SWELLING CONTROLLED SYSTEMS BASED ON IONIZABLE HYDROGELS: ROLE OF TRANSITION PHENOMENA

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BY

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DECLARATION

Certified that the work incorporated in the Thesis "Swelling Controlled Systems based on ionizable hydrogels : Role of Transition Phenomena", submitted by Mr. S.S. Patil was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

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Candidate

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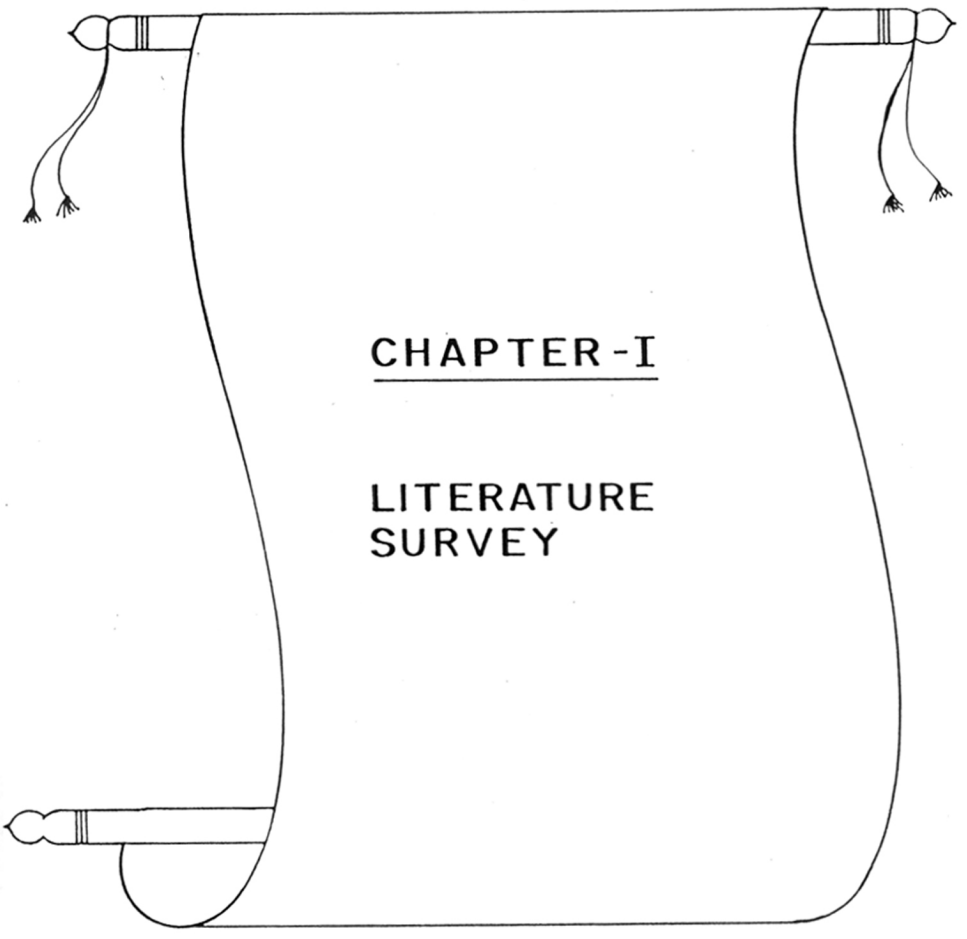


CHAPTER-I

LITERATURE SURVEY

1.0.0 INTRODUCTION

Great strides have been made in the management of diseases through the intervention of drugs such as immunizing agents, antibiotics, steroids, tranquilizers. However, these accomplishments in drug development have not been matched by a similar growth in the area of drug delivery system. Unless a drug can be delivered to its target area at the desired rate, optimum utilization of the drug is not possible. Controlled drug delivery systems enable drug administration so that an optimal amount of drug is used to bring about the desired effect.

The pharmaceutical industry today is fiercely competitive. The introduction of a new drug in the market has become prohibitive due to the phenomenal development costs involved. Hence the search is on for alternate delivery systems, which would enable the companies maintain their competitive edge. Controlled release technology has thus immense potentials in the pharmaceutical industry from both the applications and commercial view point.

1.1.1 Rationale for controlled release delivery systems.

Sustained or controlled release systems have been developed in response to the shortcomings of conventional drug delivery systems. When a conventional tablet or capsule is administered, the concentration of the drug in the bloodstream rises rapidly and may soon exceed the therapeutic range and cause undesirable side effects. Finally, the concentration drops below the minimum drug concentration required to bring about therapeutic action, rendering the drug pharmacologically inactive. When the next dose of drug is administered, the drug concentration in the blood plasma goes through the same cycle. The net effect is that the drug produces the desired effect only 40 to 60% of the time (Fig. 1.1). Thus, there is a need to control the release of a drug into the bloodstream, so that it remains within the therapeutic range for a much longer period. The benefits of using controlled release delivery systems are summarized below.

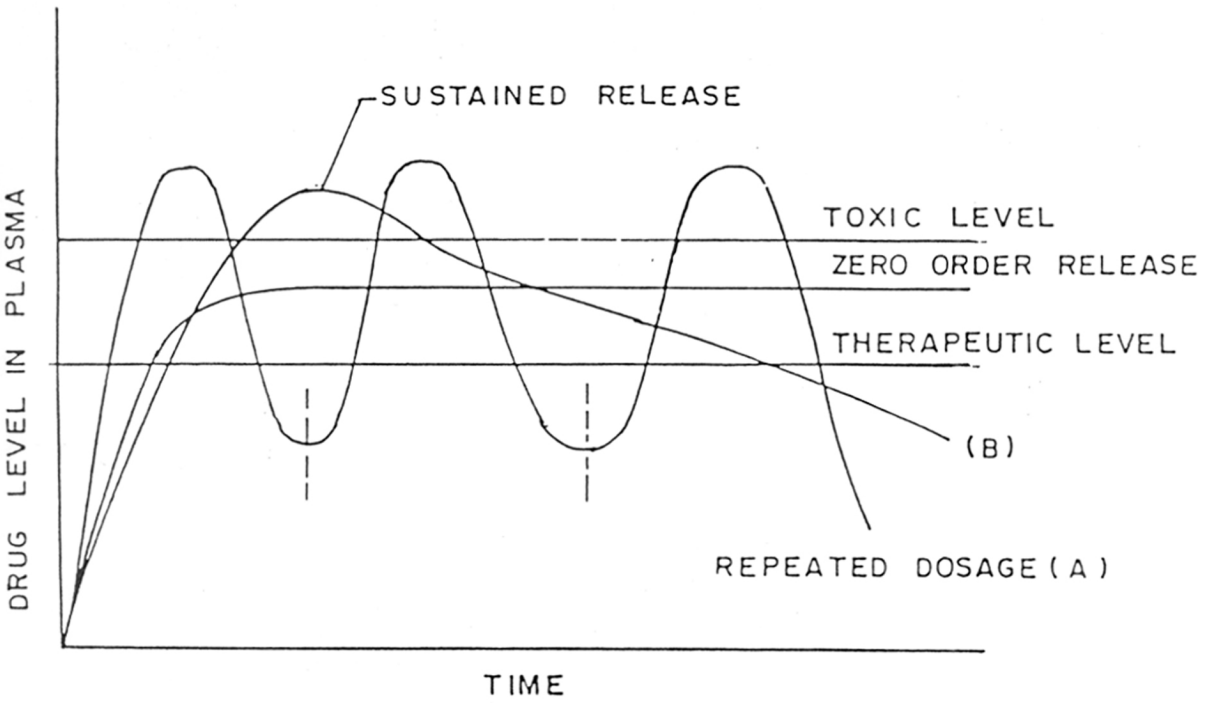


FIGURE 1·1

DRUG CONCENTRATION PROFILES FOLLOWING DRUG ADMINISTRATION

1. Since the frequency of drug administration is reduced, the patient compliance is improved. Injectables administered once a month and implants for drug delivery for an year or longer, and once a day systems for oral intake are common examples.

2. Since the blood level of drug seldom rises above the therapeutic range, the side effects can be greatly reduced if not eliminated.

3. In case of drugs with narrow therapeutic range, the drug release rate should be properly controlled in order to avoid side effects. Controlled release products are safer to use in such situations.

4. If a drug incorporated in a polymer matrix is implanted at or near its intended site of action, it can be more effective and produce fewer side effects as the dosage requirements can be brought down.

1.1.2 Importance of zero order release in pharmaceutical applications

Zero order release pattern is ideally suited for the delivery of the drugs which have short biological half life and low therapeutic index. The utility of zero order release would be clear from the pharmacokinetic model depicted in Fig. 1.2 .

The concentration of the drug in the plasma can be expressed by the equation

$$C_{plasma} = \frac{(Dose)_a}{V_d} \frac{K_a}{K_a - K_e} (e^{-K_e t} - e^{-K_a t}) \qquad 1.1$$

where K denotes the rate constant of the process indicated by the subscript and V_d denotes the volume of distribution . It is clear that the factor $(Dose)_a$ is formulation related variable whereas all the other terms are characteristics of the drug.

Zero Order Release

If the rate of drug release follows a zero order or pseudo zero order kinetics, C_{plasma} for a single compartment system is given by

$$C_{plasma} = \frac{K_o}{K_e V_d} (1 - e^{-K_e t}) \qquad 1.2$$

where, K_o denotes the rate constant for the zero order release. At some time after the

