleation theories. Typical nucleation reactions are characterised by sigmoid type curves, the slow induction period, the acceleratory phase and the decay or deceleratory phase. The unimolecular decay law and the geometric models are characterised by deceleratory type curves. In explaining the unimolecular law in terms of nucleation, Galwey (36) attributed the absence of the slow induction period, in terms of very rapid nucleation. Such rapid nucleation reduces the lag-time and conceals the initial acceleratory phase of a normal sigmoid curve. The reaction proceeds, giving a resultant deceleratory curve. The unimolecular law and the geometrical models are characterised by closely similar deceleratory type curves and mathematically the kinetic equations have been shown (114) to be approximately similar.

A thorough knowledge of solid state reaction mechanisms and crystal structure effects (186), coupled with basic principles in in reaction kinetics (5) are essential in rational approach to drug stabilization.

1.5 Stabilization Techniques for Drugs in the Solid State

Product stabilization is essential because of the need to minimise degradation of active ingredients and the maintaining of the product quality throughout the time of use. Rational approaches for the stabilization of drugs have been suggested (186). These include the synthesis of more stable derivatives relative to the parent compounds such as in the use of ergocalciferol derivatives instead of ergocalciferol; the use of high melting point esters of vitamin A which are more stable than those with lower melting point (132, 186, 187) and the use of anhydrous powders which are more stable than hydrated crystalline forms; such as dihydroxyphenylalanine and arsenous acid anhydride (186). These approaches are based on the concept of crystal engineering which is a study of factors affecting crystal packing (186). The development of the principles governing crystal packing should provide a means of preventing crystal reactivity which could be useful in the stabilization of pharmaceuticals (75). Unsaturated fatty acids in the form of urea inclusion compounds in the channels of urea crystals, have demonstrated stability from oxidation (75). This observation has been attributed to crystal packing.

In the study of the stability of cefoxitin sodium, the amorphous form was found to be less stable than the crystalline form (188). In the study of the stability and other physical properties of amorphous and crystalline forms of indomethacin, Imaizumi et al. (193) showed that the amount of water absorbed by the amorphous form increased with increasing relative humidity, and at 30^{0}C, 89% relative humidity it changed to the crystalline forms. The transition of amorphous form to crystalline forms followed first order kinetics.

The presence of water in the form of moisture is said to account for many pharmaceutical drug decompositions, through hydrolytic action (189). The suggestion to dry drugs in a moisture level of below 0.1% (190) is attractive and practicable for a large number of drugs, but maintaining that level of moisture content on storage is practically impossible for many products. However, mixing of drugs with substances which preferably adsorb moisture may find wide applicability. An example is given by the enhanced stability of aspirin when mixed with colloidal silica (191). Colloidal silica exhibited an adsorption isotherm characteristic of multilayer adsorption with limited pore volume. The silica with the greatest moisture adsorption was evaluated for its stabilising effects on aspirin in tablet form. It was observed that silica enhanced aspirin stability: a concentration of 3% offered maximum stabilization. The silica enhanced stability by acting as an internal moisture scavenger. Tablets with a higher concentration of silica (up to 15%) showed poorer stability and approached the control tablets in aspirin content after 120 days, at 40°C and 81.7% relative humidity.

The use of solid dosage forms, in fact offers solutions to many stability problems, so it could be said to be a form of drug stabilization in the context of moisture absence. Relative unreactivity of solids can be demonstrated by hydroquinone which in solution reacts with oxygen but will not react in the form of a crystalline solid (75).

Despite the problems of bioavailability (167) inherent in solid dosage forms, further treatment to enhance stability such as film coating or microencapsulation (192) are bound to affect bioavailability. Coating or microencapsulation of one or more inter-reactive ingredients in a mixture or multicomponent formulation has been used as a technique for stabilising solid mixtures of reactive ingredients (190, 192, 194). The rationale for film coating is to prevent or delay moisture or oxygen entry into the tablet core and hence the active ingredients. Drugs that are unstable to air or other environmental conditions, and volatile drugs can be given improved levels of stability by film coating or microencapsulation (192, 194). This improved level of stability was demonstrated using mixtures of aspirin and microencapsulated aspirin with chlorpheniramine maleate. The microencapsulated aspirin clearly showed improved stability even with chlorpheniramine maleate, relative to the uncoated samples (192).

In a series of studies on protective coating, Utsumi and others (195, 196) and Ida (197) have tested several polymeric materials including cellulose derivatives and identified agents suitable for film coating, intended for protection of drugs from adverse environmental factors. In their studies, the authors identified the derivatives of polyvinyl pyridine as useful in protecting aspirin, aspirin-aminophylline-phenacetin and vitamin B_1-C tablets against humidity. It was further demonstrated that (197) a coating thickness of 60-100 μ was sufficient for protection, without adversely affecting the release of the drug. In their studies of the factors which affect water vapour transmission through polymer films applied to solid surfaces, Amann and others (198) found that the type of film affected the activation energy of the absorption process, while the method of film application affected the rates of permeation at a given temperature and that the physical properties of the coated substance affected the water vapour absorption rate. It was therefore suggested that, with a given type of film the absorption rate may be decreased by ensuring that the film is in intimate contact with the dosage form. In tablets, maximum feasible compression compatible with disintegration considerations was recommended to reduce the porosity with resultant reduction in water vapour absorption. From the above recommendations, it can be deduced that proper choice of film forming polymeric material, and proper choice of film coating method are essential factors in film coating processes intended to impart stability on formulated products. It has been shown that, tablets coated with 10% polyvinyl-pyrolidone and 4% shellac attained improved stability, and that the observed improvement on the product quality was attributed to the protective ability of the film coat against moisture (199).

Additives usually present in dosage-forms as formulation factors (200) have been shown in some cases to improve the stability of a formulation. A binder-lubricant Precirol ^{R} (glyceryl palmito stearate) was found, when incorporated in aspirin tablets formulated with starch and magnesium stearate, to improve the stability of the tablets as observed over a period of 3 months at 50°C (173). Mixing of aspirin with buffer salts of various pH as an attempt to control the pH of the microenvironment was attempted (201). It was found that the decomposition followed first-order kinetics after a brief induction period and that the decomposition was dependent on the pH of the salt as the case in solution. The inhibition of stearate induced aspirin degradation by some organic acids such as malic, hexamic or maleic has been studied (202). It was found that when the acids were included in the formulations at a level of 20 percent by weight of the complete mixture, a level of inhibition was attained such that the formulations could be said to be stable with respect to salicylic acid content. Studies on thermal decomposition of silver oxalate at 133°C in the presence of diaryl polyenes were conducted; to study the effect of organic additives on the rate of thermal decomposition of solids. The organic additives were better than the inorganic additives in inhibiting the reaction. The inhibition action of the diaryl polyenes increase with the increase in chain length and by the introduction of electron donor substituents on the para or ortho positions in the aromatic rings (203). The stabilization of a water soluble preparation of vitamin A by the use of mollases from beet sugars as antioxidants and filler in capsules, as well as the use of malt extracts has been reported (204). Fat soluble vitamin A and D are claimed to be stabilised by mixing with fatty acids and long chain amines (205).

Photochemical reactions have been shown to cause fading of certified dyes when used as additives in tablet film coats. By incorporating u.v. absorbers, into the film coats, the colour stability was restored (206).

Due to instability of aspirin in solution, modern trends to formulate aspirin have been almost exclusively in the solid dosage form. Aspirin is available in a wide range of specialised formulations usually made on the basis that they give ~~use~~ rise to diminished side effects, that they promote more rapid action or give prolonged action. In the formulation of such specialised preparations, additives such as citric acid, calcium carbonate, sodium bicarboante, magnesium hydroxide or glycine have been used to impart special desired properties on the dosage form. The use of aspirin derivatives such as aluminium aspirin is based on better stability and less gastric irritation (107).

1.6 The Purpose and Scope of the Study

For the convenience of drug administration, multi-ingredient preparations in the solid dosage forms have found wide usage and acceptability to the patient in situations when two or more medicaments are required for an ailment. The basis for the manufacture of dosage forms with a number of ingredients, is probably the convenience given by drug combinations. In current use drug combinations consisting of a number of analgesics or chemotherapeutic agents (208, 209) are common.

Drug-drug and drug-excipient reactions as exemplified by aspirin with phenylephrine and aspirin with magnesium stearate respectively have been extensively reported.

It is the purpose of this study to try to understand chemical incompatibilities in the solid state using aspirin-magnesium stearate and aspirin-mepyramine maleate mixtures as models. The study involves coating the discrete particles of aspirin with film forming polymeric materials and subjecting such coated particles to stability testing programmes. The programme includes a comparative study of coated and uncoated particles with and without additives at elevated conditions of temperature and humidity. The effectiveness of film coats as barriers to drug-drug or drug-excipient reactions is studied. The observations in these tests could contribute to the knowledge of stabilization by film coating, which could eventually be applied to multi-ingredient formulations where inter-reactive species are likely to be co-formulated.

The study is essentially a pre-formulation one, where powders (simulating granules) are used in preference to tablets or capsules. This was done to avoid the inherent variables associated with tabletting or encapsulation such as variation in weight and drug content and the influence of binders, lubricants, fillers and compressional forces. The small number of additives in the formulations studied, make it easier to identify and interpret an observed effect. The slow decomposition in solids necessitates the use of high temperatures (ranging 50-60^{0}C) and rapidly reacting mixtures, so that a higher proportion of reactant decomposes to enable the development of reaction kinetics.

The problems observed in the method of stabilization, in the stability testing and in the assay procedures, as well as the probable mechanisms responsible for the observed reactions, have been discussed in detail.

CHAPTER 2

EXPERIMENTAL TECHNIQUES USED

CHAPTER 2

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2.1 Stability Testing Methods

2.1.1 Materials

Aspirin was obtained from Sigma Chemicals. Salicylsalicylic acid and Aerosil (200v) ^{R} (pharmaceutical grade) were gifts from Riker 3M, Loughborough. The following substances were obtained from British Drug House, Poole, England. Analar grades of salicylic acid, potassium chloride, magnesium chlorides and citric acid; laboratory grades of magnesium oxide, magnesium trisilicate and n-propyl-p-hydroxy-benzoate, technical grades of magnesium, calcium, zinc and aluminium stearates as well as purified sodium stearate.

Methanol (analar), ethanol (analar) and disodium hydrogen orthophosphate dodecahydrate were obtained from Fisons, Loughborough, England. Sodium chloride B.P. was obtained from Macarthys Ltd., Essex, U.K. and mepyramine maleate from May and Baker, Dangenham, Essex, U.K. Precirol-ato-5(glyceryl palmito-stearate) was obtained from Gattefosse Establishments, France.

2.1.2 Equipment

A thermostatic water bath, Tecam SB4 (Techne, Cambridge, UK), a humidity cabinet (Townson and Mercer Ltd., Croydon, UK), glass vials (Fisons Ltd., Loughborough, UK) and absorbent cotton wool (Boots Company Ltd., Nottingham, UK) were used.

2.1.3 Methods

2.1.3.1 Suspension Reaction Studies

The decomposition studies were carried out in water or in buffer solutions; McIlvaines Buffer Solutions (310). These buffer solutions were made by mixing appropriate quantities of disodium hydrogen orthophosphate dodecahydrate with citric acid. The pH value was obtained by varying the quantities of the above ingredients. The solutions at each pH value were adjusted to the desired ionic strength by addition of an appropriate amount of potassium chloride. At time zero, the drug with or without additive was added to 100 ml of the vehicle, pre-heated to 50°C in a shaking thermostatic water bath. 2.0 ml aliquots were withdrawn at pre-determined intervals and filtered through a 3 µ millipore membrane filter. The resultant filtrate was diluted with water and assayed by HPLC (high performance liquid chromatography).

2.1.3.2 Solid State Reaction Studies

Coated and uncoated discrete particles of aspirin or salsalate, were mixed with known proportions of magnesium, calcium, zinc, sodium, or aluminium stearates, citric acid, magnesium chloride, magnesium oxide, magnesium trisilicate, precirol, or mepyramine maleate. Samples of 100.0 mg quantities of each of the mixtures or of pure unmixed control materials were weighed into individual glass vials and loosely convered with cotton wool to prevent entry of condensed water droplets. The samples were then stored in a humidity cabinet maintained at 60°C. A 75% relative humidity (RH) environment was maintained at this temperature using a saturated solution of sodium chloride. Samples were taken at pre-determined intervals and assayed for aspirin or salsalate and its decomposition products by HPLC.

2.2 HPLC Analysis

The high performance liquid chromatograph was constructed from an Altex 100A constant flow solvent-metering pump, a Rheodyne 7120 valve fitted with a 20 μL loop, a Pye Unicam LC3 variable wavelength monitor, equipped with an 8 μL flow cell and operated at 285 nm with a sensitivity of 0.32 aufs, and a Pye-Unicam AR45 chart recorder. Reverse phase chromatography was performed using a 5 μ ODS Spherisorb (25 cm x 4.6 mm ID) column. The mobile phase consisted of 0.02% orthophosphoric acid and 60% methanol in water and was delivered at 1.4 ml-min^{-1}.

The solid samples were dissolved in methanol and quantitatively transferred to a 25 ml volumetric flask and made up to volume with methanol. The resultant solution was filtered, diluted and after addition of 1.0 ml (0.5 mg/ml) of internal standard (n-propyl-p-hydroxybenzoate) analysed by HPLC.

2.3 Dissolution Testing

2.3.1 Materials

Sieved pan-coated discrete particles of aspirin with a size range 710-1000 μ and microcapsules of salsalate of size range 150-300 μ were used. Double distilled water was used to make 0.1 M hydrochloric acid from concentrated volumetric solutions which were obtained from British Drug House, Poole, England.

2.3.2 Equipment

A USP rotating basket assembly was used. A Citenco FHP variable speed motor (Citenco Ltd., Herts., UK) was used to rotate the basket, the speed of which was monitored by a low speed optical tachometer (Ducklin Instruments, Portsmouth, UK). An SP8000 uv spectrophotometer (Pye Unicam) was used for monitoring the aspirin or salsalate released in solution.

2.3.3 Methods

Exactly 100.0 mg of particles to be tested were introduced into the basket and at time zero, immersed into 1000.0 mls of dissolution medium previously maintained at 37° ± 0.5°C. The motor was calibrated to rotate at 100 ± 5 rpm. 5.0 mls were removed, through a teflon filter placed at the tip of the sampling tube, at pre-determined intervals, with replacement to maintain a constant volume of dissolution medium. The samples were assayed spectrophotometrically for aspirin at 275 nm or for salsalate at 300 nm. During these tests no significant degradation of aspirin or salsalate was observed.

2.3.3.1 The Preparation of Buffer Used in Dissolution Studies

The buffer used as a medium for dissolution at pH 7 was made by mixing 18.5 mls of 0.1 M citric acid and 81.5 ml of 0.2 M disodium hydrogen orthophosphate dodecahydrate.

2.4 Pan Coating of Discrete Solid Particles

2.4.1 Materials

Cellulose acetate phthalate (CAP) was obtained from Kodak Ltd., England, hydroxypropyl methylcellulose (HPMC) was from Shin-Etsu Chemicals Co., Tokyo, Japan, Eudragit L^{R} (EL) was from Rohm Pharma GmBh Damstadt and gelatin (GEL) BP of 150 bloom was from Macarthys Ltd (Romford, Essex, UK). Analar grade solvents used were methanol, isopropyl alcohol and ethyl acetate and all were obtained from Fisons, Loughborough, UK.

2.4.2 Equipment

The glass coating pan used was made in the laboratory and had a maximum external diameter of approximately 170 mm and was rotated by a Citenco FHP variable speed motor (Citenco Ltd., Herts., UK). To spray the coating solutions a Boots Nose and Throat Atomiser (Boots Co., Nottingham, UK) was used. A hair drier (Murphy Richards, UK) was used for drying the powder bed.

2.4.3 Methods

Solutions of polymeric film-forming substances were made according to Table 2. 100.0 g of aspirin crystals with a mean particle size 280 μ were placed in the laboratory model glass coating-pan which was inclined at about 45° and rotated at approximately 50 rpm by a Citenco variable speed motor. A fine mist of the coating solution was sprayed onto the rotating powder bed in short bursts. A constant low speed stream of warm air was used for drying the coated particles. The spraying and drying continued until all the pre-calculated amount of solids was deposited on the powder bed. It was observed that during the coating process the particles formed large agglomerates. These were broken down by slightly tapping with a spatula. After the final spray of coating solution, the powder bed was well dried, removed from the coating pan and further dried in a hot air oven at 70°C for one hour. The dried coated particles were stored in well closed glass jars.

Table 2

PREPARATION OF SOLUTIONS FOR POLYMERIC MATERIALS FOR COATING 100 g OF ASPIRIN

Coating Substance	Weight of dry substance applied (g)	Approximate solvent volume to make a solution possible to spray	Solvent system
EL	3.0	50 ml	Ethanol/Water (9:1)
GEL	3.0	50 ml	Water
CAP	3.0	100 ml	Isopropyl alcohol/ Ethyl acetate (1:1)
HPMC	3.0	50 ml	Water

2.5 Microencapsulation Techniques

The encapsulation procedure used was coacervation or phase separation utilizing complex coacervation of gelatin by acacia.

2.5.1 Materials

Acacia powder was obtained from Macarthys Ltd. (Bromford, Essex, UK), gelatin from Alfred Adams and Co., West Bromwich, England while Analar grades of isopropyl alcohol, glycerol and liquid paraffin were obtained from Fisons (Loughborough, UK). Formalin solution (37-41% w/v formaldehyde) was obtained from British Drug House (Poole, England).

2.5.2 Equipment

A thermostatic water bath (Tecam SB4-Techne, Cambridge, UK) and a Citenco variable speed motor (Citenco Ltd., Herts., UK) were used.

2.5.3 Methods

2.5.3.1 Complex Coacervation or Phase Separation

Salicylsalicylic acid (Salsalate) was used as a model drug for microencapsulation by the gelatin-acacia complex coacervation method because of its stability and low aqueous solubility (0.1 G/L at $37^{O}C$ and 0.5 G/L at $50^{O}C$).

250 ml of 2% solutions of acacia and gelatin were prepared and kept at $50^{O}C$ in a water bath. 5.0 g of salsalate was triturated with 2 ml of glycerol to make a well mixed slurry. The slurry was quantitatively transferred into the 250 ml of a 2% acacia solution at $50^{O}C$ and rapidly stirred at 400 rpm. The pH of the 2% gelatin

solution was adjusted to 3.8-4.0 with 0.1 N hydrochloric acid or 0.1 N sodium hydroxide before it was added to the acacia-salsalate dispersion maintained at 50^{0}C and stirred at 400 rpm. After addition, the pH was re-checked and re-adjusted to 3.8-4.0 when necessary. The mixture was maintained at 50^{0}C and stirred at 400 rpm for a further 20 minutes, after which it was transferred quickly to an ice cold water bath. The stirring rate was maintained until the temperature of the mixture had dropped to between 5-10^{0}C. During this cooling period, soft microcapsules were clearly visible under a microscope. When the temperature of the mixture had reached between 5-10^{0}C, stirring was stopped to allow the particles to settle. The clear supernatant and any froth formed were discarded without disturbing the bed of particles. 50 ml of isopropyl alcohol, previously kept in an ice cold bath was added and stirring resumed for 2-3 minutes. Another portion of isopropyl alcohol was added after decanting and removing the supernatant of the previous isopropyl alcohol wash. The mixture was stirred as previously described. A third portion of cold isopropyl alcohol containing 2 ml of formalin 40% (equivalent to 1.6% formalin in 50 ml isopropyl alcohol) was added as on the previous two occasions. The microcapsules were given a second wash with a further volume of the cold isopropyl alcohol/formalin mixture. The particles were finally washed with cold isopropyl alcohol only, transferred to clean filter paper and left to dry overnight at room temperature. These microcapsules were further dried at 70^{0}C for one hour in a hot air oven, and kept in well closed jars.

2.5.3.2 Phase Polymerisation Method

Another technique of microencapsulation which was attempted was based on the work of Tanaka et al. (264) who made microcapsules of gelatin using mineral oil to cause phase separation. Although the microcapsules so prepared were not used for stability studies because of the failure to remove the oil completely, they served to demonstrate interesting surface properties. The concentrations of gelatin suggested by the authors were very viscous, so dilutions were made in the work performed in these studies.

2.6 Particle Size Measurements

2.6.1 Materials

Pure aspirin particles and aspirin coated with gelatin (GEL), Eudiagit L ^{R} (EL); cellulose acetate phthalate (CAP) and with hydroxypropylmethyl cellulose (HPMC) were used for particle size measurements. Salsalate and microencapsulated salsalate particles were also used.

2.6.2 Equipment

A sieve shaker and a set of test sieves of size range (63-1000 μ) were obtained from Endecotts Filters Ltd., London UK.

2.6.3 Methods

10.0 g of particles were placed on top of a set of sieves arranged from top to bottom in order of decreasing apperture size. The set of test sieves was firmly attached on to the sieve shaker which was set to vibrate for 15 minutes. The weight of material remaining on each sieve was determined and expressed as a proportion the liquid in which it floats. The method was first described by Wulff and Heigl (294) and outlined as one of the methods in density determinations for solids by the International Union of Crystallography (295). The liquids used are of wide range, the special merits governing the choice of m-xylene and bromobenzene were:

a) Miscibible with each other in all proportions.

b) Neither aspirin nor the film coats should dissolve in either of the liquids.

c) The liquids were of specific gravities which embraced that of the solid to be tested.

2.8 Melting Point Determinations

Two methods were used to determine the melting points of pure aspirin and of aspirin-magnesium stearate mixtures of varying proportions.

The first method was by the use of the standard capillary tube method, utilizing an electrothermal melting point apparatus obtained from Electrothermal, London.

The second technique was by the use of a differential scanning calorimeter (Perkin-Elmer model DSC-IB) operated at a heating rate of 8 degrees C per minute and a nitrogen atmosphere of 2 bar. 20-30 mg samples were used with aluminium as the reference material.

2.9 Electron Microscopy

In order to examine the surface characteristics of the particles used in this study, samples were prepared for examination and photographed by a scanning electron microscope S150 (Cambridge Instruments, UK).

The process of sample preparation involves placing a small sample of particles on a double sided adhesive which enables the particles to be held in place while attached to an aluminium stub. The sample on the stub was gold coated using a Speedivac Coating Unit Model 12E6/1422 (Edwards High Vacuum Ltd., Essex, UK).

2.10 Light Microscopy

A light microscope fitted with a camera (Micro-Instruments, Oxford Ltd.) was used to examine the particles, to monitor and photograph surface changes during decomposition.

2.11 Atomic Absorption Spectrophotometry

An atomic absorption spectrophotometer (Unicam SP90A) was used to determine the concentration of Mg^{++} ions in a solution. Magnesium nitrate solution was used to construct the standard curve. The absorption wavelength used was 285.2 nm with the slit width at 0.05 mm and a current of 4 amperes. The burner was set to a height of 1.0 cm, the acetylene gas pressure at 0.7 kg/cm^2 (10 psi) and the compressed air flow at 4.5 L/min.

2.12 Washing Procedure for Magnesium Stearate to Reduce Alkaline Impurities

Samples of magnesium stearate were washed by adding 5 g to 200 ml of 0.1 M hydrochloric acid to remove any alkaline impurities and filtering the residue through No. 3 sintered glass filter. The stearate was then washed by shaking with 50 ml of alcohol to remove stearic acid precipitated out during the acid wash. The powder was rinsed with several changes of double distilled water until the resultant pH was in the 6.9-7 range. After filtration, the residue was dried overnight on filter paper at room temperature and finally at 50°C for half an hour before storage in a well closed glass container.

2.13 Synthesis of Acetylsalicylsalicylic Acid

The general acetylation procedure of Chattaway (332) was adopted. Salicylsalicylic acid 2.6 g (0.01 M) was dissolved in 100 ml of 0.1 N sodium hydroxide and the solution cooled with crushed ice. 2.0 g (0.02 M) acetic anhydride was added rapidly into the cool solution. Precipitation of the product was enhanced by addition of 0.1 M hydrochloric acid. The product was washed with cold water and finally recrystallised from methanol and dilute acetic acid. The product melting point was 159-161°C (literature 159°C). The authenticity and purity were checked by uv spectrophotometer, NMR and HPLC.

2.14 Moisture Determination by the Karl Fischer Method

2.14.1 Materials

Methanol (specially dried for non-aqueous titration) and standard solution of water in methanol were obtained from British Drug House (Poole, England). Karl Fischer reagent was obtained from Fisons (Loughborough, Leics., England).

2.14.2 Equipment

The equipment for non-aqueous titration was made by Band and Tatlock Ltd. (Chadwell Heath, Essex).

2.14.3 Methods

Both the methanol (specially dried) and the standard solution of water in methanol were calibrated with the Karl Fischer Reagent, so that equivalent values of the methanol and the water solution to the Karl Fischer Reagent were obtained. An equivalent weight of water for 1.0 ml of the Karl Fischer Reagent was also obtained. Samples which were removed from the humidity cabinet were dissolved in 10 ml of methanol (specially dried). 5.0 ml of the sample were titrated. The volume of Karl Fischer reagent used is corrected for either back-titration by the standard water solution in methanol and for water present in the methanol (specially dried). The volume obtained is equivalent to the water present in the sample. From the known equivalent amount of water, the weight of water in the sample can then be calculated.

CHAPTER 3

THE EFFECT OF FILM COATING ON DRUG RELEASE

CHAPTER 3

3. The effect of film coating on drug release

3.1 Factors that influence release

The process of dissolution can be considered as a specific type of heterogeneous reaction in which a mass transfer is effected through the net result of escape of solute molecules at a solid surface (210). The dissolution kinetics are dependent on a large number of physico-chemical influences. In the study of the dissolution of benzoic acid and lead chloride, Noyes and Whitney (211) derived the following equation.

$$\frac{dc}{dt} = kS(C_S - C_t) \qquad \text{--- Eq. 20}$$

where C_t = concentration of solute at time t

$\frac{dc}{dt}$ = the rate of change of concentration with respect to time

S = surface area

C_S = the equilibrium solubility of the solute at the experimental temperature

k = rate constant

Hixson and Crowell (212) carried out research to investigate the dependence of reaction rate upon surface and agitation. A law, the "cube root law" was developed to express the velocity of dissolution as a function of surface area and concentration. In the case where the concentration gradient $(C_S - C_t)$ is maintained essentially constant by keeping the dissolution medium sufficiently dilute the cube root equation is expressed as follows.

$$Kt = W_o^{1/3} - W_t^{1/3} \qquad \text{--- Eq. 21}$$

where K = rate constant (units length/time)

W_o = initial weight of crystals

W_t = weight of crystals at any time t

Kaneniwa and Watari (213) studied the dissolution of poorly soluble drugs and quantified the dissolution rate using the cube root law.

Wagner (214) has given an excellent historical review on studies on dissolution. In the review, factors influencing the rate of dissolution, and interpretation of dissolution rate data from in vitro testing of tablets and capsules were documented. When environmental factors which influence dissolution rate such as agitation, concentration gradient, composition and temperature of the dissolution medium are controlled; the physico-chemical properties of the drug and formulation variables, are the major factors which influence the rate of dissolution.

Physico-chemical properties of drugs which are of importance in dissolution include solubility, crystallinity, dissociation constant and particle size. These factors are often interdependent making each given case quite complex, as observed in a number of publications (215-219).

The formulation factors which influence the release rate have been a subject of numerous reports (220-232). These factors include the influences due to the amount and type of additive, compressional forces in tablets, storage conditions and age of the dosage form. These factors have made it necessary to develop several testing methods (233-241) in attempts to minimise errors and attain reproducibility. Variations have been observed in collaborative dissolution studies (242). In such collaborative dissolution studies, the one major source of error identified was the level of vibration at the side of the dissolution flask. The need to quantify agitation conditions in compendial dissolution tests (243, 244) is therefore necessary. Levy (283), for example, suggested the use of appropriate agitation intensities for in vitro dissolution rate tests to reflect in vivo conditions. The author further presented evidence that solid dosage forms are exposed to relatively low agitation intensities after oral administration, and suggested the use of similar mild agitation conditions for predictive in vivo dissolution tests. A relationship between the dissolution rate constant and the square root of the stirring rate was observed and a general empirical equation (210) describing the influence of agitation on the dissolution rate constant was presented.

$$K = a(N)^b \qquad \text{--- Eq. 22}$$

where N = the stirring rate

K = the dissolution rate constant

b = constants: Diffusion: b is nearly equal to 1

: Interfacial reaction b approaches 0

a = proportionality constant

Polymeric materials used in film coating or microencapsulation have been shown to modify the release rates of drugs from the formulations (167). These modifications frequently result in the reduction of release rates (245-253). The slow release of drugs brought about by the use of polymeric materials, has been utilised in the preparation of repeat action, sustained action or prolonged action drug formulations (214). To aid the design of slow release aspirin preparations, the effects of film coating on the release of the drug were studied. A number of methods (254-270) for applying film coats to drug substances have been reported.

Film coating techniques such as the Wurster air suspension method (254, 255) have been successfully employed in coating small discrete particles which showed good sustained release profiles. Other notable techniques include the dispersal of a drug in a polymer or wax matrix (247, 251).

Microcapsules have been defined as vessels or containers of microscopic size consisting of seamless, rigid, thin polymer walls that protect enclosed fine particles of a drug substance in the core (260). A number of techniques for microcapsule preparation have been developed to suit desired purposes (194). In this study, coacervation or phase separation was used. The basic principles of coacervation were studied by Bungenberg de Jong (267) and a number of reports are available where the coacervation method has been used to encapsulate drugs (268, 269).

To evaluate the quality of the formulation, various dissolution methods both <u>in vitro</u> and <u>in vivo</u> have been used (271-273). Coletta and Rubin (255), Wood and Syarto (254) used the first order kinetic equation to evaluate and compare the release of the coated sustained release particles. In the theoretical analysis of the rate of release of solid drugs dispersed in solid matrices, Higuchi (250) found that the mechanisms for the release rate from spherical pellets did not follow a first order relationship. However, apparent first order rates have been reported for the terminal portion of the release profiles obtained with sustained release formulations (274). Higuchi (250) derived two expressions, one for a homogenous matrix and another for a granular matrix. The equations are presented as equation 23a and 23b respectively.

$$Q = \sqrt{D\ (2A - C_s)C_s t} \qquad \text{--- Eq. 23a}$$

$$Q = \sqrt{\frac{DE}{\tau}(2A - EC_s)C_s t} \qquad \text{--- Eq. 23b}$$

where Q = amount of drug released per unit time t per unit exposed area

D = diffusivity of the drug in the homogenous matrix media (Eq. 23a) or in the permeating fluid (Eq. 23b)

C_s = solubility of the drug in the matrix (Eq. 23a) or in the permeating fluid (Eq. 23b)

A = total amount of drug present in the matrix per unit volume

E = porosity of the matrix

τ = tortuosity factor of the capillary system ≈ 3

Borodkin and Tucker (275) studied drug release from hydroxypropylcellulose films and used both a first order and the Higuchi equations 23a and 23b to describe the release. The Higuchi equations were expressed in a form:

$$Q = K_H\ t^{\frac{1}{2}} \qquad \text{--- Eq. 24}$$

where K_H = $[D(2A - C_s)C_s]^{\frac{1}{2}}$ for homogenous matrix,

and K_H = $[\frac{DE}{\tau}(2A - EC_s)C_s]^{\frac{1}{2}}$ for granular matrix

However, the authors found that although both a first order equation and equation 24 could be used to describe the release, the Q versus $t^{\frac{1}{2}}$ relationship was clearly superior.

3.2 Dissolution Patterns

Dissolution studies can be used as a tool in drug design and optimization. In this study, the release patterns of coated particles were studied. Film coats applied to discrete particles or tablets act as barriers to adverse external factors (7). Since the actual process of dissolution involves penetration of water into the core, dissolving and eventually releasing the drug, the barrier action of the film coat in delaying or inhibiting water penetration would be expected to be translated into a slower dissolution rate. The effectiveness of the film coat as a barrier to external adverse conditions, could be useful in enhancing the stability of hydrolabile or volatile drugs (192). This was investigated in the present study. However, in order to evaluate the usefulness of this approach, the effect of the film coat on the drug release had to be studied first.

3.2.1 Pan Coated Particles

The pan coated particles of aspirin (Section 2.4) were subjected to dissolution testing using the USP rotating basket assembly (Section 2.3.3). The release of the drug into the dissolution medium was monitored spectrophotometrically at 275 nm for aspirin. During the dissolution test no significant degradation of aspirin was observed. The dissolution rates were determined in 0.1 M hydrochloric acid (pH 1.2), in water (pH 5.8) and in buffer (pH 7) (Section 2.3.3.1) in order to assert that the effects observed are due to the film coats only and not the medium. Since the particles used were in the form of agglomerates, held together by a film matrix, the equation presented by Borodkin and Tucker (275),

Fig. 1. Dissolution of Coated Aspirin particles in Water at 37^{o}C plotted according to first order equation.

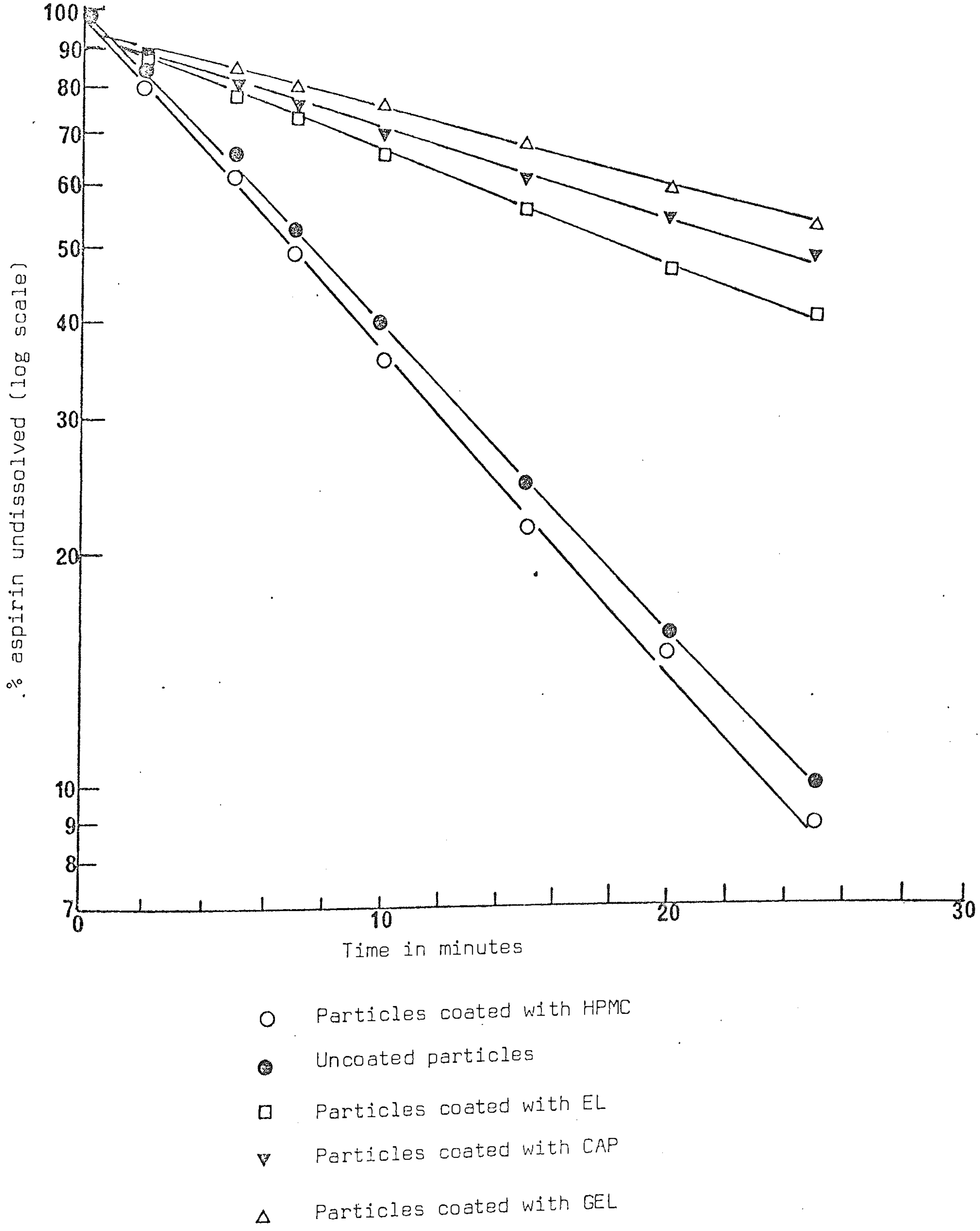
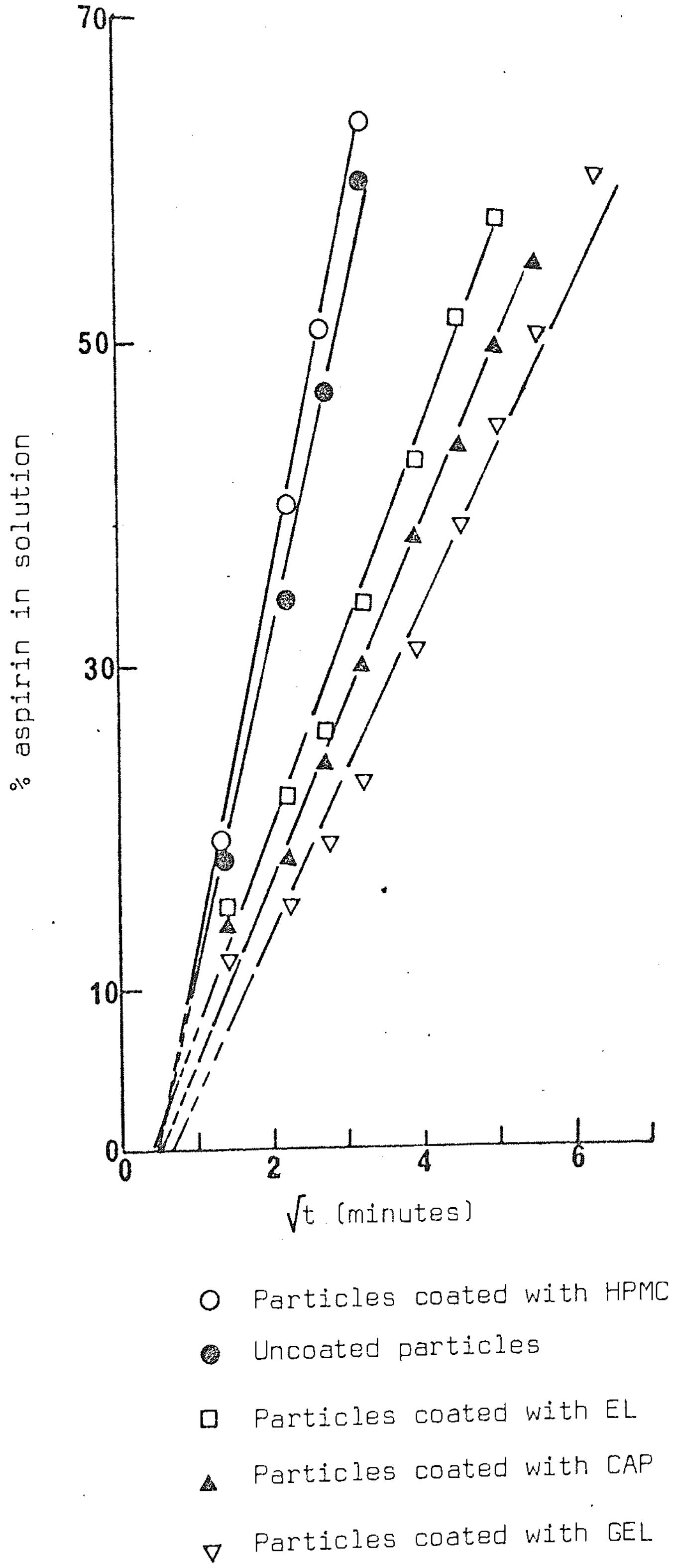


Fig. 2. Dissolution of coated aspirin particles in water at 37°C plotted according to Q versus $t^{\frac{1}{2}}$ equation 24



equation 24 was used for comparing the effects of the different film coatings on the release rate. Figure 1 shows the dissolution data obtained plotted on a log-linear graph according to first order equation. The data appear to be well described by the first order equation. The same data for the dissolution of aspirin in water at 37^0C is plotted according to equation 24, that is Q versus $t^{\frac{1}{2}}$, is shown in Figure 2. The slopes obtained from the plots in Figure 2 are shown on Table 3. These slopes serve to compare the relative effects of the film coats on the drug release. The release rate, as measured by the slopes of equation 24 appear to be strongly influenced by the type of film coat and the pH of the dissolution medium.

3.2.1.1 Discussion

The results on Table 3 indicate that drug release is faster with increasing pH. This has been shown quantitatively by Edwards (218) and can readily be explained by the higher degree of ionisation of the drug in these media. Aspirin has a pKa of 3.45 (207) with the percentage ionisation at pH 1.5, calculated as 0.99%, while at pH 5.5 this increases to 99.01% and at pH 7.5 ionisation is complete. The influence of the type of film can be observed from the values for release constants (Table 3). With the exception of hydroxypropyl methylcellulose (HPMC), the other films used appear to decrease the release rate. In alkaline media, the film coated aspirin particles appear to have a lower release rate for aspirin than the uncoated samples. The film coats also reduce the release rates in the lower pH values tested, the magnitude of reduction depending on the type of film. For example gelation film coats decrease release rates both in acid or alkaline media;

Table 3

THE DISSOLUTION OF COATED AND UNCOATED ASPIRIN PARTICLES

TYPES OF PARTICLES	RELATIVE SLOPES ACCORDING TO EQ. 24 Units $(mg\text{-}cm^{-2}\ min^{-\frac{1}{2}})$		
	pH 1.2	pH 5.8	pH 7.0
HPMC	25.14	24.52	39.42
PA	18.38	23.97	30.91
EL	11.76	11.99	14.59
CAP	10.33	10.47	17.83
GEL	7.39	10.72	10.03

HPMC = Hydroxypropylmethylcellulose

PA = Pure Aspirin

EL = Eudragit L

CAP = Cellulose Acetate Phthalate

GEL = Gelatin

compared to the release rates observed for Eudragit L^{R} and cellulose acetate phthalate. However, the observed values (Table 3) could be a manifestation of differences in the quality of the film coats. The increase of release rate with pH, reveals the influence of the film coat more clearly. The increase in release rate at pH 1.2 compared to pH 7.0 is expressed as a percentage increase for the films used as follows:

Cellulose acetate phthalate	72%
Pure uncoated aspirin	68%
Hydroxypropylmethylcellulose	56%
Gelatin	35%
Eudragit L	24%

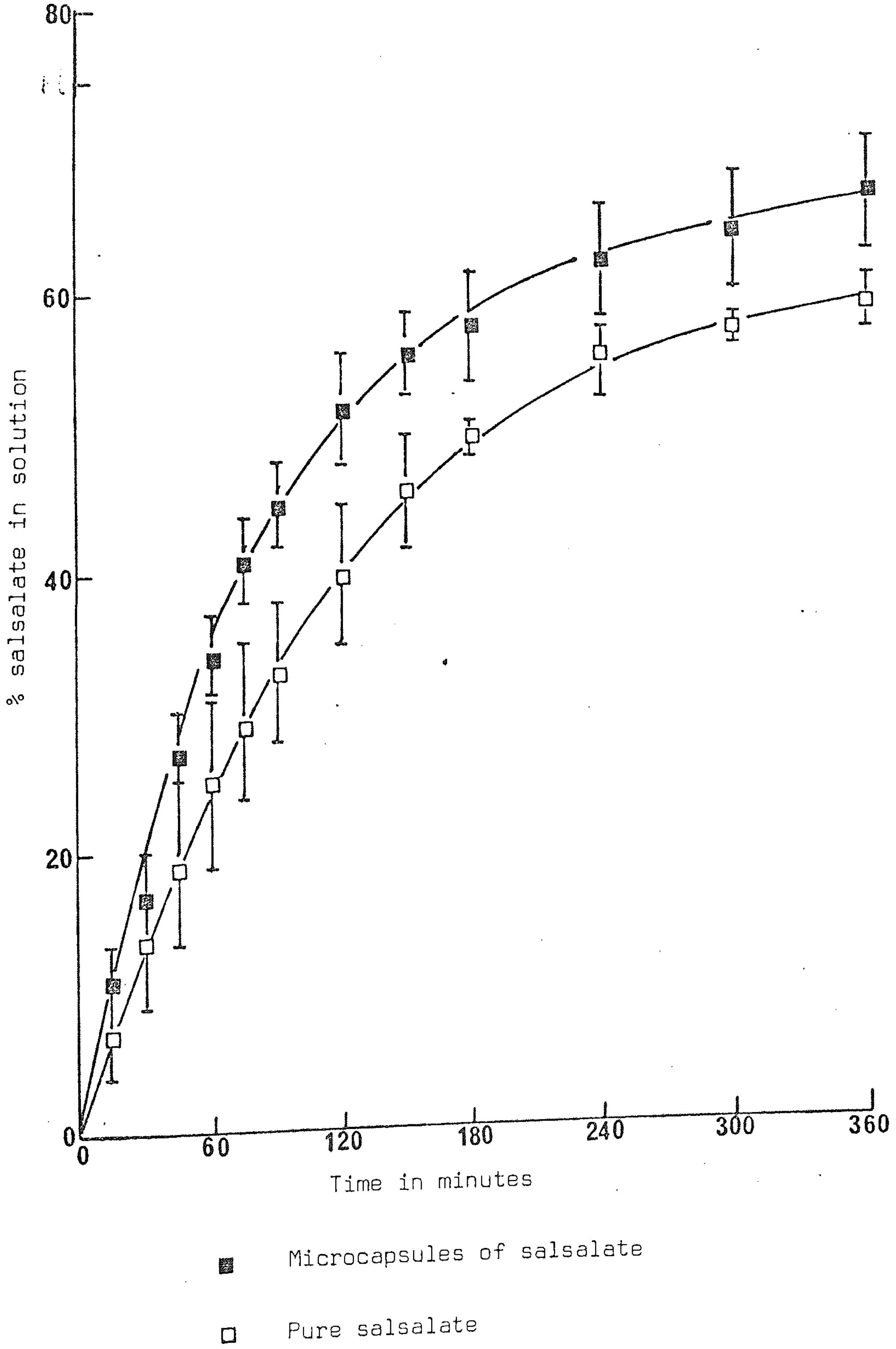
From this comparison, it is clear that cellulose acetate phthalate, which is a known enteric film coat dissolves rapidly in alkaline media while it inhibits release in acidic media. Only gelatin and Eudragit L^{R} film coats show significant retardation of the release rate of aspirin in alkaline media. The process of slowing down release of drug may be significant in solid state reactions as shown in the subsequent studies (Chapter 5).

The effect of hydroxypropyl methylcellulose in increasing rather than decreasing the release rate can be explained by an observation that dispersion of a hydrophilic binder such as methylcellulose on a surface of a hydrophobic drug, enhances the wetting characteristics of the drug and consequently increases the release rate (276).

3.2.2 The Microcapsules

The microcapsules used in this study were prepared by complex-

Fig. 3. Dissolution profiles of pure salsalate and microencapsulated salsalate in water at 37°C



coacervation, phase separation of gelatin by acacia. Salsalate powder was prefered to aspirin for microcapsule preparation because of its high insolubility relative to aspirin (Section 2.5.3.1). The release of the drug into the dissolution medium was monitored spectrophotometrically at 300 nm for salsalate. The dissolution profiles of salsalate and encapsulated salsalate (microcapsules) are shown on Figure 3 for equal amounts of active constituents in water. The microcapsules show a higher release rate than the pure non encapsulated salsalate particles.

3.2.2.1 Discussion

The effect of microencapsulation on the dissolution rate as shown in Figure 3 may be explained by a number of factors. During the dispersion process (Section 2.5.3.1) in the microencapsulation procedure, slight dissolution at 50°C would occur with subsequent re-crystallisation on reducing the temperature to 10°C. The re-crystallisation process may produce finer particles than the original salsalate particles. These small particles have been claimed to speed up dissolution (213) when in contact with larger particles due to large surface free energy. The presence of hydrophilic additives like glycerol (which was used in preparing the slurry) (Section 2.5.3.1) and gelatin/acacia capsule material, could enhance the wetting of the hydrophobic drug (276-279).

The observed profiles have shown to be important in the interpretation of the stability of the microcapsules in the solid state (Chapter 5).

The versatility of dissolution studies can further be demonstrated in a preformulation programme to study the intrinsic dissolution properties of unformulated drugs (280). Such studies have been shown to assess differences between polymorphs. In order to understand and interpret observed phenomena, of dissolution as well as stability, the effect of film coating on surface characteristics, density and size distribution were studied.

3.3 Effect of film coating on the properties of particulate materials

The application of polymeric film-forming substances on pure particles modify release rates. Less apparent changes which may affect drug release are changes in particle size and size distribution, density and porosity of granules. The influence of particle size on dissolution and gastrointestinal absorption has been widely studied (281-285) and an attempt to introduce particle size distribution in the kinetics of dissolution has been reported (286).

Carli and Simioni (287) in studying the kinetics of liquid capillary penetration into polymer matrices found that the rate of release was influenced by the pore volume effectively penetrated by the liquid. The release characteristics of drugs from dosage forms are influenced by porosity which enters directly into the Higuchi square root law for dissolution (250).

Cruaud (288) showed that there is a correlation between dissolution rate constant and porosity in the case where a tablet disintegrates into porous granules and the limiting process is the penetration of water into the dislodged granule.

3.3.1 Surface Characteristics

Kaneniwa (213) reported that surface conditions of a particle may play an important role in the initial dissolution process for poorly soluble drugs. Observation by scanning electron microscope reveals the presence of very fine particles adhering to the larger

Fig. 4. Pure uncoated aspirin crystals (PA) magnification x 50

particles. After comparing the dissolution rates of samples with and without particles adhering to the surface, the authors obtained no significant difference and attributed the observed initial dissolution rate to surface free energy which increases with decreasing particle size.

