CONTROLLED RELEASE OF DRUGS FROM POLYMER FILMS

JOSEPH ROBERT MHANDO

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SUMMARY

Controlled release of drugs from pharmaceutical formulations is an attractive concept. Most controlled release preparations are formulated in polymer bases in a manner which aims to produce specific rates of drug release. In this thesis, the formulation of controlled-release systems consisting of local anaesthetics in gelatin bases is investigated with a view to elucidating the physico-chemical factors which influence the release of drugs from such formulations.

Studies on the release of lignocaine from homogeneous films show that it depended on the dissolution rate of the matrix. The importance of temperature on the mechanism of release of lignocaine from homogeneous gelatin films is shown.

The extent to which emulsion systems is modelled by equations describing release from homogeneous films has been found to depend on the drug oil-water partition coefficient. The release of drugs with low partition coefficient from emulsion systems can be satisfactorily simulated by the homogeneous film equations. The use of diffusion equations describing release from suspension systems have also been evaluated for emulsion systems.

Predictions of release profiles from emulsion systems using equations developed for estimating the dielectric permeability of heterogeneous media were attempted. No single equation provided entirely reliable prediction for release of lignocaine from a range of alcohol-in-gel emulsions.

Zero order delivery of benzocaine was obtained from formaldehyde-hardened emulsion-type gels. With high formaldehyde levels in the films, a two-phase release profile was observed. The early phase was attributed to fast diffusive release of complexed benzocaine while the late phase was attributed to slower release of matrix-bound benzocaine.

KEY WORDS

Controlled-release
Formulation
Gelatin films
Emulsion films
Local anaesthetics

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CHAPTER 1

INTRODUCTION

1.1 THE CONCEPT OF CONTROLLED DRUG DELIVERY

The two main shortfalls of conventional drug administration are poor patient compliance and fluctuation in drug blood levels during the dosing interval. Both lead to potentially serious impairment of drug performance. Sustained-release delivery systems represent the first attempts to minimise these problems. Methods of achieving sustained release include macro-, micro and nano encapsulation, complexation, the synthesis of poorly soluble salts and the formulation of porous tablets containing dispersed drugs (1-4). Most of these preparations are for oral administration. Injectable sustained release formulations are mainly of the oil depot type (5, 6) or emulsion type (7-9) although implants are now being actively investigated.

Sustained release oral formulations are restricted by gastro-intestinal transit times. It is therefore generally not possible to obtain oral sustained delivery for more than 12 hours. The use of depot injections needs to be approached with caution since administration is irreversible; a serious problem in case of patient reaction. Finally, the mechanisms of sustained-release mostly depend on the nature of the surrounding environment. Thus, for oral preparations for example, differences in diet would elicit differences in release rates. These shortfalls restrict the

usefulness of sustained-release dosage forms.

Controlled release delivery differs from sustained release delivery by virtue of the fact that the release rate is controlled. Sustained release can of course also be obtained. For controlled release, changes in the surrounding medium should, within reasonable limits, not affect the release rate. Most controlled release delivery systems are polymer-based, release of the drug being dependent on its diffusion from the device or on the degradation of the matrix. More recently, osmotic control has been applied to the delivery of drugs from dosage forms.

1.2 POLYMERS USED IN CONTROLLED RELEASE DEVICES

Choosing a polymer for controlled release devices depends on two important criteria. First, the polymer must be usable *in vivo*. Many polymers elicit immunogenic responses when implanted. According to Bruck and Ratner (10) an ideal biocompatible polymer should not cause thrombosis; destruction of cellular elements; alteration of plasma proteins; destruction of enzymes; depletion of electrolytes; adverse immune responses; damage to adjacent tissue; cancer and/or toxic or allergic reactions. Since no single implantable material can satisfy all of the above criteria completely, the use of polymers generally depends on the overall reaction of the animal to the implant. Specific tests for specific criteria are

available (10) to provide ways of determining the cause of a particular kind of reaction.

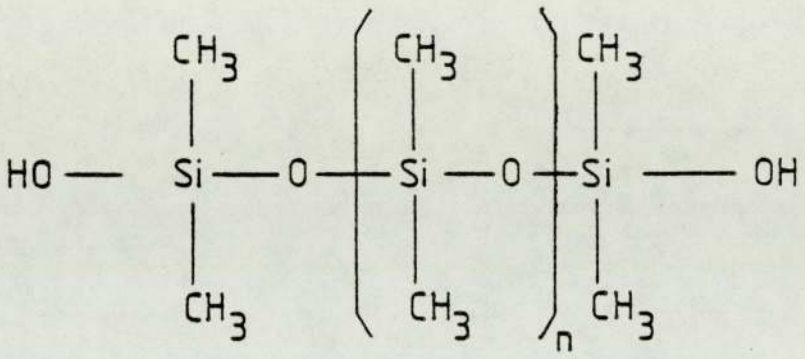
Secondly, the rate of release of the drug from the device should satisfy therapeutic requirements. This is usually established by in-vitro release studies subsequently validated by in-vivo work. The extensive research made into devising surgically useful polymers has led to a large number of biocompatible polymers. The limiting factor in the design of controlled-release devices is therefore mainly the release rate and behaviour of medicaments from such biocompatible polymers.

The following classification is developed for polymers used in controlled-release formulation, based broadly on the release behaviour obtained from them.

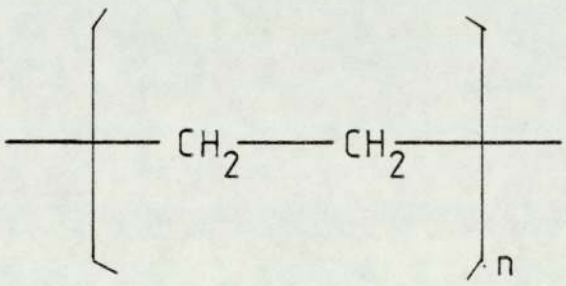
a) Non-degradable polymers
   (i) hydrophobic
   (ii) hydrophilic
b) Biodegradable polymers.

1.2.1 Hydrophobic, Non-degradable Polymers

This class includes the widely studied Silicone and polyethylene polymers. The basic structures of polyethylene and polydimethylsiloxane are given in Fig. 1.1. The most popular polydimethylsiloxane polymer in drug delivery systems design is SILASTIC '382' MEDICAL GRADE ELASTOMER (Dow Corning). Being initially in a



(a) Poly(di methylsiloxane) - as in Silastic '382' medical elastomer.



(b) Polyethylene.

Fig.1.1 The structures of some hydrophobic polymers.

viscous liquid state, formulation with Silastic '382' is very easily performed by levigation or trituration. On addition of appropriate amounts of crosslinker (Stannous octoate) devices with good mechanical properties are obtained, their shape and size depending on the molds used. The rate of hardening of the polymer can easily be controlled by varying the amount of crosslinker used. Silastic '382' is hydrophobic, biocompatible and non-degradable. It has therefore been studied for delivery of oil soluble medicaments such as steroids (11-19), prostaglandins (20-24) and p-aminobenzoate esters (25,26).

The release of medicaments incorporated in hydrophobic polymers depends on both partitioning and diffusion (27, 28). Generally, hydrophobic polymers are more permeable to hydrophobic drugs but in case of release of hydrophobic drugs from hydrophobic matrices into an aqueous receiver phase, the high oil/water partition coefficient of the drug slows down the release to the extent that diffusion across the hydrodynamic diffusion layer becomes rate controlling rather than diffusion from the polymer (17, 27). Release of hydrophilic substances from hydrophobic matrices is slower due to their low solubility in the matrix. Choice of hydrophilic or hydrophobic polymeric matrices therefore depends on the individual drug and whether slower or faster release rates are required.

The rate of diffusion of medicaments from both

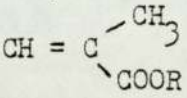
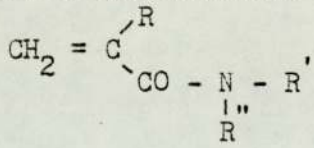
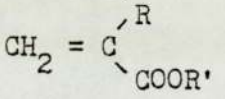
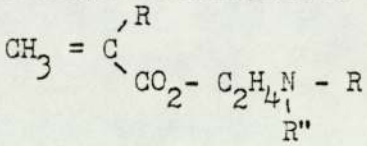
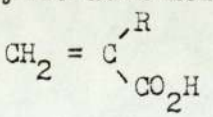
hydrophobic and hydrophilic polymers can be varied by varying the concentration of crosslinker (29, 30). Other studies have shown that release of hydrophilic drugs from silicone polymers can be enhanced by incorporation of hydrophilic carriers (31).

1.2.2 Hydrophilic, Non-degradable Polymers

Hydrophilic polymers are usually referred to as hydrogels because they imbibe appreciable amounts of water and swell considerably. Their good biocompatibility profiles have been associated with their high water contents (32). Protein adsorption and their subsequent unfolding seems to play an important role in immunogenic responses with regard to implants (33). The hydrophilic polymers do not lead to significant protein adsorption probably as a result of the low interfacial tension between polymer surface and body fluids. Most synthetic hydrogels are derivatives of acrylic acid. Ratner and Hoffman (34) have classified hydrogels according to their chemical properties (Table 1.1). Poly(-hydroxy-ethylmethacrylate) (poly HEMA) (Fig. 1.2), the contact lens material, has been widely studied for formulation of controlled release devices. Hydrogels have been studied with respect to the formulation of steroids (29, 35-37); prostaglandins (39); enzymes and proteins (39); antibiotics (40); pilocarpine (41) and narcotic antagonists (42).

TABLE 1.1

Classification of Acrylic Hydrogels.

Class	Basic Structure
Neutral	1. Hydroxyalkyl methacrylates  R= hydroxyalkyl group. 2. Acrylamide derivatives.  R",R'= H; $-CH_3$; $-C_2H_5$; $-CH_2CHOHCH_3$ R = H; $-CH_3$ 3. Hydrophobic acrylics (used as co-monomers).  R = H; $-CH_3$ R' = $-CH_3$; $-C_4H_9$; $-OCH_3$; $-CN$
Basic or Cationic	Aminoethyl methacrylates  R,R',R" = H; $-CH_3$; $-C_4H_9$
Acidic or Anionic	Acrylic acid derivatives  R = H or alkyl group.

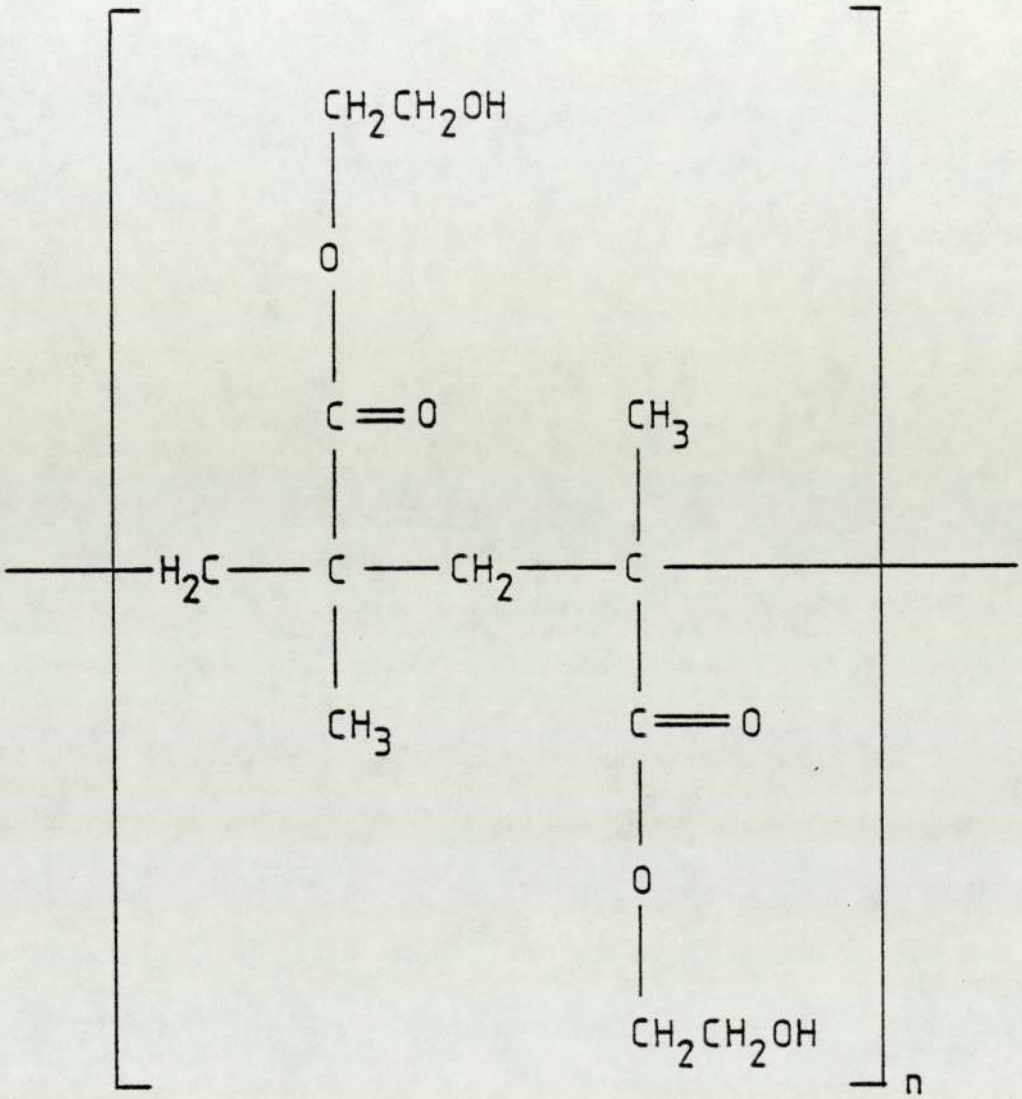


Fig 1.2 Poly(hydroxyethylmethacrylate) [poly(HEMA)]

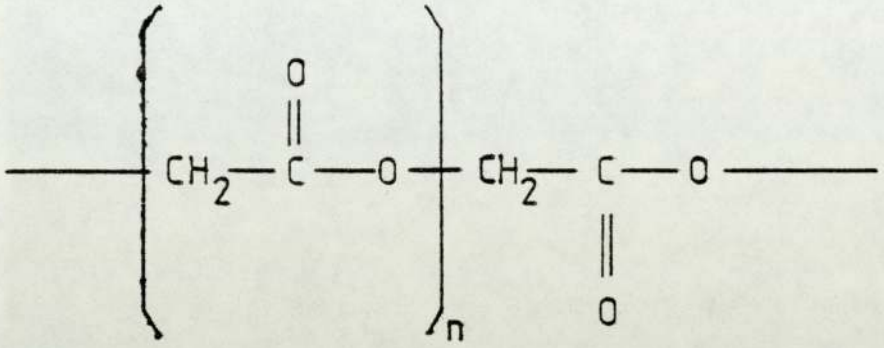
In using hydrogels, partition coefficients of the drugs between the polymer and the surrounding aqueous environment is not important since both phases are highly hydrophilic. Therefore crosslinkage density plays a very important role in control of rate of release of the drugs. The crosslinkage density can be varied depending on the amount of crosslinker used (29, 30). The most common crosslinker in acrylic polymers is ethyleneglycol dimethacrylate (EGDMA). It has also been observed that the water content in the polymer influences the rate of diffusion of substances (30).

Hydrogels are more permeable to hydrophilic drugs. For sparingly soluble drugs, their solubilities play a significant role in their release rates as will be discussed later in section 4.1

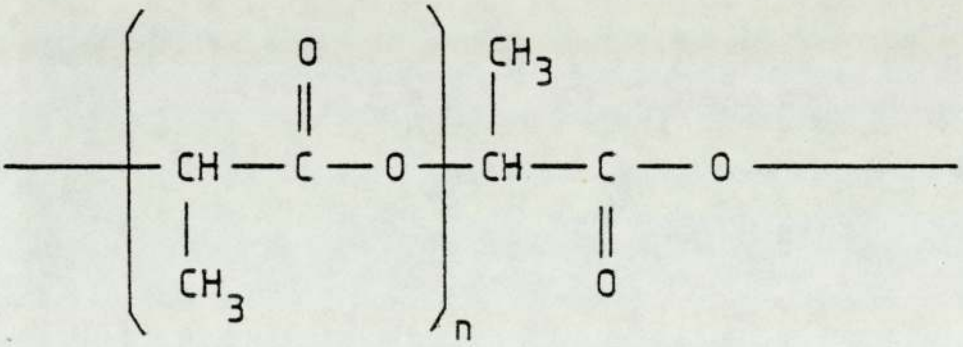
1.2.3 Biodegradable Polymers

Biodegradable polymers used in pharmaceutical formulations have been reviewed by several authors (43-46). The most commonly used biodegradable polymers are

a) Polyesters such as those of poly(lactic acid) and poly(glycolic acid). The structures of these polymers are given in Fig. 1.3. Yolles and his group have made extensive studies on the formulation of steroids (47) and narcotic antagonists (48-50) in Poly(lactic acid).



Poly(glycolic acid)



Poly(lactic acid)

Fig 1.3 Examples of biodegradable polymers (polyesters)

The use of copolymers of lactic acid and glycolic acid has also been studied (51, 52). Results show that variation of the lactate composition between 75% and 100% by weight provided degradation half-lives which increased from 2 weeks to 6 months (51). Mechanisms of release of steroids from polymers of ϵ-caprolactone, lactic acid and glycolic acid and their copolymers have also been studied (53, 54). Both diffusion and matrix degradation-controlled release mechanisms were observed. Similar observations were made on the release of local anaesthetics from poly(lactic acid) microspheres (55).

b) Poly(amino acids) such as poly(glutamic acid) (Fig. 1.4) have also been studied as potential biodegradable drug carriers for drugs such as cyclophosphomide (56) and p-phenylene mustard (57). The use of poly (hydroxyalkyl-L-glutamines) for drug delivery systems has also been studied (58).

c) The surgical adhesives, poly(alkyl-2-cyanoacrylates) have been studied for application as controlled-release delivery bases (59-61). Their general structure is shown in Fig. 1.5.

The mechanisms of degradation of these polymers depend on their chemistry (43, 62). For example, polymers

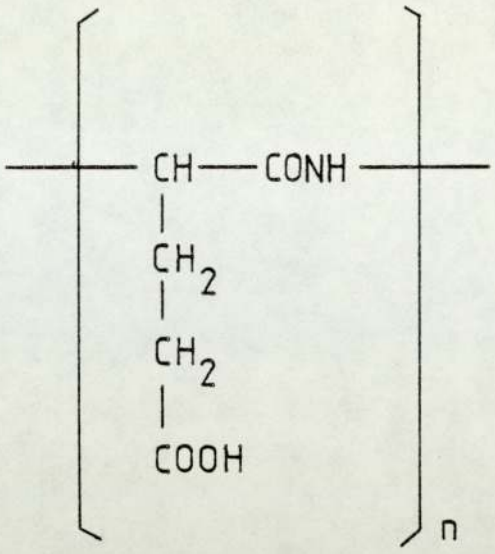


Fig.1.4 The structure of poly(glutamic acid)

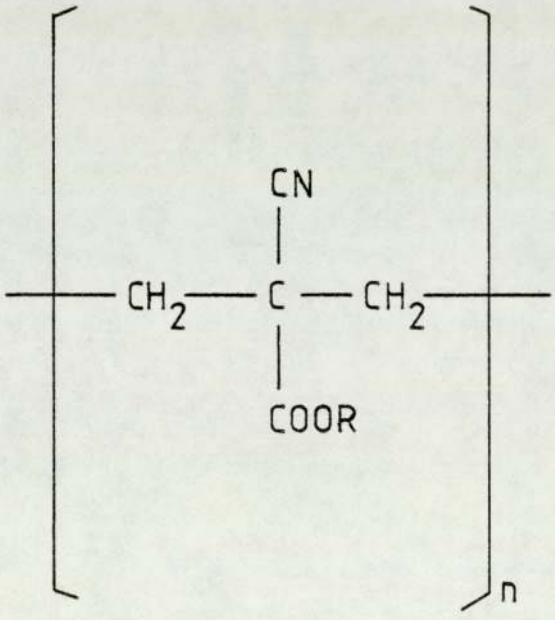
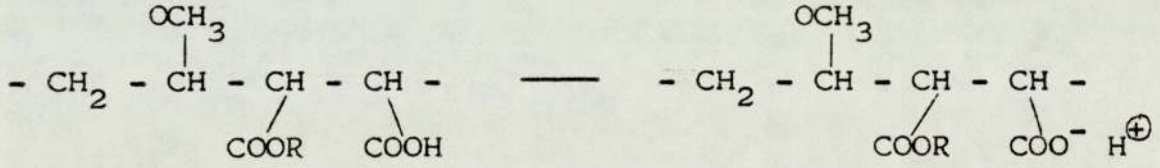


Fig.1.5 The general structure of poly(alkyl-2-cyanoacrylates).

of acrylamide and N-vinylpyrrolidone crosslinked with N, N'-methylenebisacrylamide have been shown (63, 64) to degrade through the hydrolysis of the crosslink. The products in such cases are still high molecular weight polymers since the polymer backbone is left intact. Another mechanism involves the solubilization of initially hydrophobic polymers by hydrolysis, ionization or protonation of pendant groups (65). For example, in the case of partially esterified copolymers of methyl-vinyl ether and maleic anhydride, dissolution of the polymer proceeds after ionization of the carboxyl group in the following reactions (66).



Such reactions are usually pH dependent (67).

Hydrolytic backbone cleavage of hydrophilic polymers such as poly(lactic acid) (46) produces small, water-soluble molecules. The so-called homogeneous backbone degradation occurs simultaneously throughout the polymer matrix, whereas heterogeneous degradation involves cleavage of bonds at the surface of the polymer as has been observed with poly(alkyl-2-cyanoacrylates) (61). Heterogeneous degradation therefore depends on the surface area of the device. Other mechanisms of backbone cleavage have been reviewed by Pitt et al (43).

1.2.4 Gelatin

Gelatin is a natural hydrogel. It is derived from skin (soft-tissue) and bone or dentine (hard-tissue) collagen by acid, neutral salts or alkali extraction (68, 69). Due to differences in methods of extraction, the isoelectric point of gelatin varies from acidic (4.8-5.2) in the case of alkali extraction, to basic (around 9.0) for acid extraction (70, 71). The chemical composition of gelatin also varies depending on the source of the original collagen. For example, hard-tissue collagen contains appreciable amounts of covalently bound phosphate (72-74).

Generally, proteins have three structural levels (75). The primary protein structure describes the arrangement of the amino acids on the macromolecular strand. The secondary structure of a protein is the coiling of the primary strand into an α-helix. Finally, the tertiary structures describes the recoiling and intertwining of secondary strands into a "super-helix". It has been observed (76) that gelatin is composed of protein, mainly in the secondary state. It has also been observed that the triple-helix tertiary structure (the collagen fold) can be regained by gelatin and soluble collagens to reform collagen rods (68, 76, 77). The whole gelation phenomenon can therefore be explained in terms of denaturation and renaturation behaviour.

The transition from collagen to gelatin is accompanied by changes in solubility, crystallinity and

molecular weight. Whereas collagen can be considered, in a very general sense, to be insoluble, gelatin is soluble in hot water and acetic acid. This solubility is probably due to decrease in molecular weight, as a consequence of loss of the tertiary structure, as well as breakage of primary chains (78). The increase in polar groups on hydrolysis promotes solubility of gelatin.

The change in molecular weight of gelatin has been associated with variation in the physical properties of gels (74). Molecular weight of polymeric systems is usually expressed in terms of weight average molecular weight ($\bar{M}_w$.), as determined by methods such as refractometry, or as number average molecular weight ($\bar{M}_n$), as determined by methods like osmometry (44). The ratio of the two ($\bar{M}_w/\bar{M}_n$) is usually used to indicate the molecular weight distribution; a unity value implying no variation in molecular weight at all. A high molecular weight distribution would have a ratio greater than 1. Differences in molecular weight distribution between different samples of gelatin is the source of variation of physical properties of different gelatins from the same source, as a consequence of differences in extent and manner of denaturation of collagen (78). It is therefore common practice in gelatin studies to isolate different fractions so as to maintain consistency. One approach to fractionation is based on narrowing down the molecular weight distribution in terms of size of the

molecules. Methods like ultracentrifugation are based on this principle. Ultracentrifugation of soluble collagen and gelatin produces three bands named α, β and γ components (69, 80, 81). The γ fraction, which sediments faster than the others, was shown to be composed of triple-stranded components similar to those of collagen (69, 81). Similarly, the β- fraction was observed to comprise of double-stranded components, while the α component is composed of single polymer strands (69, 81). The other approach to fractionation is based on differences in charge distribution on the polymer strands. This is exemplified by the alcohol coacervation method (82).

The official (83) method of standardizing gelatin samples involves the determination of the rigidity of gels in terms of bloom (jelly) strength. The bloom strength of a gelatin sample is the weight in grams required to move a plastic plunger, 0.5 inches in diameter, 4 mm. into a $6^2/_3$ % gelatin gel that has been held at 10°C for 17 hours (84). It is a measure of the cohesive strength of the cross-linking which occurs between gelatin molecules and is proportional to the molecular weight of the gelatin (84).

The most prominent property of gelatin is its ability to form gels. This gelation behaviour has been shown to be, in part, a tendency of reversion towards the natural collagen triple-helix configuration.

During gelation, the strands have been shown to form fringed micelles (85, 86) i.e. a matrix consisting of sections of well ordered arrays of strands, interspersed by areas of disorganized, random strands (87). This setting model emphasizes the role of crystallinity in the physics of the gel. Since the rate of formation of crystals depends on the rate of cooling from molten state, the temperature of setting and the nature of solid surfaces in contact with the gel during setting, it is important during studies involving gelation to maintain constant conditions.

The kinetics of gelation of aqueous gels have demonstrated a behaviour typical of a fast primary nucleation process followed by a slower 3-dimensional fibrillar rod growth from the primary nuclei, and a final process corresponding to secondary crystallization (88-94). The melting behaviour of gels therefore reflects this setting behaviour. The melting point of gelatin gels is a function of ageing, conditions of ageing, bloom strength and gelatin concentration (95), all of which are factors which affect gel rigidity.

1.3 RELEASE OF DRUGS FROM POLYMER MATRICES

1.3.1 Diffusion-controlled Release from Polymers

(a) Kinetics of release

The potential use of release of substances from a polymer in which it was initially absorbed, for drug

delivery, was first realised by Folkman and Long (96). Extensive efforts then followed to develop both sustained and controlled-release formulations based on the diffusion behaviour of drugs in polymers.

Desorption of drugs from polymeric matrices usually obeys Fick's laws of diffusion, the solutions for which are available in standard texts (97-99). Basically, Fick's laws relate the rate of sorption/desorption to the concentration gradient of the drug in the matrix and other parameters such as thickness and geometry. Fick's law for steady-state, unidirectional diffusion in isotropic media is given by equation

$$F = -D \frac{dc}{dx} \quad \ldots\ldots 1.1$$

where F is the diffusion flux, $\frac{dc}{dx}$ is the concentration gradient and D is a constant called the "diffusion coefficient". The diffusion coefficient usually varies with concentration due to non-ideality of the system but in dilute systems, it can be reasonably taken as constant. D has the dimensions of $(\text{length})^2.(\text{time})^{-1}$, most commonly $cm^2.sec^{-1}$. The negative sign in eq. 1.1 arises because diffusion proceeds in the direction opposite to that of increasing concentration.

Fick's second law for unidirectional non-steady diffusion in isotropic media is written as

$$\frac{dc}{dt} = \left(D \frac{d^2c}{dx^2}\right) \quad \ldots\ldots 1.2$$

The solution of this equation within limits imposed by the system under study provides expressions

useful for kinetic quantification of the diffusion process. For example, in case of two sided desorption from a slab into a perfect sink, the boundary conditions are

$$C = Co\ , \qquad 0 < x < 1 \qquad t = 0$$

$$C = 0\ , \qquad x = 0,\ x = 1 \qquad t > 0$$

i.e. there is uniform initial distribution of the drug in the polymer and that the concentration of the drug at the layer next to the edge of the polymer is zero at all times.

The solution of equation 1.2 for a slab under above boundary conditions can be obtained by two methods. The method of separation of variables (97) provides a solution useful for long times and is given as

$$Q_t = \frac{8lCo}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp\left(\frac{-D(2N+1)^2\pi^2 t}{l^2}\right) \quad \ldots\ldots 1.3$$

where Q_t is the amount of drug released per unit area from the matrix at time t, Co is the initial drug concentration in the polymer and l is the thickness of the matrix. When t is large, equation 1.3 can be simplified to

$$\frac{Q_r}{Q_\infty} = \frac{8}{\pi^2} \exp\left(\frac{-\pi^2 Dt}{l}\right) \quad \ldots\ldots 1.4$$

where Q_r is the amount of drug remaining in the device at time t, and Q_∞ is the total releasable amount of the drug from the device.

Solution of equation 1.2 by Laplace transformation leads to an expression useful for short times.

$$Q_r = 1Co\left[2\left(\frac{Dt}{l^2}\right)^{\frac{1}{2}}\left(\frac{1}{\sqrt{\pi}} + 2\sum_{n=1}^{\infty}(-1)^n \text{ ierfc } \frac{nl}{2Dt}\right)\right] \quad \ldots\ldots 1.5$$

which at short times can be simplified to

$$\frac{Qt}{Q_\infty} = 2\left(\frac{Dt}{\pi l^2}\right)^{\frac{1}{2}} \quad \ldots\ldots 1.6$$

Solutions of equation 1.2 for other geometries and under different boundary conditions are available in standard text (97-101).

Normal Fickian desorption from polymer matrices is therefore characterized by an initial $\sqrt{t}$ phase followed by a later exponential phase. Since constant delivery rates are more desirable in drug administration, simple desorption systems are not very useful. Efforts have therefore been directed towards designing systems that would lead to zero order drug delivery.

The use of suspension type matrices for drug delivery has been widely studied. Monolithic suspension type matrices also provide $\sqrt{t}$ release behaviour as expressed by the Higuchi equation (102).

$$Q_t = \sqrt{(2A - Cs)CsDt} \quad \ldots\ldots 1.7$$

where Q_t is the amount of drug released per unit area, A is the total initial concentration of the drug in the device, and Cs is the solubility of the drug in the matrix. The $\sqrt{t}$ release behaviour persists as long as solid drug remains in the device. The cause of this $\sqrt{t}$ behaviour has been recognised as the gradual increase of the diffusion path with continued desorption. There are three instances therefore under which zero order

delivery can be obtained from suspension type devices.

(i) when diffusion across the thin interfacial boundary layer at the surface of the polymer is rate limiting. This is the so-called partition controlled release (28).

(ii) Suspension-type reservoir or sandwich type devices with diffusion of the drug across a rate limiting membrane (100). The successfully marketted OCUSERT® (103), PROGESTASERT® (103) and HERCON® dispensers (104) are based on this principle. Since the dissolution rate of the solid in the suspension side of the membrane is faster than the diffusion of the drug across the membrane, constant activity is maintained in reservoir, hence steady delivery rates.

(iii) Special geometrical modifications on non constant delivery devices to balance the effect of the increasing diffusion path. Near zero order delivery rates have been obtained with the use of sectioned cylinders (105, 106) and sectioned spheres (107, 108).

In strict terms, interfacially-controlled release as discussed under (i) above is not "controlled release" as defined in the early part of this introduction. The dependence of the release rate on the interfacial boundary layer exposes it to variations in the nature and composition of body fluids. Thus, for example, a device

placed in the uterus would have fluctuating release rates depending on changes in the viscosity of uterine secretions and in uterine motility.

The use of emulsion systems for controlled release has not been as widely studied as solid-solid suspension systems. In vitro release of drugs from emulsion droplets has been observed to be a function of interfacial resistance, both electrical and physical (109). The kinetics of drug release can be quantified by modelling the systems as having a rate limiting membrane at the surface of the droplet. This model is useful for oral and topical delivery systems in which the rate limiting step is the transport of the drug from the dispersed phase. Windhauser et al (110) considered the case where diffusion of the drug in the continuous phase is rate limiting. They managed to determine the role of factors such as viscosity, particle size of droplets and partition coefficients on in-vitro and in-vivo release of injectable formulations. The use of emulsion systems for delivery of drugs by parenteral route has been reviewed (111, 112). Further kinetic considerations on release of drug from emulsion-type systems will be undertaken in Chapter 4. It suffices to mention here that zero order delivery has been achieved with emulsion-type reservoir devices (113).

(b) Polymer factors affecting diffusion

(i) State of Polymer:

Diffusion in polymers has been explained in terms of

free volume and segmental mobility (114). It follows therefore that the state of the polymer will determine the permeability of the polymer to diffusing substances.

Polymers in the glassy state are hard, rigid and usually brittle. Poor molecular and segmental mobility in the glassy state causes low diffusion of large molecules (115). Above the glass transition temperature i.e. in the rubber state, polymer diffusion is faster (115, 116). In the glassy state, polymers are composed of crystalline as well as amorphous zones. The extent of crystallinity strongly depends on the history of the polymer. It therefore follows that diffusion in glassy polymers is also dependent on storage and process history. Diffusion in glassy polymers has been shown to exhibit non-fickian behaviour (117-120). Non-fickian diffusion is now characterized into (a) Sigmoidal (120); (b) two-stage sorption (119, 121, 122); (c) Case II diffusion (123, 124) and (d) Supercase II diffusion (125). These behaviours are well reviewed in standard texts (97, 120, 126). It must be emphasized that these anomalous behaviours have been observed in glassy polymers well below their glass transition temperatures in cases of low molecular weight permeants. No such anomalous behaviour appears to have been reported in the pharmaceutical literature.

(ii) Crosslinkage

It had earlier been mentioned that the diffusion of

medicaments in hydrogels is affected by the extent of crosslinkage of the polymer (Section 1.2.2). In terms of the mechanisms of the diffusion process, increased crosslinkage affects the diffusion by increasing the average molecular weight of the polymer and decreasing segmental mobility.

(iii) Swelling

The ability of polymer to swell with a given solvent is governed by the free energy of mixing of the solvent with the polymer and the density of crosslinking (116, 127). When diffusion proceeds as swelling occurs, complex release behaviours are obtained (122). The two stage release behaviour mentioned in part (i) is also said to be caused, in part, by swelling (122).

(c) Prediction of diffusion in polymers and liquid systems

Graham (44) has utilized the empirical relationship obtained by Davis (128) to develop an expression for estimating the release profiles of medicaments from preswollen hydrogel devices. The Davis equation is given as

$$Dp = Do \exp\left[-(0.05 + 10^{-6}M)\ P\right] \quad \ldots\ldots\ 1.8$$

where Dp is the diffusion coefficient of the drug of molecular weight M in the polymer matrix containing P% w/w of polymer and Do is the diffusion coefficient of solute in pure solvent.

On combining the above equation with equation 1.6, Graham obtained the expression

$$\frac{Q_t}{Q_\infty} = 4 \left(\frac{Do \exp \left[-(0.05 + 10^{-6}M)\ P\right] t}{\pi l^2}\right)^{\frac{1}{2}} \quad \ldots\ldots 1.9$$

Since the above expression depends heavily on the value of Do, it is possible therefore to predict the whole release behaviour if the value of Do is predictable. Bretsznajder (129) has reviewed equations available for prediction of diffusion coefficients of substances in liquids. The simple, usable equations are:

(a) The Stoke-Einstein equation (130)

$$\frac{DM}{kT} = \frac{1}{6\pi r} \cdot \frac{1 + (3M/\beta r)}{1 + (2M/\beta r)} \quad \ldots\ldots 1.10$$

where k is the Boltzman constant

T is the absolute temperature

M is the kinematic viscosity

r is the radius of diffusing molecule

β is the molecular friction coefficient

which simplifies to

$$\frac{DM}{kT} = \frac{1}{4\pi r} \quad \text{if } \beta = 0 \quad \ldots\ldots 1.11$$

and

$$\frac{DM}{kT} = \frac{1}{6\pi r} \quad \text{if } \beta = \infty \quad \ldots\ldots 1.12$$

(b) The Li and Chang equation (131)

$$\frac{DM}{kT} = \frac{1}{2\pi} \left(\frac{N}{V}\right)^{\frac{1}{3}} \quad \ldots\ldots 1.13$$

where N is Avogadro's number

V is the molar volume of diffusing substance.

Though equation 1.13 was developed to reduce errors in equations 1.11 and 1.12, errors of up to 40% are obtained in some cases (131). Equation 1.10 has been shown to provide good approximations in some cases especially when $M > 1000$ (132). Other equations require extensive thermodynamic data e.g. the Eyring equation (133).

$$D = (\frac{V}{N})^{\frac{2}{3}} (\frac{kT}{h}) e^{\frac{\Delta S}{R}} . e^{\frac{\Delta H}{RT}} \quad ..... \quad 1.14$$

where h is the Plank's constant

ΔS is the entropy of activation of diffusion

ΔH is the heat of activation of diffusion

Several semi-empirical relationships are available for estimation of D such as those of Wilke and Chang (134); Scheibel (135); Ibrahim and Kuloor (136) and Othmer and Thakar (137). It suffices to say here that none of these expressions are totally reliable. It is therefore probably better to use the much simpler Stoke-Einstein or Li and Chang equations where preliminary prediction studies are required.

In this work, no attempt has been made to extend the application of equation 1.9. However, the Stoke-Einstein relationship has been used to predict release from emulsion-in-gel matrices.

1.3.2 Release from Biodegradable Polymers

Drug release from bioerodable devices should normally proceed by one of two processes; whichever is the fastest.

Firstly, the drug release may be a result of the degradation of the polymer base. In such cases it has been shown (138) that the release rate is given by

$$\frac{M_t}{M_\infty} = 1 - (1 - \frac{k_o t}{C_o a})^n \quad \ldots\ldots$$

where k_o is the zero order erosion rate constant

C_o is the uniform initial drug concentration

M_∞ is the total amount of releasable drug

M_t is the amount of drug released after time t.

For the slab, n = 1 and a is half thickness; for the cylinder n = 2 and a is its radius whereas for a sphere n = a and a is its radius. Thus only slabs can provide zero order delivery. Such behaviour has been observed in <u>in-vitro</u> studies (66).

On the other hand, when the diffusion of the drug from the matrix is much faster than the rate of degradation, the release kinetics would be similar to those of non-degradable matrices. In such cases $\sqrt{t}$ behaviour is expected.

These two cases, unfortunately, represent two extremes. In vitro studies of release of dibucaine from poly(lactic acid) microspheres has demonstrated that an intermediate case is obtained when the two mechanisms are comparable (139). The shape of the release profile is, in such cases, uncharacteristic of both individual mechanisms. The same behaviour has been observed in other cases (55, 63, 50). That the behaviour is a consequence of comparable rates of diffusion and degradation

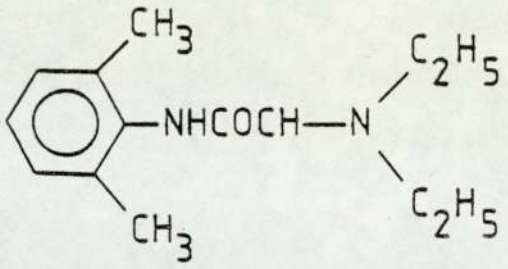
has been mathematically demonstrated by Heller and Baker (65). This behaviour could be similar to the anomalous diffusion in glassy polymers discussed in section 1.3.1 (b).

1.4 SOME ASPECTS OF LOCAL ANAESTHETIC THERAPY

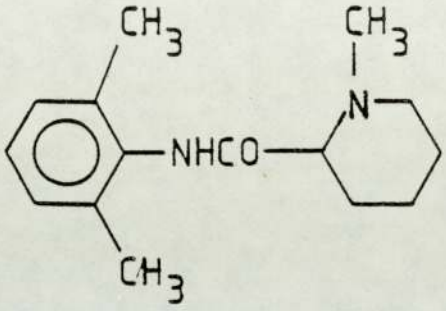
Local anaesthetics are drugs that reversibly block nerve conduction when applied locally to nerve tissue in appropriate concentrations. They seem to affect the transient increase in the permeability of the cell membranes to sodium by increasing the threshold of electrical conductivity probably through competition with calcium at some sites that control the permeability of membranes (140, 141).

The structure-activity-relationship of local anaesthetics is not fully established but according to Löfgren (142), local anaesthetics generally demonstrate a lipophilic part (usually aromatic) linked to a hydrophilic part (usually a secondary or tertiary amine) through an intermediate chain (143). The presence of the ester or amide intermediate chain is necessary to guarantee the reversibility of their action (143).

Local anaesthetics are usually classified according to the nature of their intermediate chains. Esters, such as Procaine and Tetracaine (Fig. 1.6a) are usually hydrolysed by both liver and plasma esterases (143). Amide local anaesthetics, such as Lignocaine and Carbocaine (Fig. 1.6a) undergo more complex metabolism through

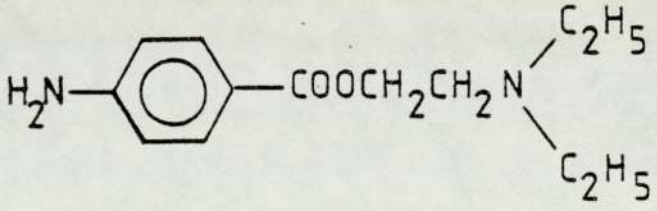


Lignocaine

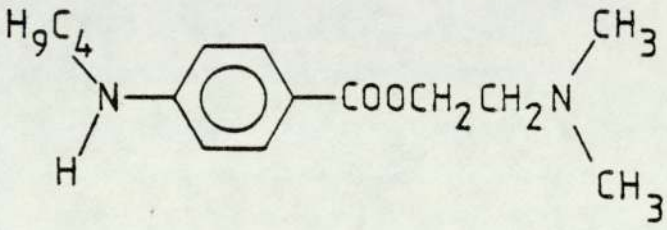


Carbocaine (Mepivacaine)

AMIDE



Procaine



Tetracaine (Amethocaine)

ESTERS

Fig 1.6(a) Structure of the local anaesthetics used in this study.

N-dealkylation followed by hydrolysis (144).

The structures of local anaesthetics used in this study are given in Figs.1.6a &b. Of all these local anaesthetics, only Procaine does not possess surface anaesthetic properties. The esters of p-aminobenzoate are used exclusively for surface anaesthesia due to their low aqueous solubility. The methyl and propyl esters of p-aminobenzoate are not used clinically. Lignocaine is also widely used as an antiarrythmic agent.

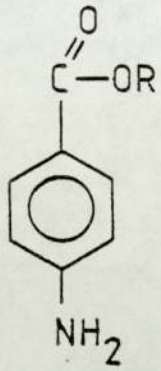


Fig 1.6(b) Esters of p-aminobenzoic acid (R is an alkyl group eg for benzocaine, R is C_2H_5).

CHAPTER 2

MATERIALS AND METHODS

2.1 MATERIALS

The sources and grades of the materials used in these experiments are given in appendix 2.1. All chemicals were used as supplied without any further purification.

Gelatin samples of four different bloom strengths were used. All the gelatins were ossein, acid produced and the bloom strength was as quoted by the manufacturer. No determination of the molecular size distribution was done. Fractionation was not performed since an earlier report (230) had shown no difference in using fractionated or unfractionated gelatin in release experiments. Since most of the release experiments were to be performed in buffered systems, it was necessary to know the isoelectric points (IEP) of the gelatins used. The IEPs were determined by turbidimetry; where the turbidity of a 1% gelatin solution at various pHs was determined by reading the absorbance of the solution at 600 nm. The pH with the maximum turbidity was taken as the isoelectric point. The plots of absorbance against pH are given in Figure 2.1. Britton and Robinson buffers (145) adjusted to an ionic strength of 0.5 molar were used. The IEPs obtained from Fig. 2.1 are the same for the gelatins of different bloom strengths (IEP of 8.8-9.1).

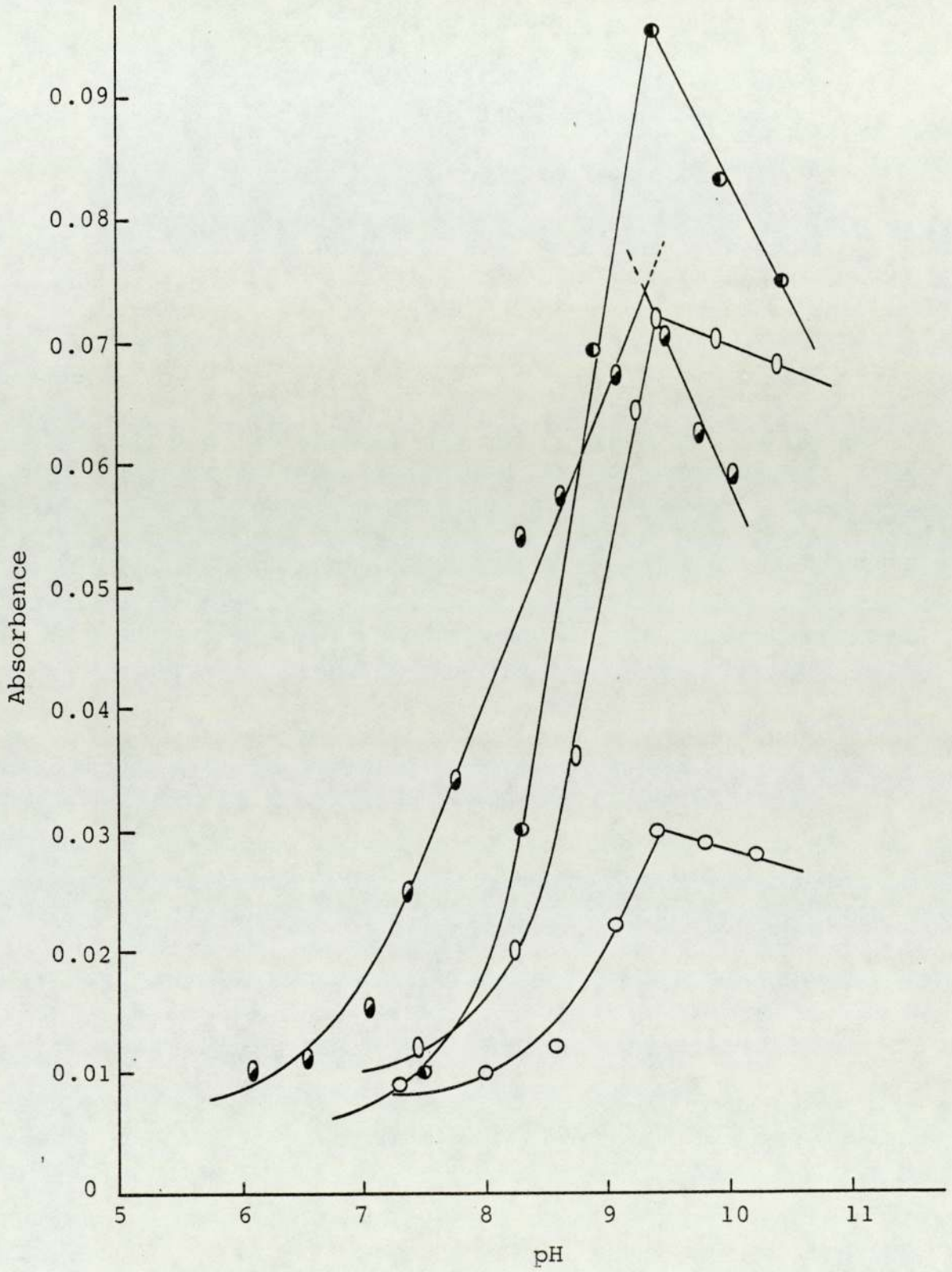


Fig 2.1 The determination of isoelectric points of gelatin by turbidimetry. O 90 bloom, ◐ 150 bloom, 0 200 bloom, ◑ 230 bloom gelatins.

Like previous studies (178), the moisture content of the gelatins was determined by drying in an oven at 100°C and reduced pressure (appr. 4.0 mm Hg) to constant weight. It was determined that all gelatins had approximately 12.4% moisture content. This content was disregarded during the preparation of gels.

2.2 PREPARATION AND STORAGE OF GELS

2.2.1 Formulation

The preparation of aqueous gelatin gels followed the following general procedure (specific quantities will be given in appropriate chapters).

Step (i) : Weighing of aqueous soluble additives and dissolving them in about 50% of the total amount of water required in the formula.

Step (ii) : Weighing the required amount of gelatin.

Step (iii) : Mixing the solution prepared under (i) above with the weighed gelatin and making up to required weight.

Step (iv) : Mixture allowed to mature for 1 hour.

Step (v) : Mixture melted at 60°C for 2 hours.

Step (v) above involved the tedious process of removing air bubbles from the gels. Early attempts to use vacuum failed due to the excessive frothing. Leaving the gel in a water bath at 60°C for a long duration was observed to rid the gel of air bubbles. However, the danger of hydrolysis of the protein molecules made this

method unsuitable. A compromise procedure was found which involved leaving the gel for 2 hours in the water bath at 60°C during which time the air bubbles rise to the surface of the gel where they can be scraped off easily using a spoon or spatula.

2.2.2 Determination of the Equilibrium Moisture Content of Gels

In some cases it was necessary to store the films before release experiments. During storage, loss of moisture would normally occur due to the high content of free water in the gels. Storage conditions had to be found that would guarantee constancy of composition of the gel.

Approximately 1.0 g. of a 20% w/w 150 bloom gelatin gel was placed in tar ed vials and weight accurately. The vials were then placed in dessicators containing saturated salt solutions for maintaining constant relative humidities. The salts used in this study are listed in table 2.1 and are described in standard reference texts (147). The vials were weighed daily until a constant weight was reached. The loss in weight was expressed as a percentage of the original weight and plotted against time (Fig. 2.2). The equilibrium values were plotted against the relative humidity (Fig. 2.3). This allowed the determination of a relative humidity which, at 25°C, would maintain the consistency of a 20% gel. From Fig. 2.3 the appropriate relative humidity was derived to be 95-96%.

Table 2.1

List of salts used in the determination of the equilibrium moisture content of gelatin.

Salt	% Relative humidity
Potassium acetate	23
Potassium carbonate	44
Sodium dichromate	56
Sodium nitrite	66
Sodium chloride	76
Potassium chloride	86
Disodium hydrogen orthophosphate(12H O)	95
Potassium sulphate	97

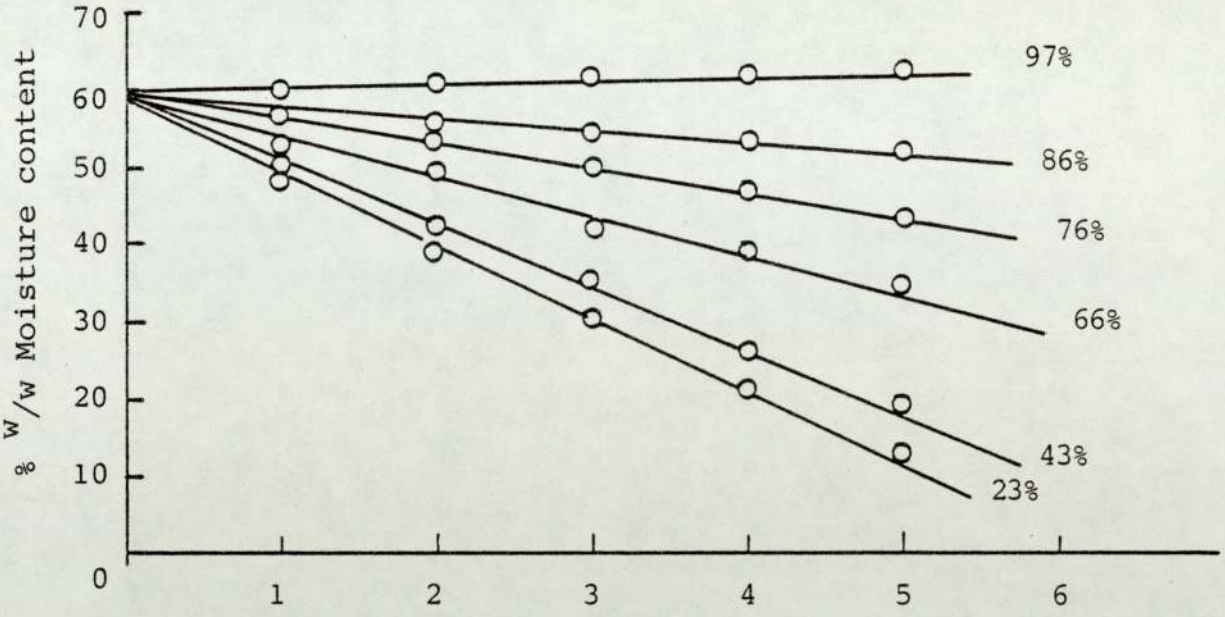


Fig 2.2 Loss of moisture from gelatin gels (originally 60% water moisture content) on storage at different relative humidities at 25°C.

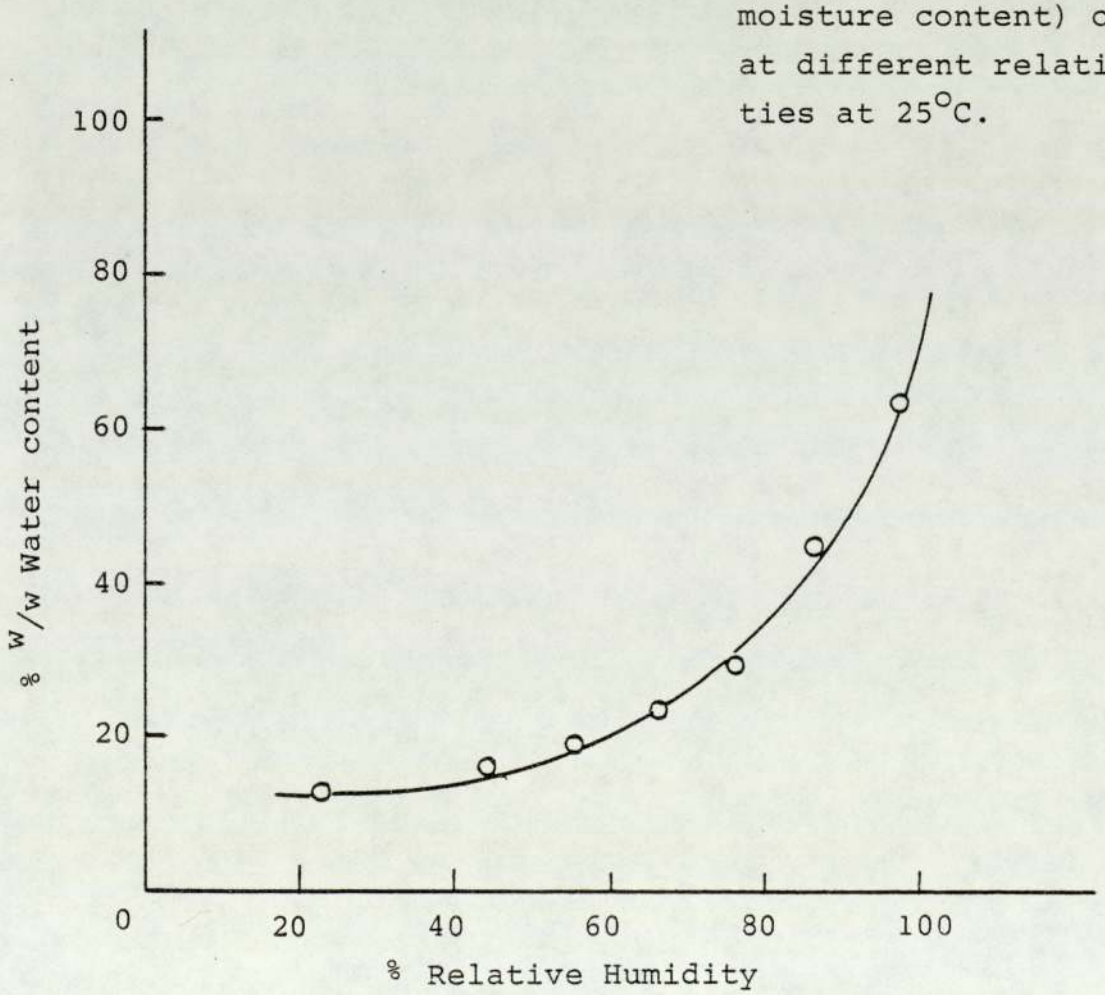


Fig 2.3 The equilibrium moisture content of 150 bloom gelatin gels.

All gels including emulsion gels with the basic formula of 20% gelatin in water were stored at 95% R.H. However, for more accurate determinations of the drug content of the films, weighing of the films immediately after casting was necessary. Film thickness was usually measured just before the individual release experiments.

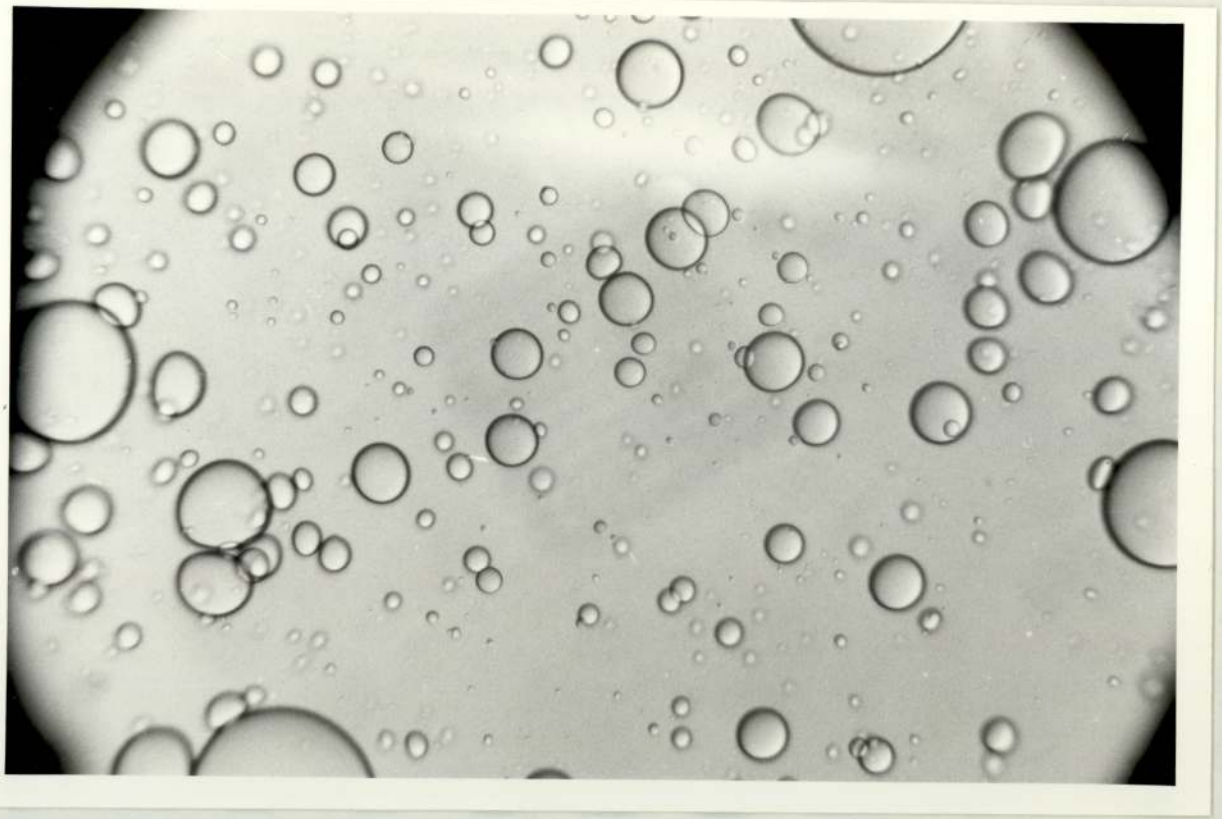
2.3 PREPARATION OF EMULSIONS

2.3.1 General Procedure

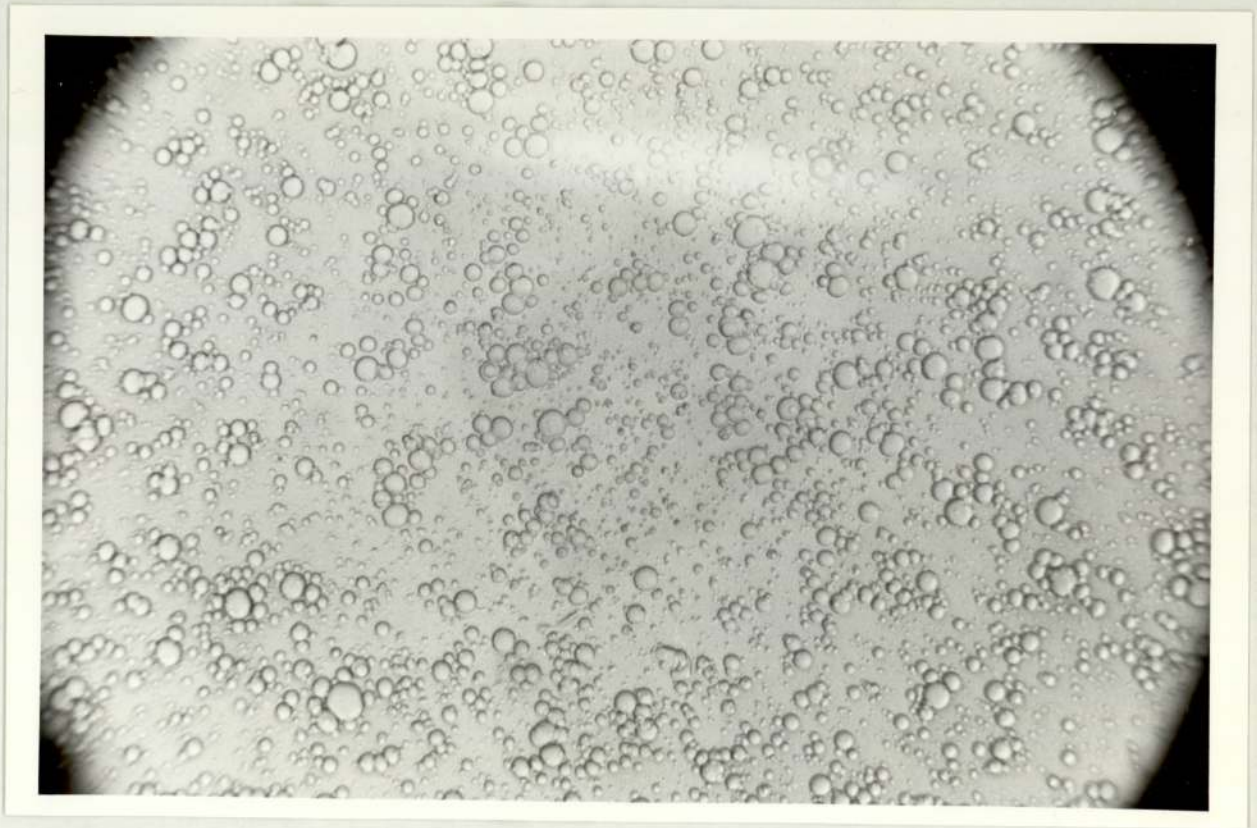
The oil-in-gel emulsions were produced without the use of any extra surfactants since gelatin itself has emulsifying properties. The general procedure involved adding the required quantity of the oleagenous phase containing the drug(s) and pre-heated to 60°C to the required amount of molten gel also at 60°C. The mixture was then stirred at 2,000 r.p.m. using a Heidolph RZR 50 motor for 2 minutes. The influence of stirring speed on the particle size of olive oil emulsion droplets is shown in Fig. 2.4. It is essential therefore, to use the same stirring speed at all times.

For the production of emulsions of different particle sizes another method of preparation was used. This involved the homogenization of the emulsion produced as explained above using a French Press. This procedure produced emulsions with oil droplets of micron-size.

Fig. 2.4 (Opposite).
The influence of stirring speed on the particle size of sunflower oil emulsion droplets. Photomicrographs taken at X 400 magnification.



1000r.p.m.



2000 r.p.m.

2.3.2 Particle Size Analysis

For the emulsions produced by stirring, the particle size distribution was determined by microscopy [146]. Unfortunately, the method was unsuitable for homogenised emulsions due to the fineness of the droplets obtained. Photomicrographs (Fig. 2.5) compared the sizes of the emulsion droplets produced by the two methods. Due to the inability to quantify the particle size distribution of the homogenized emulsions, studies involving particle size variation were qualitative rather than quantitative.