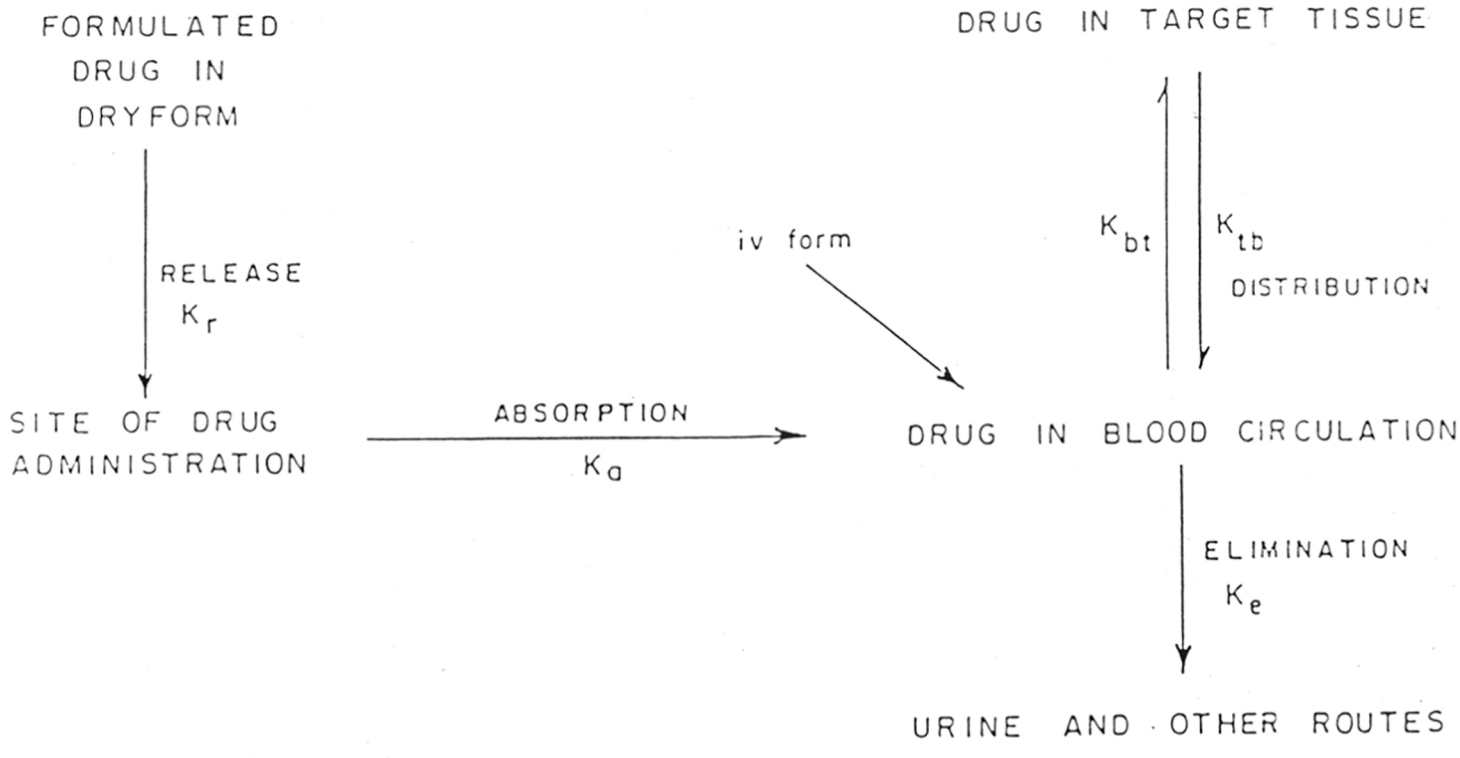


FIGURE 1·2

PHARMACOKINETIC PROCESSES IN DRUG ADMINISTRATION

administration of the drug, the $e^{-K_e t}$ term approaches zero and a steady state concentration given by

$$C_{plasma} = \frac{K_o}{K_e V_d} \quad 1.3$$

is established in the plasma. If the drug has a short biological life i.e. K_e is large, K_o will also have to be large so that an effective therapeutic level can be attained. For a multiple component system

$$(C_{plasma})ss = \frac{K_o}{\beta V_d} \quad 1.4$$

where ß is the composite rate constant for drug elimination estimated by a plot of terminal elimination phase of a ln (C_{plasma}) vs t plot. Thus a steady concentration of the drug in the plasma can be achieved by manipulating K_o.

First Order Kinetics

If the drug release from the controlled release device follows first order kinetics, the concentration of the drug in the plasma is given by

$$C_{plasma} = \frac{K_1(Dose)}{(K_1 - K_e) V_d} (e^{-K_e t} - e^{-K_1 t}) \quad 1.5$$

Equation 1.5 is a transformed form of equation 1.1 since release of drug from CRD system becomes the rate controlling step, i.e. $K_1 << K_a$.

For a multicomponent system

$$C_{plasma} = \frac{K_1(Dose)}{(K_1 - \beta)V_d} (e^{-\beta t} - e^{-K_1 t}) \quad 1.6$$

Thus, for a drug released by first order kinetic process, C_{plasma} depends not only on K_1 but also on the amount of drug (Dose) in the system . Thus, with the exhaustion of drug, C_{plasma} will fall at a rate depending on the relative magnitudes of K_1 and K_e.

It is obvious that a CRD system that contains a drug having a moderately long biological half life (, 12 hours) and release it at a constant rate, would be preferred to a system having a short biological half life released by a first order rate process.

1.2.0 Classification of Controlled Release Devices :

Release Kinetics

Controlled release systems can be classified in two different ways. The scheme of classification could be based on 1) the mechanism of release or 2) the route of administration.

Table 1.1 lists the four general mechanisms which govern the release of the active ingredient. It must be mentioned that this scheme of classification is quite general in nature. The steps involved in the release of a drug from a device are summarized below (Somasekharan & Subramanian 1980).

a) diffusion of the external medium into the matrix

b) release of the drug through the device

c) diffusion of the drug through the device to its surface

d) phase transfer

e) migration across the boundary layer

f) diffusion into the bulk phase

The mechanism of release would then depend upon which of the above steps is the rate controlling step. Ideally, the release of the drug should be rate limiting so that release is totally dependent on the device itself and not on the surrounding environment.

The release behaviour of bioactive agents is the result of diffusional phenomena in the polymer and mass transfer limitations at the polymer/liquid interface. The design of controlled release delivery systems requires an understanding of mechanism of solute diffusion through polymers. Regardless of the type of system involved, the diffusion coefficient of the active ingredient (a_i) depends on structural and morphological parameters of the a_i and the polymer. Solute diffusivity also depends on the concentration of the

TABLE 1.1 : Classification of Controlled Release Devices

I. Diffusion Controlled Systems

A) Reservoir Systems

i) Reservoir Systems with Rate Controlling Membrane

ii) Reservoir Systems without Rate Controlling Membrane

B) Matrix Systems

i) Active Ingredient Uniformly Dispersed in Matrix

ii) Laminated Structures

II. Chemically Controlled Systems

A) Bioerodible Systems

i) Bulk Eroding Systems

ii) Surface Eroding Systems

B) Pendent Chain Systems

III. Swelling Controlled Systems

IV. Magnetically Controlled Systems

solute in the polymer.

1.2.1 Diffusion controlled systems

These are the most widely used systems for the delivery of bioactive agents. The mechanism of release is governed by the rate of diffusion of the drug from the device. These systems are subdivided into two categories, viz;

A) Reservoir Systems and B) Matrix systems.

Diffusion of a solute molecule can take place through the space between the macromolecular chains with diffusion coefficient D_{ip} or through the porous network filled with aqueous medium with an effective diffusion coefficient D_{eff}, which incorporates both porosity and tortuosity.

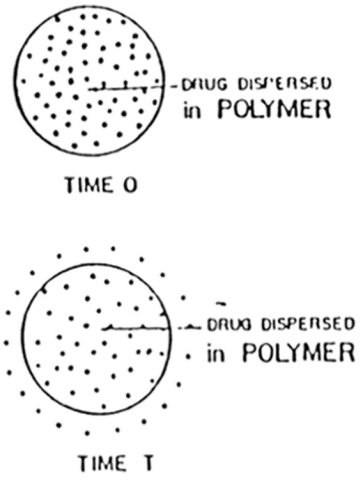
A) Reservoir systems

Reservoir systems consist of a thin membrane separating a core of bioactive agent from the environment (Fig 1.3). The active ingredient is appropriately dispersed or dissolved in a suitable medium. These systems are also referred to as "depot devices". Solute diffusion through and release from polymeric systems can be analyzed in terms of the Fick's law. For concentration independent solute diffusion coefficient in the polymer, D_{ip}, and constant thickness, δ, Langer and Peppas proposed following equation

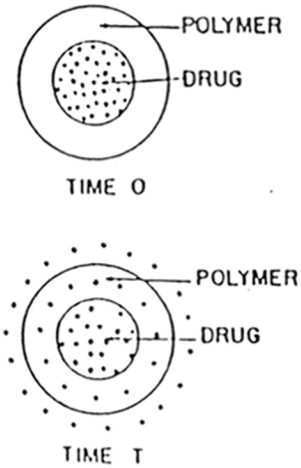
$$\frac{dM_i}{dt} = D_{ip} K A \frac{\Delta C_i}{\delta} \qquad 1.7$$

where K is the solute partition coefficient and A is the membrane area. A constant flux is possible if the transmembrane concentration difference is maintained constant. This can be achieved by maintaining a constant ΔC_i drug concentration in the internal phase by placing excess drug inside the reservoir system to maintain a saturated solution of drug as diffusion progresses. Reservoir systems exhibit nearly zero order or time independent diffusional solute release behaviour.

Most reservoir systems are planar, spherical, or cylindrical. Equation 1.7 may be solved for these systems to yield expressions of the total amount of drug (M_t) released, at



Schematic diagram of a cross section of a cylindrical diffusion-controlled matrix system.



Schematic diagram of a cross section of a cylindrical diffusion-controlled reservoir system.

FIG. 1·3

SCHEMATIC DIAGRAM OF A RESERVIOR AND MATRIX DEVICE.

time t. For membranes (neglecting side effects) Eq. 1.7 gives

$$M_t = \frac{(D_{ip} K A \Delta C_i)}{\delta} \times t \qquad 1.8$$

For cylindrical devices the corresponding expression is

$$M_t = \frac{D_{ip} K A \Delta C_i}{\ln(r_e/r_i)} \times t \qquad 1.9$$

where r_e and r_i are the external and internal radii of the cylinder, respectively, and $A = 2\pi l$ is the area of the cylinder of length l. For spherical reservoir systems

$$M_t = \frac{4 D_{ip} K \Delta C_i}{(r_e - r_i)/r_e r_i} \times t \qquad 1.10$$

Thus, it is seen that the solute release is proportional to time and can be controlled by adjusting the geometry of the device, the thickness of the membrane, the concentration gradient ΔC_i, the thermodynamic characteristics of the system, the partition coefficient, and the structure of the polymer. The partition coefficient is a thermodynamic parameter while the diffusion coefficient is a kinetic parameter.

The partition coefficient is defined as the ratio of the concentration in the polymer to that in the external solvent medium. In order to predict the release rate from a device, it is necessary to determine the drug diffusion coefficient and the partition coefficient experimentally.

Problems associated with the diffusional release from reservoir systems are time-lag and the burst effect. The time lag alters the initial release kinetics. Mathematically, the drug release is given by

$$M_t = \frac{D_{ip} A \Delta C_i}{\delta} \times (t - \delta^2 / 6D_{ip}) \qquad 1.11$$

The burst effect is related to solute accumulation at the membrane-water interface before the device is placed in contact with water. The solute release for systems exhibiting this phenomenon is expressed by

$$M_t = \frac{D_{ip} A C_i}{\delta} \left(t + \frac{\delta^2}{3 D_{ip}} \right) \qquad 1.12$$

Reservoir systems have been used extensively in the medical field. The most popularly used device is the " Occusert " used for treatment of glaucoma.

B) Matrix Systems

In matrix systems the bioactive agent is incorporated in the polymer either in dissolved or in dispersed form. Therefore, the solubility of the solute in the polymer becomes a controlling factor in release from these systems. Mathematical solutions of Eq. 1.7 can be obtained for a variety of initial and boundary conditions which represent appropriate experimental situations. Here we will concentrate on solutions applicable to diffusional solute release from slabs. Similar expressions may be obtained for other geometries.