In this study aspirin crystals examined under a scanning electron microscope are shown on Figure 4. It can be seen that in addition to small particles adhering on the larger crystals, cracks, sharp edges and fissures can be observed. The presence of cracks and fissures on the crystal surface is said to enhance the reactivity of solid substances (55, 289, 290). Such adhering particles, cracks and fissures on aspirin crystals may be of significance in interpreting stability data. The photomicrographs of coated aspirin particles are shown in Figures 5-8 where Figure 5 shows HPMC coated particles, Figure 6 shows EL coated particles, Figure 7 shows GEL coated particles and Figure 8 shows CAP coated particles. The coated particles exist as agglomerates of aspirin crystals bonded together by the adhesive action of the polymeric film-forming material. It is thought that during the application of the coating solution, a single crystal is coated but before it dries, it is bonded to other similarly coated crystals. With continuous coating, the agglomerates already formed are further coated. The resultant agglomerate is a stable, almost spherical particle consisting of aspirin crystals randomly dispersed in the matrix of the polymeric material used. The formation of agglomerates is accompanied by the presence of canals and voids between the bonded particles. However, the presence of small particles adhering to the large particles is not distinctly evident. The presence of canals and voids can influence the penetration of liquids through

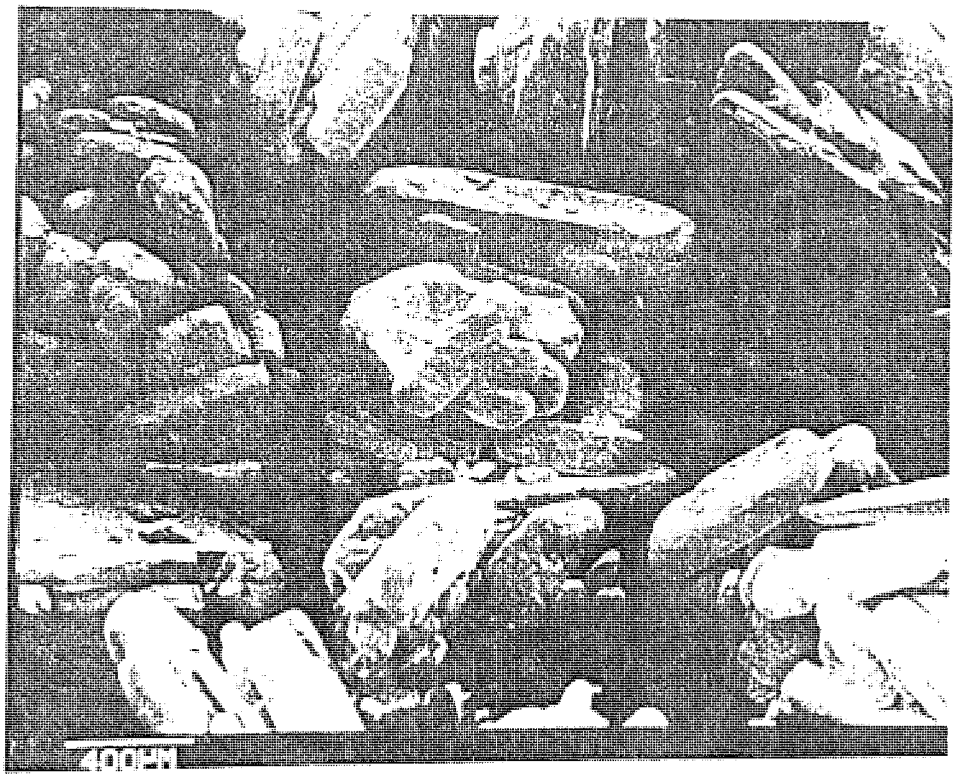


Fig. 5. Hydroxypropylmethylcellulose coated aspirin particles (HPMC)
Magnification x 50

Fig. 6. Eudragit L coated aspirin particles (EL)
Magnification x 50

Fig. 7. Gelatin coated aspirin particles (GEL)
Magnification x 50

Fig. 8. Cellulose acetate phthalate coated aspirin particles (CAP)
Magnification x 50

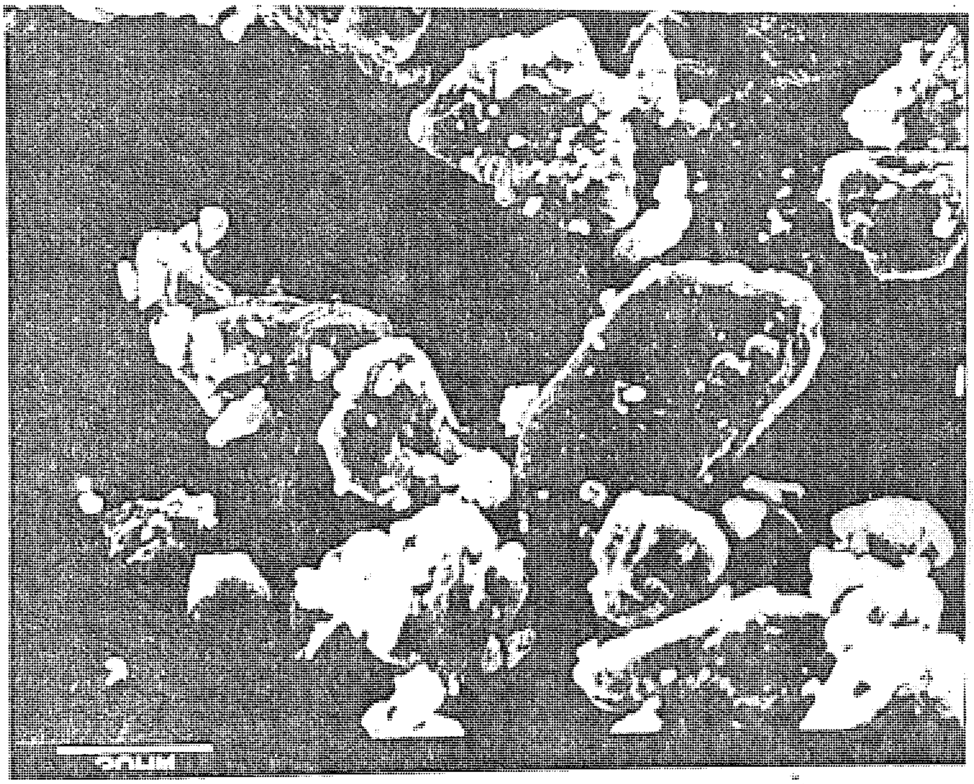


Fig. 9. Salsalate power
Magnification x 1 K

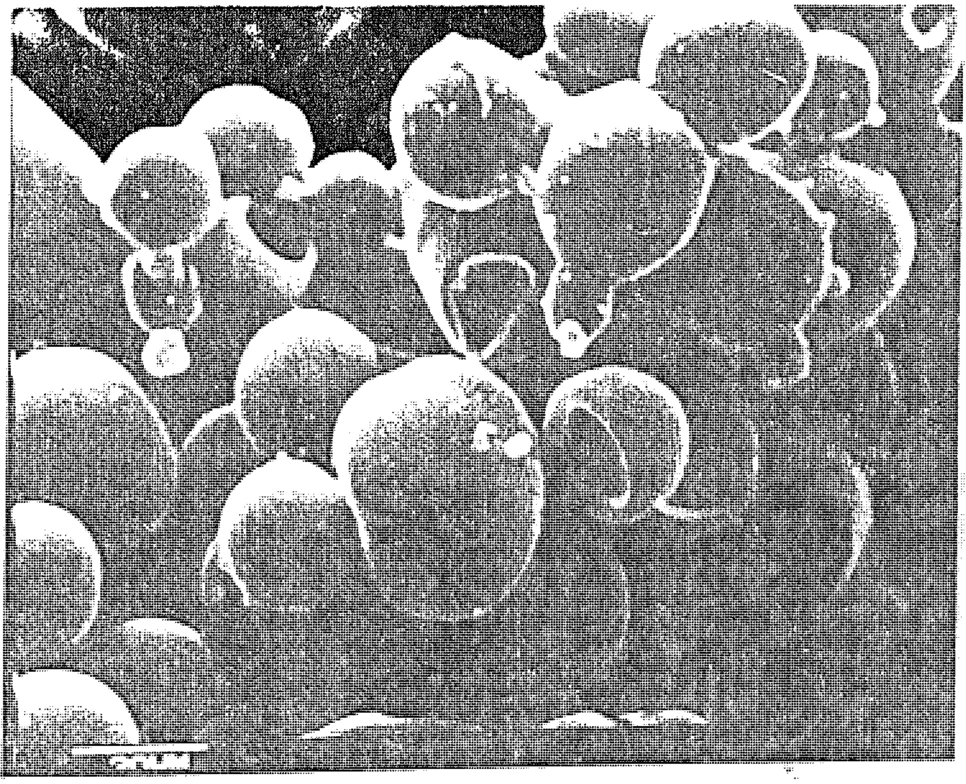


Fig. 10. Gelatin-acacia salsalate microcapsules made from powder Fig.9
Magnification x 1 K

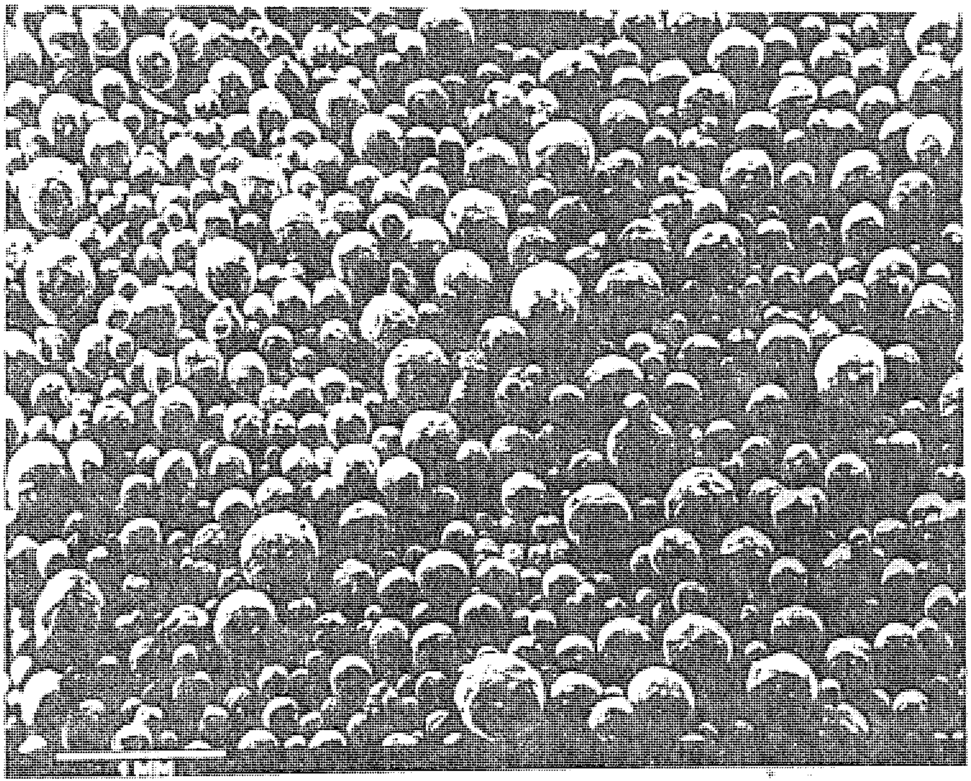


Fig. 11. Gelatin only salsalate microcapsules made by the method of Tanaka et al.
Magnification x 20

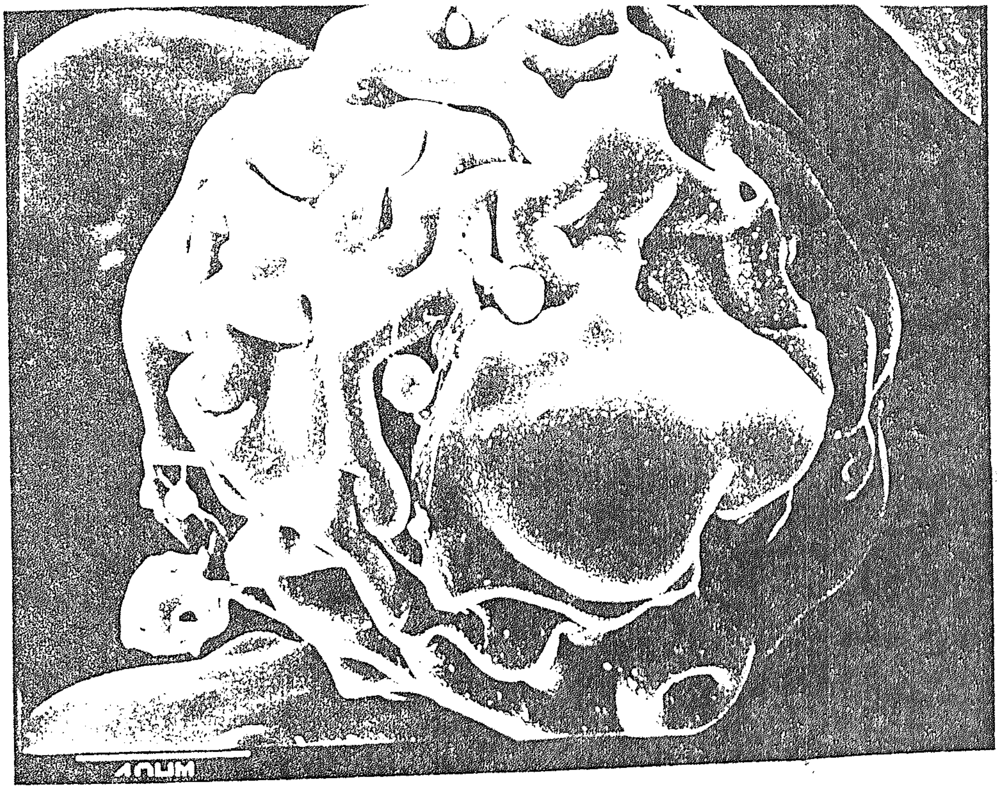


Fig. 12. Gelatin only salsalate microcapsule.
Close up surface view of microcapsules on Fig. 11.
Magnification x 500

powder bed or granules (287, 288).

Figures 9 and 10 are photomicrographs of pure salsalate powder and of salsalate microcapsules respectively. As previously observed, small particles adhere to the large salsalate particles as seen on Figure 9, while the microcapsules on Figure 10 have smooth surfaces and have attained a spherical shape. However, the presence of pores can be clearly seen. These could enhance dissolution or reactivity of the core substance, because of the possibility of moisture access through the observed pores.

Figure 11 is the photomicrograph of salsalate microcapsules made in accordance with the method of Tanaka _et al._ (264) which is essentially a phase polymerisation technique. The surfaces appear rough due to the presence of wrinkles. Figure 12 which is the photomicrograph of one particle as on Figure 11 magnified 500 times, confirms the presence of wrinkles and further demonstrates the presence of pores. The interesting feature of such particles as demonstrated by Figure 12, is that the effective surface area which influences both dissolution and reactivity is much higher than that which could be estimated from the diameter of the particles. Takenaka _et al._ (291) observed the presence of wrinkles on microcapsules treated with formalin and further observed the effect on particle size distribution as the amount of formalin added is increased.

3.3.2 Particle Size Distribution

Sieve analysis was used to determine any change in particle size and size distribution as a result of pan coating or microencapsulation (Section 2.6.3). Edmundson (292) reviewed various methods of particle size analysis. A large number of pharmaceutical powders are log-normally distributed and the particle size distribution could be described by the geometric mean and geometric standard deviation. Geometric mean, X_g is defined as the F^{th} root of the products of the variables,

$$X_g = \sqrt[F]{(x_1 \times x_2 \times x_3 \times x_F)} \qquad \text{--- Eq. 25a}$$

Equation 25 could be re-written as

$$X_g = \text{Antilog } \frac{\Sigma \log x}{F} \qquad \text{--- Eq. 25b}$$

where F = is the total frequency

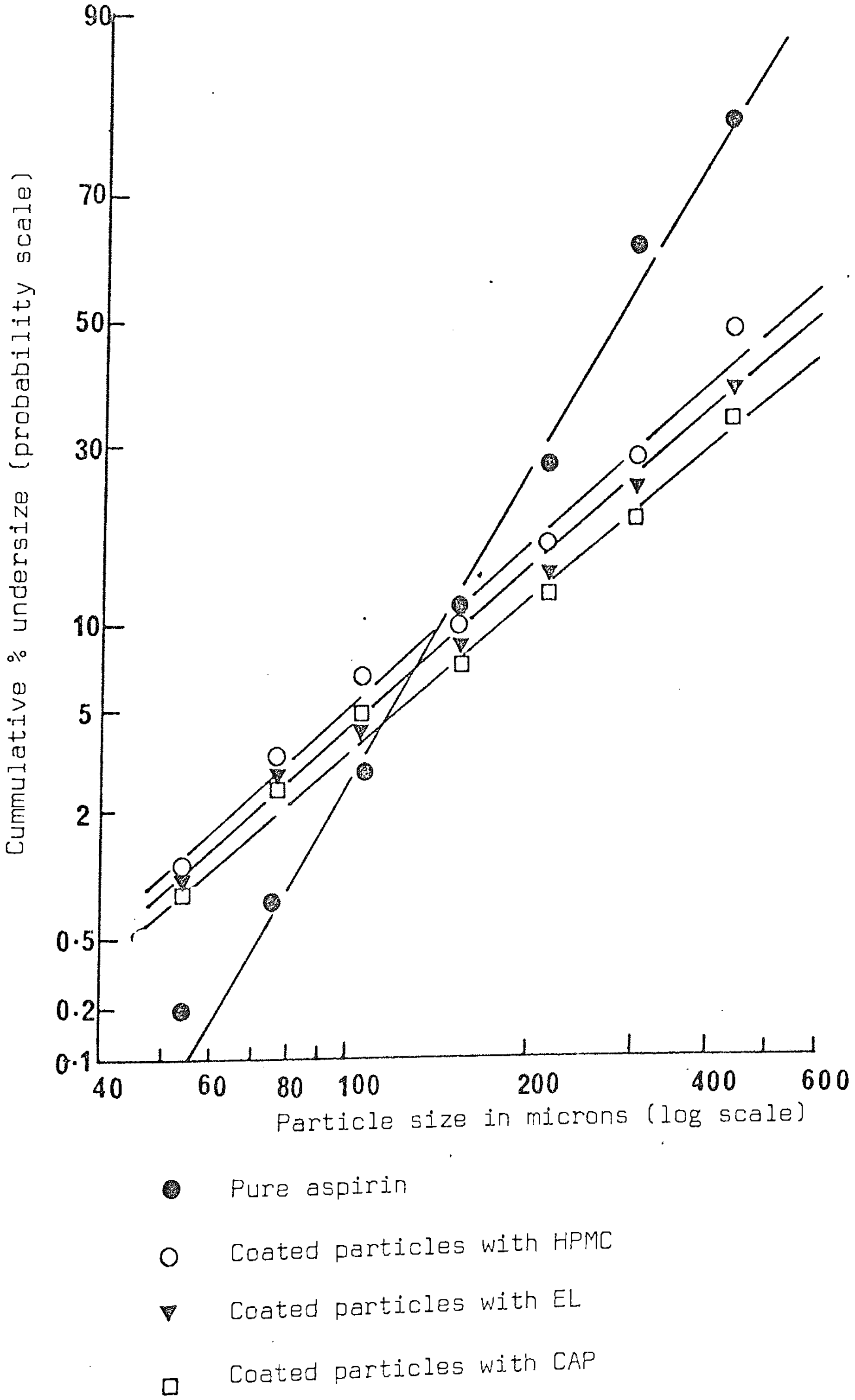
X = number of variables

These formulae are rarely used (Equations 25a and 25b) to calculate the geometric mean from frequency distribution because these means have practical significance only in special cases in which the particle size distribution happen to obey the log-normal law. When this is so, the geometric mean can be read directly from a graph of cumulative frequency against diameter (292). The geometric mean is equivalent to the median or 50% diameter. The geometric standard deviation is equivalent to the slope of the distribution when such particle size data is plotted on a log-probability graph. In this study, the size distribution of coated and uncoated aspirin particles, as well as salsalate and salsalate microcapsules were determined.

3.3.2.1 The Pan Coated Particles

The size distribution of coated and uncoated aspirin particles follow a linear relationship when plotted on a log probability

Fig. 13. Particle size distribution of pan coated aspirin particles on log-probit graph



graph. The linear relationship shows that the log-normal distribution was present. From the log-probability graph, as shown in Figure 13, the geometric mean and subsequently the geometric standard deviation were obtained. The geometric mean was graphically determined as the size that corresponds to 50% probability distribution. The geometric standard deviation was calculated from the ratio of the size that corresponds to 50% probability and 16% probability, as shown by the following expression (292, 293):

$$\sigma_g = \frac{50\% \text{ size}}{16\% \text{ undersize}} \qquad \text{--- Eq. 26}$$

where σ_g = geometric standard deviation.

The values for the geometric mean and geometric standard deviation are shown on Table 4.

3.3.2.1.1 Discussion

It can be observed in Table 4 that the geometric mean size and the deviation have increased as a result of film coating.

The increase in geometric mean size due to film coating can probably be due to agglomeration of the particles. The effect of the film coat thickness is negligible on the observed increased geometric mean since the proportion of the coat is very small (3% $^{w}/_{w}$) (Section 2.4.3 and Table 2).

The geometrical standard deviation, which defines the spread of the distribution, is also observed to be higher for the coated particles. This means there is possibility of existence of very large or very small particles in appreciable amounts in the coated samples. This observation is explained by the possibility that segregation occurs during the rotation of the coating pan such that

Table 4

RELATIVE SIZE DISTRIBUTION OF COATED AND UNCOATED ASPIRIN PARTICLES AND SALSALATE MICROCAPSULES

TYPE OF PARTICLE OR FILM COAT	GEOMETRIC MEAN μ	GEOMETRIC STANDARD DEVIATION σg
PA	280	1.65
GEL	370	2.05
HPMC	490	2.55
EL	550	2.55
CAP	660	2.73
<u>PURE SALSALATE AND SALSALATE MICROCAPSULES</u>		
Salsalate Powder	115	1.52
MICROCAPSULES:		
Made at 400 rpm	193	1.51
Made at 600 rpm	125	1.44

a size gradient exists. The gradient is such that the largest particles rotate at the outermost regions of the pan while the small particles remain almost stationary at the centre of the rotating pan. On spraying the coating liquid the large particles form aggregates with the adjacent particles. Similarly the smaller particles form aggregates. The large particles usually pack poorly (293) creating large aggregates with large void volume. Since smaller particles form well packed aggregates, it is rational to say that a uniform growth of particles does not occur. The observed phenomenon of segregation of particles during the pan coating process, make it appear that the method is not a reliable tool for applying films to small discrete particles without significantly changing the particle size or size distribution.

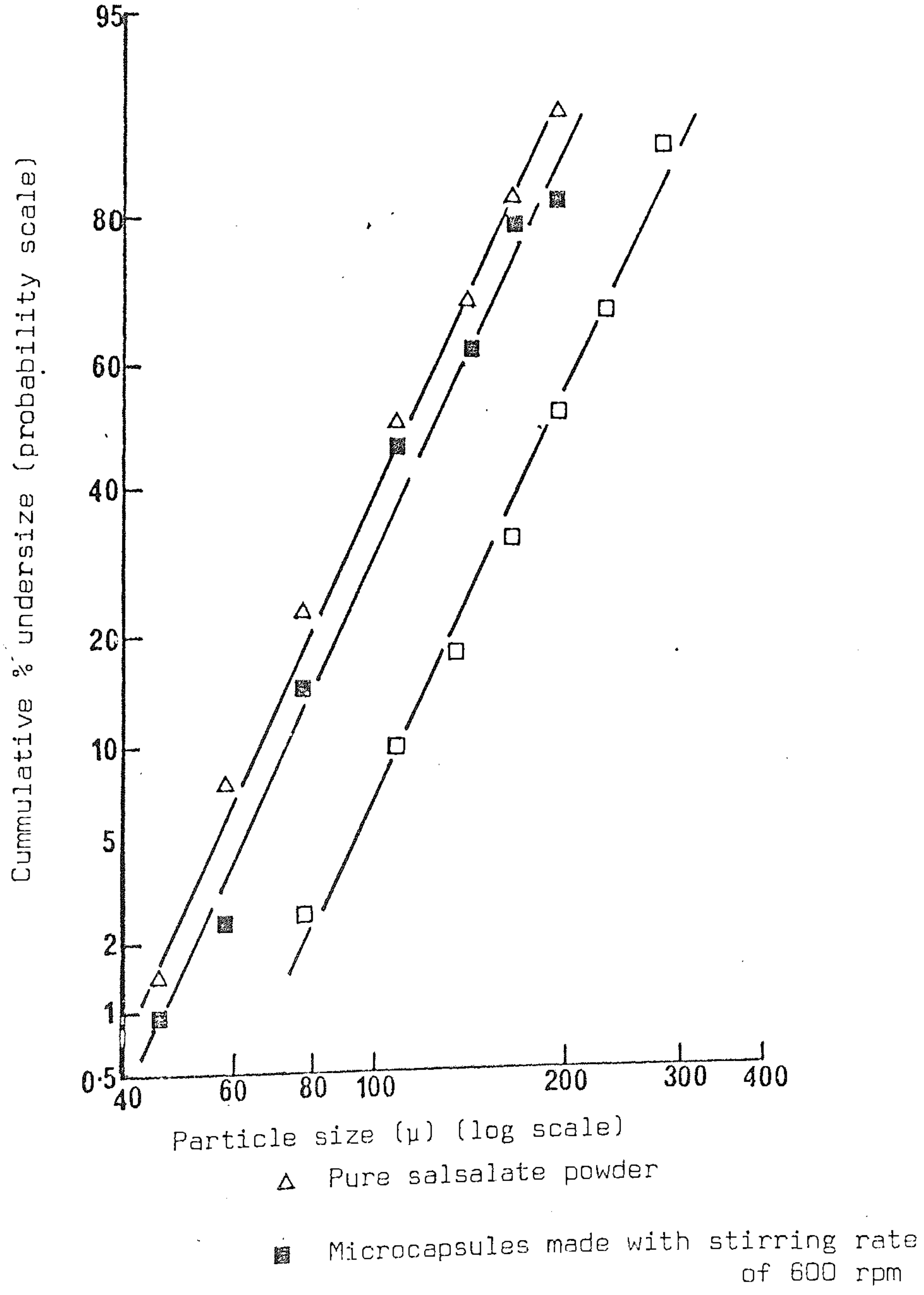
3.3.2.2 The Microcapsules

The particle size distribution of salsalate and microencapsulated salsalate as represented on a log-probability graph is shown on Figure 14. The geometric mean and geometric standard deviation are determined from Figure 14 and tabulated on Table 4.

3.3.2.2.1 Discussion

Relative to the pan coated particles, the observed changes in particle size and geometrical standard deviations of the microcapsules were modest. The size distribution of sulfamethoxazole microcapsules prepared by gelatin-acacia complex coacervation (291) method seem to corroborate the size distribution observed for salsalate microcapsules. The increase in stirring speed for dispersion during the formation of coacervates clearly reduces the mean size of the resultant microcapsules. It is not only

Fig. 14. Particle size distribution of salsalate and microcapsules on log-probit graph



speed which effects the microcapsule size but also pH and hardening agent (291).

3.3.3 The Density and Porosity of Coated Particles

The high degree of aggregation of particles observed for the pan coated particles, make it necessary to investigate the extent of crystal packing in the discrete agglomerates. The degree of packing which could be revealed through density or porosity determinations is important in some physical or chemical processes (250, 287, 288).

Density can be used to determine the porosity of particles (280, 293). Table 5 shows the percentage porosity as calculated from the experimentally determined granule densities according to equation 27 (280, 293):

$$\% \text{ Porosity } (E) = 1 - \left(\frac{\text{Density of aggregates}}{\text{Density of Pure Aspirin}}\right) \quad \text{--- Eq. 27}$$

The method for determining density has been described in chapter 2 (Section 2.7) based on the method originated by Wulff and Heige (294) and presented as one of the techniques for determining the density of crystals (295). The method is claimed to have a probable accuracy of 1%.

Cellulose acetate phthalate coated particles, with film loading ranging from 1% $^{w}/_{w}$ to 8% $^{w}/_{w}$ were used in the density determination studies. The density of the film was found to be 1.1 g/cm^3 and that an 8% $^{w}/_{w}$ film loading on aspirin crystals could give a maximum shift in density of 2%, while the real observed shift after correction for film effect is 5%.

Table 5

DENSITY AND POROSITY OF ASPIRIN COATED WITH CAP

% DRY WEIGHT OF FILM COAT	GEOMETRICAL MEAN μ	DENSITY G/cc	CALCULATED % POROSITY
0	280	1.40	0
1	330	1.39	0.7
3	660	1.38	1.4
6	1150	1.36	2.9
8	1500	1.33	5.0

The presence of voids in the aggregates could be significant in the stability, if it is considered that after drying and driving off any solvent, the voids may be filled with moist air. Depending on humidity at the time of exposure, the initial degradation of such particles may be dependent on the moisture present in the voids rather than the external experimental conditions. It has been observed that a number of degradations in pharmaceutical dosage forms is dependent upon the inherent moisture present in the diluents (184, 296).

3.4 Summary

In this chapter, an attempt has been made to define the characteristics of the coated particles and on the release of aspirin and salsalate. When film-forming polymeric substances are applied on particles as film coat, the surface characteristics- the shape, the density or porosity of the resultant coated particles are observed to differ from the original particles. Although particle surface characteristics and porosity may have less pronounced effects on dissolution (213, 250, 288), they are known to play a significant role in the enhancement of reactivity in solids (55, 63, 64).

In the study, the surface characteristics were controlled by using a similar batch of particles while the porosity was controlled by using narrow size range of particles in the solid state stability studies. In this way, the effects observed would not be due to size variables but mainly due to the film or the additives used extragranularly to test the barrier effects of the polymeric film coats as shown in the subsequent sections (Chapter 5).

CHAPTER 4

STABILITY IN SUSPENSION SYSTEMS

THE INFLUENCE OF ADDITIVES ON THE STABILITY OF SALSALATE

CHAPTER 4

4. STABILITY IN SUSPENSION SYSTEMS: THE INFLUENCE OF ADDITIVES ON THE STABILITY OF SALSALATE

4.1 Introduction

The effect of common tablet or capsule excipients and co-formulated active materials on the hydrolysis of aspirin in aqueous suspension has been studied (297, 298). In such suspension studies, the formation of salicylic acid was found to be zero order and this can be rationalised on the basis of decomposition in a saturated solution (299). In an attempt to extrapolate stability data from suspensions to tablets, Moulding *et al.* (298) examined the stability of powder mixes and tablets, and observed the influence of various excipients and antacids as well as the effect of varying the amount of water. It was observed that the rate of degradation increases linearly with an increase in moisture content, and that the relationship could be used to predict the stability of solid dosage forms from the apparent zero-order rates obtained from suspension studies.

In this study the stability of drugs in a suspension system was done in order to model the kinetics of decomposition in the solid state, and salsalate was chosen as a model drug.

Salsalate or Disalcid ^{R} (300), Diplosal or o-salicyloyl salicylic acid (301) or Salicylsalicylic acid (302) are some of the names used to describe the bimolecular ester (303) of salicylic acid (Figure 15).

Salsalate is essentially a pro-drug of salicylic acid. *In vivo*, it is hydrolysed to two molecules of salicylic acid, and the same decomposition pathway is observed when improperly stored

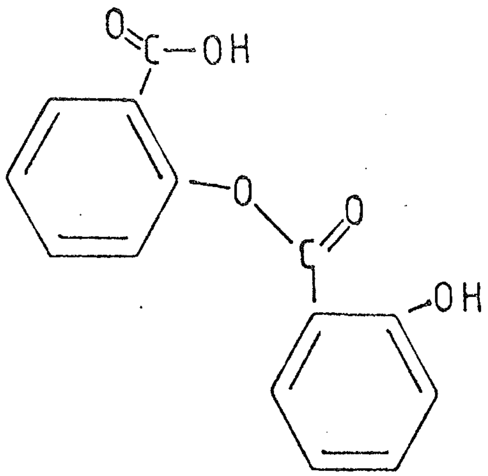


Fig. 15. Chemical structure of salicylsalicylic acid (salsalate)

in vitro (300, 304). One of its claimed advantages is its longer half-life relative to aspirin (300). The drug is said to produce less gastric irritation (300). Salsalate is therefore promoted for conditions such as rheumatoid arthritis, when long term salicylate therapy is indicated.

4.2 The Degradation of Salsalate in Suspension Systems

4.2.1 Methods

1% w/v suspensions of salsalate were used to investigate the stability of the drug at 50°C. Additives, namely 0.1% w/v magnesium stearate, 0.1% w/v sodium stearate, 0.1% w/v aluminium stearate and 0.03% aerosil were added to the suspensions and their effect on the degradation of salsalate were monitored. Samples were withdrawn as explained previously (Section 2.1.3.1) and assayed by HPLC.

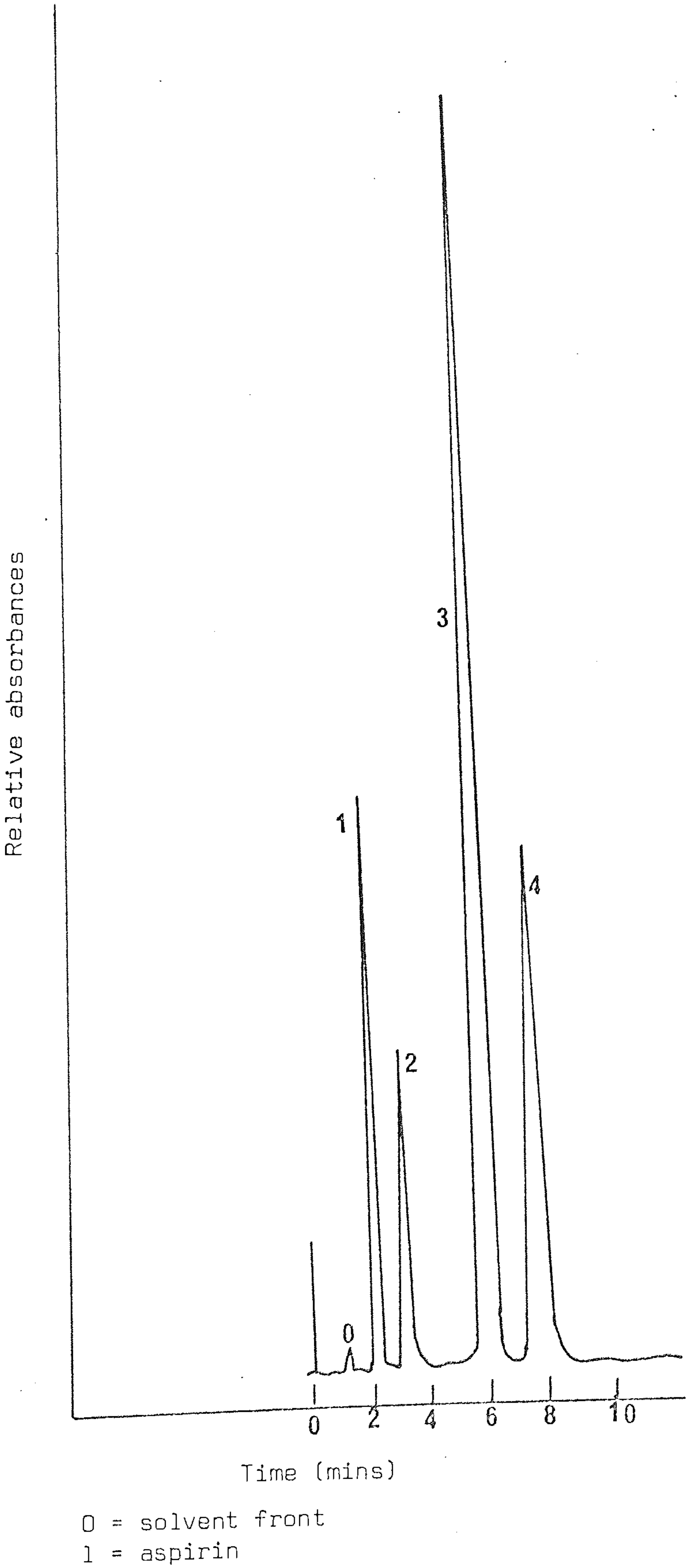
4.2.2 Results and Discussions

The HPLC method used was capable of separating salsalate, salicylic acid and the internal standard used, n-propyl-p-hydroxy benzoate, as well as aspirin and its decomposition products. An HPLC trace for the separation, using standard concentrations of the compounds is shown in Figure 16. Such a separation enables the quantification of both the reactant and the reaction product.

4.2.2.1 Degradation of Salsalate without additive

The degradation of salsalate in suspension with no excipient is relatively very slow. The formation of salicylic acid as determined by the apparent zero order rate constant was found to

Fig. 16. An HPLC trace for the separation of a standard mixture of aspirin, salicylic acid, n-propyl-p-hydroxybenzoate and salsalate at 285 nm



0 = solvent front
1 = aspirin
2 = salicylic acid
3 ~~4~~ = n-propyl-p-hydroxybenzoate
4 ~~5~~ = salsalate

be 0.033 m moles/litre/hr, while the degradation induced by magnesium stearate gave a rate constant of 0.410 m moles/litre/hr, a twelve fold change.

4.2.2.2 Influence of Additives on Salsalate Degradation

The effects of additives on the degradation of salsalate in aqueous suspensions at 50°C are presented in Figure 17, where the effects due to each of the stearates of magnesium, calcium, sodium and aluminium as well as Aerosil^R are shown. Except for Aerosil^R for which a 0.03% w/v concentration was used, the amounts for each of the stearates used was 0.1% w/v. Higher concentrations of Aerosil^R produced viscous mixtures. The stearates of divalent metals produced the largest changes in the rate of decomposition of salsalate. However, there is no clear relationship between the cationic charge and the observed effects. Several possible mechanisms could explain the difference in observed rates produced by the different additives. The presence of catalytic impurities, the direct catalytic effect of the metal ions, catalysis on the surface of excipients and solubility differences of the alkali stearates were possible mechanisms. Aerosil^R did not show any significant influence on the rate of degradation of salsalate. Sodium stearate, the most soluble of the stearates used shows less effect than magnesium stearate which is less soluble. Literature values obtained are as follows (305).

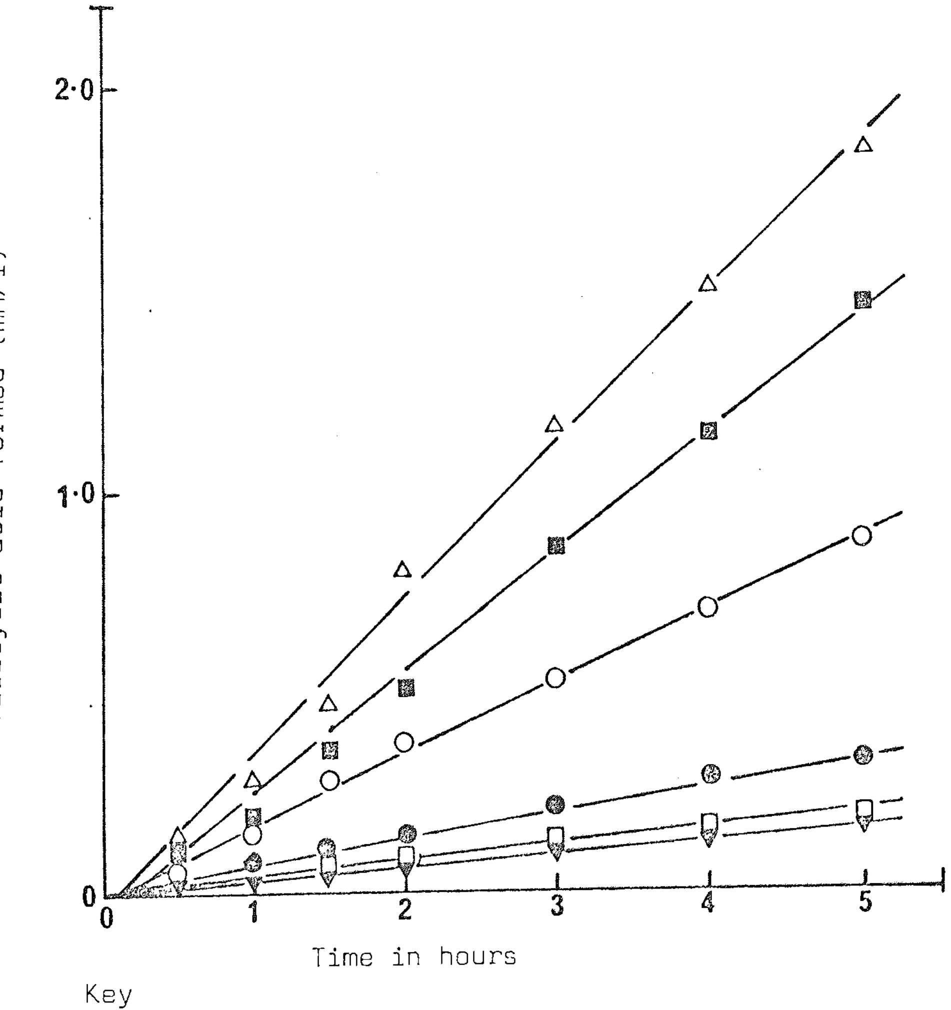
Sodium stearate 5 g/litre

Calcium stearate 0.025 g/litre

Magnesium stearate 0.04 g/litre

Sodium stearate has been described as soluble and calcium stearate as insoluble, while magnesium stearate is described as

Fig. 17. Degradation of salsalate suspension at 50^{0}C and the effect of additives



Key

▼ Pure salsalate in water
□ Salsalate + 0.03% w/v aerosil
● Salsalate + 0.1% w/v aluminium stearate
○ Salsalate + 0.1% w/v sodium stearate
■ Salsalate + 0.1% w/v calcium stearate
△ Salsalate + 0.1% w/v magnesium stearate

having a solubility of 0.03 g/litre in cold water and 0.08 g/litre in hot water (306). Aluminium stearate is described as insoluble (306) and its small effect on the degradation of salsalate and aspirin relative to the stearates of calcium, sodium and magnesium has been attributed to its insolubility (297).

In the study of the hydrolysis of aspirin in combination with tablet lubricants in aqueous suspensions, Kornblum and Zoglio (297) proposed a primary mechanism which involves alkali cations reacting with aspirin in solution to form a salt of aspirin and which in the presence of solvated aspirin, comprises a buffer system with a pH detrimental to the stability of aspirin. To investigate whether a parallel mechanism occurs with salsalate and magnesium stearate in suspensions an experiment was designed to test the effect of magnesium ions derived from a solution of magnesium stearate, on the rate of degradation of salsalate in suspension.

4.3 Influence of Magnesium Ion Concentration on the Degradation of Salsalate

4.3.1 Methods

5.0 g Magnesium stearate powder was added to 200 mls of water and the mixture was vigorously stirred overnight at room temperature after which the filtrate was recovered and was assayed for Mg^{++} ion using atomic absorption spectrophotometry (Section 2.11).

The salsalate suspension was made using solutions containing different amounts of magnesium ions. These ranged from 15 ppm to 0.15 ppm.

Fig. 18. Effect of Mg^{++} ion concentration on the degradation of salsalate in suspension at 50°C

Key

▼ salsalate alone in water

○ Mg^{++} ion 0.15 ppm

□ Mg^{++} ion 1.5 ppm

▩ Mg^{++} ion 7.5 ppm

△ Mg^{++} ion 15 ppm

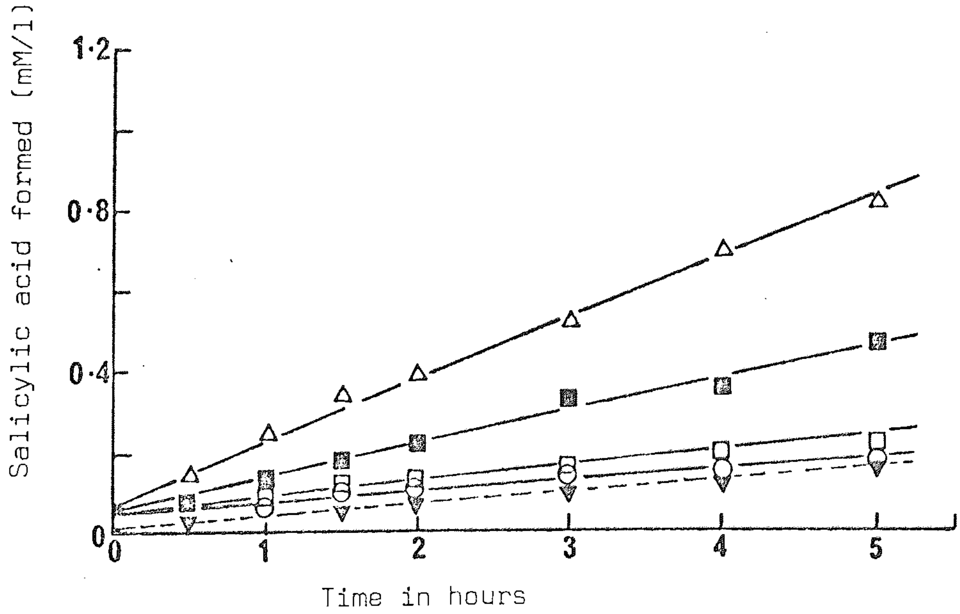
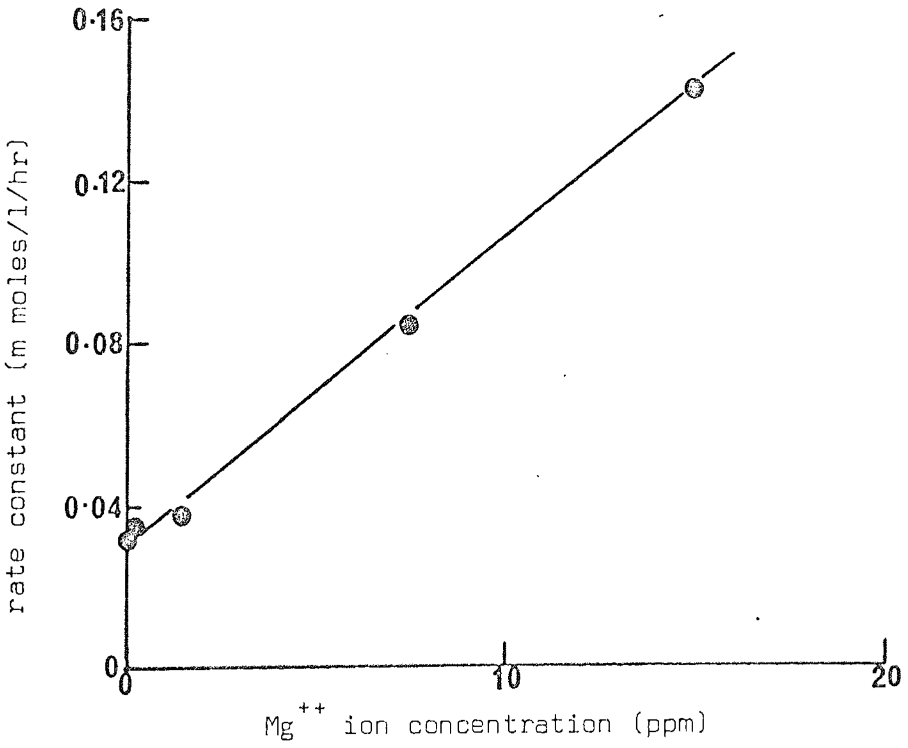


Fig. 19. Relationship between zero order rate constants and magnesium ion concentration as observed in salsalate degradation in suspension ($50^{\circ}C$)



4.3.2 Results and Discussion

The degradation of salsalate in the presence of different concentrations of magnesium ions, obtained by adjusting the magnesium stearate concentration is shown in Figure 18. The higher the magnesium ion concentration in the suspension system the higher the rate of salsalate degradation. In fact a linear relationship is observed between the apparent zero-order rate constant and the concentration of the magnesium ions. The relationship is in Figure 19 and can be described by equation 27.

$$Y = 0.008x + 0.03 \qquad \text{--- Eq. 27}$$

where Y = k, the apparent zero order rate constant with units

m moles/litre/hour

x = Concentration of magnesium ions in ppm

(r, the correlation coefficient = 0.997).

The magnesium ion concentration therefore appears to be important, but the available data does not provide the necessary proof that this was the case. Effects induced by excipient impurities for example could not be excluded. The British Pharmacopoeia (307) and the United States Pharmacopoeia (308) specify the magnesium oxide content in magnesium stearate as being between 6.5% up to 8.5%. The bulk of the magnesium ions could perhaps be expected to arise from magnesium oxide because of its higher aqueous solubility relative to magnesium stearate. Jaminet and Louis (174) in fact claimed that the magnesium oxide present in magnesium stearate was responsible for the observed acceleration of the decomposition of aspirin in the presence of the lubricant. Magnesium oxide is hydrolysed to magnesium hydroxide which will impart a high pH to the suspension system. The correlation

Table 6

THE APPARENT EFFECTS OF MAGNESIUM IONS

SYSTEM	Apparent zero-order rate constant
Salsalate alone	0.033 mM/l/hr
Salsalate + 0.1% $MgCl_2$ (1000 ppm of Mg^{++})	0.039 mM/l/hr
Salsalate + 0.1% $Mg(C_{17}H_{35}CO_2)_2$ (15 ppm of Mg^{++})	0.1499 mM/l/hr

$MgCl_2$ = Magnesium Chloride

$Mg(C_{17}H_{35}CO_2)_2$ = Magnesium Stearate observed in equation 27 and Figure 19 between the rate constant and magnesium ion concentration could be a manifestation of other factors, parallelled by the changes in the magnesium ion concentration. To test this, the decomposition of salsalate was followed in the presence of 0.1% w/v magnesium chloride.

4.3.2.1 The Influence of Magnesium Chloride

The level of magnesium chloride used gives an equivalent of 1000 ppm Mg^{++} ion in solution compared to 15 ppm Mg^{++} ion maximum concentration used in the previous test (Section 4.3.2). Despite the high concentration of magnesium ions in solutions, the rate of degradation of salsalate was not changed in the presence of magnesium chloride. This can be observed in the rate constants obtained (Table 6).

From the observed data, the magnesium ion in solution cannot account for the large increase in the rates of decomposition of salsalate when magnesium stearate is added to a suspension of the drug. Several factors made necessary an investigation of the effects of pH on the salsalate degradation. These include a) the existence of basic impurities in magnesium stearate (174), b) the observation that such alkaline additives induce the formation of a buffer system in aspirin suspensions with a pH detrimental to the stability of aspirin (297) and (c) the British Pharmacopoeial specifications for the pH of a standard solution of magnesium stearate (309).

4.4 The Influence of pH on the Degradation of Salsalate

4.4.1 Methods

McIlvaines buffer solutions (310) were made by mixing various

Table 7

COMPOSITION OF BUFFER SOLUTIONS USED IN SUSPENSION STUDIES

(Prepared according to ref. 310)

Desired pH at 25°C	Resultant pH of reaction mixture	g/l $Na_2HPO_4.12H_2O$	g/l $C_6H_8O_7.H_2O$ (citric acid)	Resultant ionic strength (m)	KCl added to make ionic strength 0.2 M g/l
3.4	3.40	20.4	15.0	0.112	6.56
3.6	3.53	21.5	14.2	0.128	5.37
3.8	3.82	25.4	13.6	0.142	4.32
4.0	4.02	27.6	12.9	0.157	3.21
4.2	4.22	29.4	12.3	0.173	2.01
4.4	4.40	31.6	11.7	0.190	0,75
4.6	4.56	33.4	11.2	0.210	0.0

proportions of disodium hydrogen orthophosphate dodecahydrate and citric acid to obtain pH values between 2.2 to 8.0. Potassium chloride was added to give a required ionic strength as shown in Table 7. Buffer solutions with pH values ranging from 3.4 to 4.6 were made, and were standardised to an ionic strength of 0.2 M with potassium chloride. In order to test the effect of pH on the stability of salsalate, 1.0g/100 ml suspensions were made in the buffer solutions kept at 50°C and samples were withdrawn at predetermined intervals for an HPLC assay for salsalate and the formed salicylic acid (Section 2.1.3.1).