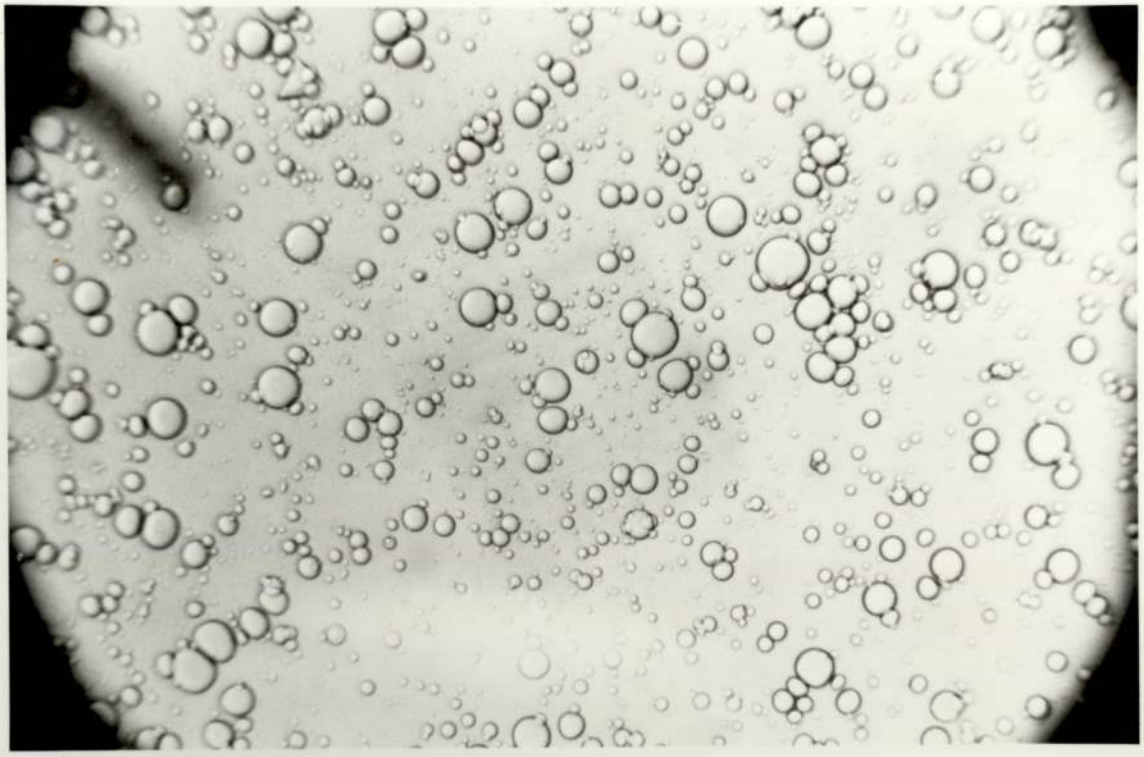
The reproducibility of the stirring technique is shown in Fig. 2.6 which compares the particle size distributions of four emulsions prepared separately by the same method.

2.4 FILM CASTING

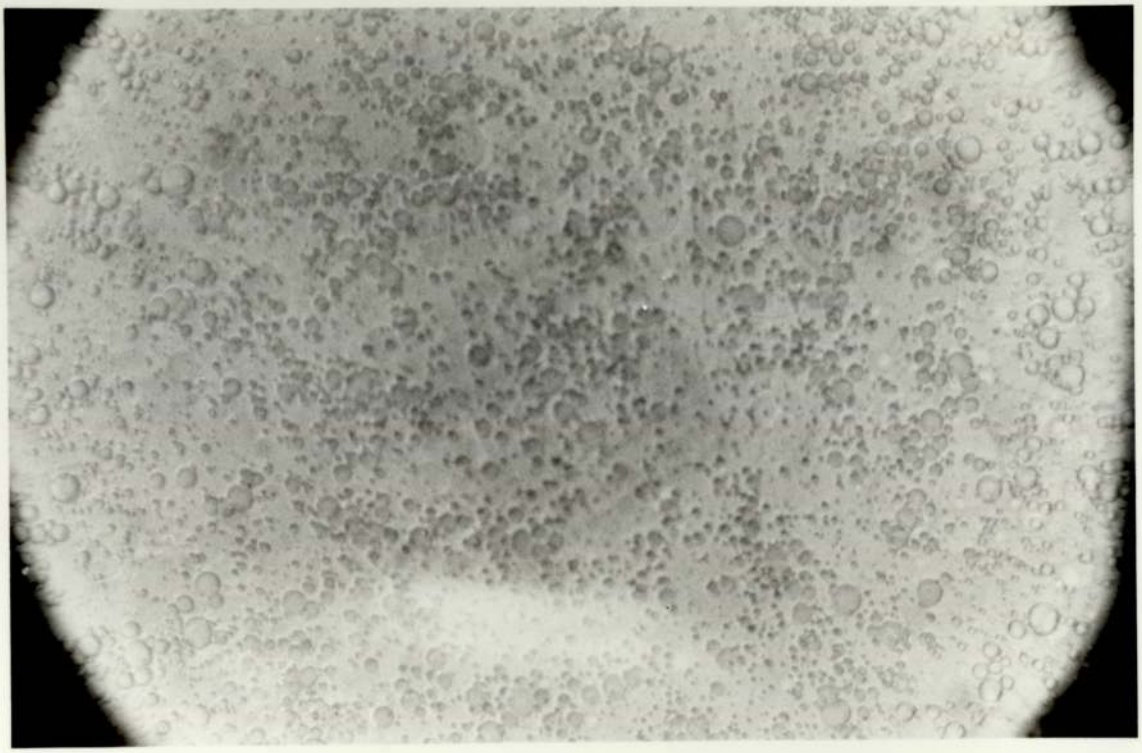
Several methods were tried in an attempt to obtain a fast and efficient method for producing thin films. The methods described in standard text [148] were either unavailable or unsuitable for gelatin gels.

2.4.1 Spreading on TLC Plates

This method has previously been used by other investigators [37,197]. On trying them the following problems were noticed.



(a) Stirred emulsion (2000 rpm).



(b) Homogenised emulsion

Fig. 2.5 Difference in particle size of homogenised and stirred emulsions. Photomicrographs of the emulsions taken at X 800 magnification.

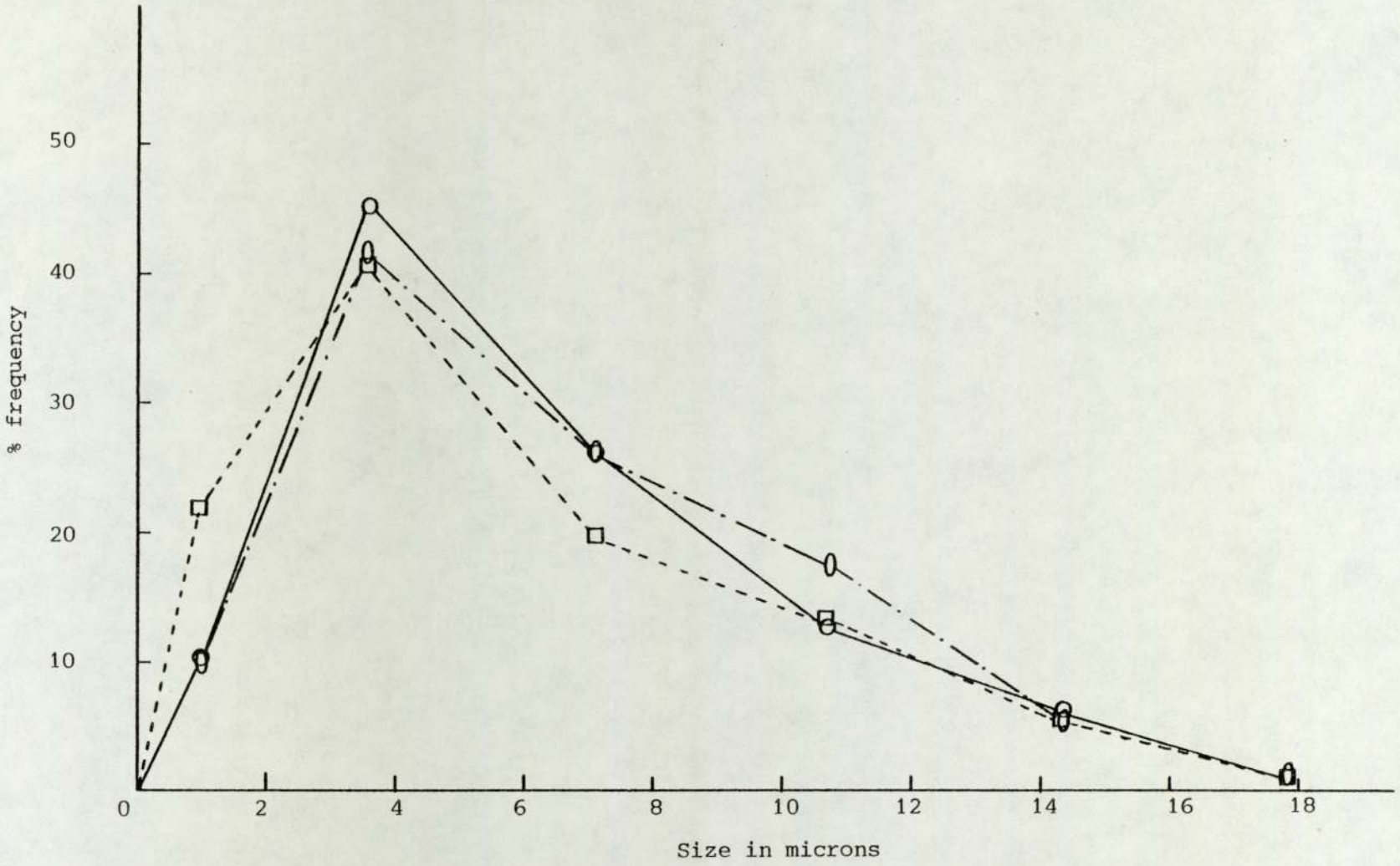


Fig 2.6 Particle size distribution of sunflower oil-in-gel emulsions prepared by stirring at 200 rpm

a) Cold areas on the equipment caused instant solidification of the gel. Pre-warming was therefore necessary.

b) Thin films (thickness approximately 0.5 mm) could not be produced with more viscous gels. Since the method was meant to be used for a wide range of gel viscosity, this was a serious setback.

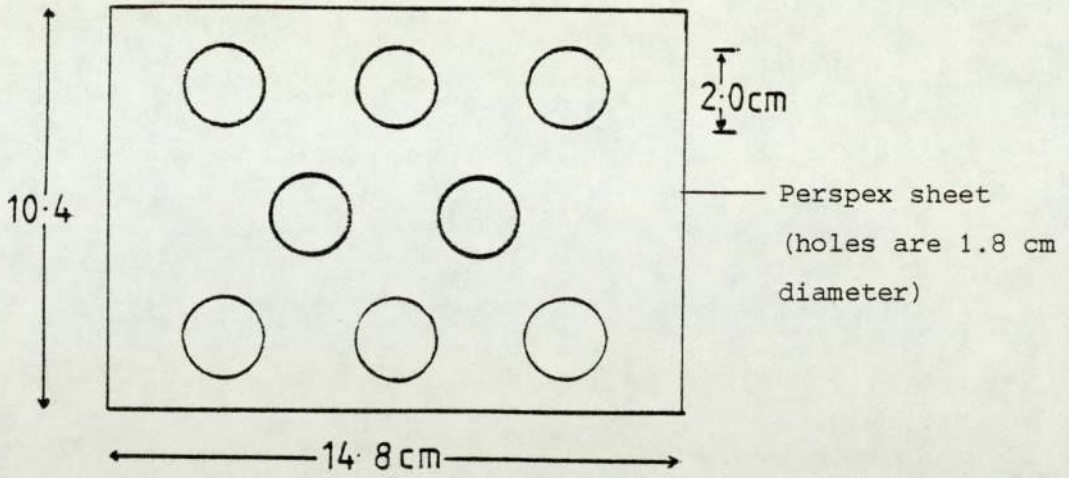
c) Some pre-treated gels adhered strongly to the glass (especially formaldehyde hardened gels), and removal from the plates yielded unusable films.

2.4.2 Die Casting

This is illustrated on Fig. 2.7.

A perspex sheet (thickness 0.33 mm.) was drilled with 8 holes of 1.8 mm. diameter. The sheet was then placed onto a flat surface and perspex disks inserted into the holes. The disks were cut such that a hole of 0.5 mm. was left (see illustration). A small amount of molten gel was placed in each of the holes and the plate was covered and compressed by another flat perspex plate. After some time (sufficient to ensure solidification of the gel) compression was stopped and the top plate removed. The thin films could then be dislodged by pressing the bottom of the disks in the holes.

This method was easy and fast to use but had the main disadvantage of requiring an almost exact amount of gel



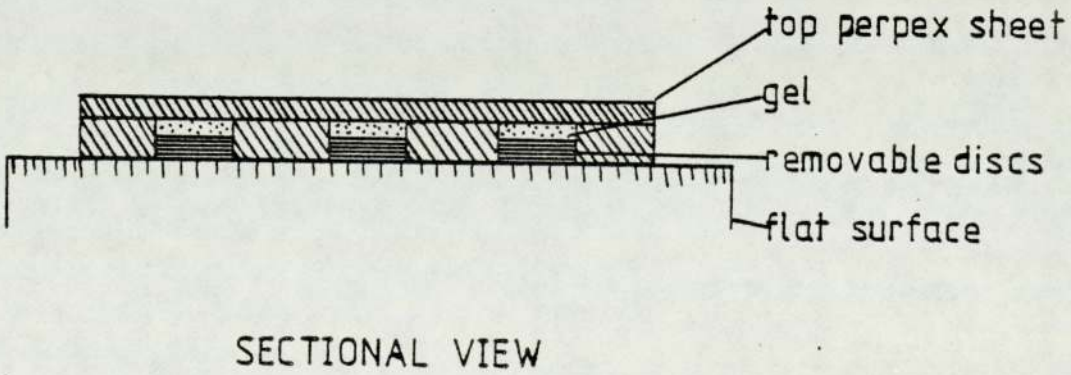


Fig 2.7 Apparatus for the "die-casting" technique

deposited in the holes. An excess amount of gel would cause it to overflow between the top plate and the perforated plate and therefore cause significant variation of film thickness.

2.4.3 The Template Box

The basic principle of molding is to solidify a gel within a preset gap. The material is placed in the gap either in the molten state or as a solid to be melted 'in-situ'. A perspex box was therefore constructed in which several perspex plates could be laid on top of each other separated by microscope slides. The gel would be introduced into the gap between perspex plates in the molten state. The thickness of the films would therefore depend on the thickness of the microscope slides used. The design of the box is as shown in Fig. 2.8.

By applying low vacuum via the outlet, the gel was sucked into compartment A, and rose through the gaps between the perspex plates into compartment B. The vacuum is switched off before any gel overflows out of the box. The gel is retained in the box by closing the entry port. The box is left in an upright position at the required temperature for not less than 12 hours.

This method of casting produced excellent films. Variation of thickness between films is greatly reduced by careful selection of gap-setting microscope slides. Table 2.2 shows weight variation of circular film pieces (diameter 1.8 cm.) cut from the rectangular films obtained. Very good reproducibility can thus be obtained.

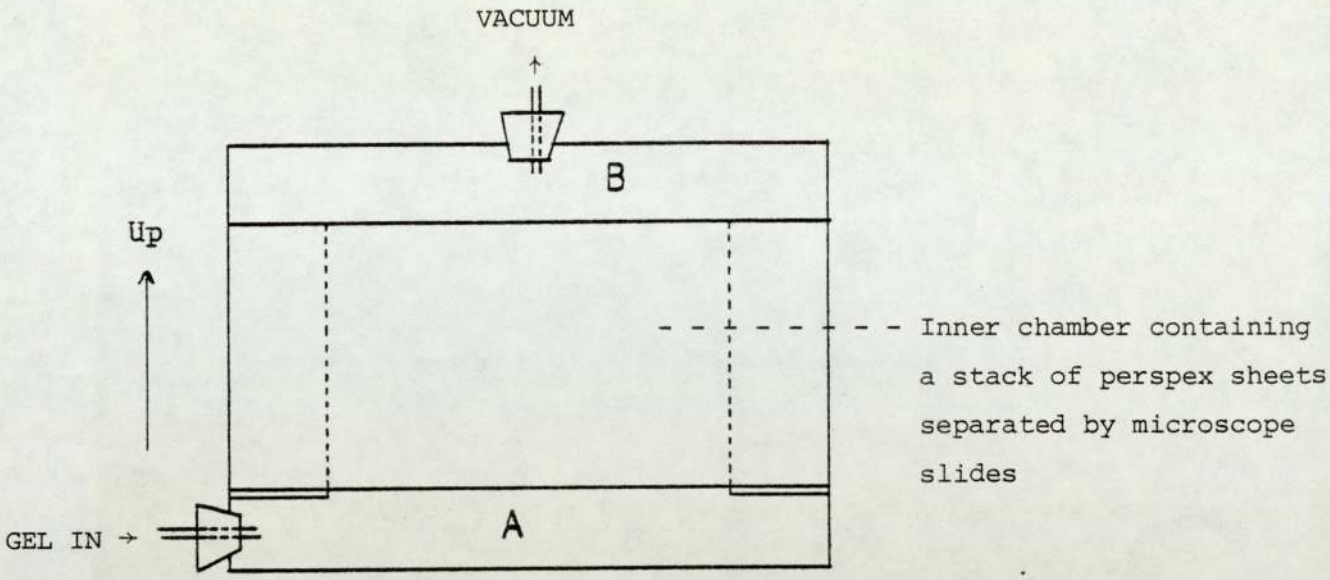


Fig 2.8 The template box

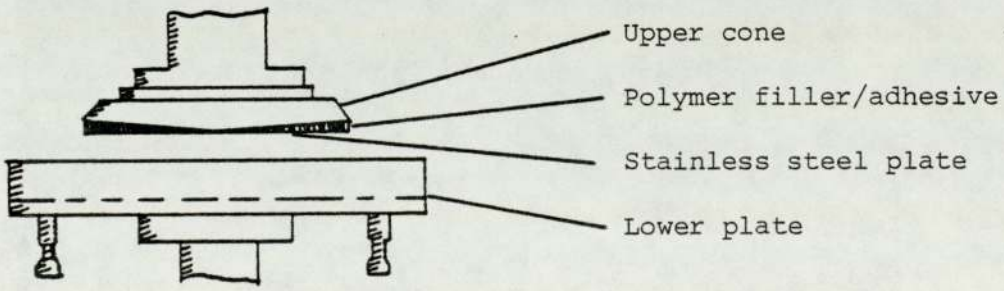


Fig 2.9 The parallel-plate film casting equipment

TABLE 2.2

(a) Weight Variation of Films Cast Using the Template Box.

Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	
Ø.5345 g.	Ø.5326 g.	Ø.5396 g.	Ø.5468 g.	Ø.5405 g.	
Ø.5549 "	Ø.5449 "	Ø.5475 "	Ø.5265 "	Ø.5193 "	
Ø.5507 "	Ø.5415 "	Ø.5454 "	Ø.5658 "	Ø.5344 "	
Ø.5601 "	Ø.5373 "	Ø.5473 "	Ø.5414 "	Ø.5662 "	
Ø.5503 "	Ø.5489 "	Ø.5555 "	Ø.5555 "	Ø.5494 "	
Ø.5349 "	Ø.5277 "	Ø.5453 "	Ø.5492 "	Ø.5322 "	
-	Ø.5260 "	Ø.5383 "	Ø.5350 "	Ø.5653 "	
Ø.5475 g.	Ø.5370 g.	Ø.5456 g.	Ø.5457 g.	Ø.5439 g.	Mean
Ø.0106 g.	Ø.0087 g.	Ø.0057 g.	Ø.0130 g.	Ø.0175 g.	Std.dev.

(b) Thickness Variation of films cast by parallel plates Technique.

Gap setting		Ø.30 mm.	Ø.40 mm.	Ø.75 mm.	1.00 mm.
*Film thickness	(1)	Ø.30 mm.	Ø.41 mm.	Ø.75 mm.	1.00 mm.
	(2)	Ø.30 "	Ø.41 "	Ø.78 "	1.00 "
	(3)	Ø.27 "	Ø.38 "	Ø.75 "	Ø.99 "
	(4)	Ø.26 "	Ø.44 "	Ø.77 "	Ø.99 "

*Each value represents a mean of six measurements at different parts of the film.

However, the method is not free of disadvantages. The volume of gel required by the box of the given dimensions is 400 ml. out of which only six 5 x 12 cm films are obtained; an obvious waste. Reduction in the size of the box was not possible due to the limiting sizes of the parts used, e.g. microscope slides, clamps and hole-plugs. Another disadvantage is the low rate of cooling due to the large mass of gel used. Films of sufficient strength can only be obtained after over 12 hours of storage.

2.4.4 Parallel Plates

Solid plastics can be cast into thin films by using compression or transfer molding technique [148]. In the case of flash molding [148], a known weight of plastic material is pressed (pressure up to 2,000 p.s.i.) between two hot plates (preset temperature depending on melting point of the material) where it melts in a space confined by a stainless steel template. The thickness of the film produced depends on the thickness of the template. Very high pressures are used to ensure that any excess material is squeezed from the gap between the template and the hot plates.

An attempt was made to use this method to cast films of preformulated gelatin gels. Apart from the necessity of knowing the melting point of the gel (which varied widely depending on the formulation), the slow rate of cocling of the hot plates made the procedure tedious.

A faster and less tedious method of casting based on the same principle was devised in which a Ferranti-Shirley viscometer was used. The top cone was levelled by gluing a flat, thin stainless steel plate using a polymeric filler (Fig. 2.9). The stainless steel plate was fixed in such a way that the apex of the original cone was in contact with the levelling plate. This was necessary so as to ensure conduction of electricity between the lower plate and the cone during gap-setting.

The casting procedure then involved pouring the molten, air-free gel onto the lower plate and bringing down the upper plate to a fixed, preset gap. After 15 minutes the upper plate is raised and the solid gel removed. Depending on the viscosity of the gel, films of up to 1 mm. thickness could be cast.

The advantages of this method are:

a) fast casting of films

b) only small quantities (5 to 10 ml.) of gel are required at any time to produce a circular film of 7.0 cm. diamater

c) where initial warming of the plates is required or where slow cooling is necessary, the system has a water circulation facility to control the temperature

d) the thickness of the film cast can be adjusted easily and very accurately using the micrometer, electrical gap setting mechanism.

The disadvantages of the method are as follows:

a) loss of water vapour from the gel takes place due to exposure of the gel to atmosphere. It is therefore essential to remove the film as soon as possible.

b) Gelatin tends to adhere strongly to stainless steel thus making film retrieval difficult. It was therefore necessary to lay a hydrophobic film on the plate, onto which gelatin does not adhere. Commercial "cling-film" was used in this case. The presence of the film produced slight undulation on the films produced because of air trapped between the cling film and the stainless steel plates. It was therefore decided not to cast films of less than 0.5 mm. thickness so as to reduce the total error in the film thickness.

Table 2.2 shows the thickness variation of films cast by this method.

2.5 RELEASE EXPERIMENTS

2.5.1 Release from Insoluble Films

For insoluble films, the USP dissolution method (149) was used after some modification. The release vessel was a 200 ml. jacketed partion cell (Fig. 2.10). Discs of the gel were introduced into the basket which was clamped onto the holder and lowered into the release medium. The medium used for release was phosphate buffer

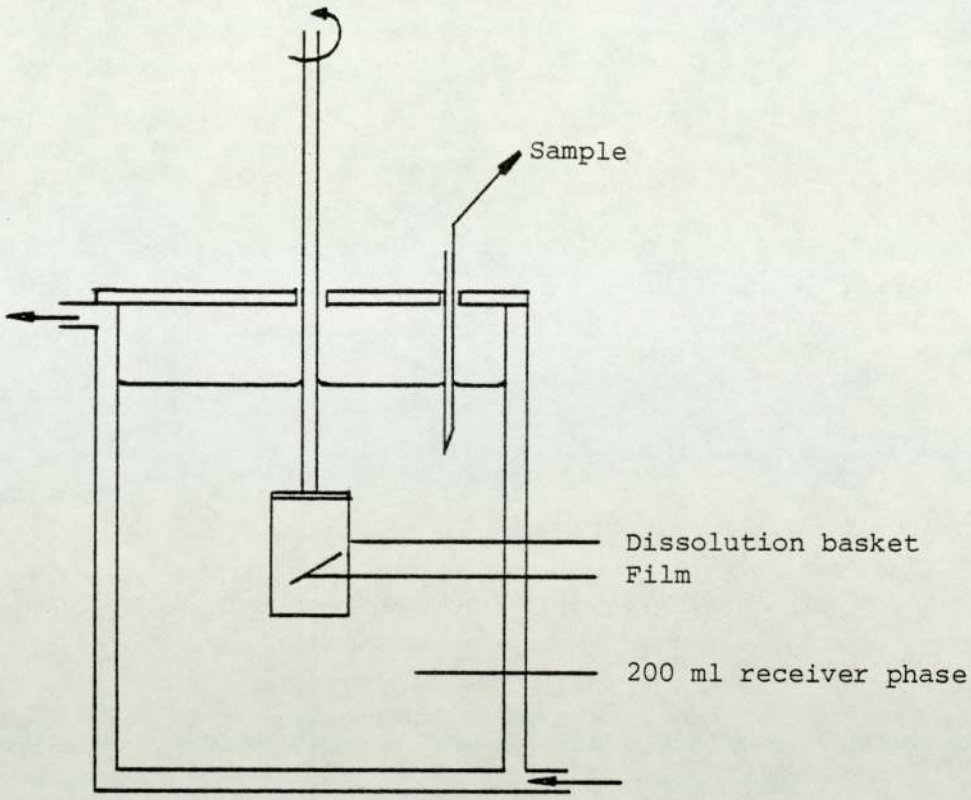


Fig 2.10 Release apparatus for insoluble films

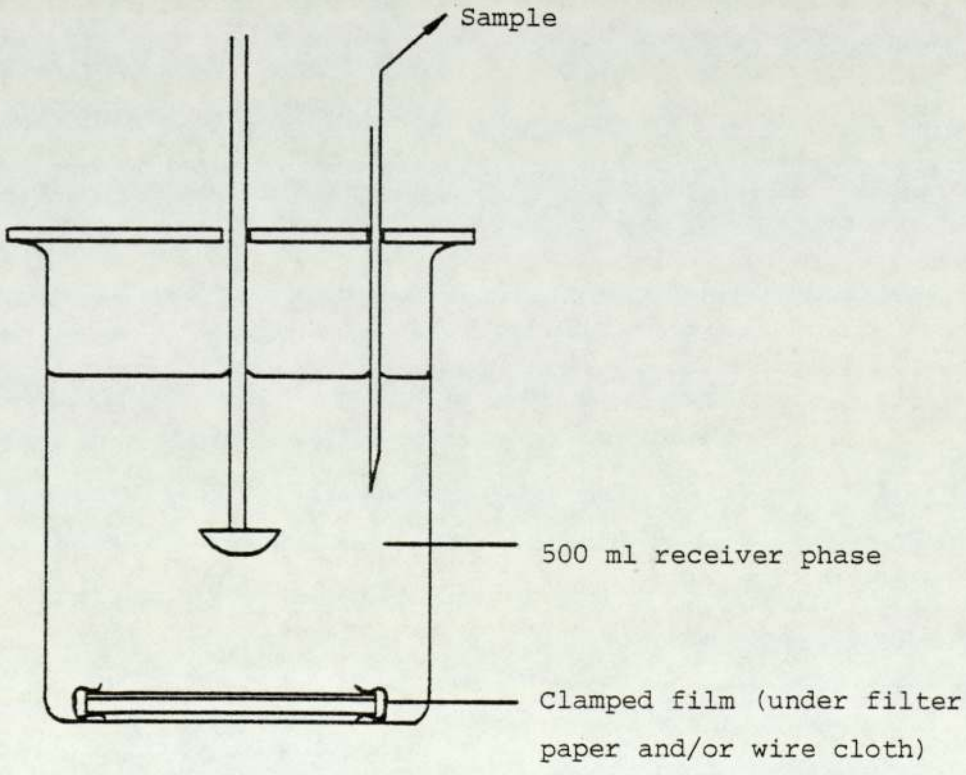


Fig 2.11 Release apparatus for soluble films

pH 7.0 prepared according to the formula available in standard text (150). The basket holder was fastened to a Heidolph RZR 50 stirrer motor and rotated at 40 r.p.m, a speed observed to be just sufficient to keep the film floating freely without adhering to the top of the basket holder. Mathematical treatment of the release behaviour therefore had to take into consideration that release is from both faces of the film. 5 ml. samples were withdrawn at given times and replaced by an equal volume of buffer at the same temperature as the release experiment. Release experiments of hardened, insoluble films were all conducted at 37°C.

2.5.2 Release from Soluble Films

Two cases are discussed in this section, that of a soluble film that had to dissolve during the experiment and that of a soluble film that was not supposed to dissolve during the experiment. In both cases the basic apparatus was the same but additional modifications were made to adapt it to the specific case under study.

The basic components of the system are illustrated in Fig. 2.11. It includes a circular perspex plate onto which the film was clamped by a perspex ring using light stainless steel spring clamps. When no dissolution of the matrix was required, a filter membrane (Millipore SM 11307) and a wire cloth (40 mesh) were placed on top of the film before clamping. The use of membranes in release from

emulsions, creams and ointments is a common practice (155, 160, 161). The popular membranes include polydimethylsiloxane (155, 160); cellulose dialysing membranes (161), membrane filters (162) and Whatman filter papers (163).

Since the sink solution was aqueous, Whatman filter papers were found to break up after some time. Dialysing membranes were found to offer a high diffusional resistance to the drug and the polydimethylsiloxane was not used since it had been reported that they also have a high diffusional resistance (164). The wire mesh placed on top of the film was observed to restrict swelling and therefore inhibit membrane dissolution. In such experiments release was performed at 25°C where the gelatin gels are below their melting points.

When dissolution of the films was under study, the set up was used without the filter paper. The presence of the wire mesh suppressed breaking up of the films, some of which were very weak mechanically. The procedure is, in principle, similar to that used by Hom et al (165) with an added advantage of a larger surface area exposed.

The clamped system was placed into a Quickfit dissolution vessel containing 500 ml. of distilled water at 25°C. Stirring was by a blade stirrer (PTFE blade on a glass holder) driven at 75 r.p.m. by a Heidolph RZR 50 stirrer motor at a height of 5 cm. above the bottom of the vessel. 5 ml. aliquots were withdrawn for analysis at given times, being replaced by an equivalent volume of distilled water.

2.6 H.P.L.C. ANALYSIS OF LOCAL ANAESTHETICS

High Pressure Liquid Chromatography (HPLC) is probably the most popular method of assay of pharmaceuticals. Like gas chromatography (GC) it has the advantage of providing analysis of complex mixtures without the need of exhaustive extraction. Unlike GC however, it allows the use of almost all types of solvents, while sample preparation is usually easier. It suffers from its present dependence on more specific detectors (mostly U.V.) which do not have the universality and precision of the flame detectors in GC. However, the development of refractive index detectors has greatly reduced this weakness. Several useful reviews [166-168] are available which outline the principles and applications of HPLC. This will not be repeated here since it is intended to emphasize on the development of systems used in studies to be reported in subsequent chapters.

The assay of local anaesthetics has probably involved the whole spectrum of analytical instruments and methods available. Lidocaine, for example, can be assayed by non-aqueous titration [169], colourimetry [170,171] and GC [151-154] in addition to ultraviolet spectroscopy. It is evident from available literature that the main problem is the isolation of lidocaine from the rest of the ingredients in the formulation or sample. This problem is greatly reduced by using chromatographic methods.

The most popular HPLC method of assaying lidocaine and its metabolites and other local anaesthetics involves

the injection of an acidic, aqueous solution of the drug(s) into a reverse phase (ODS) column [172-176]. Since the drugs are weak bases, analysis is therefore dependent on the ionized form of the drug. This method has the advantage of accepting aqueous solutions; where impure samples are to be analysed, however, the method requires double extraction of the sort

Aqueous sample (original) $\xrightarrow{\text{step 1}}$ Organic Phase $\xrightarrow{\text{step 2}}$ Aqueous phase (injectable)

so as to remove the water soluble impurities, e.g. gelatin.

A normal phase HPLC system capable of accepting organic solutions would reduce the error of analysis by requiring only one extraction (step 1). It was therefore decided to develop an assay procedure based on normal phase.

The HPLC equipment available in our laboratories consisted of the following parts.

1. Altex 100A double piston solvent metering pump.
2. Pye-Unicam LC UV detector.
3. JJ chart recorder (JJ Instruments)
4. Prepacked Si (Normal Phase) column: from
   Altex Ultrasphere Si 10 cm. 5 μm.
   Spherisorb Si 15 cm. 5 μm.
5. Shandon unpacked columns (10 cm. length; 5 mm. bore).
6. Shandon Column Packing Materials
   Hypersil Si ... 5 μm.
   ODS Hypersil ... 5 μm.

Where the Shandon columns were to be used, packing was performed using a Shandon column packing machine.

2.6.1 HPLC Analysis of Local Anaesthetics with pKa > 7.0

A normal phase system capable of simultaneous separation of lidocaine, carbocaine, tetracaine and procaine was developed. The system used the Altex Ultrasphere Si column with the following mobile phase pumped at a rate of 1.5 ml. $min.^{-1}$ (pressure 1,560 psi):

Isopropanol	15%
Strong Ammonia Soln.	0.4%
Dist. Water	0.2%
Hexane	to 100%

Detection was by U.V. at 254 nm.

The samples for injection were prepared by adding 1 ml. each of 0.1 N Sodium Hydroxide and Hexane to 1 ml. of the aqueous sample. The mixture was shaken vigorously (whirlimixed) and then centrifuged for 30 sec. 20 µl. of the top organic layer were injected into the column.

The chromatogram obtained is shown in Fig. 2.12. The method is very fast (5 min. for all the components) and quite accurate. Typical calibration curves for the local anaesthetics are shown in Fig. 2.13.

When lignocaine alone was being assayed, carbocaine was used as internal standard.

2.6.2 HPLC Analysis of Local Anaesthetics with pKa < 7.0

The analysis of the ester of p-aminobenzoic acid is discussed in this section. Due to their very low pKas

KEY:

1 Lignocaine.

2 Carbocaine.

3 Tetracaine.

4 Procaine.

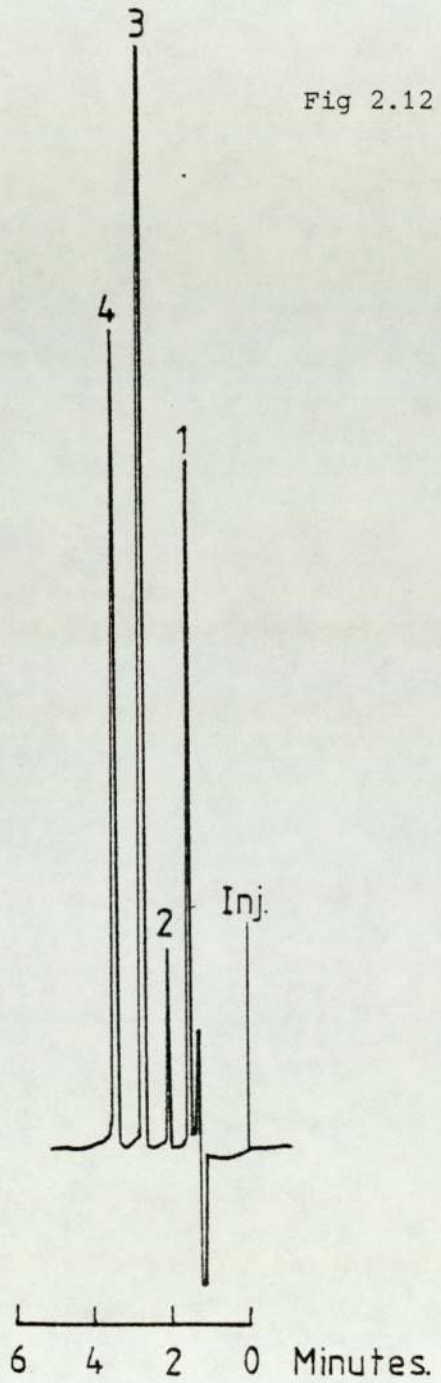


Fig 2.12 A typical chromatogram for HPLC analysis of local anaesthetics

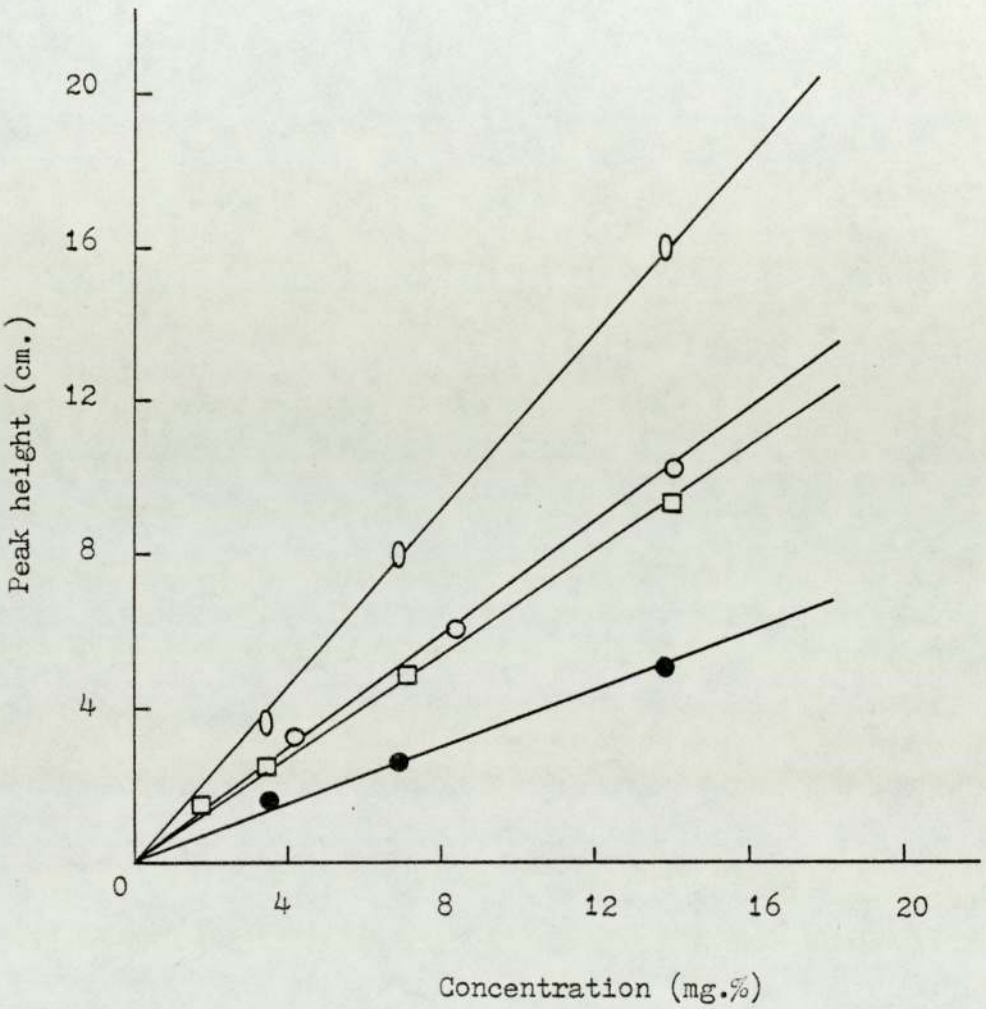


Fig.2.13 Typical Calibration Curves fo HPLC Analysis OF Local Anaesthetics.

□ Lignocaine

○ Tetracaine

0 Procaine

● Carbocaine

(Benzocaine pKa = 2.5 at 25°C), the use of normal phase column is not possible since it will require mobile phases of very low pH. A reverse phase system for the assay of benzocaine and p-Aminobenzoic acid has been reported (177). The method was, however, observed to be quite inaccurate at higher sensitivities due to the broad benzocaine peaks obtained probably caused by the long retention times (8 min) and the use of a mobile phase of pH in the proximity of the pKa of the drug. A modified reverse phase system was developed which provided a faster assay of a range of esters of p-aminobenzoic acid. The system consisted of a Shandon 10 cm. column packed with ODS hypersil 5 mm. packing material with the following mobile phase pumped at a rate of 1 ml. $min.^{-1}$ (pressure 760 psi)

Acetic acid	6%
Dilute Ammonia solution	25%
Methanol	50%
Water	to 100%

Detection was by U.V. at 285 nm.

The dilute ammonia solution was a 1:20 dilution of the strong ammonia solution B.P. The mobile phase had a pH of 4.9-5.0. The buffering was necessitated by the tailing of the solvent front due to the injection of phosphate buffer which was used as the release medium.

Extraction was not necessary since the formulation did not release any other interfering products. The

typical chromatogram obtained is shown in Fig. 2.14. As can be observed, the p-aminobenzoic acid appears on the solvent front. Although its quantitation was not necessary in this study, its presence in the solvent front was useful since it provided an indication of the stability of all the esters.

This assay procedure takes only 7 minutes for all esters. When benzocaine alone is assayed the method is as fast as 4 minutes. Propyl p-hydroxybenzoate may be used as the internal standard when all esters are studied simultaneously. For assay of Benzocaine alone, the methyl ester of PABA was used as internal standard.

Typical calibration curves for the esters are shown in Fig. 2.15.

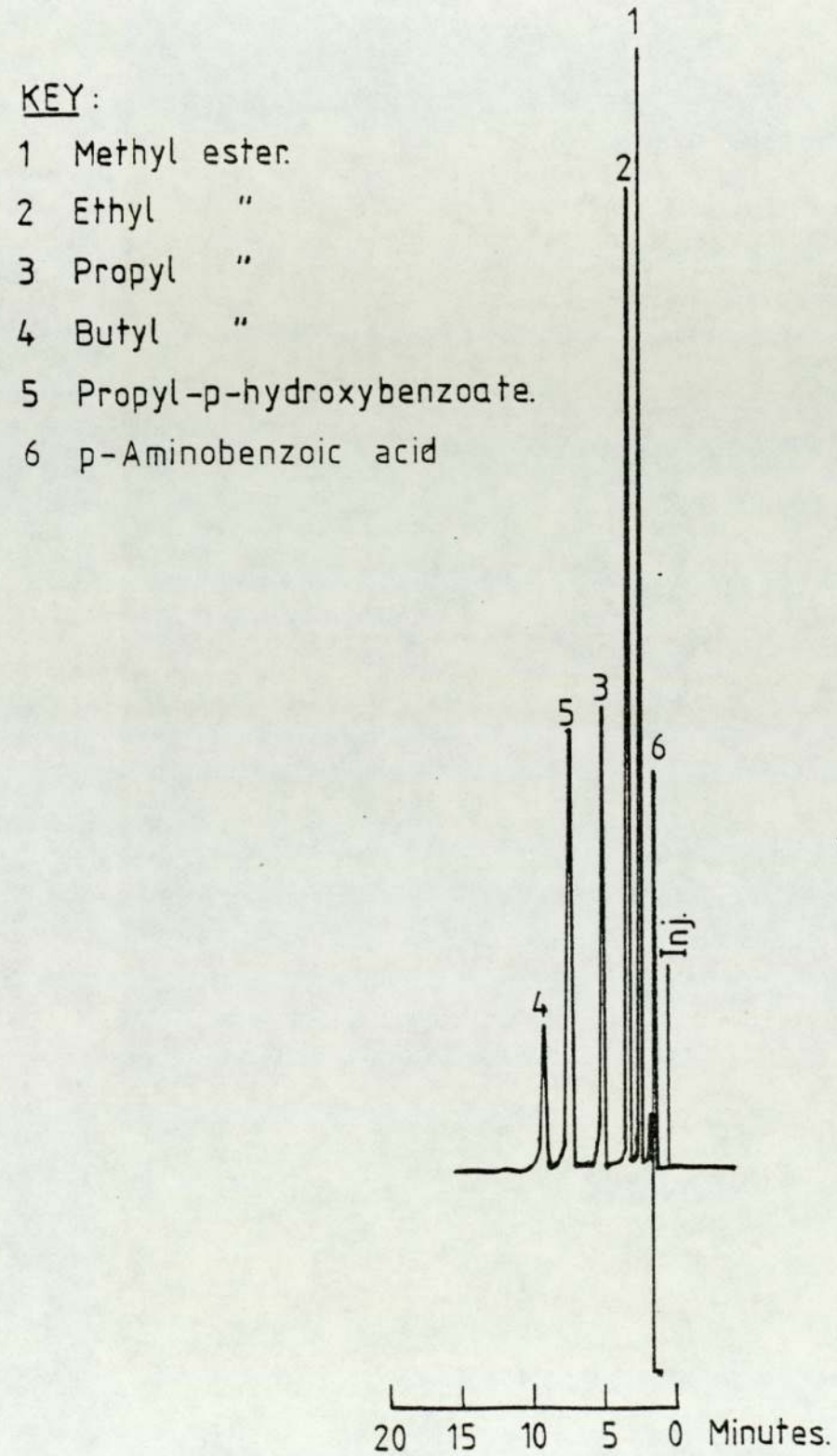
2.6.3 HPLC Analysis of Esters of p-Hydroxybenzoic Acid

A reverse phase system was developed for the assay of p-hydroxybenzoate esters. The mobile phase used was

Methanol	59%
Phosphoric acid in water (1:20)	1%
Water	to 100%

The mobile phase was pumped at a rate of 1 ml./min. (1,200 psi pressure) into an ODS Hypersil (5 μm.) column. Detection was by U.V. at 235 μm. Methyl salicylate was used as internal standard. The chromatogram obtained is shown in Fig. 2.16.

Fig. 2.14 A typical chromatogram for HPLC analysis of p-aminobenzoate esters



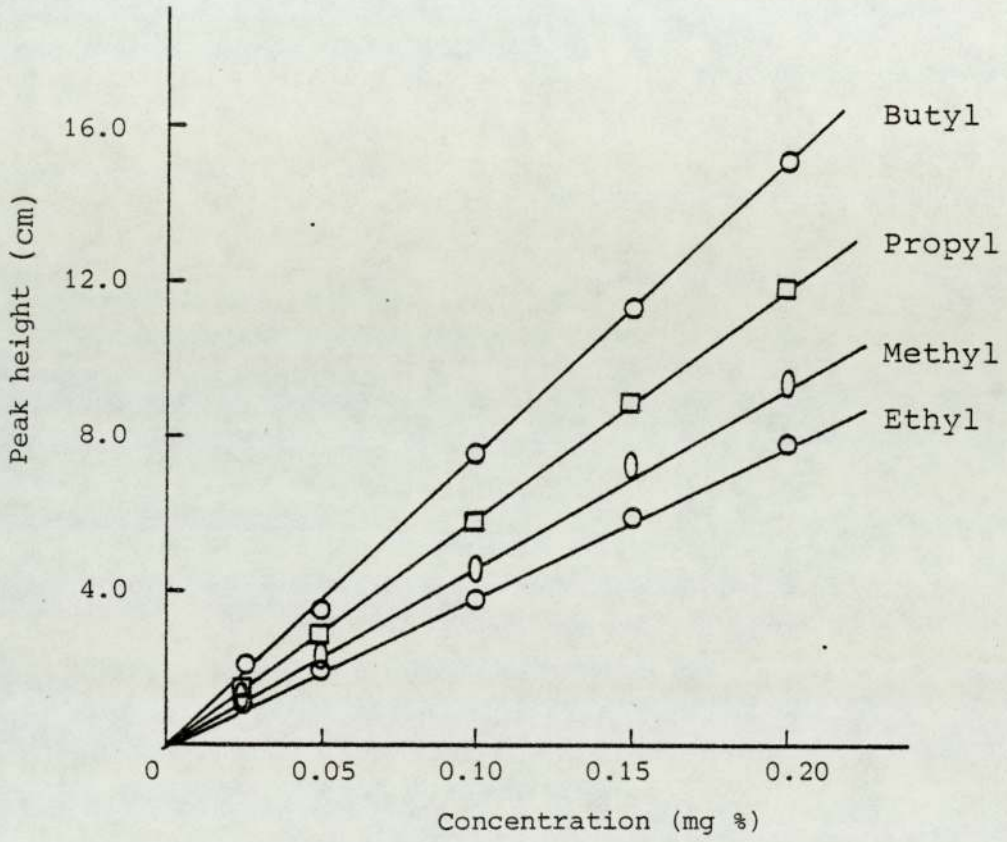


Fig 2.15 Typical calibration curves for HPLC analysis of p-aminobenzoate esters. Methyl and ethyl esters assayed at 0.08 sensitivity range, propyl ester at 0.04 range and the butyl ester at 0.02 range.

KEY:

1 Methyl ester

2 Ethyl "

3 Propyl "

4 Butyl "

5 Methyl salicylate.

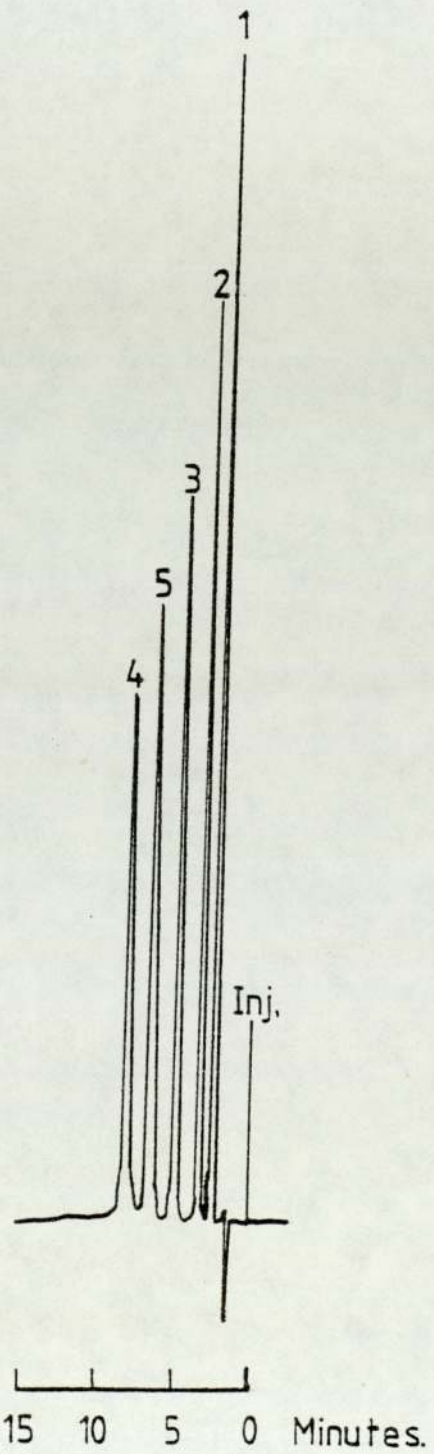


Fig 2.16 A typical chromatogram for HPLC analysis of p-hydroxybenzoate esters

2.7 DETERMINATION OF MELTING POINTS (CLOUD POINTS) OF TRIPALMITIN /TRIOLEIN MIXTURES

The amounts of tripalmitin and triolein required to make 10 g. of the appropriate composition were accurately weighed in a glass vial and melted in a water bath at 60°C. Each vial was, in turn, placed in a beaker containing melting ice and gently stirred until the cloudy point and the temperature recorded. The vial was then replaced in the 60°C water bath and the temperature at which the cloudiness disappeared was again recorded. Three samples of similar composition were used and the mean value was taken as the cloud point of the mixture.

CHAPTER 3

RELEASE OF DRUGS FROM HOMOGENEOUS GELATIN FILMS

3.1 INTRODUCTION

The release of drugs from gelatin films can be either dissolution or diffusion controlled. The kinetics of release by diffusion should be similar to those obeyed in other polymer matrices. Thus for a slab, the general release equations obtained by solving Fick's second law is given by

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{l^2}\right)^{\frac{1}{2}} \left(\pi^{-\frac{1}{2}} + 2\sum_{n=1}^{\infty}(-1)^n \operatorname{ierf}\frac{nl}{2\sqrt{Dt}}\right) \quad \text{--- 3.1}$$

or

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8 \exp\left(-D(2n+1)^2\pi^2 t/l^2\right)}{(2n+1)^2\pi^2} \quad \text{--- 3.2}$$

which simplify, at short and long times respectively, to

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi l^2}\right)^{\frac{1}{2}} \quad \text{--- 3.3}$$

and

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \exp\left(\frac{-\pi^2 Dt}{l^2}\right) \quad \text{--- 3.4}$$

In all the above equations, M_t is the amount of drug released at time t, M_∞ is the total releasable amount, l is the thickness of the film and D is the diffusion coefficient of the drug in the matrix.

In this chapter, the above equations will be used to evaluate the influence of polymer properties on drug release. Gelatin is a protein with a wide molecular weight range. Gelatins with differing characteristics and properties result from different sources and methods of manufacture (78). Due to the wide interbatch variations, attempts have been made to control the quality and properties of the gelatins used for pharmaceutical formulations (169). To a formulator, these variations together with other bulk properties, offer the prospects of a system which can be manipulated to provide the most suitable release behaviour.

Studies of diffusion of drugs through cross-linked gelatin gels has revealed a relationship between the diffusion coefficient (D) and the square root of the molecular weight ($M^{\frac{1}{2}}$) of the diffusant (180,181). This is different to the reported relationship between the diffusion coefficient and the logarithm of the molecular weight in other polymer systems (182,183) but in agreement with results reported in other studies (184,185). These discrepancies obviously point to some unresolved problems in our present knowledge of diffusion in polymer systems. Davis (128) related the diffusion coefficient to polymer concentration such that

$$D_p = D_o \exp\left[-(0.05 + 10^{-6}M)\ P\right] \quad \text{--- 3.5}$$

where D_p is the diffusion coefficient of the drug in a matrix of polymer concentration P, M is the molecular weight of the drug and D_o is the diffusion coefficient of the drug in the polymer-free solvent.

Nixon et al (186 - 188) made a systematic study of the diffusion of substances in gelatin gels. Using the method of Friedman and Kraemer (189), they observed that the diffusion coefficient decreases with increasing gelatin concentration and increasing bloom strength (186). They observed further that these changes could be wholly explained in terms of variation in the rigidity of the gels. This behaviour was attributed to decreasing porosity of the matrix with increasing gel rigidity. Thus rigidity could be taken as a measure of extent of cross-linking in the gel.

From the above discussion, it follows that any factor that affects gel rigidity will influence the diffusion of drug substances in the gel. Electrolytes, for example, are known to affect the rigidity of gelatin gels (187). An empirical equation was derived relating the rigidity of the gel to the ionic strength thus

$$G = G_o (1 \pm K \sqrt{I}) \quad \text{--- 3.6}$$

where G is the gel rigidity in presence of electrolyte

G_o is the rigidity of electrolyte-free gel

I is the ionic strength of the electrolyte

K is a constant.

It was observed that generally cations increased rigidity in glycero-gelatin gels while anions reduced it. A negative sign is therefore used in equation 3.6 for anions while a positive sign is used for cations. These empirical equations reinforce the observations made by

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Cumper and Alexander (190), that rigidity is a function of the square root of the ionic strength.

The use of gelatin in pharmaceutical preparations is mostly limited to systems which either dissolve or disintegrate to release their contents promptly; mainly as capsules or suppository bases. This probably explains the lack of interest among pharmaceutical researchers in studying diffusion behaviour in glycero-gelatin gels. Relatively more work has been done on the melting behaviour of gelatin gels. The early pioneering work of Ferry (95) on behaviour and properties of gelatin and gelatin gels has laid a firm foundation in this field.

That the melting point of gels increases with increasing gel rigidity is well documented (95 -191). Emphasis has therefore been placed on the rheological behaviour of gelatin gels. Much work has been done on this aspect and attempts have been made to explain and relate rigidity changes to gelatin concentration (95 ,195), temperature and previous storage history (192,193), bloom strength (188,194), plasticizer concentration (188) and crosslinker concentration (191,196). A series of publications by Robinson et al (197-201) systematically investigate the influence of various factors on the rheological properties of gelatin gels.

For those interested in release of drugs from gelatin gels, information on the melting point of the gels needs to be reinforced by information on the rate of melting or dissolution of the gel. It has been shown (202) that

the melting time of glycero-gelatin suppositories vary significantly depending on bloom strength and concentration of the gelatin. Since official capsules and suppositories presently in use are not meant for sustained action, the British Pharmacopoeia Commission (169) has imposed an upper limit to their dissolution time.

The dissolution behaviour of polymers has been well reviewed by Ueberreiter (203). The dissolution behaviour has been found to be strongly dependent on the physical state of the polymer and conditions under which dissolution is carried out. These are summarized in Fig. 3.1. Above the flow temperature (melting point), the polymer matrix exists as a liquid. Dissolution is therefore a simple process of mixing of two liquids. At this stage, the rate of stirring and viscosity of the two liquids control the dissolution rate. In the elastic state, i.e. between the flow temperature and the glass transition temperature (Tg) of the polymer, the surface layer is composed of an outermost liquid layer next to a gel layer (Fig. 3.1(d)). The formation of the gel layer could be the rate determining step in such cases. Below the glass transition temperature, a solid swollen layer and an infiltration layer coexist alongside the liquid and gel layers. The infiltration layer is basically the part of the polymer matrix which has been permeated by the solvent molecules but has not undergone changes in its basic properties. In this instance, the role of infiltration of the polymer by solvent molecules is important in determining the

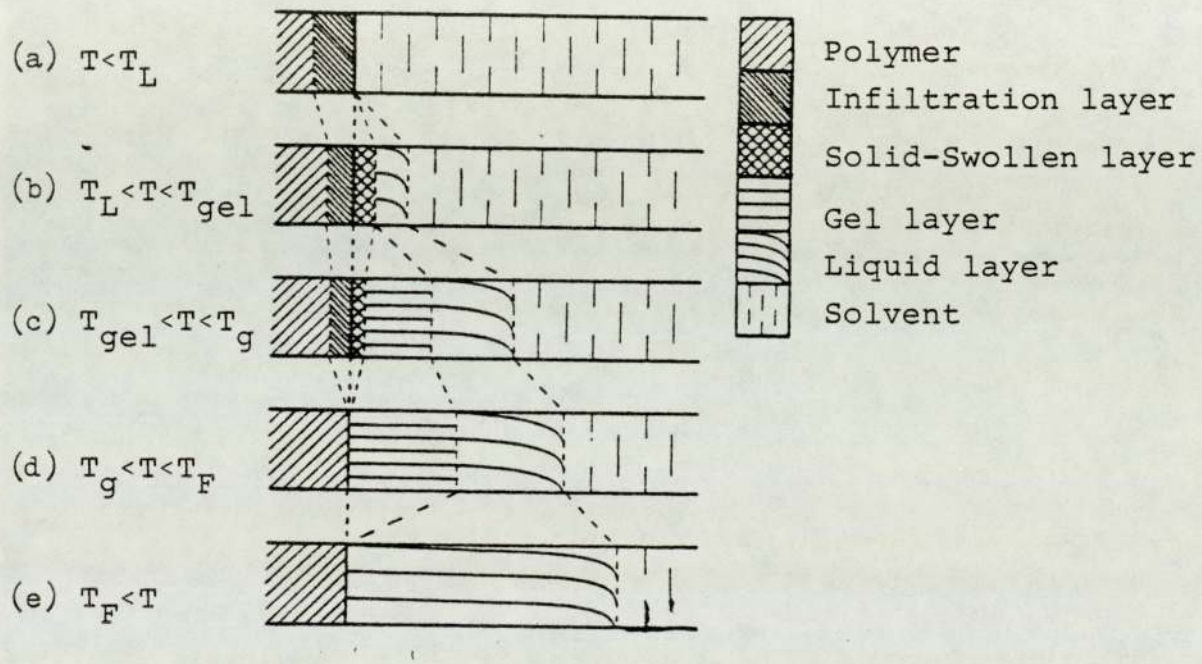


Fig 3.1 Schematic presentation of the composition of the surface layer during polymer dissolution.
T, temperature of the solution process;
T_L, solution temperature;
T_{gel}, gel temperature;
T_g, glass transition temperature;
T_F, flow temperature
(Extracted from Ref. No. 203)

dissolution rate. The rate of dissolution can also be controlled by the rate of transfer of macromolecules across the surface layers. When the surface layers are absent (i.e. below the solution temperature, T_L), the dissolution rate depends only on the infiltration of solvent molecules into the polymer. The dissolution rate in such cases is almost undetectable.

The dissolution rate of polymers is therefore dependent on the velocity of penetration of solvent molecules ($\dot{s}$) into the polymer. Ueberreiter (203) has derived the following relationship

$$\dot{s} = (\bar{D}/\delta)\ \phi_s \qquad \text{--- } 3.7$$

where δ is the thickness of the swollen surface layer and ϕ_s is the volume fraction of the solvent at the border plane of solvent and swollen layer. $\bar{D}$ is the mutual, mean volume diffusion coefficient which is a function of the diffusion coefficient of the solvent molecules and the apparent diffusion coefficient of the polymer molecules during swelling.

When considering the dissolution of a polymer at temperature T_1 in a solvent at temperature T_2 where $T_1 \angle T_2$, a complex situation arises. Firstly, due to heat transfer into the matrix, the state of the polymer will be affected. This change proceeds from the surface into the core of the matrix. Simultaneously, the dissolution process will commence, the behaviour of which will depend on the state of the surface layer which in turn depends on the temperature of the solvent and the

rate of heat transfer into the polymer. Thus dissolution of a polymer previously stored at a temperature below that of the release experiment depends on both heat and mass transfer.

It is quite obvious therefore that there is an important role played by thermal changes in the polymer. Attempts to determine the heat of fusion of gelatin were first made by Holleman et al (204) in 1934, by an indirect method. Recently, Differential Scanning Calorimetry (DSC) has been used to determine the heat of fusion of the gels and therefore explain thermal changes involved in the gelatin-collagen transition (205-207). DSC is a useful tool in thermal studies and provides a method for determining important thermal characteristics of polymers and other substances fairly accurately (87, 207). Its use in dissolution studies could provide more information on the role of heat transfer in the dissolution process.

An interesting report (165) has shown that the dissolution of gelatin gels can be explained in terms of mass transport across a diffusional layer according to the modified model of Noyes and Whitney (208)

$$\frac{dW}{dt} = k\,S\,(C_s - C) \qquad \text{--- } 3.8$$

where dW/dt is the rate of dissolution (in weight per unit time), S is the surface area of the dissolving solid, C_s is the concentration of the polymer on the liquid/solid interface, C is the concentration of the polymer in the

bulk of the solvent and k is the dissolution rate constant.

Using this equation, Hom et al (165) evaluated the influence of various factors on the dissolution of gelatin films. This successful modelling of dissolution on mass transfer processes seems to show that mass transfer overshadows the effect of heat transfer. Bearing in mind however, that mass (diffusive) transfer and heat transfer have similar kinetic patterns, it is quite possible that the above modelling does not identify the rate-limiting step.

The aims of this work

This study aims to

a) study the release behaviour of lignocaine hydrochloride from soluble gelatin films

b) investigate any possible relationship between the rate of dissolution of gelatin gels and their thermal properties

c) study the release rate of lignocaine hydrochloride from gelatin films by diffusion and the influence of matrix factors on its diffusion.

3.2 EXPERIMENTAL

3.2.1 Preparation of Gels

Gels used in this study contained 20% w/w gelatin of the appropriate bloom strength and 3% w/w lignocaine

hydrochloride in distilled water. They were prepared by adding 20 ml. of a 7.5% w/v solution of lignocaine hydrochloride in water to 20 g. of gelatin and making up to 100 g. with more distilled water. When glycerol had to be added, the appropriate amount of glycerol was mixed with 20 ml. of the lignocaine solution, made up to 80 g. with more distilled water and stirred to a clear solution before adding 20 g. of gelatin. The mixture was left standing for 2 hours before melting at 60°C for 30 minutes.

0.6 mm. films were cast using the method described in section 2.4.4

3.2.2 Release Experiments

The same apparatus described in section 2.5.2 were used. In this case the filter paper was not used, thus the film was clamped directly under the wire mesh. The receiver phase was 500 ml. of distilled water and release was performed at 25°C and 37°C for diffusion and dissolution studies respectively. The assay of lignocaine content was by the HPLC method described in section 2.6.1

3.2.3 Preparation of Formaldehyde-Hardened Gels

Method A: this involved the addition of a warm formaldehyde solution to a molten gel containing appropriate amounts of gelatin and lignocaine hydrochloride. The addition was slow, under stirring. Films were cast immediately after.

Method B: Lignocaine hydrochloride was dissolved in water. Appropriate quantities of the lignocaine solution and a formaldehyde stock solution were mixed and made up to the required weight by adding more distilled water. The appropriate quantity of gelatin was then added and the mixture allowed to stand for 2 hours. The gel was then melted at 60°C until no air bubbles remained (3 hours) before casting of the films.

All films contained 3% w/w lignocaine hydrochloride and the range of formaldehyde concentration used was from 0.02 to 0.075% w/w.

3.2.4 Differential Scanning Calorimetry (DSC)

DSC was used to determine the melting point, melting range and the heat of fusion of some gelatin gels of varying bloom strength and glycerol concentration. The instrument used was a Dupont 910 Differential Scanning Calorimeter (DSC) system linked to a Dupont 1090 Thermal Analyser, programmed to determine the melting point and to calculate the heat of fusion (213). Several reviews on the theory and applications of DSC are available (214-216).