1) Systems containing Dissolved Drug

In these systems the drug is dissolved in the polymer matrix and solute diffusion can be expressed by Eq. 1.7 . Solutions have been obtained for constant concentration of the solute at the polymer/dissolution interface. For a slab, the fractional solute release, M_t/M_∞ is

$$M_t/M_\infty = 1 - \frac{8}{(2n+1)^2 \pi^2} \exp\left(\frac{- D_{ip} (2n+1)^2 \pi^2}{\delta^2} \times t \right) \qquad 1.13$$

A convenient simplification of this equation for short times has been used quite successfully to predict solute release from most matrix systems. According to Eq. 1.14 , which may be used for $M_t/M_\infty < 0.6$, the fractional release is proportional to the square root of release time,

$$M_t/M_\infty = 4 \left(\frac{D_{ip} t}{\pi \delta^2} \right)^{1/2} \qquad 1.14$$

This shows that it is not possible to release the drug at a constant rate from matrix systems containing dissolved drug.

2) Systems containing dispersed drug.

In such systems the drug is dispersed in the polymer at a concentration c_o higher than its solubility in the polymer c_{is}. The model developed by Higuchi(1961) is a pseudo steady state solution of Eq. 1.7 . For this case

$$M_t/M_\infty = A (D_{ip} C_{is} (2C_o - C_{is}) t)^{1/2} \quad 1.15$$

As is seen from the above equation, the fraction of drug released, is proportional to the square root of time. The release rate decreases with time for devices possessing a simple geometry such as a slab.

Polymers for diffusion controlled systems

The polymers used for fabricating matrix and reservoir type of devices include swollen crosslinked polymeric hydrogels, silicones and ethylene vinyl acetate copolymers. The advantages of using these polymers are their physical and chemical stability, biological and chemical inertness, and processibility. A large number of devices have been prepared from cellullose derivatives, ethylcellulose and hydroxypropylcellulose being the most common materials.

Zero Order Release From Matrix Systems

The approaches to achieve zero order release from matrix systems include change in the geometry, nonuniform drug distribution, use of rate controlling barriers, use of polymer blends, and design of swelling controlled delivery systems. Some of the past efforts in this area are summarized below.

Geometrical modifications have lead to specially designed devices which display increasing drug availability as the distance from the surface increases. Brook and Washkuhn (1977) developed a hollow cylinder with an impermeable wall outside, and the drug was released from the inner core of the cylinder. Rhine et al (1980) fabricated a hemispherical device with an impermeable coating except for a small hemispherical cavity in the centre.This device gave an almost constant release of Progesterone from P (ethylene-vinyl acetate) matrix (Fig. 1.4).

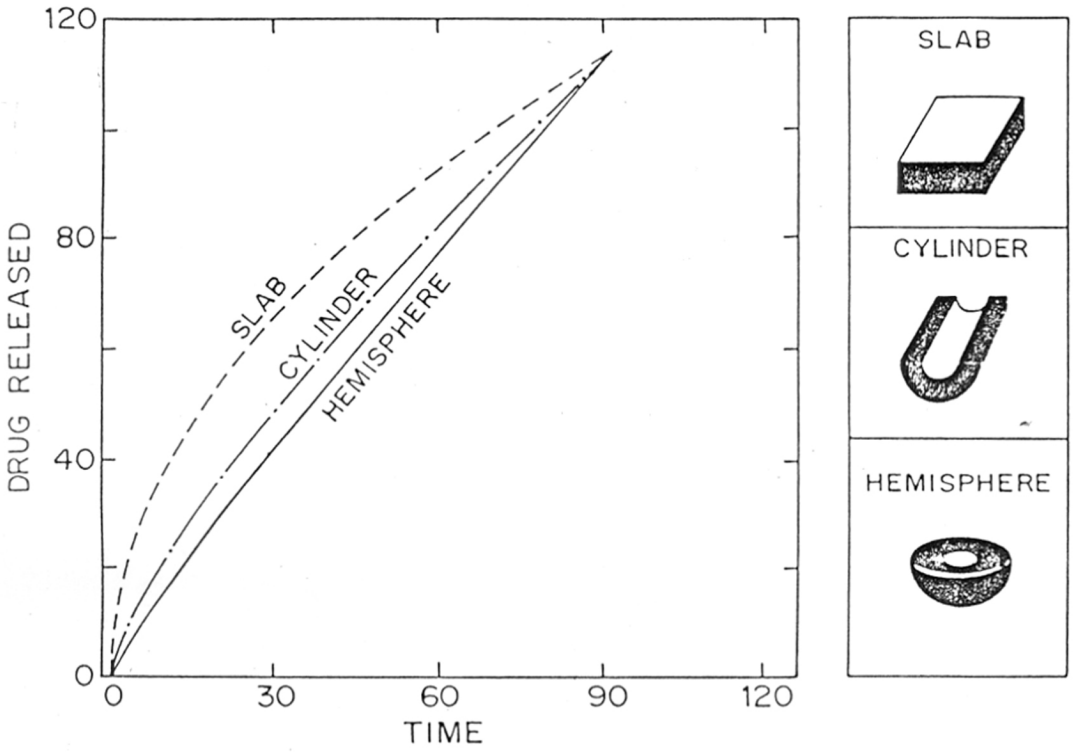


FIGURE 1·4

RELEASE CHARACTERISTICS OF MONOLITHIC DEVICES RELEASING ACTIVE INGREDIENT FROM UNSHADED AREAS

Nelson et al (1987) used a sheet of polycarbonate, with a nonpermeable backing on one side, into which many frustum shaped cells were drilled as shown in Fig. 1.5 . A similar device has been developed by Bachard and McMullen (1988).

Roorda et al (1988) reported zero order release of oxyprenolol hydrochloride from P(2-hydroxy ethyl methacrylate (HEMA)) hydrogels. As active ingredient is released from the outer layer of swollen hydrogel, the outer layers shrink around the still swollen inner core leading to ruptures in the polymer matrix, which resulted in an increase in the release rate of active ingredient.

Lee (1984) utilized the concept of nonuniform drug distribution for obtaining zero order release. A sigmoidal concentration profile of oxeprenolol hydrochloride in P(HEMA) was established by a controlled extraction process in which the polymer containing uniformly distributed drug was exposed to a swelling solvent for a specified time period followed by the freeze drying of the device. Zero order release of oxeprenolol hydrochloride was observed from such devices.

Mueller and Heiber (1982) developed interpenetrating polymer networks (IPN), and gradient -IPN polymers from P(HEMA) beads. The IPN serves as a diffusion barrier and also leads to a distribution gradient in the system. The release behaviour can be varied by changing the thickness of the IPN layer. Fairly constant release rates for oxeprenolol hydrochloride upto 24 hours were observed.

Matrix Reservoir Systems

These systems consist of a core matrix, which is encased in a polymer having lower permeability than the inner core matrix. The outer polymer shell serves as a rate controlling barrier to drug release. Roseman and Higuchi (1970) analyzed the effects of an aqueous boundary layer on the release from matrix devices and obtained a mathematical expression for the release of the active ingredient from such systems. This situation is analogous to the reservoir-matrix devices provided that the parameters assigned to the aqueous boundary layer in Roseman - Higuchi treatment are reassigned to the barrier layer of the reservoir-matrix device.

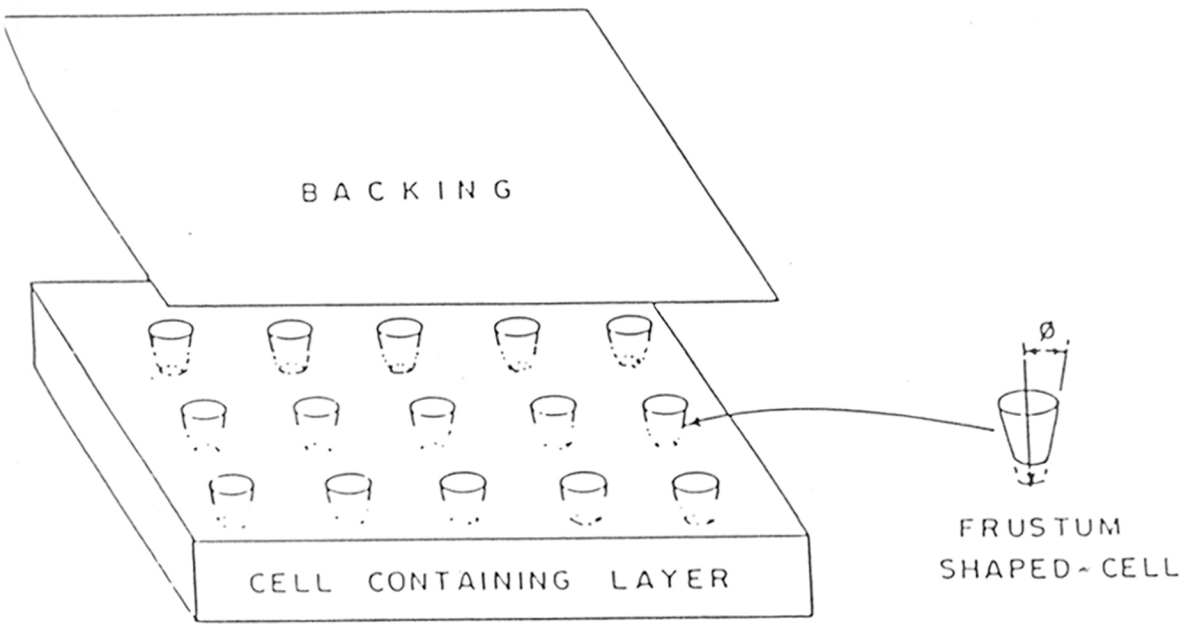


FIGURE 1·5

FRUSTUM – ARRAY DEVICE

To apply this treatment to the release of the drugs from reservoir systems of infinite slab geometry, the rate of transport of drug through a plane of unit area within the depletion zone of the core matrix can be defined as

$$\frac{dM_t}{dt} = \frac{D}{x}(C_s - C'_s) \qquad 1.16$$

where x is the thickness of the zone of depletion of the matrix, C_s is the saturation solubility of the drug in the polymer matrix, and C'_s is the concentration at the boundary between the matrix and barrier layer. The rate of transport across the barrier layer can be defined as

$$\frac{dM_t}{dt} = \frac{D_s}{\delta_D}(C'_b - C_b) \qquad 1.17$$

where D_s is the diffusion coefficient in the barrier layer, δ_D denotes the thickness and C'_b and C_b are the drug concentrations at the inner and outer edges of the barrier layer. It was shown that provided

$$\frac{\delta_m}{\delta_D} << \left(\frac{2}{k}\right)\frac{D_m}{D_s} \qquad 1.18$$

then,

$$\frac{dQ}{dt} = \frac{K C_s D_s}{\delta_D} \qquad 1.19$$

which demonstrates that under barrier controlled conditions, the release rate from a reservoir dispersed matrix system is constant with time.