4.4.2 Results and Discussions

The degradation profiles at different pH values are shown on Figure 20. The results clearly show that the rate of degradation of salsalate is related to the pH of the suspending medium. Korblum and Zoglio (297) have indeed shown that an increase in the rate of decomposition of aspirin, upon the addition of a series of lubricants was mirrored by an increase in pH, although no attempt was made to derive an expression to relate the two parameters of pH and degradation rate.

By monitoring the rate of decomposition of salsalate in the buffered and non-buffered solutions, it was possible to show the existence of a linear relationship between the logarithm of the apparent zero-order rate constant and the pH of the system over the pH range of 3.4 to 4.6. The linear relationship could be represented graphically as shown in Figure 21. The line through the points could be described by equation 28.

Fig. 20. Degradation of salsalate in suspensions of buffers at different pH values at 50°C

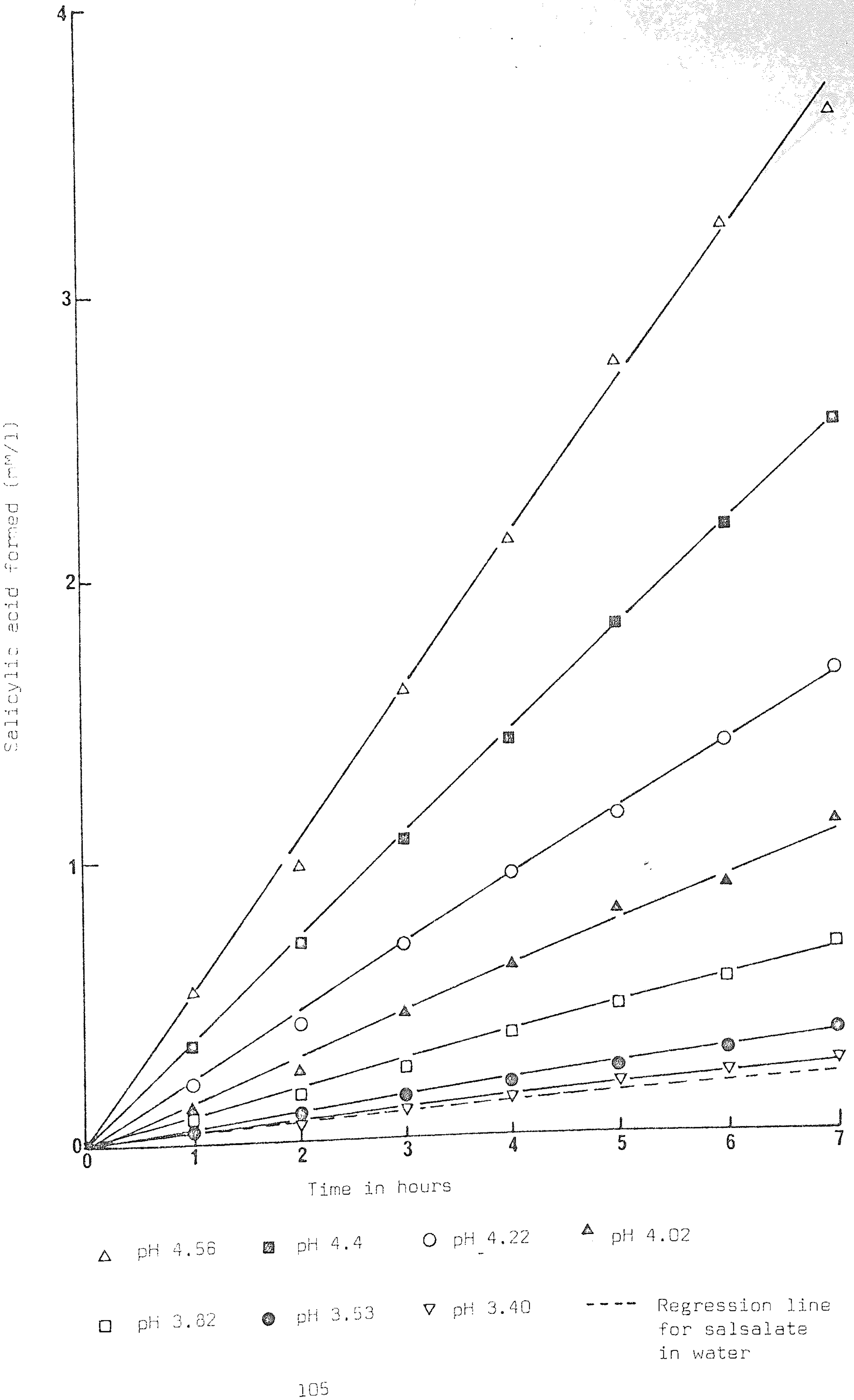
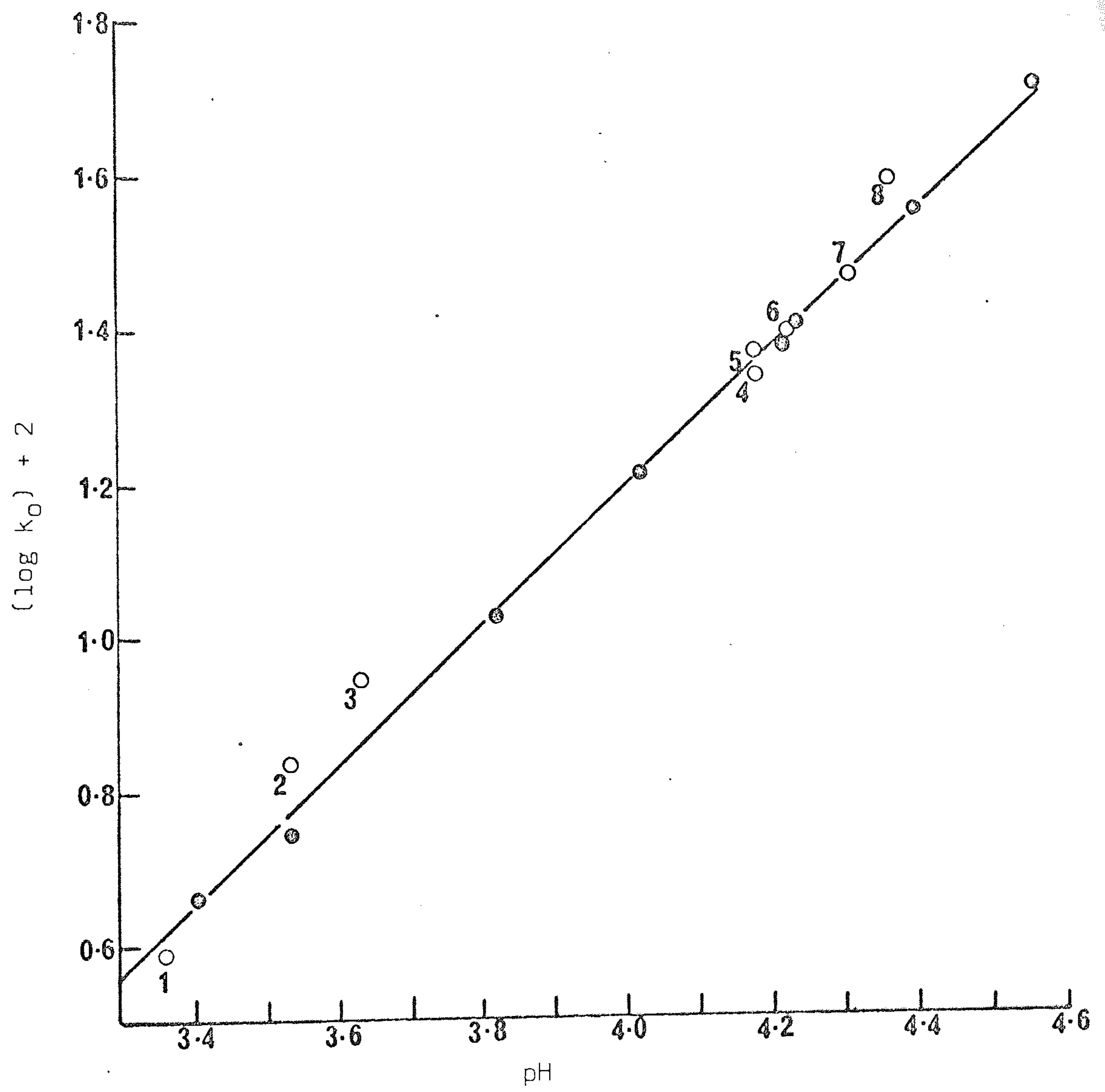


Fig. 21. Relationship between the logarithm of the zero order rate constant and pH for the degradation of salsalate in suspensions at 50°C



Key

● Salsalate in buffers ranging 3.4 to 4.56

1 Salsalate + $MgCl_2$ in water

2 Salsalate + $MgCl_2$ in buffer (pH 3.53)

3 Salsalate + Mg stearate in buffer (pH 3.63)

4 Salsalate + $MgCl_2$ in buffer (pH 4.18)

5 Salsalate + washed magnesium stearate in water (Trial I)

6 Salsalate + Mg stearate in buffer (pH 4.24)

7 Salsalate + washed Mg stearate in water (Trial II)

8 Salsalate + Mg stearate in water

$$\log k_0 = 0.93\ \text{pH} - 4.50 \quad \text{--- Eq. 28}$$

where k_0 = apparent zero order constant

r (correlation coefficient) = 0.999

Reanalysis of the data reported by Kornblum and Zoglio (297) showed that such a relationship also held for the apparent zero order decomposition of aspirin in suspension in the presence of additives. The corresponding equation was found to be as shown on equation 29, over a range of pH of 2.60 to 4.14.

$$\log k^0 = 0.72\ \text{pH} - 2.79 \quad \text{--- Eq. 29}$$

r (correlation coefficient) = 0.993

In the presence of excipients such as magnesium stearate, both compounds (drug and additive) therefore produce non buffered suspensions with pH values to which the observed reaction rates are directly proportional. However, one should not expect the linear relationship to hold for all pH values since published data on the decomposition of both salsalate (304) and aspirin (32, 33) in solution have clearly demonstrated the complex relationship between the pH and the reaction rate constant. In his studies on aspirin solutions, Edwards (32) has rationalised the linear relationship observed in the pH 2.6 - 4.14 range on the basis of six parallel reactions. There were however regions in the pH log rate constant curve where the logarithm of the reaction rate constant was inversely proportional to the pH or independent of pH.

On the basis of these observations further investigations were carried out to study whether pH has a role in excipient induced degradations of salsalate in suspension systems.

4.5 Excipient Induced Reaction

The effects of magnesium stearate and magnesium chloride in water and in buffer on the decomposition of salsalate in suspension compared with samples of salsalate with no additives in water and in buffer were investigated.

An attempt to reduce the alkaline impurities by washing magnesium stearate were also tested.

4.5.1 Methods

Suspensions of salsalate with 0.1% $^{w}/_{v}$ magnesium stearate or 0.1% w/v magnesium chloride were made in water and equilibrated at 50°C. Samples were withdrawn and assayed by HPLC as described (Section 2.1.3.1). The pH values of the samples were also determined. Likewise salsalate suspensions were made in a pH 4.24 buffer and 0.1% w/v magnesium stearate or magnesium chloride added. The effects of using washed magnesium stearate on the degradation of salsalate in suspension were also investigated.

4.5.1.1 The Washing of Magnesium Stearate

The procedure for washing magnesium stearate to reduce alkaline impurities has been outlined in Section 2.12. The samples of magnesium stearate which have been so treated, have been referred to in this thesis as "washed" magnesium stearate, to distinguish from the untreated samples.

4.5.2 Results and Discussion

The results as shown in Figures 22 and 23 suggest that pH has a role in excipient-induced salsalate degradations. The effect of magnesium stearate on salsalate degradation is controlled by the

Fig. 22. Degradation of salsalate: the effects of magnesium stearate and magnesium chloride in water and in buffer system pH 4.24 at 50°C

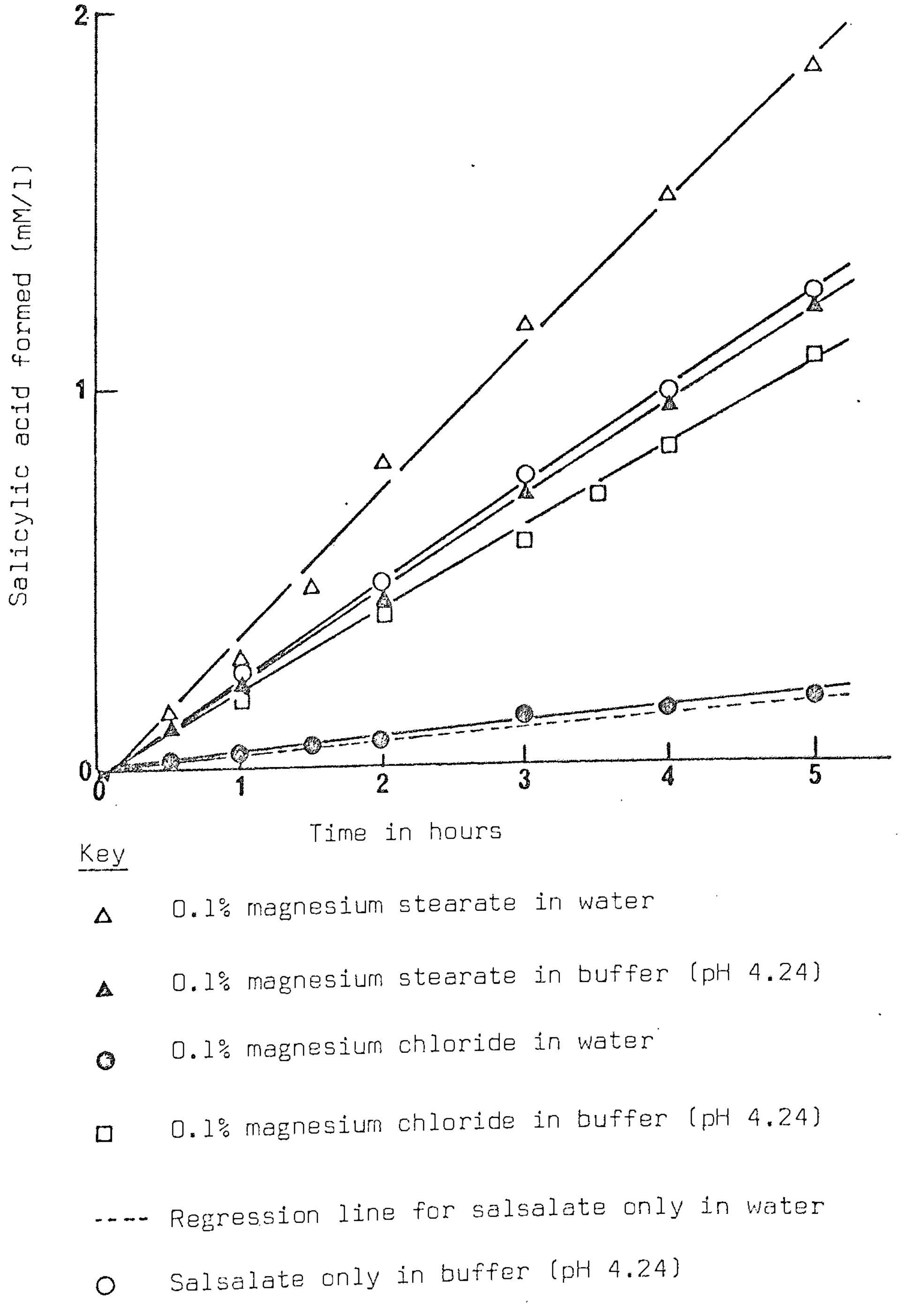
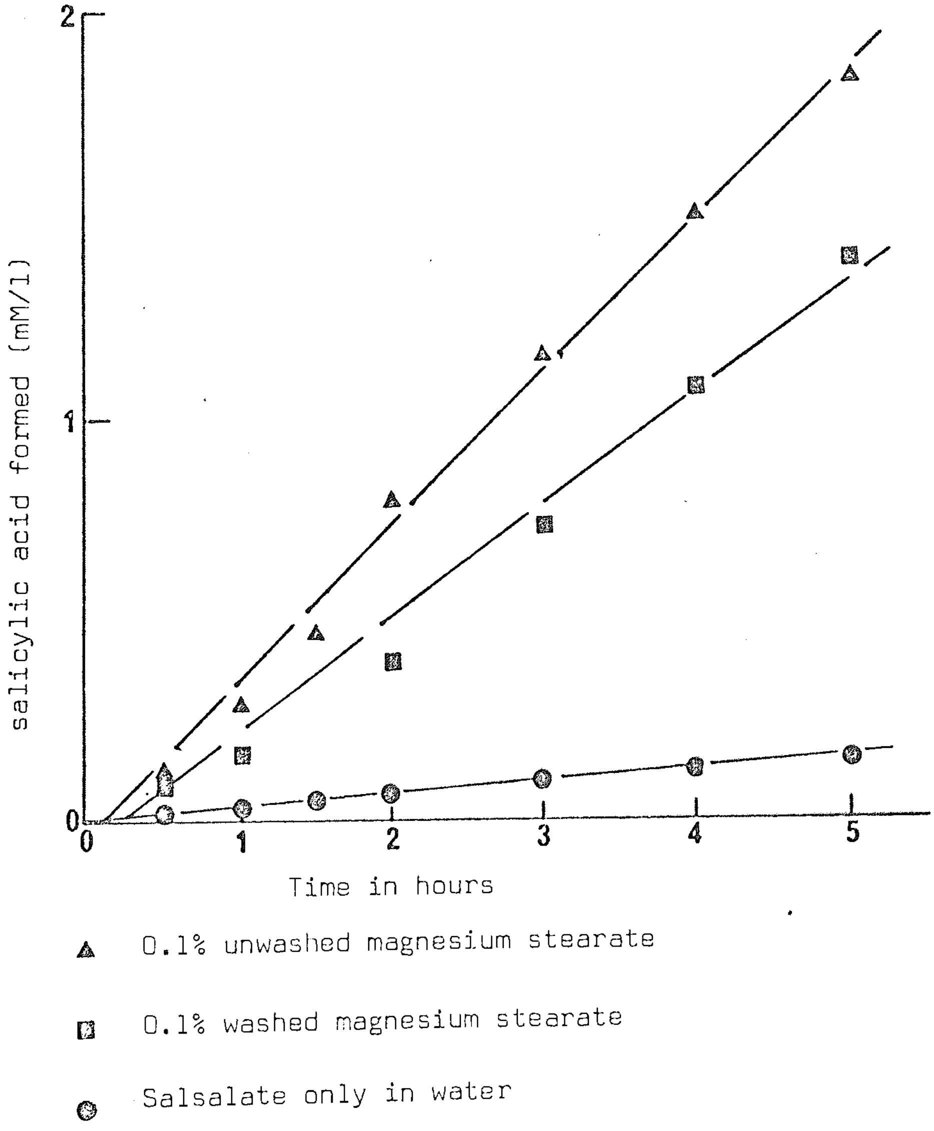


Fig. 23. The effect of washing magnesium stearate on the degradation of salsalate at 50°C



buffer system (observed decrease in rate constant) and that of magnesium chloride is also influenced by the buffer system (increase in rate constant). It is interesting to note that the reactions carried out in buffer systems (pH 4.24) show no apparent difference in the reaction rates between salsalate and salsalate with additives except those which could be attributed to minor variations in pH.

Washing of magnesium stearate had a significant influence on the decomposition of salsalate when compared to unwashed magnesium stearate (Figure 23).

The apparent zero-order rate constants for the degradation of salsalate in buffer systems and in the presence of additives are both related to the pH of the suspension system as shown on Table 8, and in Figure 21. Figure 21 shows that the pH and the apparent zero-order rate constants of the suspension in the presence of the additives were linearly related as observed in the buffer systems. An explanation can therefore be put forward to describe the observed increase in rate of reaction of salsalate on the addition of magnesium stearate.

4.5.3 The Mechanism of Excipient Induced Salsalate Degradation

The experiments that have been carried out so far show that stearates of magnesium, calcium, sodium and aluminium induced rapid degradation of salsalate in aqueous suspensions. Magnesium stearate produced the largest effect. The effects were associated with high magnesium ion contents and high values of pH. The use of magnesium ions derived from magnesium chloride was associated with lack of increase in reaction rate and low pH. The systems studied in buffer solutions have clearly indicated the relation

Table 8

RELATIONSHIP BETWEEN THE APPARENT ZERO ORDER RATE CONSTANT AND pH OF THE FORMATION OF SALICYLIC ACID IN AQUEOUS BUFFERED AND NON-BUFFERED SUSPENSIONS OF SALSALATE

The Suspension System	The pH of the Reacting Mixture	Apparent zero order rate constant K_o (mM/l/hr)	Log (k_o) + 2
Salsalate only in buffer	3.40	0.046	0.660
" " " "	3.53	0.057	0.754
" " " "	3.82	0.107	1.030
" " " "	4.02	0.167	1.224
" " " "	4.22	0.245	1.390
" " " "	4.24	0.250	1.415
" " " "	4.40	0.369	1.567
" " " "	4.56	0.543	1.735
1. SSA + $MgCl_2$ in Water	3.36	0.039	0.592
2. SSA + $MgCl_2$ in Buffer	3.53	0.069	0.839
3. SSA + MgS in Buffer	3.63	0.089	0.951
4. SSA + $MgCl_2$ in Buffer	4.18	0.224	1.351
5. SSA + Washed MgS in Water	4.18	0.240	1.380
6. SSA + MgS in Buffer	4.24	0.255	1.408
7. SSA + Washed MgS in Water	4.31	0.300	1.478
8. SSA + MgS in Water	4.36	0.410	1.613

SSA	Salsalate
$MgCl_2$	Magnesium chloride
MgS	Magnesium stearate

The Nos 1-8 correspond to identification numbers on Figure 21 between pH and the observed apparent zero order rate constant. The linear relationship (Figure 21) quantitatively confirmed a relationship between the logarithm of the zero order rate constant the the pH in the 3.4 to 4.56 range.

On the basis of these results, it can be said that the additives exemplified by magnesium stearate mediate their effects through changes in pH. For magnesium stearate, the pH formed in the suspension systems with salsalate was such that rapid degradation of salsalate occurs. Addition of magnesium stearate in buffer systems of different pH have shown that the controlling factor for the rate of reaction is pH and not magnesium ions.

4.5.4 Conclusions

The zero order rate of formation of salicylic acid from aqueous salsalate suspensions is shown to be increased by the addition of alkali stearates, an effect which is produced mainly by the alkaline impurities in the samples. A direct relationship between the concentration of magnesium ions and the rate constants was observed but was shown to be secondary to the pH changes induced by the alkaline impurities present in the sample.

The results observed may serve to interpret parallel reactions performed in the solid state (Chapter 5).

4.6 Important Observations Associated With Changes of pH in a Suspension System

The changes in pH have been shown in the previous sections to influence reaction rates in the suspensions studied. It was observed that the amount of salsalate in solution in the suspension was higher with higher pH. Salsalate is a weak acid with a pKa 3.45, a value determined by Stevens (304). A shift in pH would therefore be expected to change the amount of drug in solution. The relationship between pH and solubility for the weak acid may be of great importance in understanding reactions in the solid state. Since some solid state reactions are said to occur in solutions of adsorbed moisture on the solid surface, a substance which would change the pH of the sorbed moisture in such a way that ionisation is favoured would increase the total drug in solution. Since drugs in solution degrade faster than in the solid state (311), such a shift in pH could have a bearing on the stability of solids. It is therefore important to understand the relationships between pH, solubility and reaction rate constants.

4.6.1 Effects of pH on Solubility

The total solubility of a weak acid is the sum of the ionised and unionised species which are related to the pH and pKa by the simplified expression:

$$pH = pKa + \log \left|\frac{A^-}{HA}\right| \qquad \text{--- Eq. 30}$$

where $|A^-|$ = the concentration of the ionised species mM/l

$|HA|$ = the concentration of the unionised species mM/l at saturation solubility

At any pH value, with the knowledge of pKa of a weak acid and the total solubility, the value of $\log \left|\frac{A^-}{HA}\right|$ and $\left|\frac{A^-}{HA}\right|$ can be determined as follows:

$$|A^-| + |HA| = S \qquad \text{--- Eq. 31}$$

where S = total solubility (mM/l)

If $\left|\frac{A^-}{HA}\right| = R = \text{Antilog}(pH - pKa)$ --- Eq. 32

Then $|A^-| = R|HA|$ --- Eq. 33

By substituting equation 33 in equation 31

$R|HA| + |HA| = S$ --- Eq. 34

$|HA|(R + 1) = S$ --- Eq. 35

$|HA| = \frac{S}{(1 + R)}$ --- Eq. 36

S (experimentally determined total solubility) and R (calculated from pH and pKa according to Eq. 32) are known, so $|HA|$ can be evalulated. Similarly $|A^-|$ can be evaluated from equations 31 and 34 as described by the expression:

$|A^-| = \frac{RS}{(1 + R)}$ --- Eq. 37

The values of pH, $\left|\frac{A^-}{HA}\right|$, S, $|A^-|$ and $|HA|$, as well as the corresponding zero order rate constants in the buffer systems are shown in Table 9. From Table 9 and observing equations 36 and 37, it can be noted that $|A^-|$ changes substantially while $|HA|$ changes very little with changes in pH. Similar to the relationship earlier obtained between log K_0 versus pH (equation 28), a good linear relationship also exists between the pH and $|A^-|$ and between log K_0 and $|A^-|$ as shown by equations 38 and 39:

$pH = 1.11 \log|A^-| + 4.01$ --- Eq. 38

$\log K_0 = 1.03 \log |A^-| - 0.79$ --- Eq. 39

A complex interrelationship between log K_0, pH and log$|A^-|$ exists as described by equations 28, 38 and 39.

Table 9

RELATIONSHIP BETWEEN RATE CONSTANT, SOLUBILITY AND pH AS APPLIED FOR DEGRADATION OF SALSALATE

pH	3.4	3.53	3.83	4.02	4.22	4.24	4.4	4.56
Rate constant K_o	0.046	0.057	0.107	0.167	0.245	0.260	0.369	0.543
Log K_o + 2	0.660	0.754	1.030	1.224	1.390	1.415	1.567	1.735
Total solubility S	0.622	0.668	0.961	1.286	1.760	1.855	2.480	3.522
$R = \|A^-\|/\|HA\|$	0.891	1.202	2.344	3.715	5.888	6.166	8.913	12.882
$\|A^-\|$	0.292	0.364	0.674	1.013	1.506	1.564	2.230	3.269
Log $\|A^-\|$	-0.535	-0.438	-0.171	0.006	0.177	0.194	0.348	0.514
$\|HA\|$	0.329	0.304	0.287	0.273	0.256	0.259	0.250	0.253
Log $\|HA\|$	-0.481	-0.517	-0.542	-0.564	-0.592	-0.587	-0.602	-0.595

K_o = rate constant mM/1/hr

S = Total solubility mM/1

$|A^-|$ = Ionised species mM/1

$|HA|$ = Unionised species mM/1

N.B. There is very little change of $|HA|$ 0.079 mM/1

There is a large change of $|A^-|$ 2.977 mM/1

pKa of salsalate 3.45

4.6.2 Conclusions

From the complex interrelationships between the pH, solubility and the rate constant observed, it appears feasible that the suspension technique used may be useful in interpreting, predicting and elucidating the chemical mechanisms in solid dosage forms as well as in the evaluation of the suitability of a lubricant in a dosage form. Furthermore, the suspension model may be useful since most cases of solid state degradation encountered with pharmaceutical solid dosage forms are solvolysis, particularly hydrolysis reactions initiated by the residual moisture present in the drugs or excipients used in the formulations (184, 296).

4.7 The Effects of Buffer Ionic Strengths on the Decomposition of Salsalate

Equation 38 shows that an increase in ionised species of salsalate occurs with increasing pH. Equation 28 shows that the pH increase causes an increase in the reaction rate constant. It is rational therefore to say that ionic species participate in the observed increased reaction rate. In reactions where ionic species participate, the reaction rate may be influenced by the ionic strength of the reaction medium.

Ionic strength is defined by equation 40.

$$\mu = \tfrac{1}{2} \Sigma c_i Z_i^2 \qquad \text{--- Eq. 40}$$

where μ = ionic strength (moles)

C_i = molar concentrations M/L

Z_i = valency of the ion.

The ionic strength affects inter-ionic interactions and activity coefficients (293). The relationship between ionic strength and observed rate constants can be given by equation 41 (293):

$$\log K = \log K_0 + 1.02\, Z_A Z_B \sqrt{\mu} \qquad \text{--- Eq. 41}$$

where K = observed rate constant

K_0 = a rate constant at infinitely dilute solution where $\mu = 0$

$Z_A Z_B$ = charges of reactants

A plot of log K versus $\sqrt{\mu}$ will therefore be linear with slope value equivalent to $1.02\, Z_A Z_B$. If one of the reactants is neutral, $Z_A Z_B = 0$ then the rate constant is independent of ionic strengths in dilute solutions.

4.7.1 Methods

McIlvaines Buffer solution (310) at pH 4.0 was adjusted to the desired ionic strengths by adding appropriate amounts of potassium chloride. Solutions at pH 4.0 and ionic strengths ranging from 0.157 M to 1.0 M were prepared. A salsalate suspension (1.0 g/100 ml) in the above solutions were equilibrated at 50°C, and samples withdrawn at known intervals and assayed for salicylic acid formation by HPLC as previously described (Section 2.1.3.1).

4.7.2 Results and Discussion

It is observed on Figure 24 that the rate of formation of salicylic acid is dependent on ionic strength. As the ionic strength increases the rate of formation of salicylic acid decreases.

When the observed zero-order rate constants are determined and plotted according to equation 41, a linear relationship is obtained as shown on Figure 25. The linear relationship on Figure 25 is described by equation 42:

Fig. 24. The effect of ionic strength of buffer system on the degradation of salsalate in suspension at 50°C and pH 4.0

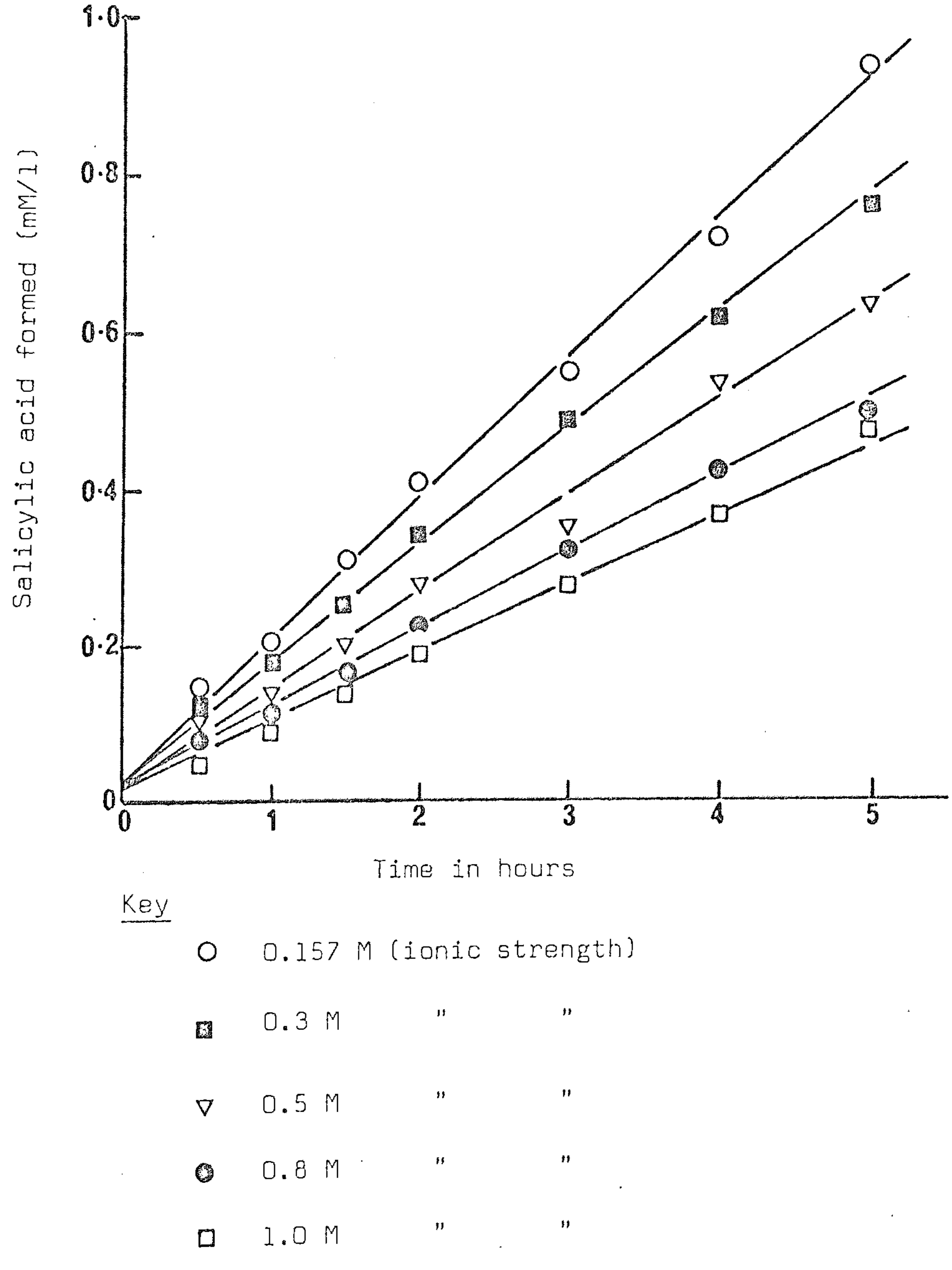
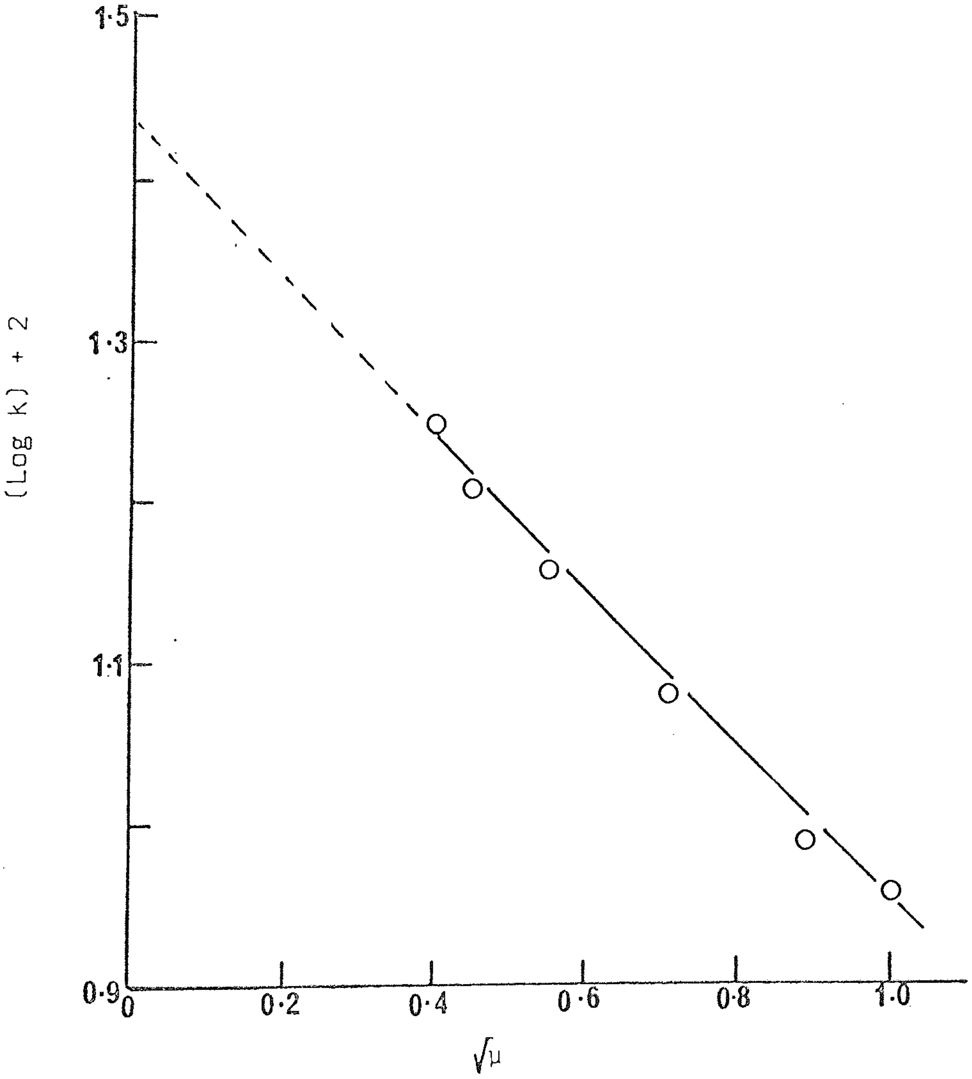


Fig. 25. Relationship between square root of buffer ionic strength (μ) and the logarithm of the zero order rate constant for the degradation of salsalate at 50°C and pH 4.0



$$\log K = -0.56 - 0.49\sqrt{\mu} \qquad \text{--- Eq. 42}$$

where K is the observed zero order rate constant.

This observation confirms the participation of ionic species in the decomposition of salsalate in suspension systems. Furthermore, additives that may contribute to the ionic strength of the reaction medium may have some influence on the rate of reaction in addition to other influences such as pH. However, the changes observed are not very large, since a large shift of ionic strength has a small bearing on the rate constant. In the case studied a six-fold change in ionic strength does appear to change the rate constant by approximately two-fold only.

4.8 Degradation of Aspirin Compared to Salsalate in the Influence of Magnesium Stearate

The influence of magnesium stearate or other common tablet lubricants on aspirin degradation has been studied extensively (180, 202, 297 and 298) while that of salsalate has not been so widely studied (304). In the presence of 0.1% magnesium stearate, both aspirin and salsalate degrade forming salicylic acid. In suspension studies, the formation of salicylic acid was observed to be an apparent zero order. The rate of formation of salicylic acid in a suspension system at 50^{0}C in the presence of 0.1% magnesium stearate was 1.140 mM/l/hr and 0.410 mM/l/hr for aspirin and salsalate respectively. This observation shows the marked difference in reactivity of aspirin and salsalate in the presence of magnesium stearate, where aspirin is six times more reactive than salsalate. (Although the rate constants quoted above differ three-fold, for every mole of salsalate that degrades, two moles of aspirin must degrade to give an equivalent amount of salicylic acid in solution). On the basis of the above observations it was rational to consider the use of aspirin for studies of stability in the solid state and to note whether the observed differences in reactivity will also be manifested in the solid state.

CHAPTER 5

STABILITY IN THE SOLID STATE: THE INFLUENCE OF ADDITIVES AND COATING ON THE STABILITY OF ASPIRIN AND SALSALATE

CHAPTER 5

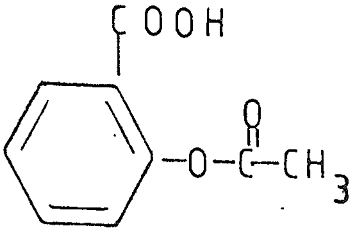
5. STABILITY IN THE SOLID STATE: THE INFLUENCE OF ADDITIVES AND COATING ON THE STABILITY OF ASPIRIN AND SALSALATE

5.1 Introduction

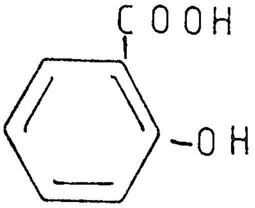
The mechanisms of decomposition of drugs in the solid state are complex and difficult to unravel (114, 186, 189). The problems are compounded by the fact that most drugs are formulated with excipients and decomposition in such systems is even more complicated. This together with the usually slow rates of decomposition in the solid state relative to solutions may explain the relatively small number of reports on the quantitation of decomposition of drugs in formulated solid-dosage forms. Many of the reports which have appeared have tended to be semi-quantitative although a few detailed studies have been reported (124, 128, 132, 134, 135, 138, 150, 151). To overcome the time-constraints, some workers have resorted to the prediction of the solid state stability of hydrolabile drugs by studying their decomposition in suspension systems. Kornblum and Zoglio (297) for example attempted to predict the stability of aspirin in the presence of tablet lubricants in the solid state by this approach. Although the method described is attractive, the mechanisms of decomposition in the solid dosage systems may be different to those observed in systems containing a higher proportion of water.

More recent studies have shown that in addition to salicylic acid (II), salicylsalicylic acid (III) and acetylsalicysalicylic acid (IV) (Figure 26) could be detected in aspirin tablets (1-2, 10-12). Since, these compounds (III and IV) have been shown (1, 3) to be potentially immunogenic, limiting their presence in formulated

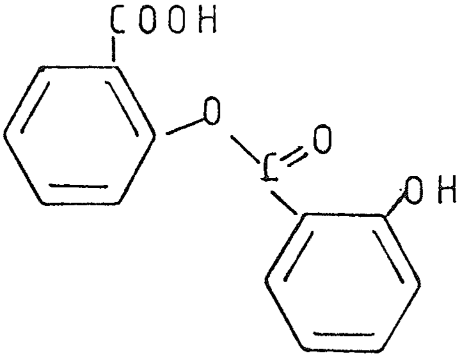
Figure 26. Decomposition of aspirin in the solid state



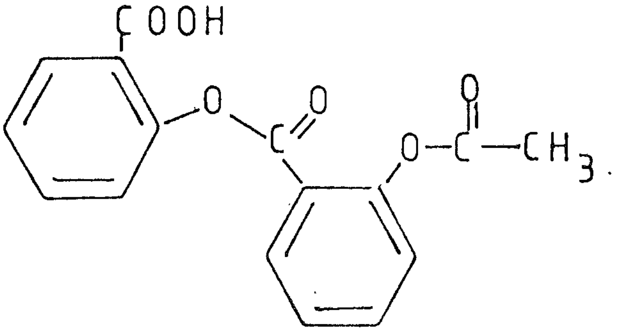
I ASPIRIN



II SALICYLIC ACID



III SALICYLSALICYLIC ACID



IV ACETYLSALICYLSALICYLIC ACID

products is important. Bundgaard and DeWeck (2) reported that although III was detected in aspirin tablets, it was not detected in various aspirin samples, thus suggesting that its formation could be excipient induced.

The study was initiated to determine whether (III) and (IV) were formed during the decomposition of aspirin in the presence of excipients in the solid state, to quantify the kinetics of decomposition of aspirin in the presence of excipients and to elucidate the mechanisms of interaction of aspirin with tablet lubricants and in particular with magnesium stearate. Other additives used included magnesium oxide, magnesium trisilicate, glyceryl palmitostearate (Precirol^R), citric acid, magnesium chloride and mepyramine maleate. Furthermore the effect of film coating on the solid state stability of aspirin was examined, as well as the protective ability of the films against extragranular additives such as magnesium stearate and mepyramine maleate. The stability of salsalate and that of the microcapsules was studied and the influence of magnesium stearate on the stability of salsalate powder was examined.

5.2 Solid State Stability of Aspirin in the Presence of Excipients: Kinetic Interpretation, Modelling and Prediction

5.2.1 Methods

The materials used have been described in Section 2.1.1. Aspirin crystals, with a geometric mean 280 ± 1.85 microns, were mixed with fixed proportions of magnesium, zinc, aluminium, sodium or calcium stearates and 100.0 mg quantities of each of the mixtures or of pure aspirin were weighed into individual glass vials and loosely covered with cotton wool to prevent entry of condensed water droplets. The samples were stored in a humidity cabinet maintained at 60°C. A 75% relative humidity environment was maintained at this temperature using a saturated sodium chloride solution. Samples were taken at pre-determined intervals and assayed for aspirin and its decomposition products by the HPLC method.

5.2.1.1 Analysis Method

Detailed descriptions of the HPLC equipment and method have been presented elsewhere (Section 2.2).

5.2.1.2 Sample Preparation for HPLC

The contents of the vial sampled were dissolved in methanol, quantitatively transferred to a 25 ml volumetric flask and made up to volume with methanol. The resultant solution was diluted and analysed by HPLC. It is known that aspirin degrades to salicylic acid and acetic acid which sublime and evaporate respectively. The sublimation process may cause sample loss in weight. In order to investigate the possibility of loss in sample weight, the sampled vials and contents were weighed. After transferring the contents of the vial, the clean dried vial was re-weighed. The difference in weight was the weight of the sample at the time of assay. Since initially the sample weight was 100.0 mg, any deviations were considered as weight gain or weight loss.

5.2.1.3 Washed Magnesium Stearate

The procedure for washing the magnesium stearate to remove basic impurities has been described in Section 2.12.

5.2.1.4 Melting Point Determinations

The melting points of aspirin and its mixtures were determined as described earlier (Section 2.8).

5.2.2 Mathematical Model

The model used for explaining the results obtained in this study is based on liquid reaction-product layer formation during the decomposition of aspirin. Jander (77) first showed that if one considers the formation of a liquid reaction product layer, during the decomposition of spherical particles and if the reaction is diffusion limited, then it is possible to derive an expression relating the fraction decomposed with time. Such a model has been previously used by Nelson and others (126).

Microscopical examination of the particles shows that the shape of the aspirin crystals used in this study were better approximated by cylinders than by spheres. Using Jander's assumptions of a diffusion limited reaction and of a rate of thickening of the liquid layer dy/dt being inversely proportional to its thickness, y, equation 43 is obtained:

$$\frac{dy}{dt} = k/y \qquad \text{--- Eq. 43}$$

On integration

$$y^2 = 2kt \qquad \text{--- Eq. 44}$$

The fraction decomposed (α) after time t, can be expressed in terms of the total weight of the cylindrical particles studied.

$$\frac{n\rho\pi r_o^2 h - n\rho\pi(r_o - y)^2 h}{n\rho\pi r_o^2 h} = \alpha \qquad \text{--- Eq. 45}$$

where

r_o = initial radius

h = height of cylinder

n = number of cylinders

ρ = density

Equation 4~~4~~5 simplifies to

$$r_o^2 - (r_o - y)^2 = \alpha r_o^2 \qquad \text{--- Eq. 46}$$

Rearranging equation 46

$$r_o \left|1 - (1 - \alpha)^{\frac{1}{2}}\right| = y \qquad \text{--- Eq. 47}$$

Substituting for y in equation 47 from equation 44 and squaring

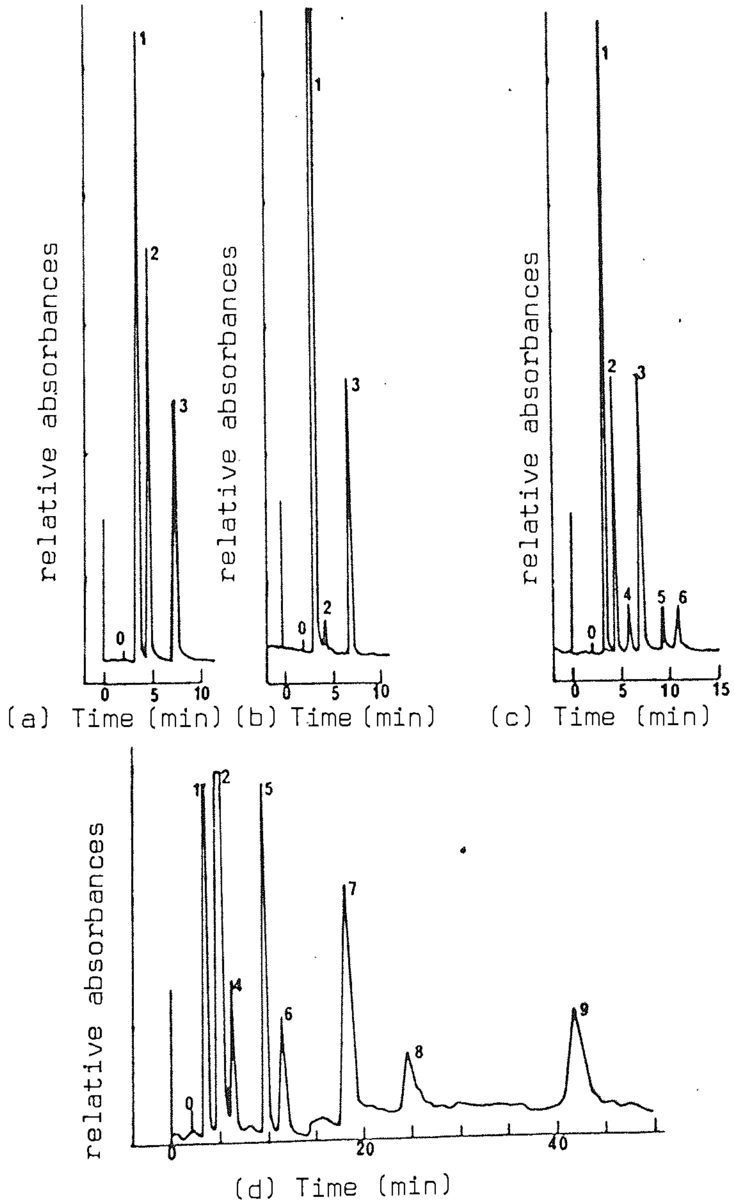
$$\left|1 - (1 - \alpha)^{\frac{1}{2}}\right|^2 = \frac{2K}{r_o^2}\, t \qquad \text{--- Eq. 48}$$

A plot of $\left|1 - (1 - \alpha)^{\frac{1}{2}}\right|^2$ against t should therefore give a straight line with zero intercept, if the liquid-layer diffusion controlled model describes the system studied. The model assumes that the length to diameter ratio of the aspirin crystals is such that end effects are negligible.