The gel samples were prepared as in the normal release experiments but without the lignocaine (section 3.2.1). They were placed in airtight glass vials and stored at 25°C for 3 days. About 20 mg. of the gel was then placed on a DSC capsule which was then hermetically sealed to restrict loss of moisture, and left at 15°C for 12 hours.

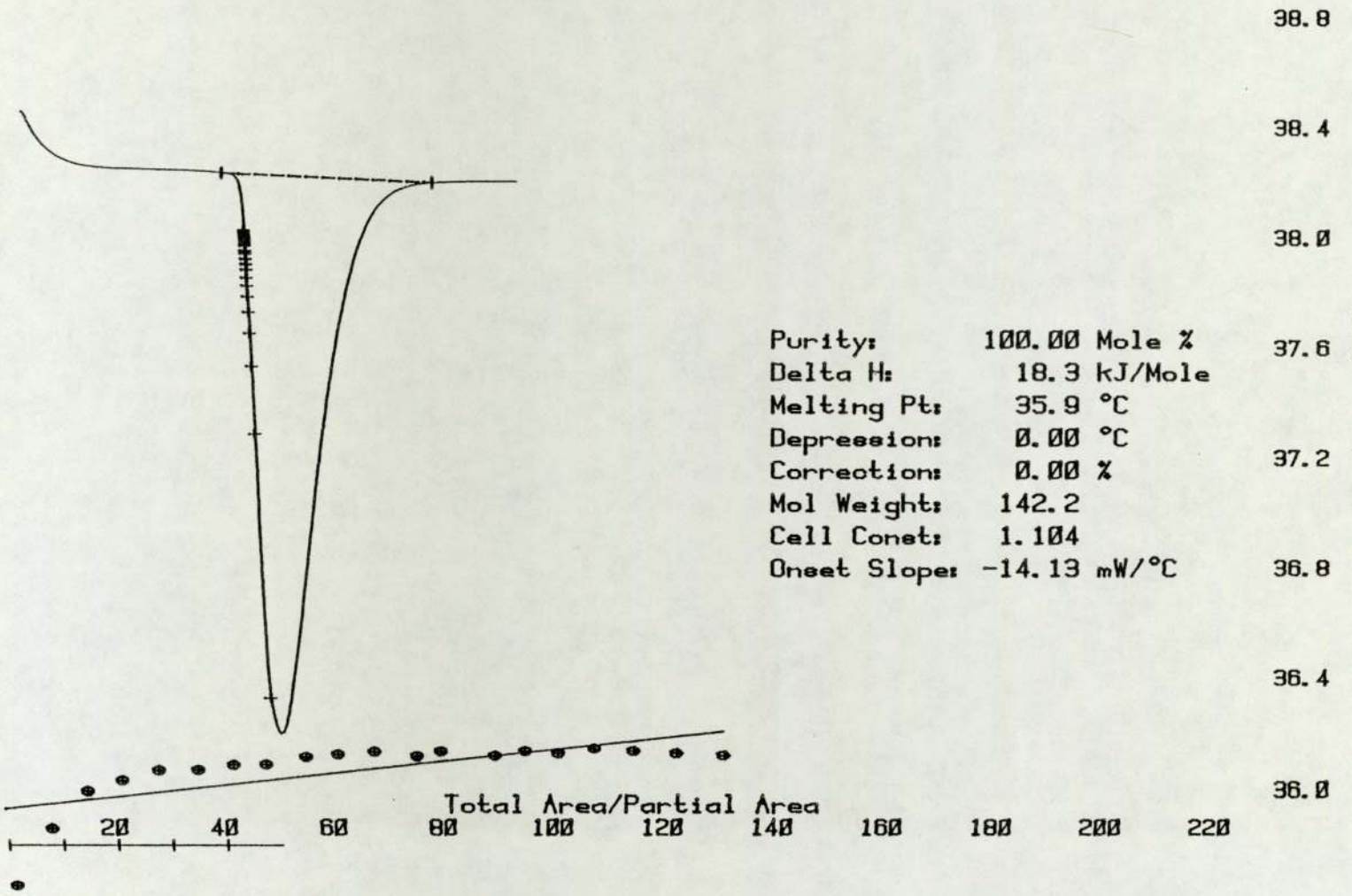
The calorimeter was calibrated using Napthol-2-hydroxyl against an empty capsule (Fig. 3.2). The samples were heated from 15°C to 60°C at a rate of 5.0°C per minute. Fig. 3.3 shows a typical DSC endotherm obtained. Generally, the values of heat of fusion obtained (Table 3.1) was much lower than that obtained by other investigators (85, 206) who obtained ΔH values of around 4.0 $cal.g^{-1}$. This was not surprising since the gelatins used in this experiment were very alkaline (Isoelectric point of 8.9) and produced very weak gels.

3.3 RESULTS AND DISCUSSION

3.3.1 The Dissolution-controlled Release of Lignocaine HCl from Gelatin Gels

The aim of this study was to investigate whether heat transfer-related changes may be rate-limiting in the dissolution of gelatin gels. The Noyes-Whitney model for dissolution of solids is applicable only where the diffusion of the dissolved solid molecules in the stagnant liquid layer at the surface of the solid is rate limiting. When steady state mass transfer conditions persist, then the dissolution rate with normalised surface area will be zero order as has been observed by Hom et al (165). Zero order kinetics are also obtainable when surface area is approximately constant and when the release is controlled by the dissolution of a polymer matrix (138). Thus if the rate of melting determines the

Fig 3.2 Calibration of DS calorimeter using Naphthol-2-hydroxy



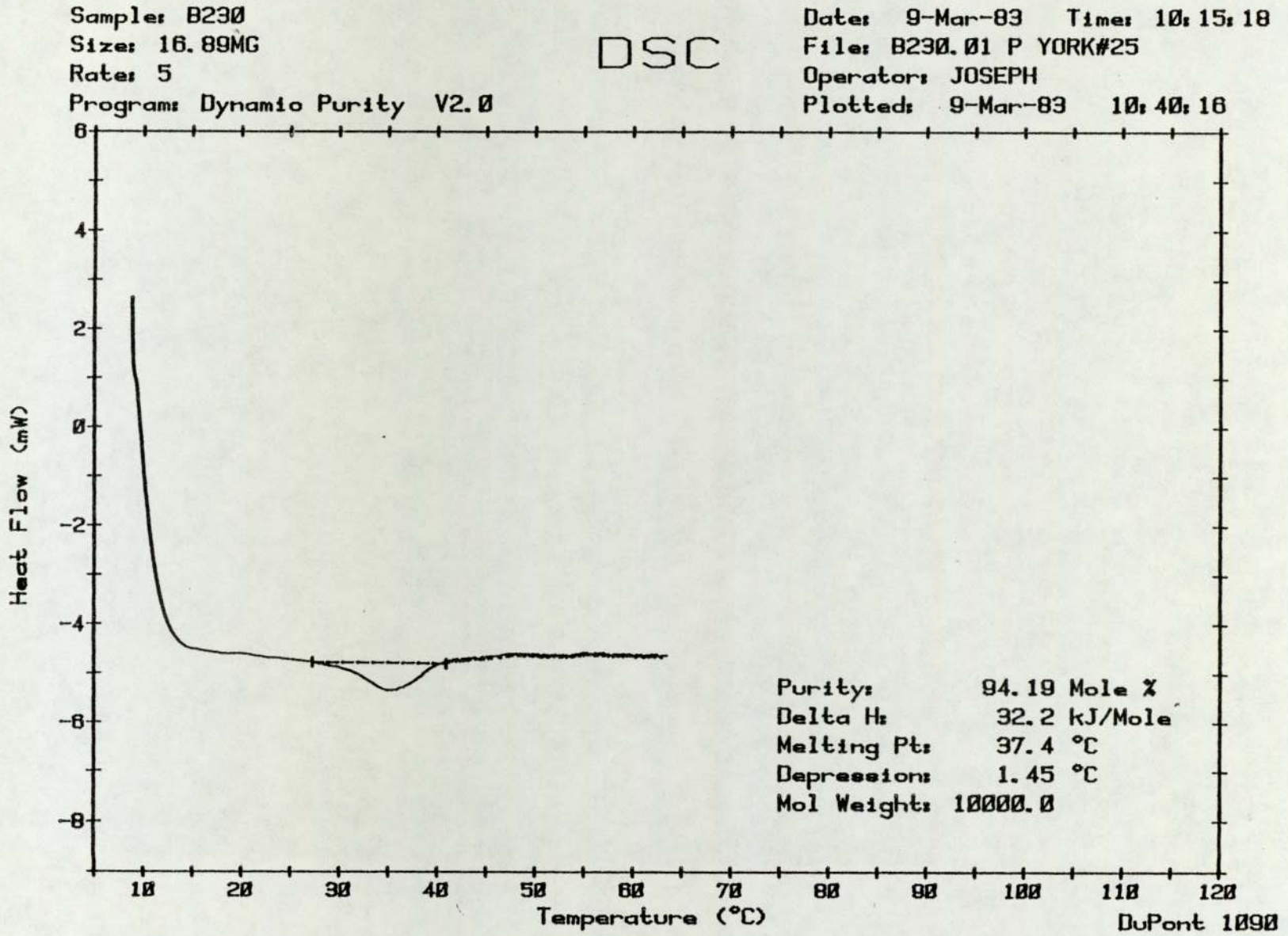


Fig 3.3 A typical DSC endotherm of a gelatin sample

TABLE 3.1

Thermal Properties of Gelatin Gels

Bloom Strength	Concn. of Glycerol (% w/w)	Approx. Melting Range	Mpt. °C (Peak)	Heat of Fusion ΔH (Cal/g.)	k' ($mg.cm^{-2}.min^{-1}$)
90	-	30-39°C	33.3	0.249	0.148
150	-	29-40	35.0	0.445	0.1031
200	-	29-40	36.9	0.645	0.0749
230	-	29-40	37.4	0.770	0.0571
200	5%	28-42	38.2	0.660	0.1001
200	10%	26-44	37.9	0.605	N/D
200	20%	23-47	38.0	0.770	0.1082
200	40%	22-50	38.2	1.286	0.1178
200	60%	22-56	39.0	2.727	0.1404

release behaviour then zero order release can also be expected.

This section examines this possibility in systems of varying bloom strength and glycerol concentrations.

a) The influence of bloom strength on dissolution

Bloom strength is a measure of rigidity which is a function of molecular weight and extent of crosslinking in the gel. When the Noyes-Whitney model is applied in the case of varying bloom strength, one expects that the term C_s in equation 3.8 will be affected by virtue of reduction in macromolecular activity due to increased molecular weight or increased cross-linkage. When melting is considered, then increased molecular weight and cross-linkage should cause an increase in the melting point. It is not certain from literature, however, if the melting temperature range, which is more significant in gels, is affected or not. The melting points and melting temperature ranges of gelatins of varying bloom strengths were therefore determined by DSC. It can be observed (Table 3.1) that the melting point increases with the bloom strength (Fig. 3.4) but the melting range remains almost constant.

Figs. 3.5 and 3.6 show the variation of release rate of lignocaine from gels of varying bloom strength. The relationship obtained in Fig. 3.6 is similar to that observed by Hom et al (165). The rate constant (k') was determined from the relationship

$$\frac{W}{S} = k' t \quad \text{--- 3.9}$$

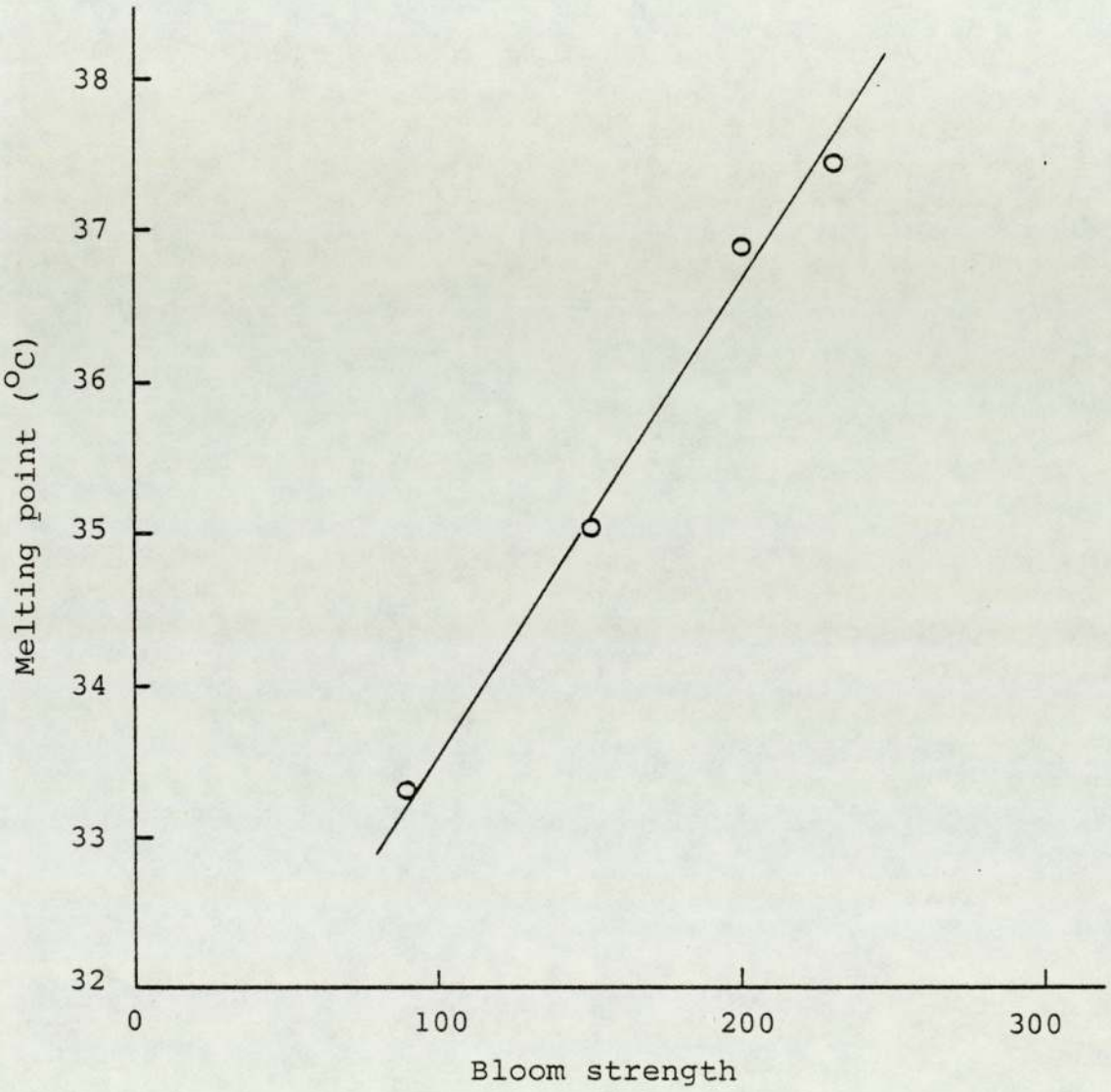


Fig 3.4 The variation of melting points of 20% $^{w}/_{w}$ gels with bloom strength.

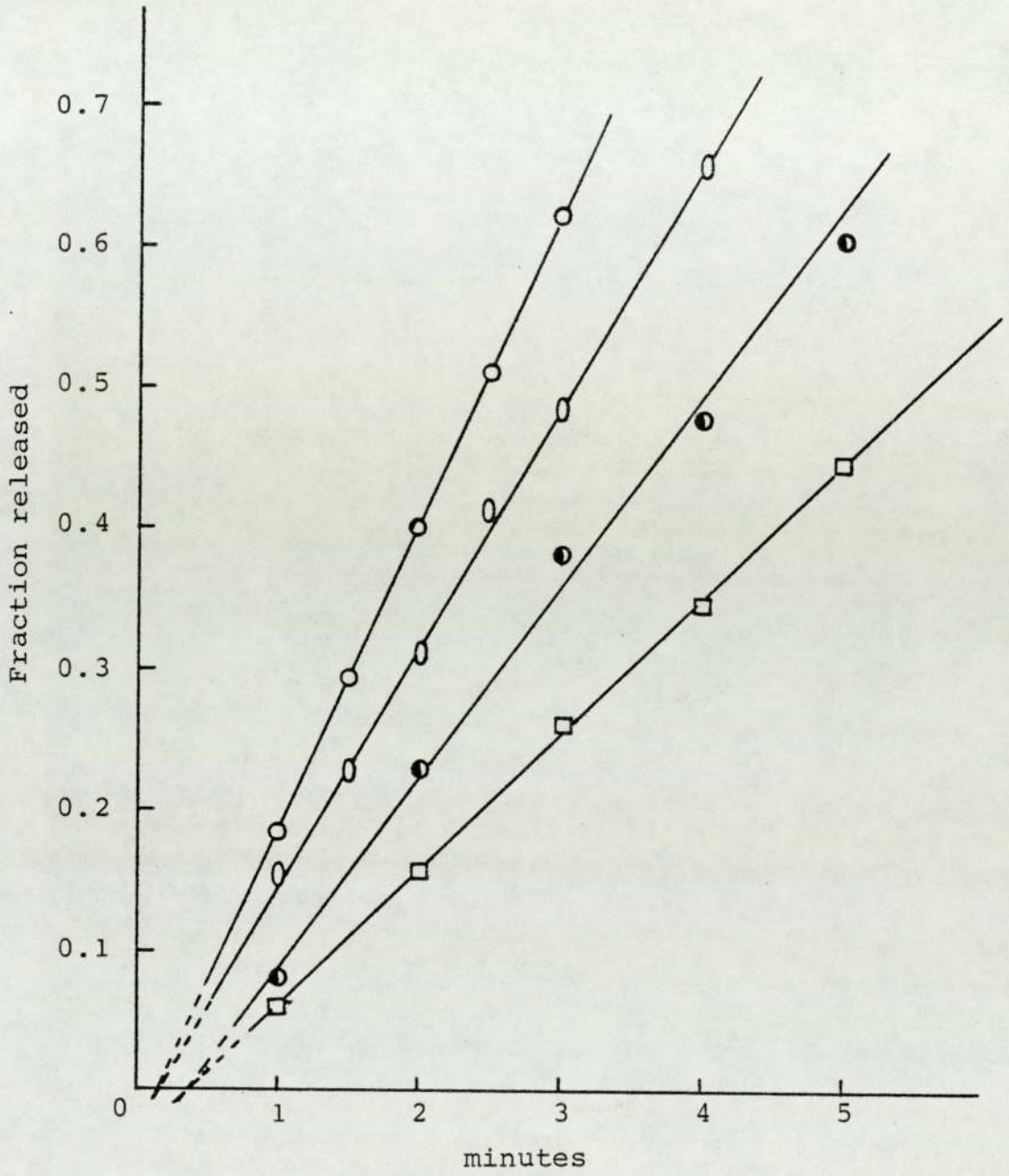


Fig 3.5 The release of lignocaine hydrochloride from 20% $^{w}/_{w}$ gelatin gels by dissolution. Influence of bloom strength. O 90 bloom, 0 150 bloom, ◐ 200 bloom, □ 230 bloom.

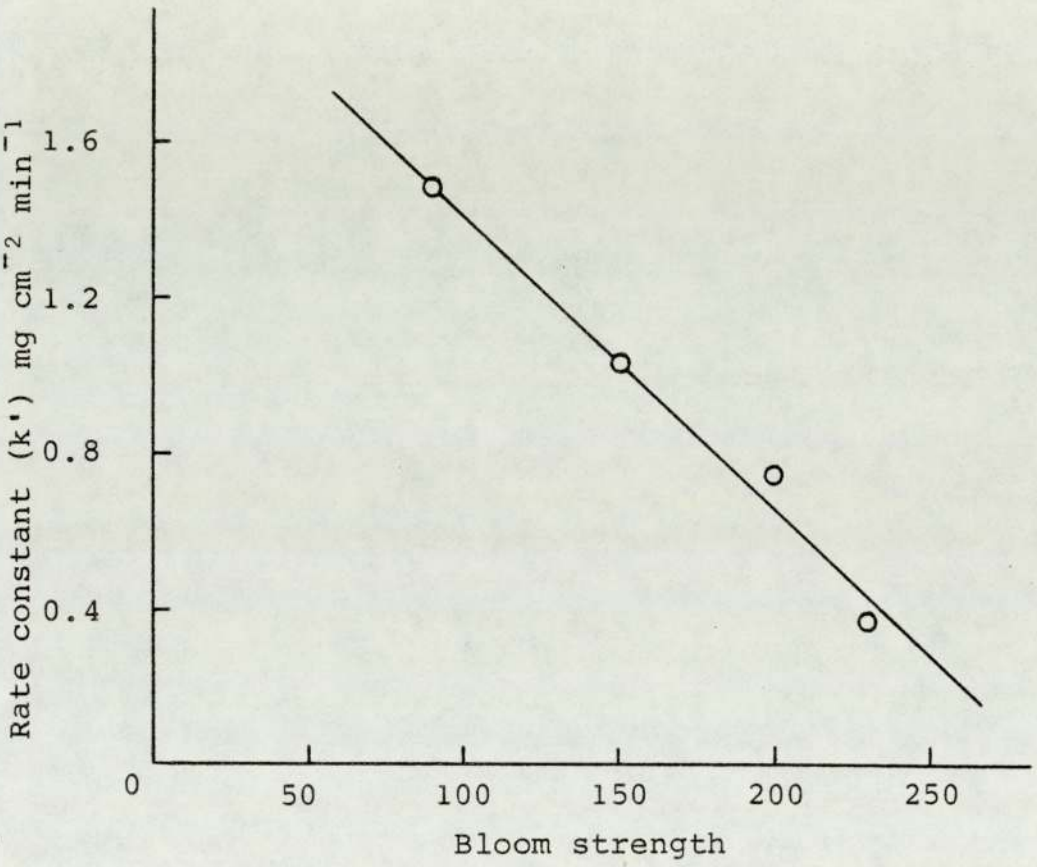


Fig 3.6 The influence of bloom strength on the dissolution rate constant of gelatin gels.

where W is the amount of drug released from the film of surface area S. It is necessary to explain at this juncture that k' is simply a zero order rate constant (units mg. cm^{-2}. min^{-1}) and should not be confused with the rate constant in equation 3.8 which has the units of distance per time.

Hom et al (165) concluded that the linear relationship obtained between k' and the bloom strength suggests that the Noyes-Whitney model is applicable. This is probably a premature conclusion since all that the relationship demonstrates is that a factor connected with bloom strength, in their case the concentration of gelatin in the gel, varies directly with the dissolution rate. It is therefore not surprising that a plot of heat of fusion of the gels (see Table 3.1) against the constant k' produces a linear relationship (Fig. 3.7). Apparently, the heat of fusion of gels vary directly with bloom strength (Fig. 3.8). Kellaway and Marriott (194) have shown that the dissolution rate of gelatin gels varies with their rigidity. Both changes in bloom strengths and gelatin concentration affect the rigidity of the gel. They also observed a direct relationship between the rigidity and melting point of the gels. Their results, together with those reported in here, strongly favour a dissolution process controlled by the solid to liquid transition (melting).

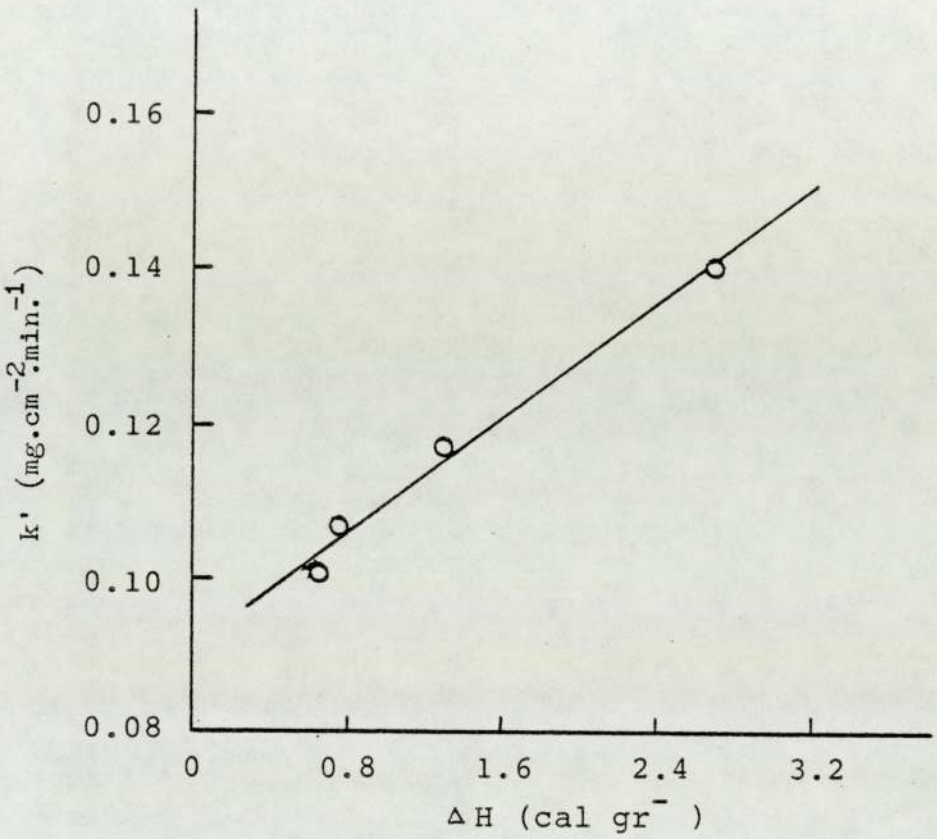


Fig 3.7 The relationship between the dissolution rate constant (k') and the heat of fusion (ΔH) of 20% $^{w}/_{w}$ gels of gelatins of different bloom strengths.

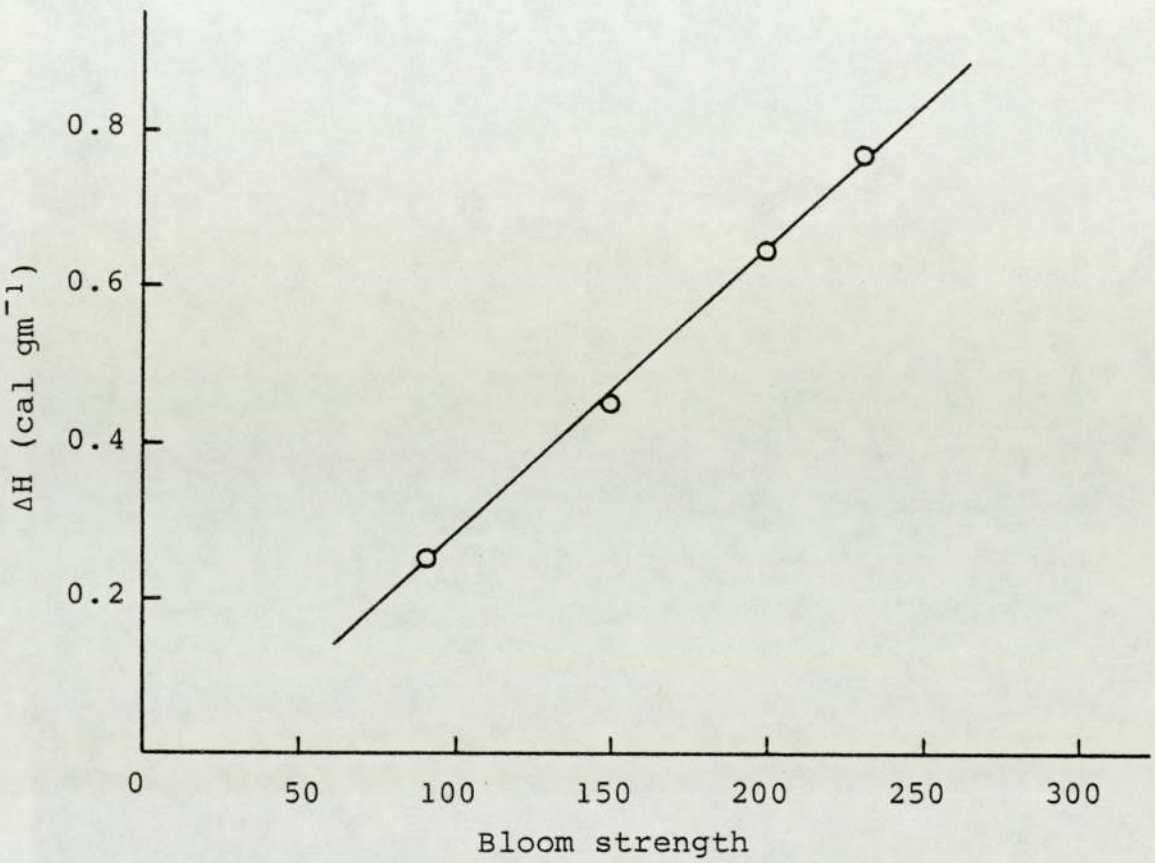


Fig 3.8 The relationship between the heat of fusion and bloom strength of 20% $^{w}/_{w}$ gels.

b) The influence of glycerol concentration

Glycerol is usually added to gelatin gels to improve mechanical properties of the gels. It has been reported to increase the rigidity of the gels (186). The system therefore provides a method of studying the role of rigidity in the dissolution of the gels. Preliminary studies of the melting behaviour of glycero-gelatin gels were initially performed. The thermal behaviour is summarized in Table 3.1. It is observed that whereas the melting point of gels with varying concentrations of glycerol remains constant, the melting range increases appreciably with increasing glycerol concentration. The heat of fusion shows a characteristic variation (Fig. 3.9), similar in shape to that of variation of the viscosity of glycerol/water mixtures (Fig. 3.10). Indeed a direct relationship is obtained between the heat of fusion of the gel and the viscosity of the glycerol/water mixture used in the preparation of gels (Fig. 3.11). It can therefore be inferred that the heat of fusion of the gels depends on the microviscosity of the gel. Ueberreitter (203) has discussed the influence of viscosity on the dissolution of polymers, explaining that the increased viscosity causes decreased freedom of movement of the macromolecular strands, hence slower diffusion-controlled dissolution. Since melting involves increased molecular movements, it is quite possible that viscosity increases the melting range by reducing such freedom of movements of the strands.

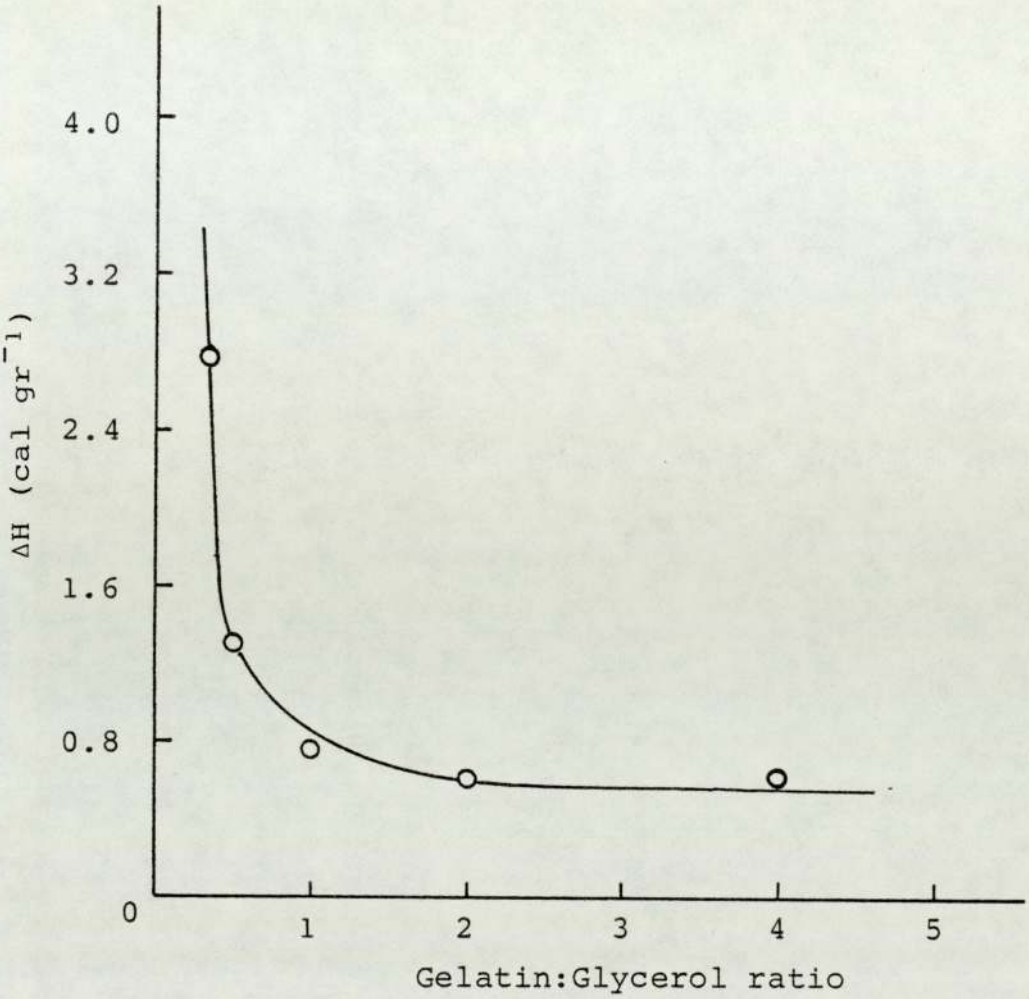


Fig 3.9 The relationship between the heat of fusion and the glycerol concentration of gelatin gels.

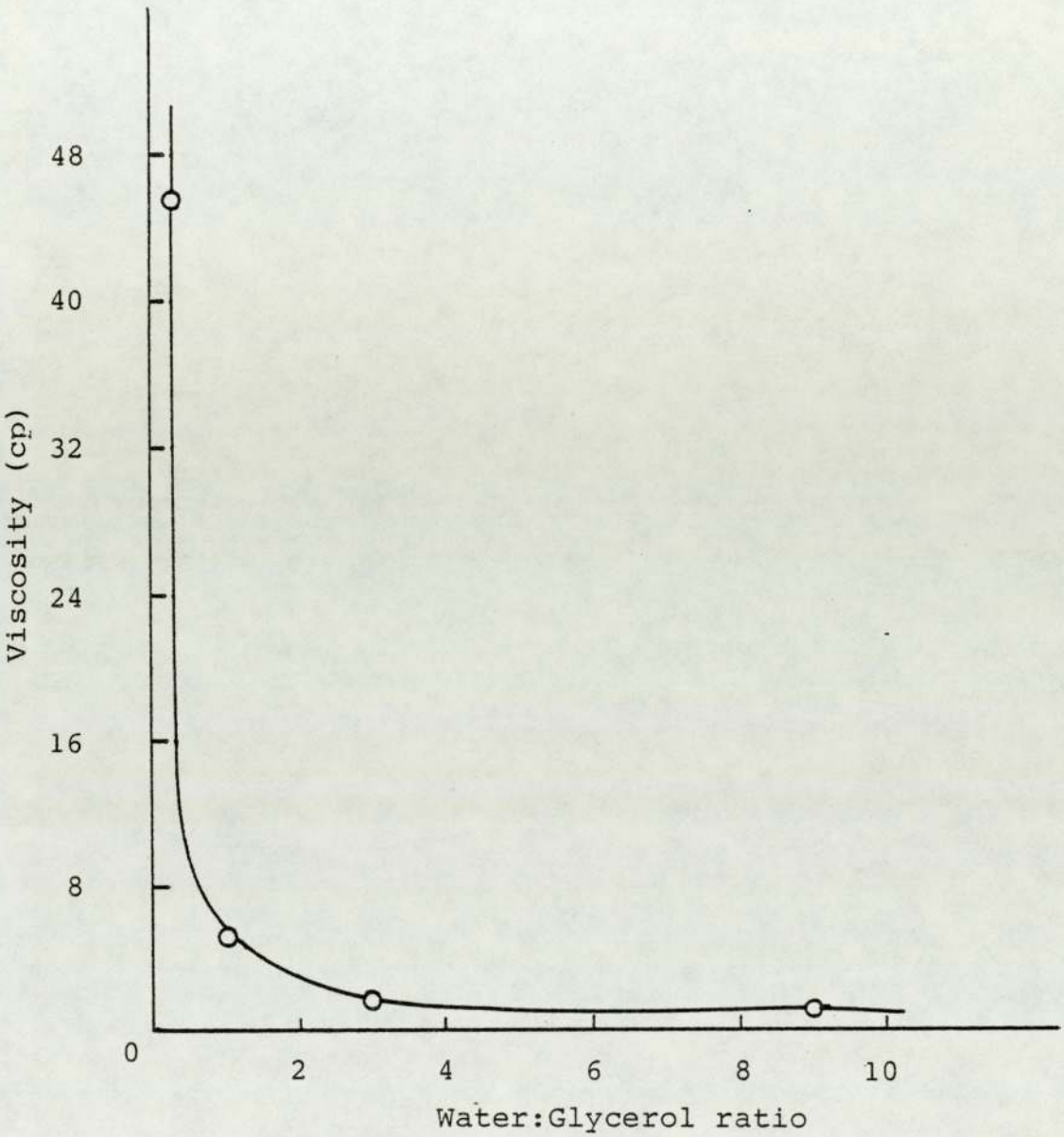


Fig 3.10 The viscosity of water/glycerol mixtures at 25°C.

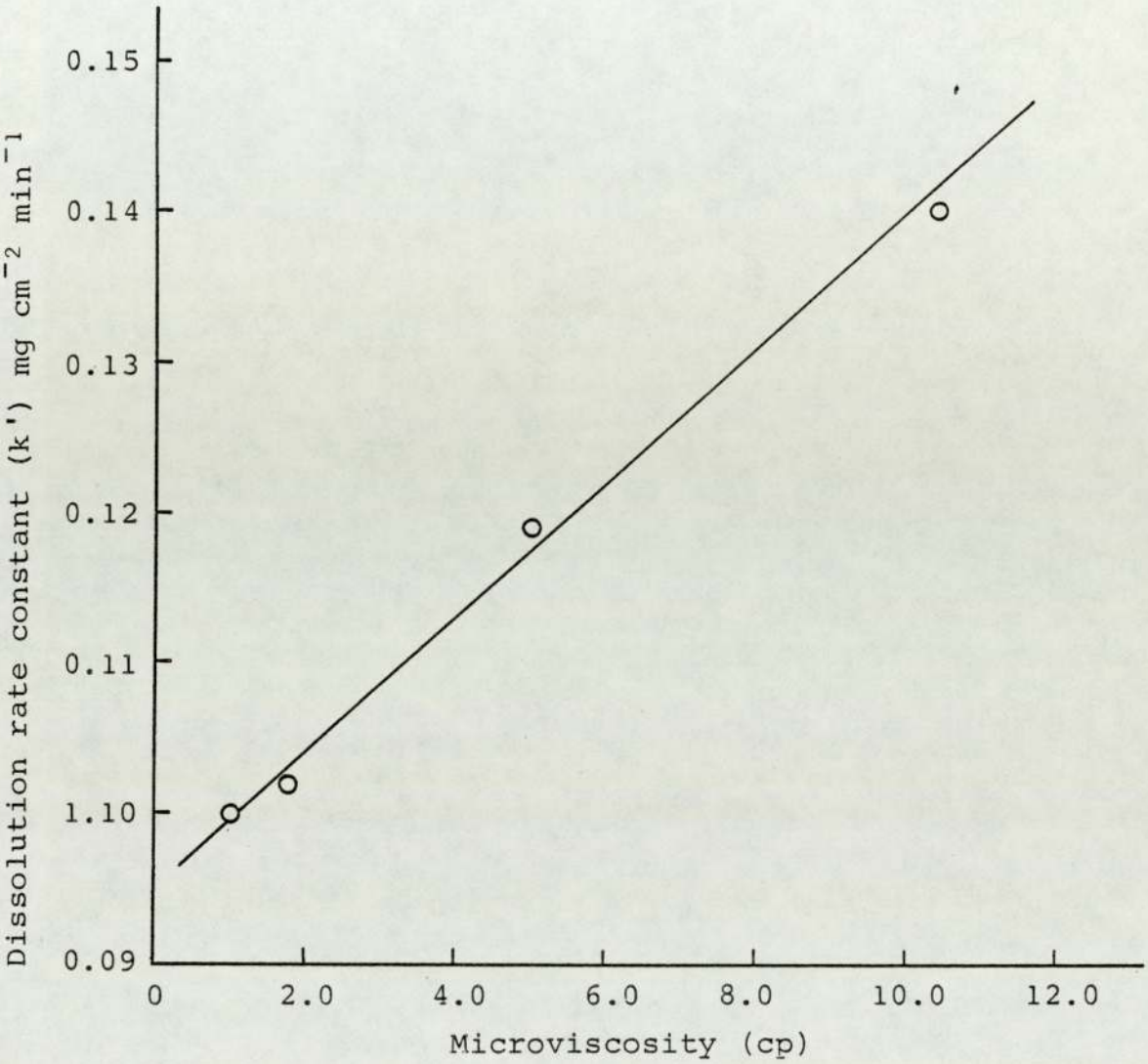


Fig 3.11 The influence of glycerol concentration on dissolution of glycerogelatin gels: The apparent relationship between the dissolution rate constant and the microviscosity of the gel.

The dissolution rate of glycero-gelatin gels was then studied. The influence of glycerol concentration on the rate constant (k') is shown in Fig. 3.12. The behaviour is similar to that reported by Hom et al (165) but does not show the second decay phase. The results therefore indicate that the dissolution rate increases with increasing glycerol concentration. The shape of the curve is again similar to those of the influence of glycerin on viscosity of water/glycerol mixtures (Fig. 3.10) and on the heat of fusion of glycero-gelatin gels (Fig. 3.9). This may lead to the conclusion that dissolution is also a function of viscosity. However, it should be noted that the dissolution rate increases with increasing glycerol concentration. This cannot be ascribed to changes in viscosity since the microviscosity increases with glycerol concentration (Fig. 3.13). If mass transfer is the rate-limiting step, the Stokes-Einstein equation would indicate that the dissolution rate should be inversely related to the microviscosity of the phase through which diffusion occurs. Fig. 3.14 shows that the rate constant increases with the heat of fusion of the gels. This is again contrary to expectations. The data however does not exclude the possibility that heat-induced phase transition is a prerequisite for dissolution. Glycerol concentration, as noted, changes the viscosity, the heat of fusion and the dissolution rate of the gel.

The use of glycerol in gelatin gel is to improve the mechanical properties of the gels. Plasticizers in general are thought to exert their effect by increasing

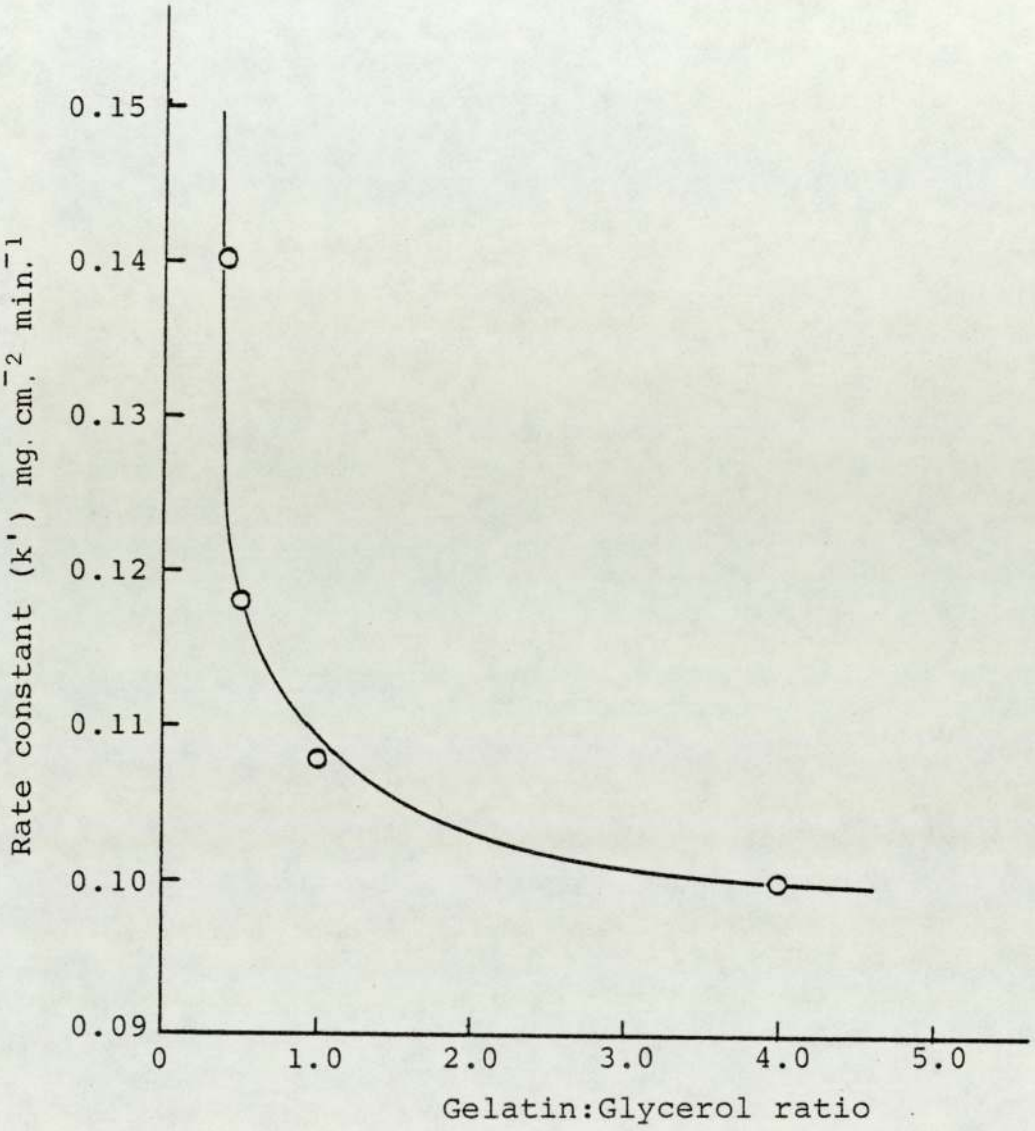


Fig 3.12 The influence of glycerol concentration on the dissolution rate constant of 20% gelatin gels at 37°C.

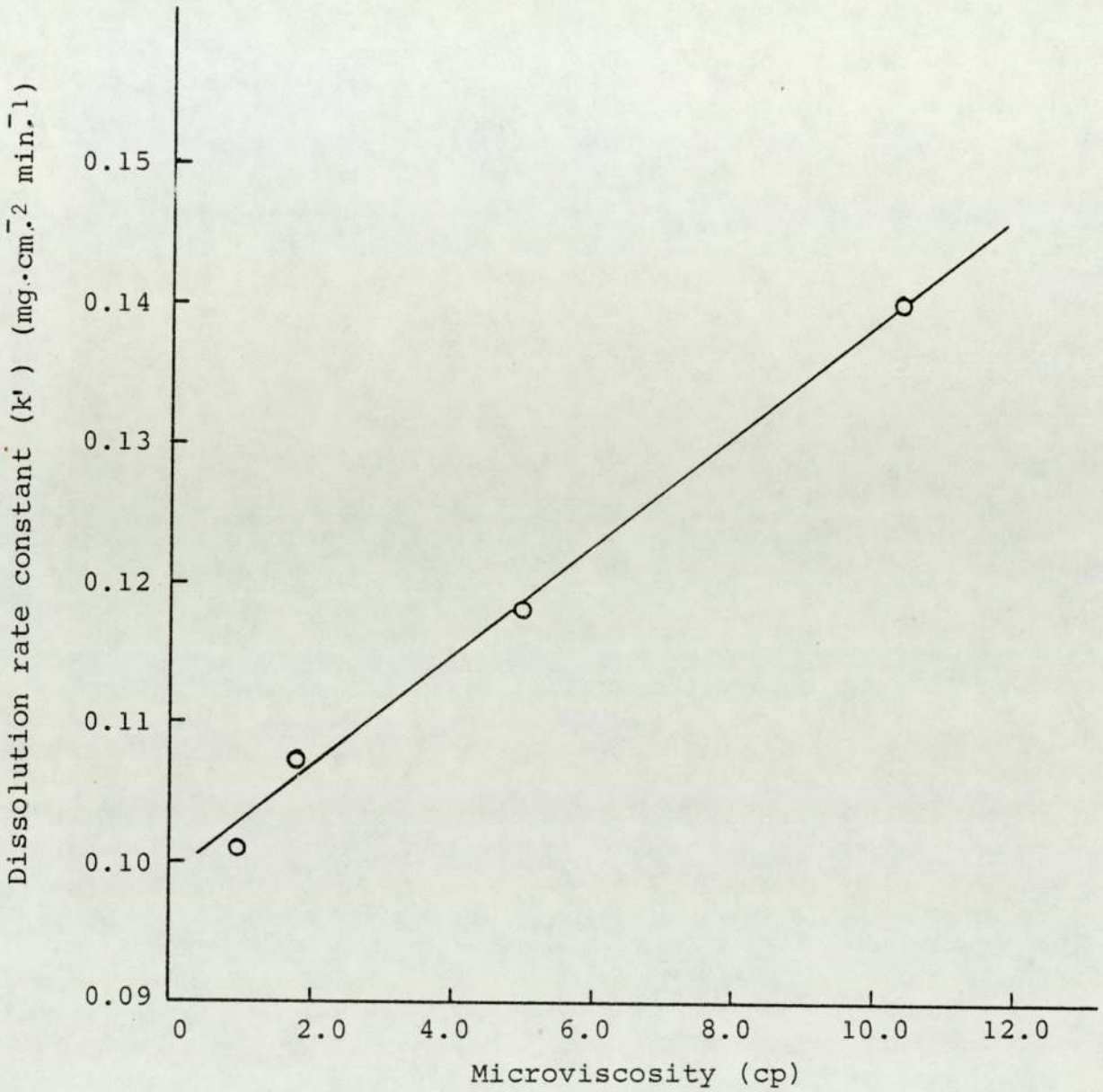


Fig 3.13 The relationship between the dissolution rate constant (k') and microviscosity of the gel.

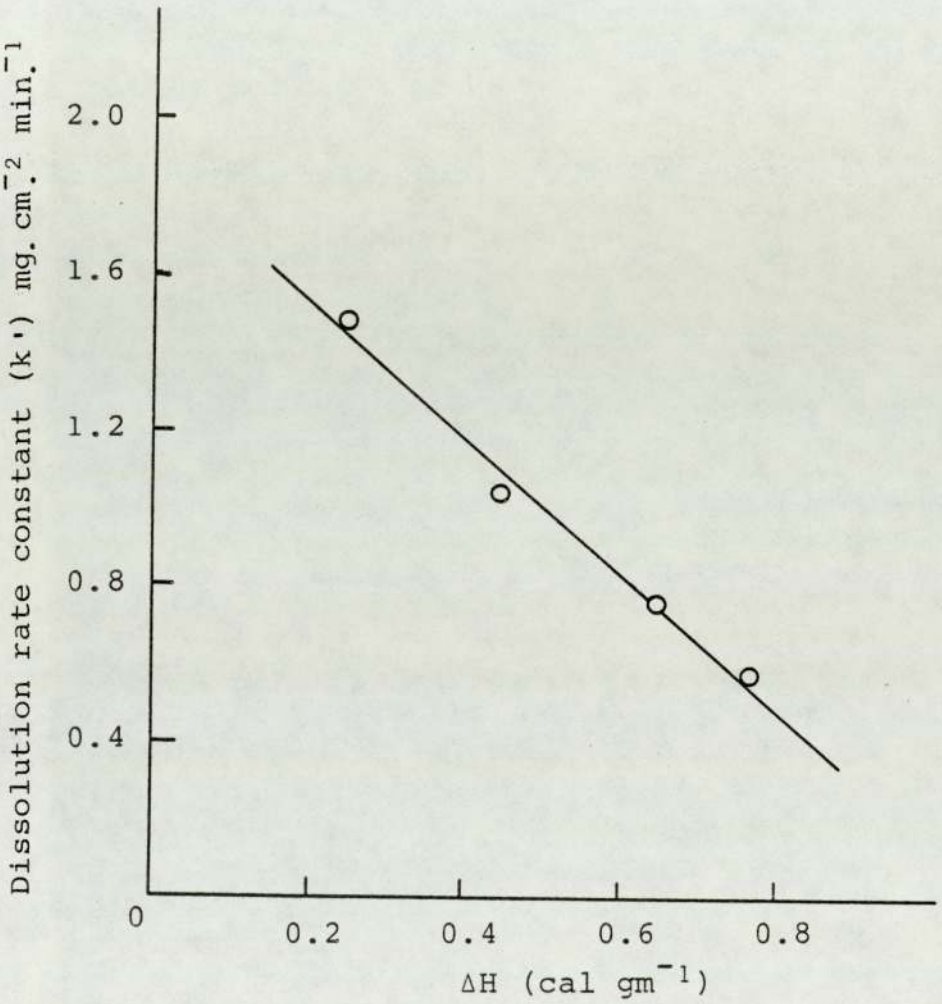


Fig 3.14 The influence of glycerol concentration on dissolution of gelatin gels: the relationship between the heat of fusion (ΔH) and the release rate constant (k')

molecular or segmental mobility of polymers by infiltrating the polymer structure (87, 210). Thus plasticization implies reduction in intermolecular forces, particularly those imparting frictional resistance within the polymer without weakening of the gels. The effect of plasticizer certainly affects cohesive forces in the polymer and this may be the cause of the increased dissolution rate. Plasticization usually causes a decrease in the glass transition temperature (Tg) (210) and hence increasing mobility in the amorphous solid state.

3.3.2 Diffusive Release of Lignocaine Hydrochloride From Gelatin Films

In the introduction it was explained that diffusive release of medicaments from gelatin gels has been shown (186-188) to depend on gel factors such as gelatin concentration, bloom strength and ionic strength. This effect was attributed to pore size of the gel network (187). It is only rational therefore, that in attempting to slow down the release of medicament from the matrix, pore size reduction would be a prime target. The influence of factors that affect the pore size of the gel on the release of lignocaine hydrochloride was therefore studied.

The release of lignocaine hydrochloride from a 20%, 200 bloom gelatin gel shows the normal initial $\sqrt{t}$ behaviour typical of diffusion-controlled release (Fig. 3.15).

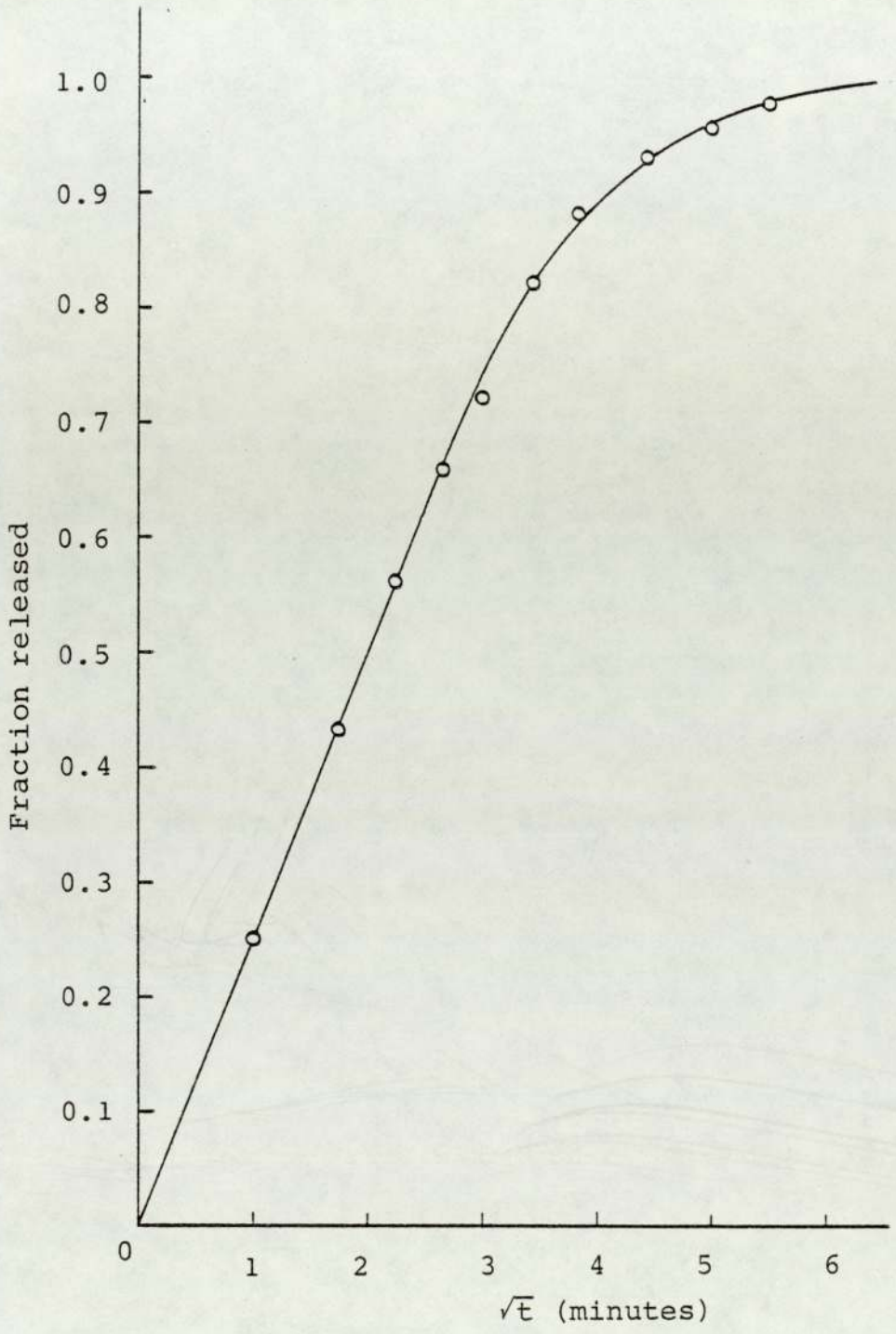


Fig 3.15 Diffusive release of lignocaine hydrochloride from 200 bloom (20% $^{w}/_{w}$) gelatin gel at 25°C.

The late phase also demonstrates the log-normal release pattern expected in such cases (Fig. 3.16). The diffusion coefficients of the drug in the gelatin gels can therefore be evaluated by using either of equations 3.3 and 3.4. The calculated value of D in the data portrayed on Figures 3.2 and 3.3 was 76.495×10^{-4} $cm^2 . hr^{-1}$.

The influence of gel factors on release was then studied. Figs. 3.17 and 3.18 show that no changes on the release of lignocaine hydrochloride are observed when gelatin concentration and the bloom strength of the gel are varied. This contradicts the previously reported behaviour (186). In the previous study the diffusant used was methylene blue, which was observed to have a tendency to aggregate. The aggregation would therefore increase the effective molecular volume and hence make it more sensitive to the pore size of the matrix. The role of molecular volumes on diffusion and the contribution of various groups has been reviewed by Flynn et al (182). It can therefore be suggested that the lignocaine hydrochloride molecules are too small to be influenced by the gelatin matrix. The release of lignocaine, like that of benzocaine in cellulose gels (209), ibuprofen in alginate gels (211) and salicylic acid in some HEMA gels (212) is solution-diffusion controlled.

Normal gelatin gels are soluble in water after considerable swelling. This solubility is greatly reduced by cross-linking agents (181, 196) which are mainly

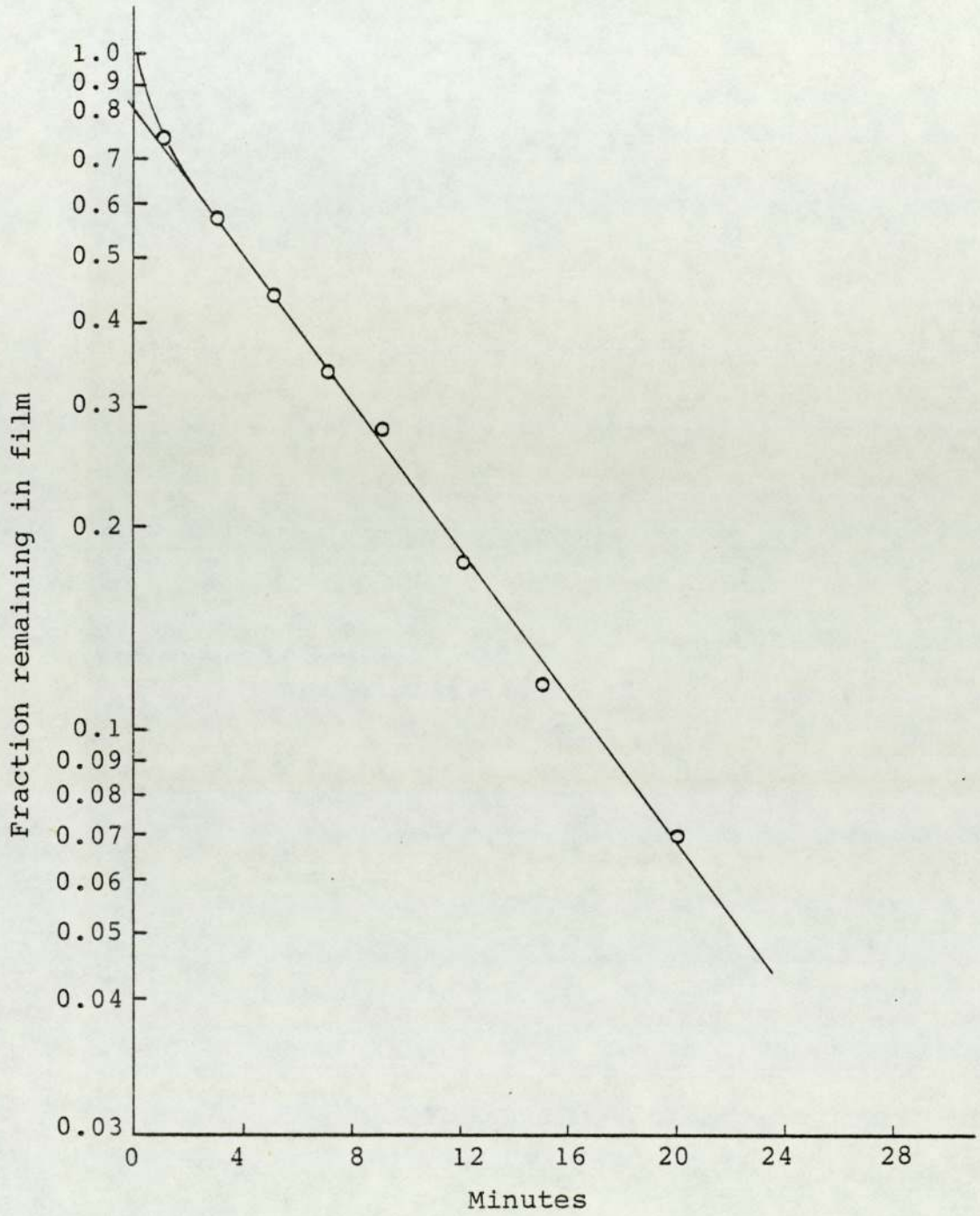


Fig 3.16 Diffusive release of lignocaine hydrochloride from 200 bloom (20% $^{w}/_{w}$ gelatin gels at 25^{o}C. Late time release.