Although reservoir matrix devices are more difficult to prepare than either reservoir or matrix devices alone, they offer advantages under certain conditions. Thus, in the case of hydrogels which are of low mechanical strength, a reservoir matrix device can be prepared to achieve a constant release rate of the drug. A review of the past efforts in making reservoir dispersed matrix systems is given below.

Lee et al (1980) developed hydrogels with rate controlling surface barriers, based on P(HEMA) or a copolymer of P(HEMA) and methoxy ethoxyethyl methacrylate. The surface barriers were formed by soaking the above monolithic devices in an ethanolic solution of ethylene glycol dimethacrylate (EGDMA), followed by exposure to UV light to create a crosslinked zone at the surface. The crosslinked zone has a lower permeability to drug than the inner core and hence serves as a rate controlling barrier, leading to zero order release of progesterone. The release rate of progesterone was found to decrease with increased soaking time in the crosslinker (EGDMA) solution. Colombo et al (1984) have reported similar results.

Cardinal et al (1980) studied the effect of P(HEMA) as a barrier membrane on the matrix based on P(methoxy ethyl ethyl methacrylate (MEEMA)) or P(HEMA-MEEMA). It was shown that a constant release rate of progesterone upto twenty days could be achieved, provided that the permeability of the barrier material was lower than that of the matrix. Anderson et al (1979) studied the release of tetracyline from trilaminated discs. The drug dispersed matrix core was surrounded by a hydrophobic outer layer, which served as the rate limiting membrane. Similar results were reported by Borodkin and Tucker (1975).

1.2.2 Chemically controlled systems

The rate of drug release in these systems is controlled by the chemical reaction occurring in the polymer matrix. These systems are subdivided into two categories.

1) Bioerodible systems and 2) Pendant chain systems

Bioerodible systems have been extensively reviewed in the literature (Heller 1984, Chasin and Langer 1990).

The literature on the synthesis and release of pendant chain systems has been reviewed by Harris and Arah (1980), Kim et al (1980), and Somashekharan and Subramaniam (1980). Shah et al (1990[a]) have investigated the various cases in the model proposed by Tani et al (1981).

1.2.3 Swelling controlled systems

In swelling controlled systems, the drug is uniformly dispersed in a glassy polymer matrix. When such a matrix is placed in a suitable medium, penetrant molecules begin to diffuse into the glassy region and the matrix swells. For designing a swelling controlled system, the knowledge of penetrant uptake as well as diffusional transport in glassy and rubbery polymers is necessary.

Diffusional transport in polymers

The classical simple limiting case of diffusion is described by Ficks law

$$D\nabla^2 c = \frac{\partial c}{\partial t} \qquad 1.20$$

where D is the diffusion coefficient assumed to be constant. However, the diffusion of small molecules into or through a polymer often follows a more complicated pattern. Even in rubbery polymers, the above equation does not hold since the diffusion coefficient normally increases with solvent concentration and hence requires the use of the generalized Ficks equation

$$\nabla [D(c)\nabla c] = \frac{\partial c}{\partial t} \qquad 1.21$$

Anomalous diffusion effects are observed in the case of glassy polymers, which cannot be explained in terms of a concentration-dependent diffusion coefficient.

Diffusional transport in polymers close to the glass transition temperature is complicated by the relaxation effects. Frisch (1980) concluded that the transport characteristics below glass transition temperature also depend on whether the penetrant is above or below the critical temperature. Dual sorption behaviour is observed for the penetrants which are effectively sorbed on the microvoids present in the glassy polymers. For penetrants below their critical temperature, anomalous diffusion behaviour is observed, which includes sigmoid sorption curves, case II and super-case II transport etc. Anomalies in sorption around glass transition temperature have been reviewed by Vrentas and Duda (1984).

Diverse diffusional characteristics in amorphous polymer-solvent system have been identified by traversing a wide range of temperature , concentration and polymer molecular weight. Alfrey (1965) and Vrentas (1975) depicted different types of diffusional transport of penetrants in high polymers by utilizing a temperature-penetrant concentration diagram. It was shown that the various regimes on this diagram could be distinguished by the ratio of the two time scales, relaxation time for polymer system and the diffusion time.

The characteristic time for penetrant diffusion is given by

$$\Theta = \frac{L^2}{D} \qquad 1.22$$

where L denotes the characteristic diffusional length and D denotes the diffusion coefficient of the penetrant in the polymer.

The characteristic relaxation time may be expressed as a mean relaxation time using (Vrentas et al 1975)

$$\lambda = \frac{\int_0^\infty s\, G(s)\, ds}{\int_0^\infty G(s)\, ds} \qquad 1.23$$

where G(s) is the shear relaxation modulus. The shear relaxation modulus can be related to the tensile relaxation modulus by using equation

$$E = \frac{9GK'}{G + 3K'} \qquad 1.24$$

where K' denotes bulk relaxation modulus. In many cases K' is greater than the shear modulus by two orders of magnitude or more (Ferry 1970). In this case the above equation becomes

$$E(t) = 3\, G(t) \qquad 1.25$$

This equation can then be used in conjunction with data obtained from simple tensile relaxation experiments to determine the characteristic relaxation time.

The dimensionless parameter diffusional Deborah number, which is used to describe the diffusional characteristics of the viscoelastic fluid is defined as

$$D_{(DEB)} = \lambda / \Theta \qquad 1.26$$

As diffusional Deborah number is a function of temperature and penetrant concentration, its magnitude changes during the diffusion of the penetrant. If the change in the penetrant concentration is small, it may be possible to describe the system by a single value of $D_{(DEB)}$. For the case where the concentration change is large , the value of $D_{(DEB)}$ may be obtained at both initial and final stage and the magnitude and the difference between the two values can be used to characterize the behaviour of the binary system. The regimes of diffusion defined by the penetrant concentration and the phase state of the polymer are shown in Fig (1.6). The regions of Fickian and nonFickian diffusion of the penetrant in the polymer defined by the limiting values of $D_{(DEB)}$ are also seen in the Fig. 1.6 (Vrentas 1975).

When the polymer is far below the glass transition temperature and the penetrant activity is very low, the time scales associated with the relaxation process are very large. One can, therefore, assume that the penetrant diffuses in a medium which is structurally invariant. Although the medium is not a purely viscous fluid, the phenomena can be analyzed using the classical diffusion theory. Diffusion in this regime is characterized by the Fickian behaviour. Since the relaxation times are large as compared to the diffusion time, the regime is characterized by $[D_{DEB}] >> 1.0$.

At the other extreme when the penetrant activity is high and polymer system is at a temperature higher than its glass transition temperature, the molecular motions are very rapid, the changes in the molecular structure can be considered to take place instantaneously as compared to the time scales associated with the diffusion of the penetrant molecule. The diffusional characteristics observed can be explained on the basis of Fickian diffusion behaviour and a concentration dependent diffusion coefficient. The regime is characterized by $[D_{DEB}] << 1.0$.

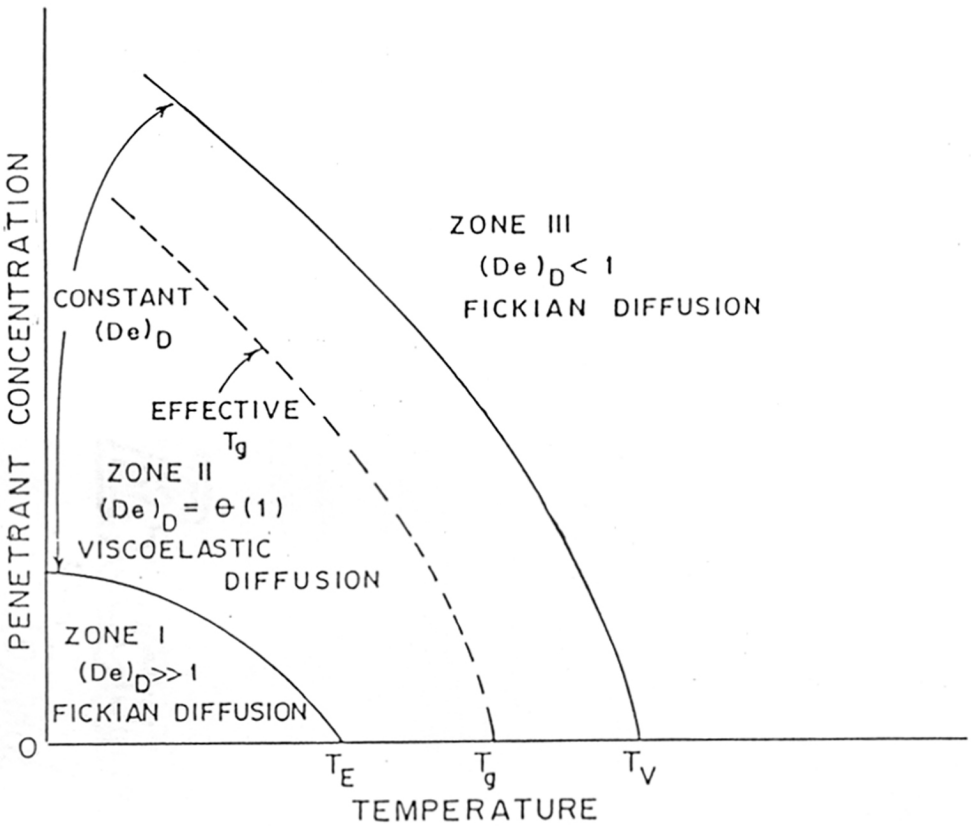


FIGURE 1·6

REGIMES OF DIFFUSIONAL TRANSPORT

In the intermediate range , wherein the penetrant activity is reasonably high and the polymer system is close to the glass transition temperature, the time scales associated with the polymer relaxation are comparable to those associated with diffusion. Characteristics of penetrant transport in terms of the phase states of the polymer and the critical temperature of the penetrant are summarized in Table 1.2 . Thus when the penetrant diffuses in the polymer, the polymer chains do not attain the equilibrium conformation instantaneously but over a period of time. Diffusion thus takes place in a viscoelastic medium. It is in this regime that a wide range of deviations are observed from the Fickian behaviour depending on the penetrant activity.Typical amongst these are a) two stage sorption and b) Case II transport

Case II transport

We have seen that the anomalous transport behaviour results from the coupling of diffusion and relaxation processes. An interesting case results when the transport process is relaxation controlled. The phenomenon was called Case II transport by Alfrey et al (1966). Case II transport depends upon

a) the choice of the penetrant

b) its size and shape

c) structural features of the polymer matrix and

d) experimental conditions

The distinctive features of Case II transport are as follows

1) The rate of sorption is linear with respect to time and not square root of time as is in the case of Fickian sorption.

2) As the penetrant is sorbed, a sharp boundary separates a glassy region ahead of the boundary from the swollen polymer behind it.

3) The swollen polymer is in its equilibrium swollen state.

4) The velocity of the boundary separating the glassy and the swollen polymer is constant and is determined by the kinetics of Case II transport.