5.2.3 Results and Discussion

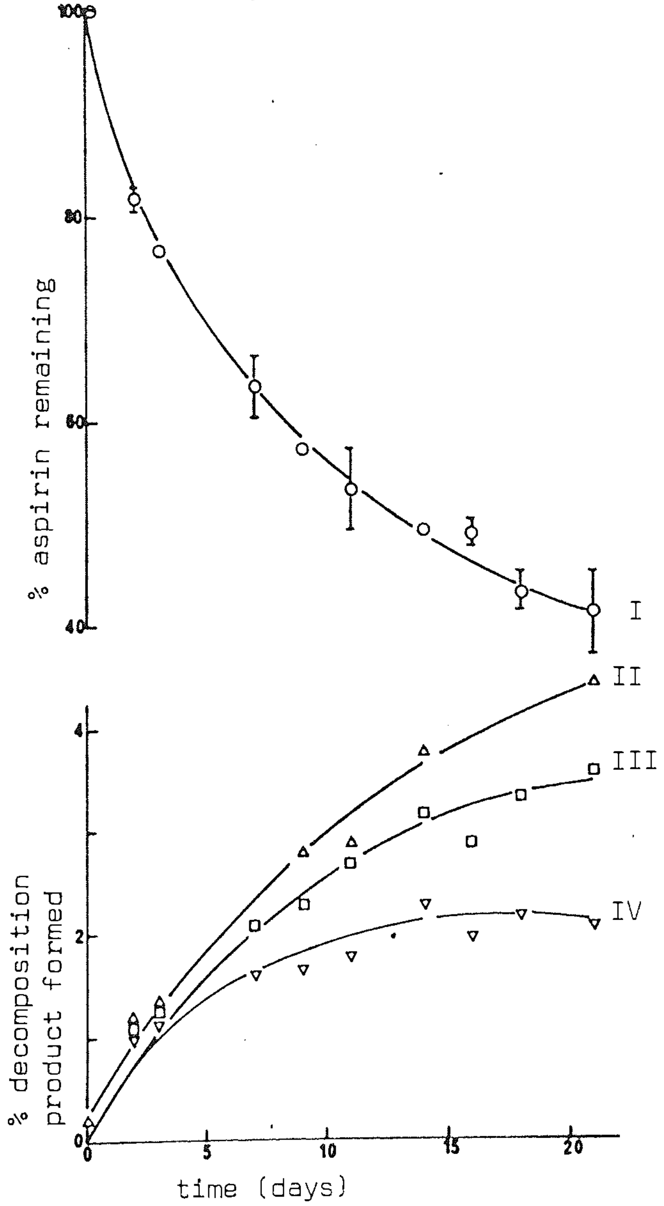
Analysis of the stored samples by HPLC showed that in addition to salicylic acid (II), salicylsalicylic acid (III) and acetylsalicylsalicylic acid (IV) (Figure 26) were formed during storage of aspirin at 60°C and 75% relative humidity in the presence of magnesium stearate. Samples of aspirin on its own stored under identical conditions did not lead to the formation of (III) and (IV) when followed over the same time period. More prolonged

Figure 27. High performance liquid chromatograms of aspirin and its decomposition products a) standard mixture of aspirin, salicylic acid and propylparaben (b) aspirin and 1% magnesium stearate c) mixture after storage for 18 days at 60°C, 75% RH and d) mixture (not diluted) after 21 days without internal standard.



Key: 0 - solvent front
1 - aspirin
2 - salicylic acid
3 - internal standard
4 - acetylsalicylsalicylic acid
5 - salicylsalicylic acid
6-9 unidentified products

Figure 28. Kinetics of decomposition of aspirin (I) in the presence of 1% magnesium stearate (60°C, 75% RH) and amounts of salicylic acid (II), salicylsalicylic acid (III) and acetylsalicylsalicyli acid (IV) formed.



storage however led to the formation of traces of the products. Figure 27 shows chromatograms of standard mixtures of aspirin, salicylic acid, and internal standard (n-propyl-p-hydroxybenzoate) (Figure 27a), non-stored samples of aspirin with 1% magnesium stearate and internal standard (Figure 27b) and stored samples of the powder mixture (Figure 27c).

Peak identification was achieved by comparison of retention times with authentic specimens as well as wavelength ratioing (16, 312). HPLC of samples stored for longer periods of time showed that the decomposition is even more complex and several products which have not yet been identified were observed (Figure 27d). These results are in agreement with those reported by Taguchi et al. (11) who showed that storage of aspirin tablets at 50°C led to the formation of (II), (III) and (IV) and that when further stressed at 95°C additional components could be detected in significant amounts. HPLC analysis of aspirin samples stored for four weeks at 60°C and 75% relative humidity showed traces of all the decomposition products detected in the presence of magnesium stearate. This therefore shows that the stearates accelerate rather than induce their formation.

The decomposition of aspirin in the presence of one percent magnesium stearate is shown in Figure 28 together with the amounts of (II), (III) and (IV) detected in the samples. It is important to note that these amounts of decomposition products can only be used as guide values since an open system was used. This particularly applies to salicylic acid (II) which has been shown to sublime readily (313). Studies in which aspirin decomposition has been followed in the solid state, by following the kinetics of formation of salicylic acid, will therefore lead to incorrect results unless closed systems were used. In the present study, an open system which allowed exposure of the samples to a constant relative humidity was preferred. Aspirin was assayed in addition to salicylic acid.

To investigate whether the concentration of lubricant present affected the rate of decomposition of aspirin, the degradation was followed in the presence of a series of concentrations of magnesium stearate. The results of these studies are shown in Figure 29. An increase in magnesium stearate concentration quite clearly accelerates the decomposition of aspirin. The data was further shown to obey equation 48. The linear relationship between $|1 - (1 - \alpha)^{\frac{1}{2}}|^2$ and time (in days) obtained is shown in Figure 30. The slope of the straight lines $\frac{2k}{r_0^2}$ is a complex function of the rate constant k, the rate of advance of the interface with units length^2 time^{-1}. The slope $\frac{2k}{r_0^2}$ day^{-1} values have been used for subsequent calculations.

Various authors have reported on the catalytic effect of excipients on aspirin decomposition (166, 169, 179). The explanation put forward for explaining the effect of magnesium stearate, has generally been based on hydrolysis taking place in an adsorbed moisture layer and on an alteration in the pH of this layer by the added excipient (174). It is indeed, known that the magnesium stearate used for tablet lubrication contains a significant amount of magnesium oxide. The British Pharmacopoeia (1973) and the United States Pharmacopoeia (1980) specifications for magnesium stearate allow for up to 8.5% of magnesium oxide (307, 308). The British Pharmacopoeia (1980) however now defines the pH range of a 5% suspension of magnesium stearate in water and states that it

Figure 29. Degradation of aspirin in the solid state: influence of increasing amounts of magnesium stearate at 60°C, 75% RH.

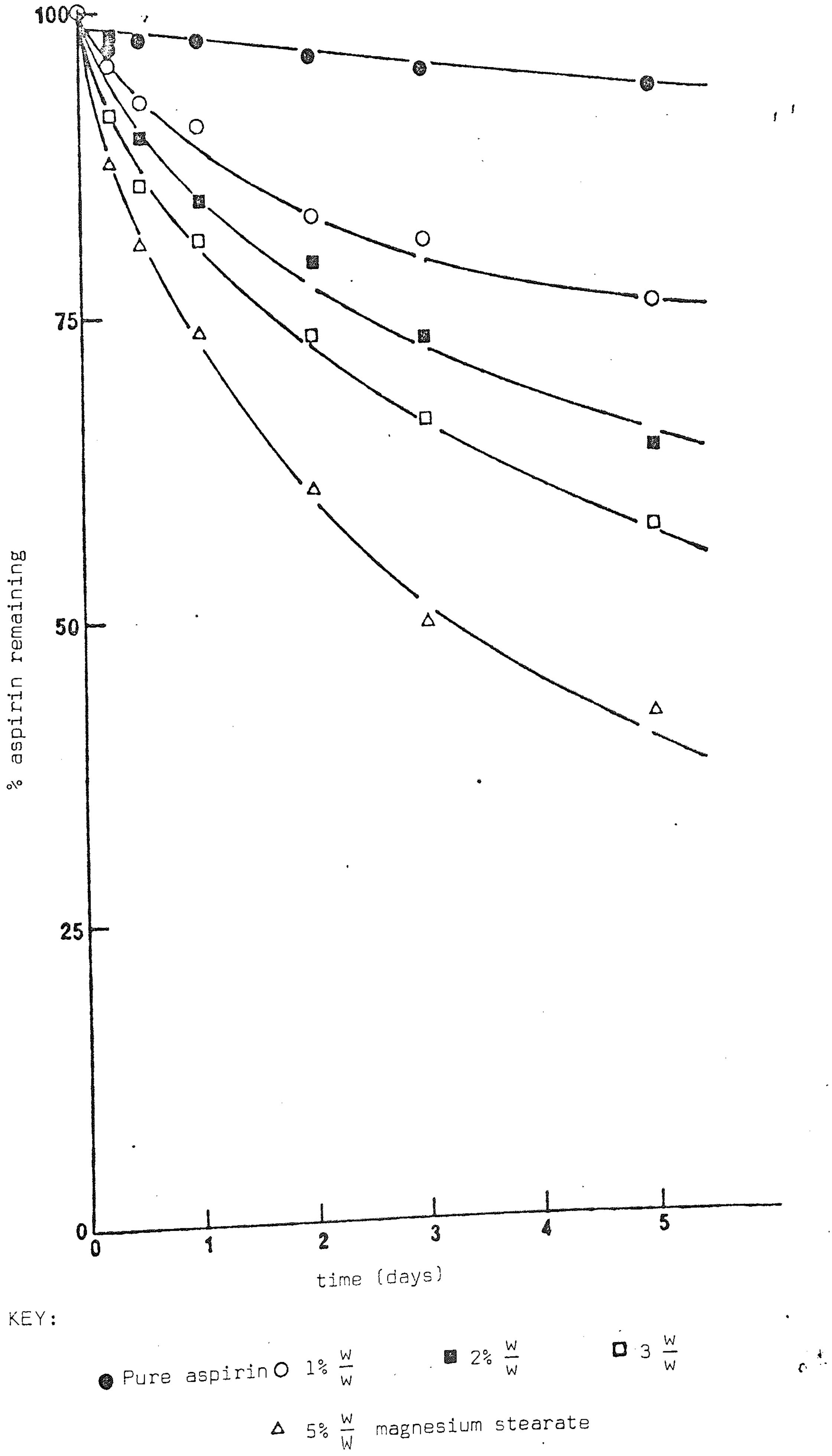
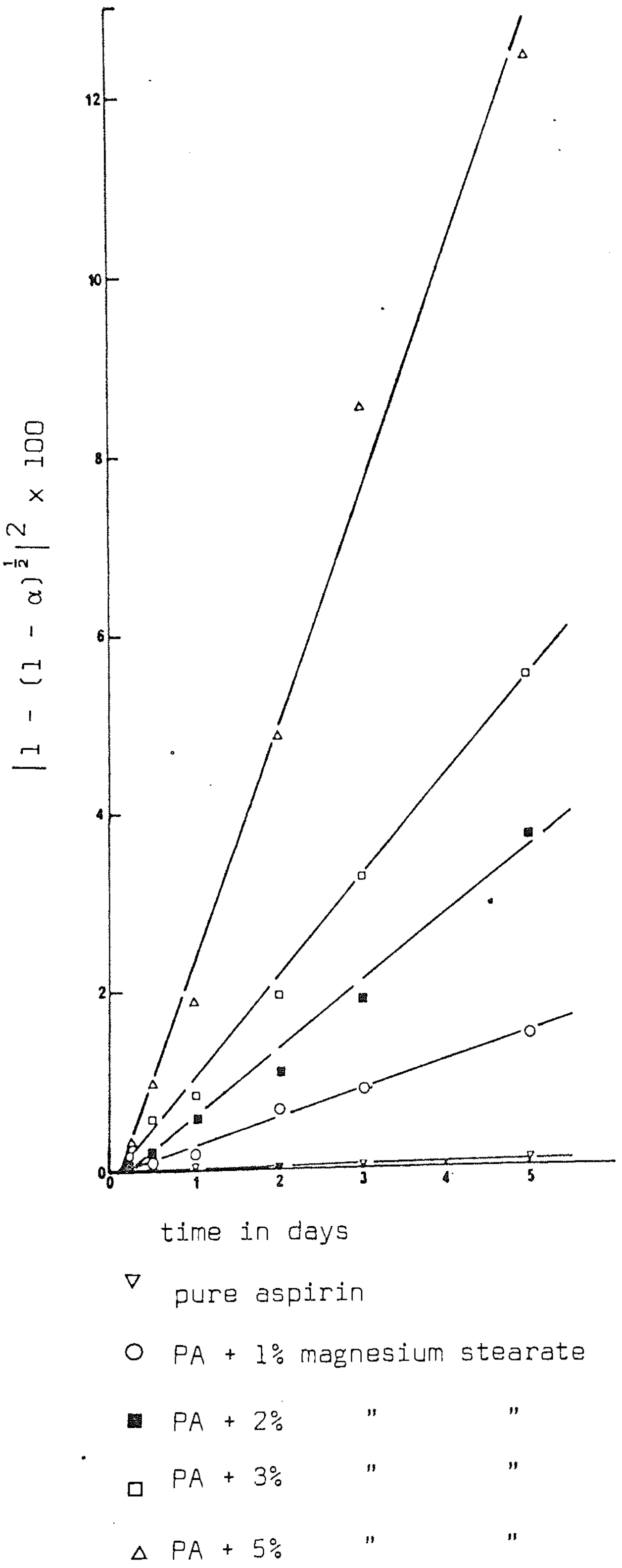


Figure 30. Effect of magnesium stearate concentration on the rate of decomposition of aspirin. Plot according to equation 48.



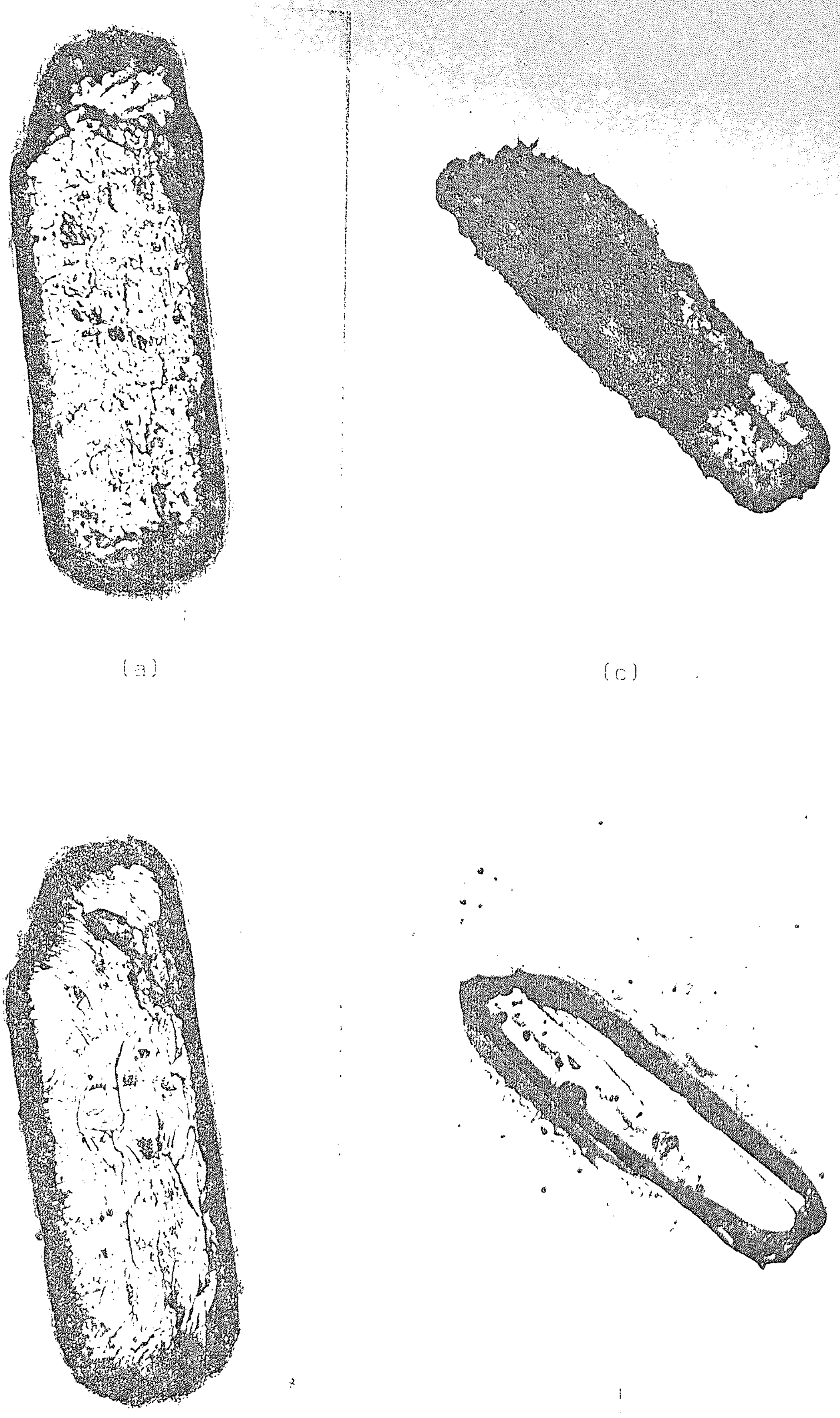
should be between 6.2 and 7.4 (309).

Additionally Kornblum and Zoglio (297) have in their aspirin-tablet lubricant suspension systems showed that there was a relationship between the observed zero order rate constant of salicylic acid formation and the pH of the suspension after addition of the lubricants. Magnesium stearate produced the largest pH shift and the highest rate constant.

It has not however been conclusively shown that pH change plays a significant role in the decomposition of aspirin in the solid state.

To test this, the rate of decomposition of aspirin powder was measured in the presence of washed and unwashed magnesium stearates. The washed sample gave a suspension (1%) with a pH near neutrality (6.9) whereas an unwashed sample prepared similarly gave a pH of 9.9. The observed rate constants as mirrored by the slopes of equation 48 were however almost identical. The slopes were 0.0033 day^{-1} and 0.0030 day^{-1} for reactions in the presence of washed and unwashed samples respectively. Clearly the results do not exclude pH induced changes in the rates of decomposition. The results however indicate that any such change was too small to be detected during the study and may have been swamped by other effects when the stability of pure aspirin is compared with aspirin in the presence of magnesium stearate.

It has been suggested (186, 191) that because sublimation of salicylic acid is observed on the surface of aspirin under stress conditions (313), factors other than those involved in solution must be operable. However sublimation out of a solution is also conceivable. Once the moisture microfilm is saturated with salicylic acid, additional formation will lead to precipitation,



(a) (c)

(b) (d)

Figure 31. Photomicrographs of decomposing aspirin crystals with and without magnesium stearate

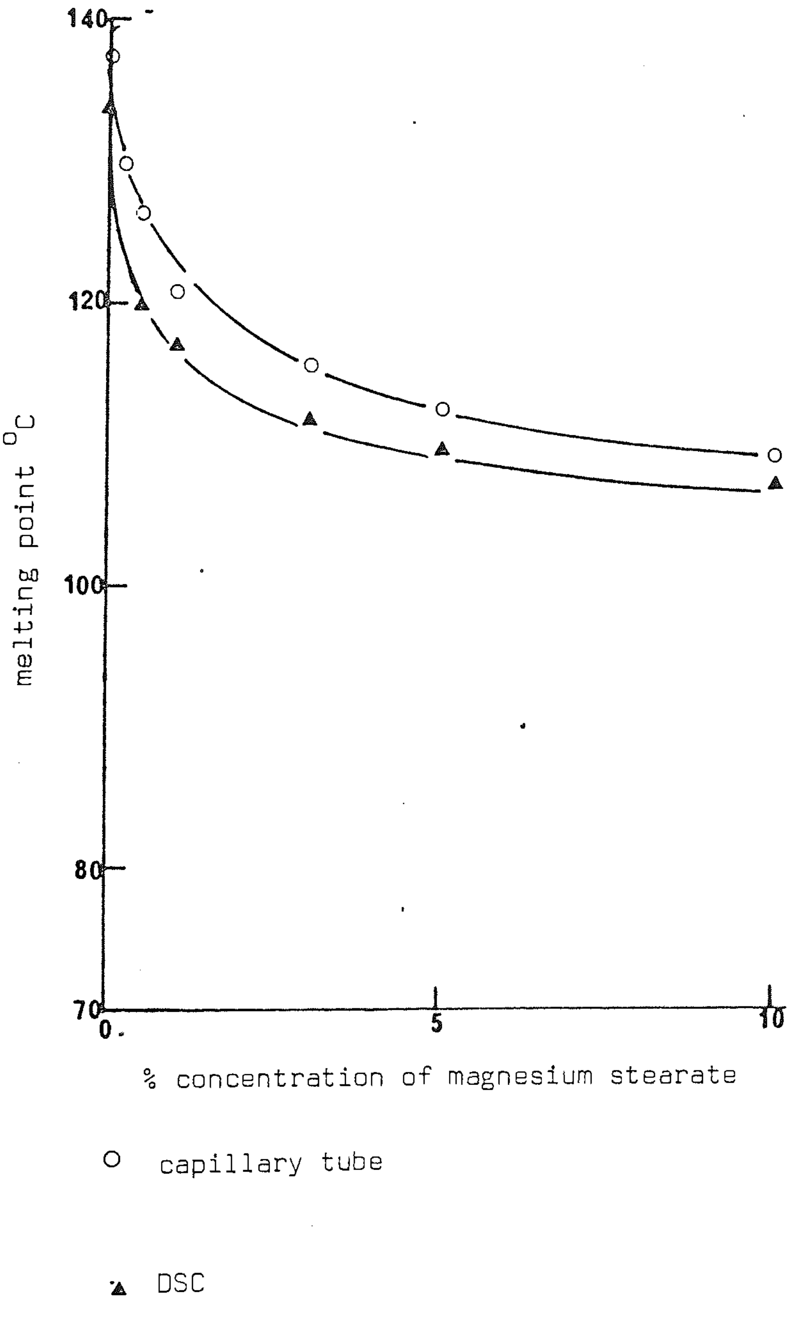
a) pure crystal on Day 0

b) pure crystal on Day 3 (at 60°C 75% RH)

c) aspirin + magnesium stearate, Day 0

d) aspirin + magnesium stearate, Day 3 (at 60°C 75% RH)

Figure 32. Effect of addition of different concentrations of magnesium stearate on the melting point of aspirin.



deposition onto adjacent surfaces and eventually sublimation.

Microscopical (Figure 31) and visual examination of the stored samples showed the presence of liquid films round the decomposing particles. Any theory put forward for observed increase in decomposition of aspirin in the presence of magnesium stearate must therefore take this into account.

Guillory and Higuchi (132) have in their work on the solid state stability of vitamin A compounds found that there was a linear relationship between the logarithm of the observed rate constant of decomposition and the reciprocal of the absolute melting temperature ($^{\circ}K$). This is derived from the relationship between the fraction of material in the liquid state (x_1) and the melting point of the pure crystalline solid (T_m) as given in equation 49.

$$\mathrm{In}\ x_1 = \frac{-Lf\cdot}{R}\left|\frac{1}{T} - \frac{1}{T_m}\right| \qquad \text{--- Eq. 49}$$

where: Lf is the molar heat of fusion and represents the difference in internal energy between the two states, the liquid being more reactive than the solid

T is the temperature of storage

R is the gas constant (8.3143 Joule mole^{-1} deg^{-1} or 1.9872 cal mole^{-1} deg^{-1})

To test whether this relationship might explain the effect of magnesium stearate on the decomposition of aspirin, the melting points of the mixtures were determined. Figure 32 shows the relationship between the melting point observed and the magnesium stearate content. The same trend was observed using both the traditional capillary tube melting point determinations and differential scanning calorimetry, although differences in absolute values were observed.

Figure 33. Relationship between the logarithm rate constant of decomposition of aspirin in the presence of alkali stearates as mirrored by the slopes of equation 48 and the reciprocal of the melting points of the mixtures.

Key: 0 aspirin alone
1 with 3% w/w Zn^{++}
2 with 3% w/w Al^{+++}
3 with 3% w/w Na^{+}
4 with 3% w/w Ca^{++}
5 with 3% w/w Mg^{++}
6 aspirin + 1% w/w magnesium stearate
7 aspirin + 2% w/w magnesium stearate
8 aspirin + 3% w/w magnesium stearate
9 aspirin + 5% w/w magnesium stearate

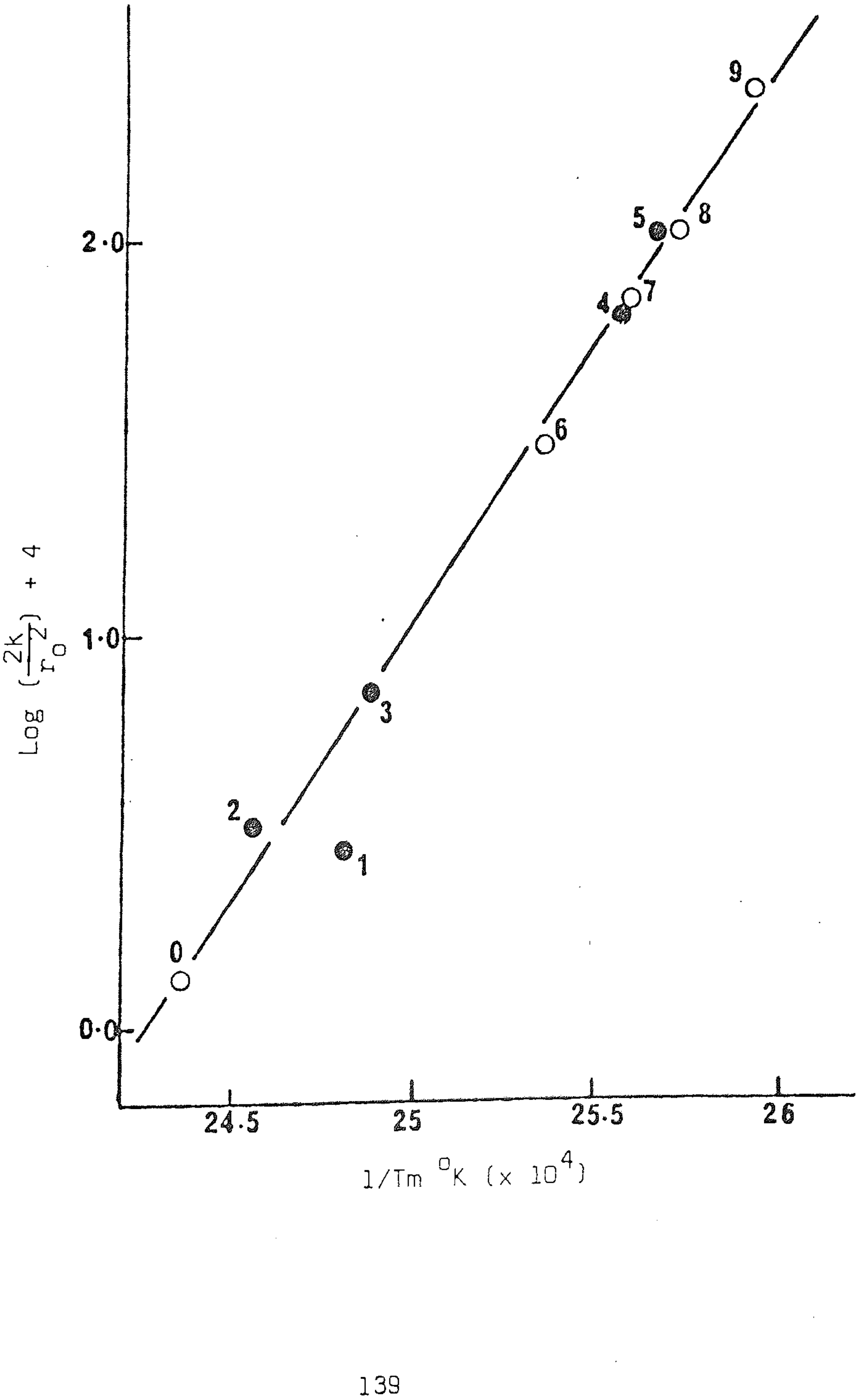
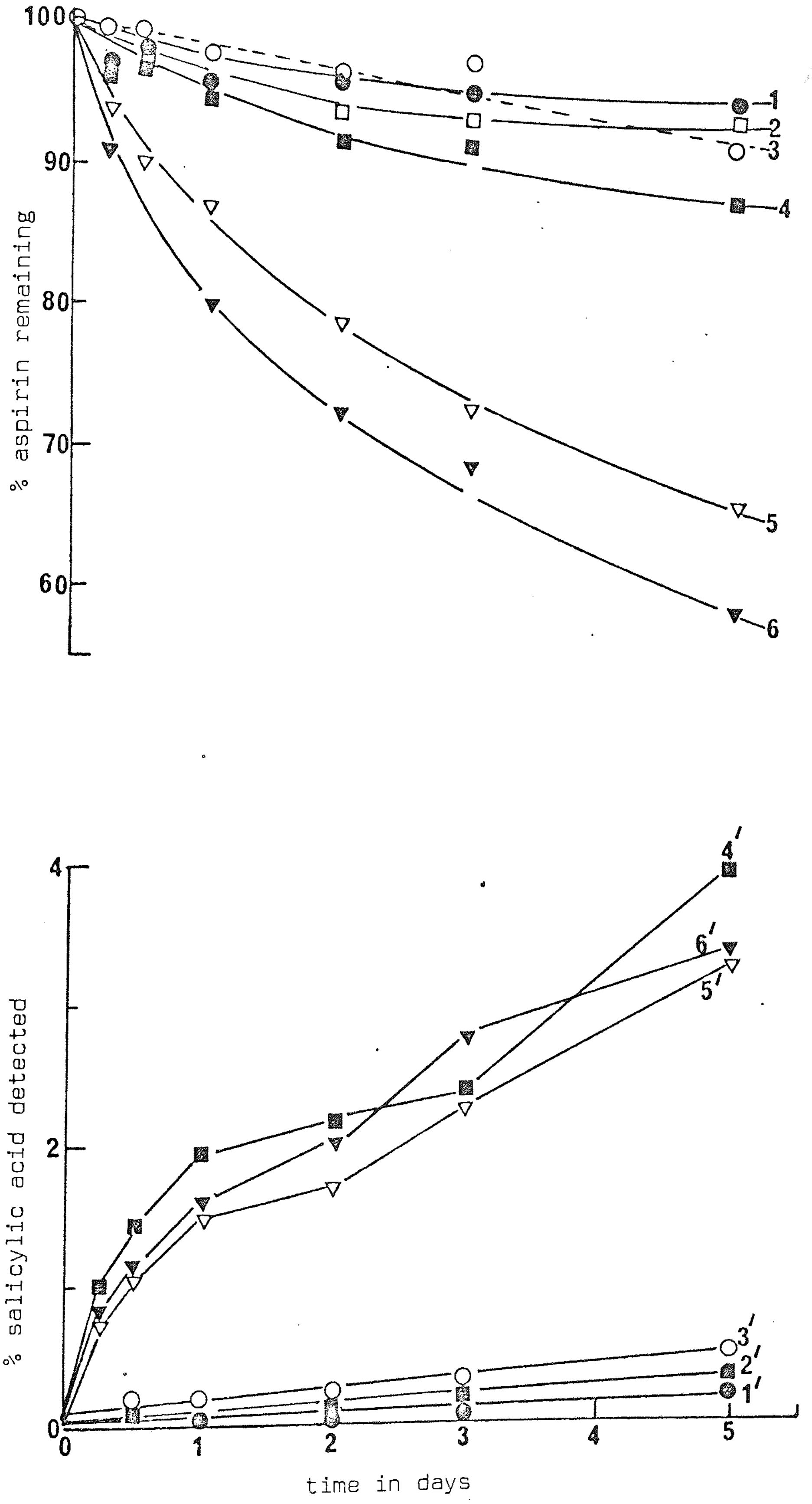


Figure 34. Effects of stearates of aluminium, zinc, sodium, calcium and magnesium on the decomposition of aspirin in the solid state (60°C, 75% RH)

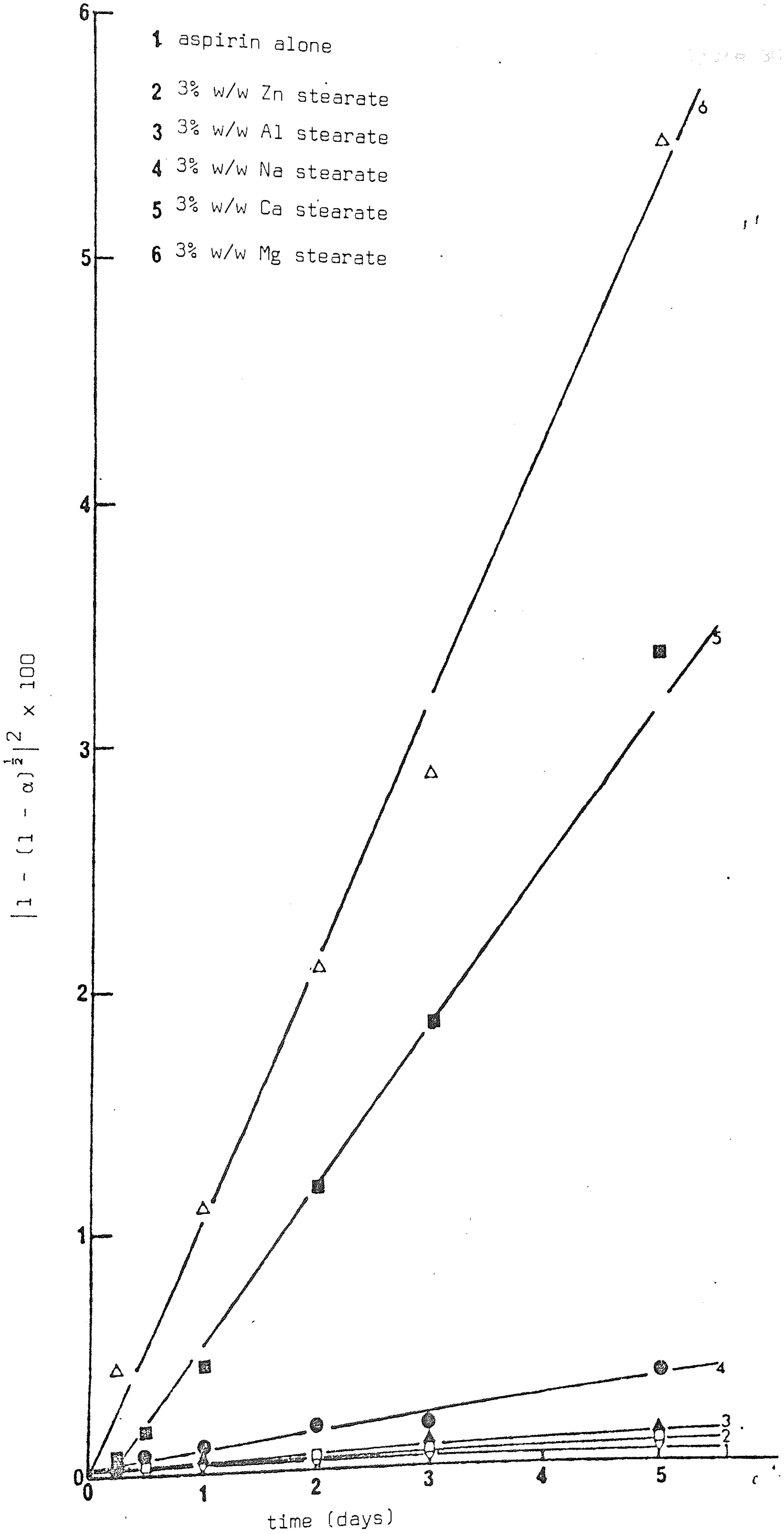


Key: stearates added

1 aspirin no additive
2 3% w/w Al^{+++}
3 3% w/w Zn^{++}
4 3% w/w Na^{+}
5 3% w/w Ca^{++}
6 3% w/w Mg^{++}

1' **6'** corresponding salicylic acid detected

Figure 35. Degradation of aspirin in the presence of stearates of zinc, aluminium, sodium, calcium and magnesium, plotted according to equation 48.



The slopes of equation 48 for the reactions shown on Figure 30, were then plotted against the reciprocal of the corresponding melting points of the aspirin-magnesium stearate powder mixtures. Figure 33 shows that this relationship holds for the system studied. One would expect that other stearates would also alter the decomposition rates of aspirin, the magnitude of the change being determined by the size of the depression in melting points.

Experiments were carried out to test whether other stearates alter the decomposition rates of aspirin. Results shown in Figure 34 indicate that different stearates in equal proportions in the mixtures exert different influences on the decomposition rates of aspirin. Magnesium stearate exerts the greatest influence. When the data in Figure 34 was kinetically treated using equation 48, linear relationships were observed as shown in Figure 35. This observation implies that the decomposition of aspirin under the influence of the stearates of zinc, aluminium, sodium calcium and magnesium, when present in proportions of 3% follow the mathematical model proposed. When the melting points of the powder mixtures were determined, and the slopes of equation 48 for the reaction as shown in Figure 35 obtained, it was observed that the relationship between the logarithm of the rate constants and the reciprocal of the absolute melting temperature appear to be superimposed on the results obtained for magnesium stearate as shown on Figure 33. It is therefore evident that the general relation holds here too.

5.2.4 Conclusions

In this study, therefore, it is shown that salicylsalicylic acid (III) and acetylsalicylsalicylic acid (IV) are decomposition products of aspirin when the latter is stored in the solid state in the presence of alkali lubricants such as magnesium stearate. III and IV were not detected in samples of aspirin without an additive stored under identical conditions for the same length of time. More prolonged storage however led to the formation of traces of the products. These data would suggest that the stearates accelerate the formation of these products and provide an explanation for earlier reports showing that III was detected in most of the commercial aspirin tablets analysed but not in bulk aspirin samples.

A direct relationship was shown between the rate constant of decomposition, as expressed by the slopes of plots of equation 48, and the concentrations of magnesium stearate present. It has further been demonstrated that there was a linear relationship between the logarithm of the slopes of equation 48 and the reciprocal of the melting points of the aspirin-stearate powder mixtures. Using a series of stearates it was shown that the relationship is of wide applicability.

Changes in melting points rather than shifts in pH of the moisture microfilms surrounding the particles, would appear to be the more plausible explanation for the observed effects of magnesium and other alkali stearates on aspirin stability. Melting point determinations would therefore appear to provide a rapid method for predicting the stability of aspirin in aspirin-lubricant solid mixtures as well as other formulations like that of sodium dicloxacillin and in the presence of additives (314) in which Differential Thermal Analysis was used. When vitamin E succinate and magnesium stearate were melted together, and cooled, the following congealing points may be observed (315):

Pure vitamin E succinate melting point is $68^{0}C$

Vitamin E succinate : Magnesium stearate 99:1 = $45^{0}C$

Vitamin E succinate : Magnesium stearate 95:5 = $30^{0}C$

Vitamin E succinate : Magnesium stearate 90:10 = $5^{0}C$

The inverse relationship between aspirin decomposition in aspirin-lubricant solid mixtures and the reciprocal of the melting points (180) is quantitatively confirmed.

5.3 The Influence of a Film Coat on the Stability of Film Coated Aspirin Particles in the Presence of Magnesium Stearate

5.3.1 Introduction

In most cases, drugs will decompose with a loss in their efficacies if they are not protected from atmospheric effects such as moisture, oxygen or light. When sugar or gelatin is used for coating drugs, the chances are that drugs having a great affinity for water will absorb some of the water from the syrup or gelatin film. Such moisture absorption may cause sugar coated tablets to have fissured and mottled surfaces (195). To overcome such problems, moisture or oxygen resistant protective coating agents would appear valuable in producing a stable product. Shellac, nitro-cellulose, acetylcellulose and waxes have been widely used as coating agents (194) because of their water resistant properties.

Although protection of tablets from moisture can be completely obtained by the use of coating agents, the active ingredients may not be well absorbed from the gastrointestinal tract because of incomplete dissolution (167). The use of very thin film coats cannot give sufficient protection against moisture.

In an attempt to obtain both a good bioavailability profile and a protective coating, Utsumi and Ida (195, 196) and Ida (197) synthesized some organic compounds such as the derivatives of polyvinyl pyridine and aminocellulose. These were tested for use as protective film coating as well as for toxicity and practical applications.

Film coats have been applied to tablets or pellets in order to attain certain desired goals such as the masking of unpleasant taste, the protection of unstable core material against adverse atmospheric influences, the separation of reactive ingredients, prolongation or delay of drug release (sustained-action), the control of the site of release (enteric coat) and the changing of the physical surface characteristics of the ingredients (7).

In an attempt to improve the stability of a product containing inter-reactive ingredients, Ball et al. (190) used multilayered granules which ensured complete separation of the drug and the reactive species. However, it was observed that reduction of the moisture content of the product to a level of 0.1% gave a better stability. Bakan and Sloan (192) used coated particles of aspirin (microcapsules) and demonstrated the protective ability of the cellulosic film coat against the adverse effect of chlorpheniramine maleate. Many reports on film coating of pharmaceutical dosage forms have centred on drug release (as shown in Chapter 3), the stability of the coated formulation (195, 313) or the interaction between drugs (192, 194). The properties of the polymeric materials in relation to their permeability to moisture has been studied (198, 316, 317). In such studies (198) it has been observed that the factors of importance include the method of film application which affects the actual rate of permeation and the physical properties of the coated material which affects the water vapour absorption rate. The activation energy of the absorption process is determined by the type of film forming polymeric material used. In the study investigating the influence of surfactants on the permeation across a cellulose acetate phthalate membrane Short and Rhodes (317) observed that although non-ionic surfactants influenced permeability they did not interact directly with the membrane. The choice of film forming materials used in this study was based on their wide usage and acceptability. Gelatin is extensively used in microencapsulation and as additive in film and sugar coating of tablets. Cellulose acetate phthalate and Eudragit L ^{R} both have solubilities dependent on shifts of pH and have been used as enteric coats and for modified release respectively. Eudragit L ^{R} is claimed (318) to be suitable for the coating of small discrete particles intended for modified release formulations.

It is the aim of this investigation to explore the barrier and protective effects of the three film forming polymeric materials described above on the decomposition of aspirin particles. The effect of extragranular magnesium stearate is studied and possible mechanisms of the protective barrier proposed.

5.3.2 Methods

The coating of the discrete particles of aspirin using gelatin, cellulose acetate phthalate and Eudragit L ^{R} has been described (Section 2.4.3). In order to assess the quality of the film coat applied the release patterns were examined as presented in Section 2.3.3 and in Chapter 3.

The materials used have been described in Section 2.4.1.

Aspirin crystals and coated aspirin particles were mixed with 1% magnesium stearate and 100.0 mg quantities of each of the mixtures were weighed into individual glass vials and loosely covered with cotton wool to prevent entry of condensed water droplets. The samples were stored in a humidity cabinet at 60°C and 75% relative humidity (Section 2.1.3.2).

5.3.2.1 Analysis Method

Detailed description of the HPLC equipment and analysis method have been presented in Section 2.2.

5.3.2.2 Sample Preparation for HPLC

The contents of the vials sampled were dissolved in methanol, quantitatively transferred to a 25 ml volumetric flask and made up to volume with methanol. For the coated particles, the film forming substances which were insoluble in methanol were filtered off using 3 μ membrane filter[§]. The resultant filtrate was diluted and after adding an internal standard, n-propyl-p-hydroxybenzoate, was analysed by HPLC.

5.3.3 Results and Discussion

5.3.3.1 Preliminary Studies at 50°C, 75% RH

Studies carried out at 50°C, 75% relative humidity have revealed that the film coats of gelatin, cellulose acetate phthalate and Eudragit L^R could be used for reducing the adverse effects of magnesium stearate on the stability of aspirin in the solid state. As shown in Figure 36, aspirin on its own at 50°C, 75% relative humidity degrades very little (about 5% only) in a period of seven weeks. Film coats of gelatin and cellulose acetate phthalate appear to enhance the stability of aspirin.

On addition of 1% w/w magnesium stearate, the gelatin film appears to give a significant inhibition to aspirin degradation relative to the cellulose acetate phthalate and the uncoated aspirin samples.

In an earlier report on the stability of cellulose coated aspirin tablets, salicylic acid was observed on the tablet surface (313). It was further demonstrated that salicylic acid sublimation could cause appreciable errors when estimating the degree of degradation of aspirin. In this study therefore, both aspirin and salicylic acid were quantified simultaneously but the values obtained for salicylic acid formed were used as a guide only. When such values are plotted as shown in Figure 37 it is seen that the pattern observed for salicylic acid detected does not correspond to the degree of aspirin degradation; the deviation being obvious for the coated samples. Concordance in the two profiles can be expected if one assumes that one mole of aspirin gives a mole of salicylic acid and acetic acid on decomposition. However, the decomposition pathway maybe more complex since other reaction products are formed as shown earlier (Figure 27).

If one compares the results in Figure 36 and those in Figure 37, it can be seen that salicylic acid detected in the films is generally higher than for the uncoated samples both with and without the addition of magnesium stearate; while the degradation of aspirin is lower for the coated samples than for uncoated samples. This observation suggests that monitoring of salicylic acid in stability assays in open systems cannot be considered reliable. In Figure 37, the coated particles retain

Figure 36. Degradation of aspirin in the solid state. Influence of 1% magnesium stearate and film coating at 50°C 75% RH.

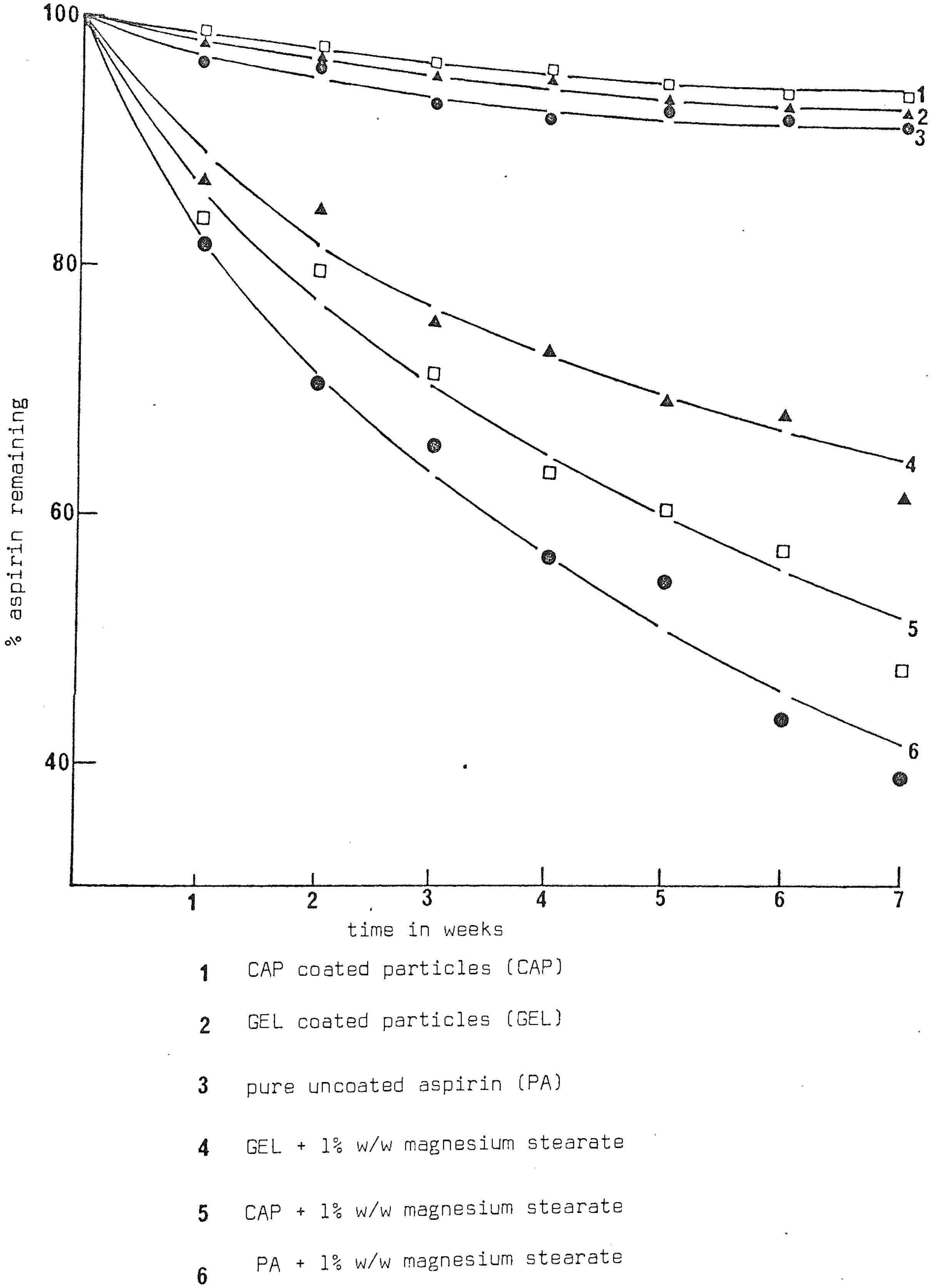
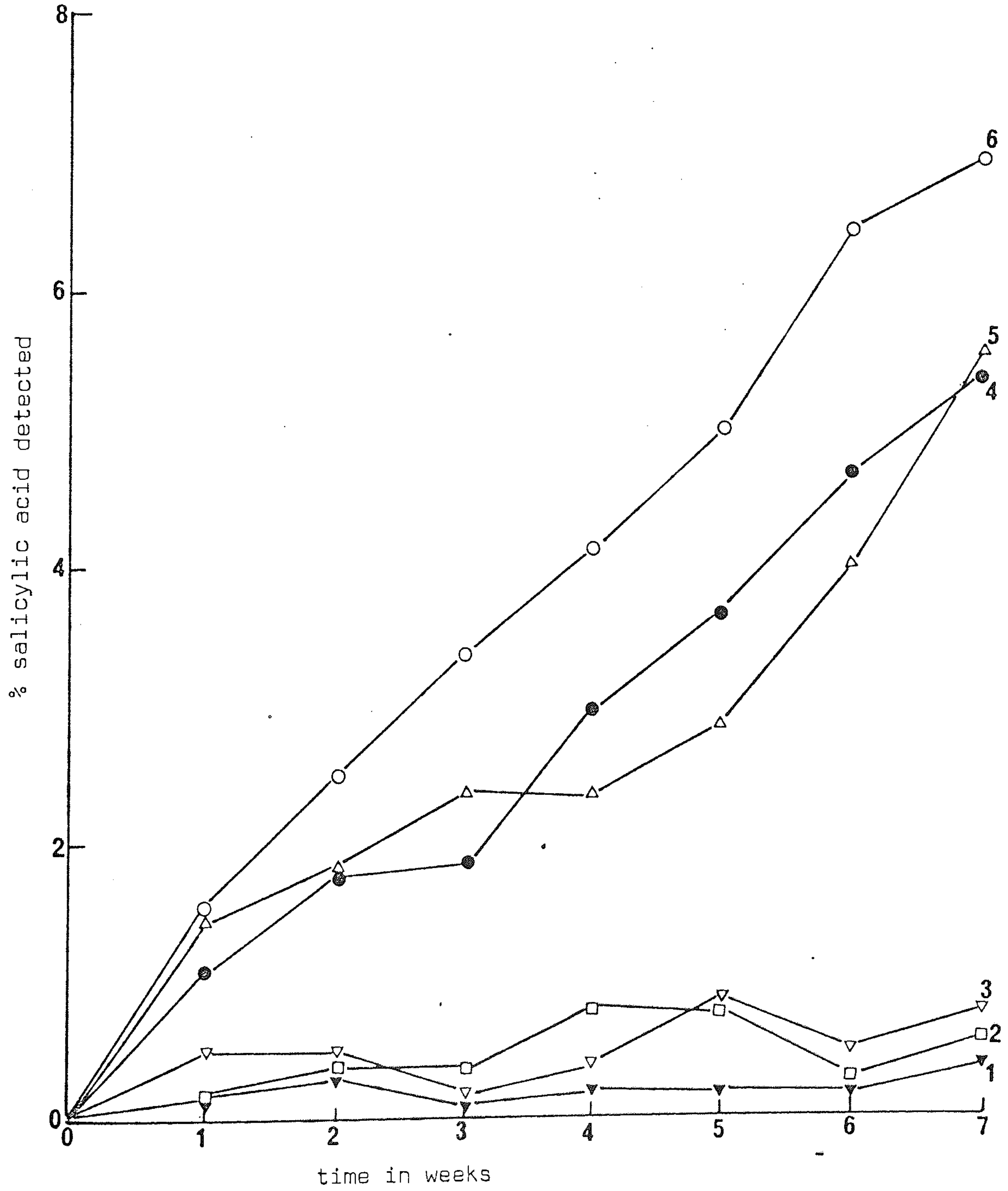


Figure 37. Salicylic acid detected in solid state decomposition of aspirin in an open system at 50°C, 75% RH



1 pure uncoated aspirin particles (PA)

2 CAP coated particles (CAP)

3 GEL coated particles (GEL)

4 GEL + 1% w/w magnesium stearate

5 PA + 1% w/w magnesium stearate

6 CAP + 1% w/w magnesium stearate

more salicylic acid than the uncoated particles, probably because the film coat inhibits sublimation of salicylic acid. These results are in agreement with those reported by Bakan and Soan (192) who have shown that vapourisation of volatile substances can be given improved protection upon film coating on microencapsulation.