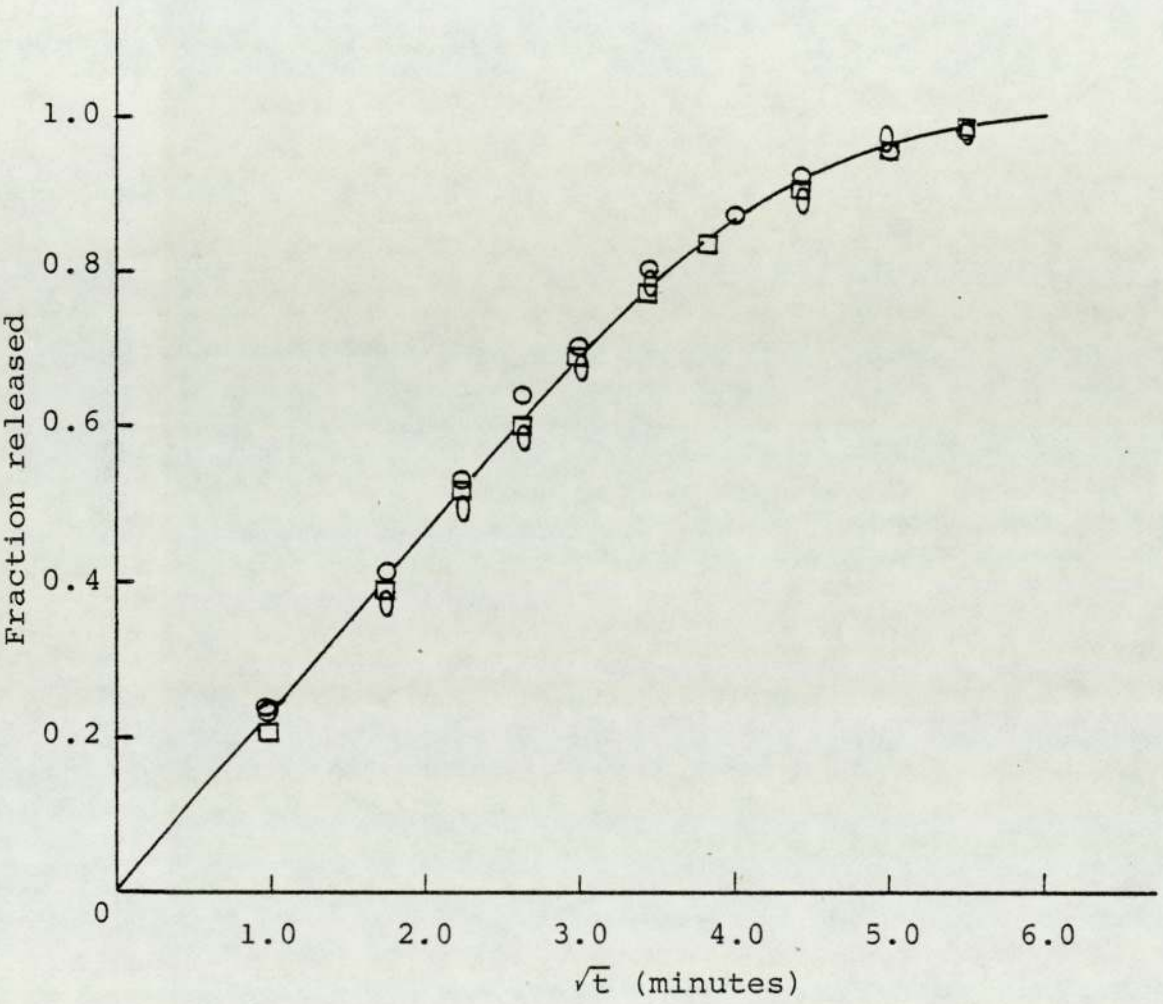


Fig 3.17 The influence of gelatin concentration on diffusive release of lignocaine hydrochloride from 200 bloom gelatin gels at 25°C. O 20%, □ 25% and 0 30% by weight gelatin in distilled water.

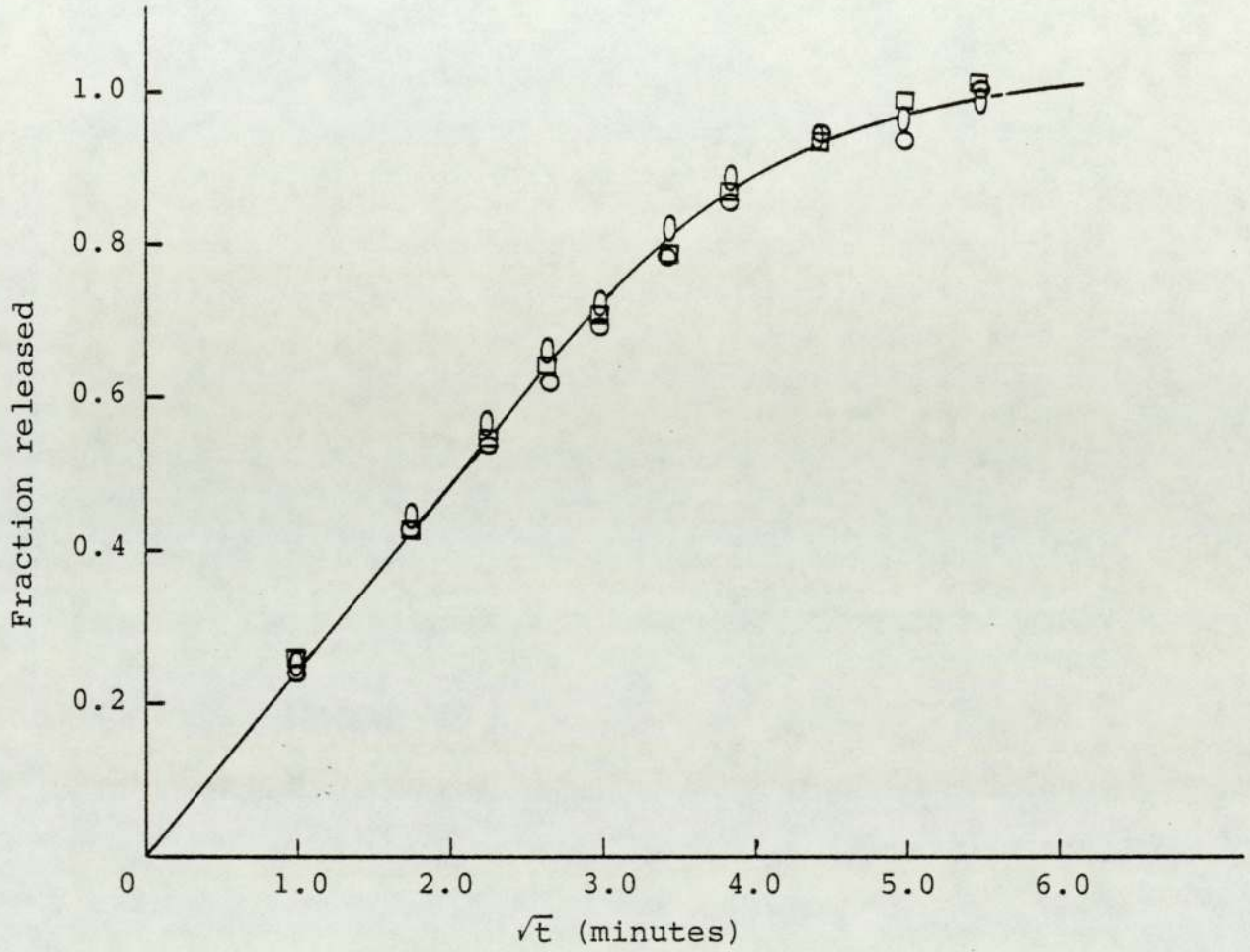


Fig 3.18 The influence of bloom strength on diffusive release of lignocaine hydrochloride from 20% $^{w}/_{w}$ gelatin gels at 25°C. O 90 bloom, 0 200 bloom and □ 230 bloom gelatins.

aldehydic compounds whose prototype is formaldehyde. These cross-linkers can also introduce a greater extent of cross-linkages than is attainable by variation of bloom strength. The influence of formaldehyde concentration on the release of lignocaine hydrochloride was therefore studied. Two procedures of preparing formaldehyde-hardened gels were tried and compared (see section 3.2).

When the formaldehyde-hardened gels were prepared using Method A, variable release rates were obtained. Evaluation of the diffusion coefficient showed an increasing D with increasing formaldehyde concentration (Fig. 3.19). On the other hand, gels prepared by Method B showed little variation (Figs. 3.19 and 3.20). It is deduced from these results that in Method A the reaction between formaldehyde and gelatin is incomplete. The free formaldehyde then forms weak complexes between lignocaine molecules, which causes the observed higher apparent diffusion coefficient. In results to be reported in Chapter 5, a similar, more prominent interaction between benzocaine and formaldehyde is observed. There seems to be no binding of lignocaine to gelatin since almost the same amounts of the drug are released when the formaldehyde concentration is varied (Table 3.2). Method B is therefore the better method of preparing formaldehyde-hardened gelatin films.

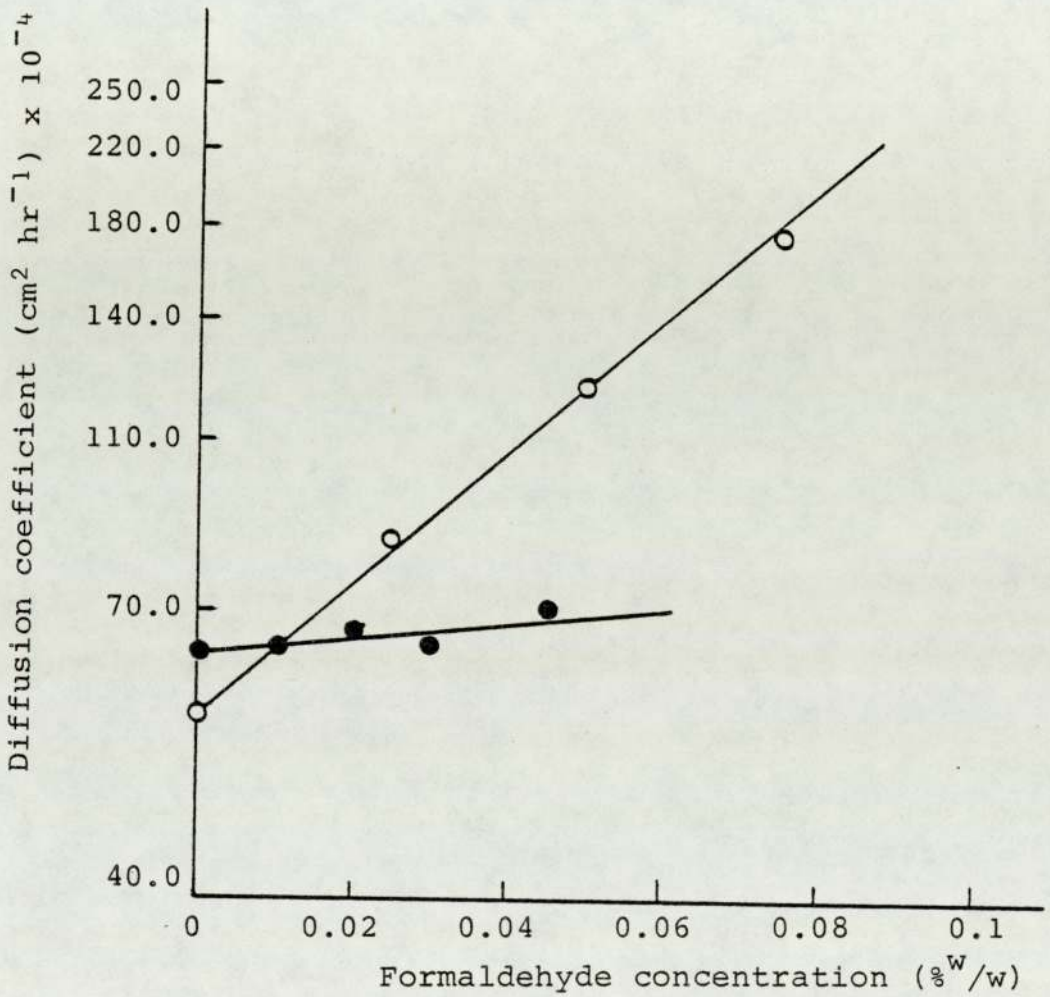


Fig 3.19 The influence of formaldehyde concentration on the apparent diffusion coefficient of lignocaine hydrochloride in homogeneous gelatin gels. O Method A and ● Method B.

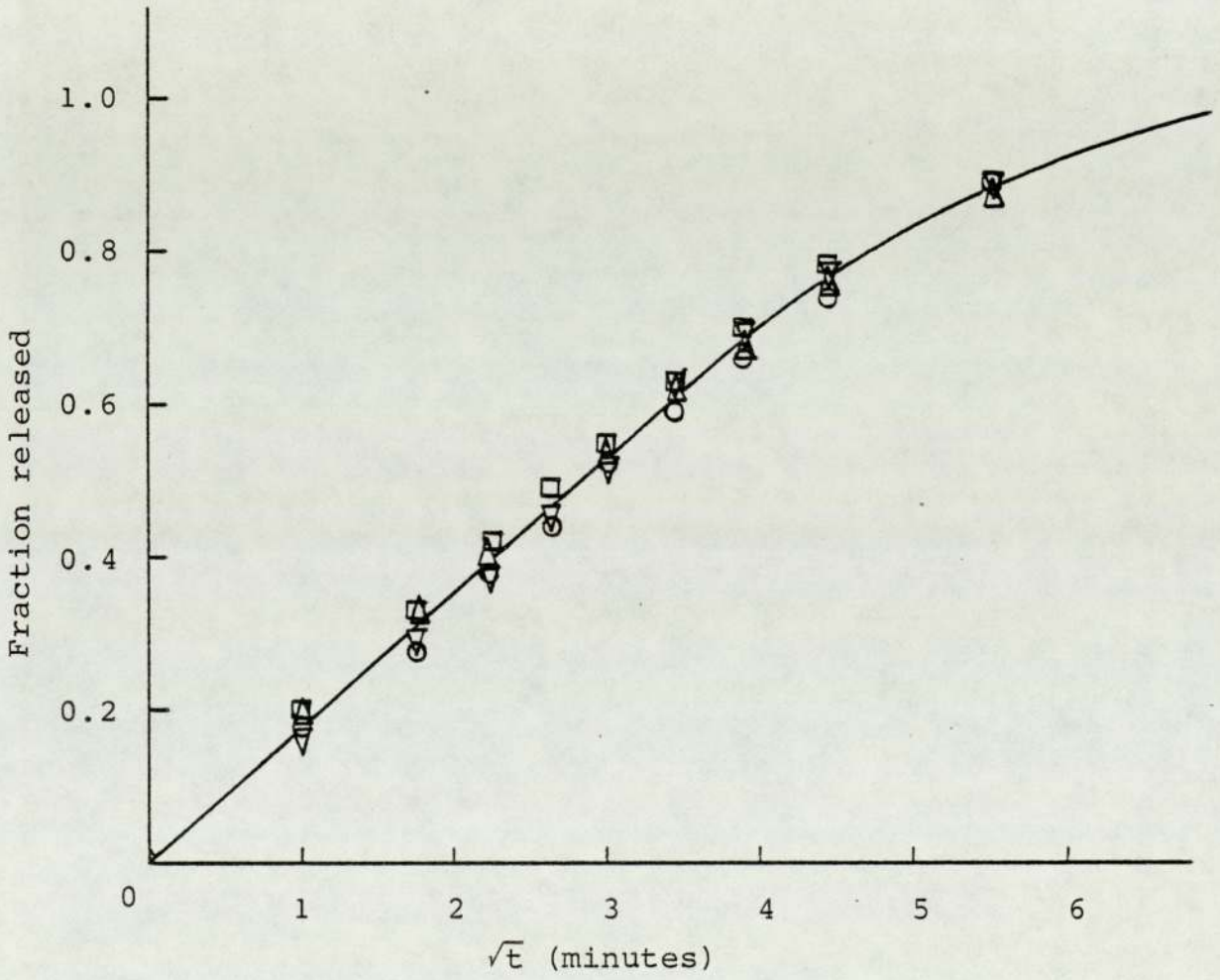


Fig 3.20 The influence of formaldehyde concentration on the release of lignocaine hydrochloride from gelatin gels - Method B.

TABLE 3.2

The influence of formaldehyde concentration on the release of lignocaine hydrochloride from homogeneous gelatin films

% w/w Formaldehyde Conc.	Method	Total Amount Released (mg.)	D_{app} $\times 10^{-4}$ ($cm^2 . hr^{-1}$)
0	A	4.55	54.6
0.025	A	4.63	84.0
0.050	A	4.29	123.0
0.075	A	4.72	176.4
0.01	B	44.69	65.95
0.02	B	44.95	68.31
0.03	B	49.68	84.24
0.05	B	46.79	70.72

CHAPTER 4

RELEASE OF DRUGS FROM EMULSION-TYPE FILMS

4.1 INTRODUCTORY THEORY

4.1.1 Theory of Drug Release From Suspension-type Devices

Solid-solid suspension-type devices have the advantage over solution-type devices in having the capacity to hold more medicament. For this reason they are often more desirable than solution devices where prolonged release is required. Like solution systems, however, release from suspension-type matrices has been shown (102) to obey the $\sqrt{t}$ law as presented by the Higuchi equation for slabs

$$Q_t = \left[D\, C_s t(2A - C_s)\right]^{\frac{1}{2}} \quad \text{--- 4.1}$$

where Q_t is the cumulative amount of drug released per unit area of device at time t, A is the total initial drug concentration in the device, C_s is the solubility of the drug in the matrix and D is the diffusion coefficient of the drug in the polymer matrix.

This $\sqrt{t}$ behaviour renders suspension-type formulations undesirable where zero order delivery is preferred. However, there are cases where suspension systems have produced zero order delivery, mainly through geometrical modifications of the devices. Brooke and Washkuhn (105) have demonstrated zero order delivery from a sectioned cylinder filled with drug suspended in a polymer matrix. The ability of such a geometry to deliver medicaments at a constant rate is based on the compensation

brought about by the geometry on the decaying release rate. The decay in release rate observed in normal suspension and solution-type devices is due to the gradual increase in the diffusion path as the solvent front recedes further into the matrix. The geometrical modification introduces an increasing area with advance of the front and this cancels out the effects of increasing path length (105,106). Following the same trend it was shown (107) that an inwardly releasing hemisphere attains better zero order delivery than a sectioned cylinder, when the outer radius is greater than three times the inner diameter. A polymeric hemispheric device based on these principles has been constructed and has been shown to produce a fairly constant delivery rate (108).

More success has been obtained by using reservoir suspension type devices where solid drug maintains constant drug activity in the environment in the core surrounded by a rate limiting membrane (36,100). In the case of a slab-type reservoir suspension device the release rate is given by

$$\frac{dM_t}{dt} = \frac{A\ D\ K\ \Delta C}{l} \qquad \text{--- 4.2}$$

where $\frac{dM_t}{dt}$ is the rate of release of the drug, A is area of the slab exposed, D is the diffusion coefficient of the drug in the membrane, K is the partition coefficient of the drug between the inner matrix and the rate limiting membrane of thickness l, and ΔC is the concentration difference across the membrane.

Equations for release from other geometries can be derived and are available in standard texts (97 - 100).

Though zero order delivery is desirable, this does not preclude the usefulness of non-zero order delivery formulations. The majority of topical formulations presently available are not constant delivery system but ordinary solution/suspension type systems. In such cases, the significance of mathematical expressions such as equation 4.1 is to enable quantitative evaluation of the parameters involved in release control. These equations therefore assist in the development and optimization of controlled-drug formulations. It is only in such a way that a rational approach to the selection of appropriate parameters such as polymer-type, quantity and particle size of the solids can be undertaken.

The irony is that where zero order delivery formulations have been achieved, most of them have not been exploited. Two important factors contribute to this contradictory situation. Firstly, most of such controlled release preparations are much more expensive. Secondly, most of such formulations have been developed for some specific chronically administered drug, mostly for implantation. The designs are therefore unsuitable for use as delivery systems for other common drugs because of specific requirements for these drugs. Some suspension-type zero order delivery formulations that have been patented are listed in Table 4.1

It is necessary to add though that these non zero-order

TABLE 4.1

Examples of Zero-Order Controlled Release Formulations Patented

Patent No.	Example of Drug	Example of Polymer	Site of Administration
U.S. 3,279,996	Heparin	Polysiloxane	Implant
U.S. 3,518,340	Various	Silicone rubber	Capsules
U.S. 3,545,439	Medroxyprogesterone	Silicone rubber	Vaginal insert
U.S. 3,630,200	Pilocarpine, Chloramphenicol	Silicone rubber and hydrogels	Ocular insert
U.S. 3,641,237	Pilocarpine	Methacrylates	Insert/ implant
U.S. 3,710,795	Progesterone, Antibiotics	Silicone rubber, natural gum rubber	Not specified
U.S. 3,742,951	Vasodilators	Silicone rubber	Bandage
U.S. 3,797,485	L-Dopa, Testosterone	PVC	Implant in blood vessels
U.S. 3,832,458	ACTH	Polysiloxane/ PVP copolymer	Eye lens
U.S. 3,845,761	Contraceptives	Various	IUD
U.S. 3,895,103	Contraceptive steroids	Ethylene, vinyl acetate copolymer	IUD
U.S. 3,896,815	Contraceptives	Various	IUD
U.S. 3,598,122	Megesterol	Silicone rubber	Bandage
U.S. 3,598,123	Chloramphenicol, contraceptives	HEMA, Silastic®	Bandage

delivery formulations currently available often do not offer the advantages of controlled release. Many have been arbitrarily formulated and are therefore often both wasteful and unpredictable.

4.1.2 Theory of drug release from emulsion-type devices

Emulsions provide another way of incorporating more drug in a system than can normally be accommodated. Emulsions have been extensively studied for their potential use as injectable formulations where particulate solids are undesirable due to the possible induction of embolism (111). Being suspensions of a liquid in another liquid, micronised droplets are much easier to obtain and their disposition in the body is much less hazardous than solid injectable dispersions. However, emulsion formulations are very unstable on storage and this might be the reason that less attention is paid to them.

To be able to formulate controlled release preparations, it is desirable to predict the release behaviour anticipated and this requires sufficient knowledge of the kinetics of release of the drug from that system. Apart from extrapolating the general release behaviour of reservoir devices to emulsions instead of suspensions, very little is known on the release kinetics of drugs from emulsion systems.

It has been known for a long time that the key to quantitative description of drug movement in emulsions lies in an acceptable definition of an effective diffusion

coefficient of the drug in the system. Movement of drug molecules through polymer membranes is similar to heat and electric conduction in that all involve diffusive processes. It is therefore a rule that mathematical solutions applicable to one of these processes would normally also be useful to the others. Physical chemists have therefore investigated the possibility of applying mathematical expressions for the dielectric permeability of heterogeneous systems to diffusion of drugs in emulsions (222, 243).

In attempting to determine the effective dielectric permeability of a heterogeneous system, Maxwell (217) considered a system so dilute that no interaction exists between neighbouring particles of the dispersed phase. He therefore derived an equation for determining the effective dielectric permeability of such a system which, by definition, is the permeability coefficient of a homogeneous matrix with a similar overall permeability/ conductivity behaviour to that of the heterogeneous system. The Wagner-Weiner (218) equation is derived from the Maxwell solution and is given as

$$\frac{P_e - P_b}{P_e - 2P_b} = Va \frac{P_a - P_b}{P_a - 2P_b} \quad \text{--- 4.3}$$

where P stands for the permeability coefficient and subscripts a and b refer to the dispersed and continuous phases respectively. Subscript e refers to the effective behaviour of the system. V_a is the volume phase ratio of the dispersed phase.

The use of equation 4.3 in cases of diffusion implies the definition of an effective diffusion coefficient fitting the Maxwell description of the effective permeability in electrical conductivity.

The Bruggeman equation (219)

$$\frac{P_e - P_a}{P_b - P_a} \cdot \left(\frac{P_b}{P_e}\right)^{\frac{1}{3}} = V_b \qquad \text{--- 4.4}$$

is another solution to dielectric permeability in heterogeneous systems which has been applied to cases of diffusion in emulsions. It has been reported (220) that the Bruggeman equation provides a better prediction of release from emulsions than the Wagner-Weiner equation.

Another expression of particular application to pharmaceutical formulations was derived by Higuchi and Higuchi (221)

$$P_e = \frac{2P_b^2(1-V_a) + P_aP_b(1-2V_a) - KP_b\left(\frac{P_a-P_b}{2P_b-P_a}\right)^2(2P_b+P_a)(1-V_b)}{P_b(2+V_a) + P_a(1-V_b) - K\left(\frac{P_a-P_b}{2P_b+P_a}\right)^2(2P_b+P_a)(1-V_b)} \qquad \text{--- 4.5}$$

This equation was derived to account for perturbations between neighbouring particles which was ignored in the Maxwell-Wagner-Weiner model. In dilute emulsions the solution provided by equation 4.5 will therefore be similar to those obtained from 4.3.

Several other expressions for the effective permeability are available (222) based on slightly different assumptions and/or modified to account for different shapes and arrangements. De Vries (223) showed that there is considerable variation in the calculated effective dielectric permeability

depending on the equation used.

Evaluation differs from prediction by the fact that parameters needed for evaluation need not be absolute but only reproducible. It was therefore suggested (231) that the equation for desorption for homogeneous systems can be extended to the heterogeneous case. Thus

$$Q_t = 2C_o \left(\frac{D_e t}{\pi}\right)^{\frac{1}{2}} \quad \text{--- 4.6 (a)}$$

where Q_t is the amount released at any time per unit area, C_o is the initial total drug concentration and D_e is the effective diffusion coefficient. Alternatively, equation 4.6 (a) can be rewritten as

$$\frac{M_t}{M_o} = 2\left(\frac{D_e t}{\pi l^2}\right)^{\frac{1}{2}} \quad \text{--- 4.6 (b)}$$

where M_t is the cumulative amount released in time t and M_o is the total releasable amount. l is the thickness of the matrix.

It is essential to note that equations 4.6 (a) and 4.6 (b) are derived from the Maxwellian definition of the effective diffusion coefficient. Whereas the release from matrices of finite thickness can be resolved into two phases; the initial $\sqrt{t}$ phase during which the matrix behaves as semi-infinite, and a late phase during which the matrix demonstrates a typical first order loss of activity (224); equation 4.6 portrays only the early $\sqrt{t}$ phase. It is therefore not surprising that deviations at late stages are observed (220) when equation 4.6 is used to simulate release from a matrix of a finite thickness. It would be interesting

therefore to investigate whether the use of the effective diffusion coefficient evaluated from the $\sqrt{t}$ phase in the appropriate equation for the late phase would satisfactorily model the complete release behaviour of the drug from the emulsion. Deviations at any stage would suggest a significant influence by other factors.

Other workers (225) have viewed emulsions as a kind of suspension. They have therefore used a modified form of equation 4.1 developed by Koizumi et al (226)

$$Q_t = \left[D_e' C_s t \left(2C_o - \frac{2}{3} C_s \cdot \frac{C_o - 0.88C_s}{C_o - 0.89C_s}\right)\right]^{\frac{1}{2}} \quad \text{--- 4.7}$$

where C_o is equivalent to A in equation 4.1, i.e. the total initial Drug concentration in the matrix. Other abbreviations remain as defined previously. More consistent values of D_e were obtained (225) when C_s was redefined to refer to the initial equilibrium drug concentration in the continuous phase ($C_{aq.}$). Thus,

$$Q_t = \left[D_e' C_{aq.} t \left(2C_o - \frac{2}{3} C_{aq.} \frac{C_o - 0.88C_{aq}}{C_o - 0.89C_{aq}}\right)\right]^{\frac{1}{2}} \quad \text{--- 4.8}$$

The values of D_e obtained using equation 5.6 (a) for the same data differed from those obtained using equation 4.8 and also varied with phase ratio.

Windhauser et al (110) demonstrated the roles of viscosity, partition coefficient and particle size on the release kinetics of drugs from emulsions. By using a steady state diffusion model they managed to demonstrate, mathematically, the roles of these parameters but they could not obtain a complete quantitative expression.

Where release from the internal phase plays an important role, knowledge of drug release from the suspended droplets is useful. Several studies on the release of drugs from emulsions or micellar systems into a surrounding sink have been reported (109,227 - 230).

In short, the basis of these quantitative analyses is consideration of release as a sum total of the drug released from individual spherical droplets by diffusion into a sink in the presence or absence of interfacial resistance. Goldberg et al have discussed the roles of both electrical (227) and physical (228) barriers at the interface. In both cases the barrier was treated as a membrane and equations for diffusion across a membrane from a spherical source applied. An electrical barrier may be introduced by the use of charged substances adsorbable at the interface such as ionic surfactants, or as a consequence of induced charges.

Brodin (229) has shown that the presence of adsorbed substances at the interface reduces the rate of solute transport by virtue of the reduction in the diffusion surface area. Bikhazi et al (109) used the electrical and physical models developed earlier (228, 227) to develop a model for transport in emulsion systems. The physical model satisfactorily described the release of drugs from an oil droplet on which a finite thickness of gelatin was adsorbed (230). Therefore, if it can be shown that the rate of release from the dispersed phase plays a significant role in the adsorption or release of drugs from heterogeneous

systems, it might be possible to quantify the role of surfactants and other forms of interfacial resistance in diffusion in heterogeneous systems; a problem which presently available conductivity models fail to model satisfactorily. Similarly, more light may be shed onto the much more complex phenomenon of transport in biological membranes.

4.1.3 The Aim of the Study

This study aims to;

a) review the equations used in the evaluation of release from emulsion systems, particularly the suspension equations

b) re-examine and compare the various equations used to quantify the kinetics of release from emulsion systems

c) study the extent to which "homogeneous behaviour" is followed in heterogeneous systems and to attempt to explain the deviations observed in the late stages of release when equations for homogeneous systems are used.

4.2 EXPERIMENTAL

4.2.1 Preparation of Emulsion Gels

(a) The influence of partition coefficients on release

The release of lignocaine (base) from alcohol-in-gel emulsions was studied. The alcohols used as internal phases were octanol, nonanol, decanol and dodecanol. The general formula for the emulsions was

lignocaine base	1.5 g.
Alcohol	8.5 g.
20% aqueous gelatin gel (pH 7.0)	40.0 g.

The preparation and casting of emulsion films was as outlined in sections 2.3.1 and 2.4.4 respectively.

The release of a series of p-hydroxybenzoate esters (methyl to butyl) from octanol-in-gel emulsions was also studied. The general formula of the gels was

Ester in octanol solution	10.0 g.
20% w/w aqueous gelatin gel	40.0 g.

The amounts of the esters used per 100 g. of emulsion were calculated to provide equimolar concentrations equivalent to 1% w/w of the butyl esters.

(b) Variation of phase ratio

Octanol-in-gel emulsions with varying phase ratios (dilution) were prepared by diluting a stock emulsion containing

15% w/w lignocaine (base) in octanol solution	15 g.
20% w/w aqueous gelatin gel	35 g.

This initial emulsion (30% oil phase content) was diluted using pure 20% gel to produce emulsions containing 25%, 20%, 15% and 10% oil phase content by weight.

A similar study was performed using benzocaine in sunflower oil emulsion gels. The stock emulsion contained

0.25% w/w benzocaine in sunflower oil	15 g.
20% w/w aqueous gelatin gel (pH 7.0)	35 g.

The emulsion was diluted into proportions similar to those of the octanol emulsion above.

4.2.2 Casting of films

Films of 0.70 mm. thickness were cast using the method outlined in section 2.4.4. They were stored at 25°C, 95% R.H. for 12 hours before release studies were performed. The actual thickness of the films was measured just before the release experiment.

4.2.3 Release experiment

The method used is the one outlined in section 2.5.2 using a filter paper on top of the membrane to stop dissolution of the film. Release experiments were performed at 25°C using 500 ml. of phosphate buffer (pH 7.0) as the receiving phase. 5 ml. aliquots were withdrawn at predetermined intervals, being replaced by 5 ml. of the phosphate buffer. Analysis of drug content in the aliquots was by HPLC methods outlined in section 2.6.

4.2.4 Viscosity determination

These were performed at 25°C using U-tube (Oswald's) viscometers. The calibration of the viscometers was done using an aqueous 80% glycerol solution whose viscosity and density values were obtained from the literature. Specific gravities of the alcohols were determined at 25°C using a 25 ml. specific-gravity bottle, from which densities were calculated using water at 25°C as reference (standard values for water were obtained from ref. no. 258).

4.2.5 Determination of partition coefficients

100 ml. of phosphate buffer (pH 7.0) saturated with the appropriate alcohol and containing 200 mg. of lignocaine base (accurately weighed) were added to 25 ml. of the alcoholic phase saturated with the buffer in a conical flask. Both solutions were previously equilibrated at the appropriate temperature. The flask was then shaken in a water-bath for 12 hours, after which a sample of the aqueous phase was withdrawn and analysed for lignocaine content by U.V. spectrophotometry at 262 nm.

Since the partition coefficients were determined at different temperatures, they could be more accurately expressed in molal terms. The appropriate phases were therefore weighed before mixing.

4.3 RESULTS AND DISCUSSION

4.3.1 Evaluation of Drug Release from Emulsion Systems

Various workers have used the short-time approximation for drug release from homogeneous films (equation 4.6 (a)) in studying the release of drugs from emulsion systems. The equation enables the determination of an effective diffusion coefficient analogous to the effective permeability coefficient defined by Maxwell. The equation is expected to be useful for release from emulsion systems for up to 30-50% of total drug release (231). Unfortunately no exhaustive studies have been performed to demonstrate this. A recent study (225) showed that the diffusion coefficient thus calculated varied considerably depending on the dilution state of the emulsion. More consistent results were obtained by using equation 4.8 (225). This observation, however, may have been complicated by experimental constraints and variables such as

a) the use of surfactants. In emulsion systems these may produce an interfacial barrier to drug transport (227,229) and dilution would also introduce changes in the barrier. In micellized systems dilution will reduce the concentration of micelles and hence the quantity of solubilized drug.

b) in the reported study (225) the receiver phase used is oleagenous and therefore miscible with

the solvent (internal phase). There is a possibility of solvent migration from the emulsion into the sink when the internal phase is soluble in the sink solvent (232). It is therefore necessary to rule out such migration.

The present study was initiated to investigate the applicability of equations 4.6 (a) and 4.8 in a more controlled system. The systems used were a series of alcohol-in-gel emulsions containing lignocaine (lidocaine). The alcohols, ranging from octanol to dodecanol, provide a variation of partition coefficient within the emulsion. The variation of the partition coefficient of lignocaine base between the alcohols and phosphate buffer pH 7.0 at different temperatures is shown in Fig. 4.1. The log-normal relationship between partition coefficients and number of carbon atoms of the alcohols reported by other investigators (233) is seen to be obeyed at temperatures higher than 25°C. At 25°C, dodecanol deviates from this behaviour. This may be due to the proximity of the experimental temperature to the melting point of dodecanol (24°C) such that some solid residues may be present. The continuous phase for the emulsions was a 20% gelatin (200-230 bloom) gel in phosphate buffer at pH 7.0. The equilibrium conditions in such emulsions can be viewed as existing between the alcohol and the aqueous part of the gel (230). It had earlier been shown that variation in the bloom strength of the gelatin used does not affect the diffusion of lidocaine in homogeneous matrices (section 3.3.2).

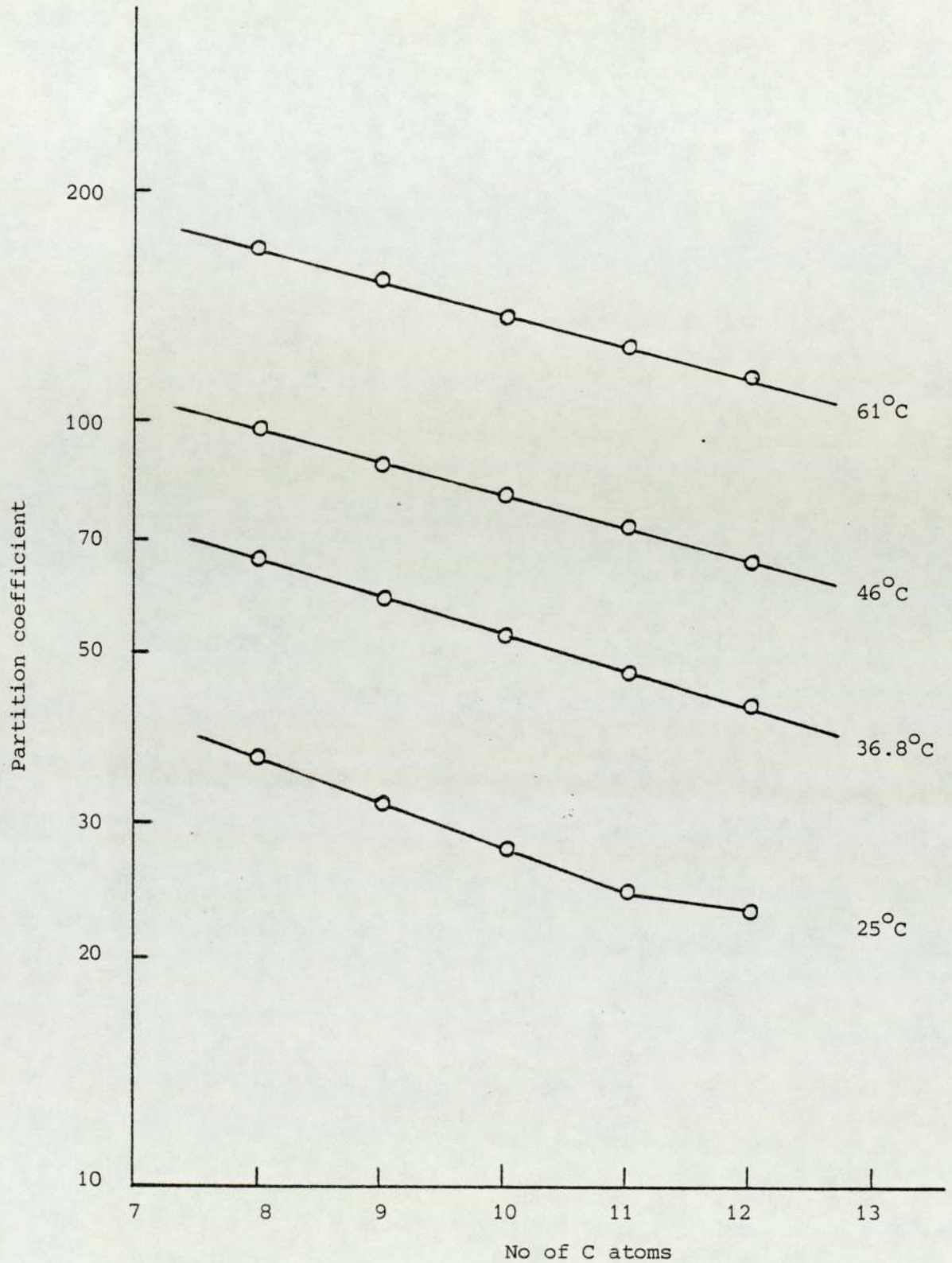


Fig 4.1 The variation of partition coefficient of lignocaine between aliphatic alcohols and phosphate buffer pH 7.0 with temperature (Partition coefficients calculated in terms of molal concentrations)

This also means that other gel behaviours such as formation of micelles does not affect the total activity of lidocaine in the gel. Binding of lidocaine to gelatin is also ruled out.

This system offers the following advantages:

a) Dilution of the emulsion with pure gel will not alter the nature of the interface since no added surfactant was present

b) Thin solid films of the emulsions can be cast thus providing a finite system from which complete release kinetics can be studied.

c) The internal phases are highly insoluble in the receiver phase, thus minimizing solvent migration. An extra precaution taken was to saturate the receiver phase with the alcohol thus ensuring no migration at all. The effect of emulsion dilution is shown in Fig. 4.2 for octanol-in-gel emulsions. As expected (220) the initial release shows a typical $\sqrt{t}$ behaviour characteristic of release from semi-infinite matrices. That the release rate is dependent on the initial concentration is evident from the profiles. Equation 4.6 (a) was then used to evaluate the values of the effective diffusion coefficients (D_e) from the Q Vs $\sqrt{t}$ slopes. Table 4.2 shows that there is no variation in the values of D_e

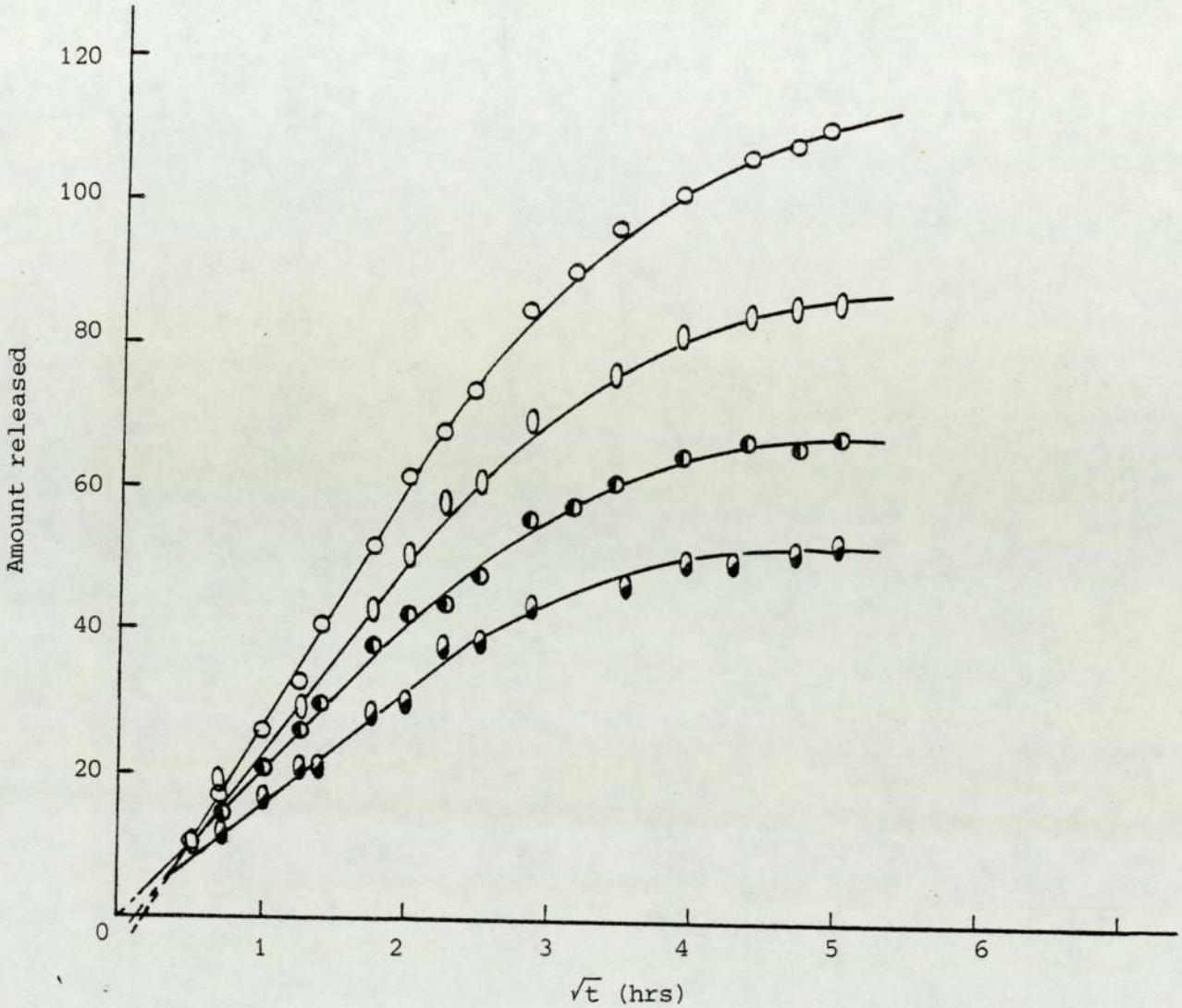


Fig 4.2 The influence of emulsion dilution on release of lignocaine from octanol-emulsion gels.

- o 30% w/w oil phase content
- 0 20% w/w oil phase content
- ◐ 15% w/w oil phase content
- ◒ 10% w/w oil phase content

TABLE 4.2

Release of Lignocaine from Octanol-in-gel Emulsions
Influence of Phase Ratio (Dilution)

% w/w oil phase	$M_t V_s \sqrt{t}$ slope$^{-\frac{1}{2}}$ (m.g. hr$^{-\frac{1}{2}}$)	M_∞ (mg.)	Thickness (1 cm.)	D_e (cm.^{2} hr^{-1})
10%	15.388×10^{-4}	48.0	0.068	3.733×10^{-4}
15%	21.6737×10^{-4}	67.0	0.068	3.789×10^{-4}
20%	26.9318×10^{-4}	86.0	0.068	3.562×10^{-4}
30%	33.9803×10^{-4}	107.0	0.068	3.663×10^{-4}

obtained with dilution. This is contradictory to the observations made by Broberg et al (225) who observed an increase in D_e with dilution.

The influence of partition coefficient was then studied. Fig. 4.3 shows the release from alcohol-in-gel emulsions containing equal concentrations of lidocaine. It is observed that the release rate decreases in the order:

dodecanol > decanol > nonanol > octanol

This order corresponds to an increase in partition coefficient (Fig. 4.1). The values of the effective diffusion coefficient (D_e) as evaluated using equation 4.6 (a) are shown in Table 4.3. It can be observed that there is a decrease in D_e with increasing partition coefficients. The direct relationship between D_e and the partition coefficient is shown in Fig. 4.4.

That diffusion in the dispersed phase does not influence the release is shown in Fig. 4.5 where the effective diffusion coefficient is plotted against the reciprocal of the viscosity of the dispersed phase. The reciprocal of viscosity is related to the diffusion coefficient by the Stoke-Einstein (130) equation

$$D = \frac{kT}{6\pi\eta r} \qquad \text{--- 4.9}$$

where k is the Boltzman constant, T is the temperature in absolute degrees, η is the absolute viscosity of the solvent and r is the radius of the diffusant.

TABLE 4.3

Release of Lignocaine from Alcohol-in-Gel Emulsions
Influence of Partition Coefficient

Internal Phase (Alcohol)	o/w Partition Coeff.	M_t Vs $\sqrt{t}$ slope ($m.g.\ hr^{-\frac{1}{2}}$)	M_∞ (mg)	D_e (Eq. 5.6) $cm^2.\ hr.$
Octanol	27.6	22.54	74.0	4.107×10^{-4}
Nonanol	23.6	26.64	74.0	5.738
Decanol	19.6	29.86	74.0	7.211
Dodecanol	17.9	32.13	74.0	8.344

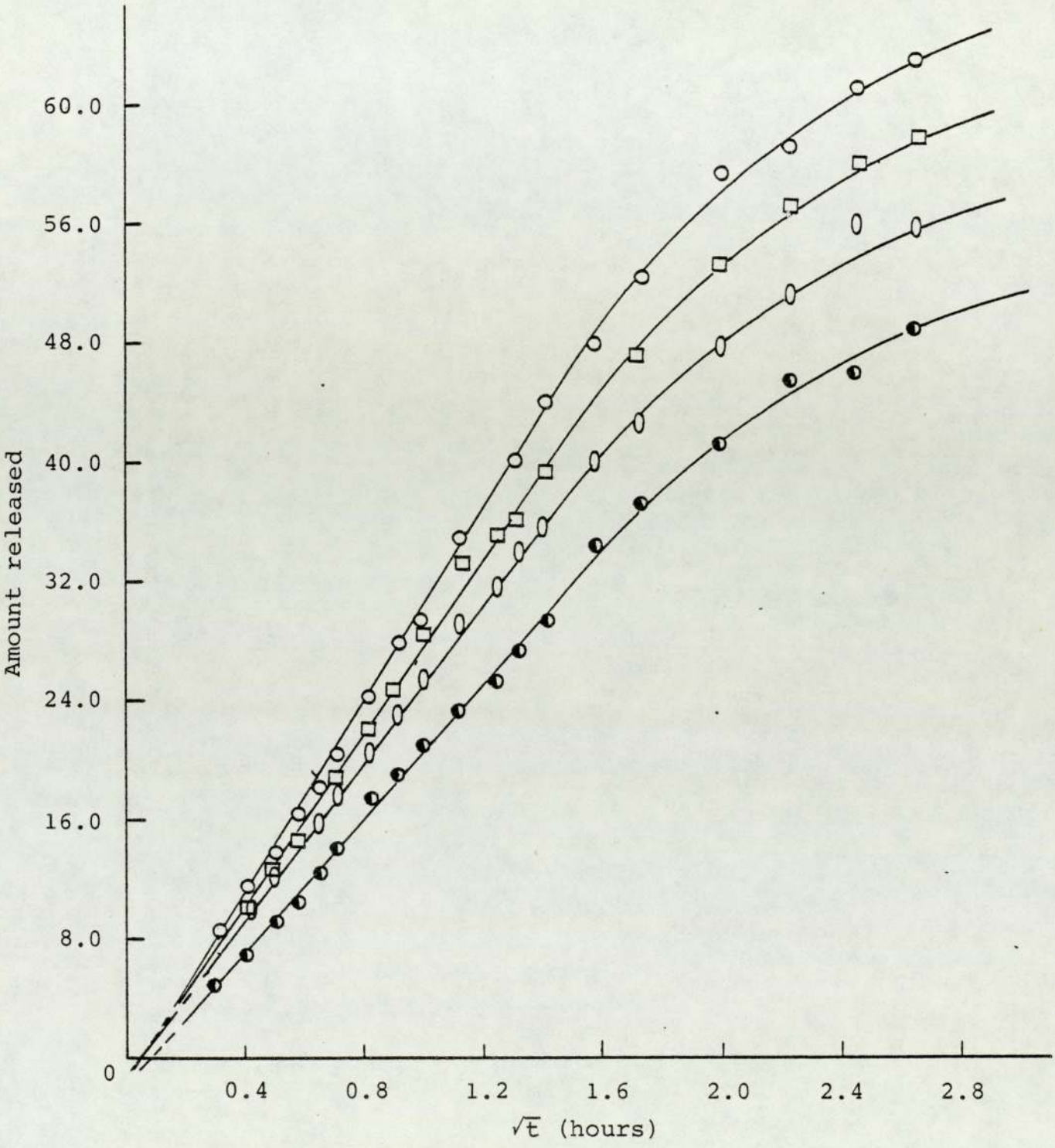


Fig 4.3 The release of lignocaine (base) from thin alcohol-in-gel emulsion films (0.075 cm thickness) at 25°C. O octanol, □ nonanol, 0 decanol and ◐ dodecanol emulsions.

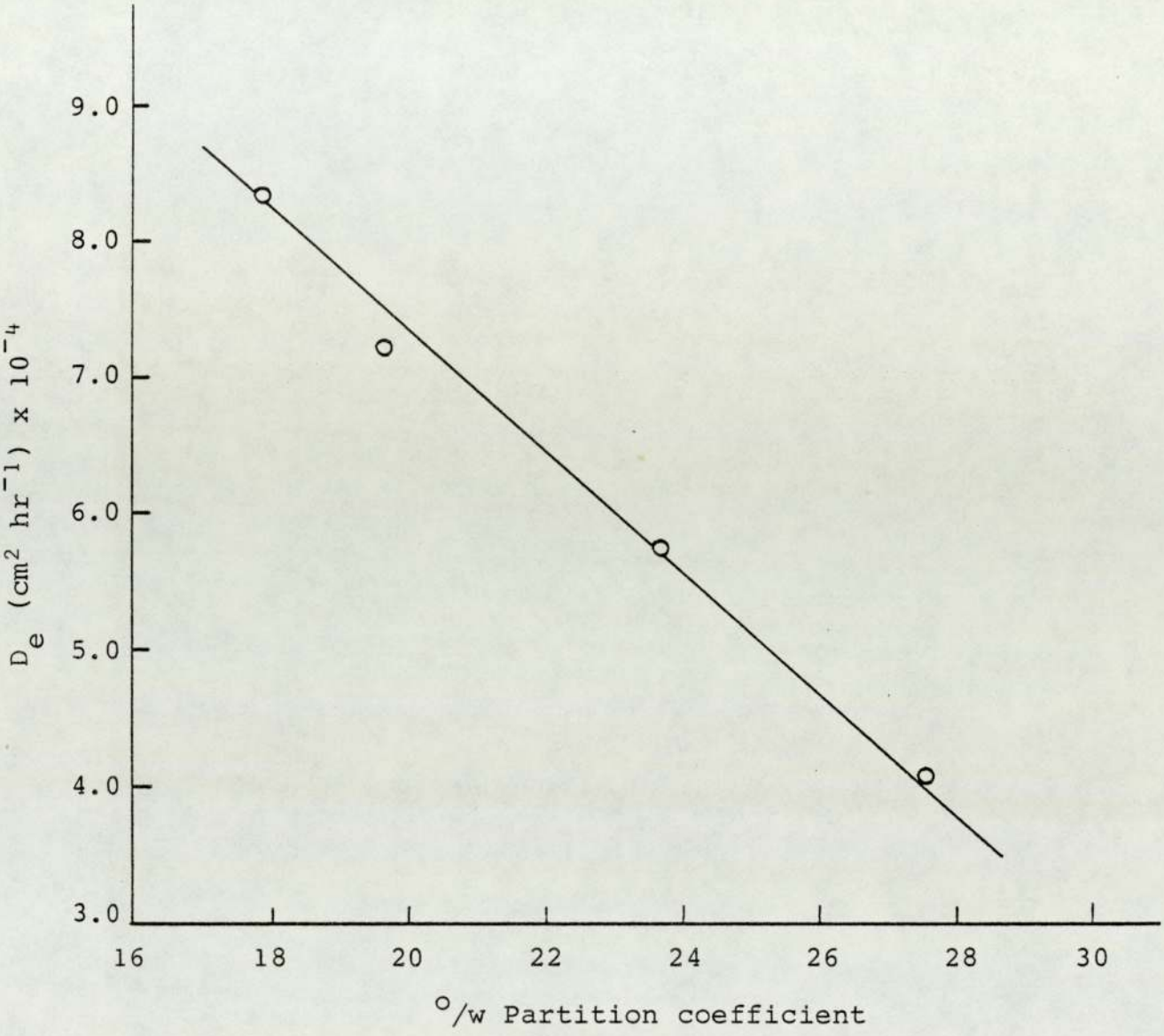


Fig 4.4 The relationship between the effective diffusion coefficient and the °/w partition coefficients.

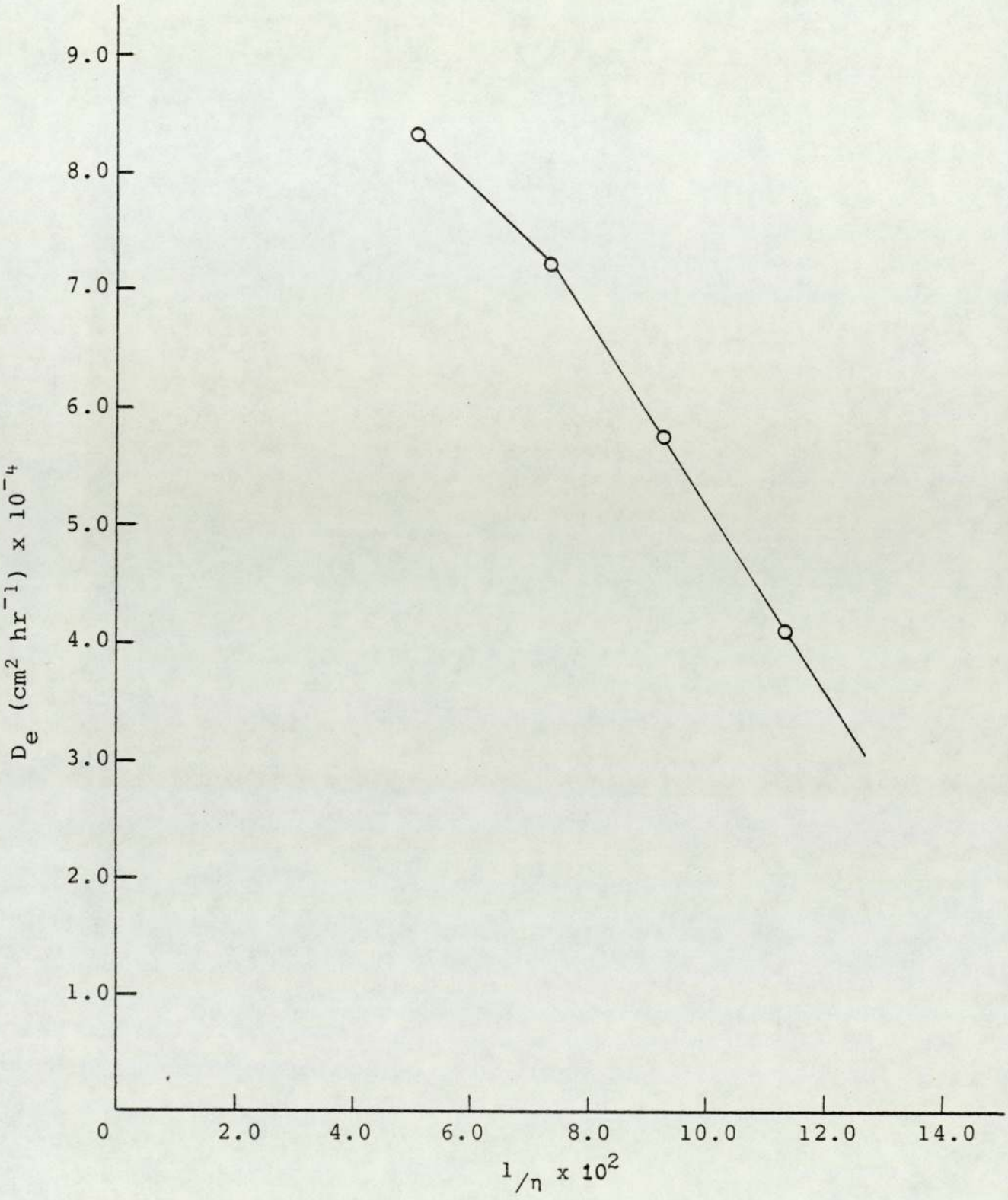


Fig 4.5 The variation of the effective diffusion coefficients with the reciprocal of the viscosity.

More confirmatory experiments were performed using esters of p-hydroxybenzoic acid. The release of the esters from an octanol emulsion gel is shown in Fig. 4.6. It can be observed that the values of D_e obtained also decrease with increasing partition coefficients (Table 4.4). This is in spite of the apparent non-sink conditions for the release since the total amounts released are lower than the original amounts in the films. In the case of the esters, the relationship between the effective diffusion coefficient (D_e) and the partition coefficient is logarithmic (Fig. 4.7). The component

$$\log \left(\frac{D_e}{D_o}\right)$$

in Fig. 4.7 is plotted instead of D_e alone so as to compensate for the difference in the diffusion coefficients of the individual esters, in the continuous phase, due to differences in molecular sizes. This observed logarithmic relationship differs from the linear relationship observed in the case of release of lidocaine in alcohol emulsion gels. The reason for this discrepancy lies in the short range of partition coefficient used in the lidocaine study. It can be seen (Fig. 4.8) that the plot of partition coefficient of the alcohols (from octanol to decanol) against the number of carbon atoms at 25°C can also be plotted on a linear scale.

Supplementary studies of release of benzocaine from sunflower oil emulsion gels of varying dilutions

TABLE 4.4

Release of p-hydroxybenzoate Esters from Octanol-in-Gel Emulsions

Ester	o/w Partition Coeff.	$M_t V_s \sqrt{t}$ slope ($mMole.hr^{-\frac{1}{2}}$)	M_∞ (mMoles)	D_e (Eq. 5.6) ($cm^2.hr^{-1}$)	D_o ($cm^2.hr^{-1}$)
Methyl	73	0.0483	0.121	6.136×10^{-4}	114
Ethyl	216	0.0398	0.121	4.165×10^{-4}	109
Propyl	664	0.0306	0.121	2.468×10^{-4}	105
Butyl	1533	0.0245	0.121	1.585×10^{-4}	93

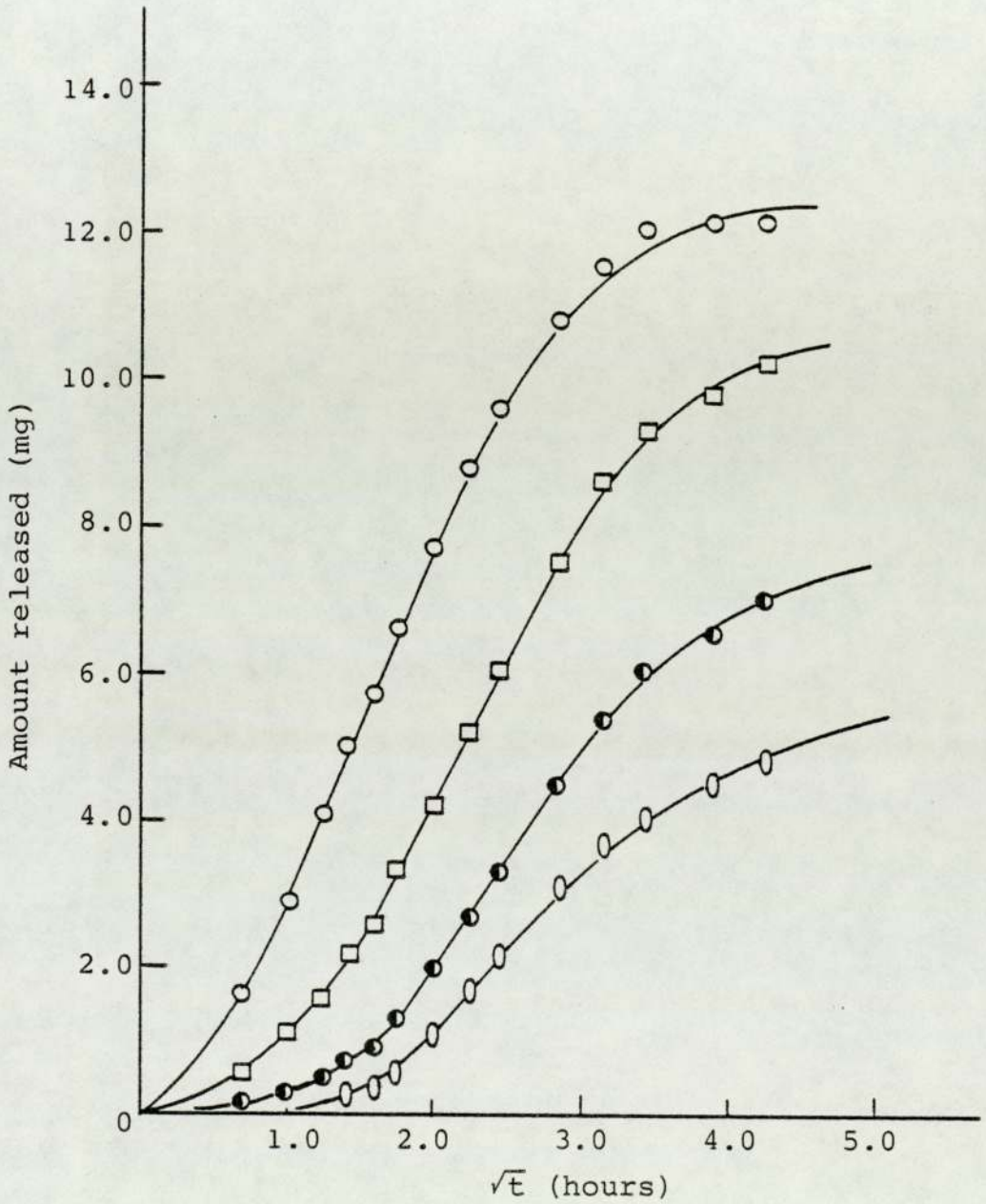


Fig 4.6 The release of esters of p-hydroxybenzoic acid from octanol-in-gel emulsions at 25°C.
O methyl, □ ethyl, ◐ propyl, and 0 butyl.

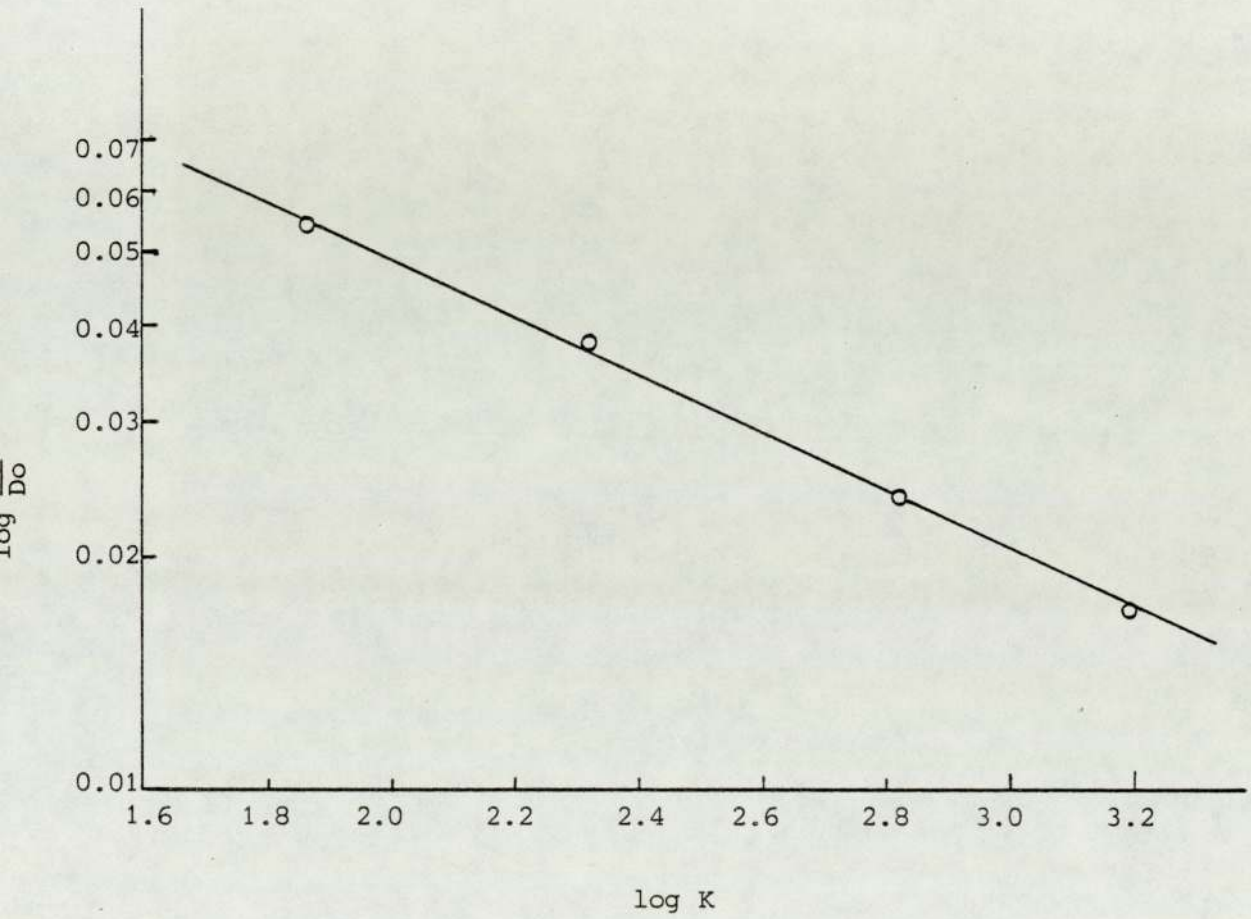


Fig 4.7 The relationship between the observed normalized effective diffusion coefficient and the partition coefficient (K) for release of p-hydroxybenzoate esters from octanol/gel emulsion systems at 25°C.