TABLE 1.2

Transport in Amorphous Polymers

$T > T_c$	$T < T_c$
Fickian diffusion, single mode sorption	
Ideal Fickian diffusion concentration independent diffusion coefficient.	Concentration dependent diffusion coefficient explained by free volume theories.
$T > T_g$ Henry's law obeyed, constant energy of activation.	Apparent energy of activation dependent on penetrant concentration and temperature.
Dual mode sorption	
$T < T_g$ Energy of shows breaks near T_g.	Non - Fickian and anomalous diffusion. Case II and super case II transport.

5) The velocity of the advancing front is sensitive to the thermal history of the specimen. It decreases with temperature as well as the penetrant activity.

6) By appropriate choice of the solvent , it is possible to superpose the characteristics of Case II as well as the Fickian transport eg. during sorption of methanol-acetone mixture in polystyrene, a Fickian front of methanol is followed by an acetone front moving at a constant velocity.

7) Specimen size effects play an important role in Case II transport .

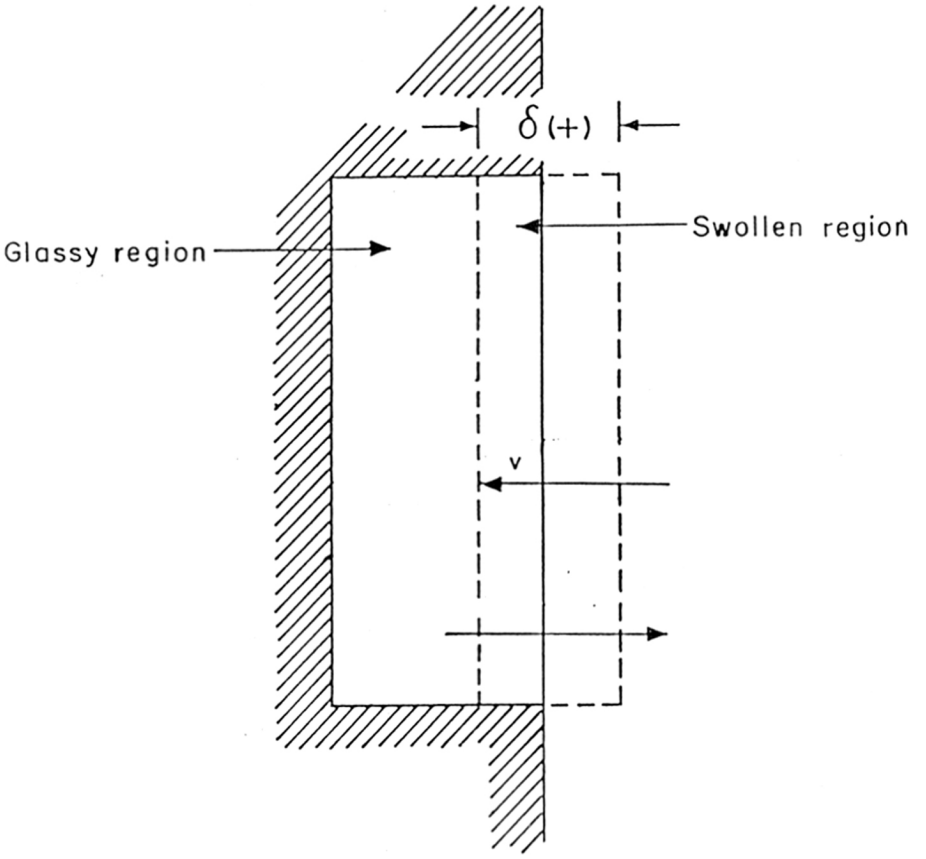
Following approaches have been proposed in the literature to elucidate Case II transport in polymers, viz., diffusion convection model (Frisch 1969), diffusion in glassy polymers with discontinuous swelling (Peterlin 1965), Case II transport as a solution of the diffusion equation (Peterlin 1977), models of Case II transport based on swelling kinetics (Sarti 1978), diffusion relaxation coupling model (Joshi and Astarita 1979), deformation model of Case II transport (Thomas and Windle 1981).

Kinetics of swelling controlled systems

In swelling controlled systems , the release kinetics is controlled by the rate of swelling of the glassy polymer. The glassy polymer matrix contains a uniformly dispersed active ingredient. When such a system is brought in contact with a penetrant, the matrix swells and controls the diffusion of solute through the continuously swelling system. This is shown schematically in Fig.1.7.

The dynamic swelling phenomenon leads to considerable volume expansion of the matrix. Initially, the surface of the polymer comes in contact with the penetrant and begins to swell whereas the inner core of the matrix remains glassy. There is a sharp boundary separating the inner glassy core from the swollen outer shell. Two fronts (interfaces) are established : a front separating the glassy core from the rubbery shell (swelling interface) which moves towards the glassy core with a velocity v; and a front separating the rubbery state from the pure penetrant (polymer interface), which moves outwards.

Hopfenberg and Hsu (1981) demonstrated that if the diffusion of the active ingredient from the relaxation boundary is rapid as compared to the rate of the movement of



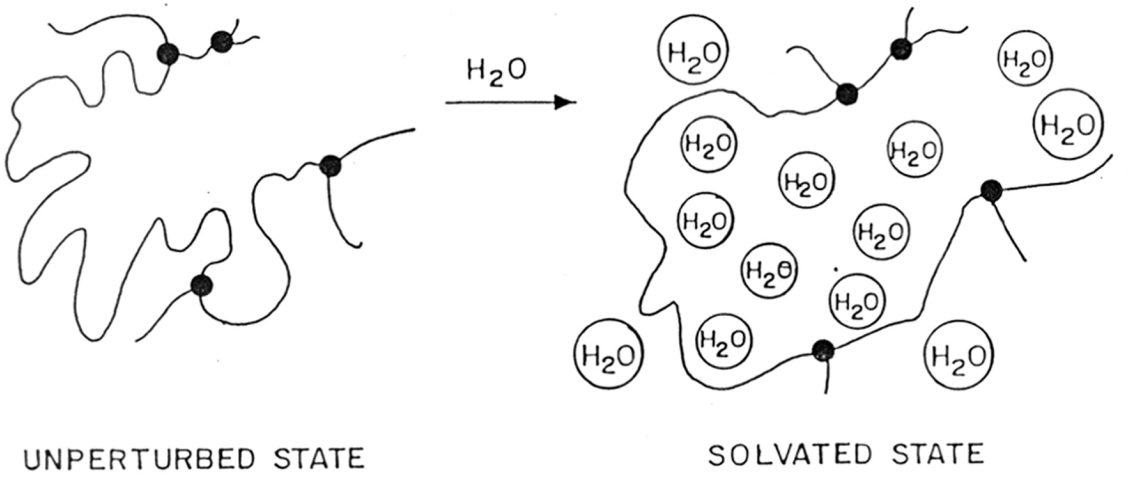


FIGURE 1·7

SWELLING CONTROLLED DELIVERY SYSTEM

the boundary, the elution of the solute would take place at a constant rate. Thus, the release of Sudan Red IV dye from polystyrene in n-hexane was found to follow zero order release kinetics.

Criteria for zero order release

Hopfenberg et al (1981) proposed the concept of a dimensionless parameter alpha, as a criterion to predict the mechanism of release. It is a measure of the relative magnitude of the penetrant velocity and diffusional transport of the active ingredient and is defined by

$$\alpha = \frac{D}{v\,\delta(t)} \qquad 1.27$$

where v is the polymer swelling rate cm/sec and $D/\delta(t)$ the diffusional conductance, cm/sec.

For very low values of the diffusional conductance or for high values of swelling rate , α is significantly lower and the release kinetics is diffusion controlled. In the early stages of polymer relaxation $\delta(t)$ being smaller , α would have a high value. In such a case, diffusive conductance will be much higher than swelling rate and zero order release can result.

Peppas and Franson (1983) introduced a new dimensionless number, viz., the swelling interface number, S_w as a criterion for the prediction of zero order release. It is the reciprocal of the dimensionless parameter alpha proposed by Hopfenberg and is defined as

$$S_w = \frac{v\,\delta(t)}{D_s} \qquad 1.28$$

where v denotes the velocity of the penetrating front, D_s the diffusion coefficient of the active ingredient and $\delta(t)$ the thickness of the swollen layer.

It was shown that the necessary and sufficient condition for zero order release is that $S_w << 1$. An equilibrium swelling interface number was introduced , which was

expressed in terms of macromolecular parameters that can be theoretically calculated or experimentally measured.

$$S_{we} = \frac{v_{max}\,\delta_{max}}{D_s} \qquad 1.29$$

where v_{max} denotes the maximum velocity of the penetration front and δ_{max} denotes the equilibrium thickness of the device. Based on the extrapolation of the plot of Sw_e vs. n , where n is the release index, it was predicted that zero order release will result for Sw_e << 1.0. However, this criterion could not explain the findings of Davidson and Peppas (1986) who demonstrated zero order release for theophylline from such devices even for $Sw_e \approx 1.0$.

Lee (1987) developed a mathematical model for the release of an active ingredient from swellable hydrogels. This model envisages a time dependent diffusion coefficient for the active ingredient to account for the role of molecular relaxations in the diffusion process. It was predicted that for the values of Deborah number for release (De_R) of the order of unity, $0.1<(De_R)< 10$, zero order release would be followed. The Deborah number for release was defined as

$$De_R = \frac{D_s}{kl^2} \qquad 1.30$$

where Ds denotes the diffusivity of the active ingredient from the swollen hydrogel, k denotes the reciprocal relaxation time and l is the half thickness of the device. It differs from the Deborah number proposed by Vrentas et al (1975), which is defined as

$$De_D = \frac{D}{kl^2} \qquad 1.31$$

where D refers to the diffusivity of the solvent molecule penetrating the polymer.

Vyavahare et al (1990[a]) introduced the dimensionless parameter $(\sqrt{D_s t})/vt$ as a criterion to predict zero order release. $(\sqrt{D_s t})$ defines a characteristic length associated with the diffusion of the active ingredient. The thickness of the swollen layer (vt) would

be a function of time. The ratio $(\sqrt{D_s}t)/vt$ would then define the relative rates of diffusion of the active ingredient and the swelling of the polymer. Obviously, the value of this parameter should be greater than unity so that the release of the active ingredient is penetration controlled. It was found that for $(\sqrt{D_s}t)/vt > 1.3$ zero order release is possible .

Swelling controlled systems : State of the art

Extensive work has been carried out in the area of swelling controlled systems for drug delivery. Some of the reported work is discussed below.

Hopfenberg and Hsu (1978) were the first to demonstrate zero order release based on such systems. They studied the release of Sudan Red IV dye from polystyrene film. In another study, Hopfenberg et al (1981) investigated sorption of water and release kinetics of sodium chloride and malachite green from P-(ethylene-vinyl alcohol) of varying copolymer composition. The release of sodium chloride followed zero order kinetics but the release of the bulkier molecule malachite green followed Fickian desorption pattern.

Gaeta et al (1982) carried out the release of lithium chloride (LiCl) from P(ethylene-vinyl alcohol) copolymer. Initially the rate of release followed the constant rate of water sorption. However, at longer times the release rate lagged behind the water uptake, exhibiting Fickian release.