5.3.3.2 The Stability of Coated and Uncoated Aspirin Particles at 60°C, 75% RH and the Influence of Magnesium Stearate

In order to reduce the time for an experimental run, a higher temperature than that previously used was adopted. The results are shown in Figure 38. The particles of aspirin coated with gelatin, cellulose acetate phthalate and Eudragit L^{R} show a rapid initial degradation. Such an initial rapid reaction is clearly shown by gelatin-coated aspirin. This initial rapid reaction is probably caused by moisture entrapped during the coating process which could not be completely removed during drying (Section 2.4.3). It is important to note that the same batches of particles were used as in the previous experiment (Section 5.3.3). The absorption of moisture may have occurred during normal usage and storage. The films used appear to impart some protection against the adverse effects of magnesium stearate, in agreement with the results observed earlier (Section 5.3.3.1).

It has been shown that changes in melting points rather than shifts in pH of the adsorbed layer of moisture surrounding the particles, would appear to be a more plausible explanation for the observed effects of magnesium stearate and other alkali stearates on aspirin stability. The film coats as shown in Figures 36 and 38 exert their action mainly through preventing or reducing the extent of direct contact between aspirin and magnesium stearate.

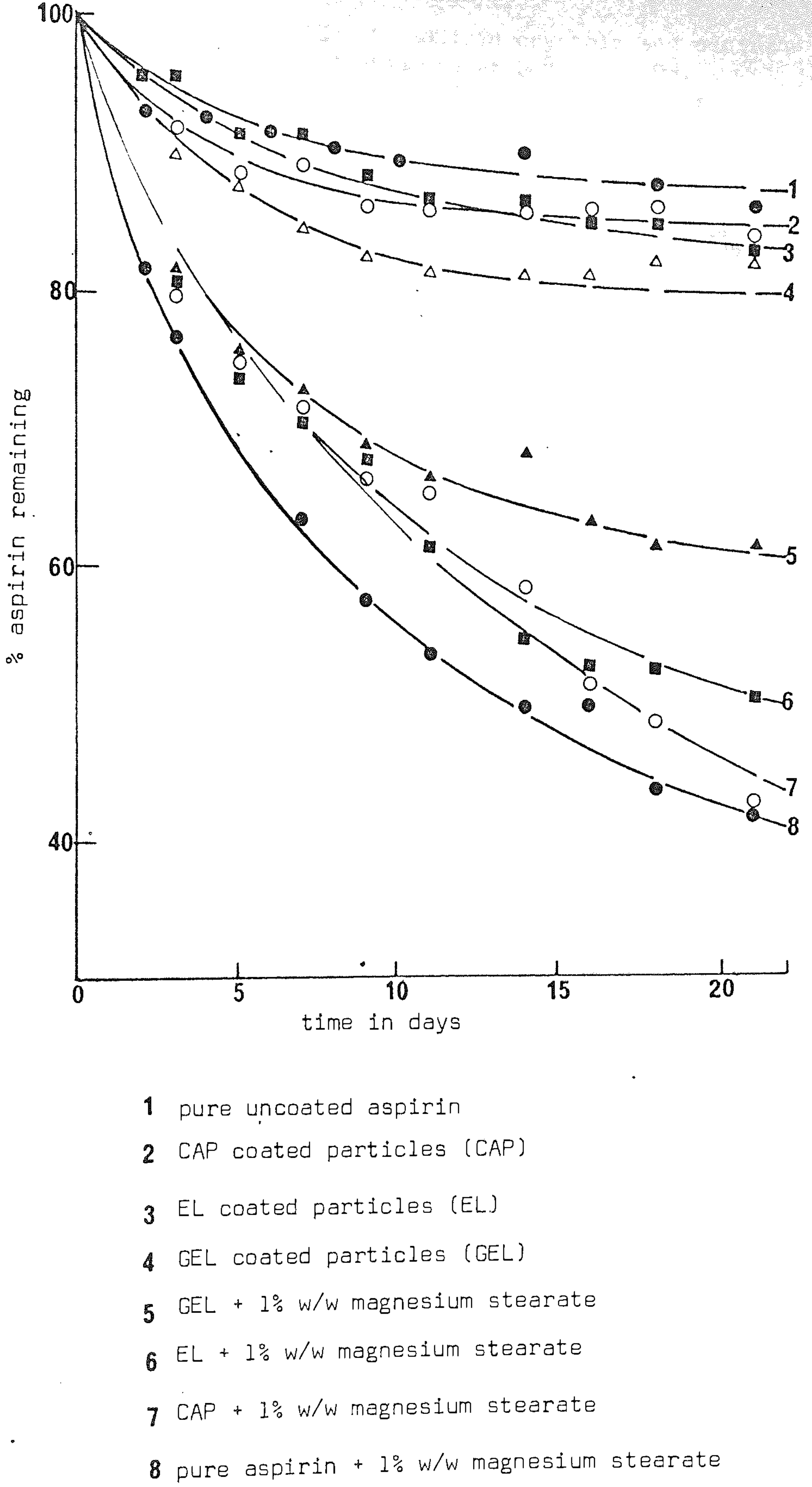
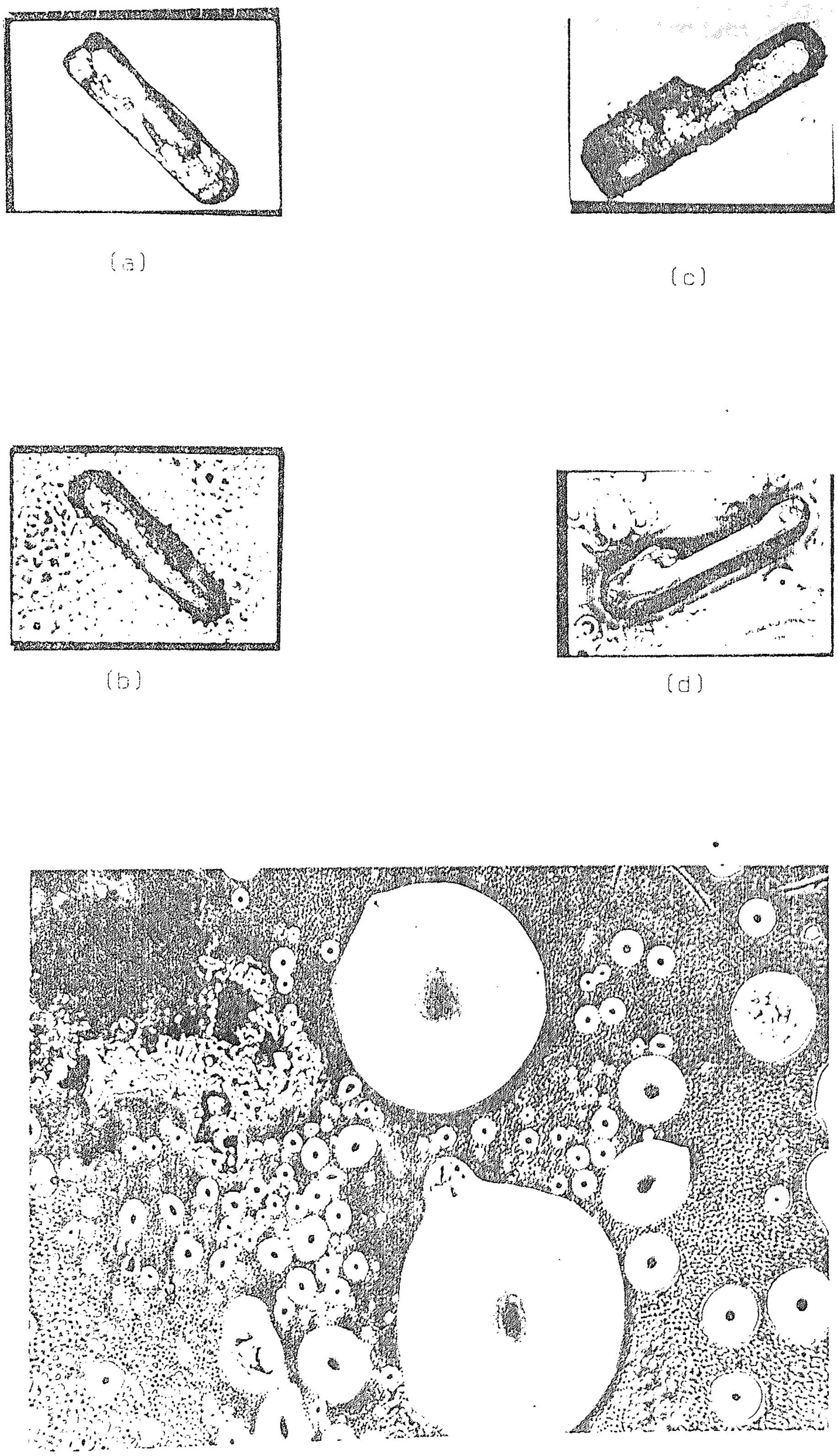


Figure 38. The degradation of aspirin in the solid state. Influence of film coating and 1% w/w magnesium stearate at 60°C, 75% RH.

Figure 39. Observed surface changes of aspirin crystals and aspirin mixed with 3% magnesium stearate at $60^{o}C$, 75% RH.



(a)

(c)

(b)

(d)

(e)

a) pure aspirin at Day 0
b) pure aspirin at Day 3 (note no extensive melting)
c) aspirin mixed with magnesium stearate at Day 0
d) aspirin mixed with magnesium stearate at Day 3 (note melting)
e) aspirin mixed with magnesium stearate at Day 3 (note the magnesium stearate alone does not melt (top left dark corner)).

The reaction between two kinds of crystals has been claimed to be caused by vibrations of the crystal molecules in the space lattice (50). These vibrations cause initial contact between the two compounds forming a molecular layer of the reaction product at the contact surface. The reaction rate was found to be directly proportional to the magnitude of the initial extent of contact of reacting solid substances (58).

Microscopical examination (Figure 39) shows an aspirin crystal before reaction (Figure 39a) and three days later (Figure 39b), as well as a crystal mixed with 3% w/w magnesium stearate at day zero (Figure 39c) and three days later at 60°C and 75% relative humidity. From Figures 39(a-d) it is observed that aspirin on its own does not show any detectable melting (Figures 39a & b) while the crystal mixed with magnesium stearate shows this quite clearly (Figures 39c & d). Careful examination of the photomicrograph of aspirin mixed with magnesium stearate after three days at 60°C and 75% relative humidity (Figure 39e) reveals that the magnesium stearate does not melt if not in contact with the aspirin (dark view of the top left hand corner in Figure 39e).

5.3.4 Conclusion

It was observed that gelatin used as a film coat on aspirin particles is capable of significantly reducing the adverse influences of magnesium stearate on aspirin degradation. Based on the dissolution data (Table 3) gelatin film gave the slowest drug release rates and the protection against decomposition demonstrated may be attributed to the barrier effect of the film coat. At 60°C the initial degradation rate is observed to be the greatest with the gelatin coated particles. This can perhaps be explained by a higher moisture uptake during storage or changes in moisture permeability with an increase in temperature. Eudragit L ^{R} and cellulose acetate phthalate, provide greater protection than gelatin where no additives are present, but are less effective relative to gelatin in the presence of 1% w/w magnesium stearate. When proper storage to prevent moisture absorption into coated particles is achieved, film coating can be an effective tool in stabilising and preventing reaction between reactive species as exemplified by the aspirin - magnesium stearate incompatibility.

5.4 Solid State Stability of Aspirin in the Presence of Mepyramine Maleate

5.4.1 Introduction

Chemical interactions between two or more drug components in the same dosage form or between active ingredients and excipients are known to occur. Such reactions may cause total loss of activity of one or both of the components or may produce toxic products (5, 7, 159). It has been claimed (164) that aspirin would readily react with drugs containing amino, phenolic or alcoholic groups. Transacetylation reactions of aspirin in admixture with other drug substances have been reported. These include reactions of aspirin with codeine (158, 159), acetaminophen (163), homatropine (164), phenylephrine (165) and chlorpheniramine maleate (192). Gentamicin and carbenicillin have been used in the treatment of Pseudomonas infections. Loss of gentamicin activity in the presence of carbenicillin can probably be attributed to a physicochemical interaction which would be most likely to occur if the two antibiotics were physically mixed, such as in iv fluids (5, 7).

Bakan and Sloan (192) showed that the reaction between aspirin and chlorpheniramine maleate (Figure 40) would be inhibited if the aspirin particles were microencapsulated. It was therefore decided that an investigation of the potential interaction between mepyramine maleate and aspirin would be useful. Mepyramine maleate BP (307) (Figure 41) or pyrilamine maleate (7) is the hydrogen maleate of N-4-methoxybenzyl-N'N'-dimethyl-N-2-pyridyl-ethylene diamine. Like chlorpheniramine maleate, mepyramine maleate is an antihistaminic compound, useful for symptomatic relief of a wide variety of allergic conditions.

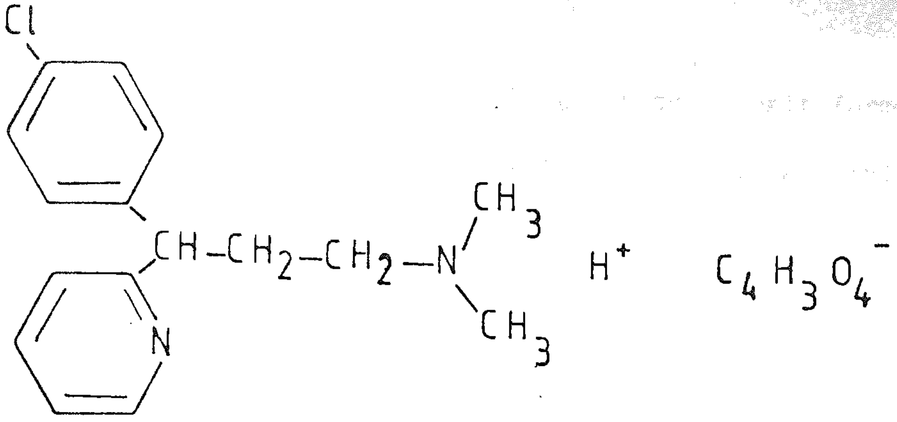


Figure 40. Chlorpheniramine maleate

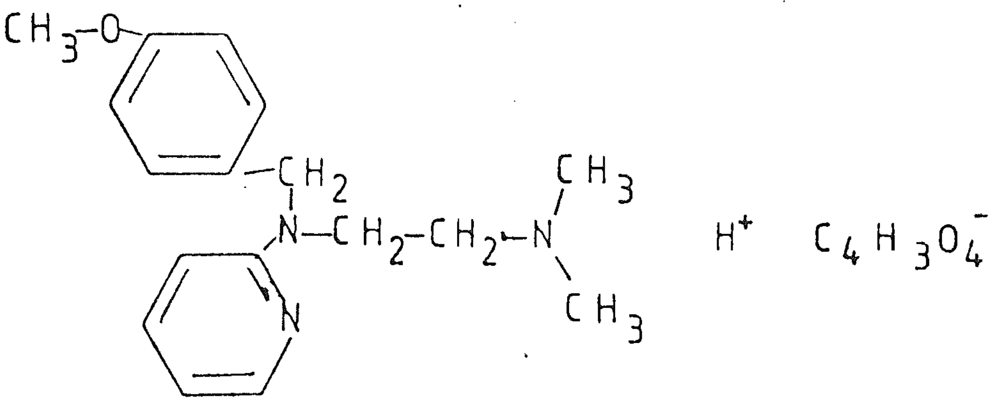


Figure 41. Mepyramine maleate

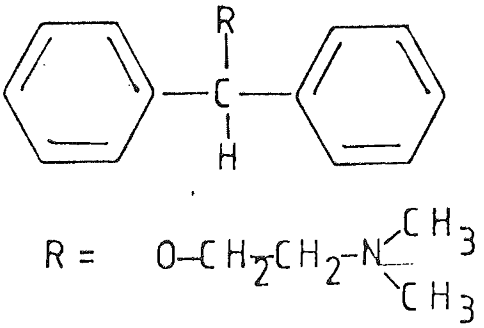


Figure 42. Diphenylmethane nucleus

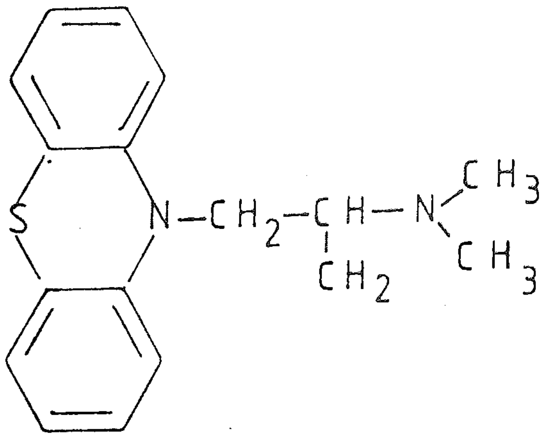


Figure 43. Promethazine

It has been shown that physical changes such as melt formation or dissolution may influence solid state reactions (8, 128, 151, 181, 311). Substances which would either lower melting points or enhance dissolution, would appear to accelerate reactions in the solid state. Mepyramine maleate has surface active properties (319). The structural similarity between mepyramine maleate (Figure 41) and promethazine (Figure 43) is evident by the presence of both the diphenylmethane nucleus (Figure 42) and an ethylene diamine side chain. Drugs having the structure as shown in Figure 42 have surface active properties and have been observed to form micelles in aqueous solutions (320). Surface active agents are known to enhance dissolution of poorly soluble drugs (167, 321). In a series of studies on the stability of dry preparations of thiamine salts, Yamamoto et al. (322-326) showed that the stability of the thiamine powder preparations was chiefly dependent on the solubility of the thiamine salt used.

The present study was initiated to determine whether mepyramine maleate would induce aspirin decomposition, to quantify the kinetics of the degradation of any such reaction and to elucidate the possible mechanisms of decomposition and interaction.

5.4.2 Methods

The materials used have been described in Section 2.1.1. Mixtures of aspirin and mepyramine maleate ranging from 0% w/w to 20% w/w of mepyramine maleate were made. 100.0 mg quantities were weighed into glass vials. The procedure for the stability testing as described in Section 2.1.3.2 was followed.

5.4.2.1 Analysis Method

Detailed description of the HPLC equipment and the method of analysis have been presented in Section 2.2. The method was suitable for assaying aspirin and its degradation products when mepyramine maleate was present in admixtures with aspirin.

5.4.2.2 Moisture Determination

The moisture content of the 100.0 mg samples of the mixtures was determined immediately after preparation and subsequent determinations were done on samples that had been stored at 60°C and 75% relative humidity over a period of 7 days. The Karl Fischer method was used for moisture determination (Section 2.14).

5.4.3 Results and Discussion

Analysis of the stored samples of solid mixtures of aspirin and mepyramine maleate shows that degradation of aspirin is enhanced by the addition of mepyramine maleate and that an increase in the proportion of mepyramine maleate in the solid mixtures, further increases the rate of degradation. Figure 44 shows the solid state degradation profiles of aspirin when admixed with 0-20% w/w of mepyramine maleate and stored at 60°C and 75% relative humidity. There are a number of possible causes for the observed phenomena, namely a direct reaction between aspirin and mepyramine, a pH effect, influence on the sorbed moisture layer or melting. If direct reaction occurs between aspirin and mepyramine maleate, it is likely that equimolar quantities would be involved in the reaction and if no other factors contributed to the reaction, it is possible to estimate only a 20% degradation after which the rate of reaction would be reduced significantly. In this study

Figure 44. Degradation of aspirin in the solid state: influence of increasing proportion of mepyramine maleate at 60°C, 75% RH

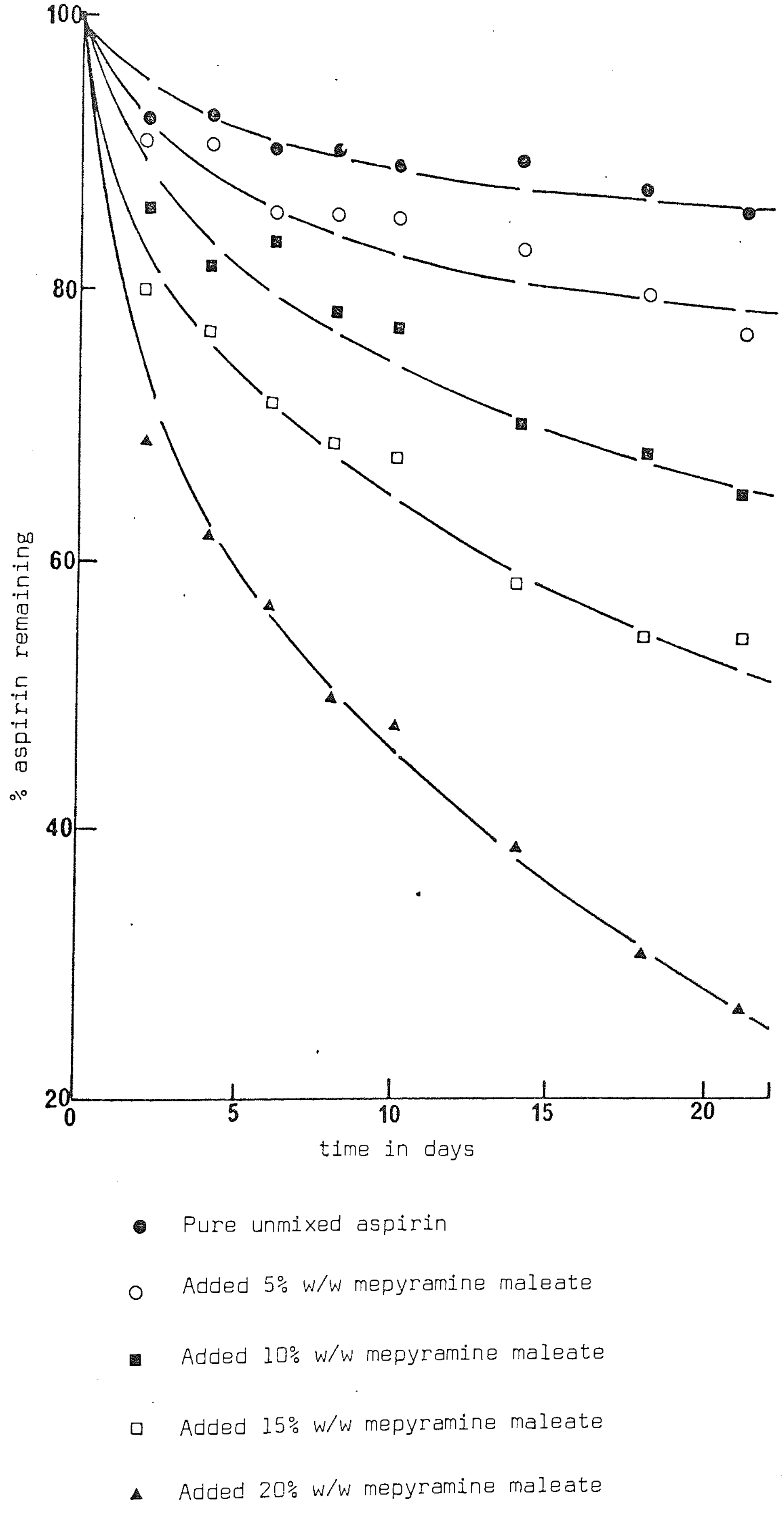


Figure 45. Relationship between moisture content in the samples and the proportion of mepyramine maleate at room temperature and at 60°C, 75% relative humidity.

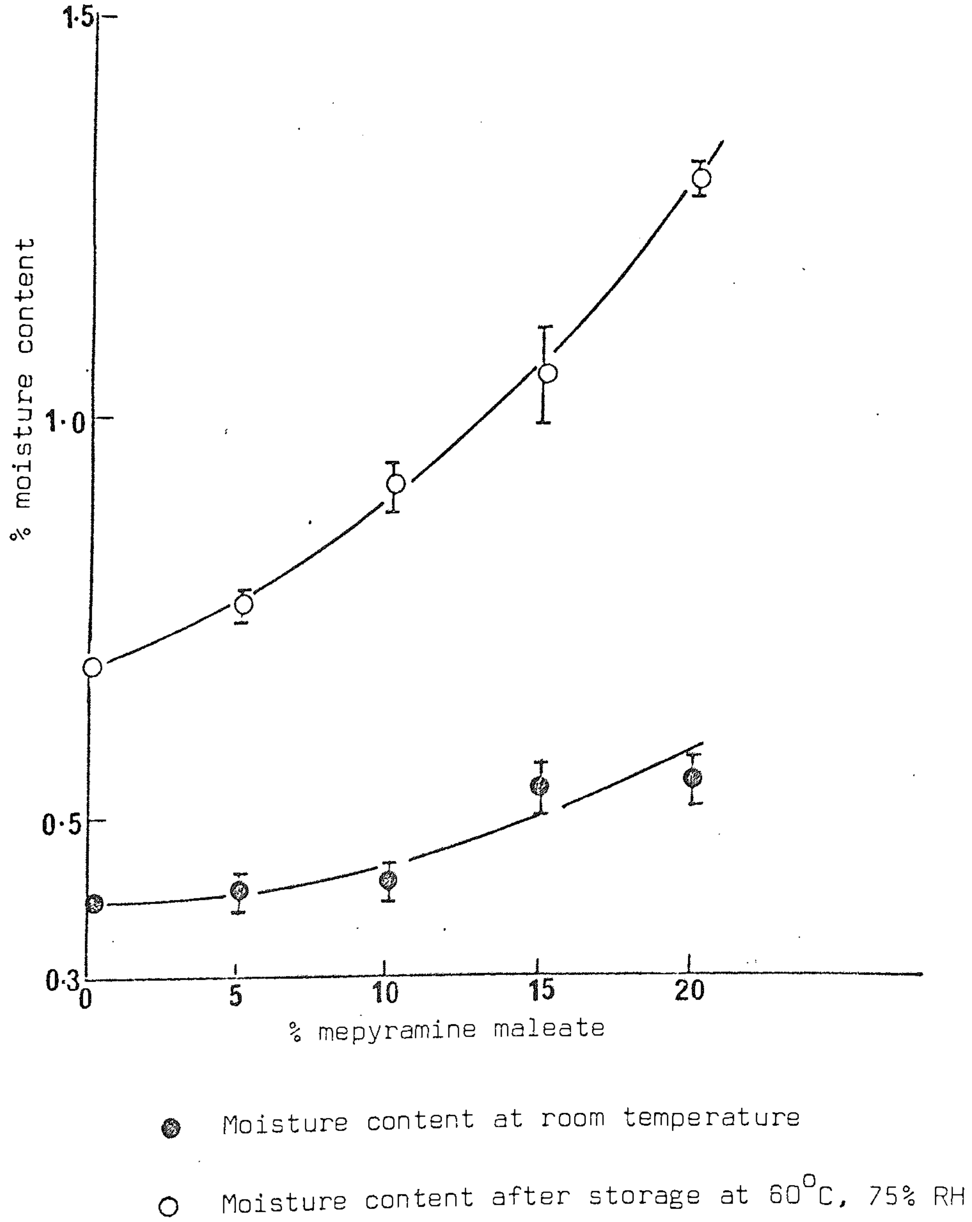
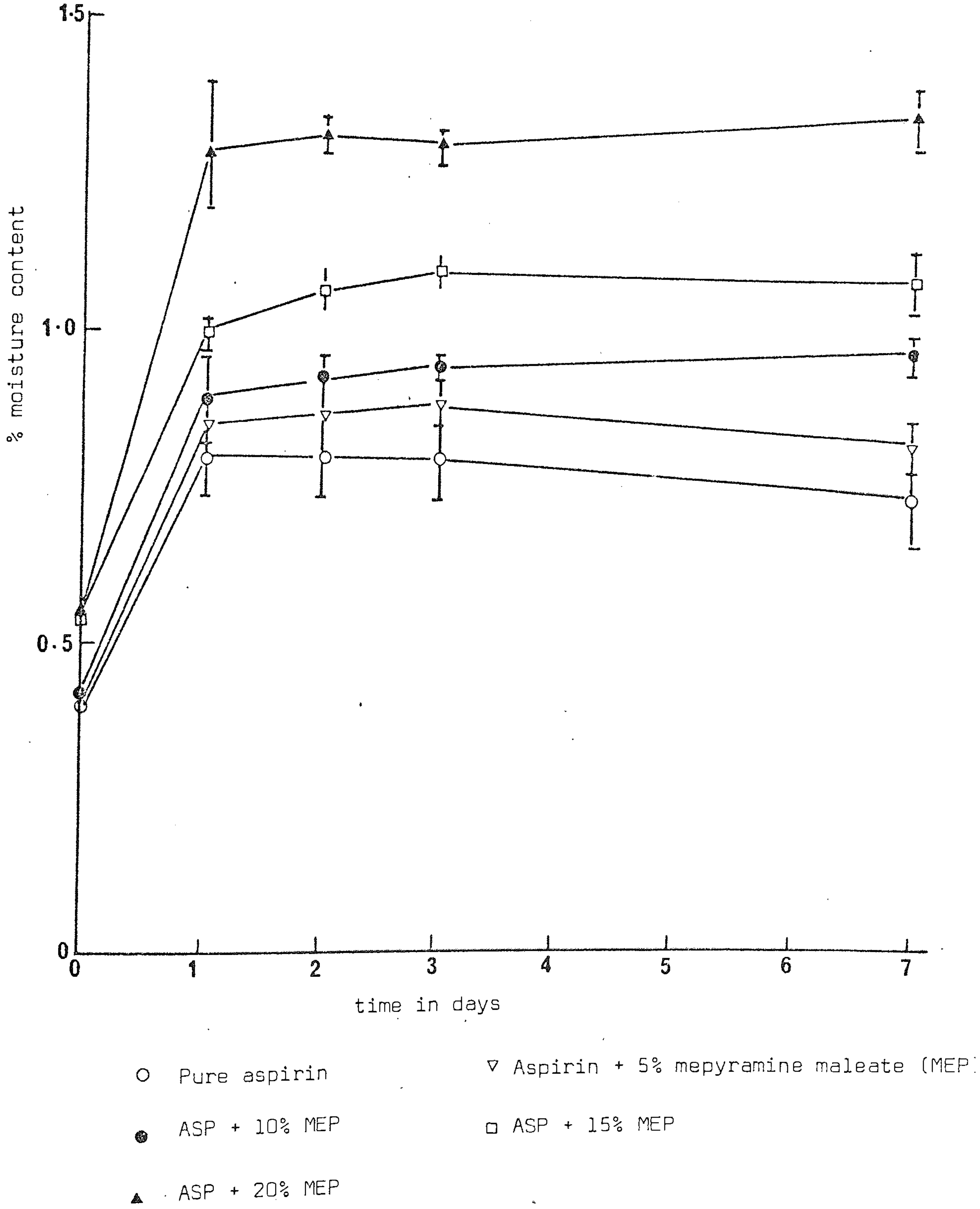


Figure 46. Moisture absorption profiles of aspirin-mepyramine maleate powder mixtures stored at 60°C, 75% relative humidity.



however, residual aspirin in the samples was monitored. It is shown quantitatively that mepyramine maleate enhances the degradation of aspirin in the solid state.

Mepyramine maleate is very soluble (302, 307) (1 g in 0.5 ml at 25°C). According to Yamamoto et al. (322) hygroscopicity of salts played a significant role in influencing drug stability through sample moisture uptake. If mepyramine maleate present in solid mixtures adsorb moisture, it is possible that under the experimental conditions of 60°C and 75% relative humidity, the salt absorbs sufficient moisture to dissolve itself. The residual increased layer of moisture on the aspirin crystals then dissolves a larger amount of aspirin.

In order to assess whether moisture sorption occurs, the samples used were tested for moisture content. As shown in Figure 45, the moisture content was higher with higher proportions of mepyramine maleate in the solid mixtures. The moisture uptake was rapid, and equilibrium appeared to be attained within 3 days as shown in Figure 46. Careful examination of Figures 44 and 45 makes it possible to say that the observed high rate of degradation of aspirin in the presence of high proportions of mepyramine maleate appear to be linked with moisture content. The higher the moisture content, the higher the amount of aspirin dissolved and the resultant higher degradation rate. The degradation of aspirin in a liquid reaction-product layer model was proposed. To test whether the reaction was diffusion controlled and whether the reaction occurs in a liquid-reaction product layer, the data for Figure 44 was treated by equation 48. Linear relationships between $|1 - (1 - \alpha)^{\frac{1}{2}}|^2$ and t with slope $\frac{2k}{r_0^2}$ and zero intercept were obtained for the whole range of mepyramine maleate concentrations used. Such linear relationships are shown on Figure 47. By plotting the logarithm of the rate constant as mirrorred by the slopes of Figure 47, with the proportion of mepyramine maleate, a linear relationship was obtained as shown in Figure 48. The linear relationship obtained can be described by equation 50.

$$\log\left(\frac{2k}{r_0^2}\right) = 0.09\ W - 3.72 \qquad \text{--- Eq. 50}$$

where $2k/r_0^2$ = the slope of equation 48 as applied to date in Figure 47

W = % amount of mepyramine maleate in the solid mixture

α (correlation coefficient = 0.997)

It was also found that the best correlations were obtained when the logarithms of the rate constants were plotted against the reciprocal of moisture content as shown in Figure 49, the linear relationship obtained can be described by equation 51.

$$\log\ (2k/r_0^2) = 0.69 - 3.4/MC \qquad \text{--- Eq. 51}$$

where MC = % moisture content of the samples

α (correlation coefficient = 0.992)

The relationship between the moisture content of the samples and the proportion of mepyramine maleate in the mixture is shown in Figure 45 and the linear relationship observed (shown in Figure 50) can be described by equation 52.

$$\frac{1}{MC} = 1.29 - 0.03\ W \qquad \text{--- Eq. 52}$$

where W and MC have been defined in equations 50 and 51 respectively.

α (correlation coefficient = 0.995)

Figure 47. Kinetic treatment of the data (Figure 44) according to equation 48.

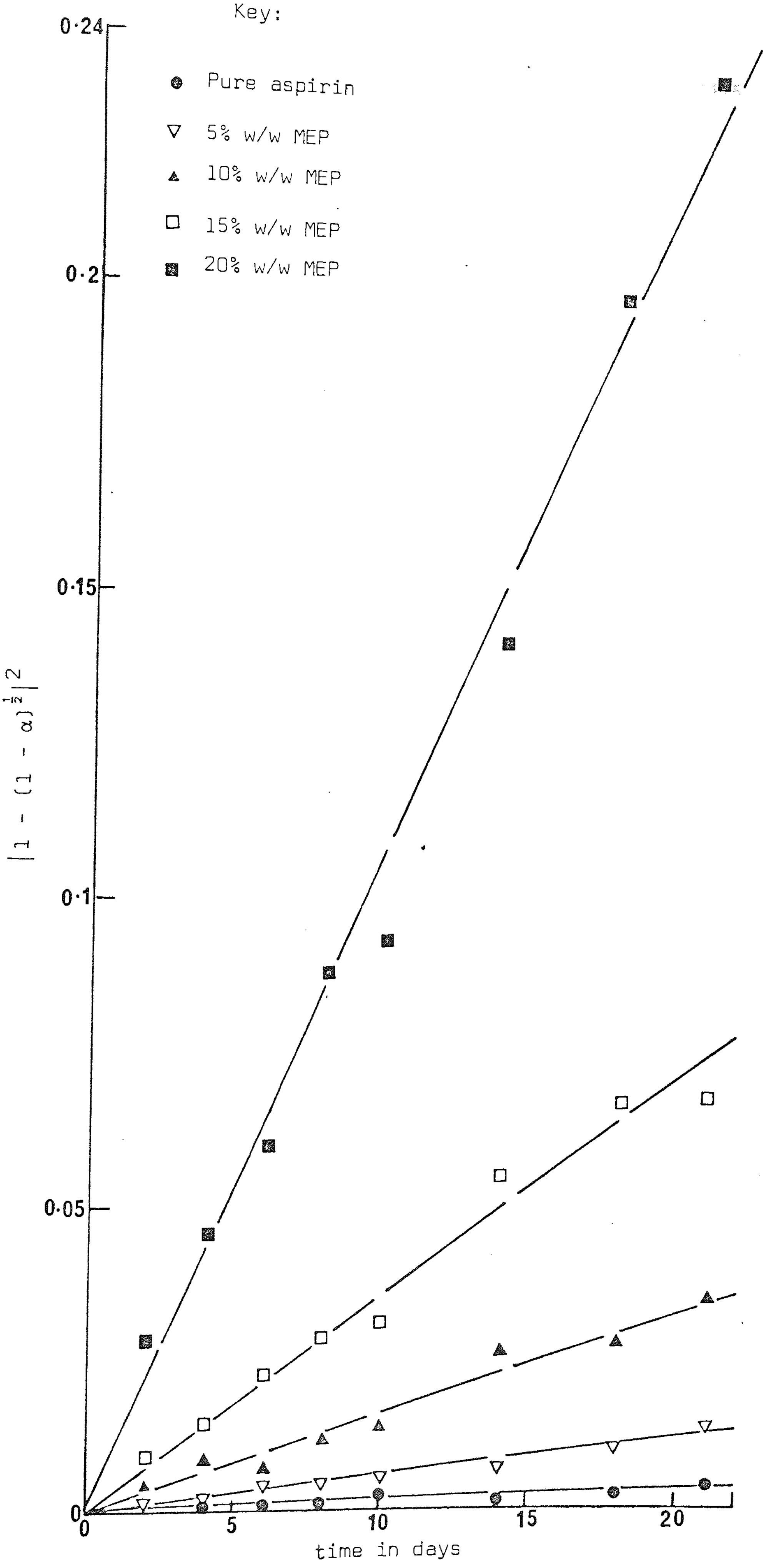


Figure 48. The relationship between the logarithm of the rate constants (slopes of Figure 47) and the proportion of mepyramine maleate in the aspirin powder mixtures.

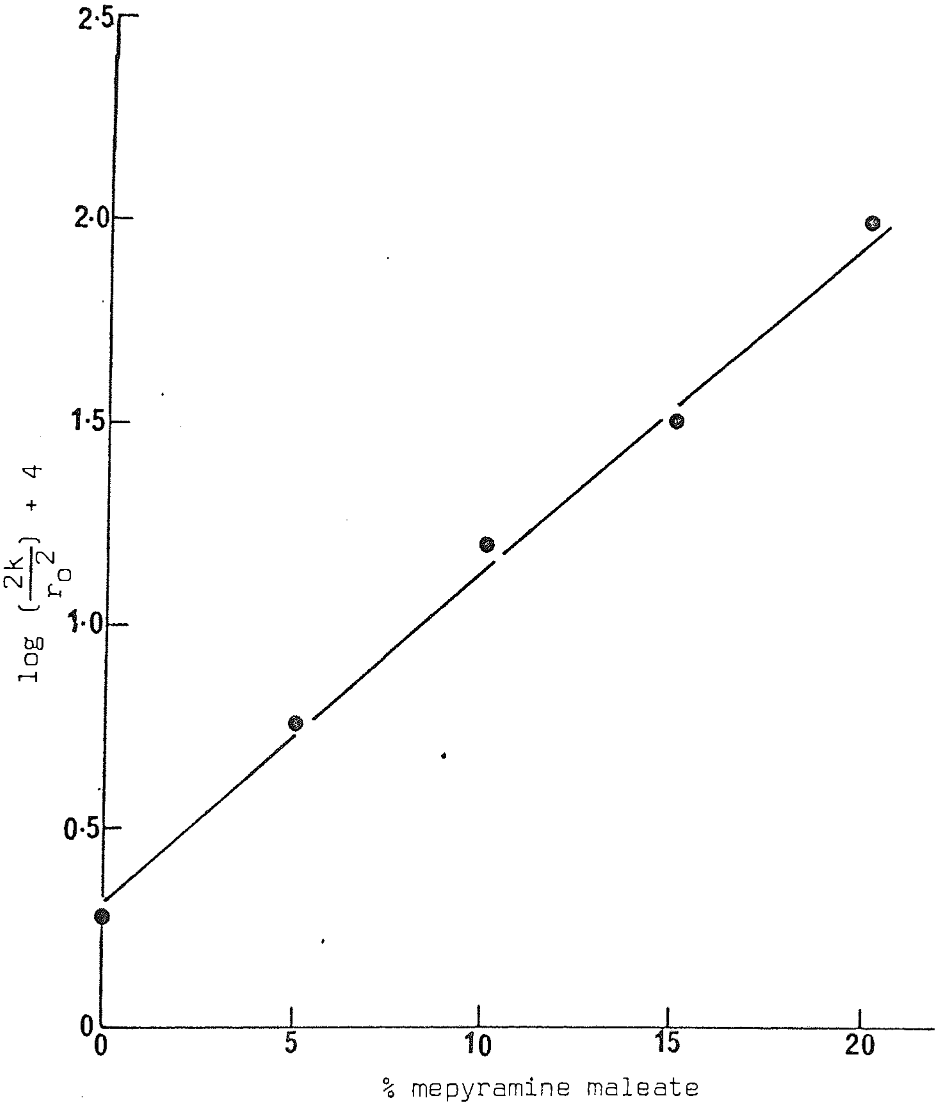
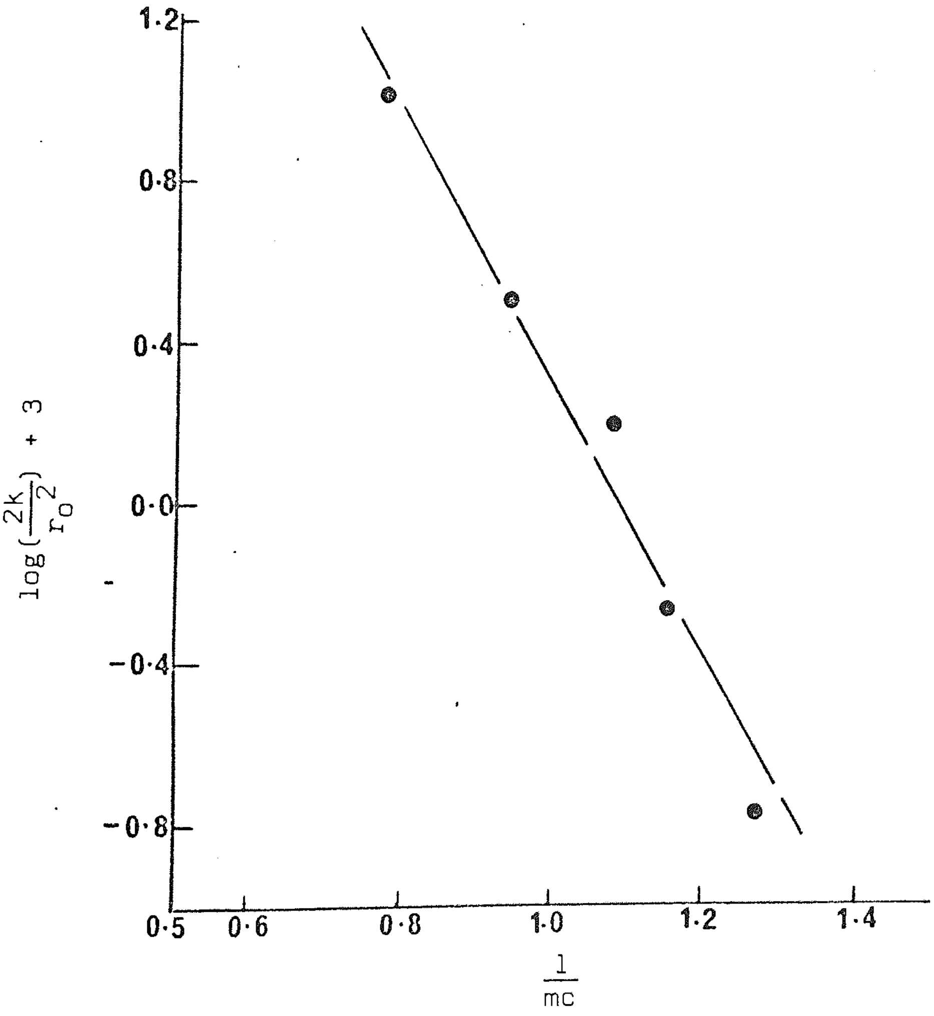
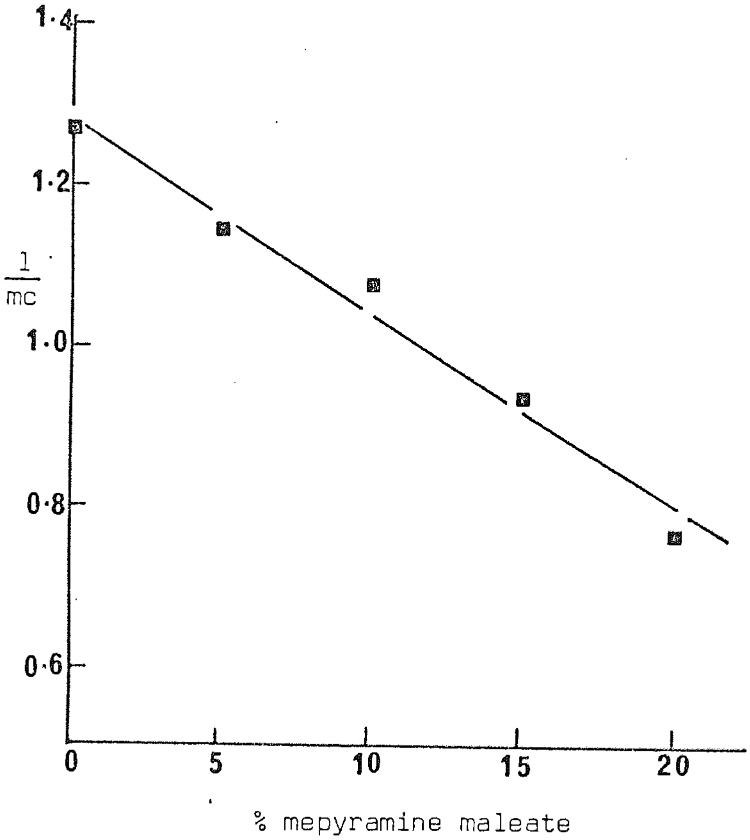


Figure 49. Relationship between the logarithm of the rate constant and the reciprocal of the moisture content.



mc = % moisture content

Figure 50. Relationship between the reciprocal of the moisture content and the proportion of mepyramine maleate in the powder mixtures.



mc = % moisture content

When MC in equation 51 is replaced by W from equation 52, one obtains equation 50. The direct relationship obtained between logarithm of the rate constant and the proportion of the mepyramine maleate in the solid admixtures with aspirin (Figure 48 and equation 50) appear therefore to be related to the moisture uptake by the samples.

The results presented so far may not be conclusive since it was shown in the study on the degradation of aspirin that increasing the amount of water in powder mixtures resulted in a higher rate of reaction. Both Kornblum and Zoglio (297) and Moulding et al. (298) showed that there was a direct relationship between the rate of formation of salicylic acid and the amount of water added. The observed relationship (Figure 49 and equation 51) suggests the concurrent participation of other factors such as pH, surface active properties or the formation of a melt.