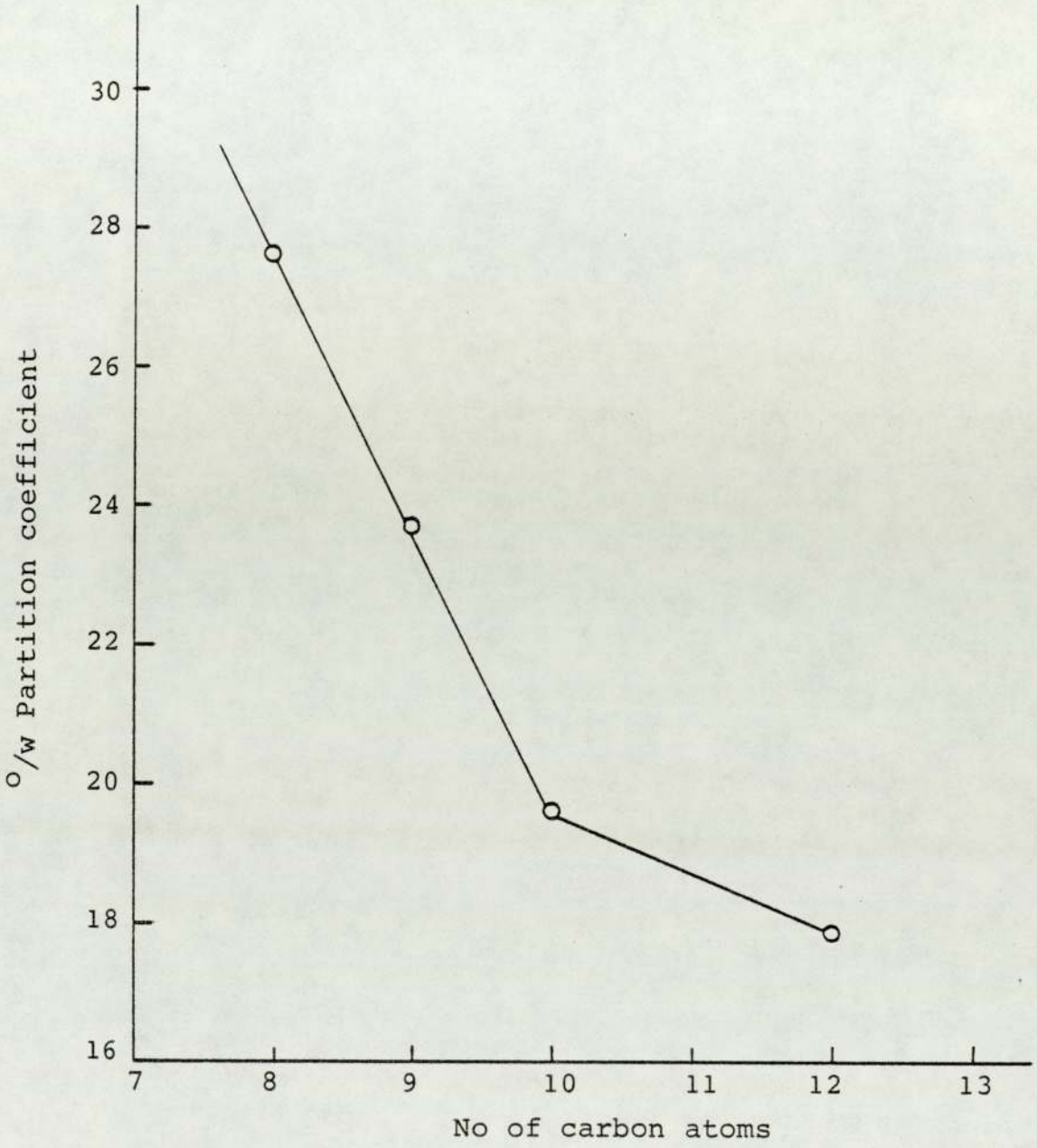


Fig 4.8 The partition coefficients of lignocaine (base) between aliphatic alcohols and phosphate buffer (pH 7.0) at 25°C.
(Partition coefficients calculated in terms of molar concentrations).

(Fig. 4.9) also produced a constant effective diffusion coefficient (Table 4.5).

In section 4.1 it was mentioned that equation 4.6 (a) is derived from Maxwell's definition of the effective permeability coefficient of a heterogeneous system. It was therefore decided to extend the study to investigate the extent to which the Maxwell model approximates the complete release behaviour.

Guy and Hadgraft (235) have developed a model that can be used to simulate and compare sink and non-sink release of drugs from homogeneous matrices based on the solution of Fick's second law by Laplace transformation. A computer program (Appendix 4.1)based on this model was written to simulate the complete release profile. The program was tested using the data on release of from homogeneous gelatin films (discussed in section 3.3.2) and the closeness of the fit can be seen in Fig. 4.10.

With the values of D_e for lidocaine alcohol emulsion systems as evaluated from experimental data using equation 4.6 (a), the program was used to simulate the appropriate "homogeneous" behaviour. A comparison of the theoretical and observed behaviours is shown in Fig. 4.11. It can be observed that whereas the dodecanol emulsion is almost entirely simulated, the other alcohol emulsions show a significant deviation in later stages. The decanol emulsion has been omitted from the diagram for the sake of clarity but also shows late phase deviation. These deviations suggest that the Maxwell model is not always applicable to

TABLE 4.5

Release of Benzocaine from Sunflower Oil Emulsion Gels
Influence of Phase Ratio (Dilution)

Oil Phase Volume Fraction	$M_t V_s \sqrt{t}$ slope (mg. $hr^{-\frac{1}{2}}$)	M_∞ (mg.)	(D_e (eq. 5.6) (cm^2. hr^{-1})
0.11	1.434	2.67	12.40×10^{-4}
0 18	2.557	5.20	10.4×10^{-4}
0.23	3.767	6.95	12.64×10^{-4}
0.29	4.685	9.22	11.10×10^{-4}
0.34	5.887	11.10	12.10×10^{-4}

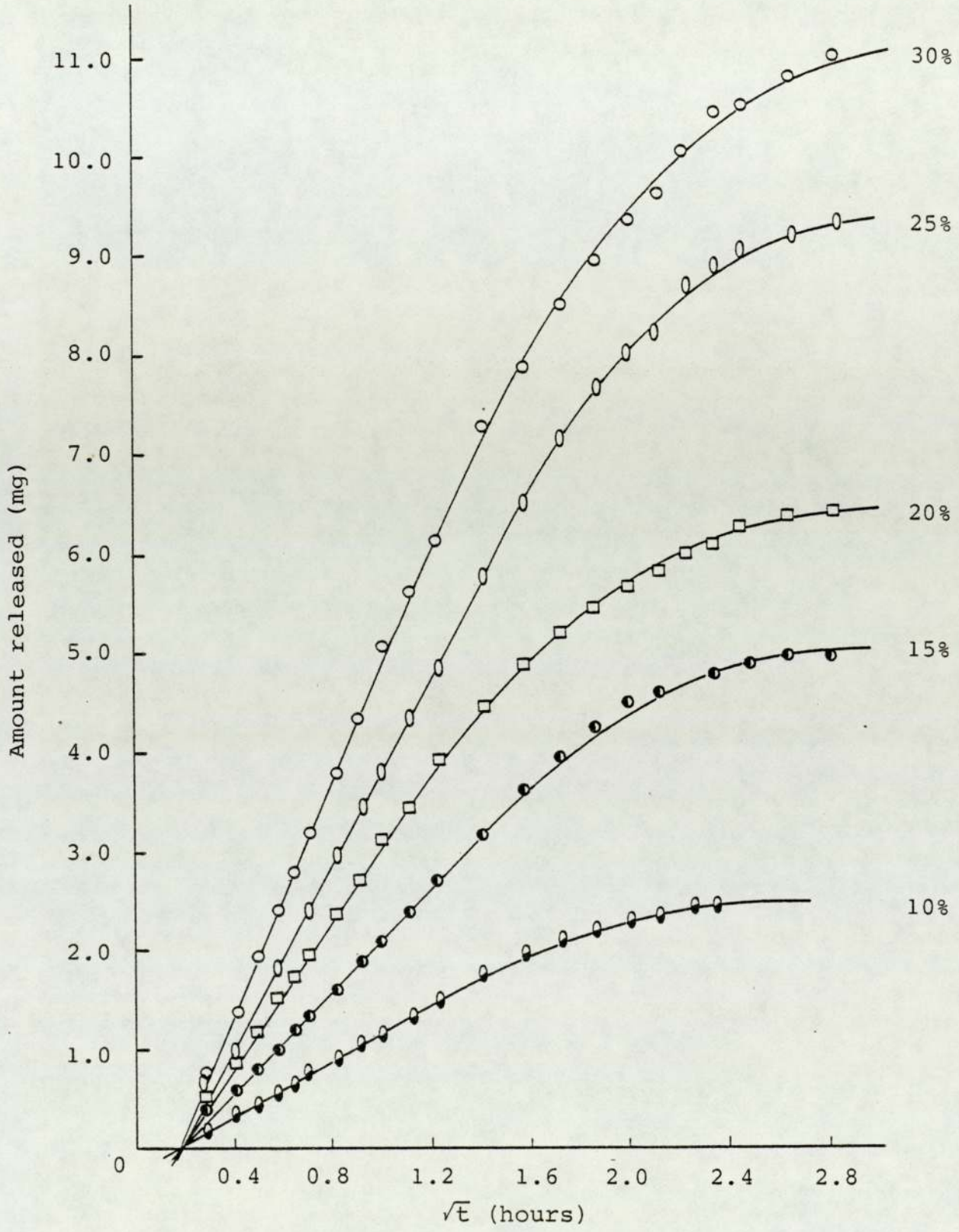


Fig 4.9 The influence of phase ratio (dilution) on the release of benzocaine from sunflower oil emulsion gels, at 25°C.

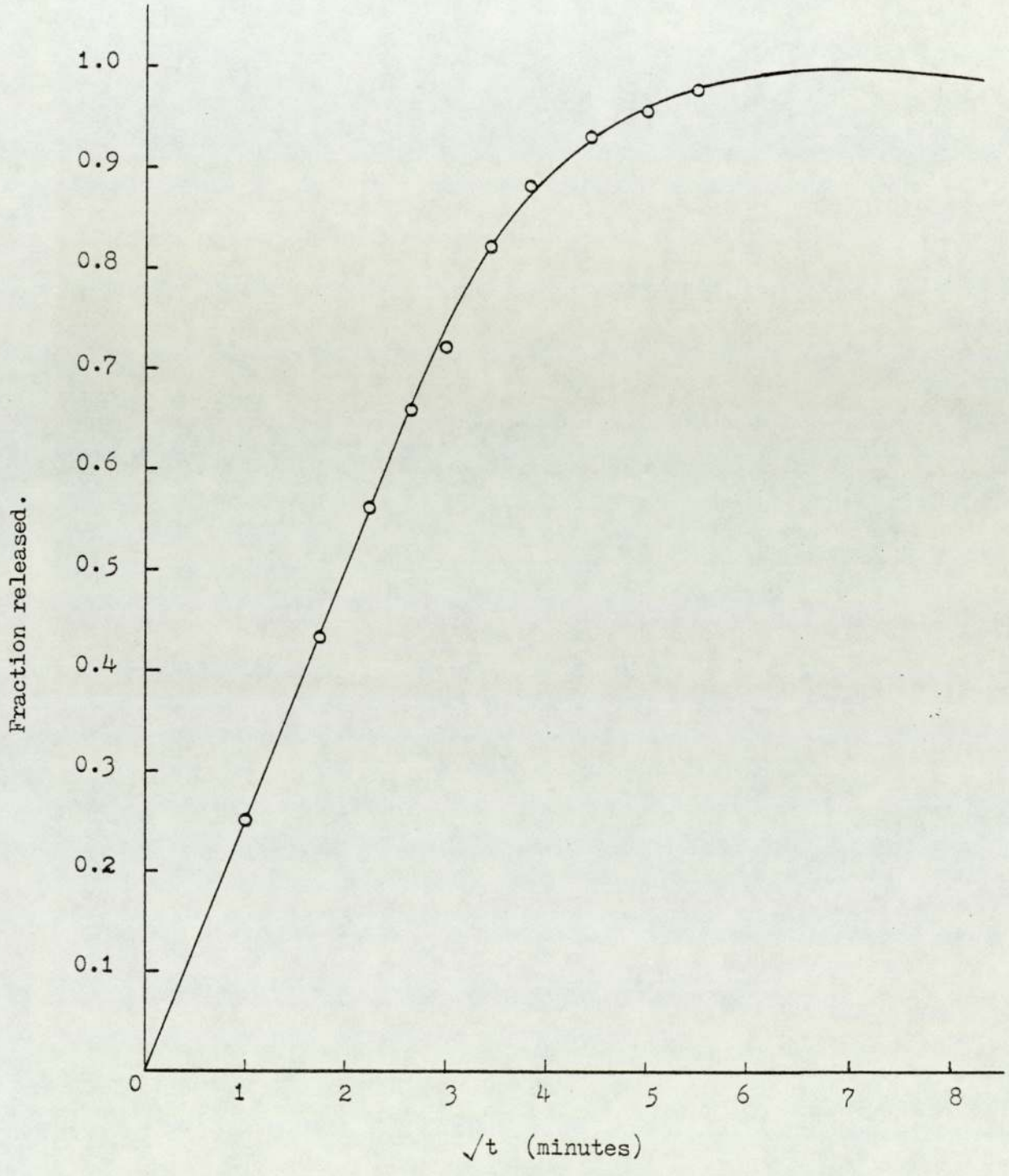


Fig. 4.10 Computer simulation of drug release from homogeneous matrices using the Guy and Hadgraft model (Appendix 4.1). Points are experimental (release of lignocaine from homogeneous gelatin films- section 3.3.2) while the line represents computer predicted release.

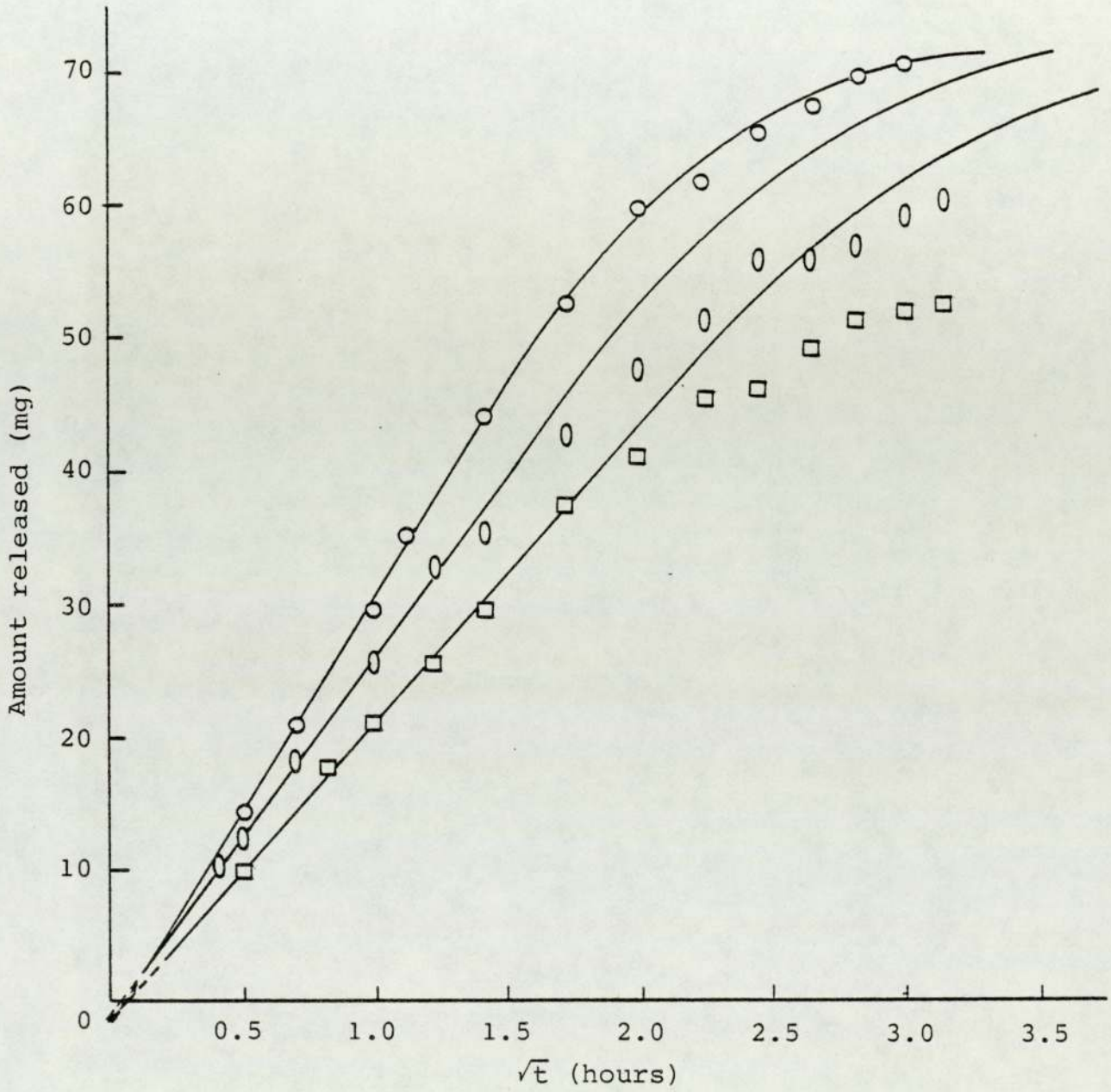


Fig 4.11 Comparison of theoretical and experimental release profiles for the desorption of lignocaine from alcohol-in-gel emulsions at 25°C. The theoretical profiles (solid lines) are computer simulated (see text). Points are experimental observations. O octanol, 0 nonanol, □ dodecanol emulsion gels. (Data on release from decanol emulsions are not included in this graph for the sake of clarity).

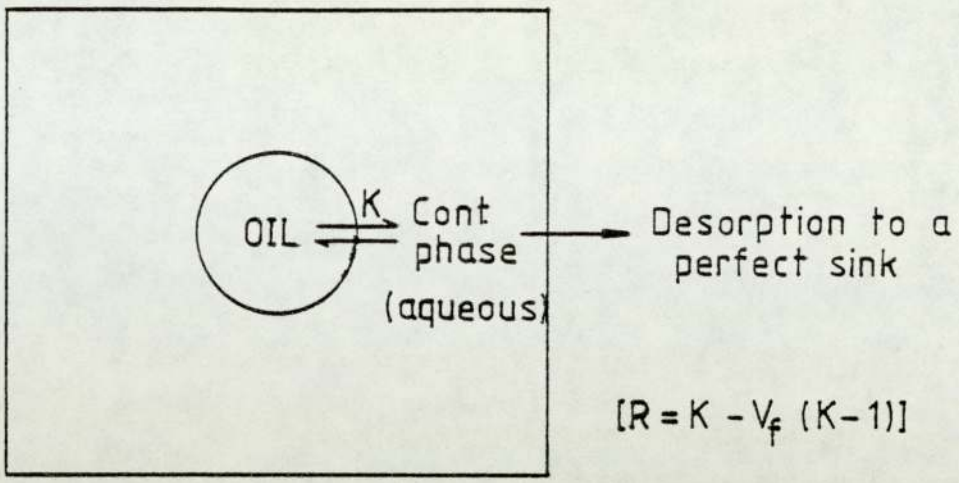
release from emulsions in all cases and is generally only applicable in the early $\sqrt{t}$ phase of release. Moreover, the assumption that equation 4.6 (a) is applicable for release of up to 30-50% of total [231] may not always be valid. The extent of concordance between experimental and theoretical values appears to be dependent on partition coefficient. Where partition coefficient is low, the extent of the fit between the Maxwell model and the homogeneous matrix is larger than when the partition coefficient is high. The extent of $\sqrt{t}$ fit therefore suggests the extent of the "simulated homogeneity" by the emulsion.

Evaluation of the effective diffusion coefficient (D_e') using equation 4.8 was then undertaken. Table 4.6 lists the values of D_e' obtained for lidocaine in alcohol emulsion systems. It is observed from the table that the value of D_e' varies with both dilution and partition coefficient. This again contradicts an earlier report [225] which showed constant values of D_e' for emulsions of varying dilutions. In another report [236], the values of D_e' as calculated from equilibrium conditions were described as "quite unrealistic". However, it has to be noted that the Maxwell model and the equations for release from monolithic suspension systems have different definitions for the observed diffusion coefficients which are not therefore directly comparable.

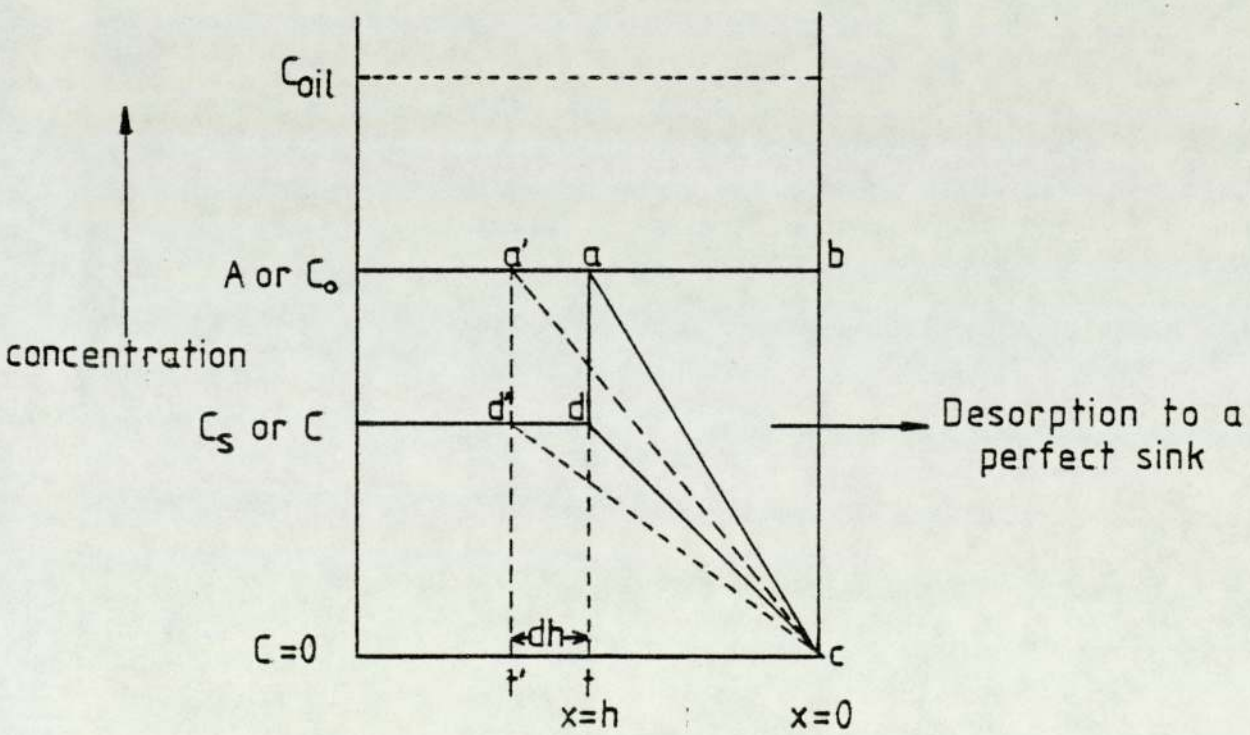
Equation 4.8 is a modification of equation 4.1 introduced by Koizumi et al [226] to correct the errors

introduced by the assumed steady-state conditions during the derivation of equation 4.1. In deriving equation 4.1, Higuchi (102) had envisaged desorption involving a receding solvent front with a fairly well defined boundary between the depleted and undepleted zones. The depleted zone was assumed to contain no solid drug and to maintain steady-state conditions. On extending the model to the case of an emulsion an extra assumption must be made; that equilibrium conditions persist throughout the matrix at all times. A correction factor is therefore required to allow for the distribution of drug between the oil and continuous phases in the zone of depletion. A model equivalent to that of the suspension may then be drawn for emulsions (Fig. 4.12). At any given time in the emulsion model, the concentration gradient in the partly depleted continuous phase is represented by dc, assuming steady-state conditions. However, due to the persisting equilibrium conditions, the mass balance in the depleted zone is correctly represented by line ac. The triangle a d c represents the amount ignored when the suspension model is directly applied to the emulsion case.

Using Fig. 4.12 and arguments similar to those used by Higuchi in deriving equation 4.1 (102), it can be shown that the amount additionally depleted by further movement of the front by dh is, in the emulsion case, given by the triangle a' a c, i.e.



(a) Diagramatic presentation of process involved in release of drugs from an emulsion-type matrix



(b) Diagramatic presentation of concentration distribution during release from an emulsion-type matrix (based on Higuchi's model for suspensions)

Fig.4.12

$$dQ = \frac{1}{2} dh\ C_o \quad \text{--- 4.10}$$

instead of that represented in the suspension case by area a' d' c d a.

Since the driving force can be assumed to be the concentration of the drug in the continuous phase, we can write

$$\frac{dQ}{dt} = D_e'' \frac{C_{aq}}{h} \quad \text{--- 4.11}$$

C_{aq} is taken to be the initial value since in the model put forward one is postulating the progression of the depletion layer. Beyond the depleted layer C_{aq} is constant and is determined by the partition coefficient and hence the phase volume ratio.

Introducing the value ofdQ from equation 4.10 into equation 4.11 gives

$$\frac{C_o dh}{2dt} = \frac{D_e'' C_{aq}}{h} \quad \text{--- 4.12}$$

which on rearrangement and integration yields

$$h = 4\left[\frac{C_{aq} D_e'' t}{C_o}\right]^{\frac{1}{2}} \quad \text{--- 4.13}$$

Since, from the model, the amount of drug desorbed at time t is given by

$$Q_t = \frac{C_o h}{2} \quad \text{--- 4.14}$$

we can therefore write

$$Q_t = \frac{C_o}{2}\left[4\ \frac{C_{aq} D_e'' t}{C_o}\right]^{\frac{1}{2}} \quad \text{--- 4.15}$$

Therefore,

$$Q_t = \left[C_o C_{aq} D_e "t\right]^{\frac{1}{2}} \quad \text{--- 4.16}$$

It can be seen that when the partition coefficient (K) is unity, equation 4.16 reduces to

$$Q_t = \left[C_o^2 D_e t\right]^{\frac{1}{2}} \quad \text{--- 4.17}$$

which differs from equation 4.6 (a) by a factor of $(\frac{4}{\pi})^{\frac{1}{2}}$. This situation resembles that discussed by Koizumi et al (226) for the suspension case. The discrepancy arises from the assumed linear concentration gradient in the depleted zone.

By adapting the Higuchi equation (4.1) to the emulsion case we obtain

$$Q'_t = \left[(2C_o - C_{aq})C_{aq} D_e "t\right]^{\frac{1}{2}} \quad \text{--- 4.18}$$

where C_o is defined similarly to A in equation 4.1 and C_s is replaced by C_{aq}, the equilibrium concentration of the drug in the continuous phase.

Equation 4.18 can therefore be rewritten as

$$Q'_t = \left[(2 - \frac{1}{R})\, C_o C_{aq} D_e "t\right]^{\frac{1}{2}} \quad \text{--- 4.19}$$

where R is a conversion factor such that

$$C_o = C_{aq} R \quad \text{--- 4.20}$$

It can be shown that

$$R = K - V_b(K - 1) \quad \text{--- 4.21}$$

where K is the partition coefficient of the drug between

the two phases and V_b is the volume fraction of the continuous phase. It can be shown that when the partition coefficient of the drug between the continuous phase and the receiver phase is unity, R is the effective partition coefficient of the drug between the complete emulsion matrix (oil + continuous phase) and the receiver phase.

Thus equation 4.19 can be written as

$$Q_t' = Q_t \left(2 - \frac{1}{R}\right)^{\frac{1}{2}} \quad \text{--- 4.22}$$

where Q_t is as given by equation 4.16.

Equation 4.22 shows that by using the expression meant for suspensions in the emulsion case, the amount released from the emulsion at any time is underestimated by a factor equivalent to

$$\left(2 - \frac{1}{R}\right)^{\frac{1}{2}} \quad \text{--- 4.23}$$

The equation for suspension can therefore be used for the emulsion case with expression 4.23 as a correction term. This term accounts only for the conversion of the suspension equation to cover for the emulsion case and does not include the normalization factor discussed by Koizumi et al (226). The use of Koizumi et al's equation (4.8) in conjunction with the factor 4.23 should format the suspension equation to the emulsion case as well as introduce a certain degree of normalization. Thus,

$$Q_t\left(2 - \frac{1}{R}\right)^{\frac{1}{2}} = \left[D_e'' C_{aq} t\left(2C_o - \frac{2}{3}C_{aq}\left(\frac{C_o - 0.88\ C_{aq}}{C_o - 0.89\ C_{aq}}\right)\right)\right]^{\frac{1}{2}} \quad \text{--- 4.24}$$

By rearranging and expressing C_{aq} in terms of

C_o using equation 4.20, equation 4.24 reduces to

$$Q_t = \left[\frac{D_e'' t C_o^2}{R(2-\frac{1}{R})} \left(2 - \frac{2}{3R}\left(\frac{R - 0.88}{R - 0.89}\right)\right)\right]^{\frac{1}{2}} \quad \text{--- 4.25}$$

When R is unity, equation 4.25 yields

$$Q_t = \left[D_c'' t C_o^2 \left(2 - \frac{2}{3} \cdot \frac{1 - 0.88}{1 - 0.89}\right)\right]^{\frac{1}{2}} \quad \text{--- 4.26}$$

which approximates

$$Q_t = (D_e t C_o^2 \frac{4}{\pi})^{\frac{1}{2}} \quad \text{--- 4.6 (a)}$$

which is the equation for release from homogeneous matrices approximated from the non steady-state derivation.

The use of equation 4.25 differs from equation 4.8 by the presence of

a) the normalization factor which varies between $(\frac{4}{\pi})^{\frac{1}{2}}$ and $\sqrt{2}$ depending on the value of R,

b) the correction term $(2 - \frac{1}{R})^2$ for the amount that remains in the dispersed phase in the depleted zone during desorption,

c) the factor R which arises on assuming that the driving force for release is C_{aq} instead of C_o as in the homogeneous case.

By comparing equations 4.6 (a) and 4.25, one can obtain the following relationship between the two diffusion coefficients

$$\frac{4}{\pi} D_e = \frac{D_e''}{2R-1} \left(2 - \frac{2}{3R} \cdot \frac{R - 0.88}{R - 0.89}\right) \quad \text{--- 4.27}$$

Values of D_e'' were evaluated from release data

using equation 4.25 for the systems studied. These are compared with the corresponding D_e and D_e' values in table 4.6. The values of D_e'' do not show any sort of consistency with variation in concentration of the dispersed phase or partition coefficient. They are, as observed by Broberg et al (225), generally higher than D_e values. That the relationship 4.27 holds is depicted in Table 4.7.

These results may lead one to the same conclusions reached by Broberg et al. It had, however, been observed in an earlier part of this study that release from the alcohol emulsions deviated from the expected homogeneous behaviour in the late stages of release, when release was much slower than expected. Fig. 4.13 shows that there is a tendency to biphasic release in such slower systems. This suggests a change in mechanisms i.e. the diffusive phase is followed by another slower release process, presumably a process in which the rate limiting step is the release from the dispersed phase instead of diffusion in the continuous phase. This suggests that the driving force for the process is lower than C_o, the initial drug concentration. Unfortunately, it is not possible to determine this real driving force (concentration) from the release profiles.

In the derivation of equation 4.25, the diffusion coefficient considered in the model was that of the drug in the continuous phase. Earlier studies of release of lidocaine from homogeneous gelatin matrices had

TABLE 4.6

Comparison of the Various Effective Diffusion Coefficients for the Release of Lignocaine from Alcohol Emulsion Gels

Internal Phase (Alcohol)	(Eqn. 4.6) D_e	(Eqn. 4.25) D_e''	(Eqn. 4.1) D_e'
Octanol	4.107×10^{-4}	39.09×10^{-4}	16.43×10^{-4}
Nonanol	5.738×10^{-4}	47.49×10^{-4}	20.16×10^{-4}
Decanol	7.211×10^{-4}	50.25×10^{-4}	21.65×10^{-4}
Dodecanol	8.344×10^{-4}	53.62×10^{-4}	23.29×10^{-4}

TABLE 4.7

Examination of the Validity of Equation 4.27

Internal Phase (Alcohol)	(1) R	(2) D_e ($\times 10^{-4}$)	(3) (2R-1)	(4) $D_e(2R-1)$ ($\times 10^{-4}$)	(5) D_e'' ($\times 10^{-4}$)	(6) $\frac{a}{(4/\pi)}$	(7) $\frac{D_e'' . a (\times 10^{-4})}{(4/\pi)}$
Octanol	7.65	4.107	14.3	58.730	39.09	1.5022	58.721
Nonanol	6.675	5.738	12.35	70.864	47.49	1.4923	70.869
Decanol	5.65	7.211	10.3	74.273	50.25	1.4780	74.270
Dodecanol	5.225	8.344	9.45	78.851	53.62	1.4708	78.837

Notes:

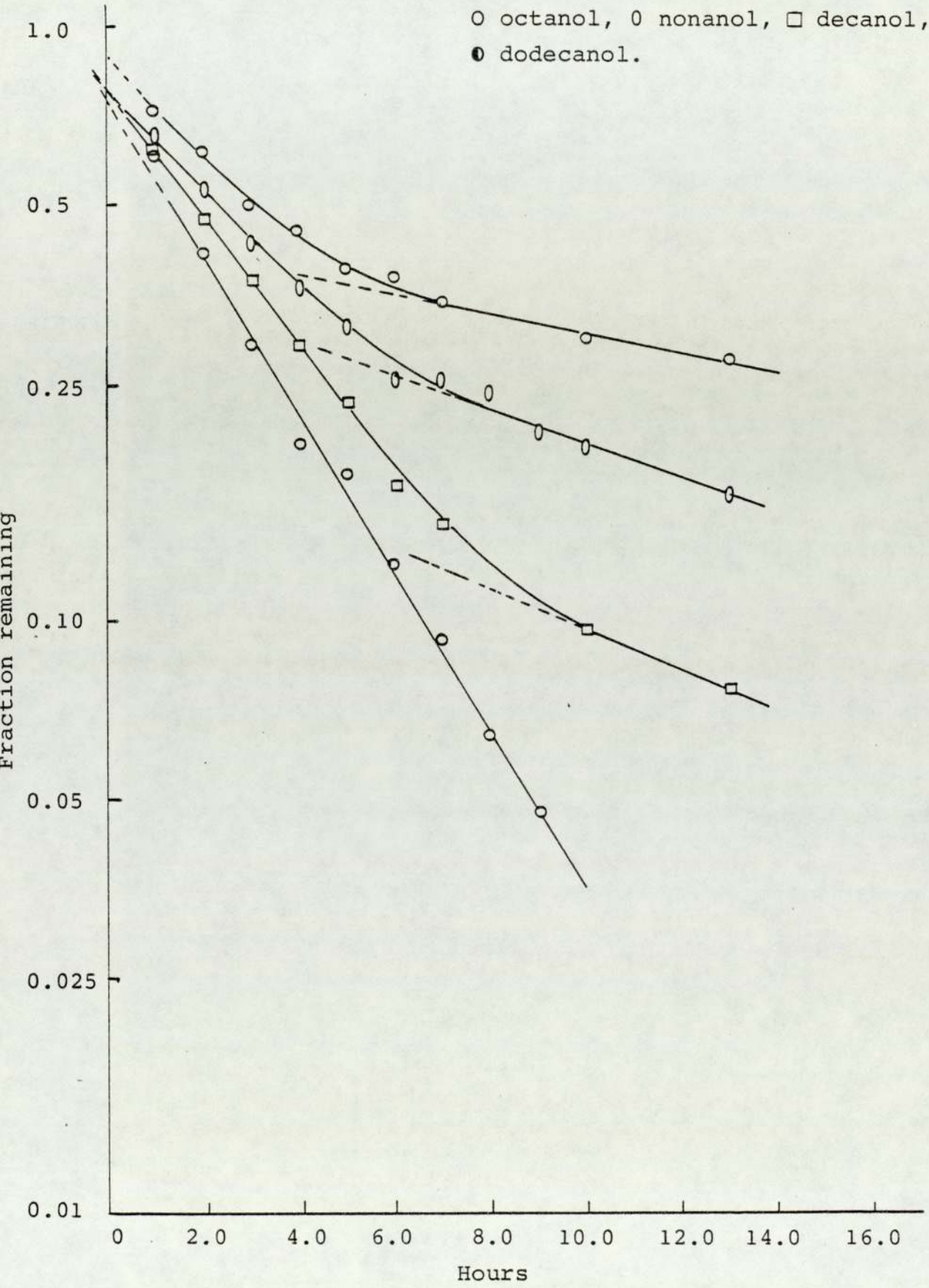
(i) $$a = 2 - \frac{2}{3R} \cdot \left[\frac{R - 0.88}{R - 0.89}\right]$$

(ii) Equation 4.27 in the form

$$D_e (2R - 1) = D_e'' \; a / \left[\frac{4}{\pi}\right]$$

is proved by the equality of columns (4) and (7).

Fig 4.13 The semi-logarithmic plot of the release of lignocaine (base) from alcohol-in-gel emulsions at 25°C. O octanol, 0 nonanol, □ decanol, ◐ dodecanol.



produced a diffusion coefficient of 76.495 x 10^{-4} cm^2. hr^{-1} (see section 3.3.2). According to studies by Carelli et al (160) and Broberg et al (225), the use of a membrane for release studies usually produces a lower diffusion coefficient than when no membrane is used. Subsequent release experiments for lidocaine from homogeneous gelatin films using a membrane filter paper similar to that used in emulsion experiments produced a diffusion coefficient of 59.034 x 10^{-4} cm^2. hr^{-1} (Fig. 4.14). Using equation 4.27 and this diffusion coefficient as D_e", the corresponding values of D_e were calculated for all the alcohol systems. Table 4.8 lists the obtained D_e values together with the hypothetical initial concentration. These hypothetical concentrations were calculated from equation 4.6 (a) using the appropriate slope obtained from experimental data and the D_e values listed in the same table. Theoretical profiles were then constructed using the computer program (Appendix 4.1) and are compared to experimental data in Fig. 4.15. A fairly good fit is observed in all cases.

These results suggest the presence of two stage release behaviour in emulsion systems. Similarities may then be drawn between diffusion in this case and the widely reported case of anomalous (non-Fickian) diffusion in gas/polymer systems (119 - 122).

TABLE 4.8

Hypothetical D_e and C_o calculated using equations 4.27 and 4.6(a) from the diffusion coefficient of lignocaine in pure gel and observed $Q\ V_s\ \sqrt{t}$ slope on release from alcohol emulsion

Alcohol	D_e"	Calculated D_e	$Q_t\ V_s\ \sqrt{t}$ slope	Hypothetical C_o
Octanol	59.034×10^{-4}	6.2018	0.7118	2.533
Nonanol	59.034×10^{-4}	7.1333	0.8412	2.791
Decanol	59.034×10^{-4}	8.4711	0.9428	2.871
Dodecanol	59.034×10^{-4}	9.1855	1.0144	2.966

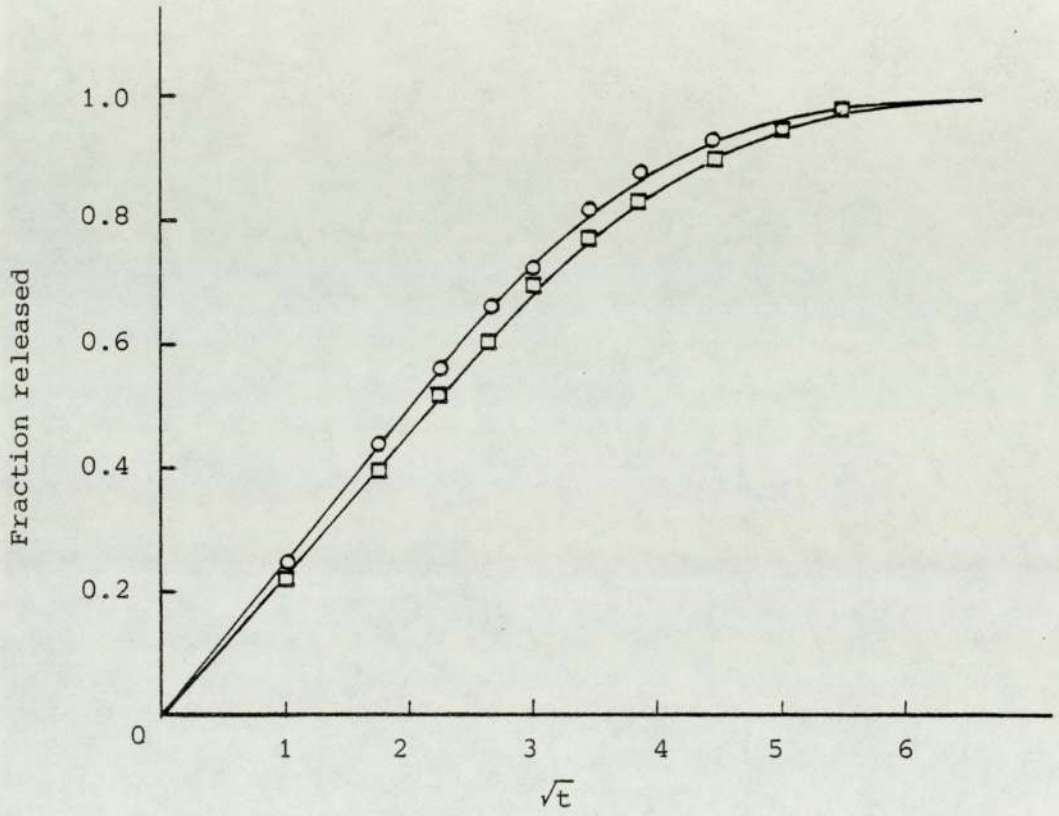


Fig 4.14 Membrane effect on release of lignocaine hydrochloride from homogeneous gelatin films (20%, 200 bloom gelatin in distilled water). O no membrane, □ membrane used. Release at 25°C.

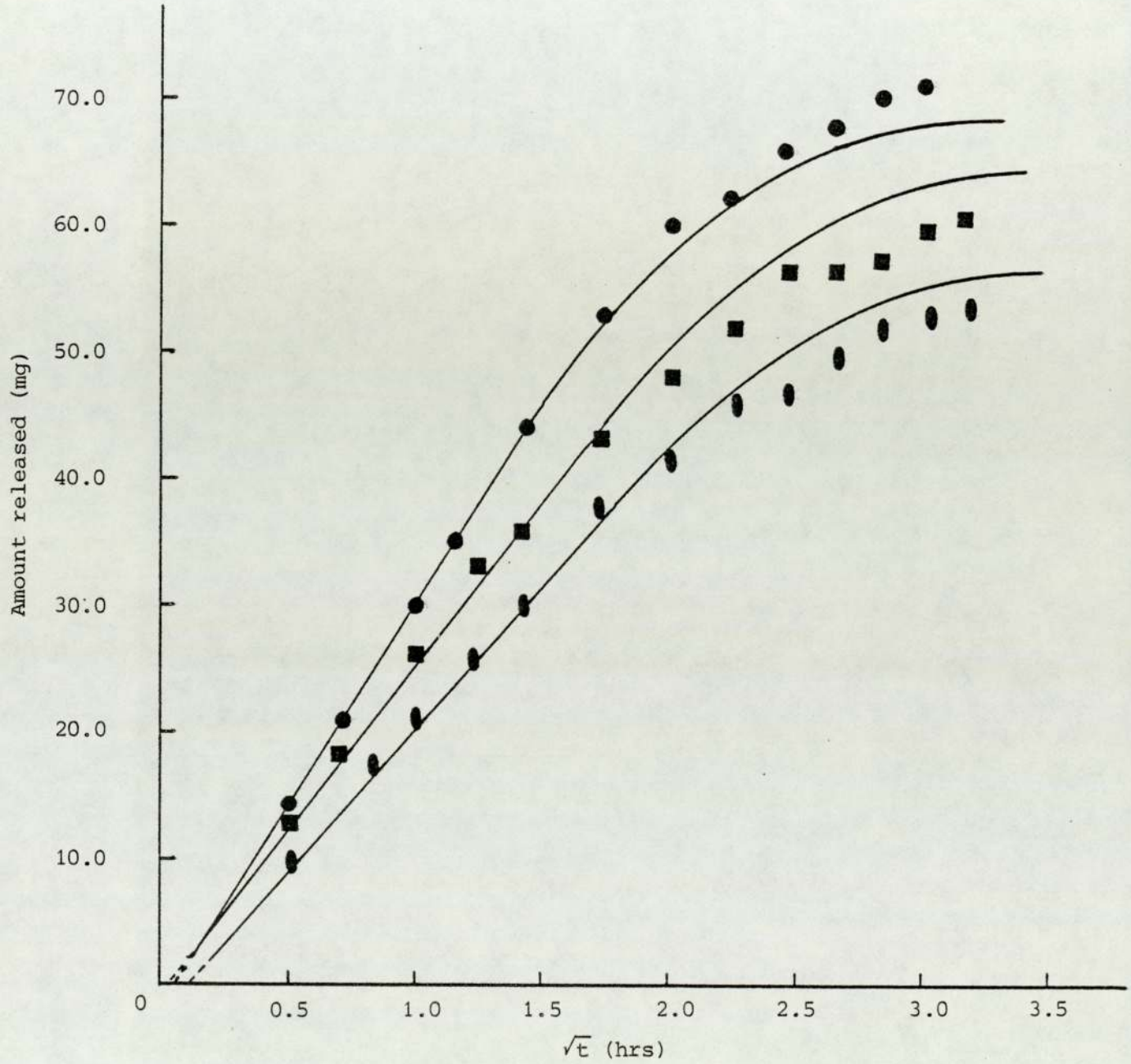


Fig 4.15 Prediction of release of lignocaine from octanol, nonanol and dodecanol emulsion gels using equations 4.27 and 4.6(a). (Decanol data has been omitted from the diagram for the sake of clarity).

4.3.2 Prediction of Drug Release from Emulsions

The use of the dielectric permeability equations in the prediction of the effective diffusion coefficient was then studied. A previous study (220) had only compared the Wagner-Weiner equation to the Bruggeman equation for one particular emulsion system. The work of De Vries (223) suggests that variation in the calculated D_e may result from changing the characteristics of the system; thus the more appropriate equation to use may also change. If this happens, the usefulness of these equations would be quite limited.

In this study it was decided to use viscosity values in the estimation of the effective diffusion coefficients (D_e) of the emulsion systems. Viscosities are generally easier and more accurately determined than diffusion coefficients and, provided a reliable relationship between the diffusion coefficient and viscosity is used, this would provide a fast method for estimating D_e values. The relationship between diffusion coefficients and viscosity of the fluid has been a subject of several studies (129, 238-240). The most popular relationship is the widely quoted Stokes-Einstein relationship (equation 4.9) which was derived from the Nernst-Einstein relationship (130). The relationship as quoted in equation 4.9 is applicable to diffusion of large molecules where frictional resistance or "sliding" between the diffusant and the molecules of the solvent is significant. For small molecules and particularly in

cases of self-diffusion, the friction factor is less significant and the appropriate relationship is

$$D = \frac{kT}{4\pi\eta r} \quad \text{--- 4.29}$$

Wilke and Chang (134,241) have observed a deviation from these relationships due, presumably, to association. They have suggested that an empirical relationship

$$D = 7.4 \times 10^{-8} \frac{(xM)^{\frac{1}{2}}T}{\eta V^{0.6}} \quad \text{--- 4.30}$$

as providing better approximations. In this case M is the molecular weight of the solvent, V is the molecular volume of the diffusant and x is an association parameter. The association parameter is experimentally determined and depends on the polarity of the solvent. The expression 4.30 therefore does not render itself accessible to quick application since preliminary experiments have to be performed to determine the value of the association parameter. On the other hand, the Stoke-Einstein relationship has been successfully used to study the influence of viscosity on the dissolution of hydrophilic polymers (242). It was therefore decided to use the Stoke-Einstein relationship in these studies. The dielectric permeability equations were therefore converted into a form which would allow the use of viscosities instead of the diffusion coefficients of the internal phases. The Bruggeman equation (4.4) was converted to the form

$$\frac{P_e - A P_b}{P_b(1-A)} \cdot \left(\frac{P_b}{P_e}\right)^{\frac{1}{3}} = V_b \quad \text{--- 4.31}$$

where

$$A = \frac{K_a \eta_b}{K_b \eta_a} \quad \text{--- 4.32}$$

where K and η abbreviate partition and viscosity coefficients respectively.

D_e could be evaluated using a computer programme (Appendix 4.2).

The Wagner-Weiner equation was rearranged to the form

$$P_e = \frac{P_b (1 + 2B V_a)}{1 - BV_a} \quad \text{--- 4.33}$$

where

$$V = \frac{K_a/\eta_a - K_b/\eta_b}{K_a/\eta_a + 2K_b/\eta_b} \quad \text{--- 4.34}$$

Finally, the Higuchi-Higuchi equation was rearranged to

$$P_e = \frac{P_b \left[2(1 - V_a) + A(1 - 2V_a) - X\right]}{(2 + V_a) + A(1 - V_a) - X} \quad \text{--- 4.35}$$

where

$$X = K B^2 (2 - A)(1 - V_a) \quad \text{--- 4.36}$$

Fig. 4.17 shows the variation of the calculated values of D_e with the partition coefficients for the lidocaine in alcohol emulsion systems. The D_e values are evaluated from P_e values using the relationships

$$P_e = K_e D_e \quad \text{--- 4.37}$$

and

$$K_e = V_a K_a + V_b K_b$$

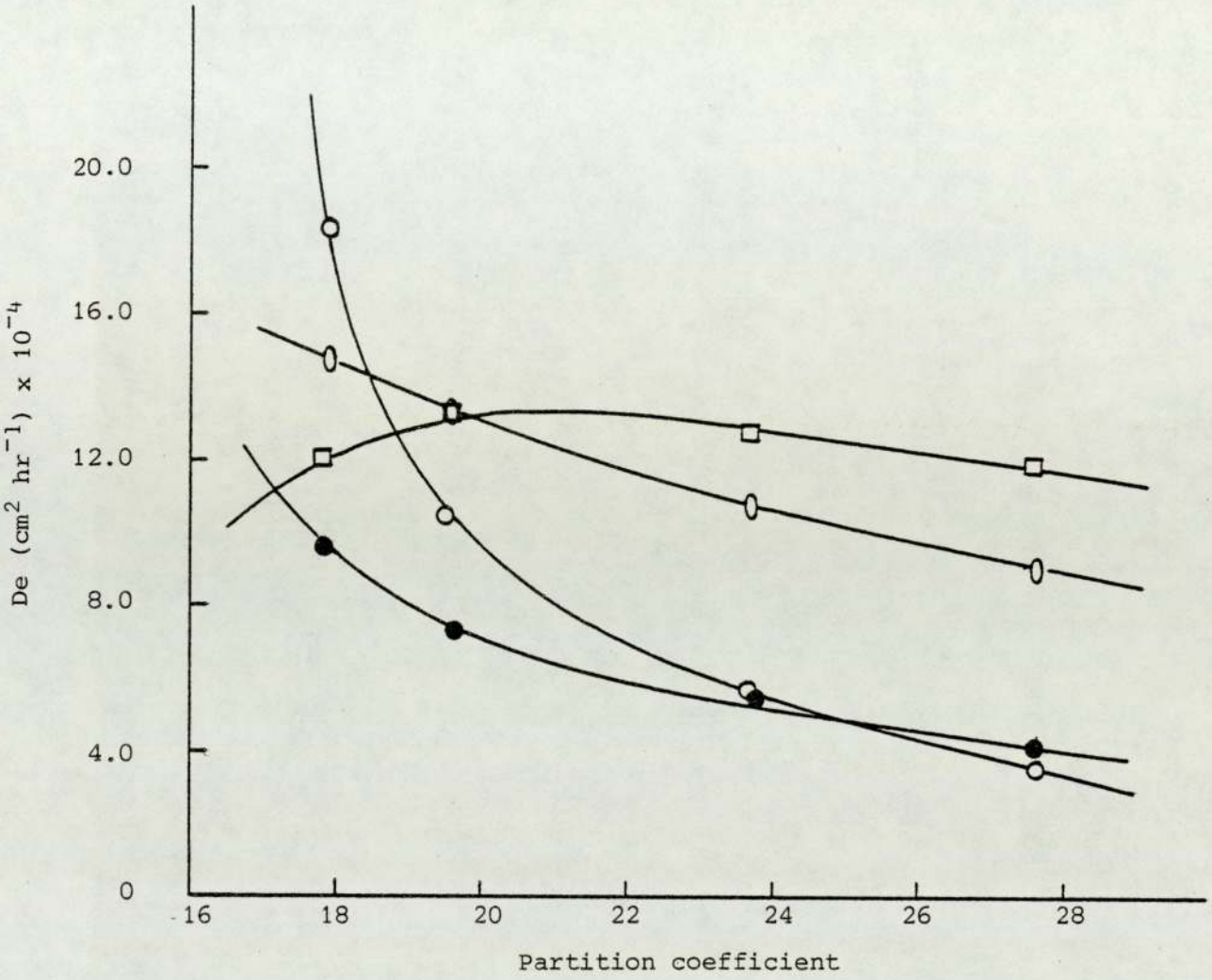


Fig 4.17 Comparison of predicted and observed effective diffusion co-coefficients for lignocaine in alcohol emulsion systems. The effective diffusion coefficients are plotted against the respective alcohol/water partition coefficients. O Bruggeman, O Wagner/Weiner, and □ Higuchi's equation. Shaded circles represent experimentally determined values.

where K_e is the effective partition coefficient of the drug between the emulsion matrix and the receiver phase.

For comparison purposes, the values of D_e as evaluated using equation 4.6 (a) from experimental data are also plotted on the same graph. It can be observed that all predictions have significant deviations at certain stages and therefore cannot be relied on entirely. The Bruggeman equation deviates at low partition coefficients, presumably due to higher levels of perturbations. It, however, provides better approximations at higher partition coefficients than the other two equations. The Wagner-Weiner equation provides a variation almost parallel to the observed behaviour. It might, therefore, be more useful in qualitative comparisons.

In a more general sense, none of the equations provides predictions that are wholly reliable. This is well illustrated in figures 4.18-4.21 which compares computer simulated theoretical profiles (Programme in Appendix 4.1 is used) to experimental results. It is observed that whereas the Bruggeman equation provides excellent predictions in case of octanol and nonanol emulsions, the Higuchi-Higuchi equation is the better one in the case of the dodecanol emulsion, although at a poorer level.

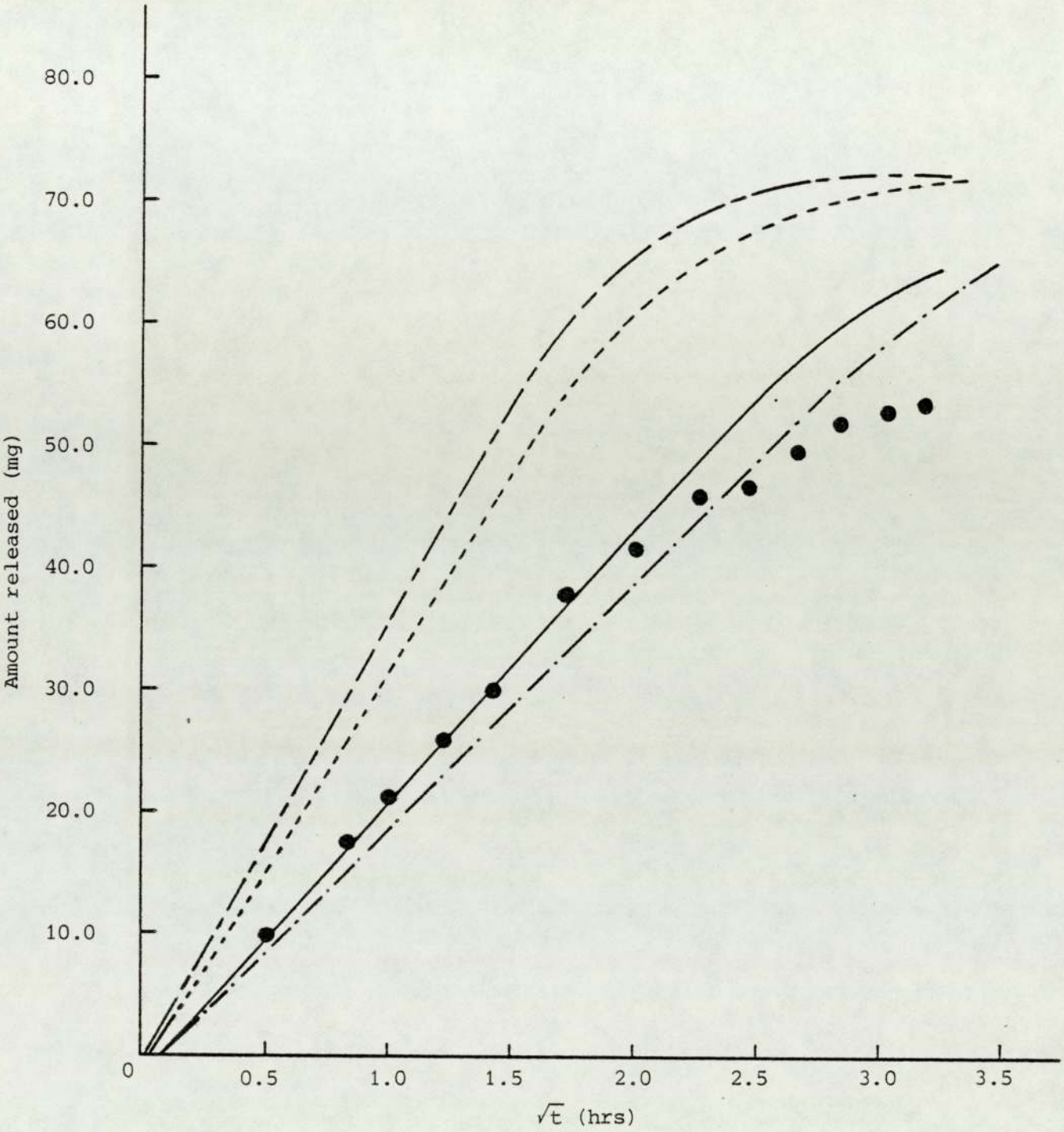


Fig 4.18 Prediction of release of lignocaine from octanol emulsion gels at 25°C. The points are experimental and the continuous line was constructed by computer to represent homogeneous release behaviour using the observed diffusion coefficient (Hadgraft model Appendix 4.1). -·-·- Bruggeman, ----- Wagner/weiner, and ——————— Higuchi's models.

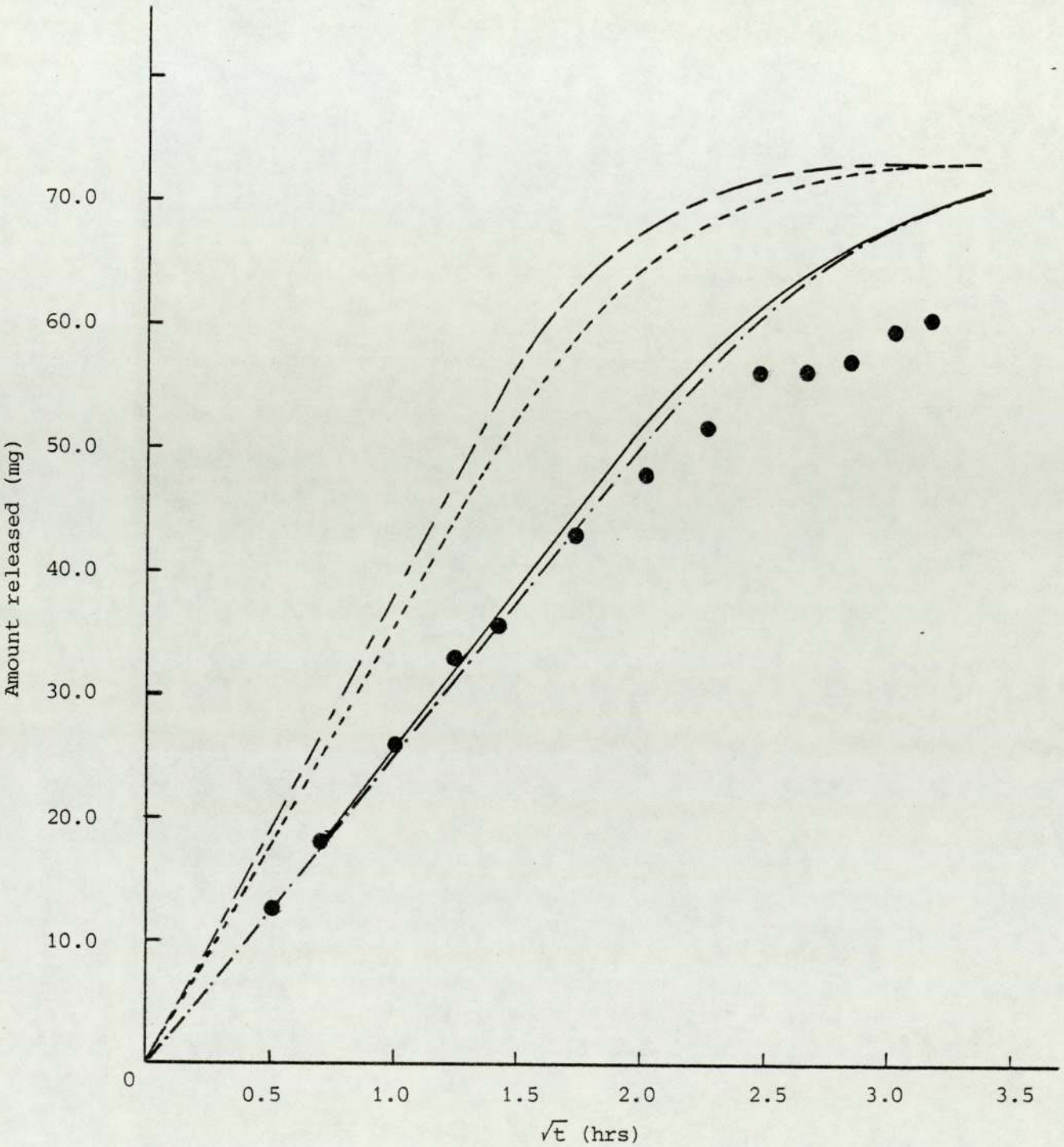


Fig 4.19 Prediction of release of lignocaine from nonanol emulsion gels at 25°C. The points are experimental data and the continuous line was constructed by computer (Hadgraft model, Appendix 4.1) to represent homogeneous release behaviour using the observed diffusion coefficient. -•-•- Bruggeman, ----- Wagner/Weiner, and ——————— Higuchi's models.