Korsemeyer and Peppas (1981) used glassy as well as swollen matrices of polyvinyl alcohol crosslinked with gluteraldehyde to release theophylline. Release from swollen polymers followed Fickian behaviour (n = 0.46-0.50), whereas for the glassy polymer the release index increased from 0.47 to 0.76. It was observed that an increase in the degree of crosslinking led to slower release rates. A similar effect was observed when crosslinked polyvinyl alcohol matrices were used. At lower crosslink densities the release index increased upto 0.76.(Korsemeyer and Peppas 1981)[a] . Lee (1983) studied the water uptake and concomitant release of thiamine hydrochloride from glassy P(HEMA) beads. It was shown that the drug release was dependent on the drug loading. Horbett et al (1983, 1984) developed glucose sensitive membranes for the release of insulin. Glucose

oxidase was immobilized in a crosslinked polymer prepared from dimethlyamino ethyl methacrylate, 2-hydroxyethyl methacrylate and tetramethylene glycol dimethacrylate. When glucose diffuses into the membrane, it is oxidized by glucose oxidase to gluconic acid which protonates the amino groups present in the polymer and increases the porosity of the membrane, due to increase in the swelling of the membrane. The increased porosity allows insulin to diffuse through the membrane. Similar studies were carried out by Kost et al (1985), and Kaetsu (1979).

Ishihara et al (1984) developed a polymer membrane which released methyl orange at a rate controlled by the concentration in the external medium. The formation of a charge transfer complex between the nitro group on the polymer and the amino group in the medium leads to enhanced swelling and hence an increase in the rate of release of the drug.

Korsemeyer and Peppas (1984)[b] reported the release of theophylline from the copolymers of (2-hydroxyethyl methacrylate -N Vinyl pyrrolidone) viz., P (HEMA-NVP). The release behaviour was found to vary with the copolymer composition and sample thickness.

Peppas and Franson (1983) carried out the release of theophylline from the copolymers of (HEMA - methyl methacrylate) viz., P(HEMA-MMA) using ethylene glycol dimethacrylate (EGDMA) as a crosslinker, to study the effect of change in the hydrophilicity of polymer matrix.

Davidson and Peppas (1986)[a] investigated the release of theophylline from P(HEMA-MMA) copolymers of varying HEMA content. It was shown that both swelling interface number and diffusional Deborah number are necessary to predict the release behaviour from swellable systems.

Sigel et al (1988) studied the release of caffeine from P(methyl methacrylate - diamino ethylmethacrylate) viz., P(MMA-DMA) copolymer as a function of pH. The enhanced swelling during the course of release at pH 3 and 5 led to near zero order kinetics, whereas no caffeine was released at neutral pH. The release profiles at pH 3 and 5

superposed when plotted against the normalized swelling ratio on a master curve.

Similarly, Peppas and Peppas(1989) demonstrated pH dependent release from the copolymers of 2 (HEMA) and methacrylic acid (MAA) and maleic anhydride (MAH) using EGDMA as a crosslinking agent.

Chicq and Peppas (1986) studied the transport of water and homologous alcohols and subsequent release of theophylline from semicrystalline P(ethylene - vinyl alcohol) copolymers. It was observed that the release is governed by the porosity and the degree of crystallinity of the polymer matrix.

Korsemeyer et al (1986)[a,b] developed a mathematical model to describe the diffusion of the penetrant and the solute in a swellable polymer slab. The model described the concept of concentration dependent diffusion coefficient and volume change during penetrant sorption to predict a wide range of release profiles.

Lustig and Peppas (1987) developed a model to describe penetrant transport and the solute release from continuously swelling polymers to explain the changes in the shape of the matrix, penetrant sorption and the solute release.

Ritger and Peppas (1987) introduced the exponential relation $M_t/M_\infty = Kt^n$ to describe the Fickian and nonFickian release behaviour of swelling controlled systems. It was shown that the equation can adequately explain the release of solutes from slabs, cylinders and spheres. Fickian behaviour was observed for the value of release exponent (n) between 0.43 to 0.5.

The model proposed by Klier and Peppas (1988) indicates that the penetrant and solute transport are dependent on free volume parameters and the velocity of glassy/rubbery front. It was shown that the linear penetrant uptake and diffusivity of penetrant concentration may provide constant release rate.

1.3.0 Hydrogels

Hydrogels are polymers characterized by hydrophilicity and insolubility in water. They swell in water, but preserve their shape. The hydrophilicity is due to the presence of

hydrophilic groups such as -OH, -COOH, -CONH2, -CONH, -SO3H etc. The insolubility and stability of shape are due to the presence of a 3-dimensional network.

Hydrogels comprise both natural as well as synthetic materials such as gelatin , cuprophan, crosslinked dextrans and crosslinked collagens. A number of biomedical applications for hydrogels have been reported in the literature. Synthetic polymers are used in prosthetic materials, soft lenses , and as membranes for controlled drug release. The wide range of biomedical applications for hydrogels are attributed to their 1) biocompatibility, 2) ability to be fabricated into a wide range of morphologies, 3) ease of tailoring physical properties for a particular application, and 4) their permeability to small molecules.

The greatest advantage hydrogels offer is their biocompatibility with the living tissues. They resemble living tissues in their physical properties more than any other class of synthetic materials. The low interfacial tension between a hydrogel surface and an aqueous solution, reduces the tendency of the proteins in the body fluids to adsorb onto hydrogels and to unfold on desorption (Hoffman 1974). The most remarkable property of hydrogels is that they can be tailormade for a wide range of applications. Hydrogels can often be prepared in a variety of forms such as porous sponges, non porous gels, optically transparent films, foams, sheets, beads, powders, tubes and blocks.

A brief outline of the various classes of synthetic hydrogels is given below :

1) Based on methacrylic and acrylic esters

To form a gel, a monomer must be copolymerized with a crosslinking agent, most often ethylene glycol dimethacrylate (EGDMA) is used. Other crosslinkers used are 3-Oxapentamethylene dimethacrylate and 3,6,9-trioxaundecamethylene (TEGDMA).

2) Based on hydroxyalkyl methacrylates or acrylates

Most widely used is poly (2-hydroxyethyl methacrylate) i.e. P(HEMA). It is highly stable to hydrolysis.

3) Copolymers of hydroxyalkyl methacrylates with enhanced hydrophilicity.

Copolymers of HEMA and Methoxy ethoxy ethyl methacrylate (MEEMA) are used.

4) Copolymers with ionogenic comonomers

HEMA is copolymerized with methacrylic acid (MAA) or acrylic acid (AA), to introduce anionic charge in the Poly (HEMA) chain, which are weakly acidic in nature.

5) Copolymers with low hydrophilicity and superior mechanical properties.

Copolymers of HEMA with hydrophobic monomers such as ethyl acrylate/butyl acrylate (35-36% wt.) are used.

6) Copolymers with hydrophilic and hydrophobic constituents eg. Poly-(2-HEMA-co-MMA-co-N-vinyl pyrolidone-co-DVB).

7) Copolymers incorporating presynthesized macromers or oligomers.

The most important property of hydrogels is their ability to imbibe water. The resulting osmotic swelling is opposed by the elastic contractility of the stretched hydrogel network. The net force is the swelling pressure. If the osmotic pressure of the solution in contact with the gel is increased by the presence of solute , the swelling pressure increases and swelling decreases. Mathematically,

$$P_{sw} = k \times c^{n} \qquad 1.32$$

i.e. swelling pressure increases with the concentration of polymer. Swelling of a hydrogel can be expressed in weight, volume and length units. The weight fraction of water W_f in a hydrogel is

$$W_f = \frac{\text{(Wet weight - Dry weight)}}{\text{(Wet weight)}} \qquad 1.33$$

The weight % of water $W_p = W_f \times 100$

Swelling related to the dry state is called hydration. Thus, percent hydration, water regain or swelling index is expressed as

$$H_p = \frac{100 \times \text{(Wet weight - Dry weight)}}{\text{(Dry weight)}} \qquad 1.34$$

The degree of swelling is expressed as

$$D_{sw} = \frac{\text{(Wet weight)}}{\text{(Dry weight)}} \qquad 1.35$$

The swelling ratio is defined as

$$R_{sw} = D_{sw}\frac{d_o}{d_{sw}} = \frac{\text{Wet volume}}{\text{Dry volume}} \qquad 1.36$$

where d_o is the density of the dry gel, and d_{sw} is the density of the swollen gel.

Hydrophilicity can be increased by using ionic monomers such as, N-vinyl pyrolidone (NVP), dihydroxy propyl methacrylate (DHPMA), and methoxyethoxyethyl methacrylate (MEEMA). Ionogenic or charged gels form a special group, with swelling and strength properties dependent on the pH of the environment. Copolymers of lower hydrophilicity can be synthesized from hydrophobic monomers such as glycidyl methacrylate (GMA), methyl methacrylate (MMA) and methoxy ethyl methacrylate (MEMA) etc. The monomers used in synthesis of hydrogels are listed in Table 1.3 .

Hydrogels have been used principally in the field of medicine. They are used in diagnostic devices (eg. catheters) therapeutic devices (hemodialysis membranes, blood oxygenators, soft contact lenses) and implants for short term or long term applications (artificial corneas, intraocular lenses). Membranes made from polyelectrolyte complexes exhibit remarkable transport properties in dialysis and in pressure driven processes. They also show remarkable promise in the recovery of toxic metal oxyions and cations.

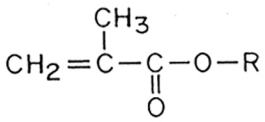
1.4.0 Volume phase transitions in polymers

A gel is a crosslinked polymer which has imbibed a liquid medium. The network prevents the gel from flowing away. Drastic changes in the state of the gel can be brought about by small changes in the external conditions. When temperature is lowered, polymer network loses its elasticity and therefore becomes increasingly compressible. The gel can shrink/swell several folds when the temperature is varied. Under appropriate conditions, the swelling or shrinking is discontinuous, so that an infinitesimally small change in temperature can cause a large change in volume. It can also be brought about by altering the composition, the pH or the ionic strength of the solvent in which the gel is immersed, or by imposing an electric field across the gel.