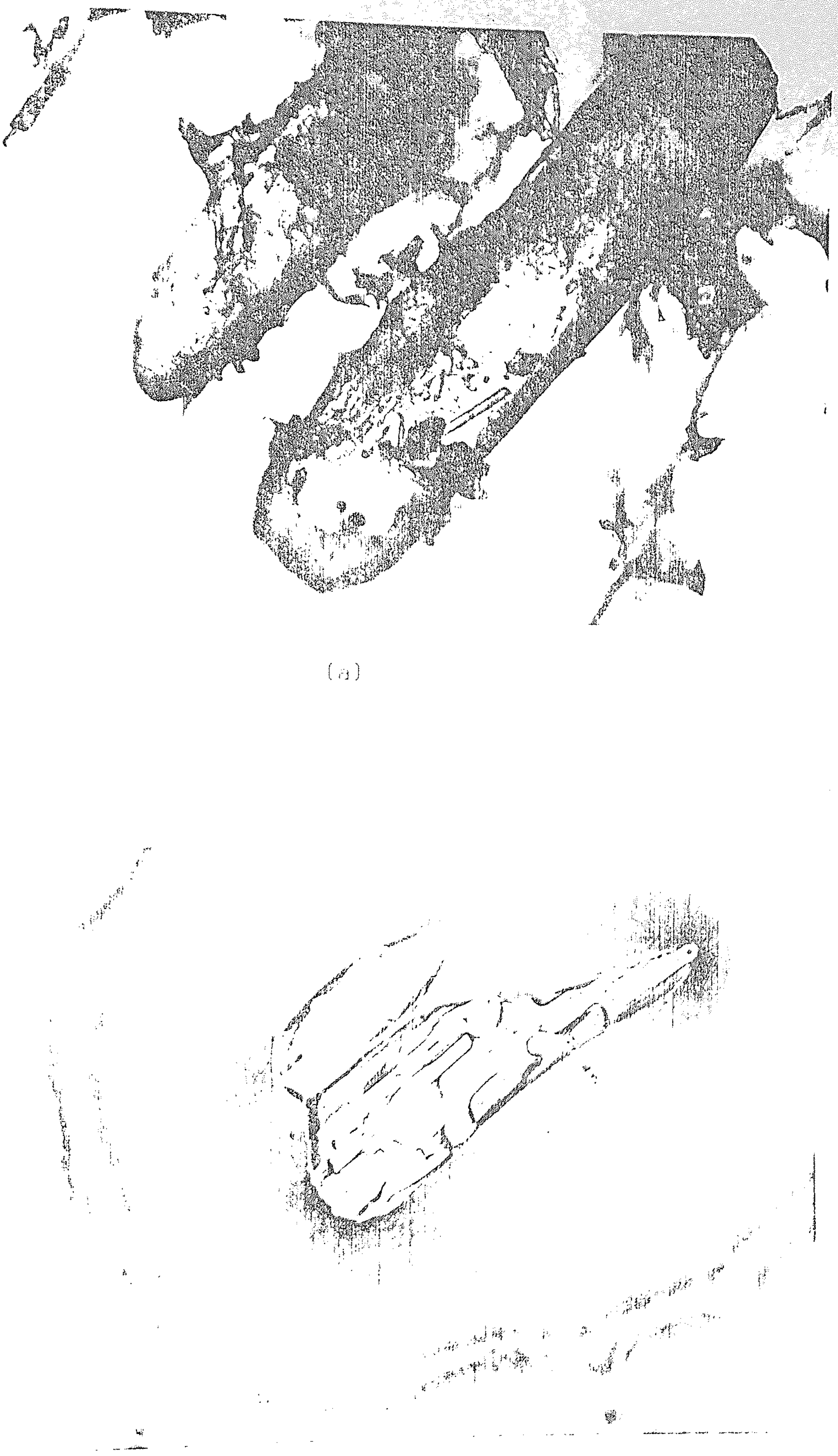
It has been reported that mepyramine maleate forms a solution with pH of about 4.7-5.2 (302). In our study, the pH values of solutions ranging from 0.1% to 200% were found to lie between 5.14 and 5.43. Within this range, the degradation of aspirin is relatively high and according to Edwards (32) the rate of degradation is independent of changes in pH in that range.

The property of surface activity inherent in antihistamines and drugs with similar structures (319, 320) implies that the salt may induce aspirin solubility in the adsorbed moisture layer through increased wetting or solubilization.

Changes in melting points of pure drugs when mixed with other drugs has been investigated by Guillory et al. (25) using differential thermal analysis. The formation of eutectic mixtures was observed with depression of melting points. The relationship between melting point and reaction rate has been quantified by Guillory and Higuchi (132) and Carstensen and Musa (150) while in this study (Section 5.2) the depression of melting point of aspirin by magnesium stearate and other alkali stearates was found to influence reaction rate. Microscopic observation of aspirin crystals mixed with 10% mepyramine maleate (Figure 51) reveals the rapid formation of a liquid layer. This observation led to the use of the model developed for the study of aspirin-magnesium stearate interaction to evaluate the results obtained.

On the basis of these reports on the melting point depression and microscopic observation (Figure 51) the melting points of our mixtures were determined in order to evaluate the influence of melting on the observed reactions.

The capillary method (Section 2.8) was used to determine melting points of aspirin and mepyramine maleate as well as that of their mixtures as used in the stability experiments. It was observed that aspirin melts at 137.5°C and mepyramine maleate at 103°C (literature values (302) are 135°C and 99-100°C respectively). In mixtures of aspirin with mepyramine maleate, rapid melting of the mepyramine maleate occurred far below the observed melting point of the pure salt. In fact a mean of 76.3°C was observed for all proportions of mepyramine maleate in the mixtures. The mepyramine maleate had melted completely at 100°C leaving the intact crystals of aspirin clearly visible. Beyond this temperature, the crystals of aspirin appear to dissolve slowly in the melted mepyramine maleate. The higher the volume of the melt, the faster the expected dissolution of aspirin. The aspirin melting point was also observed to be depressed.



(a)

(b)

Figure 51. Microscopic view of aspirin crystals mixed with 10% mepyramine maleate.
a) Day 0
b) Day 1 (at 60°C, 75% relative humidity)

Figure 52. Melting point of aspirin-mepyramine maleate powder mixtures.

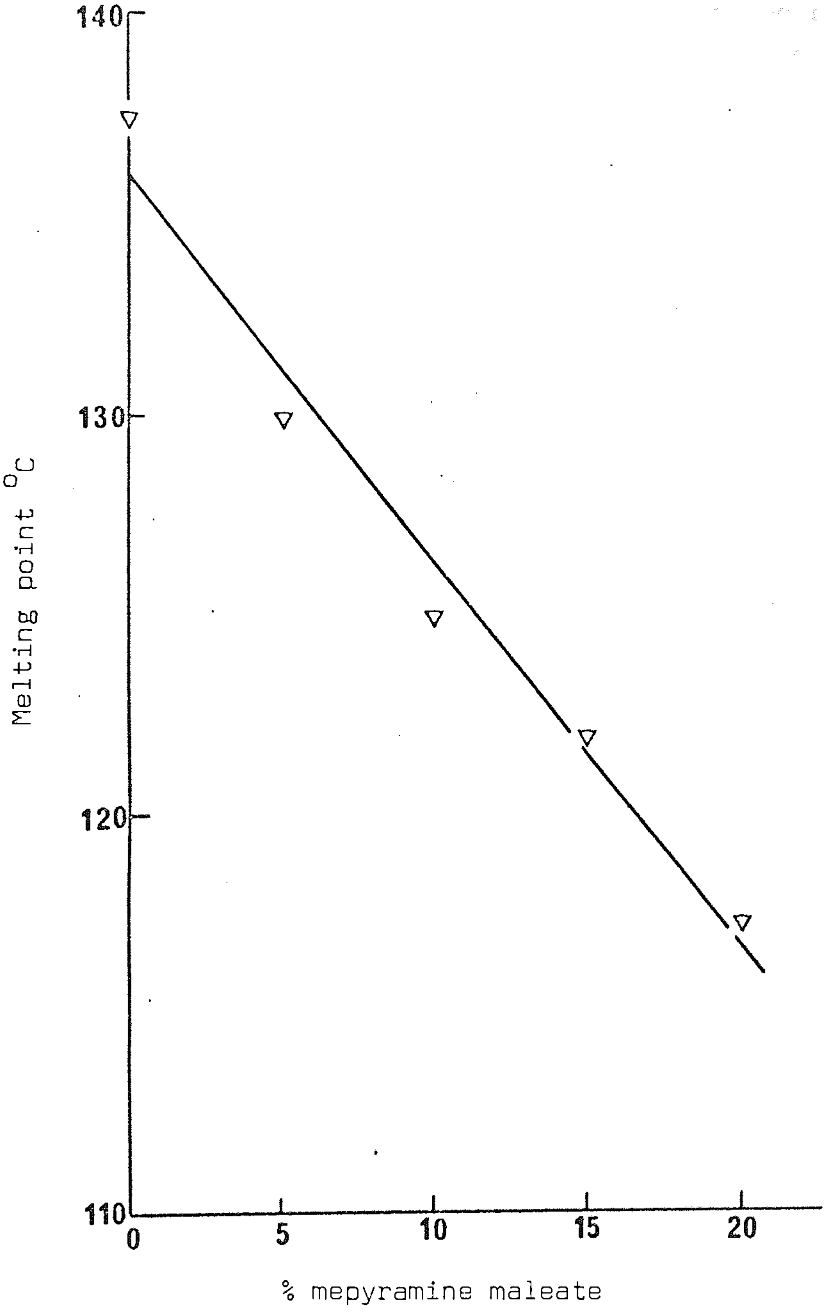
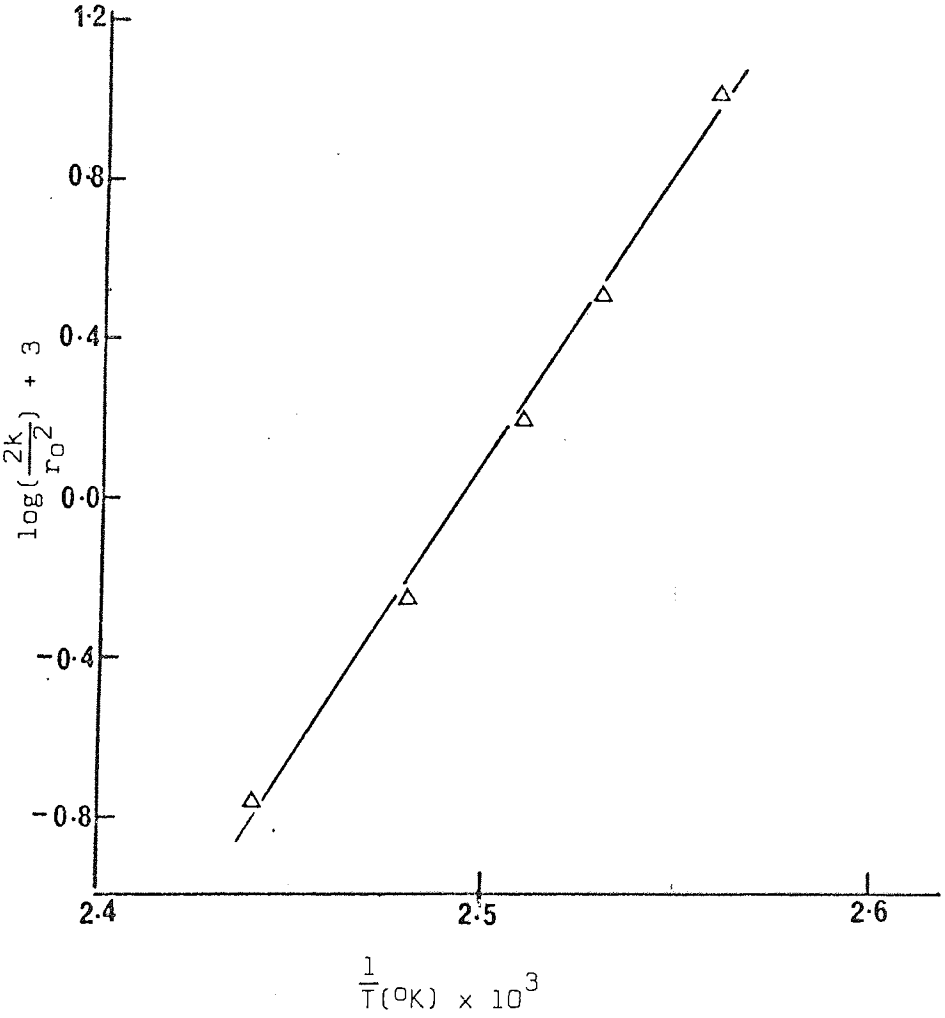


Figure 53. Relationship between the logarithm of the rate constants and the reciprocal of the absolute melting temperature for aspirin-mepyramine maleate mixtures.



A relationship was obtained between the proportion of mepyramine maleate and the apparent depression of melting point and is shown in Figure 52. If the amount of drug in the liquid layer determines the rate of reaction, then equation 49 which relates the rate constant and the melting temperature, will describe the data obtained. By plotting the logarithm of the slopes of Figure 47 and the reciprocal of the absolute melting temperature of the mixtures, Figure 53 is obtained. Equation 53 describes the line plot obtained.

$$\log\left(\frac{2k}{r_o^2}\right) = \frac{14109.68}{T_m} - 38.68 \qquad \text{--- Eq. 53}$$

T_m the melting temperature of the mixture

α (correlation coefficient = 0.995)

By comparing equation 53 above and equation 54 which describes a plot obtained for aspirin-magnesium stearate interaction, one observes the similar values of slope and intercept.

$$\log\left(\frac{2k}{r_o^2}\right) = \frac{14643.28}{T_m} - 39.57 \qquad \text{--- Eq. 54}$$

α (correlation coefficient = 0.999)

Guillory and Higuchi (132) claimed that the slopes of plots (Figures 33 and 53) may be related to the values of heat of fusion of the parent compound.

5.4.4 Conclusions

Aspirin degradation is enhanced by the presence of mepyramine maleate in solid mixtures stored at 60°C and 75% relative humidity.

The rate of degradation was shown to be higher the higher the moisture content, and a linear relationship was obtained between the logarithm of the rate constants and the reciprocal of the moisture content.

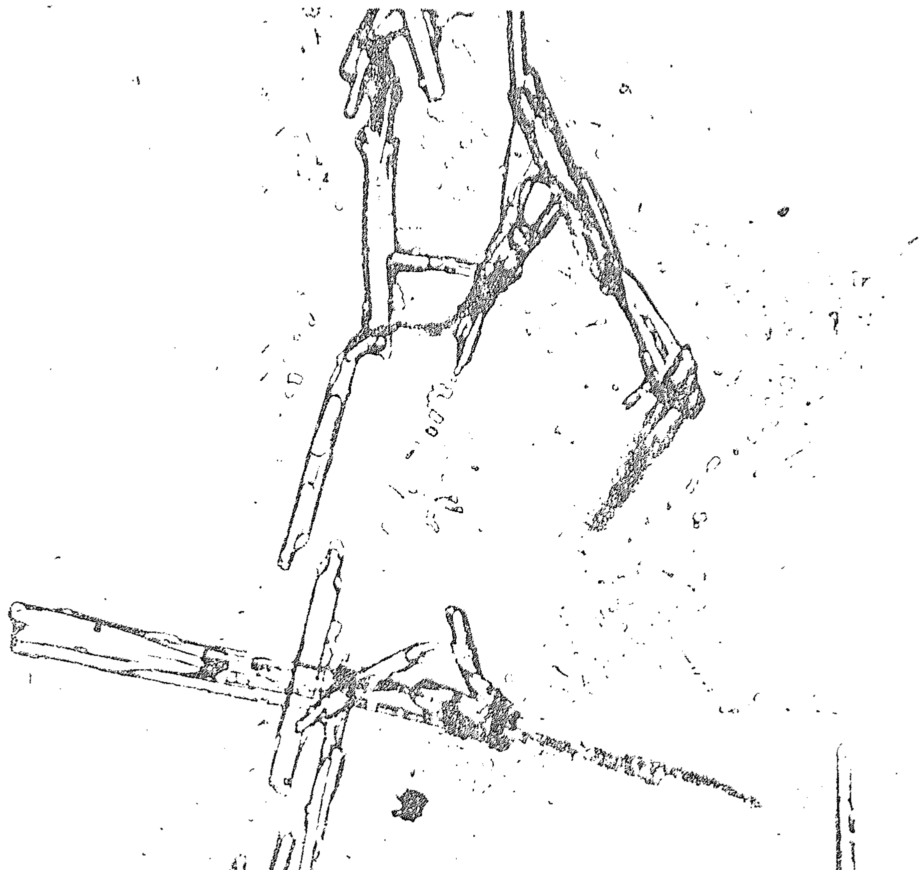
A depression in the melting point of aspirin was observed on addition of mepyramine maleate. It was further shown that the logarithm of the rate constants and the reciprocal of the absolute melting temperature of the powder mixtures were directly proportional.

On the basis of these observations, it is thought that the participation of both moisture and melt formation are responsible for the observed degradation of aspirin in the presence of mepyramine maleate. It was further shown that the relationship between the logarithm of the rate constants and the reciprocal of the melting points of the aspirin-mepyramine maleate powder mixtures (equation 53) closely resemble the similar relationship obtained with aspirin-magnesium stearate powder mixtures (equation 54). On the basis of these similarities, the predominant mechanisms appear to involve melting of the mepyramine maleate and the resultant dissolution of the aspirin crystal in the melt. The breakdown of aspirin to salicylic acid and acetic acid will always require a mole of water for each mole of aspirin decomposed. Moisture is therefore essential for the reaction to proceed.

It is likely that contact between aspirin and mepyramine maleate is of great importance in inducing the rapid formation of a melt. Crystals of mepyramine maleate placed on a microscopic slide and stored at 60°C, 75% relative humidity do not appear to change much after one day or even after seven days (Figure 54) while mepyramine maleate crystals in contact with an aspirin crystal (Figure 55) are observed to have disappeared after only a single day.

Figure 54. Microscopic appearance of mepyramine maleate crystals.

(a) After 1 day at 60°C, 75% RH



(b) After 7 days at 60°C, 75% RH

Figure 55. Microscopic appearance of aspirin crystal mixed with mepyramine maleate.

(a)
At time zero

(b)
After one day at
60°C, 75% RH

The mechanism therefore proposed for the observed degradation of aspirin in the presence of mepyramine maleate is mediated through the formation of a melt of mepyramine maleate in which aspirin dissolves with subsequent decomposition. The role of moisture may be important as a reagent with aspirin to form salicylic acid and acetic acid and may further be responsible for modifying the reaction pathway since reaction products other than salicylic acid were not detected in aspirin-mepyramine interactions while more than six products were observed in the aspirin-magnesium stearate interaction.

5.5 The Influence of a Film Coat on the Stability of Film Coated Aspirin Particles in the Presence of Mepyramine Maleate

5.5.1 Introduction

Reports of physical and chemical interactions occurring between medicinal ingredients and between medicinal ingredients and excipients in solid dosage forms have been appearing in the literature with increasing frequency (25).

Pharmaceutical analysts, recognising the fact that interactions within solid dosage forms may be responsible for observed modifications in therapeutic response have intensified their search for methods for detecting interactions and more so for methods of preventing their occurrence. Ball et al (190) observed that a syrup granule formation intended for use in tropical markets, was found to be insufficiently stable because of an interaction between the drug and sodium methyl-p-hydroxybenzoate included as a preservative in the presence of moisture from aqueous granulating process. Two approaches to prevent interaction were the use of layered granules to separate the ingredients and the lowering of moisture content of the drug, excipients and preservatives.

In their study on the microencapsulation of drugs, Bakan and Sloan (192) observed that drugs normally incompatible when present in the same environment often can be stabilised by encapsulation of one or more of the components. The observed improved stabilization was demonstrated with aspirin and chlorpheniramine maleate. Lachman (125) stated that the velocity of degradation of drugs generally increases with increased moisture content, and that the effect could be significantly reduced by a container which provides an impervious barrier between the drug product and environmental factors such as humidity and light. Film coating of drug substances has been shown to provide such an impervious barrier with the resultant enhancement of the stability of the enclosed components (192, 194 & 195).

In this study, the use of coated particles of aspirin and their stability in the presence of extragranular mepyramine maleate is investigated. An attempt is also made to elucidate the reaction mechanisms involved and to define the kinetics of the degradation.

5.5.2 Methods

The preparation of the coated particles used has been described in Section 2.4.3. Mixtures of coated particles of aspirin were mixed with 10% mepyramine maleate. 100.0 mg samples were weighed into glass vials for stability testing as described in Section 2.1.3.2.

5.5.2.1 Analysis Method

The HPLC technique described in Section 2.2 was suitable for assaying aspirin and its degradation products, in the presence of mepyramine maleate and the film coats. No interference was observed in the assay from either the film coats or mepyramine maleate.

5.5.2.2 Drug-Film Coat Interaction

50.0 ml solution of 1.0 mg/ml mepyramine maleate was added to 1.0 g of either gelatin, cellulose acetate phthalate or Eudragit L ^{R} in powder form and the resultant mixtures were placed in a shaking water bath at 60°C for a period of 22 hours. Reference samples were also made by adding 50.0 ml water to 1.0 g of the film coat substances. Samples were withdrawn at 1, 4 and 22 hours to assay for mepyramine maleate in solution by UV spectrophotometer at 300 nm (Section 2.3.2). Mepyramine maleate did not decompose after 22 hours at 60°C.

5.5.3 Results and Discussion

Samples of aspirin and coated aspirin particles admixed with 10% w/w mepyramine maleate, when stored at 60°C, 75% relative humidity degraded faster than control samples. Mepyramine maleate therefore appears to enhance the degradation of aspirin in both coated and uncoated particles. The results in Figure 56 indicate that film coats of gelatin and cellulose acetate phthalate offer no protection to aspirin against mepyramine maleate. It is also important to note that the gelatin film coat offered the best protection of aspirin against magnesium stearate effects. When gelatin coated particles were mixed with 10% mepyramine maleate, the degradation observed was greater than for uncoated particles similarly treated.

Coated aspirin particles with no additive show a rapid initial degradation. The cause of the rapid initial degradation

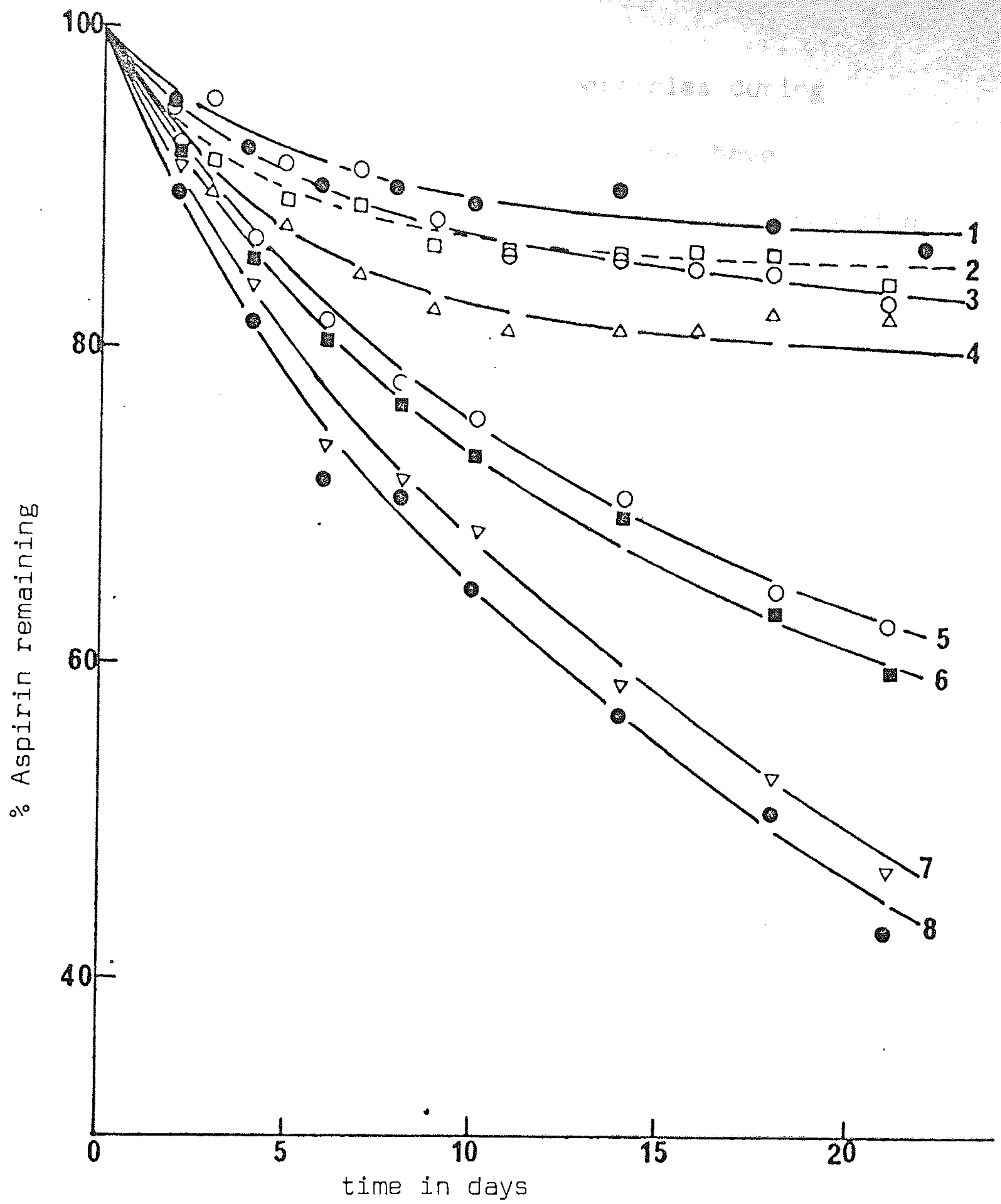


Figure 56. Effect of 10% w/w mepyramine maleate on coated aspirin particles stored at 60^oC, 75% RH

1 Pure aspirin (PA)

2 CAP

3 EL

4 GEL

5 EL + 10% mepyramine maleate (MEP)

6 PA + 10% MEP

7 CAP + 10% MEP

8 GEL + 10% MEP

EL = Eudragit L coated particles
CAP = cellulose acetate phthalate coated particles
GEL = gelatin coated particles

is thought to be the inherent moisture in the particles during the period of usage. The added mepyramine maleate may have intensified the initial rapid degradation. For the initial reaction rate to be maintained over a longer period, it is important that a continuous supply of moisture must be available. Since mepyramine maleate has wetting properties, it is possible that the moisture permeability may be enhanced. It is also possible that mepyramine maleate may be adsorbed or absorbed by the film coat material and mediate its effects on the adsorbed surface. Mepyramine maleate that comes in contact with aspirin may preferentially melt and aspirin may dissolve in the melt formed. All these processes influence permeation, adsorption or melting and may therefore increase the rates of degradation.

The influence of surface active agents on film permeation have been extensively studied (316, 317, 321, 327). The permeation of a liquid through a polymeric film is said to be enhanced by wetting. Wetting is the displacement from a surface of one fluid by another. A wetting agent is a surface active agent (328, 329). When a liquid on a solid surface remains as a drop it forms a definite angle of contact, ϕ, with the solid surface. Wetting is therefore achieved by the reduction of the angle of contact. Surface active agents and drugs which have such properties are capable of causing wetting. Wetting is particularly important when air in a very fine pore or capillary is to be displaced by penetrating solvent. The rate at which a liquid penetrates a small cylindrical capillary of radius, r, is given by equation 55 (328).

$$\frac{dl}{dt} = \frac{Pr^2}{8\eta l} \qquad \text{--- Eq. 55}$$

where l = distance of penetration

P = driving pressure

η = viscosity

t = time

The driving pressure is equivalent to the capillary pressure, produced by the curved surfaces of the capillary:

$$P_a - P_i = P = \frac{2\gamma \cos\phi}{r} \qquad \text{--- Eq. 56}$$

where P_a = atmospheric pressure

P_i = pressure just below the meniscus

γ = surface tension

r = radius

ϕ = contact angle

Substituting for P in equation 55 leads to:

$$\frac{dl}{dt} = \frac{\gamma \cos\phi . r}{4\eta l} \qquad \text{--- Eq. 57}$$

From equation 57, an increase in r and $\gamma \cos\phi$ will increase the penetration rate. The increase in viscosity will reduce the penetration rate. The diffusion release of drugs from polyethylene tablets used for delayed release (328), was found to be dependent on the penetration of the solvent into the pores of the tablet. The contact angle changes were significant and appeared to be responsible for determining the observed increase in release rate. In the system studied here, mepyramine maleate would dissolve in the sorbed moisture, and a solution which easily penetrates the film coats is probably formed. The enclosed aspirin is therefore exposed to the adverse effects of mepyramine maleate.

In the preceding section (Section 5.4), aspirin mixed with mepyramine maleate was said to form a liquid layer, in which aspirin is preferentially degraded. Both moisture and melting appear to be responsible for the observed reactions. It was further shown that contact between aspirin and the mepyramine maleate was essential for a rapid formation of a liquid layer. Since the coated particles were shown (Figures 5-7) to have cracks, fissures and pores, it is possible for the core aspirin to be exposed to mepyramine maleate with the resultant formation of a liquid layer and consequent degradation. However, this process would not account for the observed higher degradation observed with the film coated particles when compared to the uncoated particles.

Adsorption of drugs onto polymeric materials is known to occur. In the degradation of thiamine hydrochloride tabletted with microcrystalline cellulose (129) it was proposed that the thiamine dissolves in the water, adsorbed on the microcrystalline cellulose and that the thiamine present in the monolayer degrades totally. It was therefore necessary to carry out an investigation to test whether mepyramine maleate adsorbs on the polymeric film forming substances used and the influence of such adsorption on the rates of reaction. Table 10 shows that mepyramine maleate strongly adsorbs on the Eudragit L ^{R} film coat and less strongly on cellulose acetate phthalate and on gelatin. The rate of degradation of aspirin in the coated particles in the presence of mepyramine maleate was found to be inversely related to the amount of mepyramine maleate adsorbed on the film coats. The higher the adsorption on the film coat, the lower the rate of reaction. Such results are shown on Table 11. The adsorption appears to stabilise rather than destabilise the aspirin in the coated particles. The adsorbed mepyramine maleate appears not to influence the aspirin degradation. Eudragit L ^{R}, with the highest adsorption ratio, gives the best stability profile for aspirin.

Table 10

OBSERVED ADSORPTION (OR ABSORPTION OF MEPYRAMINE MALEATE ON THE FILM FORMING POLYMERIC MATERIALS

Observations	Pure solution	Added GEL	Added EL	Added CAP
Assay at 1 hr mg/ml	1.015	0.833	0.4997	0.761
Assay at 4 hr mg/ml	1.003	0.804	0.499	0.615
Assay at 22 hr mg/ml	1.017	0.809	0.512	0.673
Mean conc. in water	1.012(.006)	0.815(0.02)	0.504(0.007)	0.683(0.07)
Mean in film	0.0	0.197	0.508	0.329
Ratio $\frac{\text{film (mg)}}{\text{water (mg)}}$	-	0.242	1.008	0.482

GEL = Gelatin

EL = Eudragit L

CAP = Cellulose acetate phthalate

Table 11

THE RELATIONSHIP BETWEEN THE REACTION RATE CONSTANT AND THE ADSORPTION RATIO OF THE MEPYRAMINE MALEATE ONTO THE FILM COATS

Type of film coat	Rate constant $\frac{2k}{r_o^2}$ (day^{-1})	Adsorption ratio: $\frac{\text{amount in film}}{\text{amount in water}}$
GEL coated particles	5.375×10^{-3}	0.242
CAP coated particles	4.638×10^{-3}	0.482
EL coated particles	2.137×10^{-3}	1.008

GEL = Gelatin

CAP = Cellulose acetate phthalate

EL = Eudragit L ^{R}

5.5.4 Conclusions

Mepyramine maleate causes a rapid degradation of aspirin coated with Eudragit L^{R}, cellulose acetate phthalate and gelatin. Gelatin and cellulose acetate phthalate film coats appear to cause higher degradation relative to the uncoated samples. This phenomenon was explained by the observed rapid initial degradation caused by inherent moisture in the coated particles coupled with the ability of mepyramine maleate to induce an enhanced moisture permeability into the film coats. The difference in the rates of degradation of the film coated aspirin particles in the presence of 10% w/w mepyramine maleate may be due to the observed differences in their ability to adsorb mepyramine maleate.

At the present stage of this study it appears that gelatin and cellulose acetate phthalate cannot be used as film coats intended to protect against mepyramine maleate induced increase in decomposition rate.

5.6 The Effect of Acidic, Neutral and Basic Additives on the Stability of Aspirin in the Solid State

5.6.1 Introduction

Many tablet formulations are designed to provide rapid dissolution. Examples of such preparations include soluble aspirin formulations. These formulations utilise a reaction between an acid such as anhydrous citric acid and a base such as sodium bicarbonate, which is associated with gas evolution. The turbulance caused by the evolved gas and the rapid disintegration of the tablet help to bring about rapid dissolution. Other formulations are based on reactions which result into a soluble salt of aspirin, aimed at a higher level of bioavailability. Soluble or effervescent tablet formulations of aspirin (207, 208) are examples of preparations which are commercially available. In addition to anhydrous citric acid and sodium bicarbonate, other additives are used.

It was the aim of this study to investigate the stability of aspirin in a series of additives. Some of these are not normally used as tablet excipients but were included so as to give an insight into changes observed with common excipients. The effects of acidic substances such as citric acid, neutral salts like magnesium chloride and Precirol^{R}, and basic additives such as the antacids magnesium trisilicate and magnesium oxide were studied. The effects of magnesium stearate, a neutral salt which may contain alkaline impurities (307, 308) were also studied.

5.6.2 Methods

Aspirin powder mixtures containing 2% w/w each of citric acid, magnesium chloride, glyceryl palmito stearate (Precirol ^{R}), magnesium trisilicate, magnesium oxide and magnesium stearate were prepared. 100.0 mg samples were weighed into glass vials as previously described (Section 2.1.3.2). Samples were analysed by HPLC (Section 2.2).

5.6.3 Results and Discussion

The degradation of aspirin in the presence of citric acid, magnesium chloride, Precirol ^{R}, magnesium trisilicate, magnesium oxide and magnesium stearate is shown in Figure 57. Only magnesium stearate is observed to induce a rapid degradation of aspirin at 60°C and 75% relative humidity. Under the same conditions, citric acid, magnesium chloride, magnesium trisilicate, Precirol ^{R} and magnesium oxide show only small influence on the stability of aspirin.

An interesting observation is the degradation of aspirin in the presence of magnesium oxide. In the suspension studies, it was observed that magnesium stearate increased aspirin degradation, most probably through a change in pH. An increase in pH induced by magnesium stearate was attributed to impurities present, the notable impurity being magnesium oxide. In the solid state, 2% w/w magnesium oxide induces very little degradation of aspirin. This observation, as well as the solid state degradation of aspirin in the presence of 1% washed or unwashed magnesium stearate further confirms that pH does not appear to be a major factor in determining aspirin degradation in the solid state. Figure 58 shows a trace for the degradation of aspirin in the presence of 1% w/w washed magnesium stearate and the effect of 1% w/w unwashed magnesium stearate. The lack of significant difference in the rates of the reactions means that both sets of graphical points could be represented by a single curve.

Figure 57. Effects of acidic, neutral or basic additives on the stability of aspirin in the solid state at 60°C, 75% RH.

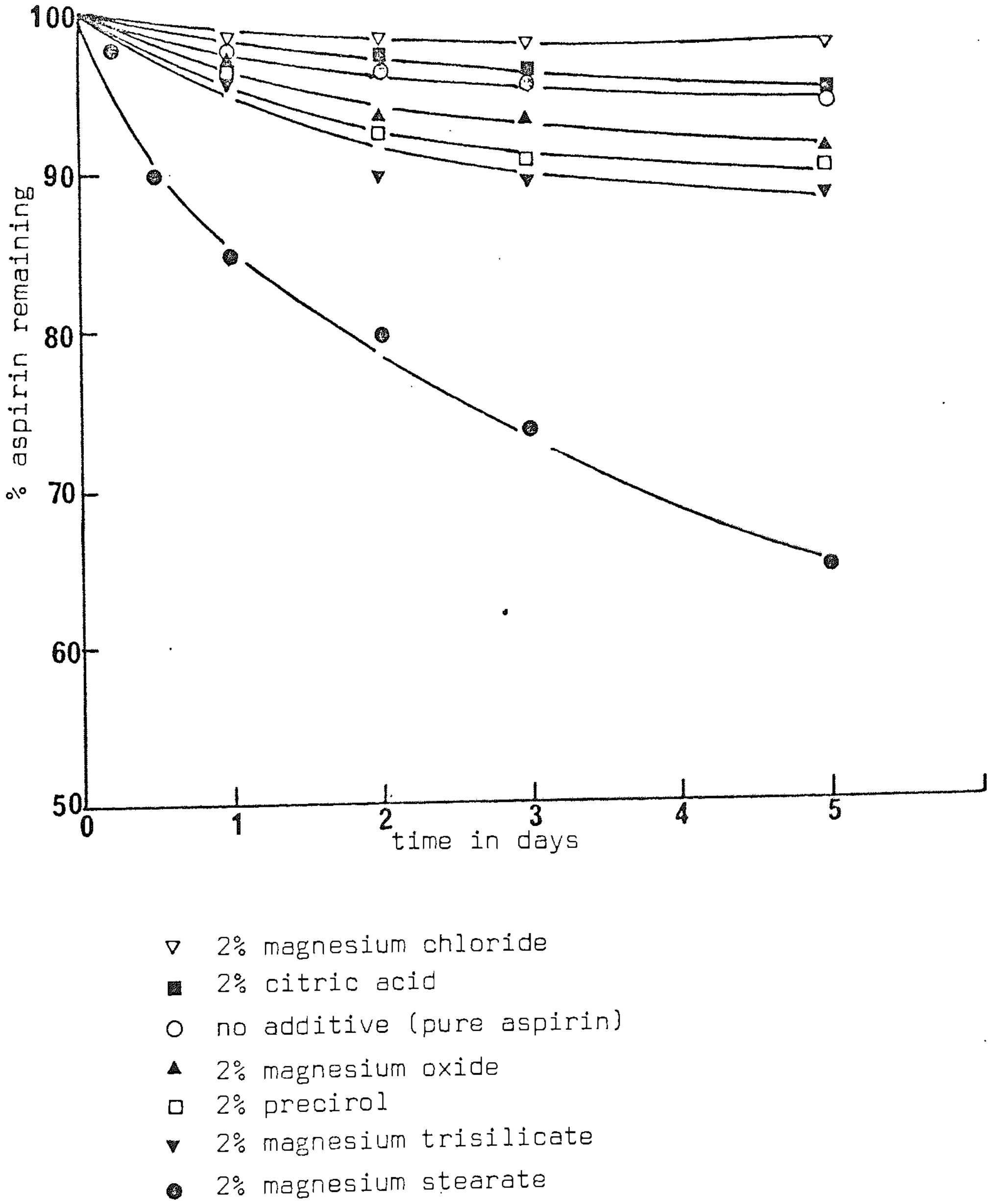
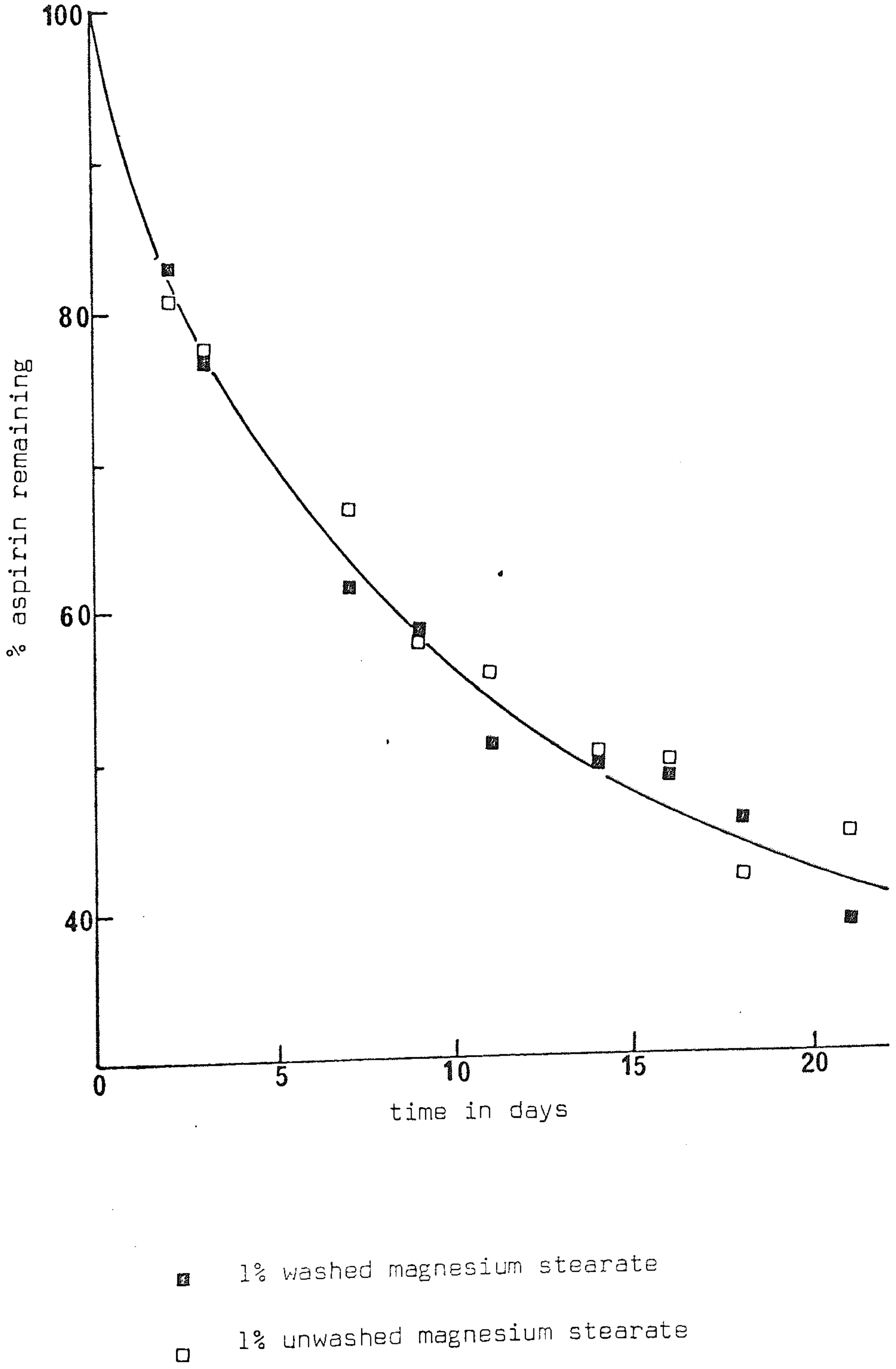


Figure 58. Effect of washing magnesium stearate on the decomposition of aspirin in the solid state at 60°C, 75% RH



5.6.4 Conclusion

Aspirin degradation in the solid state is not significantly influenced by either acidic or basic additives used in this study. Magnesium stearate induces a rapid degradation of aspirin in the solid state at 60°C and 75% relative humidity. In section 5.2 magnesium stearate was shown to mediate such rapid degradation of aspirin through depression of melting point. The other additives used, citric acid, magnesium chloride, magnesium trisilicate, Precirol ^{R} and magnesium oxide do not appear to depress the melting point of aspirin at the proportions used. The mechanisms observed for magnesium stearate-aspirin mixture do not appear to be responsible for the modest reactions observed with the other additives.

5.7 The Stability of Salicylsalicylic Acid (Salsalate) in the Solid State

5.7.1 Introduction

In Chapter 4, the degradation of salsalate in suspension systems was studied. It was shown that the rate of reaction was sensitive to changes in pH. Additives such as magnesium stearate increased salsalate decomposition through changes in the pH of the suspending medium.

In this section, studies on the stability of salsalate in the solid state, as well as that of salsalate microcapsules are described. Since microcapsules are often tabletted or filled into hard gelatin capsules (167) it is important to study the influence of lubricants such as magnesium stearate on the stability of such microencapsulated particles.

5.7.2 Methods

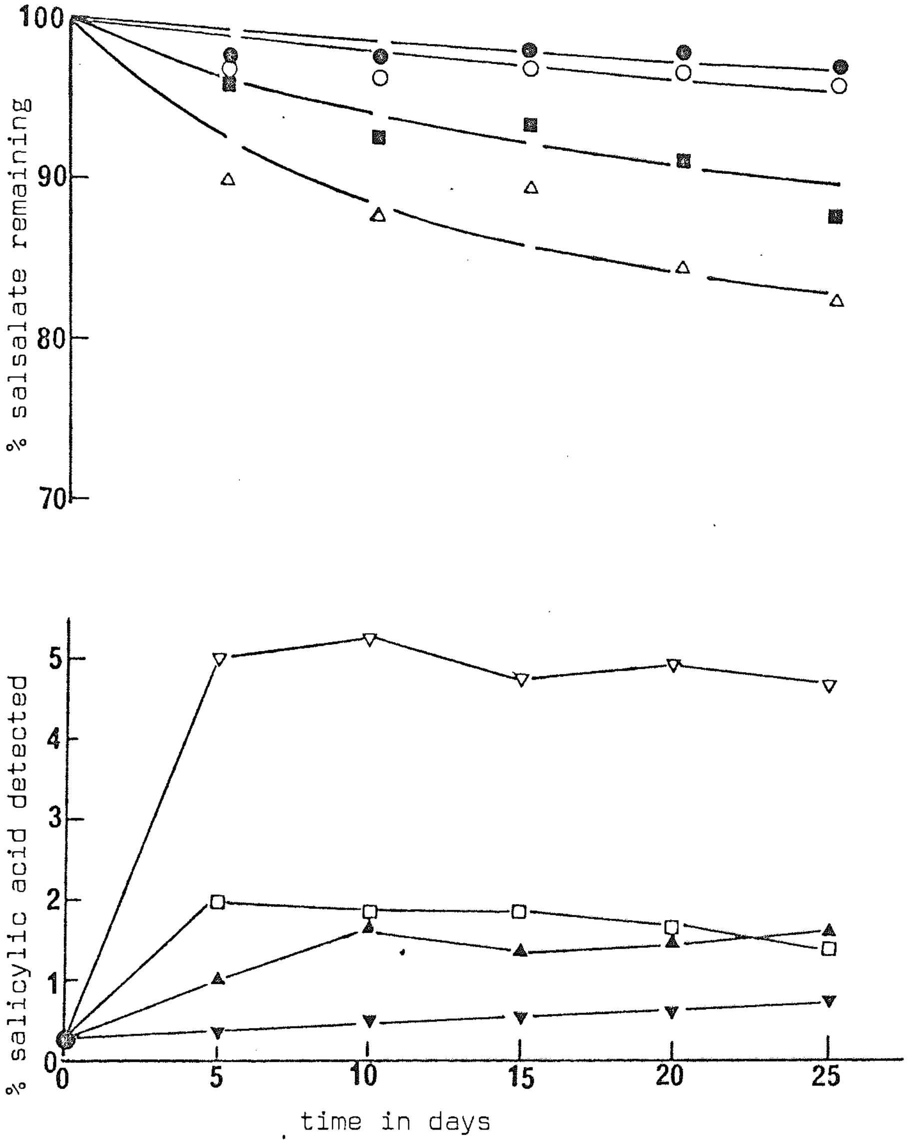
The microencapsulation procedure used for the particles of salsalate is described in Section 2.5.3.1.

Salsalate or the microencapsulated salsalate powders were each mixed with 3% w/w of magnesium stearate. 100.0 mg samples of the mixed powders or of pure control samples were weighed into glass vials which were then loosely covered with cotton wool to prevent entry of water droplets; and placed in a humidity cabinet at 60°C and 75% relative humidity. At predetermined intervals samples were removed and dissolved in methanol. To ensure complete dissolution of the drug from the microcapsules, the flasks were placed in an ultrasonic bath for 2-3 minutes. The dissolved samples were quantitatively transferred to 25 ml volumetric flasks and made to volume with methanol. The solutions were finally filtered, diluted and assayed by HPLC (Section 2.2).

5.7.3 Results and Discussion

The decomposition of salsalate in the solid state and in microcapsules at $60^{\circ}C$ and 75% relative humidity was less than 4% after 25 days; as shown in Figure 59. This observed modest degradation, even in the presence of magnesium stearate, appear to confirm the higher stability of salsalate relative to aspirin, both in suspension and in the solid state in the presence of magnesium stearate. Figure 59 further shows the amount of corresponding salicylic acid detected in the stored samples. The microcapsules appear to retain a higher proportion of the salicylic acid formed when compared to the standard powders. This observation suggests that salicylic acid sublimation may be hindered by the microcapsule. Takenaka et al. (291) showed that microcapsules prepared by gelatin-acacia complex coacervation method had porosity values of between 0.158 and 0.277. Furthermore, photomicrographs of the microcapsules under study shows the presence of pores (Figure 10 in Chapter 3). Higher porosities may lead to higher moisture contents (330, 331) and may partly explain the observed rapid initial degradation rate. Microcapsules therefore appear to be less stable than the uncoated particles, at least initially. A mixture of salsalate and magnesium stearate did not show any melting point depression. The observed degradation in the presence of magnesium stearate is relatively small and can be rationalised on the basis of the low moisture content of such mixtures.

Figure 59. Decomposition of salsalate in the solid state. Influence of microencapsulation and of magnesium stearate upon decomposition at 60°C, 75% RH



Key:

● pure salsalate ▼ Corresp. SA detected (pure SSA)

○ pure SSA microcapsules ▲ SA from microcapsules

■ SSA + 3% w/w mag. stearate □ SA from SSA + 3% mag. stearate

△ SSA microcapsules + 3% w/w magnesium stearate ▽ SA from microcapsules + 3% w/w magnesium stearate

5.8 Some Observations in the Study of Aspirin Decomposition in the Solid State and the Influence of Additives

5.8.1 Introduction

In the solid state decomposition of aspirin in the presence of additives, observations which should be taken into account during the setting up of stability testing programmes were made:

a) Loss in sample weight accompanied by decomposition.

b) A number of degradation products which could not be detected when aspirin degraded in suspensions, were observed in its solid state decomposition in the presence of magnesium stearate.

5.8.2 Loss in Sample Weight

At the time of assay, the vials removed from the humidity cabinet were weighed, and after dissolving the sample in methanol, the clean dry vials were re-weighed. The difference in weights gives the weight of the sample at the time of assay. Since the sample weights were initially 100.0 mg the weight changes could therefore be calculated. Some initial weight gain in the samples was expected as a result of moisture uptake. Invariably however, all samples of aspirin alone or in combination with magnesium stearate or mepyramine maleate showed significant losses in weight. These losses increased as decomposition of aspirin increased. The loss in weight profiles in samples of aspirin mixed with magnesium stearate ranging from 0.1% w/w to 5% w/w are shown in Figure ~~59~~ 60. The loss in weight was paralleled by a loss in aspirin content (Figures 60 and 61) and by an increase in salicylic acid content (Figure 62). When the weight losses were plotted against changes in aspirin, a linear relationship was obtained between percentage loss in sample weight and the percentage aspirin degraded (Figure 63). This relationship can be described by equation 58:

$$W = 0.25\,A - 1.4 \qquad \text{--- Eq. 58}$$

where W = % loss in sample weight

A = % aspirin degraded (100 - % aspirin remaining)

The loss in weight accompanying aspirin decomposition means that sampling from bulk powders in solid state stability would introduce significant errors. It is also a common practice in assays for tablets, to crush a number of tablets and take a weighed powder sample for assay. If during storage, significant weight losses occur, powder samples obtained at various stages of the decomposition will not give the true extent of degradation. In Figure 63 the loss in weight was not detected until about 5% degradation of aspirin had occurred. It is thought that moisture adsorption during the initial stages of storage, masks any loss in weight. The percentage salicylic acid detected (Figure 63) does not appear to vary linearly with the extent of aspirin degradation. In this study, open systems were used and the lack of linearity can be explained by the loss in weight arising from salicylic acid sublimation. No study has been done to relate the amount of salicylic acid formed to the extent of aspirin decomposition in the solid state in closed systems. Absolute values of aspirin content cannot be obtained by measuring salicylic acid alone because of the proven concurrent formation of other degradation products during the degradation of aspirin.

5.8.3 Reaction Products of Aspirin

The HPLC column used (Section 2.2) was capable of resolving

Figure 60. Solid state degradation of aspirin. Observed sample weight loss with time for mixtures of aspirin with increasing amounts of magnesium stearate at 60°C, 75% RH.