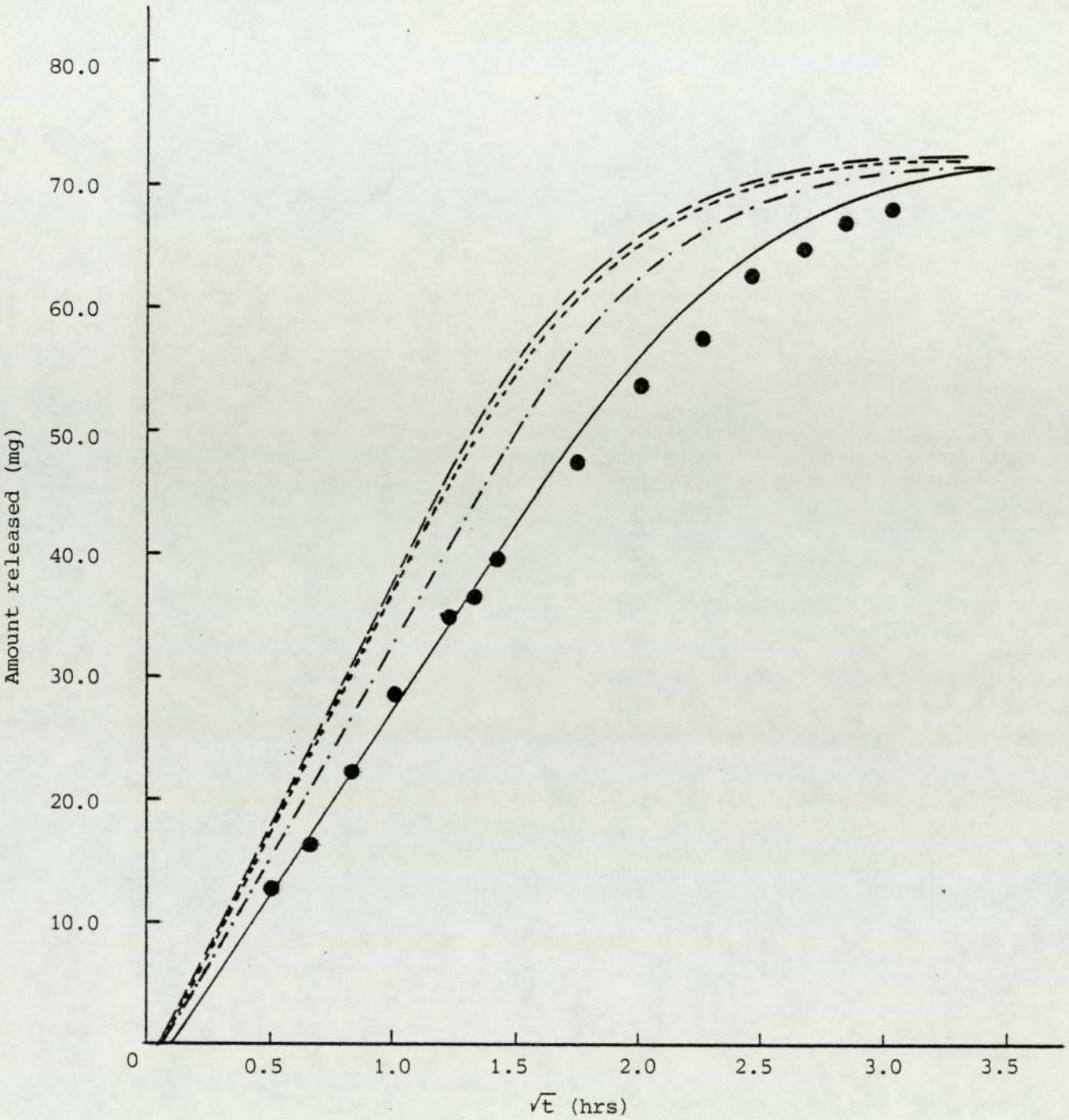


Fig 4.20 Prediction of release of Lignocaine from dexanol emulsion gels at 25°C. The points are experimental data and the continuous line was constructed by computer (Hadgraft model, Appendix 4.1) to represent homogeneous release behaviour using the observed diffusion coefficient. -·-·- Bruggeman, ----- Wagner/Weiner, and ——————— Higuchi's models.

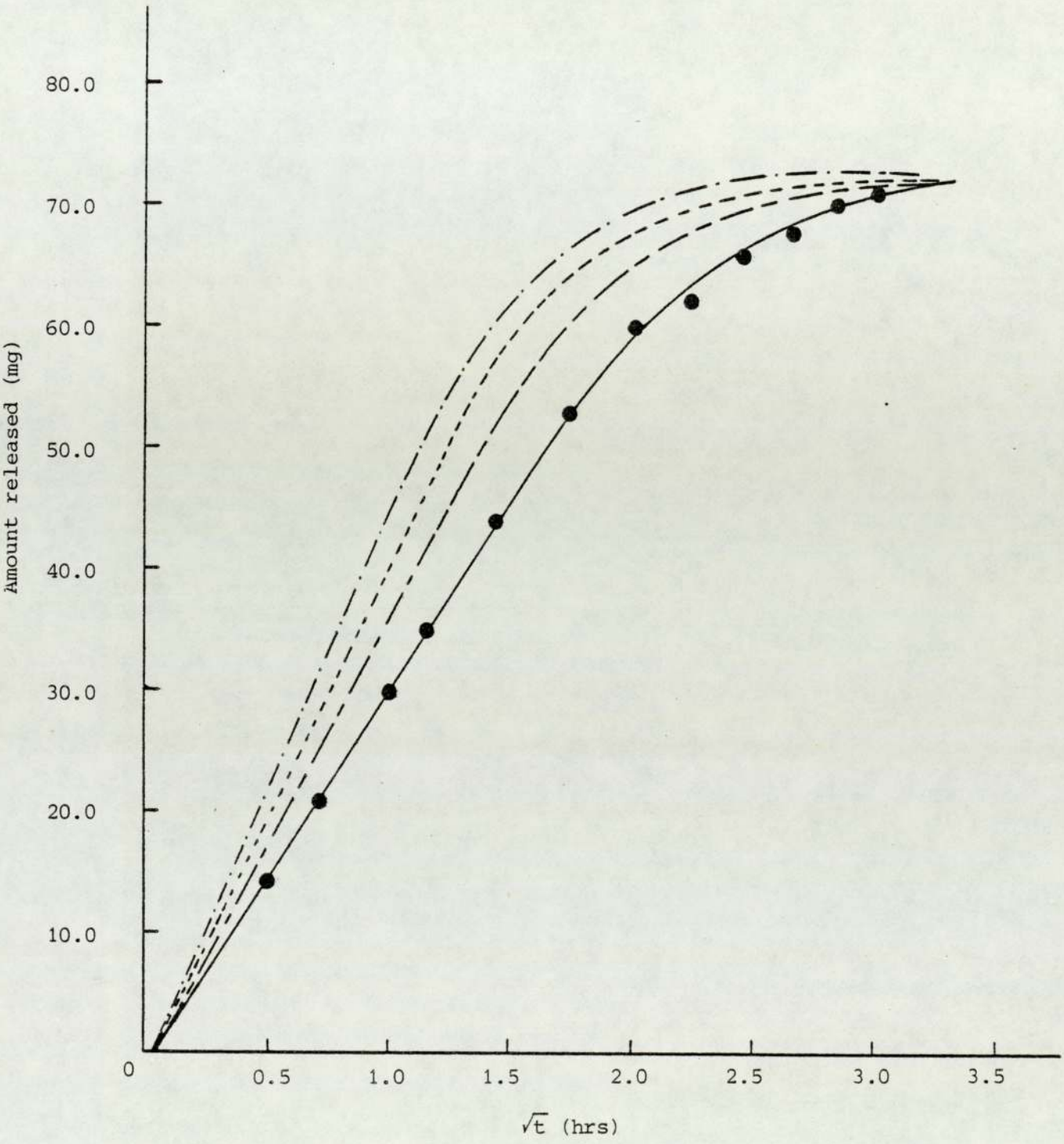


Fig 4.21 Prediction of release of Lignolcaine from dodecanol emulsion gels at 25°C. The points are experimental data and the continuous line was constructed by computer (Hadgraft model, Appendix4.1) to represent homogeneous release behaviour using the observed diffusion coefficient. -·-·- Bruggeman, ----- Wagner/Weiner and ——— Higuchi's models.

CHAPTER 5

RELEASE OF BENZOCAINE FROM FORMALDEHYDE-HARDENED OIL-IN-GEL EMULSIONS

5.1 INTRODUCTION

Benzocaine, together with other p-aminobenzoate esters, are local anaesthetics possessing a primary amino group. There is a possibility of exploiting the presence of the amino group to effect reversible binding to a suitable matrix. Since the process of crosslinking of proteins chemically involves amino and other groups, there is a possibility that benzocaine present during the crosslinking process could also get bound to the gelatin strands. If the binding is sufficiently reversible, then the subsequent release of benzocaine could be useful for drug delivery. This chapter investigates this possibility in a benzocaine-gelatin-formaldehyde system.

5.1.1. The Reaction Between Aromatic Amines and Formaldehyde

The reaction of formaldehyde and amines has been a subject of intense study (156 - 159). The chemistry is complex and dependent on the conditions under which the reaction is carried out. A range of products can be formed most of which are formed through Schiff and Mannich-type reactions. It is now accepted that most of these reactions proceed through the formation of arylaminomethylol intermediates (158,159). In strongly alkaline solutions, for

example, aniline forms bi(phenylamino)methane

$$2\ C_6H_5NH_2 + HCHO \longrightarrow C_2H_5NHCH_2NHC_6H_5 + H_2O$$

The reaction has been shown to proceed through a Mannich-type reaction.

For neutral solutions, there is formation of triaryltrimethylene triamines, possibly through a Schiff-type reaction (178).

For acid solutions, aromatic amines form resins with formaldehyde probably involving rearrangements and condensation (179). In strongly acid solutions, aromatic monoamines yield a number of complicated compounds including heterocyclic hydroquinazolines.

The pH dependence of the reactions has been demonstrated (237). This dependence varies from compound to compound, depending on the individual drug. For example, it has been observed that whereas the binding of formaldehyde to amino acids increases near neutral pH, amines bind more strongly in acidic conditions (24).

5.1.2. The Reaction of Gelatin with Formaldehyde

The reaction of formaldehyde with gelatin has also been extensively studied especially by Fraenkel-Conrat and his group (245-248). Through their work it is now known that primary amino, amido and guanidyl groups are involved in the crosslinking process. The series of reactions demonstrated by Fraenkel-Conrat et al are

i. $R_1 - NH_2 + HCHO + R_2 - NH_2 \longrightarrow R_1 - NHCH_2NH - R_2$

ii. $R_1 - NH_2 + HCHO + NH_2 - \overset{O}{\overset{\|}{C}} - R_2 \longrightarrow R_1 - NHCH_2NH\overset{O}{\overset{\|}{C}} - R_2$

iii. $R_1 - NH_2 + HCHO + NH_2 - \overset{NH}{\overset{\|}{C}} - NHR_2 \longrightarrow R_1 - NHCH_2NH\overset{NH}{\overset{\|}{C}} - NHR$

The reactions have been shown to proceed in two stages. First there is the aminomethylation of the primary amino group to form an aminomethylol

$$R_1 - NH_2 + HCHO \rightleftharpoons R - NH - CH_2OH$$

followed by the condensation with the secondary amine, amide or guanidyl group to form the methylene bridge. The reaction may involve the formation of the cation $R_2\overset{+}{N}C$ from formaldehyde and the amine, which then condenses with the anion of a reactive hydrogen compound (237). This may explain the pH sensitivity of the process since excessive acid will inhibit the formation of the anion while the formation of the cation will be inhibited by excessive alkalinity (244). The methylene bridges established during crosslinkage of proteins with formaldehyde has been shown (249) to be very stable in alkaline conditions; a general property of methylene amines and formals. Formaldehyde is slowly generated when crosslinked gelatin is treated with warm water but decomposition is much faster on exposure to cold hydrochloric acid (250). It has been observed however, that some formaldehyde is bound irreversibly (251-255).

The capacity of protein to combine with formaldehyde depends on the properties of the protein itself. Thus it has been shown that whereas gelatin can bind 4.0 to 4.8 grams

of formaldehyde per 100 g. of protein, casein can only bind 0.6 to 2.5 grams per 100 grams (256). It has also been shown (257) that higher bloom strength gelatin requires less formaldehyde to make it insoluble than the lower grades.

The increased crosslinkage in proteins results in

a) increased molecular weight

b) increased hardness

c) reduced water sensitivity.

5.1.3. The Formulation Implications of Using the Benzocaine-Formaldehyde-Gelatin System

From the above discussion, it is obvious that no prediction can be made as to the behaviour of the benzocaine-formaldehyde-gelatin system. The presence of many reactive groups makes it even more difficult to expect one particular reaction to proceed sufficiently because this depends on the relative reactivities of the groups present. The situation is complicated even further by the possibility of either Schiff-type or Mannich-type reactions taking place.

Generally, the system would demonstrate the following reactions

i. Benzocaine + HCHO $\longrightarrow$ Benzocaine complex(es)

ii. Gelatin + HCHO $\longrightarrow$ Crosslinked gelatin

iii. Benzocaine + Gelatin + HCHO $\longrightarrow$ Bound Benzocaine.

That the formaldehyde induced methylene links in gelatin are reversible in acidic conditions has been shown (250). But reports suggest that such links are very stable

at neutral and alkaline pH. The possibility of release of any gelatin-bound benzocaine in a near neutral formulation is therefore doubtful.

Since the degradation of the methylene bridges in crosslinked gelatin has been shown to liberate formaldehyde (250), this would constitute a very dangerous situation in drug administration due to the toxicity of formaldehyde. However, formaldehyde is being used in this study only as a prototype crosslinker. It is possible to find and use a safer crosslinker if these attempts are successful.

5.1.4. The Aims of this Work

The work reported in this chapter was undertaken specifically as a first effort into designing a new effective and cheap controlled release delivery system for medicaments. It was therefore intended to investigate

a) whether it is possible for a benzocaine-gelatin formaldehyde system to have sufficient free benzocaine for effective therapeutic use
b) the kinetics of benzocaine release from such formulations
c) depending on the observations in (a) and (b), to perform preliminary stability studies.

The system used in this case is an oil-in-gel emulsion system. The use of an emulsion system has been necessitated by the very low solubility of benzocaine in the aqueous gels.

5.2 EXPERIMENTAL PROCEDURES

5.2.1. Preparation of Formaldehyde-hardened Emulsion Gels

The initial emulsion gel was prepared by the method outlined in section 2.3.1. Thin films of a given thickness were cast using the method described in section 2.4.4 Small disks of 1.8 cm diameter were cut, placed on individual microscope slides and stored at 95% R.H. over formaldehyde vapour. The formaldehyde environment was created by placing 2 ml. of commercial formalin (38% w/w formaldehyde) on a piece of cotton wool, which was placed at the bottom of the storage tank.

When films had to be removed from the formaldehyde environment, they were stored in a dessicator at 25°C and 95% R.H. The 95% relative humidity was attained by using a saturated solution of disodium hydrogen orthophosphate dodecahydrate.

(All emulsions contained 0.5%w/w benzocaine in 20% O/gel emulsion).

5.2.2. Release Experiments

The films were washed with 10 ml. of 50% methanol in water before release experiments. The release experiments were performed at 37°C according to the method outlined in section 2.5.1.Aliquots (5 ml.) were withdrawn at predetermined times and replaced with 5 ml. of pure buffer. Assay for benzocaine was by HPLC (section 2.6), using methyl-p-aminobenzoate as internal standard.

5.2.3. Determination of Solubility of Benzocaine in Suppository Bases

An excess of benzocaine was added to 25 g. of the molten suppository base in a test tube at 70°C. The mixture was cooled to the required temperature while maintaining vigorous shaking. After 6 hours at that temperature, a 5 ml. sample was withdrawn and filtered using a prewarmed syringe and membrane filter. The filtrate (1 g.) was diluted with 200 ml. of 50% methanol in water and assayed for benzocaine content by HPLC.

5.3. RESULTS AND DISCUSSION

5.3.1. Mechanisms of Release of Benzocaine From Formaldehyde-Treated Films

5.3.1.1. The General Release Behaviour

Fig. 5.1. shows the trend of release of benzocaine from sunflower oil emulsion gels stored over formaldehyde vapours for different periods. It can be observed that a "burst" effect is obtained in all cases; the burst amount initially increasing with storage duration followed by a decline (Fig. 5.2). Also observed is the change in release kinetics. Whereas films stored for 3 and 4 days showed zero order release behaviour, those stored for over 11 days demonstrated non-zero order release kinetics.

The zero order release behaviour is particularly

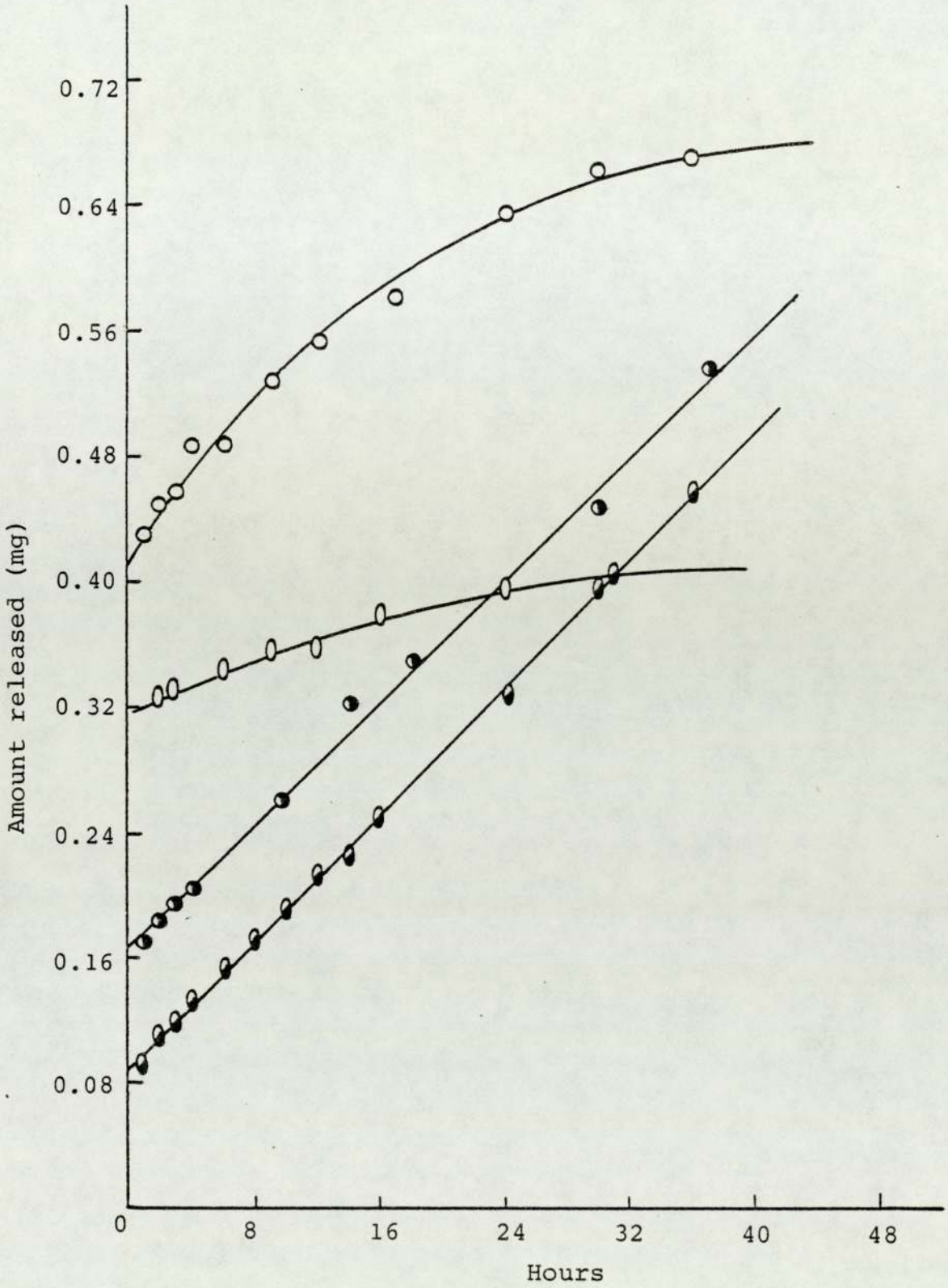


Fig 5.1 Release of benzocaine from sunflower emulsion films stored over formaldehyde for different durations. Storage durations: ◑ 3 days, ◑ 4 days, O 11 days and O 24 days.

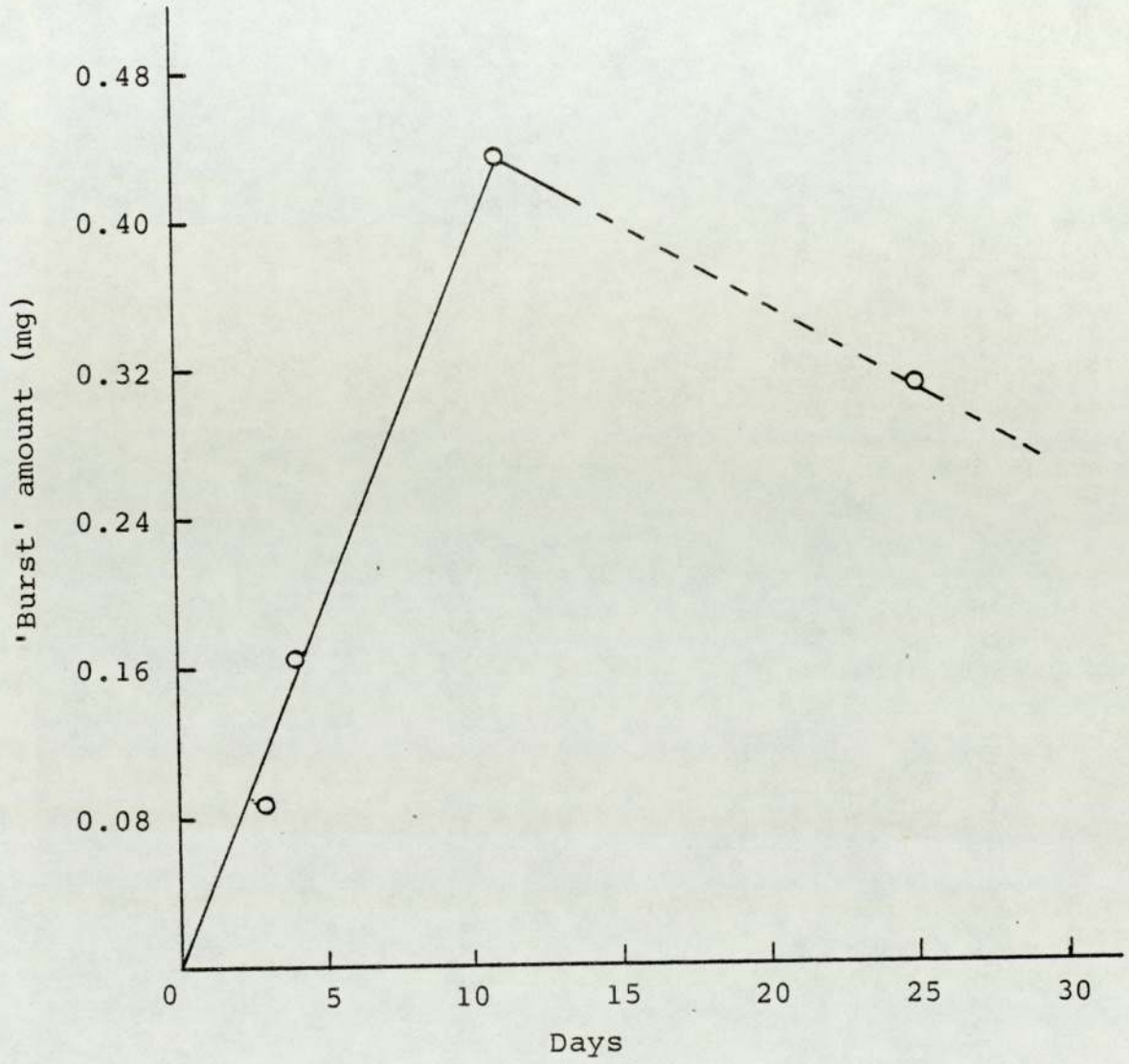


Fig 5.2 Variation of 'burst' amount on continuous storage of benzocaine emulsion films over formaldehyde. Burst amounts are approximated from intercepts on the abscissa in Fig 5.1.

interesting since steady delivery of medicaments is the aim of most studies aimed at producing controlled release. A detailed study of the observed behaviour was therefore necessary to establish

a) the cause of the initial burst effect,

b) the mechanisms for the zero and first order release behaviours and therefore the explanation for the change in the kinetic order of release,

c) the cause of the decline in total releasable amount in the presence of formaldehyde.

The initial burst behaviour could be a consequence of two factors. Firstly, it could represent the amount of drug that is on the surface of the matrix before the commencement of the release study. This could be brought about by either syneresis of the oil from the matrix or concentration in the condensate on the film caused by the high humidity storage conditions. It was therefore decided to wash the film in a limited volume of a 50% methanol in water mixture before the release experiments. The washings would then be assayed so as to facilitate the determination of the total releasable amount of benzocaine.

The second possible cause of the burst effect could be the presence of a fast release phase followed by a slower release one. Cases of two-stage release behaviour have been reported in which the drug exists in two states; one of which releases faster than the other (119-122). Fig. 5.3 shows the processes involved in the release of

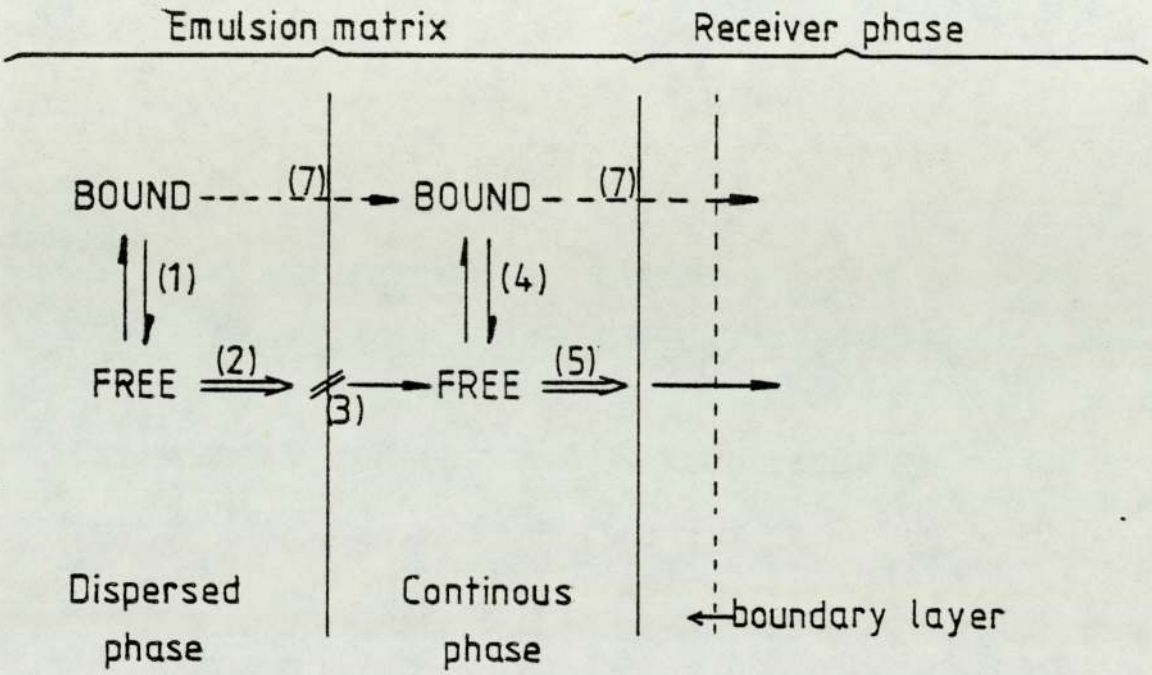


Fig 5.3 Schematic presentation of processes possibly involved in control of benzocaine release from formaldehyde-treated emulsion-gels

(1) Release of drug bound in dispersed phase

(2) Diffusion controlled release from dispersed phase

(3) Interfacial barrier-controlled release (electrical or physical)

(4) Release of matrix-bound drug

(5) Diffusion controlled release from continuous phase

(6) Diffusion across laminar sublayer

(7) Release of drug in complex form

medicament from emulsions. When the diffusion of the drug in the continuous phase is slower than that of the dispersed phase, release follows the $\sqrt{t}$ behaviour (as discussed in Chapter 4). Where release from the dispersed phase is much slower than that of the continuous phase, it is possible to obtain two stages of release, the first representing the fast release from the continuous phase, and the later phase representing release from the dispersed phase. In normal studies of release from heterogeneous (227) systems, it is a usual procedure to introduce a small quantity of the formulation into a sink solution making up the receiving phase and then monitor the rate of increase of drug in the receiving phase. In subsequent calculations, the release profile shows an initial burst which is postulated as representing the amount that was originally in the continuous phase of the formulation, and is considered as having been released instantaneously (109). Ostrenga et al (163) performed release experiments of fluocinonide from FAPG® creams, in which the formulation was separated from the receiving phase. They observed a two-stage release pattern which they explained in terms of an early diffusion controlled release of the solubilized fraction followed by a slower, zero-order phase during which release was controlled by the dissolution of the undissolved fraction. The presence of a two-stage release behaviour in the present study is therefore a possibility. Its presence can be better visualised by more frequent sampling during

the early phase of release and Fig. 5.4 shows a typical release profile.

A $\sqrt{t}$ plot of the released amounts (Fig. 5.5) shows that the 'burst' phase is in fact an independent gradual release phase during which the $\sqrt{t}$ law is obeyed. Release is therefore biphasic with an initial $\sqrt{t}$ phase and a later zero or first order phase. Since the $\sqrt{t}$ release behaviour is associated with diffusion, it is safe to conclude that release during the early phase is diffusion controlled. It was therefore thought necessary to establish the causes and mechanisms for this two-stage release and how formulation parameters such as phase ratio and thickness affect them.

5.3.1.2. The Early Phase

Fig. 5.6 compares the early release of benzocaine from films stored under two different conditions. One group of films was stored in formaldehyde vapour for 3 days followed by storage at 95% R.H. in a formaldehyde-free environment. The other group of films was stored continuously over formaldehyde vapour. At a given number of days, two films from each group were subjected to release studies to monitor the release behaviour.

It can be observed from Fig. 5.6 that the early release from films stored continuously over formaldehyde remains constant after 5 days of storage. On the other hand, the films removed from the formaldehyde environment demonstrate a gradual decline in the total amount

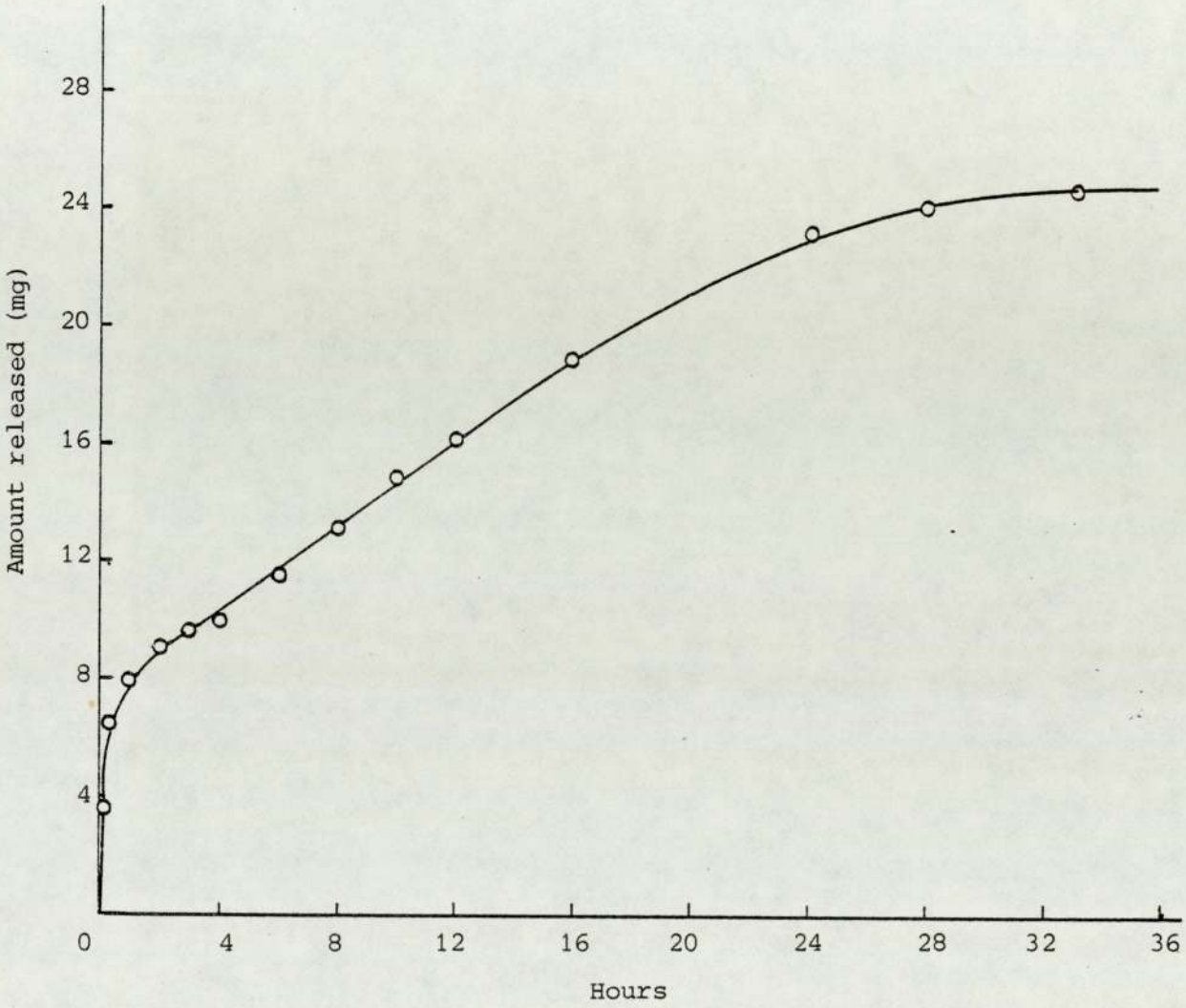
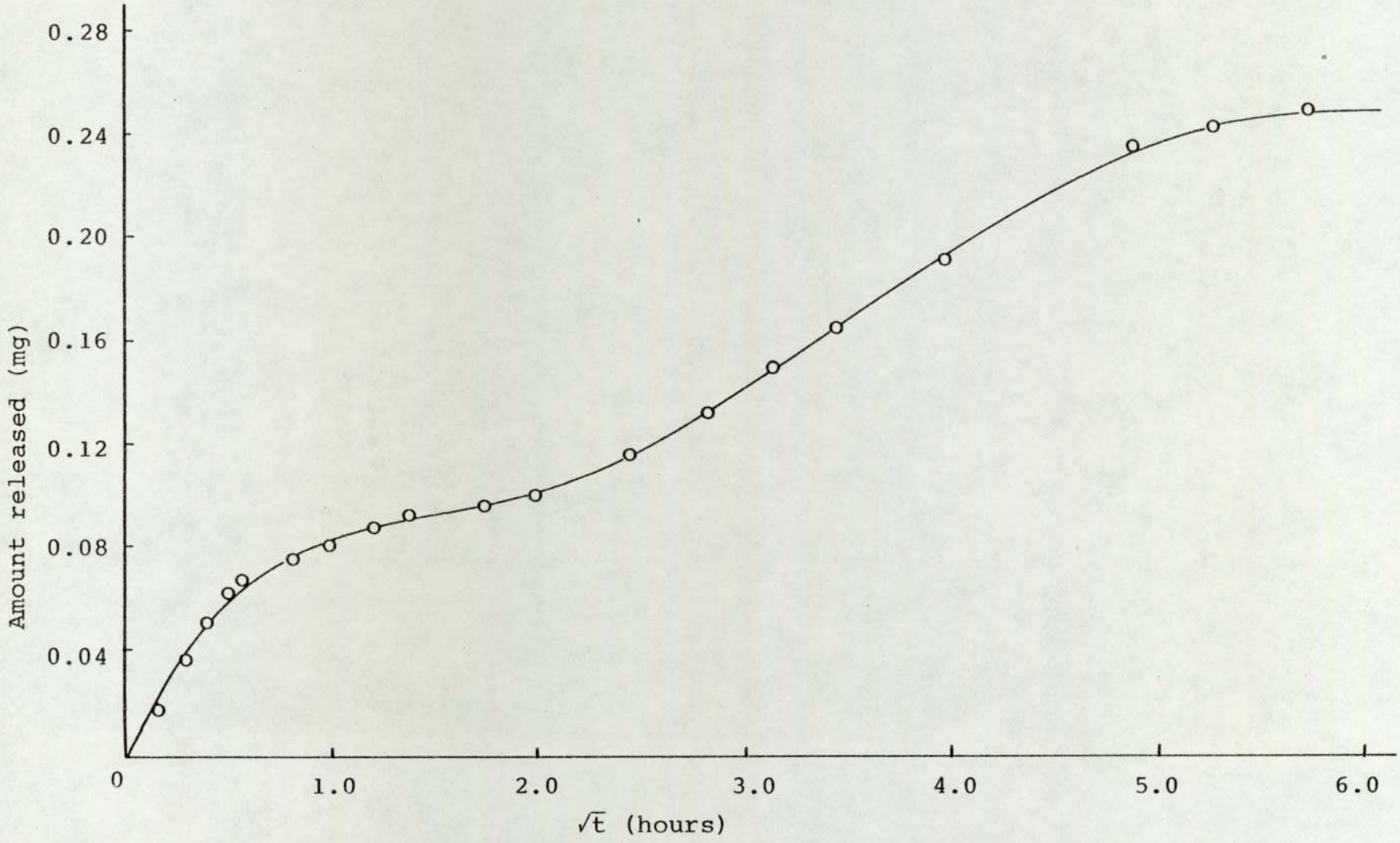


Fig 5.4 A typical benzocaine release profile from formaldehyde-treated sunflower oil emulsion films at 37°C.


0.28
0.24
0.20
0.16
0.12
0.08
0.04
Amount released (mg)
0
1.0
2.0
3.0
4.0
5.0
6.0
√t (hours)

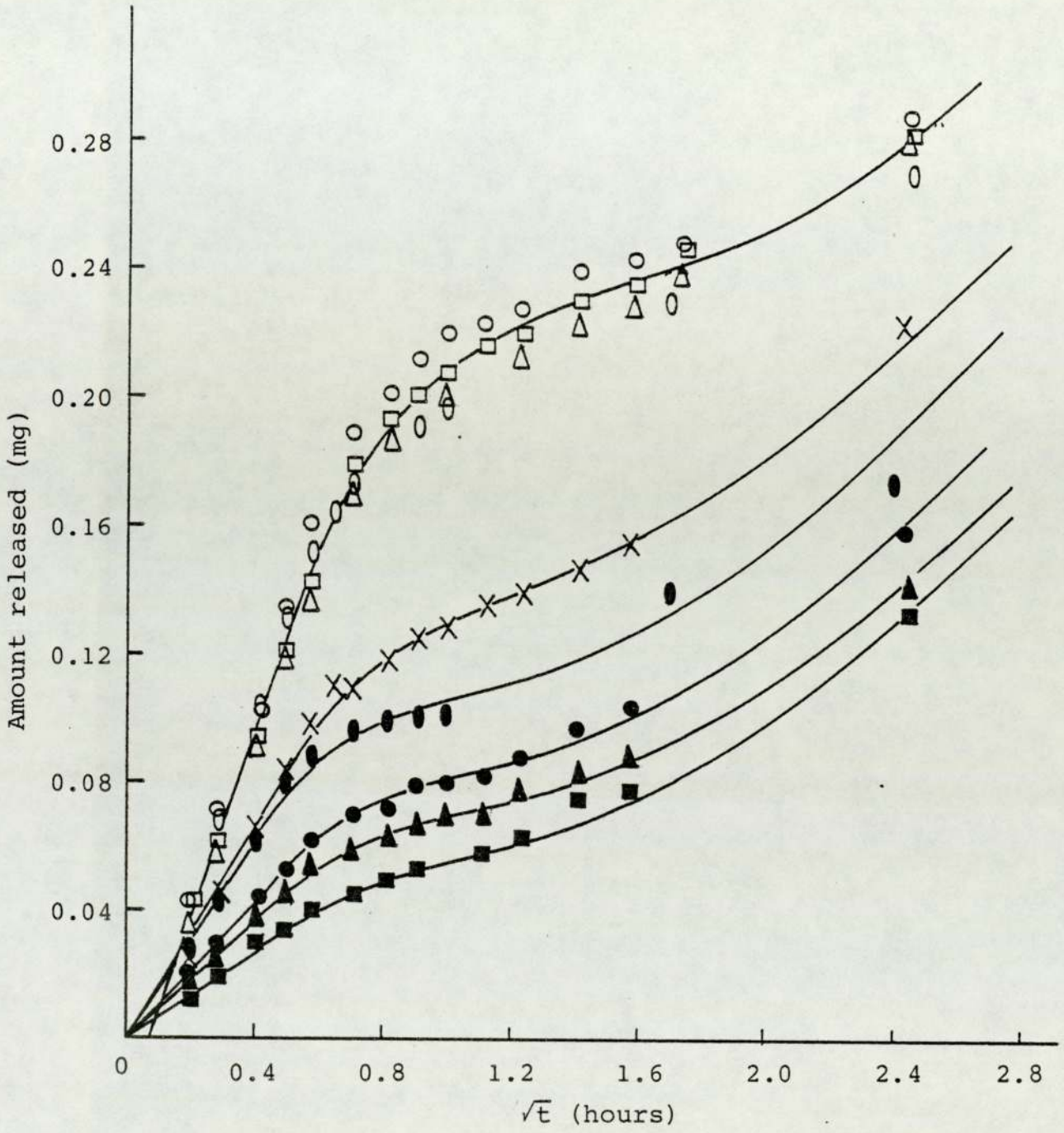


Fig 5.6 The influence of formaldehyde environment on the early release of benzocaine from stored films. Open symbols represent films continuously stored in formaldehyde while shaded symbols represent films stored in formaldehyde-free environment after the initial 3 days in formaldehyde environment. Storage duraticns: X 3 days, 0 4 days, O 5 days, Δ 6 days and □7days.

released during the early phase accompanied by a slower release rate. The total amount released during the early phase was estimated from the quasi-equilibrium of the profiles and are plotted in Fig. 5.7. Whereas the films stored over formaldehyde demonstrate a constant quasi-equilibrium, the films stored in formaldehyde-free environment demonstrate an exponential decline in the amount released during the early phase. The values for the apparent diffusion coefficients calculated from the slopes of the profiles and the quasi-equilibrium quantities using equation 4.6 (b) also demonstrate a semi-logarithmic decline with storage time (Fig. 5.8).

The release of benzocaine from sunflower oil emulsion gels not treated with formaldehyde was then studied as a control experiment. As Fig. 5.9 shows, $\sqrt{t}$ release persists to around 60% of total releasable amount. The calculated effective diffusion coefficients for a non-hardened emulsion of 0.2 oil phase ratio was 12.0×10^{-4} $cm^2.hr^{-1}$. Diffusion of benzocaine across a homogeneous film (Fig. 5.10) provides a diffusion coefficient of 106×10^{-4} $cm^2.hr^{-1}$. The apparent diffusion coefficient of films stored over formaldehyde for more than 5 days (as estimated from slope and the quasi-equilibrium assymptotes) is 83.3×10^{-4} $cm^2.hr^{-1}$, which is significantly higher than that for the control emulsion but lower than that of a homogeneous gelatin film. From table 5.1, it can be observed that the apparent diffusion coefficients for films removed from the formaldehyde environment after 3 days show a decline from

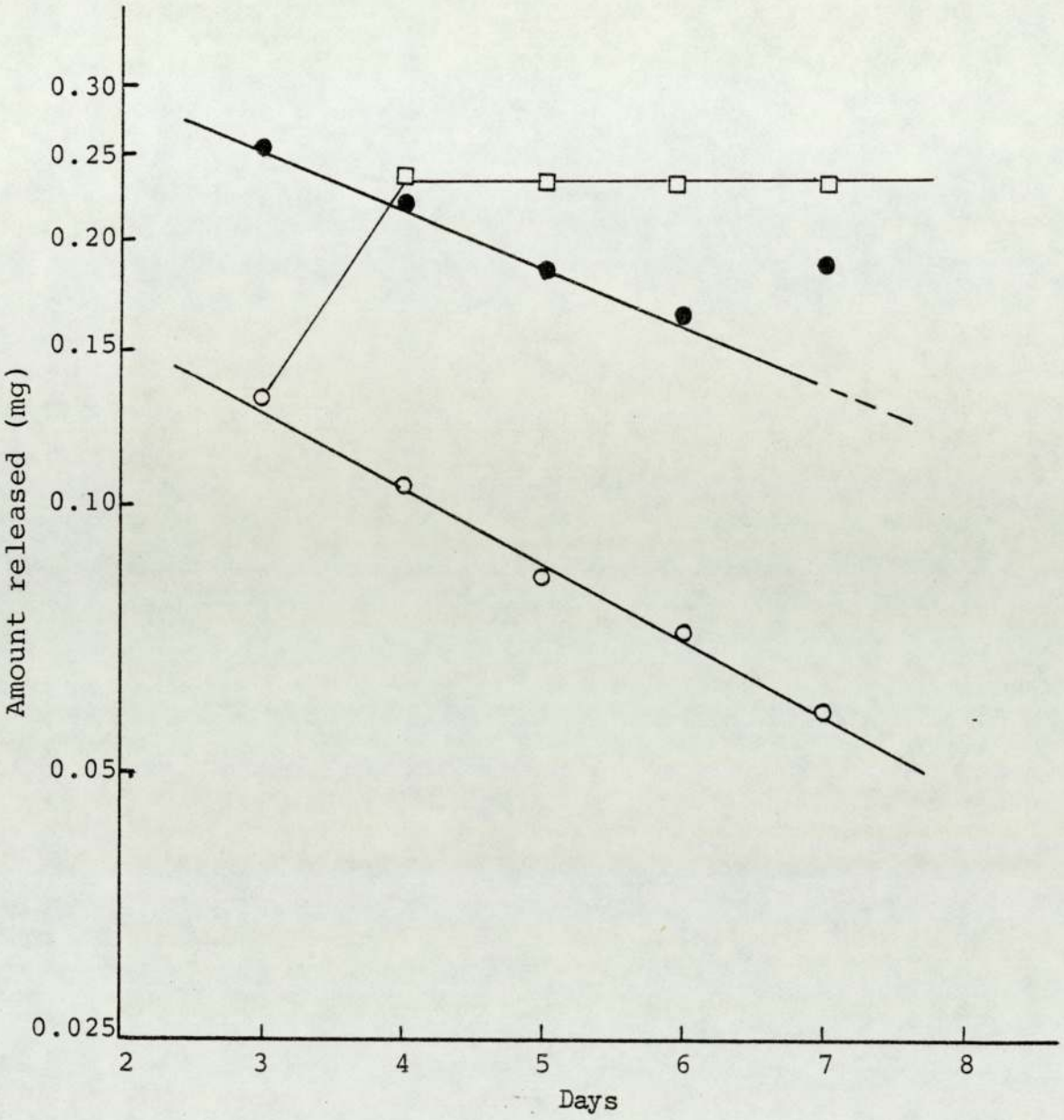


Fig 5.7 Change of the amount of benzocaine released from emulsion films during the early stage on removal of films from the formaldehyde environment. Open circles represent amounts released as approximated from the assymptote of the quasi-equilibrium. Shaded symbols - includes amounts washed off before release experiments.

○, ● Films removed from formaldehyde enviroment,

□ Films stored in formaldehyde enviroment.

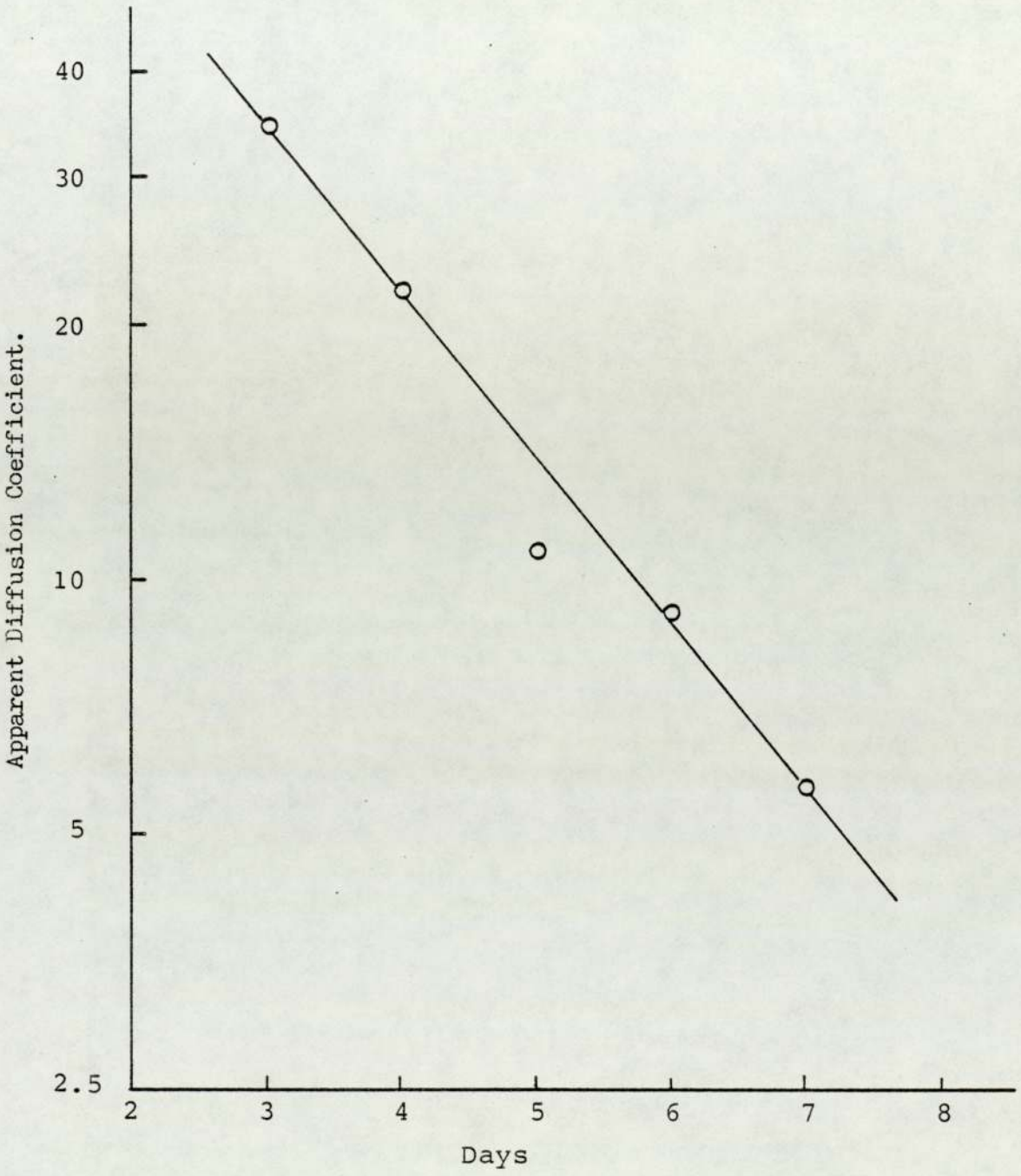


Fig 5.8 Variation of the apparent diffusion coefficient of benzocaine with time on removal of the emulsion films from formaldehyde environment.

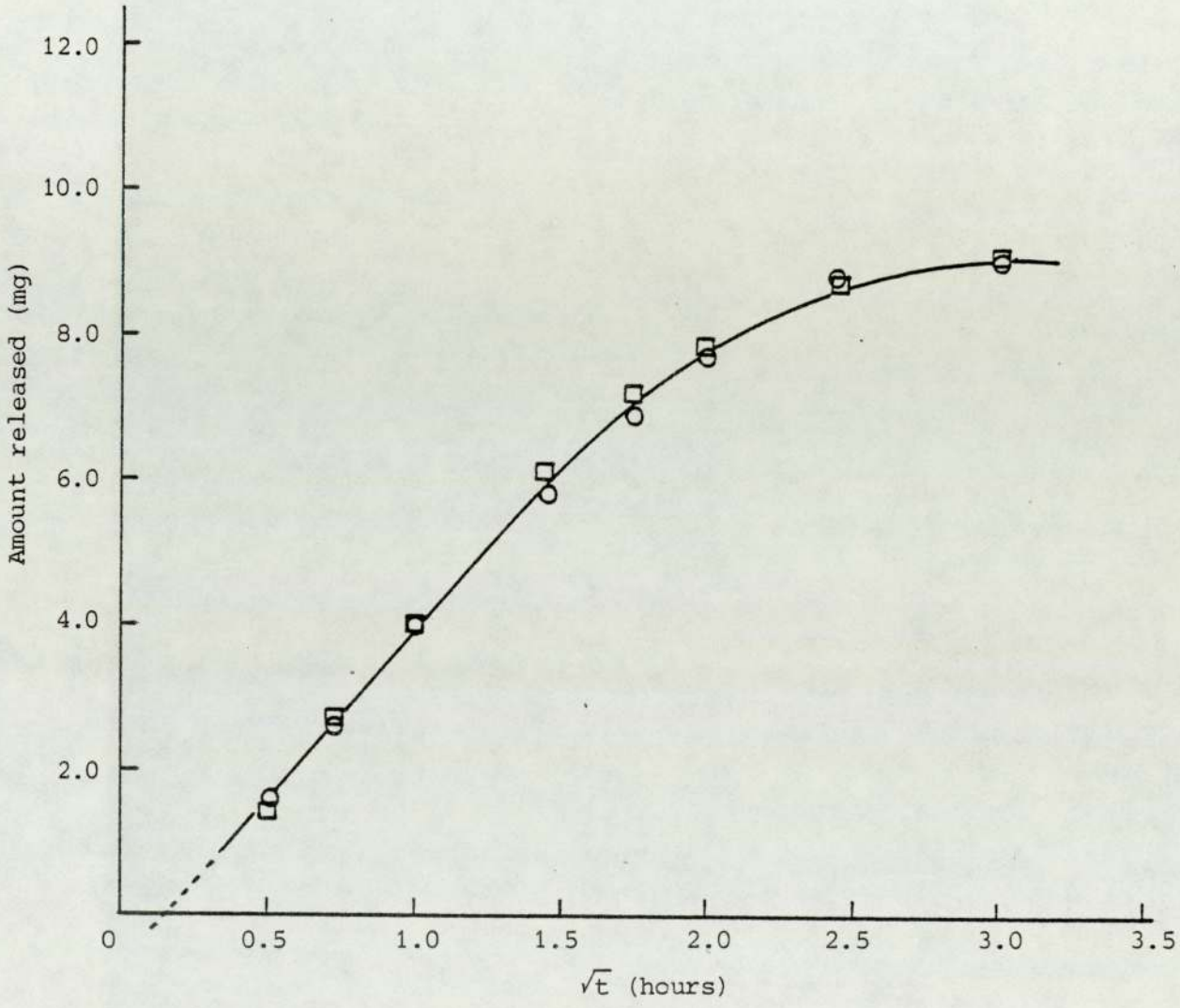


Fig 5.9 Release of benzocaine from untreated sunflower oil emulsion films. The films contained 20% oil phase and 0.5% $^{w}/_{w}$ benzocaine concentration. O homogenised emulsion, □ stirred emulsion.

TABLE 5.1

Effect of Continued Storage over Formaldehyde on Early Release of Benzocaine

Duration of Storage	Storage Condition	Reduced Slope [1]	Asymptote [2]	Diff. Coeff. ($cm^2.hr^{-1}$)
3 days	Formaldehyde	13.2×10^{-2}	0.132 mg.	34.21×10^{-4}
4 days	Formaldehyde	20.62×10^{-2}	0.236 "	83.3×10^{-4}
5 days	Formaldehyde	21.76×10^{-2}	0.245 "	93.0×10^{-4}
6 days	Formaldehyde	19.4×10^{-2}	0.238 "	73.9×10^{-4}
7 days	Formaldehyde	20.6×10^{-2}	0.241 "	83.3×10^{-4}
4 days	No Formaldehyde	10.6×10^{-2}	0.102 mg.	22.06×10^{-2}
5 days	No Formaldehyde	7.40×10^{-2}	0.082 mg.	10.74×10^{-2}
6 days	No Formaldehyde	6.83×10^{-2}	0.072 mg.	9.15×10^{-2}
7 days	No Formaldehyde	5.37×10^{-2}	0.059 mg.	5.66×10^{-2}

Note: Counting of days starts from the day they were first placed in formaldehyde. All films were initially stored in formaldehyde for 3 days, then one group was removed. The storage condition was 95% R.H. at room temperature.

Footnotes:
1. The slope of $M_t V_s \sqrt{t}/l$ plot.
2. Estimated from the quasi-equilibrium at the end of the early phase.

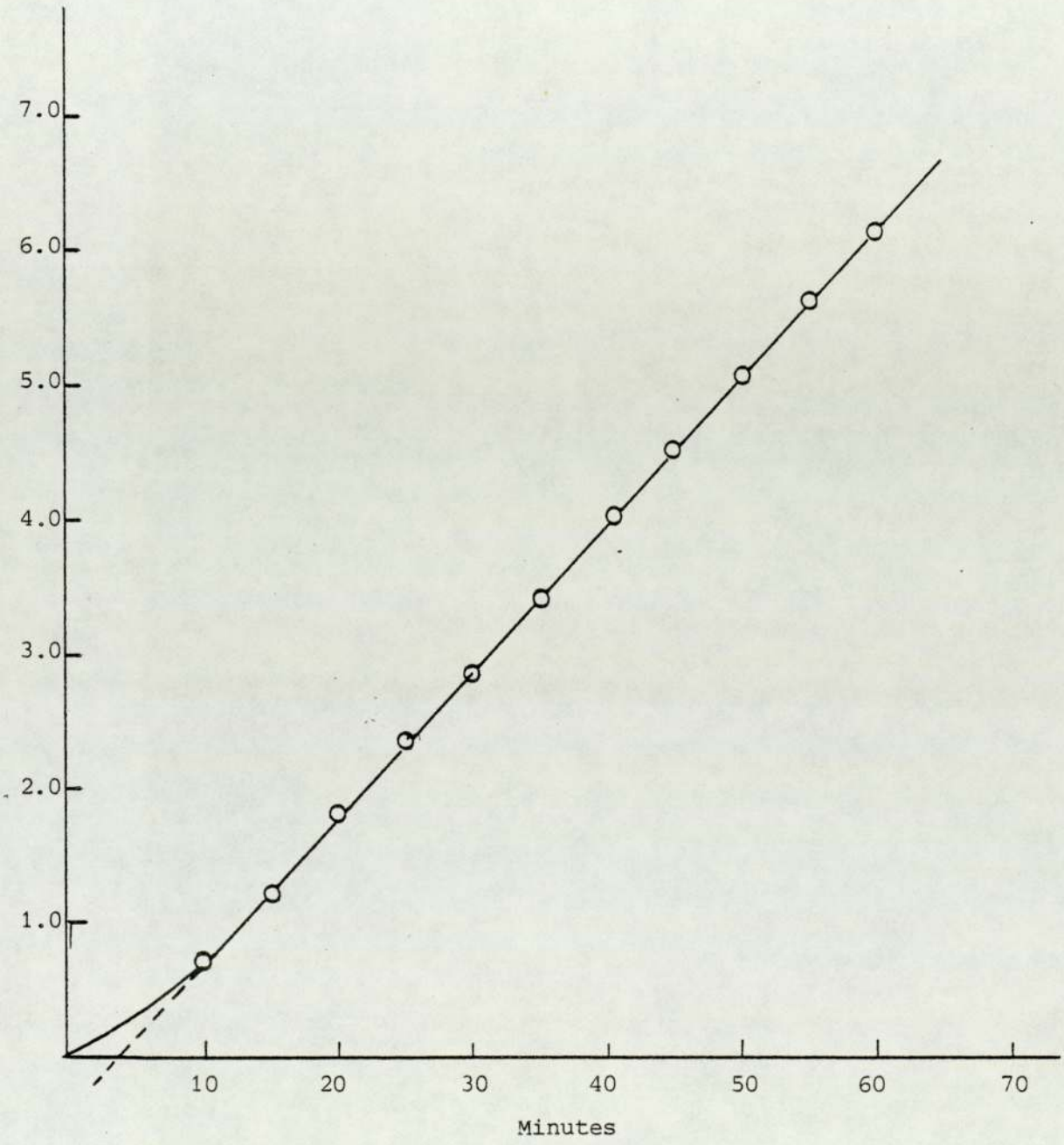


Fig 5.10 The diffusion of benzocaine through homogeneous gelatin films. Each point is a mean of three determinations.

34.212×10^{-4} $cm^2.hr^{-1}$ to 5.66×10^{-4} $cm^2.hr^{-1}$. There is therefore, an apparent faster release of benzocaine from formaldehyde treated films than from untreated films. Since the decline in diffusion coefficient is apparently proportional to formaldehyde levels in the films (as derived from the total amounts released during the early phase), it is possible to conclude that formaldehyde facilitates the diffusion of benzocaine.

Further storage of treated films away from formaldehyde (Table 5.1) shows that the apparent diffusion coefficient decreases to values below that of the untreated emulsion film (i.e. below 12.0×10^{-4} $cm^2.hr^{-1}$). Thus the possibility that benzocaine is released in a complex-reversible form cannot be discounted; especially in view of the possible chemical interactions discussed in the introduction.

The amount of benzocaine released from the films during the early phase is generally far in excess of that expected in the aqueous phase from equilibrium values. For example, in Fig 5.4, the quasi-equilibrium amount for the early phase is approximately 35% of the total amount released, whereas equilibrium conditions would allow only 15% of the total amount (Partition coefficient of 22 and 0.2 oil phase ratio). This suggests that benzocaine accumulates in the aqueous phase in excess of that predicted by the partition coefficient thus supporting the conclusion that benzocaine is bound to the gelatin or complexed with formaldehyde in the aqueous phase. It can be observed

that release from emulsion films of varying phase ratios is initially at the same rate (Fig. 5.11), suggesting a constant driving force regardless of the phase ratio. This is not consistent with release from normal emulsion systems (Fig. 4.2). A constant driving force in films of different phase ratios suggests that the quantity of benzocaine in aqueous phase is determined by the levels of formaldehyde in the surrounding environment. It has been mentioned in the introduction that the reaction between formaldehyde and aromatic amines involves the formation of intermediates, notably the methylol derivatives. The rate of the reactions was also said to be strongly dependent on pH. The observed release behaviour is strongly consistent with the chemistry and suggests that the reaction involving the utilization of the intermediates is very slow. It also demonstrates the reversibility of the conversion of benzocaine to the complex(es).

Fig. 5.11 shows that although the release rate from films with varying oil phase ratios is initially constant, the quasi-equilibrium amount increases with increasing phase ratio. There seems to be a direct relationship between the quasi-equilibrium amount and the release rate in the late phase. Thus the amount released during the early phase depends on the replenishment rate of the late phase. This behaviour is similar to the behaviour observed in two-stage sorption of gases from polymer matrices below their glass transition temperatures (119-122).

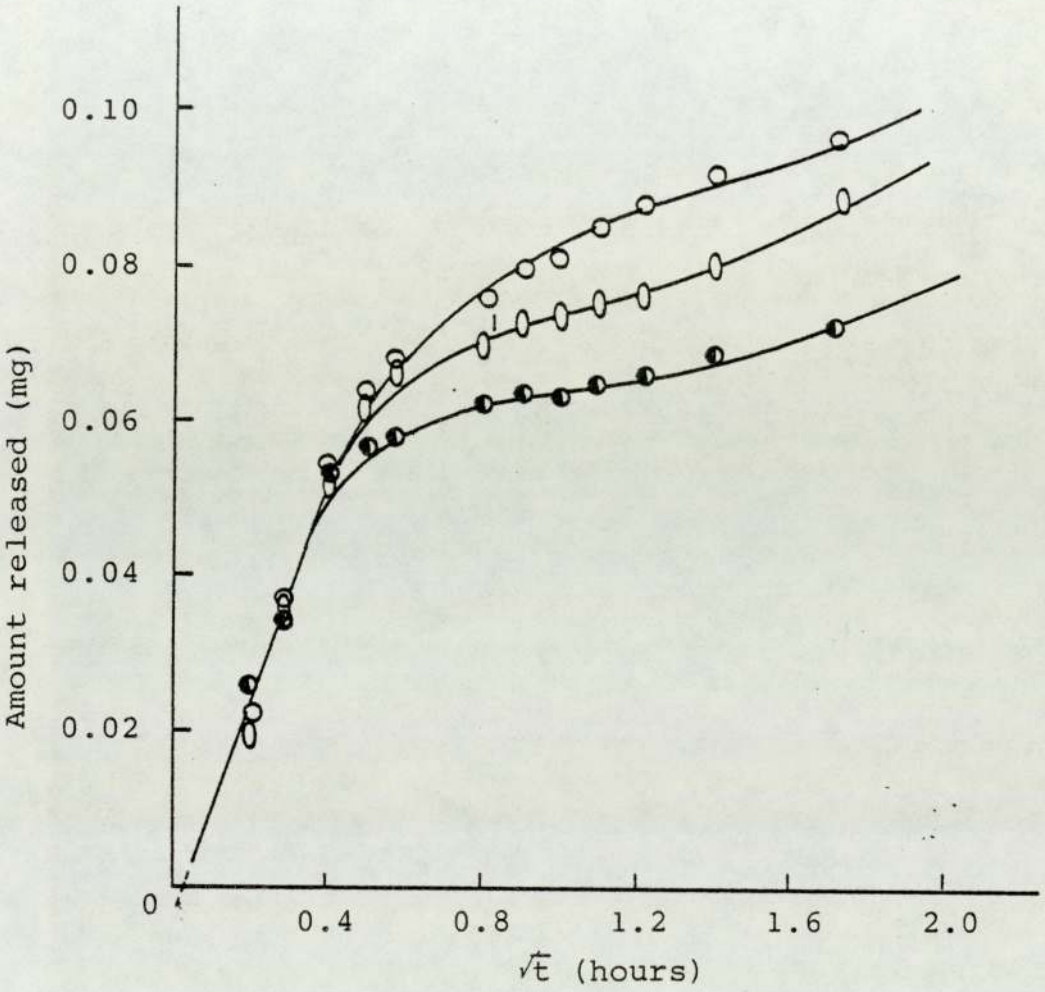


Fig 5.11 The variation of the release of benzocaine from formaldehyde-treated films with phase ratio (dilution) oil phase ratios: O 20% $^{w}/_{w}$, O 15% $^{w}/_{w}$ and ● 10% $^{w}/_{w}$.