TABLE 1·3 : Monomers Used in Hydrogels

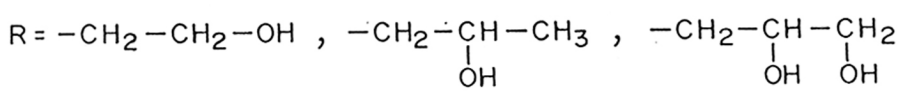
A) Neutral

General Formula

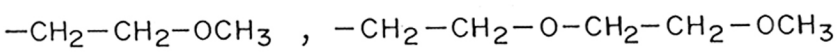


i) Hydroxyalkyl methacrylates

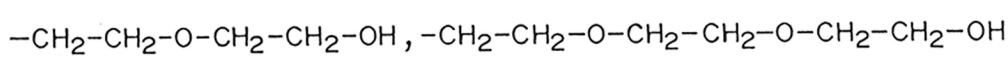
Where



HEMA HPMA GLYMA

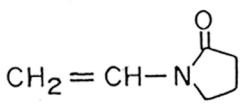


MEMA MEEMA

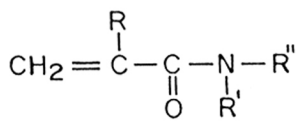


HEEMA HDEEMA

ii) N-vinyl pyrrolidone



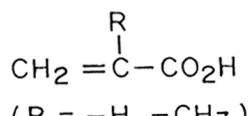
iii) Acrylamide derivatives



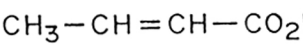
Where (R = −H, −CH3) (−R', −R'' = −H, −CH3, −C2H5, −CH2−CH(OH)−CH3) etc.

B) Acidic or Anionic Hydrogels

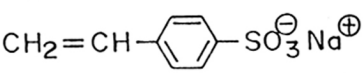
i) Acrylic acid derivatives



ii) Crotonic acid

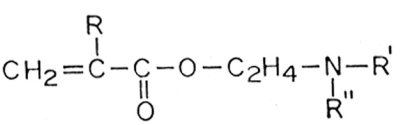


iii) Sodium styrene sulfonate



C) Basic or Cationic Hydrogels

i) Aminoethyl methacrylate derivatives



(R, R', R'' = −H, −CH3, −C4H9)

ii) Vinyl pyridine

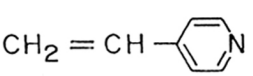
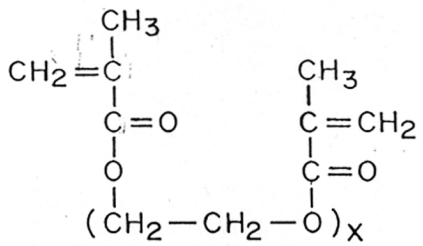


TABLE 1·3 (Continued)

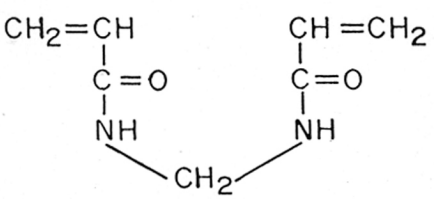
D) Typical Crosslinkers Used in Hydrogels

i) Ethyleneglycol dimethacrylate derivatives

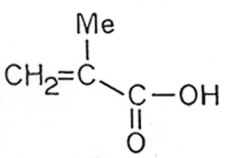


Where X = 1 EGDMA , X = 2 DEGDMA , X = 3 TEGDMA

ii) Methylene bis acrylamide



E) Typical Gel Modifiers Used in Hydrogels



MAA

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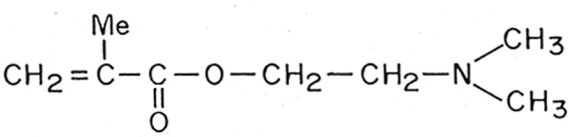
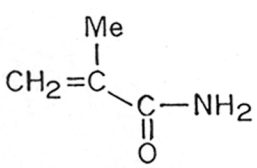


DMAEMA



MAM

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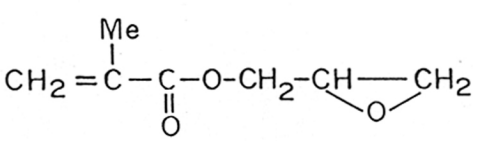
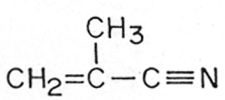


GMA



MAN

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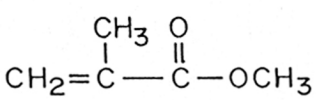


MMA

The most significant property of the gels relevant to the scope of this work is the volume phase transition of polymer gels. Tanaka et al (1978) have reported the swelling behaviour of swollen crosslinked polyacrylamide gels in acetone-water mixtures of varying composition. When such a gel is immersed in acetone-water mixtures of increasing acetone concentration, the gel shrinks progressively. A plot of swelling ratio (q) vs. solvent composition for hydrolyzed polyacrylamide is shown in Fig 1.8 . As the degree of hydrolysis increases the swelling curve initially continuous , shows a point of inflection at about 40 % acetone concentration. Beyond this point, the swelling curve becomes increasingly sensitive to acetone concentration. Eventually a discontinuity is observed in the swelling curve, the swelling ratio at transition increases with further increase in the degree of hydrolysis of polyacrylamide. The volume changes take place over a period of time much longer than that required for the solvent mixtures to diffuse through the matrix. Similarly, the discontinuity in the swelling behaviour has been observed by varying the temperature (Fig 1.8). Further, the shrinking of a hydrolyzed polacrylamide gel on exposure to a high concentration of acetone is fully reversible.

The total pressure acting on a gel is the sum of three components :

1. the rubber elasticity
2. the polymer-polymer affinity and
3. the hydrogen ion concentration.

It is the changing balance between the three components that gives rise to phase transitions. As a result of Brownian motion , a freely jointed chain assumes a equilibrium end to end distance. The thermal motion gives rise to a compressive force when the end to end distance is greater than the equilibrium distance. Alternatively , if the end to end distance is smaller than the equilibrium value, the chain tends to expand. The magnitude of this force is proportional to temperature . The polymer -polymer affinity creates a negative pressure which tends to collapse the gel. The magnitude of this pressure increases as the solvent becomes poorer. The hydrogen ion pressure arises due to the re-

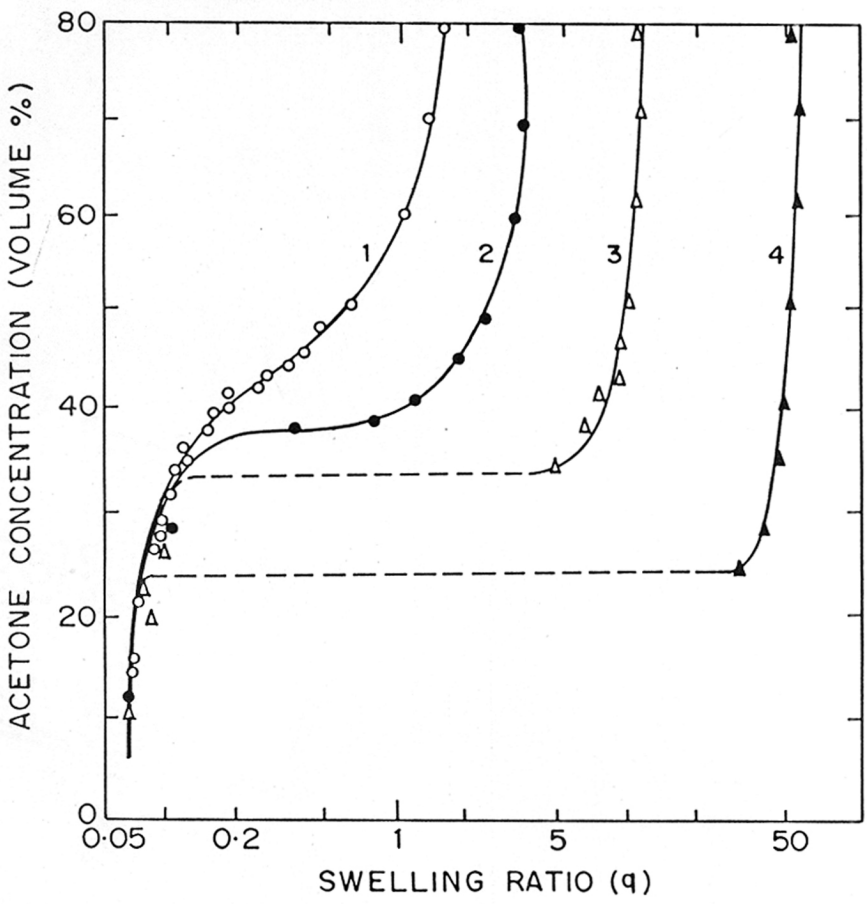


FIGURE 1·8

SOLVENT DEPENDENT VOLUME PHASE TRANSITIONS FOR PAM GELS IN ACETONE / WATER MIXTURE

lease of hydrogen ions from the polyelectrolyte into the gel. At constant volume , the magnitude of this pressure is directly proportional to temperature.

Thus, in principle, we can construct a plot of osmotic pressure vs volume at constant temperature or solvent composition. In practice the swollen polymer always attains an equilibrium volume so that its total osmotic pressure is always zero. If the pressure is positive , it takes up the fluid and swells. If the pressure is negative , it loses the fluid and collapses. The swelling or shrinking continues until equilibrium is reached, when the osmotic pressure is zero.

The continuous variation of swelling ratio with temperature or solvent composition and the existence of the critical point can be explained on the basis of variation of the three components of osmotic pressure with temperature and solvent composition. The region of negative compressibility in the p-v isotherm has been attributed to the forces arising from the polymer - polymer affinity. The contribution to the osmotic pressure due to the rubber elasticity and hydrogen pressure are positive above the critical point. However as the gel expands the magnitude of the contribution decreases. The negative pressure due to the polymer - polymer affinity also decreases with the gel expansion, but it is slower than the decrease in the other two components. Hence the total osmotic pressure decreases with increasing volume. Below the critical temperature, the decrease in osmotic pressure due to polymer - polymer affinity is faster than the other two components. This leads to increase in the net osmotic pressure with increase in the volume. However the local minimum is not reached in practice. Instead, when the Maxwell line is reached, two domains, a swollen one and a shrunken one are formed. Unlike in the gas-liquid transition it is more convenient to discuss the swelling curves, which describe the gel volume at which the total osmotic pressure is zero. It thus defines the intercepts of all isotherms on the zero pressure axis. When the transition temperature is greater than the critical temperature, the volume change is continuous. When it becomes equal to the critical temperature, an inflection is reached. As the temperature is further lowered, the

width of the Maxwell line increases and the swelling curve exhibits discontinuous transitions.

The phenomenon of volume phase transitions has been used imaginatively by a number of workers for a variety of applications. Thermally reversible hydrogels i.e. temperature dependent volume phase transitions have been reported in the literature for controlled drug delivery systems. Thermally reversible hydrogels find applications in the area of biotechnology. In biotechnology a large amount of dilute solutions have to be handled in order to get purified products. The use of hydrogels for the concentration and separation of macromolecules has been reported in the past by Vartak et al (1983). Badiger et al (1987) discussed the strategies for semicontinuous and continuous operations as well as regeneration for the packed bed continuous operations. The use of gel beads exhibiting LCST behaviour as size selective extracting solvents was discussed by Freitas and Cussler (1987) and Gehrke et al (1986). Affinity bioseparation process in which the biomolecule is bound to polymer by suitable ligand have been reported by Cole et al (1987). Dong and Hoffman (1986) utilized the thermally reversible poly(N-isopropyl acrylamide-co-acrylamide) hydrogels for the on/off triggered release of the enzyme Aspariginase. It was found that above the LCST the enzyme lost its activity and below LCST it maintained its activity reversibly. Hoffman et al (1987) extended the use of these polymers for the on/off release of active ingredients.