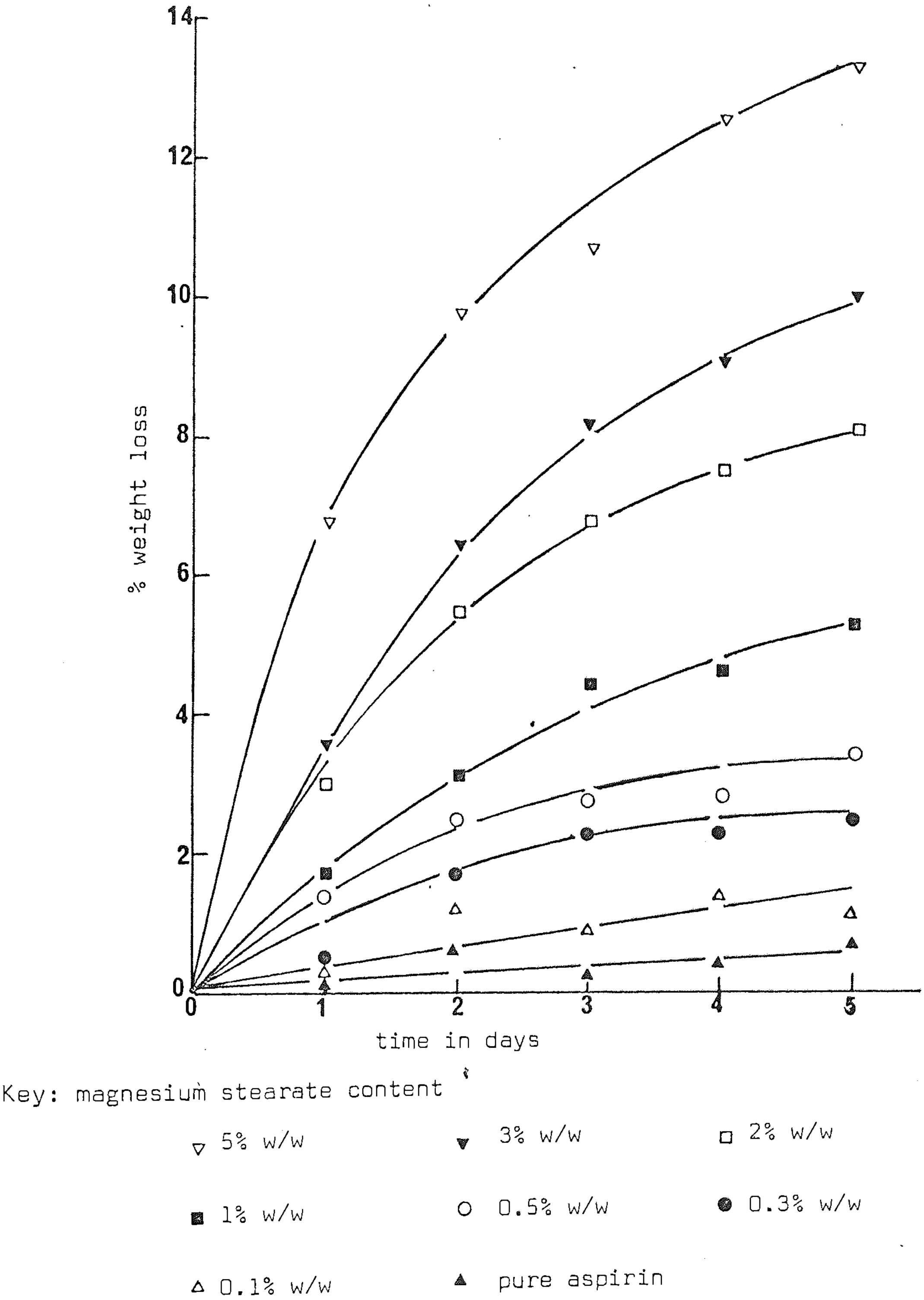


Figure 61. Solid state degradation of aspirin: profile of amounts of aspirin degraded in the presence of increasing amounts of magnesium stearate at 60^{o}C, 75% RH.

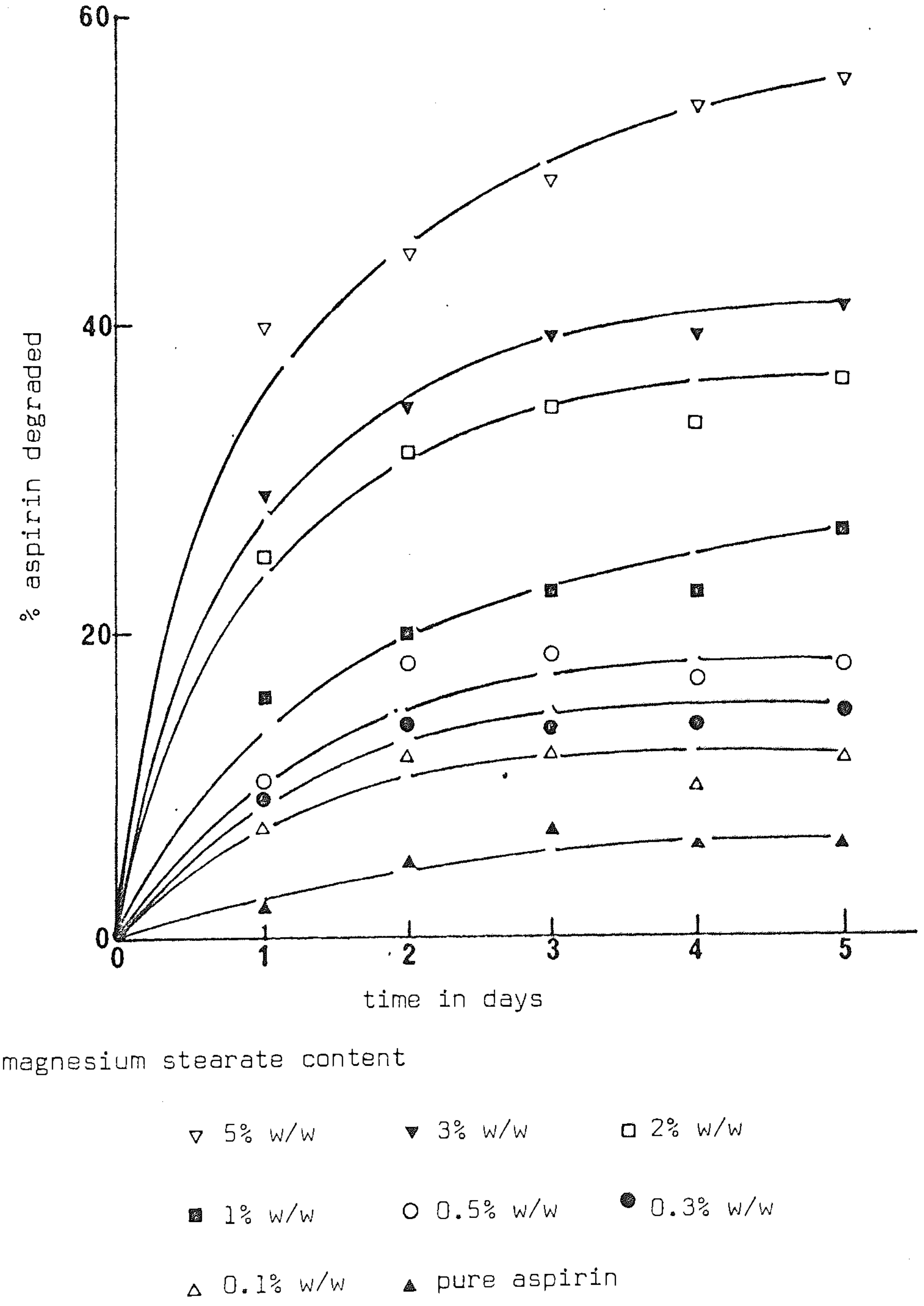
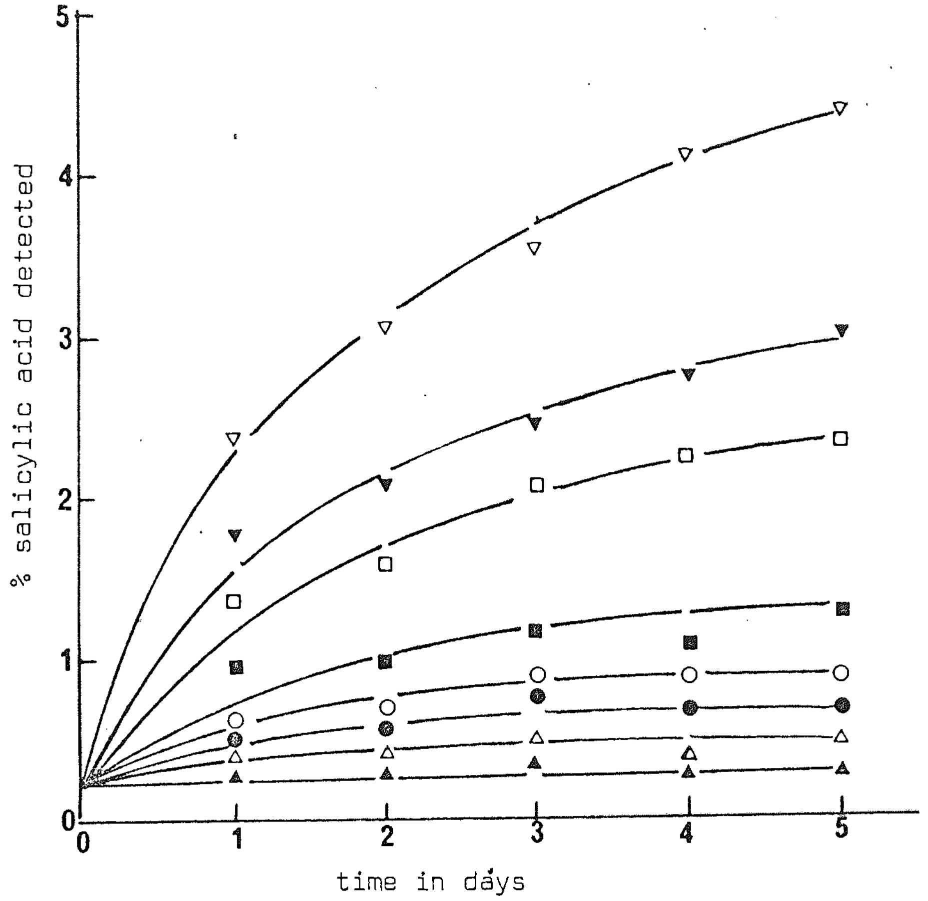


Figure 62. Salicylic acid detected in solid state aspirin degradation containing increasing amounts of magnesium stearate at 60°C, 75% RH



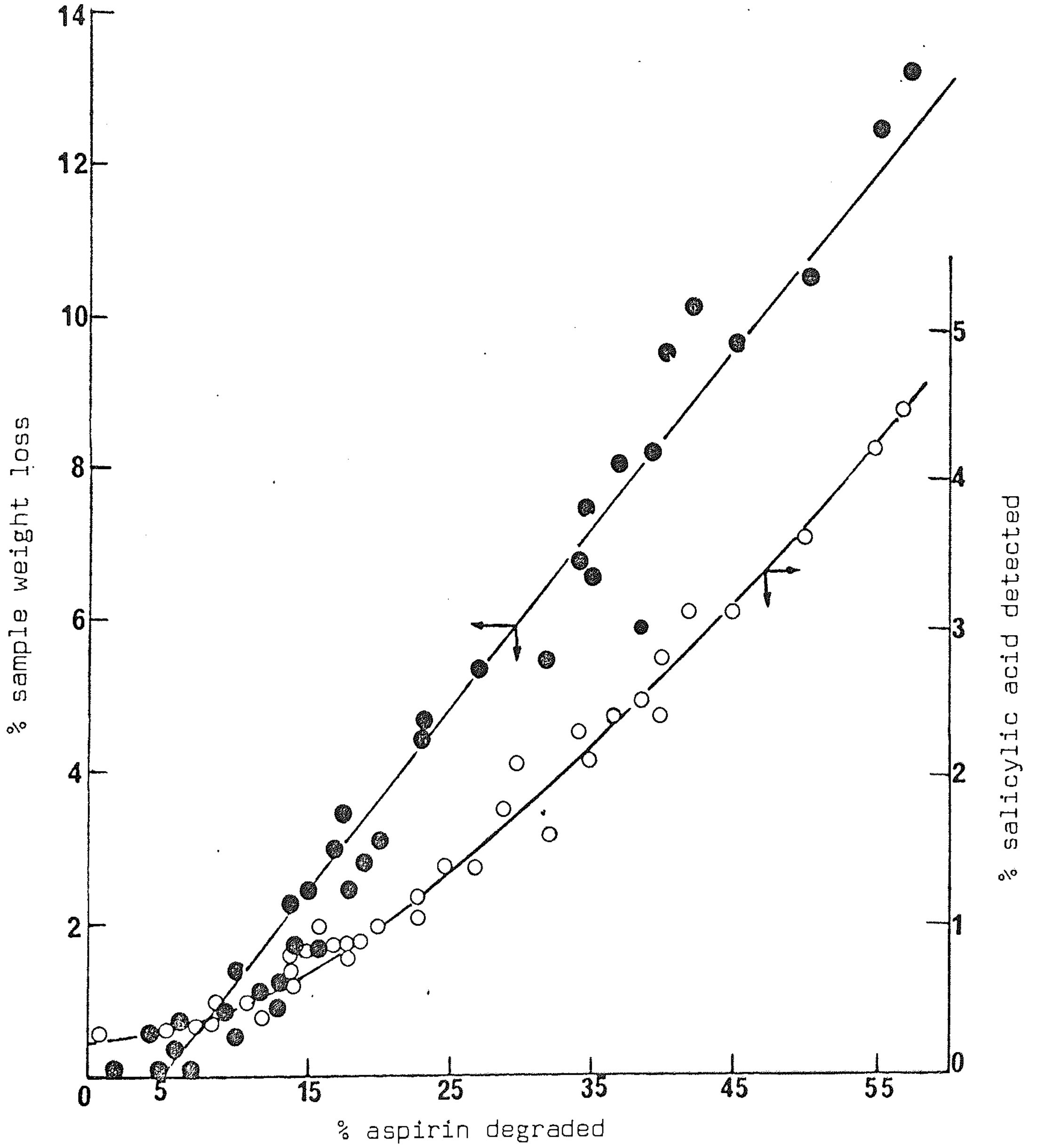
Key: magnesium stearate content

▽ 5% w/w ▼ 3% w/w □ 2% w/w

■ 1% w/w ○ 0.5% w/w ● 0.3% w/w

△ 0.1% w/w ▲ pure aspirin

Figure 63. Decomposition of aspirin in the solid state. Relationship between sample weight loss or salicylic acid detected with the % amount of aspirin degraded (60^{o}C, 75% RH).



● weight loss versus aspirin degraded

○ salicylic acid detected versus aspirin degraded a number of reaction products in samples of aspirin degrading in the presence of magnesium stearate. In this study an attempt to identify the products was made. The usefulness of HPLC in product identification is discussed.

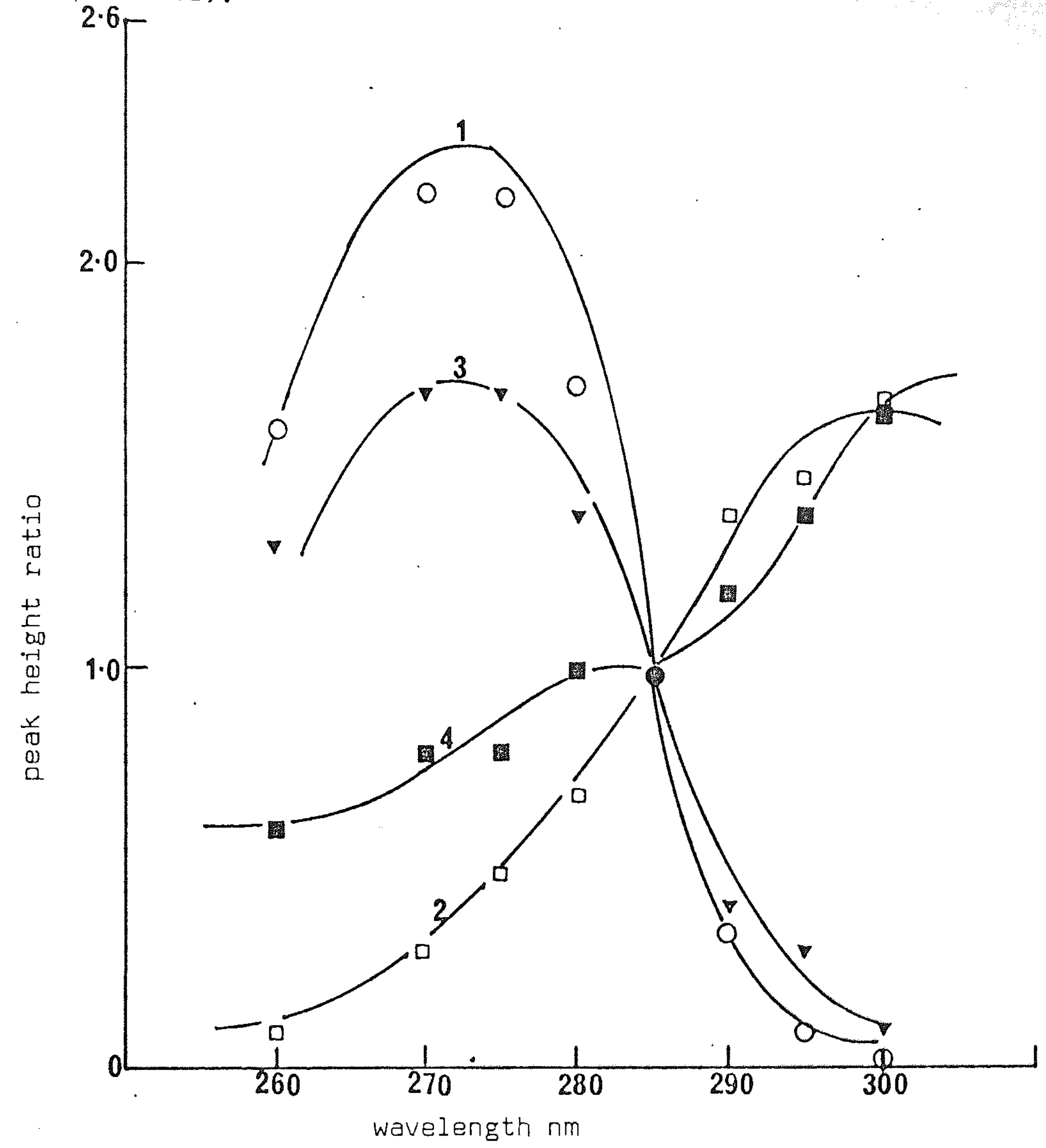
5.8.3.1 Methods

A sample of degraded aspirin was injected into the HPLC column and the peak heights of the traces were measured at 285 nm. The same sample was re-injected and the analysis done at wavelengths varying between 260 nm to 300 nm. Using 285 nm as the baseline, a peak height ratio for each wavelength of analysis was then calculated. Similarly a standard mixture of aspirin, salicylic acid, acetylsalicylsalicylic acid and salicylsalicylic acid were analysed. By plotting the peak height ratios against the wavelength, a trace similar to a UV is obtained for each of the products.

5.8.3.2 Results and Discussion

Figure 64 shows the traces obtained using authentic specimens (continuous line) and the ratios obtained with the decomposition products (points on the curves). It can be seen that there was a good degree of superimposition between the authentic speciments and the unknown decomposition products with the same retention times. From the traces in Figure 64, it appears that in addition to aspirin and salicylic acid, acetylsalicylsalicylic acid and salicylsalicylic acid were also present in degraded samples of aspirin. Figure 65 shows the peak height ratio-wavelength plots for some other unidentified degradation products. Figure 66 is the superimposition of Figures 64 and 65, prepared in order to give a complete insight into the complexity and number of the degradation

Figure 64. Relative UV absorption patterns of aspirin degradation products compared to authentic samples (NB authentic samples are shown by line trace, the points are for the degradation products).



Key:

1 aspirin

2 salicylic acid (SA) II

3 acetylsalicylsalicylic acid (ASSA) IV

4 salicylsalicylic acid (SSA) III

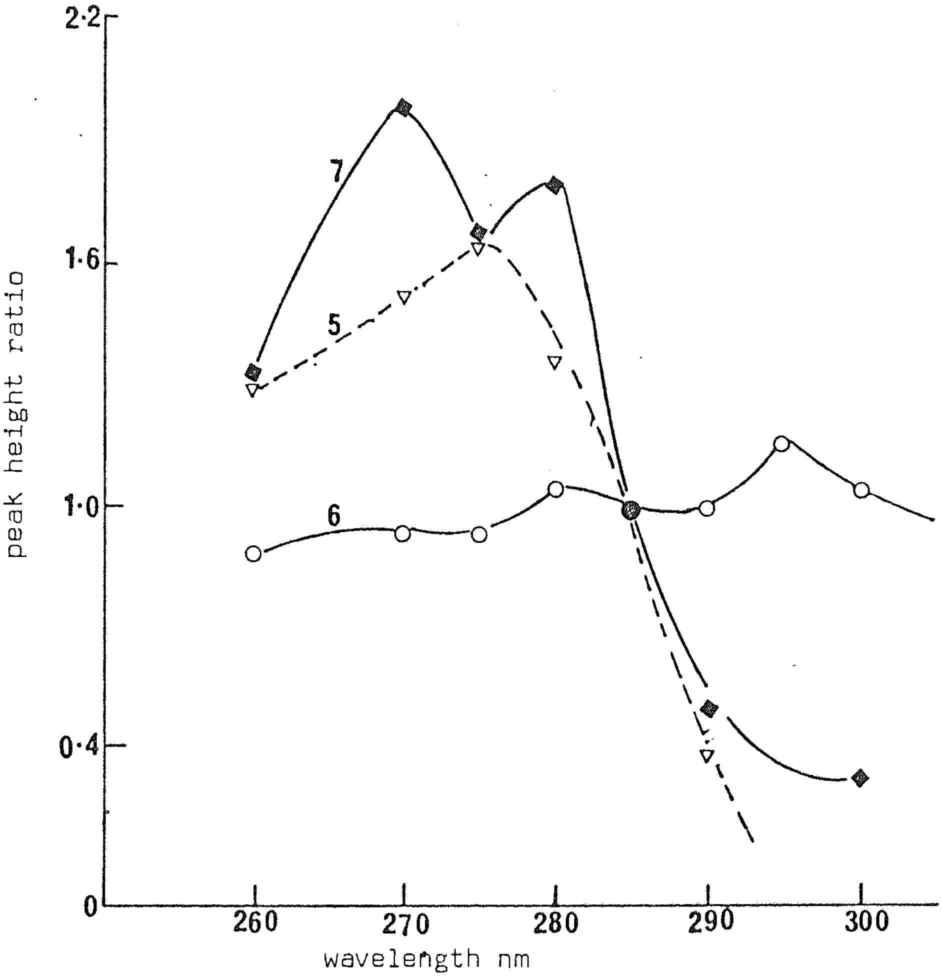
○ product that corresponds to 1

□ product that corresponds to 2

▼ product that corresponds to 3

■ product that corresponds to 4

Figure 65. UV absorption patterns of products of degradation of aspirin (these products were not identified).



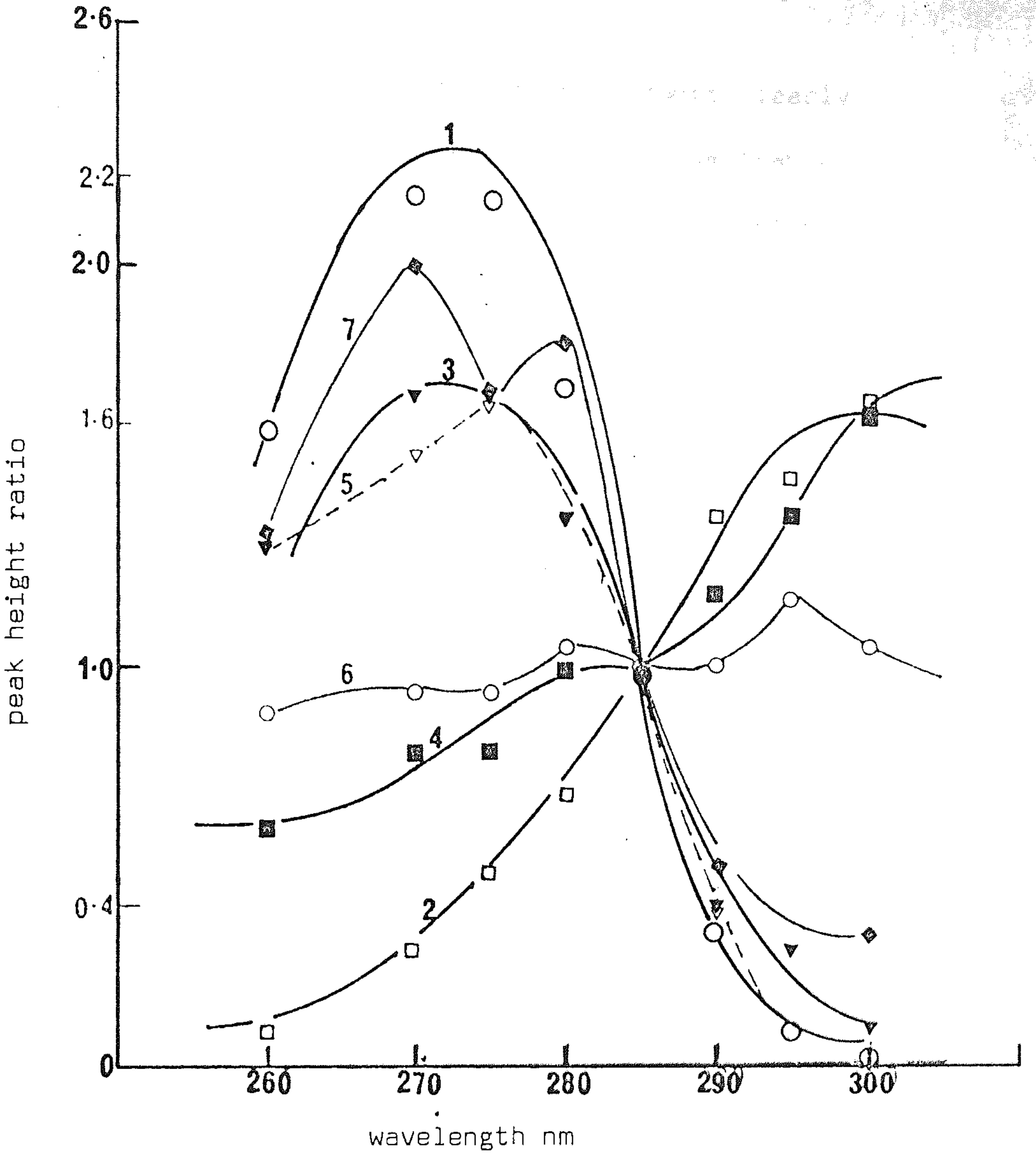
Key:

5 Peak with retention time 10.5 min

6 Peak with retention time 16.5 min

7 Peak with retention time 21.5 min

Figure 66. Superimposition of Figure 64 and Figure 65 giving a complete picture of the number of products formed in the solid state decomposition of aspirin (60°C, 75% RH)



1 aspirin (relative retention time 3.5 min)

2 salicylic acid (relative retention time 5.0 min)

3 ASSA (IV) (relative retention time 6.5 min)

4 SSA (III) (relative retention time 9.0 min)

○ degradation product identified as aspirin

□ degradation product identified as SA

▼ degradation product identified as ASSA

■ degradation product identified as SSA

5 degradation product not identified (10.5 min)

6 degradation product not identified (16.5 min)

7 degradation product not identified (21.5 min)

products of aspirin.

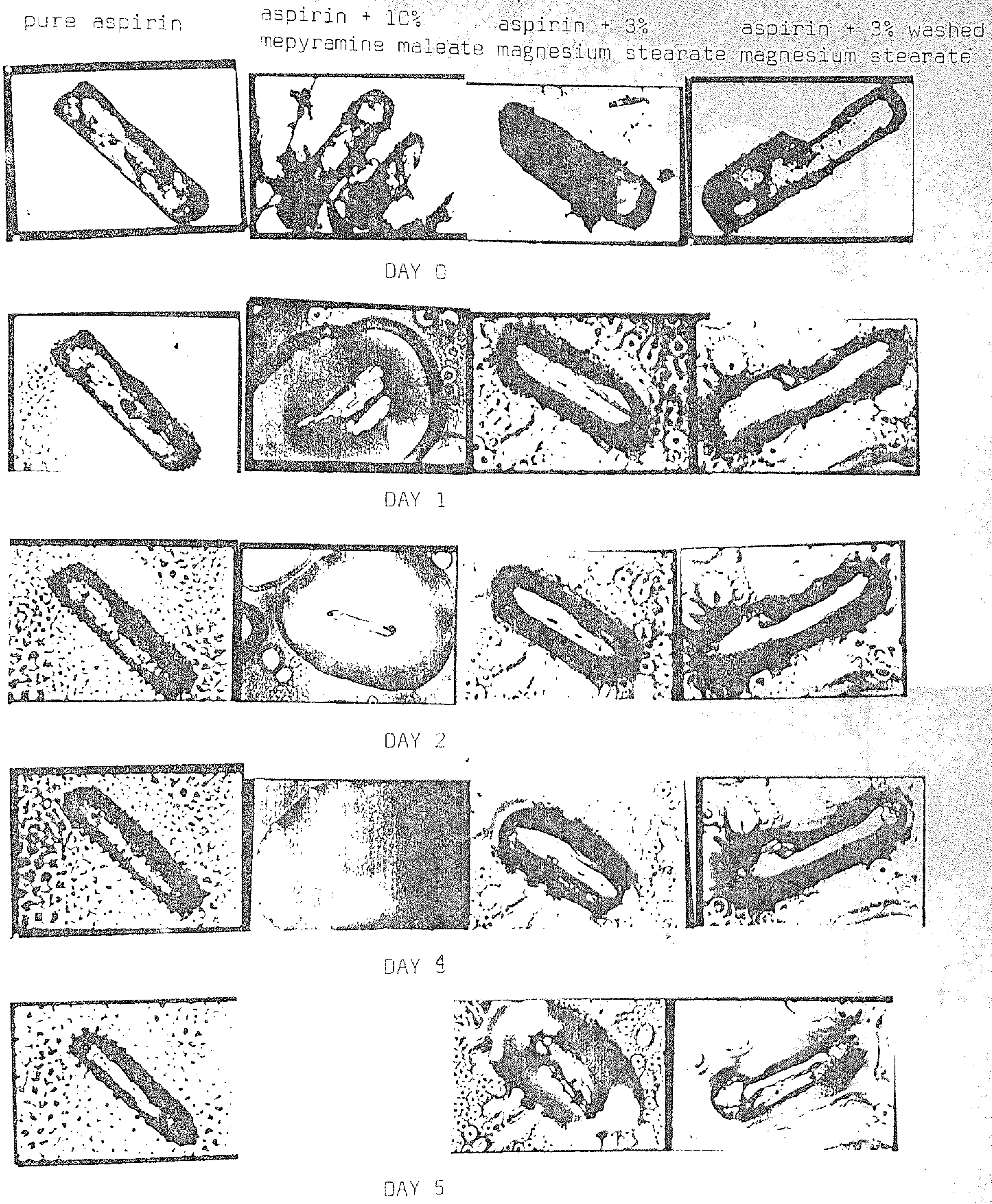
The high absorbances of the decomposition products clearly show that an ultra-violet spectrophotometry assay is unsuitable for following aspirin decomposition in our system unless prior separation of the products is obtained.

5.9 Conclusion

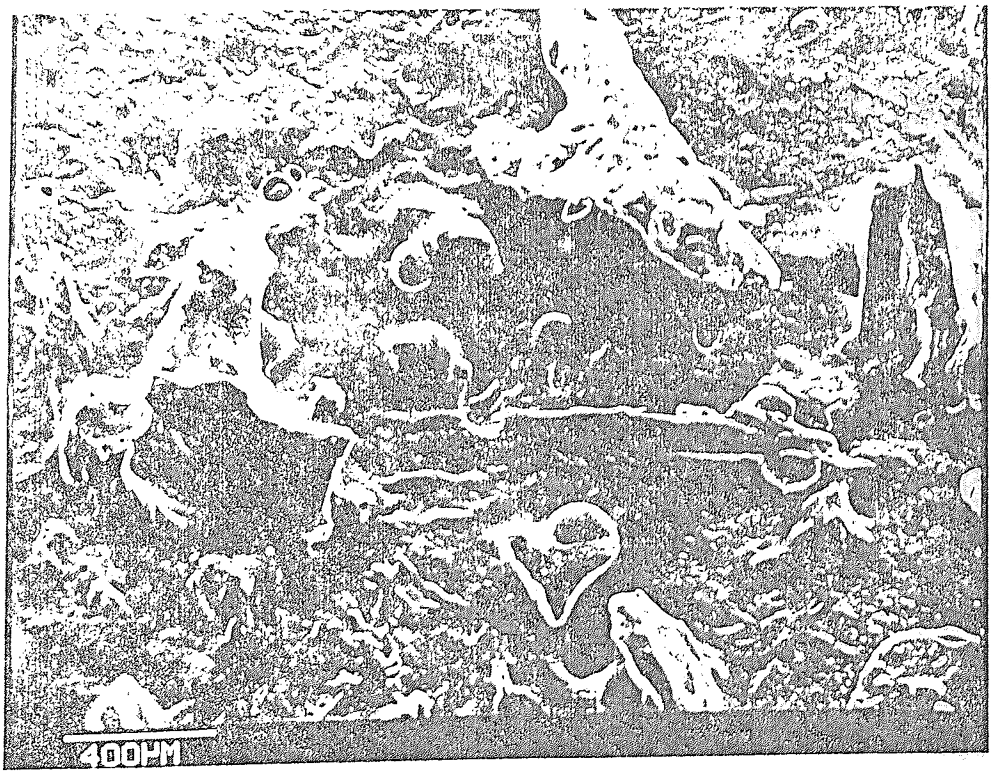
In this chapter, the stability of aspirin in the solid state and the influence of film coating and additives was studied. Both magnesium stearate and mepyramine maleate induce rapid degradation of aspirin in the solid state. The kinetics of aspirin decomposition in the presence of the additives appear to take place in a liquid layer in a diffusion controlled step. The formation of a liquid phase was demonstrated in both aspirin-magnesium stearate and aspirin-mepyramine maleate mixtures as shown in Figure 67. Photomicrographs (Figure 68) show aspirin crystals after storage at 50°C, 75% relative humidity for 15 weeks (Figure 68a) and aspirin + 1% w/w magnesium stearate after similar storage (Figure 68b). It is clearly shown that on addition of 1% w/w magnesium stearate to aspirin crystals, reaction occurs, which involves the destruction of aspirin crystal structure. The intact crystals (Figure 69a), when re-examined after being stored for 15 weeks, at 50°C and 75% relative humidity (Figure 69b) show obvious but relatively modest surface changes. These modest changes (Figure 69) appear to correspond with the small degree of degradation observed for aspirin alone, while the more intense changes (Figure 68) appear to explain the rapid degradation of aspirin induced by the presence of magnesium stearate.

These changes (observed in Figures 67, 68 and 69) which include the formation of a liquid phase, appear to be the main factors responsible for the reactions observed.

Figure 67. Comparative crystal surface changes for aspirin and in the presence of additives at 60^{o}C, 75% RH (magnification × 100).

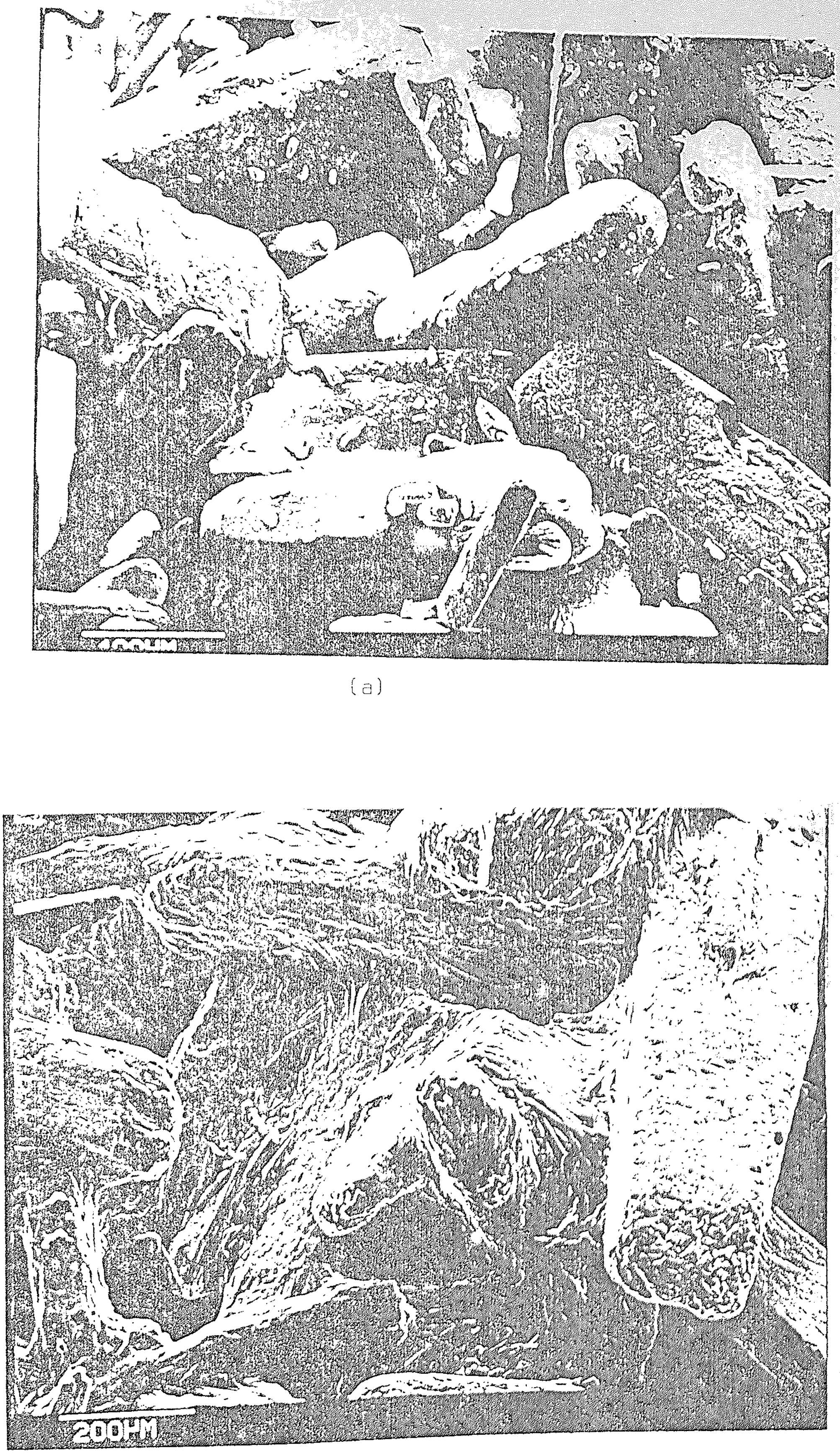


(a)



(b)

Figure 68. Photomicrographs of (a) aspirin after 15 weeks at 50°C, 75% Rh and (b) aspirin + 1% magnesium stearate at 50°C, 75% Rh after 15 weeks (magnification x 50).



(a)

(b)

Figure 69. Photomicrographs of (a) aspirin at time zero and
(b) aspirin after 15 weeks at 50°C and 75% RH
NB (a) magnification x 50
(b) magnification x 100 (for clearer surface view of
Figure 67a)

CHAPTER 6

GENERAL DISCUSSION AND SUMMARY

CHAPTER 6

General Discussion and Summary

The chemical stability of solids and solid dosage forms is influenced by a number of physical processes exemplified by dissolution, melting or vaporisation which facilitate mass transfer. An explanation for the observed reactions has to take the physical processes involved into account. Examples of reactions which have been explained with special emphasis on the physical processes involved will be examined in order to justify the proposed mechanisms given in this thesis.

In studying the aspirin-magnesium stearate interaction, the formation of a melt was observed. By microscopic examination contact between the aspirin and the magnesium stearate particles was observed to be essential to initiate melting. It was further shown that an increase in the proportion of magnesium stearate in the aspirin-magnesium stearate powder mixtures, lowers the melting point of the mixture and increases the reaction rate. The reaction rate constants were shown to be related to the melting points of the mixtures. The increase in reaction rate is due to an increased amount of drug in the melt, which degrades faster than the solid drug (311). The mechanism proposed takes into account the melt and the diffusional barrier formed. The observation that a number of reaction products are formed during aspirin decomposition in the solid state suggests that the reaction is more complex. Salicylsalicylic acid and acetylsalicylsalicylic acid are two of the decomposition products which have been identified. The salicylsalicylic acid could potentially be formed by self-esterification of salicylic acid in the presence of magnesium stearate. Storage of a 1:1 mixture of salicylic acid and magnesium stearate however failed to produce the bimolecular ester detected when aspirin was used.

The degradation of aspirin in the presence of mepyramine maleate was also explained on the basis of the formation of a liquid reaction layer. Microscopic examination of mepyramine maleate and aspirin-mepyramine maleate powder mixtures indicated that contact between the aspirin and mepyramine maleate particles was again essential for initiating rapid formation of a liquid layer. It was further demonstrated that an increase in the proportion of mepyramine maleate in the admixtures lead to a more rapid moisture uptake, a lower melting point and a higher reaction rate. All these processes contribute to increasing the amount of drug in the liquid layer. The logarithm of the rate constants (obtained by the use of equation 48) was inversely related to the reciprocal of the moisture content and directly proportional to the reciprocal of the absolute melting points of the powder mixtures. The linear relationship observed between the logarithm of the decomposition rate constant of aspirin and the reciprocal of the absolute melting point observed with aspirin-magnesium stearate mixtures was also seen with the mepyramine maleate-aspirin combination. This similarity is demonstrated by the equations obtained (equations 5~~4~~3 and 5~~5~~4). The slopes and intercepts of the equations were similar. The absence of multiple reaction products for aspirin-mepyramine maleate in contrast to observations made with aspirin-magnesium stearate mixtures suggests a difference in the reaction pathways. The overall loss of aspirin however followed similar kinetics.

The role of a film coat as a barrier when applied to discrete particles was found to be influenced by the type of additive present in the mixture. Gelatin, for example, stabilised aspirin poorly. The observed relative instability is thought to be due to sorbed moisture during the period of storage and use. When magnesium stearate was added to gelatin coated aspirin particles, significant degradation was observed but relative to the other films, it appears to be the best in inhibiting the adverse effects of the lubricant. The observed inhibition was explained in terms of the film acting as a good barrier, to prevent or reduce extensive contact between aspirin and magnesium stearate.

When mepyramine maleate was added to coated aspirin particles, a different pattern to that observed with magnesium stearate was obtained. Gelatin for example, was poorest in protecting aspirin against the adverse effects of mepyramine maleate when compared to the other films used. Three known properties of mepyramine maleate namely:

a) High solubility

b) Formation of solutions with pH 5

c) Surface activity.

may help to explain the observed phenomena. The increased moisture content of aspirin in the presence of mepyramine maleate means a higher proportion of the analgesic in solution. The surfactant solution formed would enhance the permation of the dissolved drug through the film coat into the core. The observed increase in decomposition of the aspirin particles coated with gelatin relative to the uncoated samples was attributed to a more rapid initial degradation. It was further observed in these studies that mepyramine maleate is strongly adsorbed or absorbed by the film forming substances used. The rate of reaction of the coated particles in the presence of mepyramine maleate was found to be inversely related to the degree of drug uptake by the polymeric substances. Gelatin coated particles which showed the highest degradation were found to have a low uptake ratio, while Eudragit L ^{R} coated particles which exerted an apparent stabilization (low reaction rate constant) relative to uncoated samples was found to take up much more mepyramine maleate. The adsorption/absorption appears to reduce the adverse effects of mepyramine maleate on aspirin. The sorption process reduces the effective amount of mepyramine maleate in solution, which would consequently reduce the amount of dissolved aspirin with the resultant lower rate of reaction.

The decomposition of aspirin in the presence of citric acid, magnesium chloride, Precirol ^{R}, magnesium oxide, magnesium trisilicate and magnesium stearate were studied, in an attempt to rationalise the effect of pH changes, induced by excipients, on aspirin decomposition in the solid state. In solution and suspension studies, magnesium stearate exerted a large adverse effect on the degradation of aspirin and salsalate. The observed adverse effects of magnesium stearate have been explained in terms of the presence of magnesium oxide, an impurity of which is claimed to mediate its effects through changes in pH. The use of magnesium oxide as an additive in the stability of aspirin in the solid state was done in order to see whether changes observed in suspension systems were paralleled by those seen in the solid state. The relatively modest degradation observed when aspirin was mixed with 2% w/w magnesium oxide showed that this was not so. Clearly then magnesium stearate does not increase aspirin decomposition solely because impurities present in it alter the pH of the moisture layers surrounding the aspirin particles. The evidence gathered in fact shows that this parameter is relatively unimportant.

In the solid state, the decomposition of salsalate was much slower than aspirin, even in the presence of magnesium stearate. No melting was observed. The higher degradation observed with the microcapsules with or without magnesium stearate, was attributed to a higher initial moisture content in the microcapsule coats and to a higher moisture uptake relative to the uncoated drug during the stability studied carried out at high humidity. With gelatin, the proportion of coat material in the microcapsules was about 45% in contrast to the 3% found with pan coated particles.

In this study the formation of a liquid layer was demonstrated in both aspirin-magnesium stearate and aspirin-mepyramine maleate powder mixtures stored at 60^{0}C and 75% relative humidity. Reactions usually are carried out at temperatures far below the melting temperatures of the reactants. Tamman (333) observed that sintering among reacting substances may occur at temperatures as low as 0.57 Tm where Tm is the absolute melting temperature of the pure components. A careful check of the reaction temperatures at which the work of Jander was performed, and the melting points of the substances involved show that sintering temperatures were obtained (Table 12). On addition of magnesium stearate to aspirin samples, the melting point of the mixture is lowered, to an extent which was proportional to the amount of magnesium stearate in the powder mixtures as shown in Table 13.

The lowering of melting points of pure substances by impurities has been explained by Vogel (334). At the melting point of a pure substance, both the solid form and the liquid melt co-exist in an equilibrium at atmospheric pressure. On addition of a small quantity of impurity, it will dissolve in the melt and lower the vapour pressure of the pure substance, which will then pass into

Table 12

MATERIALS AND TEMPERATURES USED BY JANDER (77) TO INVESTIGATE THE KINETICS OF SOLID-SOLID REACTIONS

Materials	Melting Point ^{o}C	Reaction Temperatures ^{o}C	Sintering Temperature $^{o}C*$
Calcium Carbonate	1339	800-890	645.8
Barium Carbonate	1740	800-890	874.4
Calcium Silicate	1604	800-890	796.9
Barium Silicate	1540	800-890	760.4

$*^{o}C$ This temperature is calculated as follows:

$$^{o}C* = (\text{Melting Temp} + 273)\ ^{o}K \times 0.57 = {}^{o}T - 273$$

These are products as a result of reaction of $CaCO_3$ and $BaCO_3$ with SiO_2

Table 13

MELTING POINTS OF ASPIRIN AND MIXTURES OF ASPIRIN WITH METALLIC STEARATES

Substance	Melting Point*
Pure Aspirin	137.5
Aspirin + 1% Magnesium Stearate	121.5
Aspirin + 2% Magnesium Stearate	118
Aspirin + 3% Magnesium Stearate	116
Aspirin + 5% Magnesium Stearate	113
Aspirin + 3% Aluminium Stearate	134
Aspirin + 3% Zinc Stearate	130
Aspirin + 3% Sodium Stearate	129
Aspirin + 3% Calcium Stearate	118

*Determined by the Capillary Method

the liquid phase, if the temperature is maintained constant. If no heat is supplied to such a system, the melting process will lower the temperature. The temperature falls to a new equilibrium where both the liquid and the solid co-exist. With a further addition of an impurity the temperature is further lowered, since a solid with a given vapour pressure cannot co-exist with a liquid phase of lower vapour pressure. Impurities therefore alter the melting of pure substances by lowering the vapour pressure of the liquid phase of the pure substance. The melting point attains a limiting temperature known as the eutectic point, below which both pure substance and an added impurity exist as solids. The solid mixture is known as a eutectic mixture and consists of definite quantities of the components which melts and freezes as a pure substance; at a definite temperature, the eutectic temperature. A eutectic mixture is not a definite chemical compound but an intimate mechanical mixture or conglomerate of the two solid components.

In studying interactions between pharmaceutical compounds by differential thermal analysis, Guillory _et al_. (25) observed that pure compounds which do not exhibit polymorphism or are not solvates and do not decompose prior to melting exhibit a single endothermic peak corresponding to fusion temperature. The resolidified melt of a binary mixture corresponding to the eutectic composition will also exhibit a single peak. Other binary mixtures will typically exhibit more than one peak, and as a rule two peaks are observed, the first corresponding to the eutectic melting temperature at which complete liquefaction occurs. Data presented by the authors show that phenacetin-phenobarbital, acetaminophen-phenobarbital and aspirin-phenobarbital mixtures form eutectic mixtures. The aspirin-magnesium stearate powder mixtures used in this study show an initial endothermic peak at 75^{o}C corresponding to the eutectic melting temperature. The use of differential thermal analysis for screening for incompatibilities appears suitable not only for binary mixtures but also for more complex finished dosage forms.

The kinetic equations reported in the literature have either been based on observed phenomena or developed empirically. A summary of some of the kinetic equations which have been reported to explain reactions in the solid state is presented in Table 14. The diversity of the kinetic equations probably reflect the complex nature of reactions in the solid state. In most of the equations presented in Table 14, the degradation has been expressed as a fraction of drug decomposed, α. Most of the equations however are only applicable for small values of α. This problem has led to the development of a relatively large number of equations to describe the kinetics of solid state reactions. Many modifications of the Jander's equation (84-89) further illustrate the problems associated with the development and application of kinetic equations used in describing solid state decomposition.

To conclude, the more notable aspects of the present study are:

(i) The development of an HPLC assay for aspirin, salsalate and their degradation products.

(ii) The development of equations for describing the kinetics of degradation of aspirin in the solid state in the presence of magnesium stearate (excipient) and mepyramine maleate (drug).

(iii) Investigation of the problems associated with film coating of powders and the effect of additives on such film-coated particles.

(iv) The interpretation of the effect of additives on the rate of decomposition of aspirin in the solid state, in terms of physico-chemical processes such as melting and dissolution.

(v) The detection, identification and quantitation of some of the observed degradation products of aspirin in the solid state in the presence of magnesium stearate.