5.3.1.3 The Late Phase

Fig. 5.1 demonstrates that most of the drug is released during a slow process which is either zero or first order depending on the duration of storage over formaldehyde. The mechanisms involved in the release during this late phase will now be considered.

Generally, the release during the late phase could be attributed to one of the following processes:

i. release from the oil phase in accordance with the normal thermodynamic law. Normally first order delivery is expected in the late phase and the total amount of drug released will be a sum of the amount released from individual droplets at any time.

ii. interfacially controlled release from the dispersed oil phase. This is a behaviour expected if there is an electrical or physical barrier at the oil-water interface. Since benzocaine is uncharged at pH 7.0, the pH to which the system is buffered, an electrical barrier should not affect its release i.e. if it is released as benzocaine and not in any other ionizable form. This leaves physical resistance as the most probable source of interfacial resistance. Such resistance could be introduced by gelatin molecules at the interface. Both zero and

first order release are possibilities in such cases if the barrier behaves as a membrane and a sufficiently high concentration of the drug is in the dispersed phase.

iii. release of benzocaine bound in the dispersed phase. This behaviour has to be considered in a system which is as complex as the one used.

iv. release of matrix-bound drug. Under this heading is included binding to the protein or the complexes formed in the continuous phase between the drug molecules and formaldehyde, and which can reversibly release the benzocaine.

Since the rate of release of medicament as controlled by the first three processes is sensitive to changes in the surface area of the o/w interface, changes in particle size of the dispersed phase would affect the release rate. The results of studies of release from formaldehyde-treated emulsion films with different particle sizes are shown in Fig. 5.13. The lack of influence of particle size variation on both the early and late phases suggests that the first three processes could not be the release-determining processes. In fact, particle-size variation does not affect the release rate of benzocaine from untreated emulsion-type gels (Fig. 5.14) suggesting that gelatin molecules at the oil/water interface do not affect the rate of drug transport across the interface. This

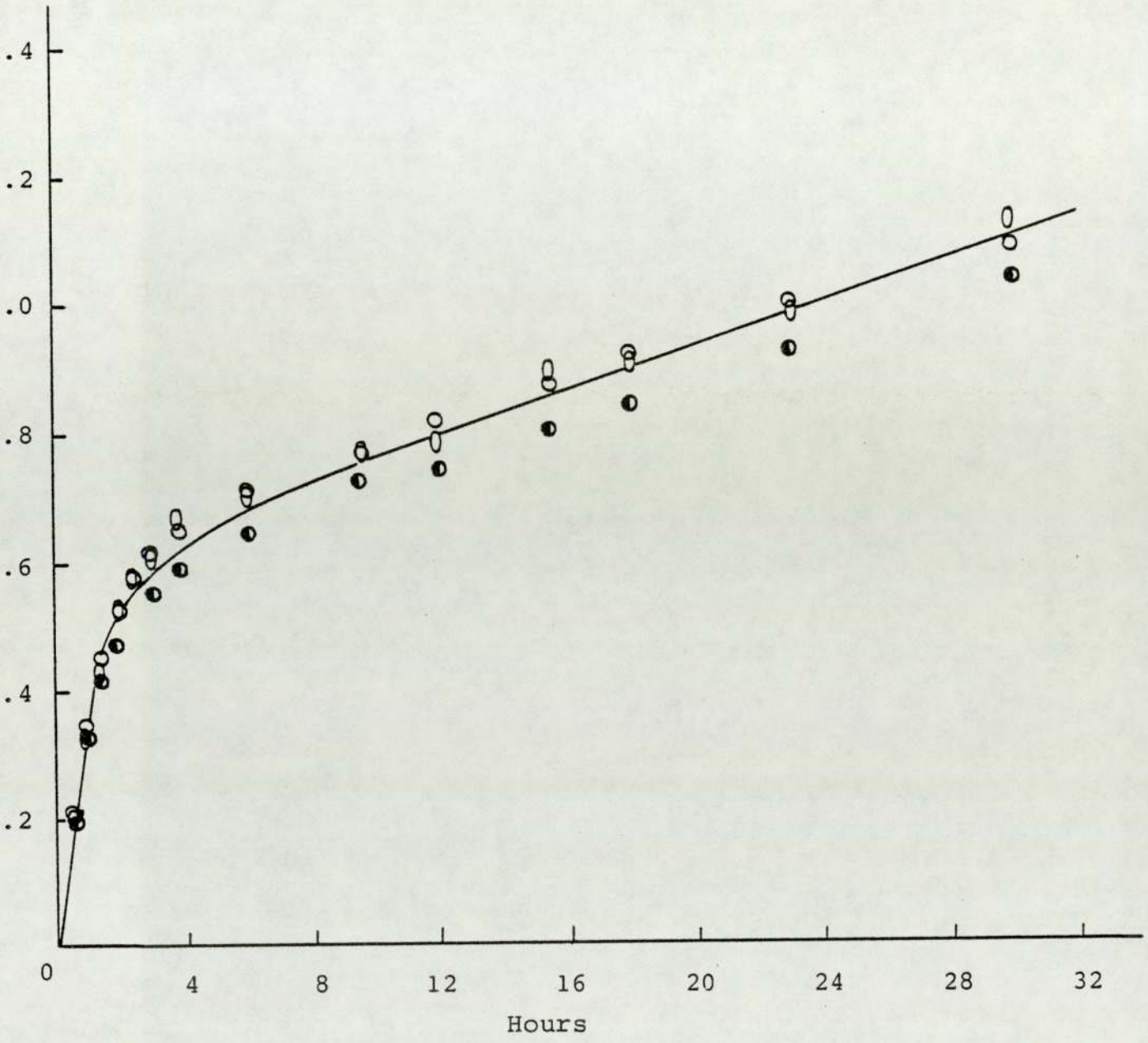


Fig 5.13 The influence of emulsion particle size on the late release of benzocaine from formaldehyde treated sunflower oil emulsion film.
● homogenised, 0 stired at 2000 rpm, and
O 50% $^{w}/_{w}$ mixture of the stirred and homogenised emulsions.

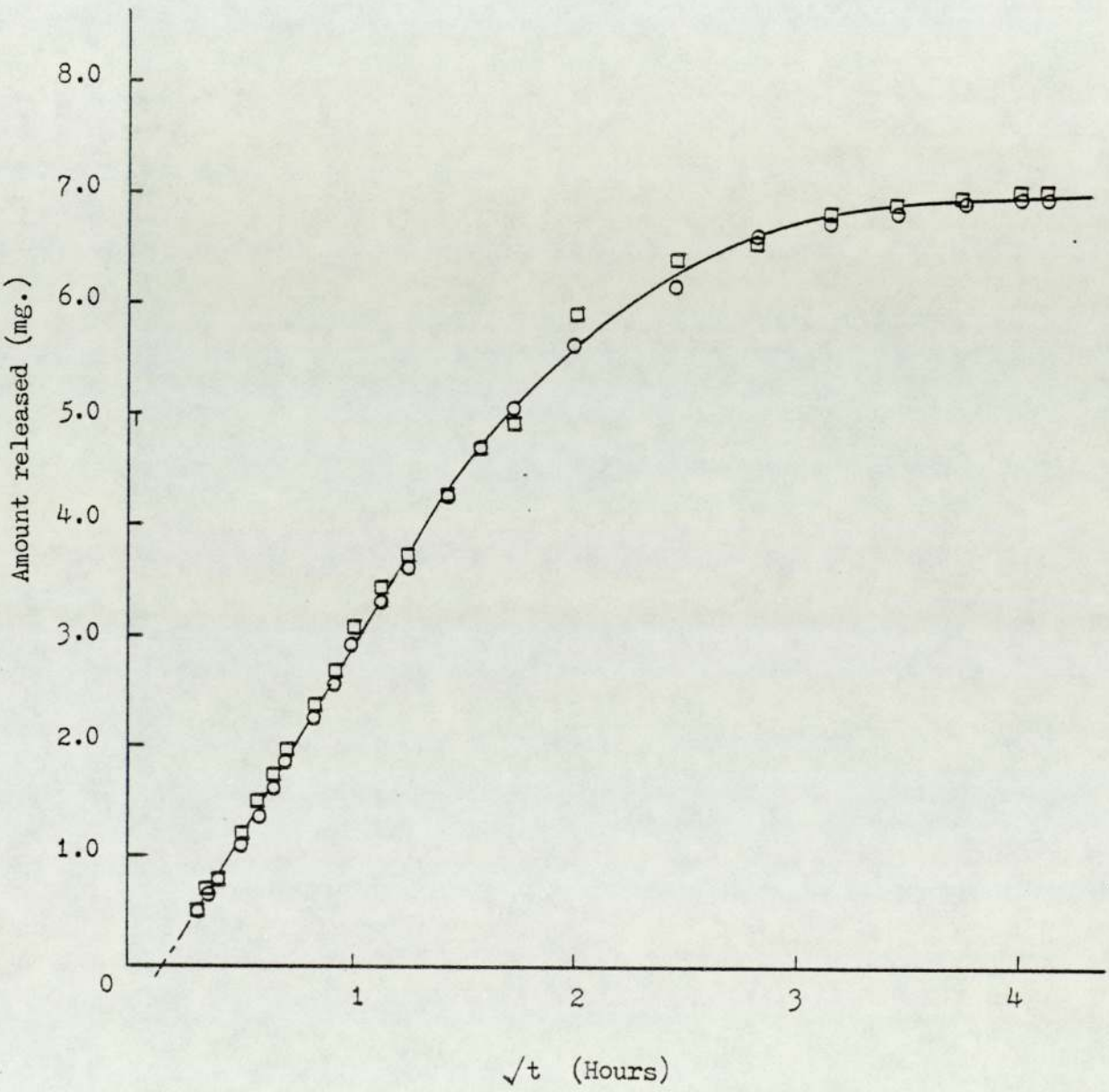


Fig. 5.14 The influence of particle size on release of benzocaine from ontreated sunflower oil emulsion gels at 25°C. O, homogenised emulsion; □, stirred emulsion.

observation is consistent with the conclusion reached in Chapter 3 that Lignocaine's diffusion is not affected by the matrix network but is solution controlled.

Late release from films of different phase ratios show an increasing release rate with increasing phase ratio (Fig. 5.15). There is a direct relationship between the steady release rate and the total amount of benzocaine released during the late phase (Fig. 5.16). However, the data on release from 10% and 15% emulsion films can also be plotted semi-logarithmically (Fig. 5.17), while that of the 20% emulsion does not provide a linear relationship. This suggests that the order of release is a function of the initial drug loading. The parallel profiles in Fig. 5.17 suggest a similar rate constant in the two cases. Fig. 5.18 shows that kinetic changes are also obtained on longer storage of the films in a formaldehyde environment. It can be seen from Fig. 5.18 that there is a corresponding decrease in the total amount of benzocaine released with increased storage duration. Both Figs. 5.17 and 5.18 suggest that the change, in the order of release, is a function of the drug loading in the matrix.

Since first order kinetics are associated with processes which depend on the concentration of the species under study and zero-order release behaviour indicates the presence of a rate limiting process, it is possible that the mechanism involved in the control of release during the late phase is saturable. Since studies on the influence of particle size on release have ruled out the

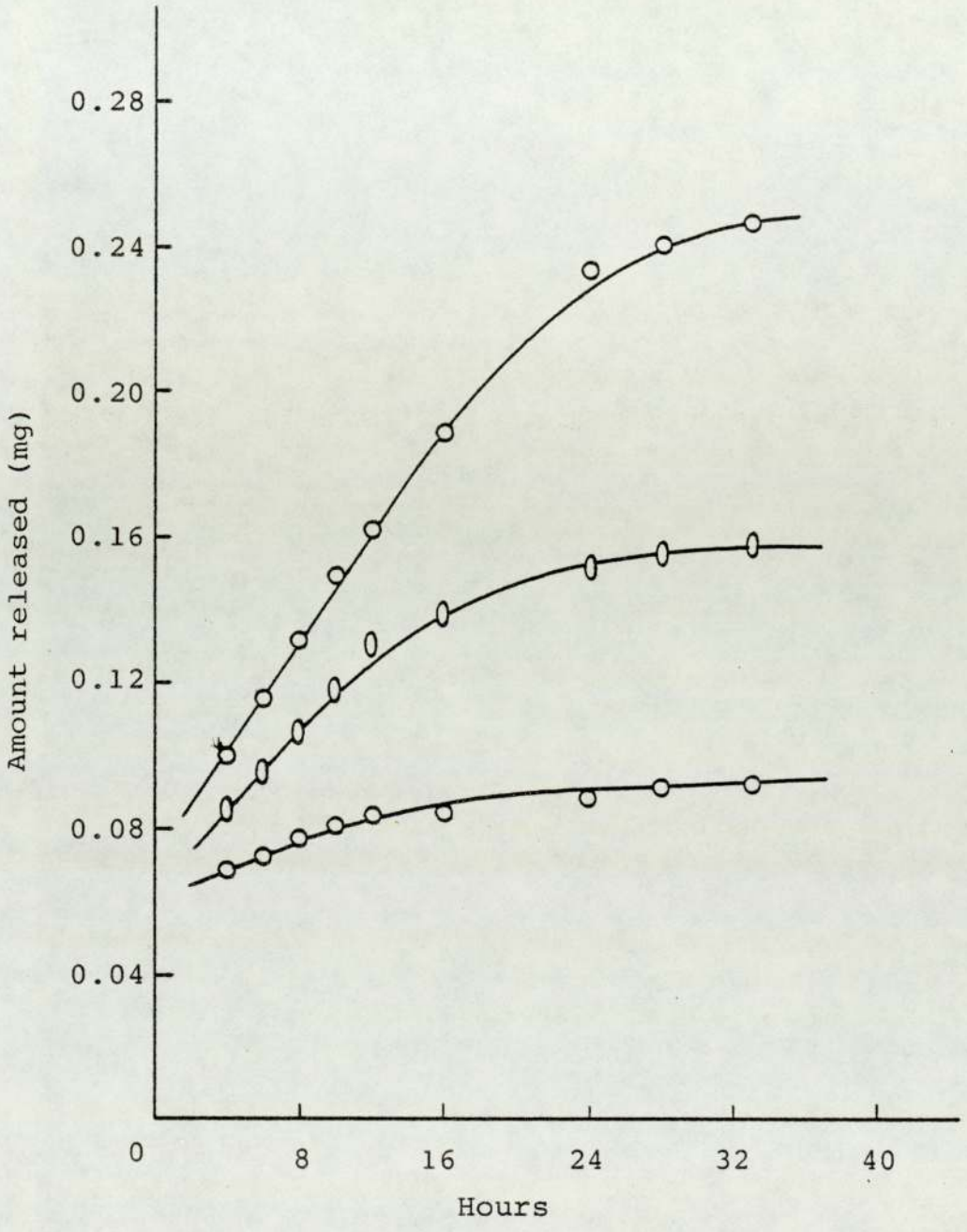


Fig 5.15 The variation of benzocaine release during the late phase with phase ratio (dilution). Oil Phase content: O 20%, 0 15%, and ● 10% $^{w}/_{w}$.

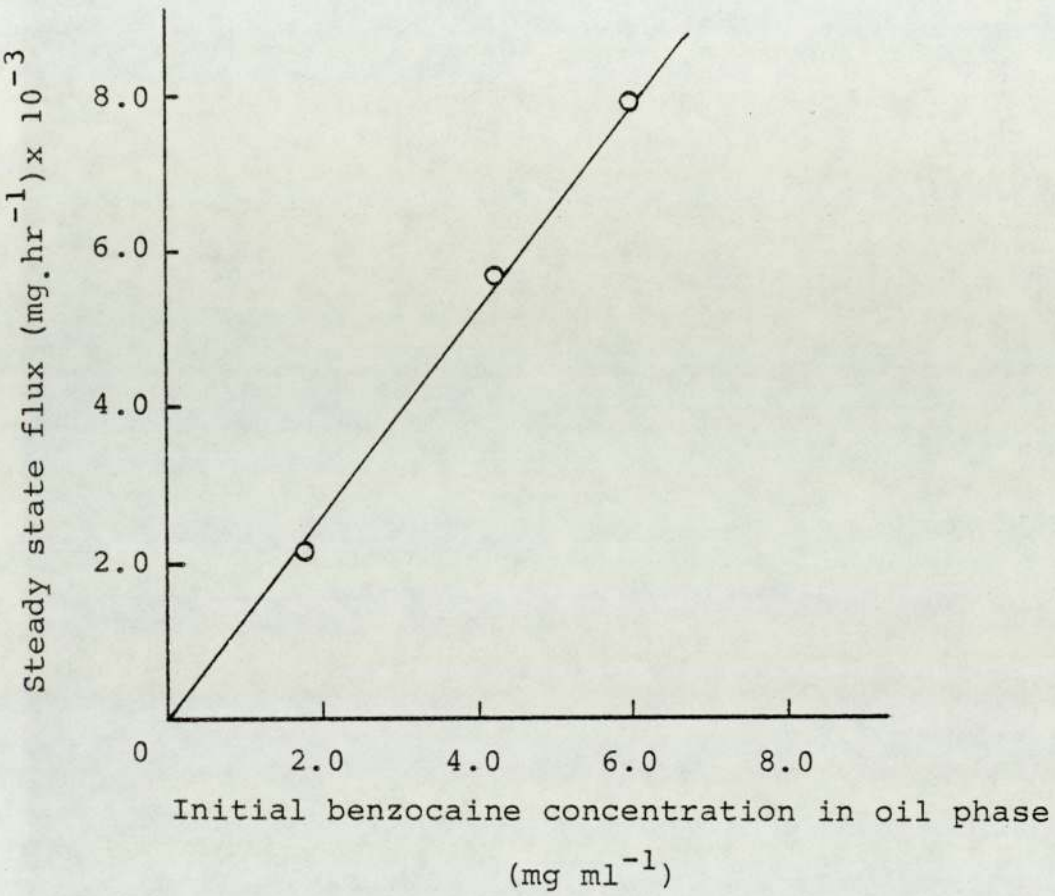


Fig 5.16 The relationship between the late phase release rate and the drug concentration in the oil phase at the onset of the late phase (ie amounts released during the early phase are not included in concentration calculations).

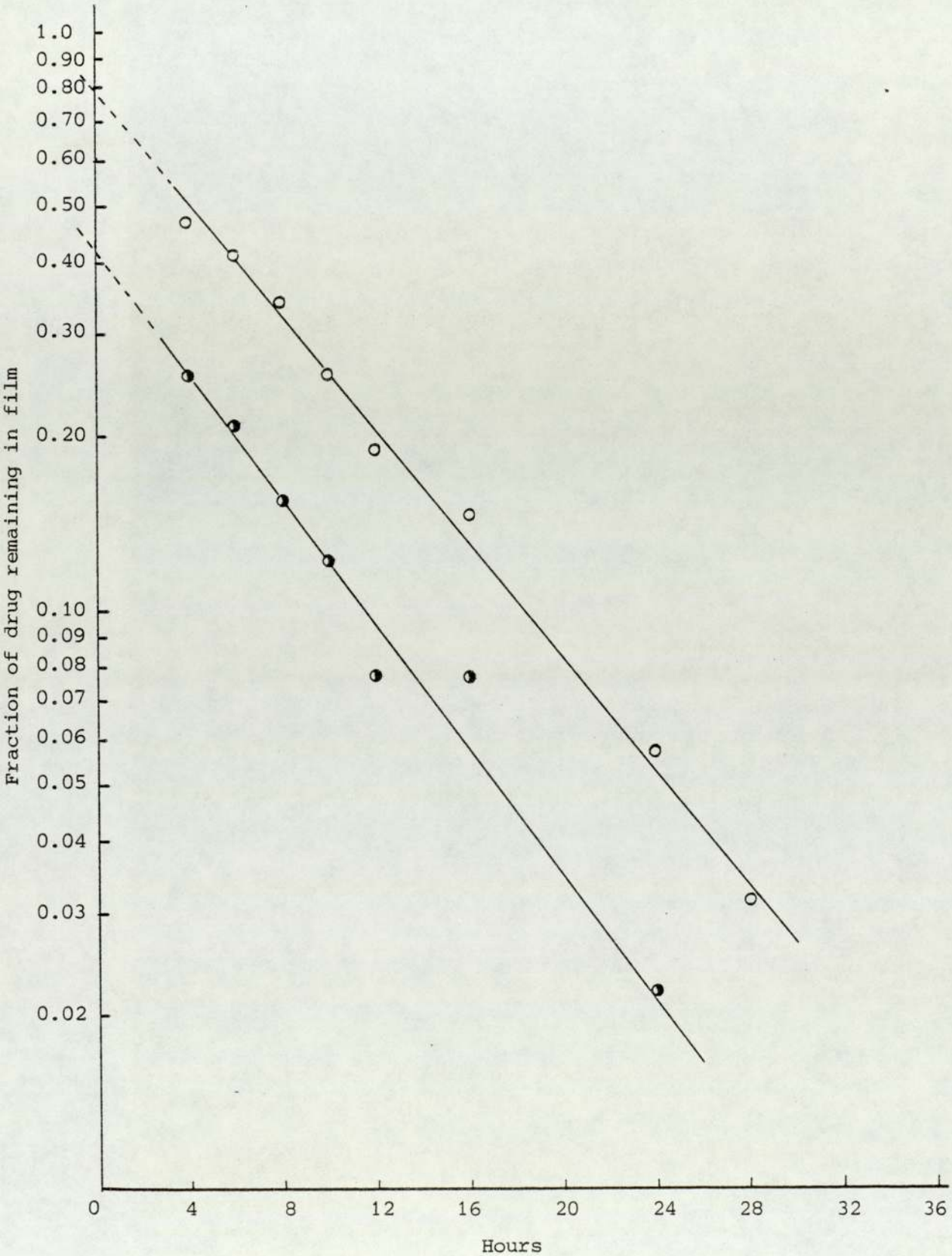


Fig 5.17 First order release of benzocaine from formaldehyde- hardened films during the late phase for emulsions of low drug content. O 15% $^{w}/_{w}$ oil phase content and ◑ 10% $^{w}/_{w}$ oil phase content.

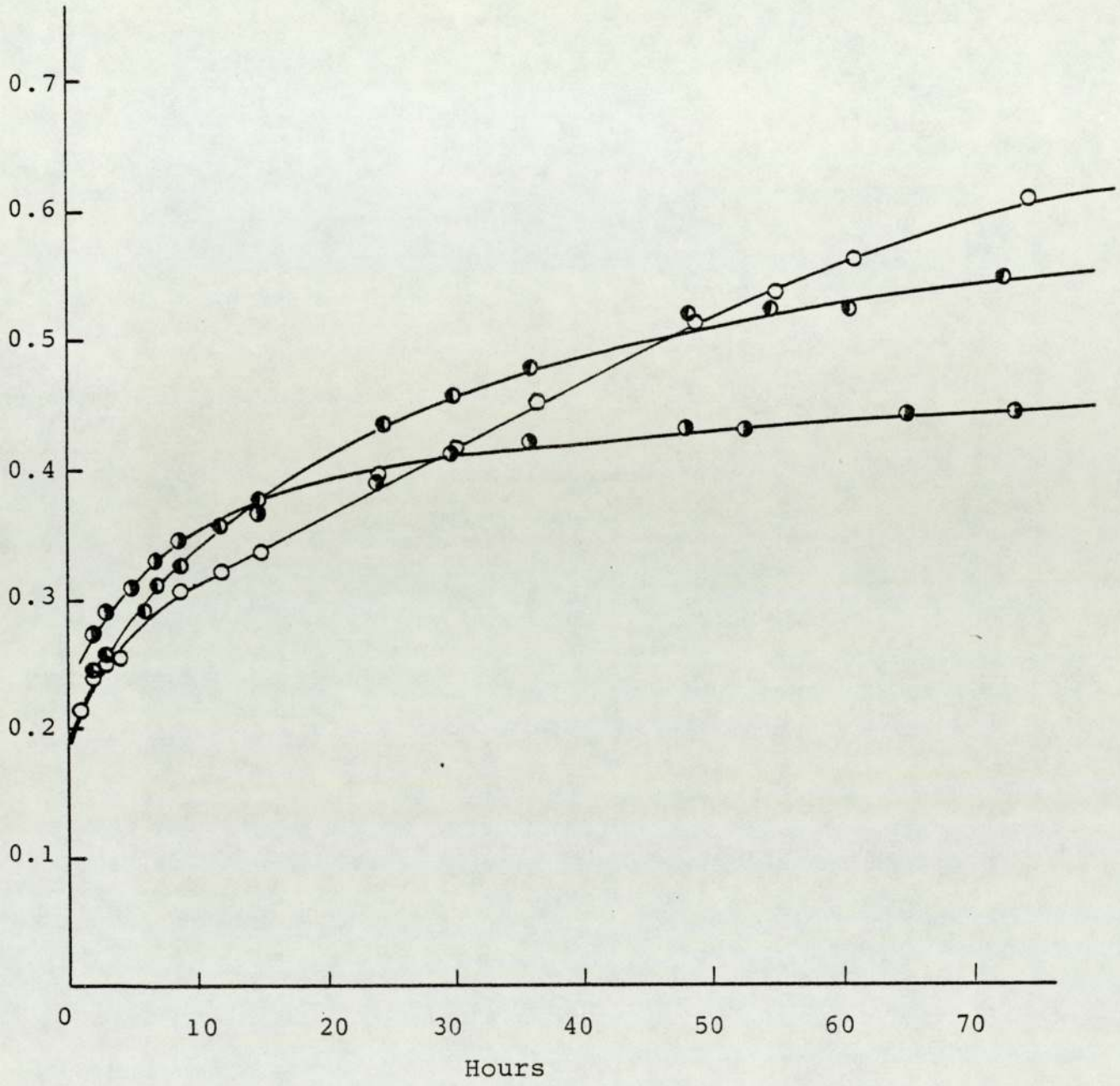


Fig 5.18 The late phase release of benzocaine from sunflower oil emulsion gels stored over formaldehyde for different periods. ○ 5 days, ◐ 12 days and ◑ 19 days. Films stored for longer than 5 days do not provide zero-order delivery.

role of interfacial barriers, it follows that the reversible binding suggested in these studies appears to be saturable. No definite conclusions can be made as to whether the mechanism undelaying the zero and first order release behaviours is the same since there is no available mathematical expression to relate the two constants. Moreover, due to the possible presence of several products, it is possible that the change in release order is due to a complex interplay of degradation of the different products.

5.3.2. Stability in Formaldehyde-treated Emulsion type Gels

Where an ester has to be formulated in an aqueous environment, the main problem would be that of the hydrolysis of the ester. For this reason, the gels were prepared in a buffered system at pH 7.0. This is the pH at which benzocaine has been reported to be most stable (177). Moreover, the assay procedure was designed in such a way as to demonstrate any appreciable degradation (Section 2.6). However, the formulation was very stable to hydrolysis even during the long release experiments since there was no trace of p-aminobenzoic acid in the chromatograms.

When an emulsion system containing a liquid dispersed phase which is lighter than the continuous phase is formulated, syneresis is a possibility. This is the gradual loss of the dispersed phase from the formulation and is also known as "bleeding" (244). An attempt was made

to monitor any syneresis in sunflower oil emulsion gels by weighing the films after wiping them with a clean and dry filter paper. No significant difference was observed in the weight of the film for a period of 2 weeks, apart from a small change which was attributable to a small loss of moisture when compared with control films.

A more certain way of avoiding syneresis is to use dispersed phases which are solid at normal room storage temperatures but liquid at body temperature. This description is well fitted by suppository bases, which have been developed to possess this particular behaviour. Stability studies were therefore performed using sunflower oil, coconut oil and a series of suppository bases.

The Suppocire range of suppository bases was tested for their ability to form oil in gel emulsions. The Suppocire range is composed of suppository bases with different solubilizing properties attained by slight structural modifications or the presence of some specific additions (Table 5.2). The solubility of benzocaine in the bases is shown in Fig. 5.19. Of all the bases used, only Suppocire 'AM' and Suppocire 'AS2' provided stable emulsions. An emulsion was considered stable if no sign of phase separation was noticeable on being left for 1 hour at 60°C.

Since suppository bases and vegetable oils are composed of triglycerides, it was decided to study the release behaviour of an emulsion containing pure triglycerides as the internal phase. The melting points

TABLE 5.2

Properties of Suppocire Suppository Bases

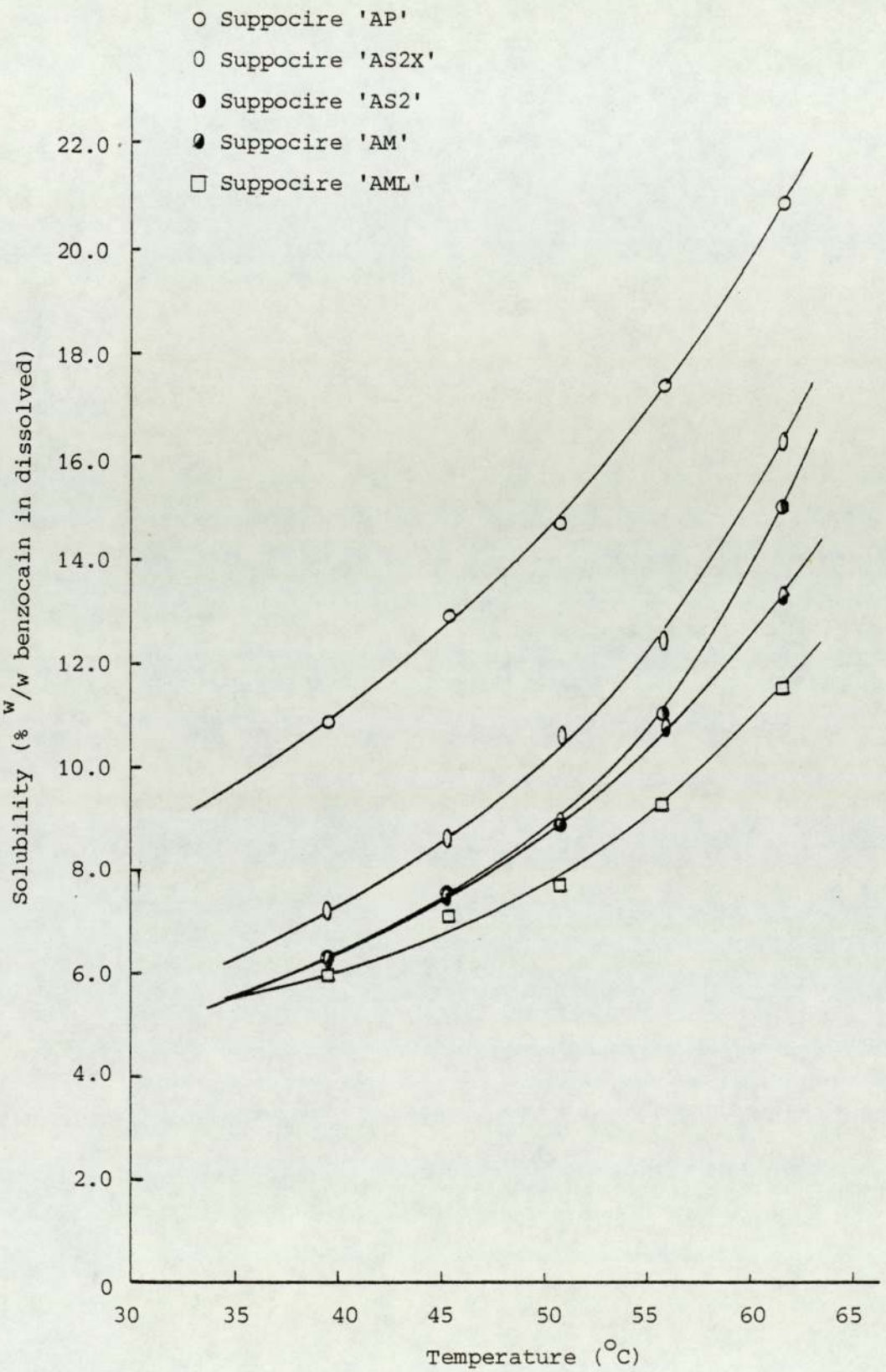
Title	Emulsion Stability	Melting Point Range	Hydrophilic Additives	Saponification Value	Hydroxyl Value
AM	Stable	35-36.5°C	-	225 - 245	<6
AML	Not Stable	35-36°C	✓	225 - 245	<6
AS2	Stable	35-36°C	-	225 - 245	15 - 25
AS2X	Not Stable	35-36.5°C	✓	225 - 245	15 - 25
AP	Not Stable	34-37°C	✓	200 - 220	30 - 50

Explanatory Notes:

1. The hydrophilicity can generally be determined, in case of bases without additives, from the hydroxyl value index. A higher hydroxyl value favours hydrophilicity.

2. The hydrophilic additives referred in this table include the use of modified (mainly ethoxylated) semi-synthetic triglycerides or other undisclosed additives specially selected to improve the hydrophilicity of the base.

Fig 5.19 The solubility of benzocaine in Suppocire® suppository bases



(cloud points) of mixtures of triolein and tripalmitin is shown in Fig. 5.20. A 20% tripalmitin in triolein mixture was selected since it has a melting point of around 36°C. The mixture could produce a stable emulsion. Also used for stability studies was Witepsol W45 suppository base.

Fig. 5.21 compares release from emulsion systems containing Witepsol W45 as the internal phase of a series of p-aminobenzoate esters at 25°C and 37°C; in non-treated films. Since the melting point of the suppository base is approximately 36°C, it therefore exists as a solid at 25°C and as a liquid at 37°C. The release at the two temperatures shows a significant difference as expected on using the same internal phase existing in two different states. At lower temperatures, the drugs are expected to possess a lower diffusion coefficient and a lower oil/water partition coefficient. The lower partition coefficient will favour a faster release rate initially because of the increased initial driving force in the continuous phase. However the lower diffusion coefficient will favour a slower release rate. The total behaviour will therefore be a balance between the two processes. The general belief is that solid emulsion systems will show slower release than liquid systems because the diffusion of drugs in solids is generally slower than in liquids. The results obtained (Fig. 5.21 and Table 5.3) indicate that this is the case and that the solid probably exerts its influence mainly through the lower initial driving force.

The release of benzocaine from emulsion systems

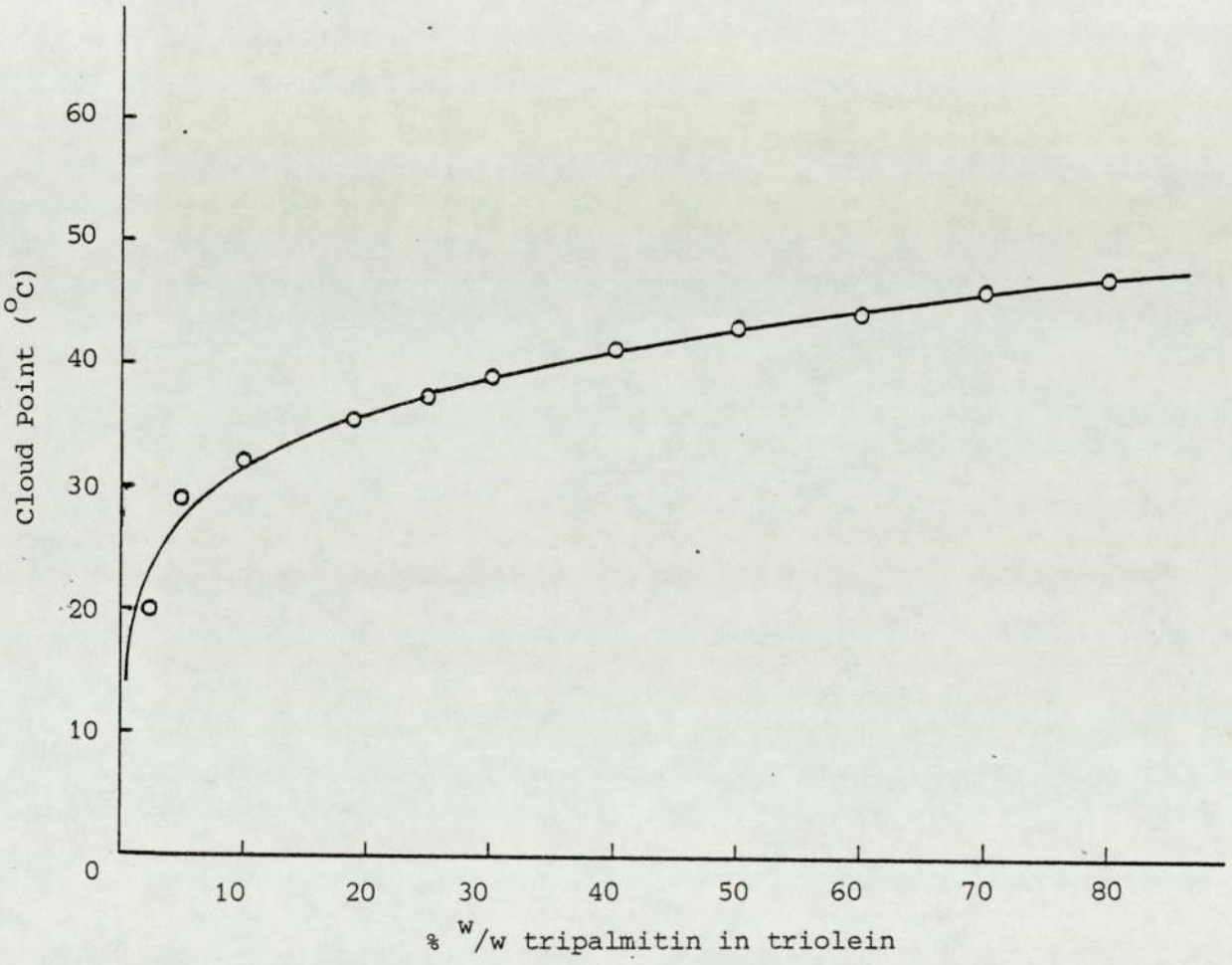


Fig 5.20 The melting (cloud) points of tripalmitin/triolein mixtures. (For method of determination see Section 2.7).

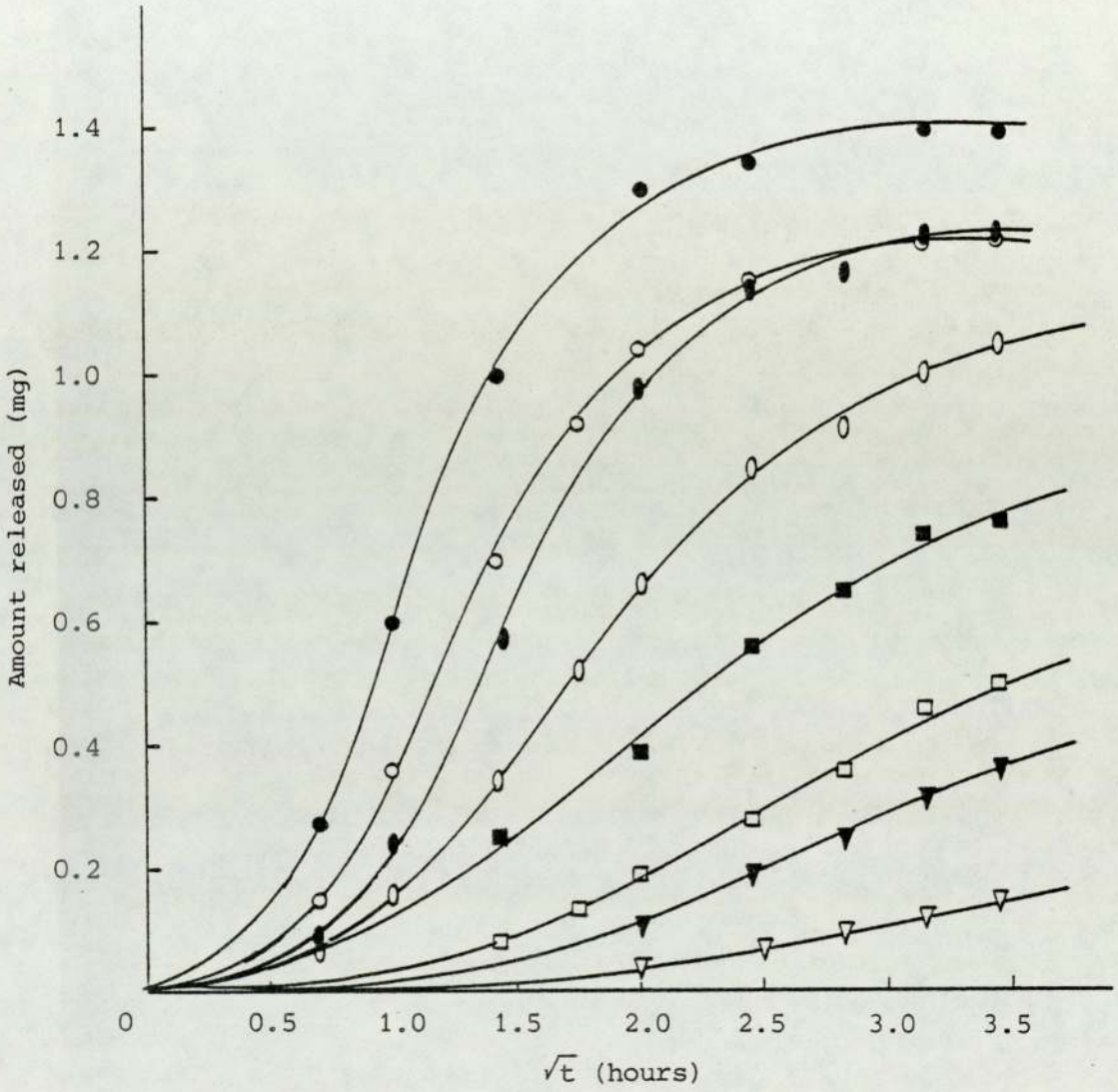


Fig 5.21 Release of esters of p-aminobenzoate from Witepsol-W45 emulsion-type gels at 25°C (open symbols) and 37°C (shaded symbols). O methyl, O ethyl, □ propyl and ▽ butyl esters.

TABLE 5.3

Comparison of release of p-aminobenzoate esters from Witepsol W45 emulsion gels at 25°C and 37°C

25°C

Esters	$M_t V_s \sqrt{t}$ Slope ($mg.hr.^{-\frac{1}{2}}$)	M_∞ (mg.)	D ($cm.^2 hr^{-1}$)
Methyl	0.7822	1.22	19.14×10^{-4}
Ethyl	0.4985	0.98	12.05×10^{-4}
Propyl	0.2084	N/D	N/D
Butyl	0.0739	N/D	N/D

37°C

Esters	$M_t V_s \sqrt{t}$ Slope ($mg.hr.^{-\frac{1}{2}}$)	M_∞ (mg.)	D ($cm.^2 hr^{-1}$)
Methyl	1.023	1.40	24.86×10^{-4}
Ethyl	0.732	1.22	16.76×10^{-4}
Propyl	0.360	N/D	N/D
Butyl	0.177	N/D	N/D

containing different bases from formaldehyde-treated films was then studied. These are shown in Figs. 5.22-5.27. It can be observed that all systems produced non-linear release kinetics which also demonstrate a gradual decline in the total amount of benzocaine released with increased storage time. The first order plots for sunflower and Suppocire 'AM' are shown in Figs. 5.28 and 5.29. It can be observed that for both emulsion systems release from films stored for less than 8 days has a different (faster) rate constant compared to the films stored for over 8 days. This surprising behaviour is also demonstrated by the other bases (summarized in Table 5.4). This behaviour suggests a change in the mechanism of release. It is difficult at present to offer an explanation for this complex behaviour.

Figs. 5.30 to 5.32 show that release during the early phase gets slower and the amount of benzocaine released smaller with longer storage times. From previous discussions, this behaviour can be attributed to either the lower compensation offered by the late phase or due to loss of formaldehyde from the storage tank. Most probably, both factors contribute to this behaviour.

The total amount of benzocaine released from the emulsion films decreases at a constant rate on continued storage over formaldehyde (Fig. 5.33). This suggests a constant rate of loss of the benzocaine which may be a consequence of an irreversible binding or complexation

TABLE 5.4

The Stability of Benzocaine in Sunflower Oil-in-Gel Emulsions Stored over Formaldehyde Vapour

Internal Phase	Storage Duration (days)	Amount Released (mg.)	Amount in Washings (mg.)	Total Amount Released (mg.)	First Order Release Rate Constant (hr^{-1})
Sunflower oil	5	.5240	.1021	.6261	70.3×10^{-4}
Sunflower oil	8	.4902	.1028	.5930	68.6×10^{-4}
Sunflower oil	11	.4380	.0985	.5365	49.3×10^{-4}
Sunflower oil	15	N/D	N/D	N/D	N/D
Sunflower oil	21	.3697	.1010	.4707	48.0×10^{-4}
Sunflower oil	29	.3000	.1023	.4023	49.9×10^{-4}
Witepsol W45	5	.5840	.1021	.6861	69.8×10^{-4}
Witepsol W45	8	N/D	N/D	N/D	N/D
Witepsol W45	11	.4690	.1011	.5701	
Witepsol W45	15	.4128	.0994	.5122	32.57×10^{-4}
Witepsol W45	21	.3206	.0977	.4183	29.9
Witepsol W45	29	.2950	.0982	.3832	22.7×10^{-4}
Suppocire 'AM'	5	.4999	.1006	.6005	69.0×10^{-4}
Suppocire 'AM'	8	.5159	.1032	.6191	68.7×10^{-4}
Suppocire 'AM'	11	.4843	.1036	.5879	33.4×10^{-4}
Suppocire 'AM'	15	.4376	.0993	.5369	42.3×10^{-4}
Suppocire 'AM'	21	.3703	.1005	.4708	34.1×10^{-4}
Suppocire 'AM'	29	.2850	.1000	.3850	N/D
20% Tripalmitin in Tridein	5	.625	.058	.680	37.5×10^{-4}
	12	.600	.053	.653	41.1×10^{-4}
	19	.575	.051	.626	17.9×10^{-4}
Coconut oil	5	.605	.045	.645	33.2×10^{-4}
Coconut oil	12	.575	.039	.614	33.9×10^{-4}
Coconut oil	19	.520	.041	.561	24.2×10^{-4}

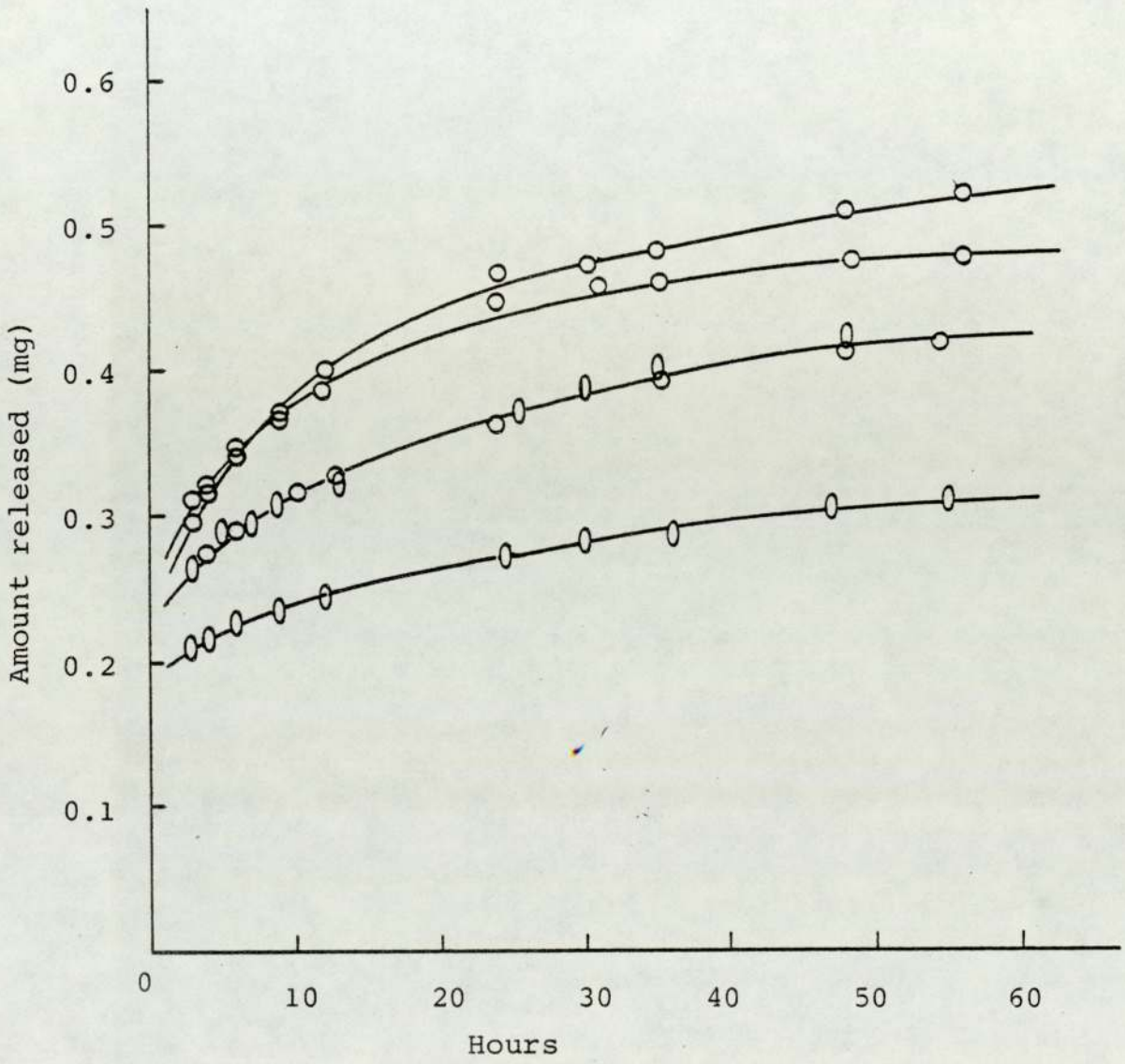


Fig 5.22 The influence of storage duration on the release of benzocaine from sunflower-in-gel emulsion films stored in formaldehyde. O 5 days, ◐ 8 days, 0 11 days, ◑ 15 days and ◕ 21 days.

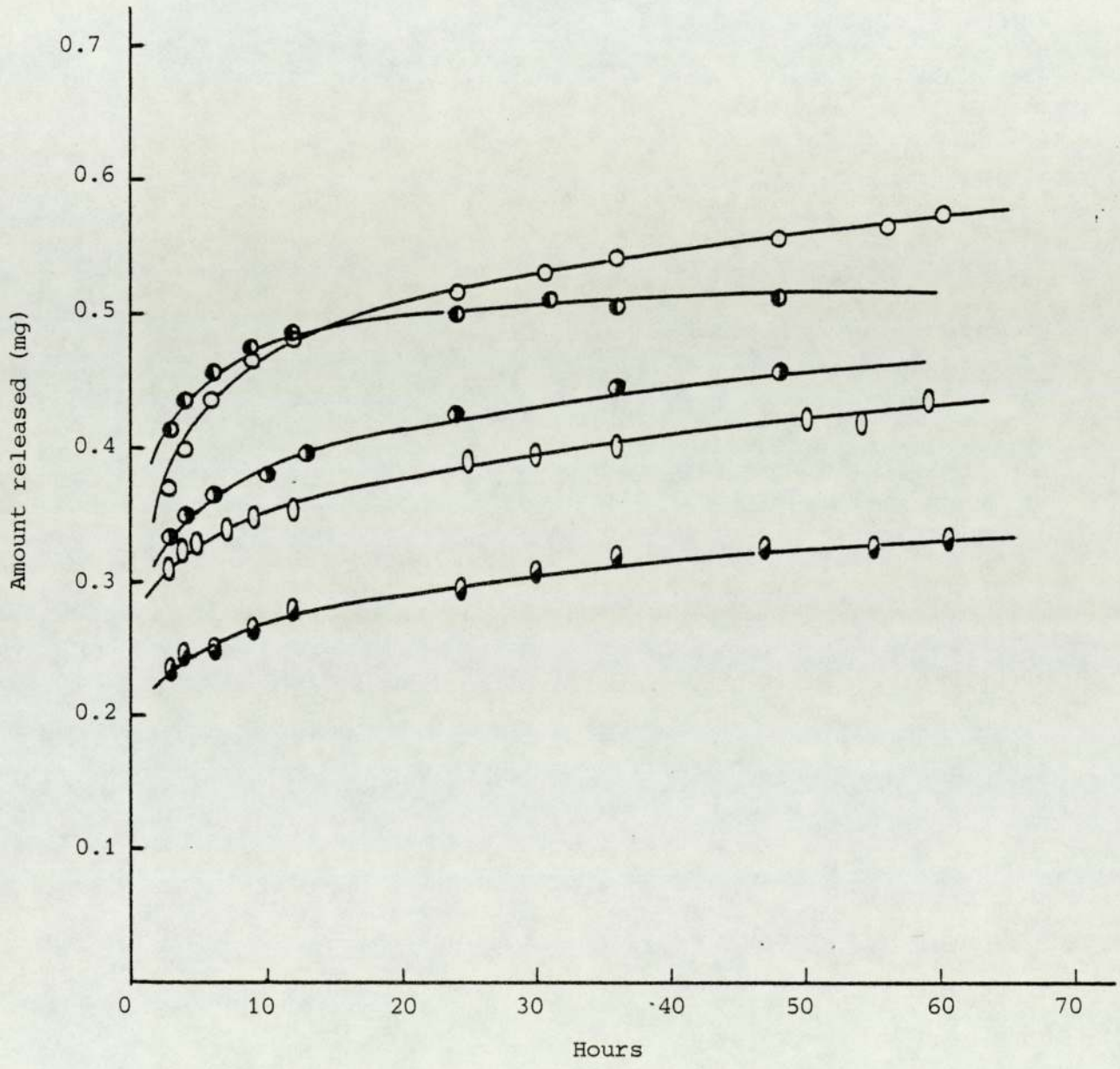


Fig 5.23 Influence of storage duration on the late release of benzocaine from Witepsol 'W45' emulsion gels stored in formaldehyde. O 8 days, ◐ 11 days, ◑ 15 days, O 21 days and ◕ 29 days.

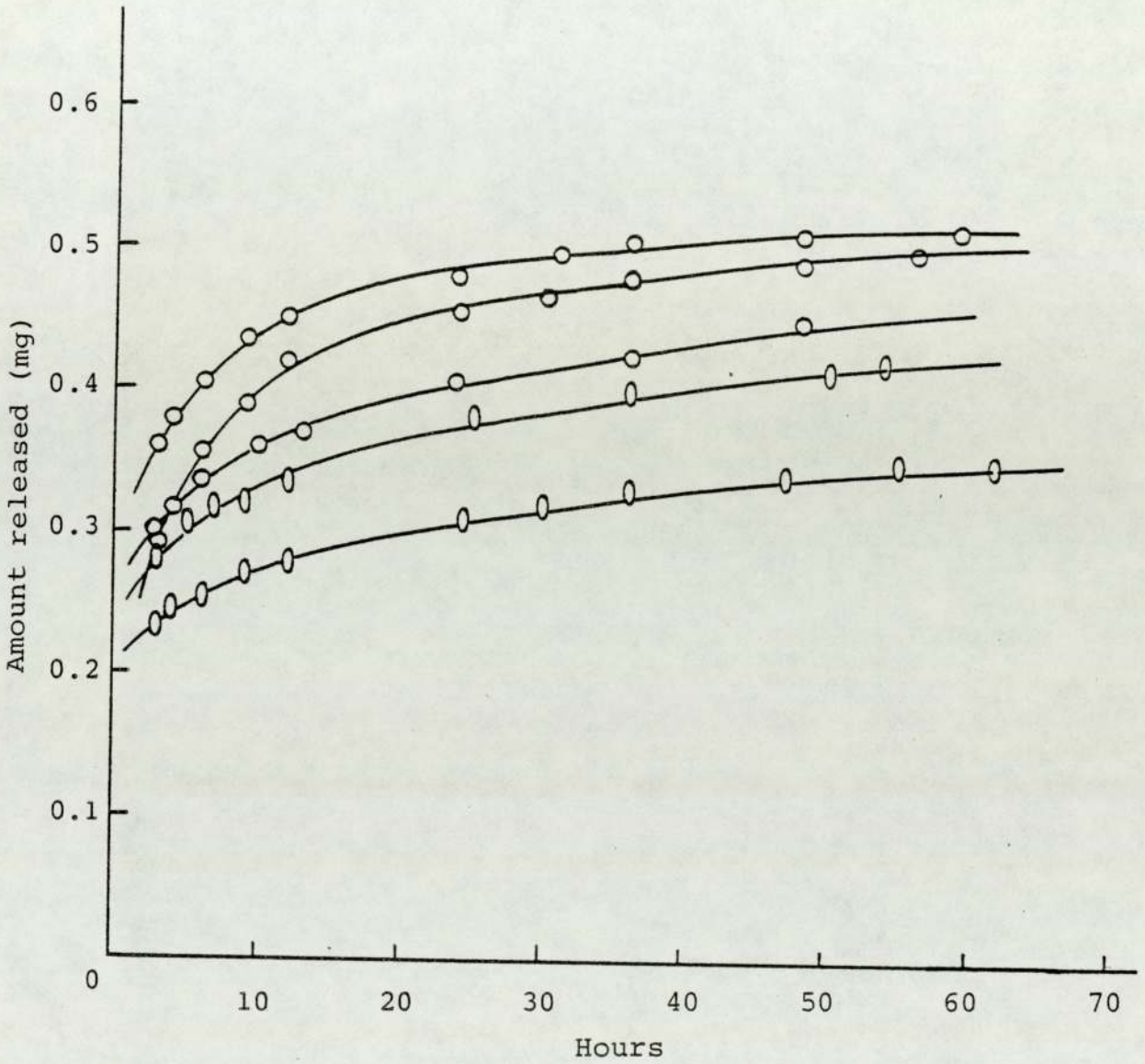


Fig 5.24 The influence of storage duration on the release of benzocaine from Suppocire 'AM' emulsion films stored in formaldehyde. O 5 days, ◐ 8 days, ◑ 11 days, 0 15 days and ◒ 21 days.

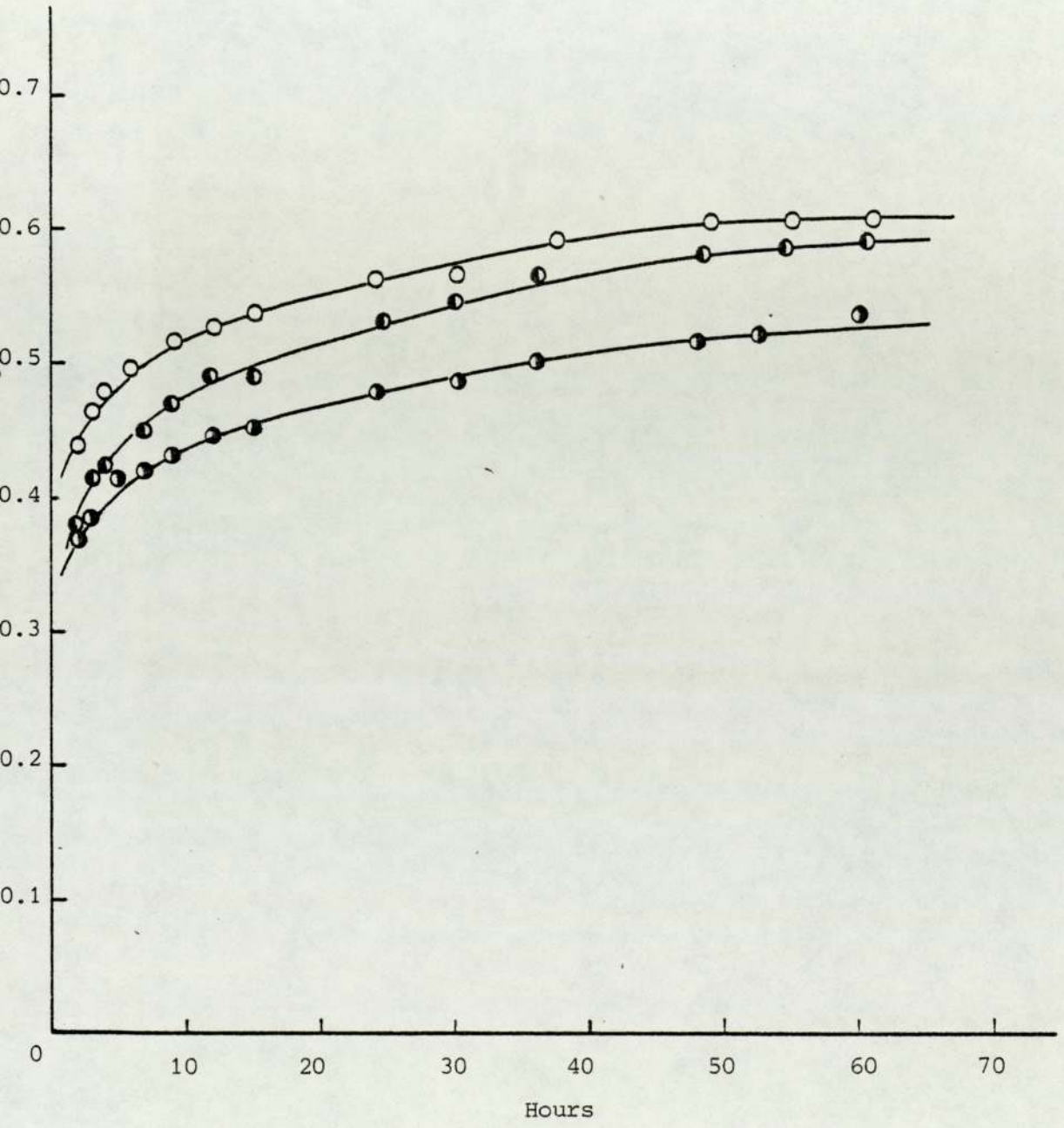


Fig 5.26 Influence of storage duration on the late release of benzocaine from 20% $^{w}/_{w}$ tripalimitin in triolein emulsion gels stored in formaldehyde. O 5 days, ◐ 12 days and ◑ 19 days storage.