(vi) The correlation of weight losses with the extent of aspirin degradation.

Suggestions for Further Work

The results reported in this thesis, support an earlier observation (172) that magnesium stearate increases the degradation of aspirin in the solid state. The mechanism for the observed degradation of aspirin in the presence of calcium and magnesium stearates in tablets stressed at 45°C for four weeks were not discussed. It would therefore be interesting to study whether the lowering of melting point also controls the degradation at lower temperatures.

An investigation into different methods of coating, to see whether it is possible to reduce particle agglomeration would also be worthwhile.

The use of differential thermal analysis as a technique for screening for possible drug-drug or drug-excipient interactions offers exciting possibilities.

Table 14

SOME KINETIC EQUATIONS OF SOLID STATE REACTIONS

EQUATION	THEORY	NAME OR REFERENCE
1. $\lvert 1-(1-\alpha)^{1/3}\rvert^2 = \frac{2k}{r_o^2} t$	Advance of Interface by Diffusion	Jander Equation Ref. 77
2. $\lvert (\frac{1}{1-\alpha})^{1/3} - 1\rvert^2 = \frac{2kD}{r_o^2} t$	as Jander	Zhuravlev, Lesokhin and Tempelman Ref. 85
3. $\lvert 1-(1-\alpha)^{1/3}\rvert^2 = \frac{2k}{r_o^2} \ln t$	as Jander	Kroger & Ziegler Ref. 84
4. $1-\frac{2}{3}\alpha-(1-\alpha)^{2/3} = \frac{2kDt}{r_o^2}$	as Jander	Ginstling & Brownshtein, Ref. 86
5. $Z-(Z-1)(1-\alpha)^{2/3} - \lvert 1+(Z+1)\alpha\rvert^{2/3} = \frac{2kD(Z-1)}{r_o^2} t$	as Jander	Carter Ref. 87
6. $\lvert (1+\alpha)^{1/3} - 1\rvert^2 = \frac{2kD}{r_o^2} t$	"Counter Diffusion"	Komatsu & Uemura Ref. 88
7. $\frac{d\alpha}{dt} = k(1-\alpha)^{1/3}/\lvert 1-(1-\alpha)^{1/3}\rvert$	as Jander	Pozin & Ginstling Ref. 119
8. $\frac{d\alpha}{dt} = k(1-\alpha)^{1/3}$	Rate Law	Pozin & Ginstling Ref. 119
9. $kt = 1-(1-\alpha)^{1/3}$	Geometrical	Cizmaru & Vass Ref. 113
10. $\frac{d\alpha}{dt} = k(a-\alpha)^{2/3}/\alpha^{1/3}$	Empirical devoloped Empirically	Hoffman & Patai Ref. 336
11. $\mathrm{In}(1-\alpha) = Kt$	First Order developed Empirically Also Nucleation (Unimolecular decay)	Tzentnershver & Boruzs, Ref. 111 Mampel, Ref. 110
12. $\log \frac{\alpha}{1-\alpha} = kt$	Initially Empirical Then based on Nucleation	Prout & Tompkins Ref. 107
13. $Bt^n = \frac{\alpha_t}{1-\alpha_t}$	Nucleation	Avrami Ref. 101-103

cont'd. ...

Table 14 cont'd.

EQUATION	THEORY	NAME OR REFERENCE
14. $\frac{d\alpha}{dt} = (1-\alpha)^{M} K^{l+1} t^{l}$	Empirical	Hasegawa *et al*. Ref. 145
15. $\frac{d\alpha}{dt} = k\alpha^{n}(a-\alpha)$	Nucleation	Kawakita Ref. 147
16. $-\log(1-\alpha) = Kt^{n}$	Nucleation	Avrami-Erofeev Ref. Galwey (36) Johanson-Mehl-Avrami-Erofeev-Koglomorov after the authors. Ref. Sestak (30)
17. $\ln \frac{6}{\pi^{2}(1-\alpha)} = \frac{\pi^{2}D}{r^{2}} t$	Fick's Laws of Diffusion	Dunwald-Wagner Equation Ref. 89
18. $\log \left\| \frac{Ao(Do^{\frac{1}{2}} + C^{\frac{1}{2}})^{2}}{D_{o}^{\frac{1}{2}} + C_{o}^{\frac{1}{2}})^{2}A} \right\| = \frac{D_{o}^{\frac{1}{2}} kp^{3n/2} t}{2.303}$	Sorbed moisture layer theory	Leeson & Mattoks Ref. 124
19. $y^{2} = 2kte^{-py}$	Advance of Interface	Rastogi *et al* Ref. 140, 141

APPENDIX 1

Data for Degradation of Aspirin in the Presence of Different Proportions of Magnesium Stearate at 60°C, 75% RH

% MS	Parameters	DAYS					
		0	1	2	3	4	5
0.0	% A. Remaining	100.0	98.01	94.82	92.51	93.67	93.67
	% A. Degraded	0.0	1.99	5.18	7.49	6.33	6.33
	% Salicylic A	0.02	0.25	0.34	0.43	0.29	0.32
	% Weight Loss	0	0.05	0.6	0.1	0.4	0.7
0.1	% A. Remaining	100.0	91.36	87.80	87.48	89.83	88.43
	% A. Degraded	0.0	8.64	12.20	12.52	10.17	11.57
	% Salicylic A	0.02	0.45	0.42	0.52	0.44	0.46
	% Weight Loss	0.0	0.1	1.2	0.9	1.4	1.1
0.3	% A. Remaining	100.0	95.67	85.96	85.55	85.89	85.2
	% A. Degraded	0.0	4.33	14.04	14.45	14.11	14.8
	% Salicylic A	0.02	0.57	0.61	0.77	0.73	0.75
	% Weight Loss	0.0	0.6	1.8	2.3	2.3	2.4
0.5	% A. Remaining	100.0	89.59	82.29	80.99	83.21	82.43
	% A. Degraded	0.0	10.41	17.71	19.01	16.79	17.57
	% Salicylic A	0.02	0.65	0.75	0.88	0.86	0.93
	% Weight Loss	0.0	0.5	2.5	2.8	3.0	3.5
1.0	% A. Remaining	100.0	84.12	80.17	76.53	76.72	73.40
	% A. Degraded	0.0	15.88	19.83	23.47	23.28	26.60
	% Salicylic A	0.02	0.98	1.02	1.21	1.11	1.35
	% Weight Loss	0.0	1.7	3.1	4.5	4.7	5.4
2.0	% A. Remaining	100.0	74.92	68.43	65.18	65.77	63.28
	% A. Degraded	0.0	25.08	31.57	34.82	34.23	36.72
	% Salicylic A	0.02	1.39	1.64	2.14	2.30	2.37
	% Weight Loss	0.0	3.0	5.5	6.9	7.6	8.2
3.0	% A. Remaining	100.0	71.32	64.71	60.25	59.81	57.80
	% A. Degraded	0.0	28.68	35.29	39.75	40.19	42.2
	% Salicylic A	0.02	1.84	2.06	2.48	2.77	3.10
	% Weight Loss	0.0	3.6	6.6	8.3	9.7	10.3
5.0	% A. Remaining	100.0	59.66	54.96	49.74	44.68	43.34
	% A. Degraded	0.0	40.34	45.04	50.26	55.32	56.66
	% Salicylic A	0.02	2.44	3.08	3.58	4.19	4.47
	% Weight Loss	0.0	6.8	9.8	10.8	12.8	13.5

MS = Magnesium Stearate

APPENDIX 2

Relationships between Rate Constants and Melting Points for Mixtures of Aspirin with Alkaline Metal Stearates and Mepyramine Maleate

Powder Mixtures	Slope $2k/r_0^2$ $\times 10^{-4}$	log(slope) + 4	Melting Point °C	$\frac{1}{0T}$ (K^{-1}) $\times 10^4$
Pure Aspirin	1.34	0.127	137.5	24.361
Asp + 1% MgS	30.80	1.489	121.5	25.349
Asp + 2% MgS	76.34	1.883	118.0	25.575
Asp + 3% MgS	112.80	2.053	116.0	25.707
Asp + 5% MgS	264.60	2.423	113.0	25.907
Asp + 3% AlS	3.23	0.509	134.3	24.552
Asp + 3% ZnS	3.31	0.520	130.1	24.808
Asp + 3% NaS	7.25	0.860	129.0	24.876
Asp + 3% CaS	69.80	1.844	118.3	25.556
Asp + 3% MgS	108.43	2.035	116.8	25.656
Asp + 5% MEP	5.73	0.758	130.2	24.802
Asp + 10% MEP	16.14	1.208	124.7	25.145
Asp + 15% MEP	33.82	1.529	121.7	25.336
Asp + 20% MEP	108.59	2.036	117.3	25.621

MgS = Magnesium Stearate

AlS = Aluminium Stearate

ZnS = Zinc Stearate

NaS = Sodium Stearate

CaS = Calcium Stearate

MEP = Mepyramine Maleate

Asp = Aspirin

APPENDIX 3

Effect of Ionic Strength on Degradation of Salsalate Suspension (in buffer pH 4.0) at 50°C

(μ) Ionic Strength	$\mu^{\frac{1}{2}}$	K_o M/n/l/hr (Rate Constant)	Log (K_o + 2)	Log K_o
0.157	0.396	0.1784	1.251	-0.749
0.20	0.447	0.1674	1.214	-0.776
0.30	0.548	0.1446	1.160	-0.840
0.50	0.707	0.1226	1.088	-0.912
0.8	0.894	0.0969	0.987	-1.014
1.0	1.00	0.0915	0.961	-1.039

APPENDIX 4

Observed Moisture Content in Aspirin-Mepyramine Maleate Powder Mixtures

% MEP	Moisture Content	1/Mc	Rate Constant $2K/r_o^2$	Log Rate	Log Rate +3
0	0.78 (0.03)	1.28	0.173×10^{-3}	-3.762	-0.762
5	0.86 (0.03)	1.16	0.573×10^{-3}	-3.242	-0.242
10	0.94 (0.04)	1.06	1.614×10^{-3}	-2.792	0.208
15	1.07 (0.05)	0.93	3.382×10^{-3}	-2.471	0.529
20	1.32 (0.03)	0.76	10.859×10^{-3}	-1.964	1.036

MEP = Mepyramine maleate

MC = Moisture Content

APPENDIX 5

Solubilities and Melting Points of Some of the Substances Used in the Stability Studies

Substances	Solubility g/l	Melting Point ^{o}C	Values of M.pt or Solubility Determined	References
Aspirin	3.3	135	137.5^{o}C	302
Magnesium Stearate	0.03	86-88	113^{o}C Unwashed 95^{o}C Washed	306
Calcium Stearate	0.04	147-149 179-180	160^{o}C	302, 306
Sodium Stearate	5.0	-	Charres on heating to reddish brown colour	305
Zinc Stearate	Insoluble	120 130	124^{o}C	302 306
Aluminium Stearate	Insoluble	103 117-120	180^{o}C	302 306
Mepyramine Maleate	2500.0	99-101	103^{o}C	302
Salsalate	0.17	148	0.1 g/l (at 37^{o}C)	304
Acetyl salicyl-salicylic acid	Insoluble	152 159	159^{o}C	302
Magnesium oxide	Insoluble	2800.0	-	302 306

REFERENCES

1. H. Bundgaard,
   J. Pharm. Pharmacol., 26 18 (1974)
2. H. Bundgaard and A. L. DeWeck,
   Int. Arch. Allergy Appl. Immunol., 49 119 (1975) (through Chem. Abstr. 83: 71990x)
3. A. L. DeWeck,
   ibid, 41 393 (1971) (through Chem. Abstr. 75: 139 922g)
4. D. L. Simmons, H. S. L. Woo, C. M. Koorengevel and P. Seers,
   J. Pharm. Sci., 55 1313 (1966)
5. Ho-Leung Fung,
   In Modern Pharmaceutics. Eds. G. S. Banker and C. T. Rhodes, Marcel Dekker, New York (1979) pp. 227
6. W. B. Deichmann and H. W. Gerarde,
   In Toxicology of Drugs and Chemicals, Academic press, London (1969) pp. 94
7. H. C. Ansel,
   In Remingtons Pharmaceutical Sciences, 16th ed. Ed. A. Osol, Mack Publishing Co., Easton (1980) pp. 1715
8. W. E. Brown, D. Dollimore and A. K. Galwey,
   In Comprehensive Chemical Kinetics, Vol. 22. "Reactions in the Solid State. Eds. C. H. Bamford and C. F. H. Tipper, Elsevier, N.Y. (1980)
9. E. R. Garrett,
   J. Pharm. Sci., 51 811 (1962)
10. S. Patel, J. H. Perrin and J. J. Windheuser,
    ibid, 61 1794 (1972)
11. V. Y. Taguchi, M. L. Cotton, C. H. Yates and J. F. Millar,
    ibid, 70 64 (1981)

12. J. C. Reepmeyer and R. D. Kirchhoefer,
ibid, 68 1167 (1979)

13. W. J. Irwin, A. Li Wan Po and D. K. Scott,
J. Clin. Hosp. Pharm., 4 25 (1979)

14. R. D. Kirchhoefer and W. E. Juhl,
J. Pharm. Sci., 69 548 (1980)

15. E. Townley and P. Roden,
ibid, 69 523 (1980)

16. A. Li Wan Po and W. J. Irwin,
J. Clin. Hosp. Pharm., 5 107 (1980)

17. E. R. Garrett,
J. Amer. Pharm. Ass. Sci. Ed., 48 676 (1959)

18. S. M. Blaug and J. W. Wesolowski,
ibid, 48 691 (1959)

19. C. A. Kelly,
J. Pharm. Sci., 59 1053 (1970)

20. M. I. Pope and M. D. Judd,
in "DTA, a guide to techniques and its applications",
Heyden Chaltham (1977) pp. 60

21. H. Jacobson and I. Gibbs,
J. Pharm. Sci., 62 1543 (1973)

22. W. W. Wendlandt,
J. Chem. Ed., 38 571 (1961)

23. W. L. Chiou and S. Niazi,
J. Pharm. Sci., 62 498 (1973)

24. H. E. Kissinger,
Anal. Chem., 29 1702 (1957)

25. J. K. Guillory, S. C. Hwang and J. L. Lach,
J. Pharm. Sci., 58 301 (1969)

26. W. H. Wu, T. F. Chin and J. L. Lach,
ibid, 59 1122 (1970)

27. W. H. Wu, T. F. Chin and J. L. Lach,
ibid, 59 1234 (1970)

28. J. L. Lach and L. D. Bighley,
ibid, 59 1261 (1970)

29. D. G. Pope and J. L. Lach,
Pharm. Acta Helv., 50 165 (1975)

30. J. Sestak, V. Satava and W. W. Wendlandt,
in "The study of heterogeneous processes by thermal analysis".
Ed. W. W. Wendlandt, Amsterdam (1973) pp. 403 (a continuation
of Vol. 7(5) Thermochemica Acta (1973) p. 333-556)

31. A. A. Frost and R. G. Pearson,
in Kinetics and Mechanism, 2nd Ed., John-Wiley & Son,
London (1961)

32. L. J. Edwards,
Trans. Faraday Soc., 46 723 (1950)

33. E. R. Garrett,
J. Amer. Chem. Soc., 79 3401 (1957)

34. W. Gomes,
Nature, 192 865 (1961)

35. E. N. Yeremin,
The Foundations of Chemical Kinetics. Mir Publishers,
Moscow (1976) (English Translation 1979) Chapter 13.

36. A. K. Galwey,
Chemistry of Solids, Chapman Hall, London (1967)

37. E. R. Garrett and R. F. Carper,
J. Amer. Pharm. Ass. Sci. Ed., 44 515 (1955)

38. S. Arrhenius,
Z. Physik. Chem., 4 226 (1889)

39. M. Polanyi and E. Wigner,
Z. Physik. Chem., A139 439 (1928)

40. K. A. Connors, G. L. Amidon and L. Kennon,
In Chemical Stability of Pharmaceuticals, A handbook for pharmacists. John-Wiley & Sons, New York (1978) pp. 18

41. W. Komatsu,
J. Chem. Soc. Japan (Pure Chem. Sect.) 76 504 (1955)
(through Chem. Abstr., 49: 15333)

42. R. Tardif,
J. Pharm. Sci., 54 281 (1965)

43. J. G. Slater, H. A. Stone, B. T. Palermo and R. N. Duvall,
ibid, 68 49 (1979)

44. J. T. Carstensen,
In the Theory of Pharmaceutical Systems, Vol. II, Academic Press, New York (1973) pp. 295

45. G. Cohn,
Chem. Reviews, 42 527 (1948)

46. A. Sieverts and H. Theberath,
Z. Physik. Chem., 100 463 (1922) (through Chem. Abstr. 16: 2249)

47. C. N. Hinshelwood and E. J. Bowen,
Phil. Mag., 40 569 (1920)

48. J. W. Cobb,
J. Soc. Chem. Ind., 29 69 (1910)

49. J. A. Hedvall,
Z. Anorg. Chem. 86 201 (1914) (through Chem. Abstr. 8: 1715)

50. W. Jander,
Angew Chem., 47 235 (1934) (through Chem. Abstr., 28: 3956)

51. V. V. Boldyrev,
Kinetika i Kataliz, I(2) 203 (1960) (through Chem. Abstr., 55: 2250)

52. J. R. Bristow and B. L. Rees,

Nature, 198 178 (1963)

53. J. Benard,

Bull. Soc. Chim. France, 13 511 (1946) (through Chem. Abstr., 43: 2065)

54. C. N. Hinshelwood and B. Topley,

J. Chem. Soc. (Transactions) 123(1) 1014 (1923)

55. M. M. Pavlyuchenko,

Dokl. Akad. Nauk. Belorussk SSR, 4 113 (1960) (through Chem. Abstr., 57 11865)

56. H. Forestier,

Bull. Soc. Chim. Belges, 67 528 (1958) (through Chem. Abstr., 53: 5812c)

57. C. N. Hinshelwood and R. E. Bunk,

J. Chem. Soc. (Transactions) 127 1105 (1925)

58. K. S. Kutateladze and V. I. Lutsenko,

Ogneupory, 15(1) 39 (1950)(through Chem. Abstr., 44: 6222 & 6327e)

59. H. Sasaki,

Zairyo, 13 (133) 759 (1964) (through Chem. Abstr., 64: 7409c

60. H. Sasaki,

J. Amer. Ceram. Soc., 47(10) 512 (1964)

61. W. Feitknecht,

Pure Appl. Chem., 9(3) 423 (1964)

62. D. Nicholson,

Trans. Faraday Soc., 61 990 (1965)

63. E. E. Petersen,

Chem. Eng. Sci., 20(6) 587 (1965)

64. R. A. W. Hill, L. E. Sutton, R. B. Temple and A. White,

Research (London) 3 569 (1950)

65. P. P. Budnikov and A. M. Ginstling,

Uspekhi Khim., 23 491 (1954) (through Chem. Abstr., 48: 10413a)

66. W. Komatsu,

J. Chem. Soc. Japan (Pure Chem. Sect.) 75 1078 (1954) (through Chem. Abstr., 48: 2457, 7407 and 49: 9369)

67. W. Komatsu,

ibid, 75 1269 (1954) (through Chem. Abstr., 49: 13747)

68. H. Forestier and C. Haasser,

Compt. Rend., 225 240 (1947) (through Chem. Abstr., 44: 3774, and 43: 6059h)

69. F. Taradoire,

Chimie and Industrie, 45 334 (1941) (through Chem. Abstr., 38: 6168)

70. F. Taradoire,

Bull. Soc. Chim., 7 720 (1941) (through Chem. Abstr. 36: 2198)

71. R. Perrin and M. Roubault,

Compt. Rend. Soc. Geol. France (1939) 76-78 (through Chem. Abstr., 33: 4499)

72. H. Marawetz,

Science, 152 705 (1966)

73. A. Li Wan Po and W. J. Irwin,

J. Pharm. Pharmacol., 32 25 (1980)

74. M. K. Gluzman and D. G. Arlozorov,

Zhur. Priklad. Khim., 31 657 (1958) (through Chem. Abstr. 52: 15415, 2828f, 16856, and 17234i)

75. I. C. Paul and D. Y. Curtis,

Science, 187 19 (1975)

76. R. J. Zeto,

Dissert. Abstr., 24(12) 5033 (1964)

77. W. Jander,

Z. Anorg. Allgem. Chem., 163 1 (1927) (through Chem. Abstr., 21: 3798)

78. W. Jander,

ibid, 166 31 (1927) (through Chem. Abstr., 22: 1518)

79. W. Jander,

ibid, 168 113 (1927) (through Chem. Abstr., 22: 1085)

80. W. Jander,

ibid, 174 11 (1928) (through Chem. Abstr.,22: 4037)

81. W. Jander and W. Stamm,

ibid, 190 65-78 and 397-406 (1930) (through Chem. Abstr., 24: 4197)

82. W. Jander and E. Hoffmann,

ibid, 200 245 (1931) (through Chem. Abstr., 26: 24 and 30: 4744)

83. A. M. Ginstling and T. P. Fradkina,

Zhur. Priklad. Khim., 25 1134 (1952) (through Chem. Abstr., 48: 9794i)

84. C. Kroger and G. Ziegler,

Glastech. Ber., 26 346 (1953) (through Chem. Abstr., 48: 1643c & 49: 7205e)

85. V. F. Zhurablev, I. G. Lesokhin and R. G. Tempelman,

J. Appl. Chem. USSR, 21 887 (1948) (through Chem. Abstr. 43: 8826d)

86. A. M. Ginstling and B. I. Brounshtein,

J. Appl. Chem. USSR, 23 1327 (1950) (through Chem. Abstr. 46: 9959c)

87. R. E. Carter,

J. Chem. Phys., 34 2010 (1961)

88. W. Komatsu and T. Uemura,

Z. Phys. Chem. (Frankfurt am Main) 72 59 (1970)

89. H. Dunwald and C. Wagner,

ibid, B24 53 (1934)

90. G. Cohn,

J. Amer. Ceram. Soc., 27 308 (1944)

91. J. A. Cooper and W. E. Garner,

Trans. Faraday Soc., 32 1739 (1936)

92. B. E. Bartlett, F. C. Tompkins and D. A. Young,

Nature, 179 365 (1957)

93. S. V. Izmailov,

Physik. Z. Sowjetunion, 4 835 (1933) (through Chem. Abstr., 28: 2982)

94. J. Hume and J. Colvin,

Phil. Mag., 8 589 (1929)

95. M. K. Goldstein and T. B. Flanagan,

J. Chem. Ed., 41 276 (1964)

96. H. Hashimoto,

Nippon Kagaku Zasshi, 82 1456 (1961) (through Chem. Abstr., 57: 5337d)

97. W. E. Garner,

Trans. Faraday Soc., 34 940 (1938)

98. A. Wischin,

Proc. Roy. Soc., A172 314 (1939)

99. W. Komatsu,

Intern. Symp. Reactivity Solids, 5th Munich (1964) pp. 182-91 (published in 1965) (through Chem. Abstr., 66: 14392d)

100. I. S. Kainarskic and N. A. Sidorov,

Zhur. Priklad. Khim., 29 1785 (1956) (through Chem. Abstr., 51: 7816)

101. M. Avrami,
J. Chem. Phys., 7 1103 (1939)

102. M. Avrami,
ibid, 8 212 (1940)

103. M. Avrami,
ibid, 9 177 (1941)

104. J. B. Austin and R. L. Rickett,
Metals Technology TP No. 964 Vol. 5(6) 23 (1938)

105. W. Komatsu,
Nippon Kagaku Zasshi, 78 1452 (1957) (through Chem. Abstr., 52: 12526)

106. M. Okamura, M. Hanano and S. Awazu,
Chem. Pharm. Bull., 28 578 (1980)

107. E. G. Prout and F. C. Tompkins,
Trans. Faraday Soc., 40 488 (1944)

108. B. V. Erofeev and I. I. Smirnova,
Zhur. Fiz. Khim., 25 1098 (1951) (through Chem. Abstr., 46: 2889i)

109. P. I. Belkevich,
Sbornik Nauch Rabot. Akad. Nauk Beloruss SSR Inst. Khim., 5 21 (1956) (through Chem. Abstr., 52: 6906)

110. K. L. Mampel,
Z. Phys. Chem., A187 235 (1940)

111. M. Czentnerszwer and B. Bruzs,
ibid, 119 405 (1926) (through Chem. Abstr., 20: 3623)

112. B. Lewis and H. J. Schumacher,
Nature, 125 129 (1930)

113. D. Cismaru and M. Vass,
Rev. Chim. Acad. Rep. Populaire Roumaine, 6 125 (1961) (through Chem. Abstr., 56: 5435)

114. J. T. Carstensen,
J. Pharm. Sci., 63 1 (1974)

115. C. Eyraud,
Pure Appl. Chem., 9(3) 397 (1964) (through Chem. Abstr., 62: 13897c)

116. J. Zawadzki and S. Bretsznajder,
Bull. Intern. Acad. Polon. Sci., Classe Sci. Math. Nat., Ser. A (1940-6) 60 (1948) (through Chem. Abstr., 43: 7307)

117. B. Topley and J. Hume,
Proc. Roy. Soc. (London) A120 211 (1928)

118. G. F. Huttig,
Kolloid Z., 94 258 (1941) (through Chem. Abstr., 35: 5379)

119. M. E. Pozin and A. M. Ginstling,
J. App. Chem. USSR, 24 37 (1951)

120. A. M. Ginstling,
J. Appl. Chem. USSR, 25 795 (1952)

121. E. A. Prodan and M. M. Povlyuchenko,
Geterogennye Khim. Reaktsu Inst. Obshch i Neorgan Khim. Akad. Nauk Belorussk SSR (1965) pp. 20-63 (through Chem. Abstr., 64: 11924)

122. J. Zawadzki,
Festskr. J. Arvid Hedvall (1948) 611-634 (through Chem. Abstr., 42: 7648)

123. B. V. Erofeev,
Zhur. Fiz. Khim., 29 1136 (1955) (through Chem. Abstr., 51: 4108, 5520g, 7811c and 15230)

124. L. J. Leeson and A. M. Mattocks,
J. Amer. Pharm. Ass. Sci. Ed., 47 329 (1958)

125. L. Lackman,
J. Pharm. Sci., 54 1519 (1965)

126. E. Nelson, D. Eppich and J. T. Carstensen,
ibid, 63 755 (1974)

127. S. S. Kornblum and B. J. Sciarrone,
ibid, 53 935 (1964)

128. J. T. Carstensen and R. C. Kothari,
ibid, 70 1095 (1981)

129. J. T. Carstensen, M. Osadca and S. H. Rubin,
ibid, 58 549 (1969)

130. F. Y. Tripet and U. W. Kesselring,
Pharm. Acta Helv., 50 318 (1975)

131. T. Eble and E. R. Garrett,
J. Amer. Pharm. Ass. Sci. Ed., 43 536 (1954)

132. J. K. Guillory and T. Higuchi,
J. Pharm. Sci., 51 100 (1962)

133. D. Genton and U. W. Kesselring,
ibid, 66 676 (1977)

134. J. T. Carstensen,
J. Pharm. Sci., 53 839 (1964)

135. J. T. Carstensen and P. Pothisiri,
ibid, 64 37 (1975)

136. G. M. Enezian,
Rev. Prod. Probl. Pharm., 23 1 (1968) (through Chem. Abstr.,
69: 31888k)

137. F. W. Goodhart, M. E. Everhard and D. A. Dickcius,
J. Pharm. Sci., 53 338 (1964)

138. E. R. Garrett,
ibid, 43 539 (1954)

139. T. Aoyama, T. Maeda and M. Horioki,
Chem. Pharm. Bull., 25 3376 (1977)

140. R. P. Rastogi, P. S. Bassi and S. L. Chadha,
J. Phys. Chem., 66 2707 (1962)

141. R. P. Rastogi and N. B. Singh,
ibid, 70 3315 (1966)

142. J. Vaughan and L. Phillips,
J. Chem. Soc. (1947) 1560

143. S. Hirota, S. Osugi, T. Hayashi, S. Kaga and Y. Takeya,
CHem. Pharm. Bull., 16 1972 (1968)

144. D. T. Lacey, J. H. Bowen and K. S. Basden,
Ind. Eng. Chem. Fundamentals (I & E Fund) 4 275 (1965)

145. J. Hasegawa, M. Hanano and S. Awazu,
Chem. Pharm. Bull., 23 86 (1975)

146. E. G. Prout and F. C. Tompkins,
Trans. Faraday Soc., 43 148 (1947)

147. K. Kawakita,
Rev. Phys. Chem. Japan, 14 79 (1940) (through Chem. Abstr.,
35: 961(s))

148. G. L. Pratt and J. H. Purnell,
Proc. Roy. Soc., 260 317 (1961)

149. G. L. Pratt and J. H. Purnell,
Trans. Faraday Soc., 58 692 (1962)

150. J. T. Carstensen and M. N. Musa,
J. Pharm. Sci., 61 1112 (1972)

151. J. T. Carstensen and R. C. Kothari,
ibid, 69 123 (1980)

152. T. Canback,
Svensk Farm Tid., 47 621 (1943) (through Chem. Abstr., 38:
5644)

153. O. N. Yakindag and E. Onur,
Turk. Hij. Tecr. Biyol. Deg., 30(3) 239 (1970) (through Chem. Abstr., 75: 132967d)

154. C. A. Brownley and L. Lachman,
J. Pharm. Sci., 53 452 (1964)

155. S. K. Seth and H. C. Mital,
Indian J. Pharm., 27 119 (1965)

156. J. Bird and R. Shelton,
J. Amer. Pharm. Assoc. Sci. Ed., 39 500 (1950)

157. J. Campbell and H. McLeod,
ibid, 44 263 (1955)

158. A. L. Jacobs, A. E. Dilatush, S. Weinstein and J. J. Windheuser,
J. Pharm. Sci., 55 893 (1966)

159. R. N. Galante, A. J. Visalli and D. M. Patel,
ibid, 68 1494 (1979)

160. I. Grabowska and G. Towarzyst,
Nauk. Wydzial. Nauk. Mat. Przyrodniczych Rozprawy Wydzialu III No. I 193-206 (1964) (through Chem. Abstr., 64: 14029a)

161. K. Akira,
Kyushu Yakugakai Kaiho, 23 27 (1969)

162. I. Lippmann and A. M. Mattocks,
Sci. Sect. Amer. Pharm. Ass. Reprint of Papers - Las Vegas, Nevada (1962) (through Chem. Abstr., 60: 1544e)

163. K. T. Koshy, A. E. Troup, R. N. Duvall, R. C. Conwell and L. L. Shankle,
J. Pharm. Sci., 56 1117 (1967)

164. E. Shami, J. Dudzinski, L. Lachman and J. Tingstad,
ibid, 62 1283 (1973)

165. A. E. Troup and H. Mitchner,
ibid, 53 375 (1964)

166. M. R. Nazareth and C. L. Huyck,
ibid, 50 608 (1961)

167. J. E. Rees,
Pharm. J. (Sept. 21) (1974) pp. 226

168. H. Delonca,
J. Pharm. Belg., 24 317 (1969 (through Chem. Abstr., 72: 35755p)

169. H. Delonca, A. Puech, G. Segura and J. Youakim,
ibid, 24 243 (1969) (through Chem. Abstr., 71: 105171a)

170. M. W. Goudah and E. P. Guth,
J. Pharm. Sci., 54 298 (1965)

171. H. Okano, H. Kawata, S. Tsutsumi and Y. Umezaki,
Yakuzaigaku, 23 279 (1963) (through Chem. Abstr., 61: 537)

172. D. Ribeiro, D. Stevenson, J. Samyn, G. Milosovich and
A. M. Mattocks,
J. Amer. Pharm. Ass. Sci. Ed., 44 226 (1955)

173. F. Jaminet and G. Evrard,
Pharm. Acta Helv., 41 601 (1966)

174. F. Jaminet and G. Louis,
ibid, 43 153 (1968)

175. Y. G. Trakman,
Farmatsiya, 17(1) 18 (1965) (through Chem. Abstr., 68: 98609g)

176. W. Wisniewski and H. Piasecka,
Acta Pol. Pharm., 24(3) 291 (1967) (through Chem. Abstr.,
68: 62653c)

177. G. Gold and J. A. Campbell,
J. Pharm. Sci., 53 52 (1964)

178. S. Lee, H. G. DeKay and G. S. Banker,
ibid, 67 1631 (1978)

179. M. R. Nazareth and C. L. Huyck,
ibid, 50 620 (1961)

180. H. V. Moulding, M. A. Zoglio and E. J. Johnston,
ibid, 57 1873 (1968)

181. E. R. Garrett, E. L. Schumann and M. F. Grostic,
J. Amer. Pharm. Ass. Sci. Ed., 48 684 (1959)

182. P. H. List,
Dtsch. Apoth. Ztg., 117 451 (1977) (through Intern. Pharm.
Abstr., 15 (1978)

183. Y. Kata and M. Suguira,
Gifu Yakka Daigaku Kiyo, 6 59 (1956)

184. K. N. Wai, H. G. DeKay and G. S. Banker,
J. Pharm. Sci., 51 1076 (1962)

185. H. Leuenberger and W. Becher,
Pharm. Acta Helv., 50 88 (1975)

186. S. R. Byrn,
J. Pharm. Sci., 65 1 (1976)

187. K. Nilou, H. Lindholm and P. Terp,
J. Pharm. Pharmacol., 3 57 (1951) (abstracted from Arch.
Pharm. Chem., 57 332 (1950))

188. E. R. Oberhotzer and G. S. Brenner,
J. Pharm. Sci., 68 863 (1979)

189. E. R. Garrett,
in Advances in Pharmaceutical Sciences Vol. 2, Eds. H. S. Bean,
A. H. Beckett and J. E. Carless. Academic Press London
(1967) pp. 1

190. D. Ball, T. Lee, J. Ryder, H. Seager and D. Sharland,
J. Pharm. Pharmacol., 30 43P (1978)

191. A. Y. Gore and G. S. Banker,
J. Pharm. Sci., 68 197 (1979)

192. J. A. Bakan and F. D. Sloan,
Drug Cosmetic Ind., 110 34 March (1972)

193. H. Imaizumi, N. Nambu and T. Nagai,
Chem. Pharm. Bull., 28 2565 (1980)

194. J. A. Bakan and J. L. Anderson,
in The theory and practice of Industrial Pharmacy, Eds.
L. Lachman, H. A. Lieberman and J. L. Kanig, 2nd Ed.
Lea & Febiger, Philadelphia (1976) pp. 420

195. I. Utsumi, T. Ida, S. Takahashi and N. Sugimoto,
J. Pharm. Sci., 50 592 (1961)

196. I. Utsumi, T. Ida and T. Usuki,
J. Pharm. Soc. Japan, 78 115 (1958)

197. T. Ida,
ibid, 79 276 (1959)

198. A. H. Amann, R. E. Lindstrom and J. Swarbriek,
J. Pharm. Sci., 63 931 (1974)

199. S. Nikolov, L. Nedeleva and E. Velikova,
Farmatsiya (Sofia) 17(3) 60 (1967) (through Chem. Abstr.,
67: 111383e)

200. C. H. Bibart,
Drug Dev. Ind. Pharm., 5(4) 349 (1979)

201. N. Tanaka, K. Figimoto and I.Utsumi,
Yakugaku Zasshi, 86(4) 282 (1966) (through Chem. Abstr., 65:
2069).

202. M. A. Zoglio, H.V. Moulding, R. M. Haller and S. Briggen,
J. Pharm. Sci., 57 1877 (1968)

203. V. V. Bodyrev, I. V. Schmidt, V. I. Pis'menko, M. S. Shvartsberg, I. L. Kotlyarevskii, V. N. Andreivskii and V. F. Komarov, Kinetika i Kataliz, 6(4) 766 (1965) (through Chem. Abstr., 63: 14106)

204. R. P. Nikolaev, M. P. Zakharova, S. I. Korolkov and A. F. Romanova, USSR Patents: 104881 & 104991, March 25 (1957) (through Chem. Abstr., 51: 10846h & i)

205. N. V. Denkavit (Inventor J. A. H. Knop), Dutch Patent 85791, July 15 (1957) (through Chem. Abstr., 52: 13200h)

206. B. R. Vaidya, Dissert. Abstr., B26 6655 (1966)

207. B.K. Martin, in "Advances in Pharmaceutical Sciences" Vol. 3. Editors: H. B. Bean, A. H. Beckett and J. E. Carless, Academic Press, London (1971) pp. 107

208. The Martindale Extra Pharmacopoeia, 27th Edition, The Pharmaceutical Press, London (1977)

209. Monthly Index of Medical Specialities (MIMS), C. Duncan, Editor. November 1981 - Medical Publication Ltd. Heymarket Publishing, Teddington (1981)

210. D. E. Wurster and P. W. Taylor, J. Pharm. Sci., 54 169 (1965)

211. A. A. Noyes and W. R. Whitney, J. Amer. Chem. Soc., 19 930 (1897)

212. A. W. Hixson and J. H. Crowell, Ind. Eng. Chem., 23 923 (1931)

213. N. Kaneniwa and N. Watari, Chem. Pharm. Bull., 25 867 (1977)

214. J. G. Wagner,
in Biopharmaceutics and Relevant Pharmacokinetics,
1st Ed. Drug Intell. Publ. Hamilton, Illinois (1971) pp. 110

215. J. W. Poole and C. K. Bahal,
J. Pharm. Sci., 59 1265 (1970)

216. C. J. deBlaey and H. van der Graaft,
ibid, 66 1696 (1977)

217. S. S. Kornblum and J. O. Hirschorn,
ibid, 59 606 (1970)

218. L. J. Edwards,
Trans. Faraday Soc., 47 1191 (1951)

219. W. E. Hamlin, J. I. Northam and J. G. Wagner,
J. Pharm. Sci., 54 1651 (1965)

220. Song-Ling Lin, J. Menig and L. Lachman,
ibid, 57 2143 (1968)

221. P. H. Elworthy and F. J. Lipscomb,
J. Pharm. Pharmacol., 20 923 (1968)

222. K. Ho Kim and C. Jorowski,
J. Pharm. Sci., 66 1536 (1977)

223. J. E. Sutton, J. L. Lach and R. S. Wagner,
Amer. J. Hosp. Pharm., 34 1323 (1977)

224. G. Levy and B. A. Hayes,
New Engl. J. Med., 262 1053 (1960)

225. E. Shotton and G. S. Leonard,
J. Pharm. Pharmacol., 24 798 (1972)

226. L. C. Schroeler, J. E. Tingstad, E. L. Knoechel and J. G. Wagner,
J. Pharm. Sic., 51 865 (1962)

227. G. Levy,
ibid, 50 388 (1961)

228. B. F. Cooper and E. A. Brecht,
J. Amer. Pharm. Ass. Sci. Ed., 46 520 (1957)

229. S. Kitazawa, I. Johno, Y. Ito, S. Teramura and J. Okada,
J. Pharm. Pharmacol., 27 765 (1975)

230. S. Solvang and P. Finholt,
J. Pharm. Sci., 59 49 (1970)

231. W. Feinstein and A. J. Bartilucci,
ibid, 55 332 (1966)

232. Y. K. C. Yen,
Canadian Pharm. J. (Nov. 1964) 15

233. Song-Ling Lin, J. Menig and C. J. Swartz,
J. Pharm. Sci., 59 989 (1970)

234. J. E. Tingstad and S. Riegelman,
ibid, 59 692 (1970)

235. P. J. Niebergall and J. E. Goyan,
ibid, 52 29 (1963)

236. R. A. Castello, G. Gellinek, J. M. Konieczny, K. C. Kwan and R. O. Toberman,
ibid, 57 485 (1968)

237. S. Kitazawa, I. Johno, T. Minouchi, Y. Ito and J. Okada,
J. Pharm. Pharmacol., 29 585 (1977)

238. F. Langenbucher and H. Rettig,
Drug Dev. Ind. Pharm., 3(3) 241 (1977)

239. T. E. Needham, K. Shah, J. Kotzan and H. Zia,
J. Pharm. Sci., 67 1070 (1978)

240. L. C. Schroeter and J. G. Wagner,
ibid, 51 957 (1962)

241. H. Weintraub and M. Gibaldi,
ibid, 59 1792 (1970)

242. A. C. Cartwright,
J. Pharm. Pharmacol., 31 434 (1979)

243. J. T. Carstensen, T. Lai and V. K. Prasad,
J. Pharm. Sci., 66 607 (1977)

244. J. E. Rees, T. A. Yearsley and K. A. M. Kuria,
British Pharm. Conference, Coventry (1978)

245. C. R. Willis Jr. and G. S. Banker,
J. Pharm. Sci., 57 1598 (1968)

246. S. J. Desai, A. P. Simonelli and W. I. Higuchi,
ibid, 54 1459 (1965)

247. J. Lazarus, M. Pagliery and L. Lachman,
ibid, 53 798 (1964)

248. T. J. Roseman and W. I. Higuchi,
ibid, 59 353 (1970)

249. H. E. Huber, L. B. Dale and G. L. Christenson,
ibid, 55 974 (1966)

250. T. Higuchi,
ibid, 52 1145 (1963)

251. A. Dakkuri, H. G. Schroeder and P. P. DeLuca,
ibid, 67 354 (1978)

252. M. Friedman, M. Donbrow and Y. Samuelov,
Drug Dev. Ind. Pharm., 5(4) 407 (1979)

253. K. Lehman and D. Dreher,
Pharm. Techn. Intern., April (1979) pp. 33.

254. J. H. Wood and J. Syarto,
J. Pharm. Sci., 53 877 (1964)

255. V. Coletta and H. Rubin,
ibid, 53 953 (1964)

256. M. Friedman and M. Donbrow,
Drug Dev. Ind. Pharm., 4(4) 319 (1978)

257. R. E. Singiser and W. Lowenthal, [illegible]
J. Pharm. Sci., 50 168 (1961)

258. M. J. Robinson, G. M. Grass and R. J. Lantz,
ibid, 57 1983 (1968)

259. A. S. Ridolfo, C. M. Gruber Jr. and R. C. Carmichael,
J. Amer. Pharm. Ass. Sci. Ed., 47 869 (1958)

260. A. Kondo,
in Microcapsule Processing and Technology, Ed. J. Wade van Valkenburg
Marcel Dekker, Basel (1979) pp. 2

261. J. A. Herbig,
in Encyclopedia of Chemical Technology, 2nd Ed. Vol. 13.
Interscience London, pp. 436

262. L. A. Luzzi,
J. Pharm. Sci., 59 1367 (1970)

263. G. S. Banker,
ibid, 55 81 (1966)

264. N. Tanaka, S. Takino and I. Utsumi,
ibid, 52 664 (1963)

265. M. A. El. Egarkey, F. El-Khawas, A. G. Iskandar and M. M. A. Khalek,
Pharmazie, 29(7) 466 (1974)

266. P. L. Madan,
Pharm. Tech. (December 1977) pp. 29

267. H. G. Bungenberg de Jong
in Colloid Science, Ed. H. R. Kruyt, Vol. 2, Elsevier,
New York (1949) pp. 232

268. P. L. Madan,
Pharm. Tech. (Feb. 1978) pp. 31

269. R. E. Phares Jr. and G. J. Sperandio,
J. Pharm. Sci., 53 515 (1964)

270. P. L. Madan, L. A. Luzzi and J. C. Price,
ibid, 61 1586 (1972)

271. L. C. Lappas and W. McKeehan,
ibid, 56 1257 (1967)

272. R. J. Nessel, H. G. DeKay and G. S. Banker,
ibid, 53 882 (1964)

273. H. P. Merkle and P. Speiser,
ibid, 62 1444 (1973)

274. R. G. Wiegand and J. D. Taylor,
Drug Std., 27 165 (1959)

275. S. Borodkin and F. E. Tucker,
J. Pharm. Sci., 63 1359 (1974)

276. C. F. Lerk, M. Lagas, L. Lie; A. Huen, P. Broersma and
K. Zuurman,
ibid, 68 634 (1979)

277. K. Yamamoto, M. Nakano, T. Arita, Y. Takoyama and Y. Nakai,
ibid, 65 1486 (1976)

278. C. F. Lerk, M. Lagas, J. T. Fell and P. Nauta,
ibid, 67 935 (1978)

279. P. Finholt,
in The influence of formulation on dissolution rate in
"Dissolution Technology", Eds. L. J. Leeson and J. T. Carstensen,
Acad. Pharm. Ass. Washington (1974) pp. 106

280. J. E. Rees,
Boll. Chim. Farm., 116 125 (1977)

281. E. J. Middleton, J. M. Davies and A. B. Morrison,
J. Pharm. Sci., 53 1378 (1964)

282. J. Fincher,
ibid, 57 1825 (1968)

283. G. Levy,
J. Pharm. Sci., 52 1039 (1963)

284. K. A. Lees,
Pharm. J. (1963) pp. 289

285. J. G. Dare,
Australian J. Pharm., 45 S58 (1964)

286. J. T. Carstensen and M. N. Musa,
J. Pharm. Sci., 61 223 (1973)

287. F. Carli and L. Simioni,
Pharm. Acta Helv., 53 320 (1978)

288. O. Cruaud, D. Duchene, F. Puisieux and J. T. Carstensen,
J. Pharm. Sci., 69 607 (1980)

289. J. A. Hedvall,
Ber. Scandinaviske Natur-fur-skermode Copenhagen (1929)
pp. 314-324 (through Chem. Abstr., 24: 2673 (1930)

290. F. S. Stone,
in "Reactivity of Solids", Ed. J. H. DeBoer et al., Elsevier,
London (1961) pp. 7

291. H. Takenaka, Y. Kawashima and S. Y. Lin,
J. Pharm. Sci., 69 513 (1980)

292. I. C. Edmundson,
in "Advances in Pharmaceutical Sciences", Vol. 2, Eds.
H. B. Bean, A. H. Beckett and J. E. Carless, Academic Press,
London (1967) pp. 95

293. A. N. Martin, J. Swarbrick and A. Cammarata,
in "Physical Pharmacy", 2nd Ed., Lea & Febiger, Philadelphia
(1969) pp. 467

294. P. Wulff and A. Heigl,
Z. Phys. Chem., A153 187 (1931) (through Chem. Abstr., 25:
2890

295. The International Tables for X-ray Crystallography Vol. III, The Keynoch Press, Birmingham (1968) pp. 17

296. J. T. Carstensen, in "Pharmaceutics of Solid and Solid Dosage Forms", Wiley Interscience Publ., London (1977) pp. 11, 182 & 194

297. S. S. Kornblum and M. A. Zoglio, J. Pharm. Sci., 56 1569 (1967)

298. H. V. Moulding, M. A. Zoglio, F. E. Pigois and M. Wagner, ibid, 58 1359 (1969)

299. E. R. Garrett, J. Amer. Pharm. Ass. Sci. Ed., 46 584 (1957)

300. Riker 3M Laboratories - Product Data Sheet (Salsalate), March (1979)

301. Dictionary of Organic Compounds, Vol. 5, Eyre and Spo Hiswoode Publishing Ltd. (1965)

302. The Merck Index, 9th Edition M.S.D. Ltd. (1976)

303. Chemical Abstracts, Eighth Collective Index, Vol. 66-75 (1967-71)

304. L. A. Stevens, Ph.D. Thesis, Bath University (1977)

305. "Solubilities of inorganic and organic compounds", Editors: H. Stephen and T. Stephen, Vol. 2, pt. 1, Macmillan, New York (1964) Table 870 pp. 275.

306. Handbook of Chemistry and Physics, Eds: R. C. Weast and M. J. Astle, Vol. 61, CRC Press Inc., Boca Raton, Florida (1980-1981)

307. British Pharmacopoeia (1973) The Pharmaceutical Press (London)

308. United States Pharmacopoeia, 20th Edition (1980) United States Pharmacopoeial Convention

309. British Pharmacopoeia (1980) The Pharmaceutical Press (London)

310. P. J. Elving, J. M. Markowitz and I. Rosenthal,
Anal. Chem., 28(7) 1179 (1956)

311. C. E. H. Bawn,
in "Chemistry of the Solid State", Ed. W. E. Garner,
Butterworths, London (1955) pp. 254

312. J. K. Baker, R. E. Skeleton and C. Y. Ma,
J. Chromatogr., 168 417 (1979)

313. A. Y. Gore, K. B. Naik, D. O. Kildsig, G. E. Peck, V. F. Smolen
and G. S. Banker,
J. Pharm. Sci., 57 1850 (1968)

314. H. Jacobson and G. Reier,
ibid, 58 631 (1969)

315. J. T. Carstensen, J. B. Johnson, D. C. Spera and M. J. Frank,
ibid, 57 23 (1968)

316. T. Higuchi and A. Aguiar,
J. Amer. Pharm. Ass. Sci. Ed., 48 574 (1959)

317. M. P. Short and C. T. Rhodes,
J. Pharm. Pharmacol., 23 239S (1971)

318. K. Lehman,
Acta Pharm. Techn., 21(4) 255 (1975)

319. D. Attwood and O. K. Udeala,
J. Pharm. Pharmacol., 26 854 (1974)

320. D. Attwood, A. T. Florence and J. M. N. Gillan,
J. Pharm. Sci., 63 988 (1974)

321. J. A. Rees and J. H. Collett,
J. Pharm. Pharmacol., 24 154P (1972)

322. R. Yamamoto and Tamoo Takahashi,
J. Pharm. Soc. Japan (Abstracts in English) 76 7 (1956)

323. R. Yamamoto, T. Takahashi and M. Harada,
ibid, 76 853 (1956)

324. R. Yamamoto, T. Takahashi and K. Inazu,
ibid, 77 82 (1957)

325. R. Yamamoto and T. Takahashi,
ibid, 79 415 (1959)

326. R. Yamamoto and T. Takahashi,
ibid, 79 419 (1959)

327. S. C. Penzotti and A. M. Mattocks,
J. Pharm. Sci., 57 1192 (1968)

328. G. Zografi,
"Interfacial Phenomena" in Remington's Pharmaceutical Sciences,
16th Edition, A. Osol Editor. Mack Publishing Co., Easton,
Pennsylvania (1980) pp. 264

329. D. J. Shaw,
in "Introduction to Colloid and Surface Chemistry",
Butterworths, London (1980) pp. 127

330. J. T. Carstensen, P. Toure, L. Van Campen and G. Zografi,
J. Pharm. Sci., 69 742 (1980)

331. M. El-Sabaawi and D. C. T. Pei,
Ind. Eng. Chem. Fund., 16 321 (1977)

332. F. D. Chattaway,
J. Chem. Soc., 134 2495 (1931)

333. G. Tamman,
Z. Anorg. Allgem. Chem., 149 21 (1925) (through Chem. Abstr.,
20: 324 & 3373)

334. A. I. Vogel,
in "Textbook of Practical Organic Chemistry", 3rd Ed.
Longman's London (1956) pp. 21

335. G. Parravano,

Chem. Eng. News (C & EN) 40(12) pp. 111 (March 1972)

336. E. Hoffmann and S. Patai,

J. Chem. Soc. (1955) 1797-1802