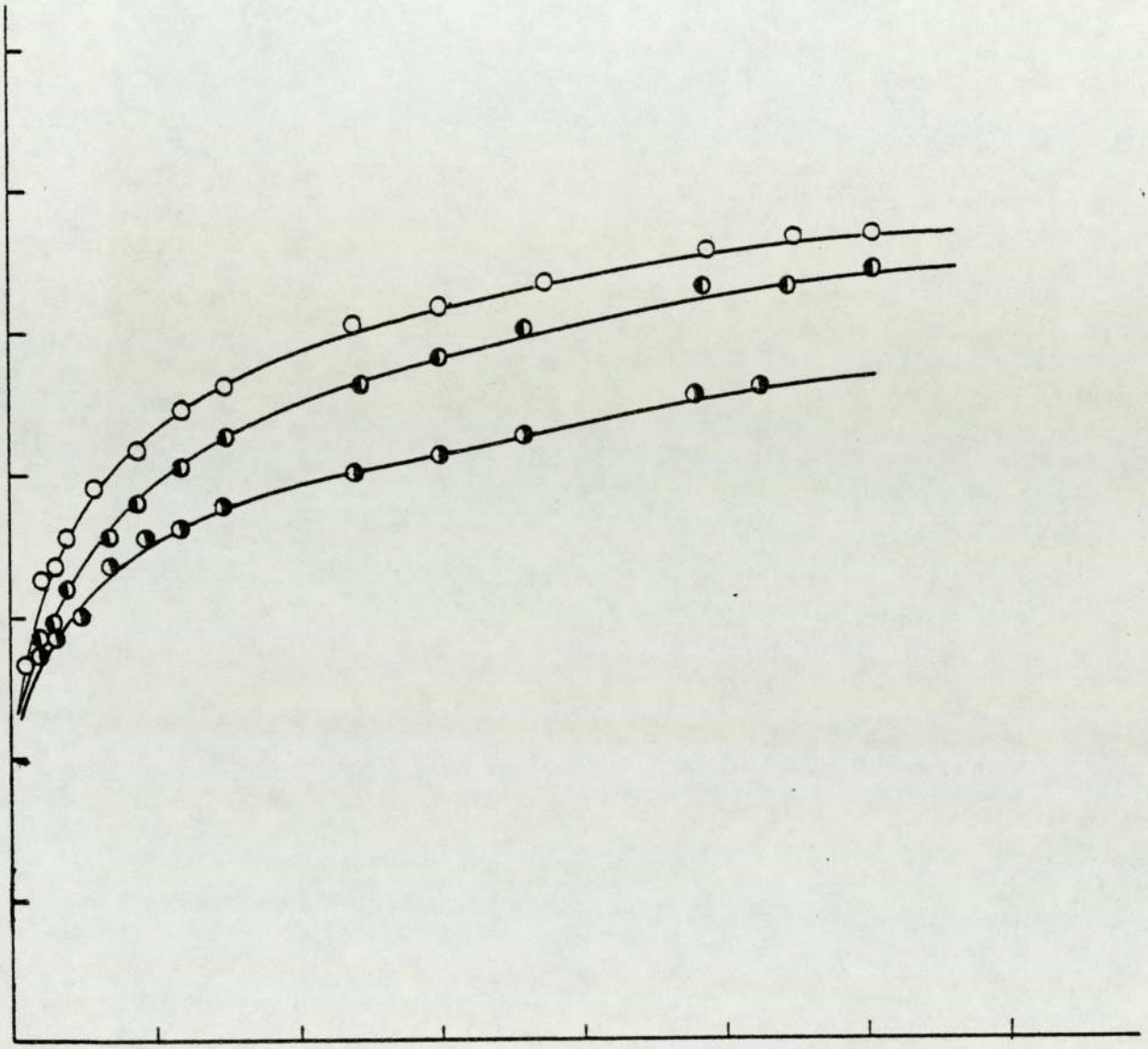


Fig 5.27 The influence of storage duration on the late release of benzocaine from coconut oil emulsion gels stored in formaldehyde. ○ 5 days, ◐ 12 days, and ◑ 19 days storage.

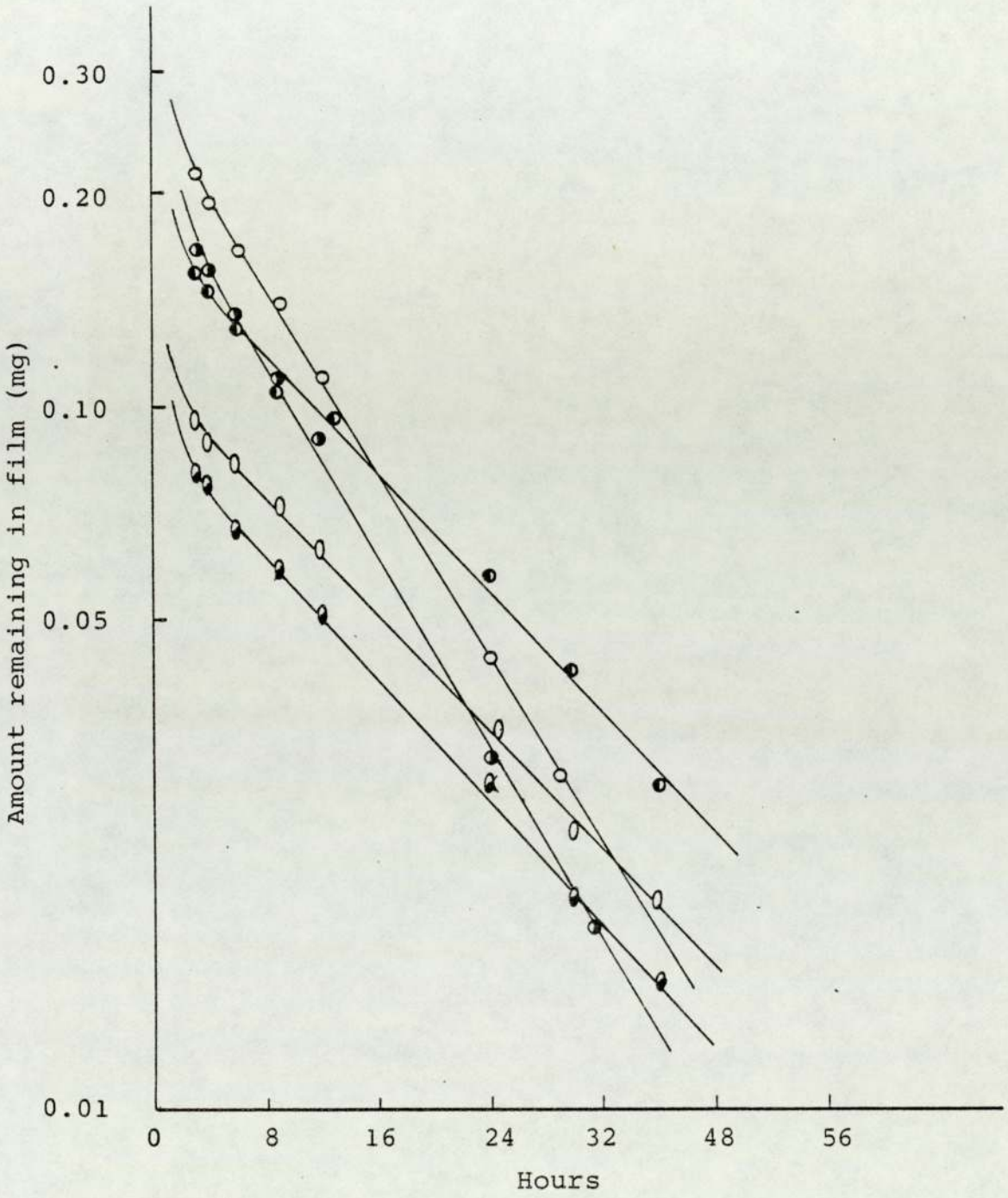


Fig 5.28 The influence of storage on the kinetics of release of benzocaine from formaldehyde-treated sunflower oil emulsion gels. O 5 days, ◑ 8 days, ◐ 11 days, 0 15 days, and ◕ 21 days.

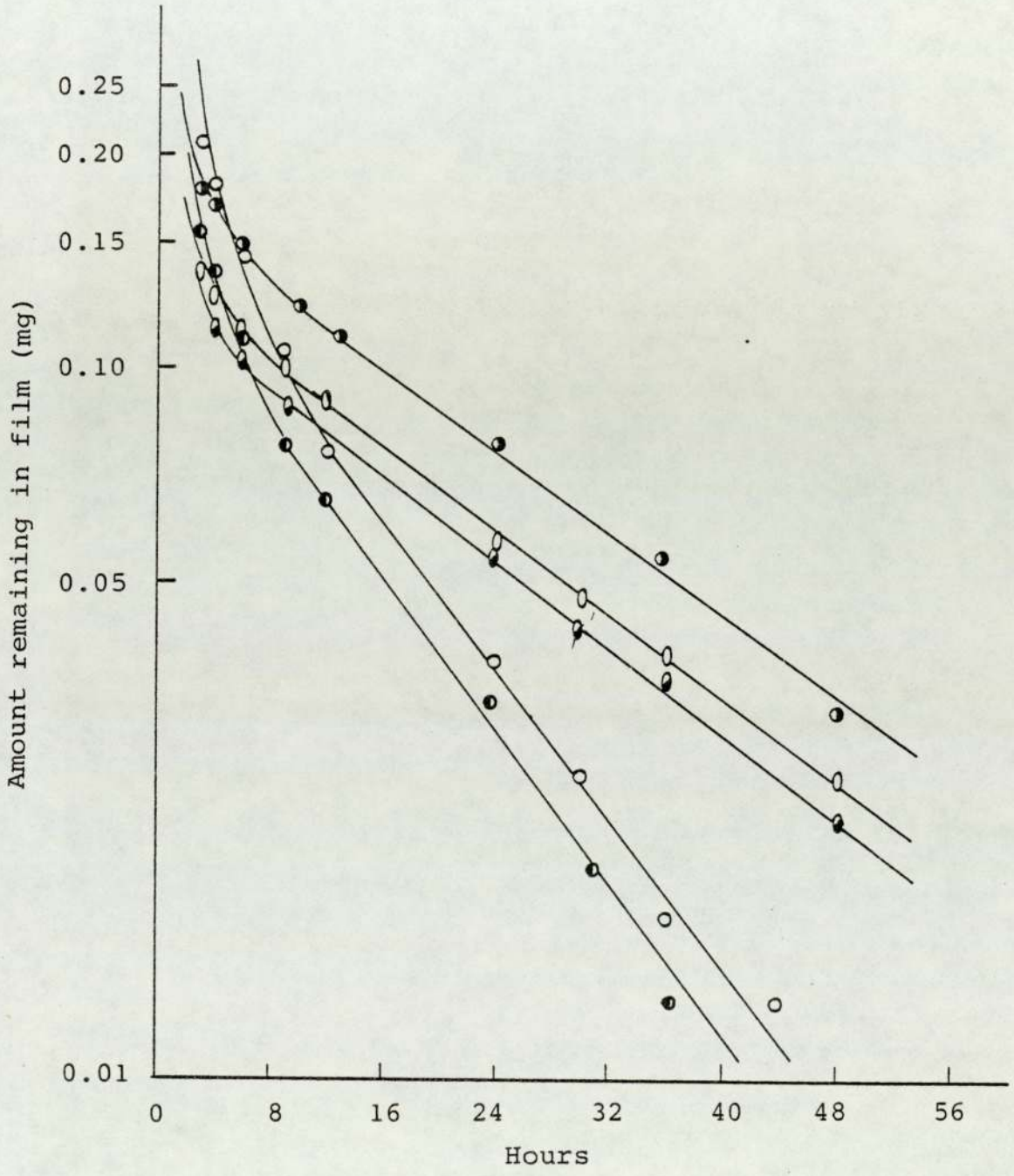


Fig 5.29 The influence of storage on the kinetics of release of benzocaine from formaldehyde-treated Suppocire 'AM' emulsion gels. O 5 days, ◐ 8 days, ◑ 11 days, 0 15 days and ◐ 21 days.

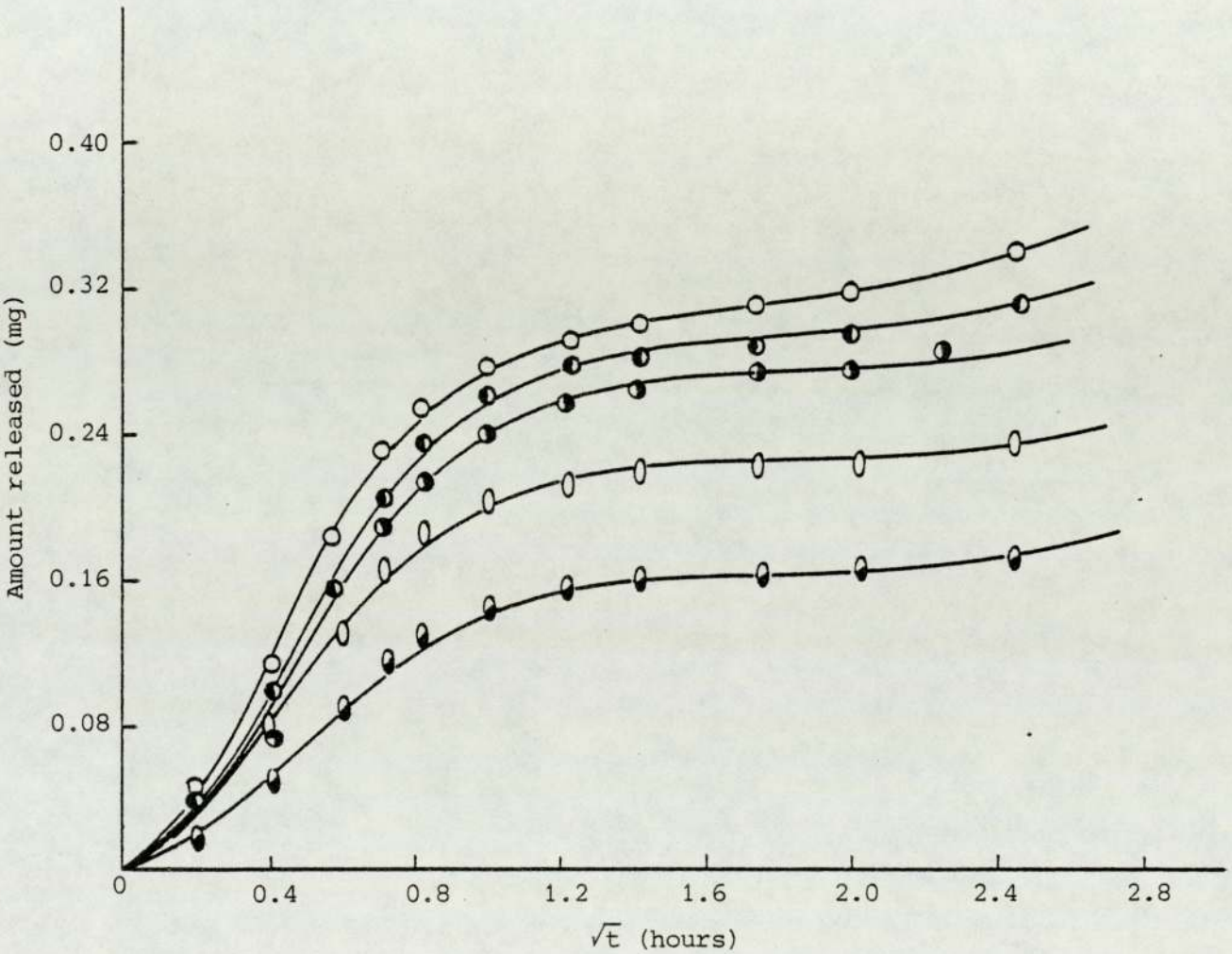


Fig 5.30 The influence of storage duration on the early phase release of benzocaine from sunflower oil emulsion-type gels stored in formaldehyde. O 8 days, ◐ 11 days, ◑ 15 days, 0 21 days and ◕ 29 days storage.

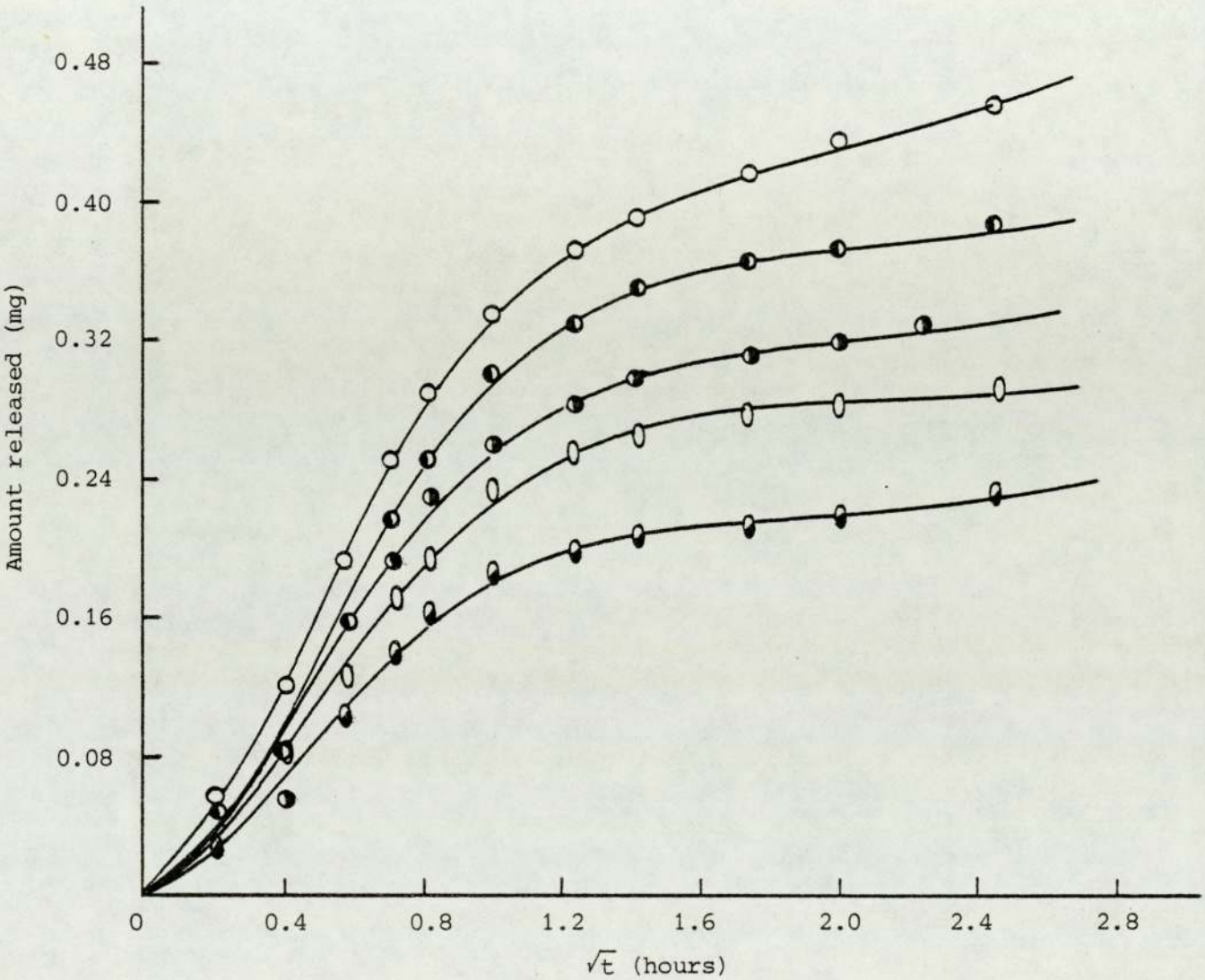


Fig 5.31 The influence of storage duration on the early phase release of benzocaine from Witepsol 'W45' emulsion-type gels stored in formaldehyde. O 8 days, ◐ 11 days, ◑ 15 days, 0 21 days and ◒ 29 days storage.

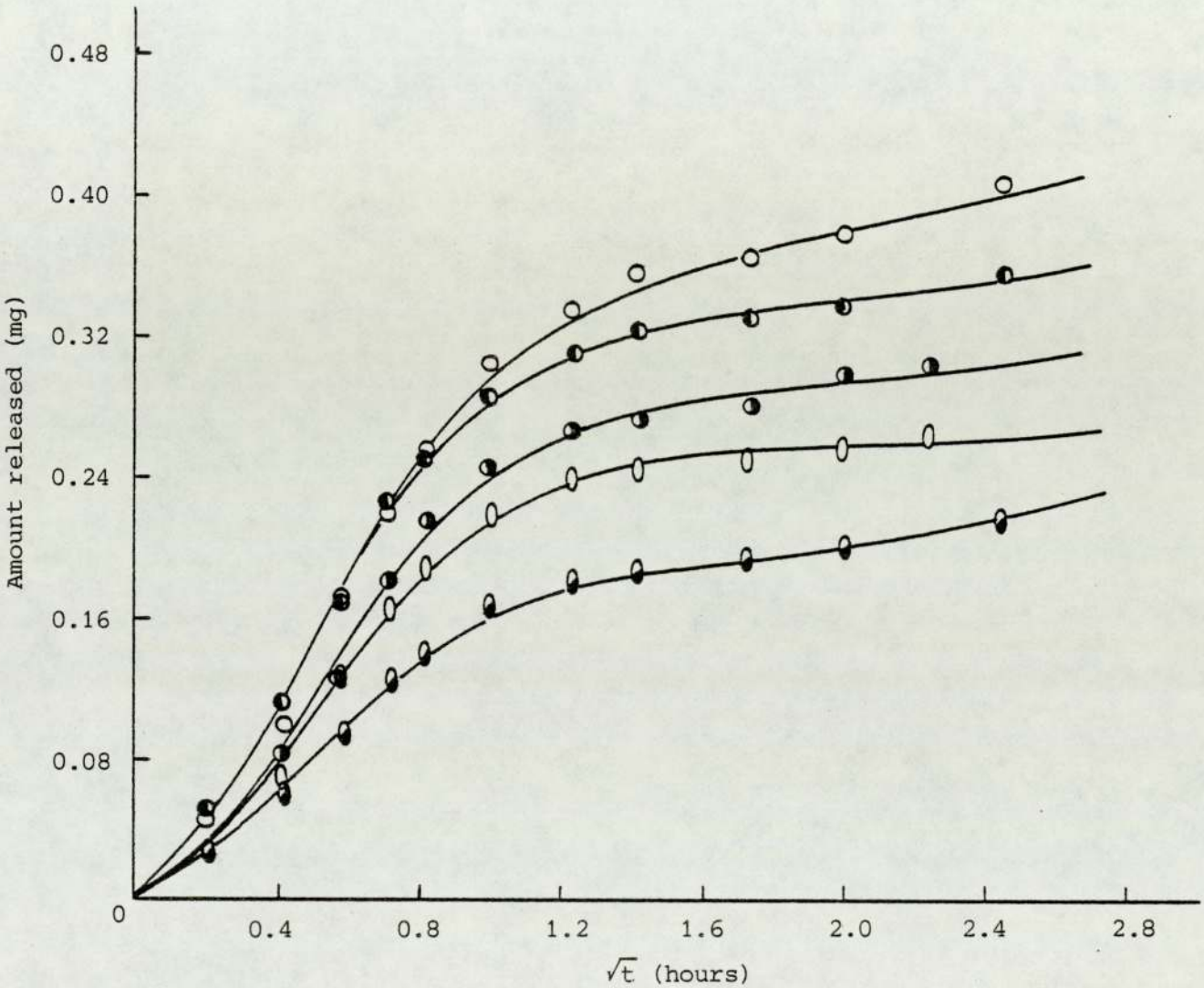


Fig 5.32 The influence of storage duration on the early phase release of benzocaine from Suppocire 'AM' emulsion-type gels stored in formaldehyde. O 8 days, ◐ 11 days, ◑ 15 days, 0 21 days and ◕ 29 days storage.

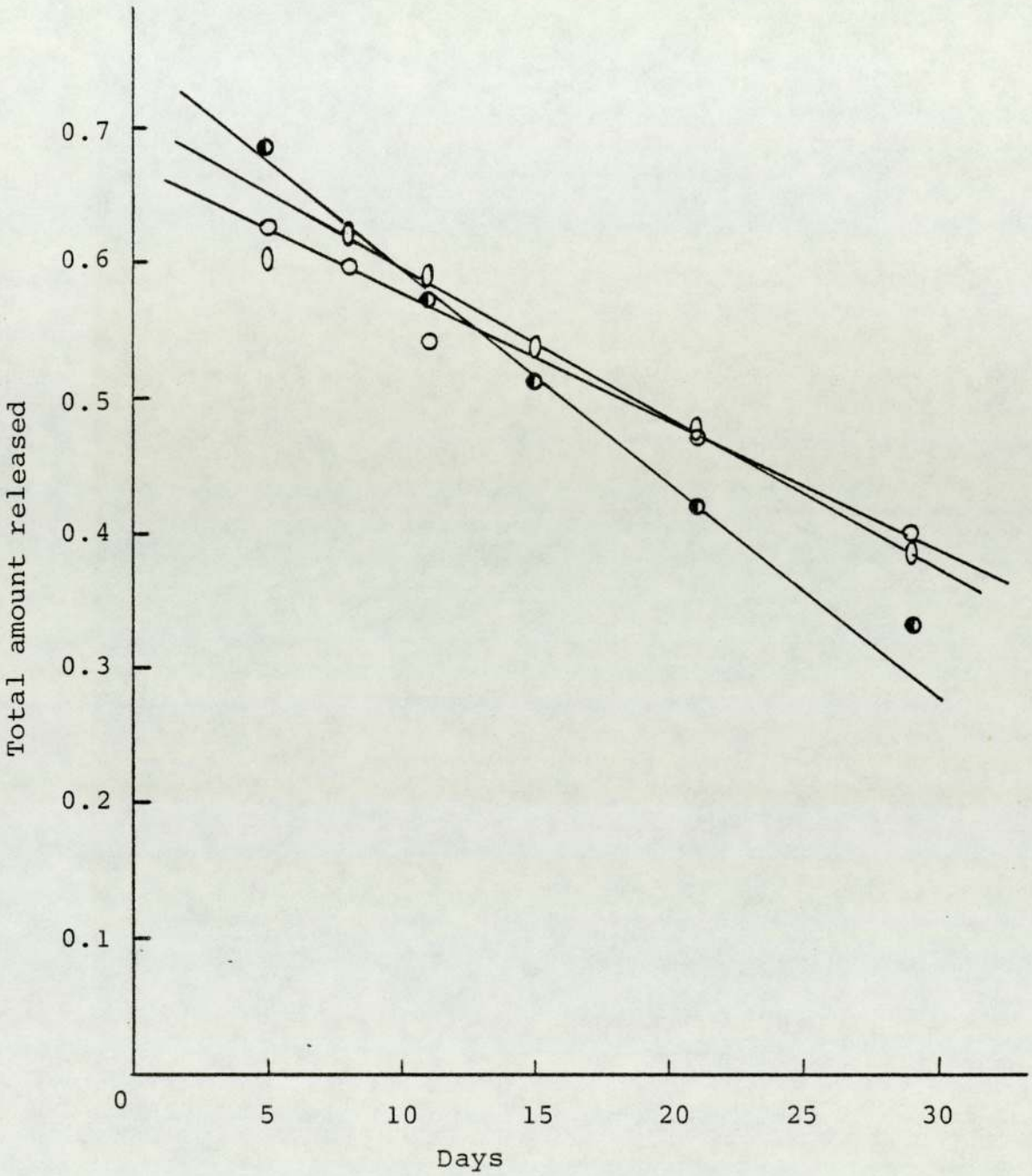


Fig 5.33 Loss of activity of the benzocaine in emulsion-type gels on continued storage in formaldehyde. O Sunflower oil, ◐ Witepsol and ◑ Suppocire 'Am'.

reaction. The presence of such a reaction would not be surprising since there are reports of irreversible binding of formaldehyde to proteins (251-255). In this context, the differences in the slopes of the stability profiles in Fig. 5.33 can be taken as a measure of the protective behaviour of the bases. Sunflower oil seems to offer the greatest protection when compared to Witepsol W45 and Suppocire 'AM' suppository bases. It would be interesting to see if there is any relationship between the protective behaviour of the internal phases and their corresponding oil/water partition coefficients. The total amount of benzocaine released from the other systems shows a similar behaviour (Table 5.4).

The release of benzocaine from formaldehyde-treated sunflower oil emulsion films which were removed from the formaldehyde tank after 3 days of hardening is shown in Fig. 5.34. The release rate is fairly constant for up to 8 weeks and the total amount released from the films is also constant (Table 5.5). The release profiles indicate a gradual decrease in release rates during the initial 16 hours to a constant rate which is maintained for over 80 hours and ends quite abruptly. It is obvious from the profiles that the absence of formaldehyde provides a very stable system. More studies are necessary however, to investigate if the slightly faster release after eight weeks of storage is an indication of subsequent degradation of the system.

TABLE 5.5

The Stability of Benzocaine in Formaldehyde-Treated Sunflower Oil Emulsion Gels Stored in Formaldehyde-Free Environment

Storage Duration	Total Amount Released (mg.)	Late Phase Steady Release Rate (mg. hr^{-1})
3 Days	0.352	-
1 Week	0.346	0.00338
3 Weeks	0.359	0.00342
8 Weeks	0.372	0.00350

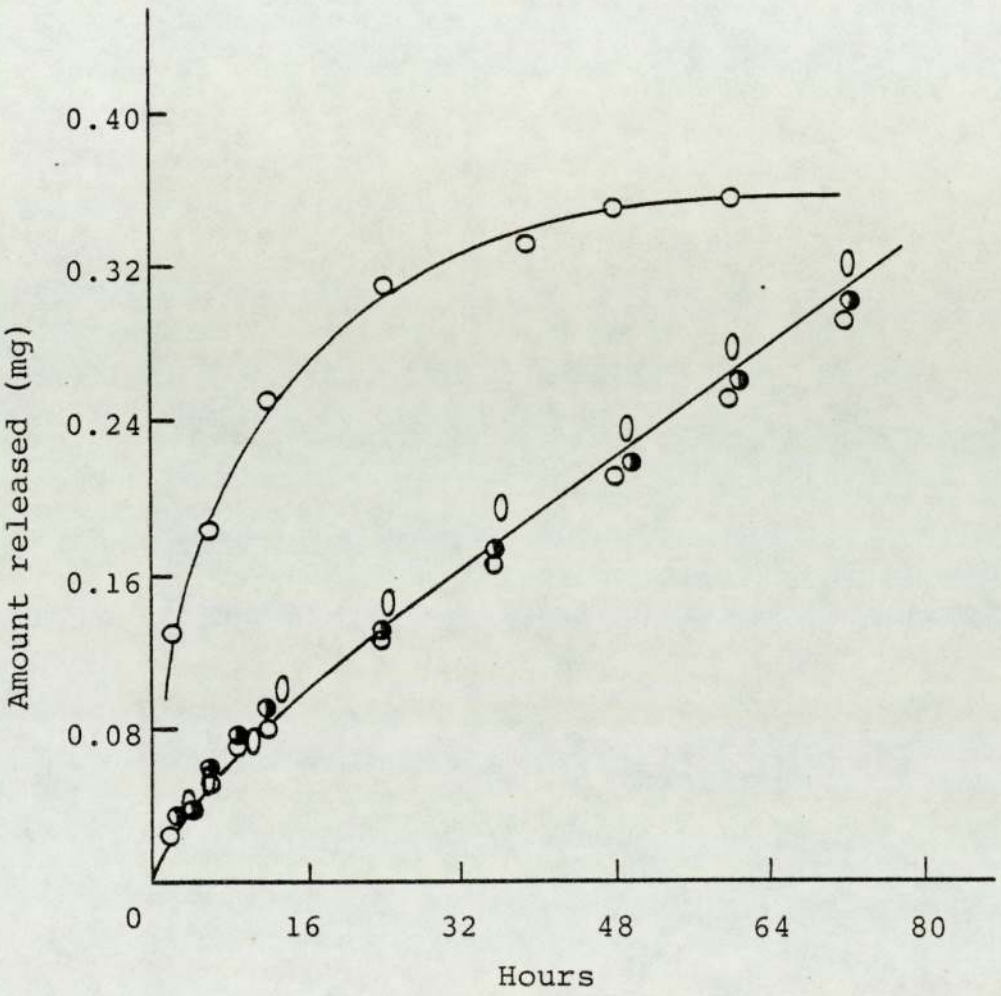


Fig 5.34 Release of benzocaine from a sunflower oil emulsion formulation. The films were initially stored in formaldehyde for 3 days and the formaldehyde was then removed by storage in formaldehyde-free environment with circulating air supply. O on the day of removal from formaldehyde, O after 1 week, ◑ after 3 weeks and 0 after 8 weeks of storage in formaldehyde free environment.

5.3.3. Formulation Variables and Possible Modifications

The results depicted by Fig. 5.34 are very encouraging indeed. However, there is a need to understand the various parameters that are available for manipulation of the total amount incorporated in the dosage form and its rate of release. The most important parameters are:

a. Initial drug concentration: The role of the initial drug loading has been discussed. It has been observed that the initial drug loading determines the rate of drug release especially during the late phase. It is difficult at this stage to provide a complete relationship because, as has been evident throughout this study , the late phase loading depends on the amount released during the early phase as well as the irreversible loss of the drug. Only after these two processes are well understood and quantifiable can significant prediction of the influence of initial drug concentration be performed. It should be mentioned, however, that the total amount of drug incorporated in the dosage form will be limited by its solubility in the dispersed phase at the storage temperature. It is quite possible too that a higher partition coefficient could reduce the irreversible loss of the drug.

b. Oil-phase ratio in the emulsion: An increase in the oil phase ratio means a higher amount

of drug can be incorporated in the device and consequently, it favours a higher release rate. The ideal phase ratio therefore depends on the amount of drug that is incorporated and the rate at which it is released. It should be remembered that it has been observed, in this study, that late release is controlled by the continuous phase and the role of the dispersed phase seems to be merely to deliver a higher amount of the drug during the binding process.

c. Thickness of the film: The early release has been shown to obey Fick's Law and thus is a function of the thickness of the film. The late phase however seems to respond to thickness changes as shown by variation in the amount of drug released (Fig. 5.35). Thus a thicker film will have a higher release rate because it contains more drug. The direct proportionality between thickness and release rate is shown in Fig. 5.36.

In usable form, the films will obviously have a significantly less prominent early phase. This is because most of the formaldehyde would have been removed from the formulation. The regeneration of formaldehyde on the breakage of bonds to release benzocaine during the late phase should therefore be the main cause of concern. More studies are therefore necessary to monitor the amounts of formaldehyde released in this process. There may be a need to replace formaldehyde with a less toxic crosslinker.

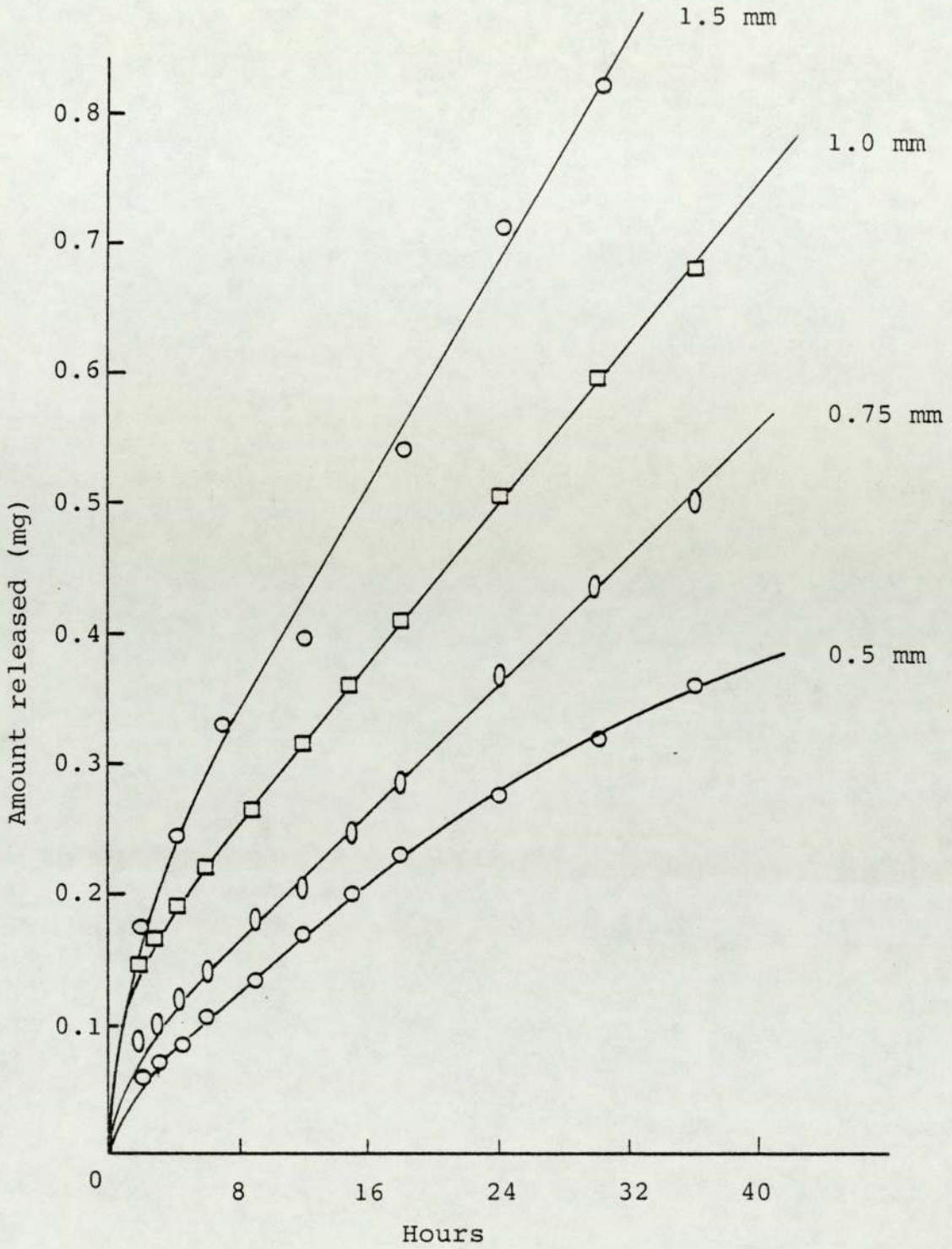


Fig 5.35 The influence of thickness on release of benzocaine from formaldehyde-treated sunflower oil emulsion films.

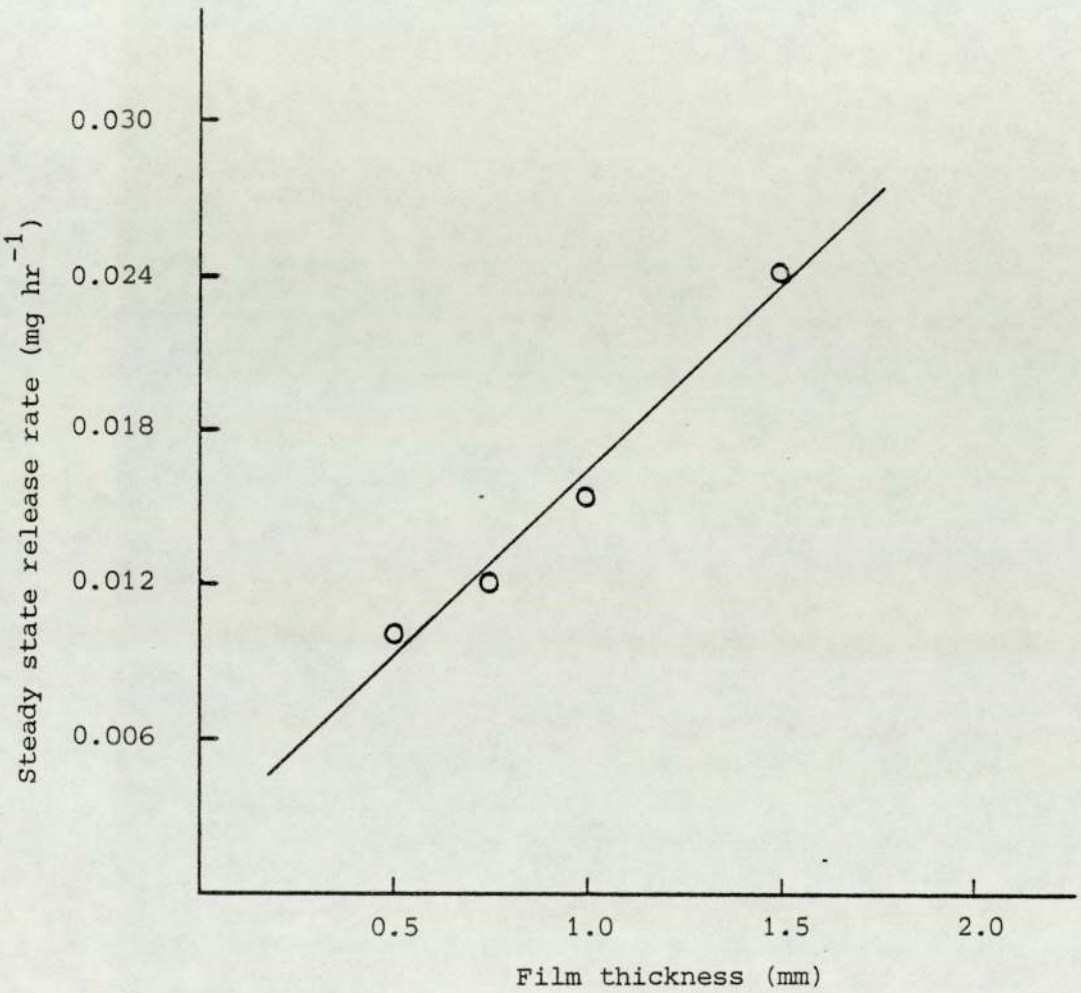


Fig 5.36 The relationship between the late phase steady release rate and film thickness for formaldehyde treated films.

CHAPTER 6

CONCLUSION AND SUGGESTIONS FOR FURTHER WORK

6.1 CONCLUSION

An attempt has been made to systematically formulate a controlled-release preparation of a local anaesthetic in gelatin gel. The choice of gelatin as the polymeric base was based on its cost and on its safety profile. Moreover, since one of the potential applications of the formulation was for the relief of mouth ulcers, the adhesive properties of gelatin were attractive.

The possibility of release from such a system being controlled by heat transfer and heat induced phase transition was investigated, an approach which other investigators have neglected in their analysis of dissolution behaviour. Heat and mass transfer are modelled by the same mathematical equations and they both therefore give similar qualitative results. In attempting to resolve this problem, the dependence of the dissolution rate of gels on their bloom strength and glycerol concentration was studied, together with the thermal properties of the gels. It was observed that the dissolution rate was a function of bloom strength and glycerol concentration. The melting point of the gels were affected by the bloom strength of the gelatin used but glycerol concentration affected the melting range rather than the melting point. The heat of fusion of the gels increased with both bloom strength and glycerol concentration, leading to the

conclusion that the dissolution behaviour might be related to the heat of fusion, since both mirror the energetics of the system. Such was the case for bloom strength variation since gels with higher heat of fusion dissolved much slower. In case of glycerol, it was observed that the dissolution rate was enhanced by the glycerol concentration regardless of the fact that the heat of fusion of the glycero-gelatin gels increase with glycerol concentration. This led to the conclusion that rigidity of the gels was not the determining factor in the dissolution of the gels. The results therefore rule out a direct relationship between the heat of fusion and the dissolution rate of the gels.

Due to the fast release of the drug by dissolution, studies were made on diffusion-controlled release. Earlier reports (181,186) suggested that the diffusion of substances in gelatin gels is a function of gel factors such as bloom strength, gelatin concentration and the extent of crosslinking. The release of the drugs could therefore be controlled by manipulation of such gel factors. The release of lignocaine hydrochloride from homogeneous gelatin films was observed to be independent of all these factors thus leading to the conclusion that the structural framework of the gel did not affect the diffusion of lignocaine from the formulations investigated.

The release of medicaments from emulsion-type solid gels was then studied. The study was aimed at

investigating the limits of application of the equations available for evaluation of the release behaviour of drugs from emulsion systems. Contrary to Higuchi's suggestion (231) that the equation for release from homogeneous matrices can be applied to heterogeneous matrices up to 30-50% of the total amount released, it was found that the limits vary considerably depending on the partition coefficient of the drug between the two emulsion phases. Thus in case of low partition coefficients, the homogeneous behaviour was almost entirely simulated, whereas in case of higher partition coefficients, the proportion that fits the homogeneous model decreases.

Regarding the use of the suspension equation (102) for modelling release from emulsions, it was suggested that minor modifications were necessary to correct for the thermodynamic conditions peculiar to emulsions and which do not apply to suspensions. Thus a simple rederivation of Higuchi's equation for suspension (102) was performed taking into account the amount of drug remaining in the dispersed phase in the depleted zone. Another modification of the suspension equation was the adoption of a term introduced (226) to correct for the assumptions made in the derivation of the suspension equation that linear concentration gradients exists in the zone of depletion. The rederived equation provided a fairly good fit for release of lignocaine (base) from alcohol emulsion gels when the diffusion coefficient of lignocaine in the continuous phase was used. The model could not be applied

to results of other release experiments because of the apparent non-sink conditions persisting in the release medium. The need for further testing of the equation is therefore obvious. The equation offers an easier way of predicting release from emulsion systems than those presently available.

The studies of release from emulsions was then extended to the use of equations developed by Wagner (218), Bruggeman (219) and Higuchis' (221) to predict the effective dielectric permeability coefficient of heterogeneous systems. Due to similarities between dielectric permeability and diffusion, it has generally been felt that the same mathematical equations can be used for describing both. Instead of using the diffusion coefficient of the drug in the continuous phase as required by the equations, their corresponding viscosity values were used on the basis of Stoke-Einstein relationship between the diffusion coefficient and the viscosity of the solvent. The results obtained showed that for the drug with high partition coefficients the Bruggeman equation provided the best approximation. At lower partition coefficients, the other equations provided better approximations. Generally, no single equation provided satisfactory predictions throughout, with the Wagner and Higuchi equations being the worst. The use of viscosity data in the prediction was far more successful than expected, bearing in mind the limitations of the Stoke-Einstein relationship when used for describing such complex systems.

Attempts were then made to produce a reversibly bound formulation of benzocaine to gelatin. For the preliminary studies, formaldehyde was used although it was appreciated that it will probably have to be replaced if the model proved successful due to its potential toxicity. The reaction between formaldehyde and nitrogen-containing compounds and especially with amines is very complex and leads to formation of a number of compounds (156). It was therefore initially doubtful whether sufficient benzocaine could be bound to gelatin instead of formaldehyde. Moreover, the reversibility of such binding was also a potential complication. It was therefore quite surprising when the system provided reproducible zero order delivery. The release was observed to occur in two stages with an early, fast, diffusion-controlled stage and a late, slower zero or first order delivery stage. The early stage was found to be due to drug accummulated in the continuous phase possibly in complex form. The amount released during the early phase was found to be dependent on the content of formaldehyde during storage since there was a marked decrease in the diffusive release rate and the amount released during the early phase when the films were removed from the formaldehyde environment. By observing the change of the apparent diffusion coefficient with time on the removal of the films from the formaldehyde environment, it was concluded that the benzocaine released during the early phase was most probably diffusing out as a complex whose

concentration decreased as formaldehyde was being lost. Since formaldehyde is reported to react with amines in Schiff and Mannich-type reactions through the formation of weak methylol intermediates (156), it is a possibility that these methylol complexes are responsible for the behaviour observed during the early phase.

Release during the late phase was found to be independent of particle size of the oil phase (sunflower oil). This led to the conclusion that surface area-controlled mechanisms at the oil-continuous phase interface could not be the controlling mechanisms during the late phase. Possible alternative explanations include binding of the drug to the protein molecules and complexation between benzocaine and formaldehyde.

The release kinetics during the late phase were observed to be dependent on the initial drug loading. Thus when very high levels of formaldehyde were used, first order kinetics were obtained in this late stage. In such cases, most of the drug existed as complexes in the continuous phase which were released during the early stage. For example, when films of varying phase ratio were used, the emulsions with lower phase ratio (hence lower drug loading) tended to release by first order kinetics during the late phase while those with a higher drug loading (i.e. higher oil phase content) tended to release by zero order kinetics. The early phases tended to be constant regardless of the phase ratio, thus supporting the earlier observation that the amount released during the early phase is determined by the

level of formaldehyde in the storage tank. The thickness of the films was also demonstrated to influence the late phase release rate only in terms of drug loading.

Limited stability studies were performed to monitor the fate of benzocaine in the formulation on continued storage in formaldehyde. Two important observations were made. Firstly the total amount of benzocaine released from the films was seen to decrease at a constant rate on continued storage. This suggested that an irreversible reaction was taking place in the film. Secondly, the amount released during the early phase also decreased with storage time. This was thought to have been caused by either the reduction in the replenishment rate of the drug during the late phase or by the loss of formaldehyde from the tank. Most probably the behaviour was a result of both factors.

Other bases, mainly suppository bases, were then used to determine whether the type of dispersed phase could affect the release behaviour. The suppository bases were also selected so as to reduce the possibility of syneresis when liquid dispersed phases are used in solid systems. The results obtained suggested a similar trend of events as in the case of sunflower oil with slight differences in the rate of loss of releasable benzocaine from the films on continued storage over formaldehyde. If this was taken as a measure of the protective effect against irreversible binding which the

dispersed phase offers to the drug, then it seems that sunflower oil is better than Witepsol (W45) or suppocire 'AM' suppository bases.

The release of benzocaine from films removed from formaldehyde exposure after 3 days' storage was observed to provide zero order release. The release rate remained almost constant even after eight weeks of storage. The initial diffusive phase was much less dominant and zero order delivery lasted from 16 to 80 hours. These results were quite encouraging. It was therefore concluded that the system could offer a useful delivery formulation but the use of alternatives to formaldehyde as cross-linking/binding agent should be explored.

6.2 SUGGESTIONS FOR FURTHER WORK

Of the many questions which have arisen during the course of this work, the following are worth investigating:

1. As far as dissolution-controlled release is concerned, further studies on the thermal behaviour of gelatin gels is necessary. The influence of aging, blending (additives) and gelatin concentration on the thermal behaviour needs to be determined. The mechanisms of dissolution need further investigating following observations that rigidity as such does not have any direct effect on the dissolution rate (Section 3.1).

2. In the diffusion work (Section 3.2) on lignocaine from glycerin-free aqueous gelatin films,

no difference in diffusion coefficient was observed with changes in concentration of gelatin thus suggesting that the matrix did not provide the diffusion control as is commonly assumed (181). It would be interesting to investigate the limiting molecular size of the diffusant which would bring about a change in diffusion-control from solution to matrix.

3. In emulsion systems, the validity of the modified suspension equations needs to be confirmed. Moreover, the behaviour of release from solid matrices when resistance at the oil/continuous phase interface is significant might offer another useful method of formulating controlled-release dosage forms; since the expected two-stage release behaviour could provide a system with an initial loading dose followed by a maintenance dosage significant interfacial resistance to drug transport could be introduced by using combinations of surfactants which could provide a more condensed film at the interface.

4. It is necessary to establish the exact nature of the interaction between benzocaine, formaldehyde and gelatin. Following this, the presence of binding of benzocaine to gelatin under the conditions used for preparation of the formulation could be demonstrated and quantified.

APPENDIX 2.1

LIST OF CHEMICALS

1. Acetic acid (glacial) - Fisons
2. p. Aminobenzoic acid (SLR) - Fisons
3. Ammonia solution (SLR) - 0.88 Sp. Gr. - Fisons
4. Boric acid (BDH)
5. Butyl - p-aminobenzoate - Sigma
6. Butyl - p-hydroxybenzoate - Sigma
7. Butylated hydroxyanisole - BDH
8. Carbocaine (base) - Pharm. Man. Co., Epsom Surrey
9. Coconut oil - Richard Daniel & Son, Derby
10. Decan-1-ol (SLR) - BDH
11. Dodecan-1-ol - Fisons
12. Ethyl - p-aminobenzoate - Sigma
13. Ethyl - p-hydroxybenzoate (LR) - BDH
14. Formaldehyde soln. (38% w/v) - Fisons
15. Gelatin - Alfred Adams & Co.
16. Glycerol - Macarthy's
17. Glycerol - trioleate (Triolein) - BDH
18. Glycerol - tripalmitate (Tripalmitin) - BDH
19. Hexane (HPLC Grade) - Fisons
20. Lignocaine (base) - Sigma
21. Methanol (AR) - Fisons
22. Methyl - p-aminobenzoate - Koch-light Laboratories
23. Methyl - p-hydroxybenzoate (LR) - BDH
24. Nonan-1-ol (Grade 1) - Sigma
25. Octan-1-ol (AR) - Fisons
26. Phosphoric acid - BDH
27. Potassium acetate (LR) - BDH
28. Potassium carbonate (AR) - Fisons
29. Potassium chloride (AR) - Fisons
30. Potassium sulphate (LR) - BDH
31. Procaine (base) - Sigma
32. Propan-1-ol (HPLC Grade) - Fisons
33. Propyl - p-aminobenzoate - Pfultz & Bauer Inc.
34. Propyl - p-hydroxybenzoate - BDH
35. Sodium chloride - Fisons
36. Sodium dichromate (Tech. grade) - Fisons
37. di-Sodium hydrogen orthophosphate $12H_2O$ (AR) - Fisons
38. Sodium hydroxide (IOM) - BDH
39. Sodium nitrite (SLR) - Fisons
40. Sunflower® oil - Macarthy's
41. Suppocire® suppository bases - Gattefosé
42. Tetracaine (base) - Sigma
43. Undecan-1-ol (99%) - Sigma
44. Witepsol W45 suppository base

APPENDIX 4.1

```
C JOB :SHP740,NJ(DIFF,NO(J760,MZ40X)
1 U:FORTRAN SAVE  JDIFFE
2       MASTER DIFFREL
3 C     PROGRAM TO MODEL DIFFUSIONAL DRUG RELEASE UNDER SINK AND NON-SINK
4 C     CONDITIONS.
5 C     R.H. GUY AND J. HADGRAFT, J. PHARM. SCI., 1981,70,1243-1245
6 C     INPUT DATA IS :
7 C        CARD 1      : IOPT ,  ISCALE     (2I1)
8 C                      IOPT = 0  FINISH RUN
9 C                      IOPT = 1  NORMAL RUN - SWAP MODELS WHEN T>1
10 C                     IOPT = 2  SHORT TIME APPROXIMATION THROUGHOUT
11 C
12 C                     ISCALE= 1 PLOT SCALED TO MINF
13 C                     IOPT = 3  LONG  TIME APPROXIMATION THROUGHOUT
14 C        CARD 2      : NAME  (20A4)
15 C                      : NAME = TITLE OF RUN
16 C        CARD 3      : DD,K,VR,A,L    (E10.4,4F10.4)
17 C                      DD    = DIFFUSION COEFFICIENT
18 C                      K     = PARTITION COEFFICIENT
19 C                      VR    = VOLUME OF RECEIVER PHASE
20 C                      A     = INTERFACIAL AREA
21 C                      L     = THICKNESS OF DONOR PHASE
22 C        CARD 4      : CO, T1, T2    (3F10.4)
23 C                      CO    = INITIAL CONCN OF DRUG IN DONOR PHASE
24 C                      T1    = INITIAL TIME
25 C                      T2    = FINAL TIME
26 C     REPEAT CARDS 1,2, 3, 4 FOR SUCCESSIVE RUNS
27 C     TERMINATE WITH A BLANK CARD
28 C     MINF IS THE INITIAL TOTAL AMOUNT OF DRUG IN THE DONOR PHASE
29 C                    MINF = A * L * CO
30 C     WHERE CO IS THE INITIAL DRUG CONC IN THE DONOR PHASE
31 C     MTSINK AND MTNONS ARE THE CUMULATIVE AMOUNTS OF DRUG PENETRATING INTO
32 C     THE RECEIVER COMPARTMENT AT TIME T
33       DIMENSION NAME(20),IPLOT(51,121),TI(13)
34       REAL L,K,MINF,MTSINK,MTNONS ,MINFA,MINFB
35       INTEGER SU,S1,NO,N1,BO,B1
36       COMMON /A/ NAME,DD,K,VR,A,L,MINF,T1,T2,T3,CO
37       DATA  SU,S1,NO,N1,BO,B1/1HS,1HT,1HM,1H*,1H ,1H*/
38   10  READ (5,20) IOPT
39   20  FORMAT (2I1)
40       IF (IOPT .EQ. 0) GOTO 220
41       READ (5,30) NAME
42   30  FORMAT (20A4)
43       READ (5,40) DD,K,VR,A,L
44   40  FORMAT (E10.4,4F10.4)
45       READ (5,50) CO,T1,T2
46   50  FORMAT (3F10.4)
47       T3  =(T2-T1)/50.0
48       MINF=A*L*CO
49       Q   =A*L/(VR*K)
50       T4=(T2-T1)/12.0
51       DO 55 I=1,13
52    55 TI(I)=T1+FLOAT(I-1)*T4
53       IWARN=0
54       YNO =50.0
55       XNO =120.0
56       T=DD*T2/L/L
57       MINFA=2.0*MINF*SQRT(T)*0.5641896
58       MINFB=MINF*(1.0-EXP(3.0*T))
59       IF (MINFB .GT. MINFA) MINFA=MINFB
60       IF (MINFA .GT. MINF) MINFA=MINF
61       IF (ISCALE .EQ. 1) MINF=MINF
62       YSCALE=YNO/MINFA
63       XSCALE=XNO/(T2-T1)
64       TSWAP=0.1
65   57      DO 60 I=1,51
66       DO 60 J=1,121
```

```
      57      DO 60 I=1,51
              DO 60 J=1,121
      60      IPLOT(I,J)=BO
              CALL TITLE
              WRITE (6,70)
      70      FORMAT (1H0,10X,'TIME',10X,'NON-SINK RELEASE',10X,'SINK RELEASE')
              TIME=T1-T3
      80      TIME=TIME+T3
              IF (TIME .GT. T2) GOTO 150
              T=DO*TIME/(L*L)
              IF (IOPT .EQ. 3) GOTO 90
              IF (T .GT. TSWAP  .AND.  IOPT .EQ. 1) GOTO 90
C             SHORT TIME APPROXIMATION
C                 NON-SINK CONDITIONS
              X1=G*Q*T
              X2=SQRT(X1)
              CALL ERROF (X2,ERFX)
              MTNONS=MINF/Q*(1.0-EXP(X1)*ERFX)
              IF (MTNONS .GT. MINF) MTNONS=MINF
C                 SINK CONDITIONS
              MTSINK=MINF*SQRT(T)*1.1283792
              IF (MTSINK .GT. MINF) MTSINK=MINF
              GOTO 110
C             LONG TIME APPROXIMATION
C                 NON-SINK CONDITIONS
      90      MTNONS=MINF/(1.0+Q)*(1.0-EXP(-3.0*(1.0+Q)*T))
C                 SINK CONDITIONS
              MTSINK=MINF*(1.0-EXP(-3.0*T))
              IF (IWARN .EQ. 1) GOTO 110
              WRITE (6,100) TSWAP
      100     FORMAT (1X,'MODEL CHANGE FOR ',F5.2)
              IWARN=1
      110     WRITE (6,120) TIME,MTNONS,MTSINK
      120     FORMAT (1X,4X,F15.4,10X,F10.4,10X,F10.4,10X)
              IY1=INT(MTNONS*YSCALE)+1
              IY2=INT(MTSINK*YSCALE)+1
              IX =INT((TIME-T1)*XSCALE)+1
              IF (IY1 .EQ. IY2) GOTO 140
              IF (IWARN .EQ. 1) GOTO 130
              IPLOT(IY1,IX)=NO
              IPLOT(IY2,IX)=SO
              GOTO 80
      130     IPLOT(IY1,IX)=N1
              IPLOT(IY2,IX)=S1
              GOTO 80
      140     IPLOT(IY1,IX)=B1
              GOTO 80
      150     CALL TITLE
              DO 190 K1=1,51
              I=52-K1
              II=(I-1)/5*5
              IF (II .EQ. I-1) GOTO 170
              WRITE (6,160) (IPLOT(I,J), J=1,121)
      160     FORMAT (6X,'I',121A1)
              GOTO 190
      170     II=II*INT(MINFA)/50
              WRITE (6,180) II,(IPLOT(I,J), J=1,121)
      180     FORMAT (2X,I5,' +',121A1)
      190     CONTINUE
              WRITE (6,200)
      200     FORMAT (6X,'++',12('----------+'))
              WRITE (6,210) (II(I), I=1,13)
      210     FORMAT (2X,13(F9.2,1X))
              WRITE (6,215)
      215     FORMAT (1H0,50X,'T  I  M  E')
              TSWAP=TSWAP+0.1
              IF (TSWAP .GE. 1.0) GOTO 10
              GOTO 57
      220     STOP
```

```
      TSWAP=TSWAP+0.1
      IF (TSWAP .GE. 1.0) GOTO 10
      GOTO 57
  220 STOP
      END
      SUBROUTINE ERROIF (X,ERFX)
C     SUBROUTINE TO CALCULATE ERROR FUNCTION
C      X IS THE OPERAND, ERFX IS THE FUNCTION VALUE AND D  IS THE POWER OF X
C      USED IN THE APPROXIMATION
      IF (X .LE. 0.0) GOTO 50
      S=1
      S0=X
      S1=X
      D0=1.0
      D1=1.0
      X0=X
   10 X0=X0*X*X
      IF (X0 .LE. 1E-70) GOTO 20
      IF (X0 .GE. 1E70)GOTO 20
      D=2.0*D0+1.0
      S0=S0-X0/(D1*D)*S
      IF (ABS((S0-S1)/S1) .LE. 1E-7) GOTO 40
      S1=S0
      S =-S
      D0=D0+1.0
      D1=D1*D0
      GOTO 10
   20 WRITE (6,30) X0,D
   30 FORMAT (1H0,'EXTREME CORRECTION: X**N = ',E10.5,
     1' AT POWER = ',F5.1/)
   40 ERFX=S0/D.8862269
      IF (ERFX .GT. 1.0) ERFX=1.0
C     RETURN COMPLEMENT OF ERROR FUNCTION
      ERFX=1.0-ERFX
      RETURN
   50 ERFX=0.0
C     RETURN COMPLEMENT OF ERROR FUNCTION
      ERFX=1.0
      RETURN
      END
      SUBROUTINE TITLE
      DIMENSION NAME(20)
      REAL L,K,MINF,MTSINK,MTNONS
      COMMON /A/ NAME,DD,K,VR,A,L,MINF,T1,T2,T3,CO
      LP=6
      WRITE (LP,10) NAME
   10 FORMAT (1H1,10X,20A4//)
      WRITE (LP,20) DD,K,VR,A,L,MINF,CO
   20 FORMAT (1H ,'DIFFUSION COEFFICIENT = ',E10.4,10X,'PARTITION COEFFI
     1CIENT = ',F10.4 /' RECEIVER VOLUME = ',F10.4,16X,'AREA = ',F10.4 /
     2' DONOR THICKNESS = ',F10.4,16X,'M (INFINITY) = ',F10.4/
     3' INITIAL  CONCN  = ',F10.4/)
      WRITE (LP,30)T1,T2,T3
   30  FORMAT (1X,'TIMED FROM ',F10.4,' TO ',F15.4,' IN INCREMENTS OF ',
     1F10.4/)
      RETURN
      END
      FINISH
1
 TEST DATA 1
2.0E-5     200.0      100.0      50.0       10.0
2.0        0.0        500000.0
1
 TEST DATA 2
2.0E-3     200.0      100.0      50.0       10.0
2.0        0.0        100000.0
1
 TEST DATA 3
2.0E-5     200.0      100.0      50.0       10.0
```

APPENDIX 4.2

```
10 '*************************************************************************
20 'SOLUTION OF DIFFUSIONAL CUBIC EQUATION DERIVED VIA :
30 'BRUGGEMANS EQUATION J. PHARM. SCI., 57(1968)87
40 '::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
50 CLS : READ B$ : ' TITLE OF RUN
60 READ N0, K0, V0, P1 : 'SYSTEM CONSTANTS
70 LPRINT B$ : LPRINT : LPRINT "SYSTEM CONSTANTS ARE :"
80 LPRINT TAB(12);"VISCOSITY =    ";N0
90 LPRINT TAB(12);"PARTN.COEFF = ";K0
100 LPRINT TAB(12);"PHASE RATIO = ";V0 : LPRINT
105 LPRINT TAB(12);"PERMEABILITY CONST =";P1 : LPRINT : LPRINT
110 LPRINT "COMPOUND";TAB(12);"VISCOSITY";TAB(24);"PARTITION K";
120 LPRINT TAB(36);"DIFFUSION K";TAB(54);"X"
130 READ A$ : IF A$="" THEN 320
140 READ N1,K1,D1 : ' VISCOSITY, PARTN. COEFF., DIFF. COEFF.
150 R1 = K0/K1*N1/N0
160 ' SET COEFFICIENTS
170 A=EXP(LOG(P1)/3) : B=V0*P1*(R1-1) : C=P1*EXP(LOG(P1*R1)/3)
180 X0=EXP(LOG(P1)/3)  : ' INITIAL ESTIMATE
190 F1=A*X0*X0*X0 - B*X0 - C : F2=3*A*X0*X0 - B
200 X1=X0-F1/F2 : IF ABS((X1-X0)/X0) < 1E-5 THEN 220
210 X0=X1 : GOTO 190
220 'S=SGN(X1) : X=EXP(LOG(ABS(X1))/3) * S
221 X=X1*X1*X1
230 LPRINTA$;TAB(12);N1;TAB(24);K1;TAB(36);D1;TAB(50);X
240 GOTO 130
250 DATA "BRUGGEMAN EQUATION - TEST DATA "
260 DATA 0.89, 1, 0.8, 7.6495E-3
270 DATA "OCTANOL", 8.799, 27.6, 4.107E-4
280 DATA "NONANOL", 10.732, 23.7, 5.738E-4
290 DATA "DECANOL", 13.535, 19.6, 7.211E-4
300 DATA "DODECANOL", 19.345, 17.9, 8.344E-4
310 DATA ""
320 END
```

```
BRUGGEMAN EQUATION - TEST DATA
SYSTEM CONSTANTS ARE :
            VISCOSITY =    .89
            PARTN.COEFF =  1
            PHASE RATIO =  .8
            PERMEABILITY CONST = 7.6495E-03
COMPOUND    VISCOSITY   PARTITION K DIFFUSION K        X
OCTANOL      8.799        27.6         4.107E-04     2.66802E-03
NONANOL      10.732       23.7         5.738E-04     3.73893E-03
DECANOL      13.535       19.6         7.211E-04     5.78012E-03
DODECANOL    19.345       17.9         8.344E-04     9.57427E-03
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