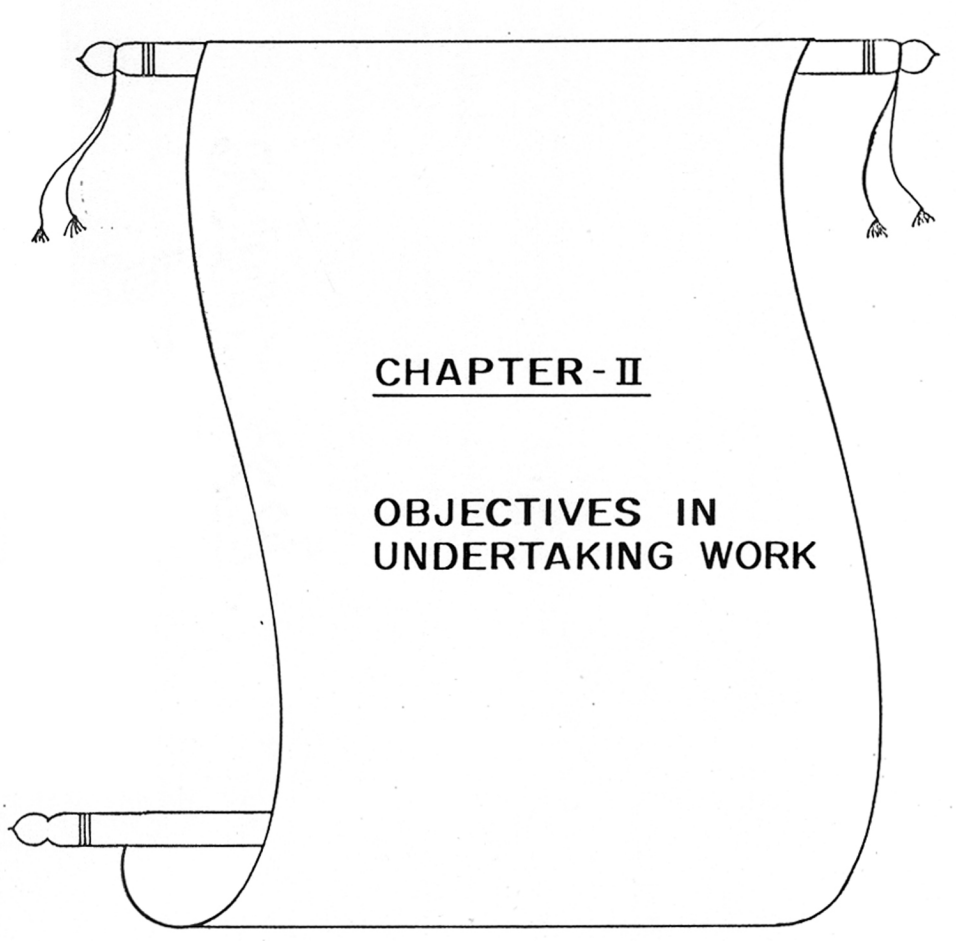
Iwata and Matsuda (1988) prepared an environment sensitive membrane by copolymerization of polyacrylamide and polyacrylic acid onto a porous membrane. The polyacrylic acid membrane being very sensitive to pH, the filtration rate sharply decreased with increasing solution pH. Together with this decrease in filtration rate, the membrane gained the ability of ultrafiltration of macromolecular solutes such as dextran (MW = 2,000,000) and albumin (MW = 67,000).

Glucose sensitive membranes were prepared by Albin et al (1985). The copolymer of P(HEMA) with dimethylamino ethyl methacrylate, with pendant amino groups serves as a membrane, in which glucose oxidase is entrapped. As glucose diffuses into the gel,

glucose oxidase catalyzes its conversion to gluconic acid, resulting in a lower pH within the gel microenvironment. This in turn leads to a increased ionization of the pendant amino groups and swelling of the gel. Hence the permeability of the hydrogel to insulin is increased. Similar work has been reported by Ishihara et al (1983). pH responsive permeation across membranes has also been reported by Okahata et al (1984) and Okahata and Seki (1986).

1.5.0 Conclusions:

This chapter gives a brief overview of controlled release delivery systems for drugs. Different types of controlled release devices and the release kinetics from such systems are described. A literature survey of past efforts for achieving zero order release from matrix systems and the various criteria proposed for swelling controlled zero order release has been made. The utilization of volume phase transitions in hydrogels for controlled release of drugs, has also been reviewed.



CHAPTER - II

OBJECTIVES IN UNDERTAKING WORK

2.0.0 Objective in undertaking work.

A) SWELLING CONTROLLED SYSTEM

The release mechanism from matrix type devices is known to follow diffusion controlled mechanism i.e., the release rate drops with time. On the other hand, matrix devices are easy to fabricate, cost less and are amenable to mass production. Thus there is a need to achieve constant rate of release from matrix devices using novel approaches. A number of approaches have been reported in the past to achieve constant release rates from matrix devices. This work reports the use of swelling controlled systems to achieve zero order release. The aims of this study are

a) to validate the quantitative criteria proposed by Lee et al (1987) and Vyavahare et al (1990)[a] for zero order release.

b) to bring about pH controlled structural changes in the polymer matrix to facilitate constant release of theophylline.

B) CONSTANT RATE DELIVERY SYSTEMS BASED ON SWOLLEN HYDROGELS

In the case of swollen hydrogels also, the release is diffusion controlled, the rate of release being proportional to the square root of time. Mathematically the release is governed by the following equation

$$Q = [(2A - C_p)C_pD_mt]^{1/2}$$

where Q denotes amount of drug released.

From the equation, it is seen that release is controlled by three parameters viz; A, C_p and D_m. In the past zero order release has been achieved from systems wherein the area (A) across which the release takes place increases with time (Rhine et al 1980) or the concentration (C_p) profile is nonuniform (Lee 1984). It is also possible to achieve zero order release by increasing the diffusivity (D) of the active ingredient during release.

The aim of this work is to demonstrate zero order release from rubbery hydrogels by enhancing the diffusivity of active ingredient during the period of release.

Matrix Reservoir Devices for zero order release

In matrix reservoir systems, as long as the permeability of the rate controlling barrier layer is lower than that of the core matrix, zero order release is possible. (Section 1.2.3). Various methods have been used in the past to form a barrier on the surface of a matrix. Olanoff et al (1979) formed a barrier layer by laminating the matrix whereas Lee et al (1980) sorbed a crosslinking monomer into the surface layers and polymerized it. However these barriers are irreversible in nature.

Volume phase transitions in polymers have been discussed in Section 1.4.0 . The phenomenon has been exploited for a variety of applications in the past. (Okahata et al 1984, Bae et al 1987, Hoffman 1987, and Badiger et al 1990). In this work, it has been used to form a surface barrier on the monolithic device.

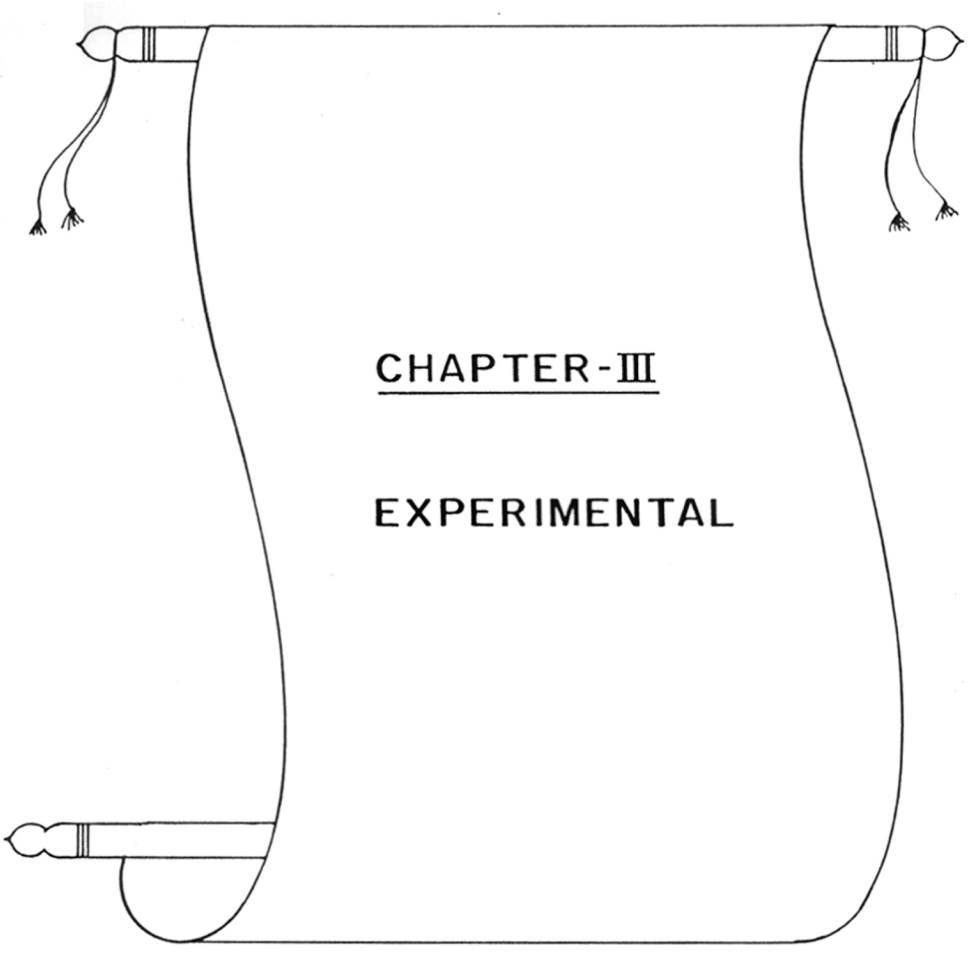
Summary

The proposed investigation has been undertaken with the following objectives

a) to understand and validate the criteria for zero order release.

b) to demonstrate zero order release from glassy hydrogels.

c) to design reservoir systems from matrix devices by utilizing the phenomenon of volume phase transitions in hydrogels.



CHAPTER-III

EXPERIMENTAL

3.0.0 Experimental

3.1.0 Materials

Monomers 2-hydroxyethyl methacrylate (HEMA), hydroxypropyl methacrylate (HPMA) were obtained from Fluka (Switzerland) and purified by distillation at 80°c/4mm and 57°c/0.5 mm Hg respectively and stored at 0°c. 4-methyl 7 hydroxy coumarine was obtained from local supplier. t-butyl hydroperoxide (Wilson Laboratories) was used as an initiator for polymerizations.

3.2.0 Synthesis of 4 methyl 7 oxy coumarine methacrylate (MOCM)

4 methyl 7 hydroxy coumarine (0.11M) was dissolved in 170 ml of dry dimethyl acetamide solvent in R.B. flask. Methacryloyl chloride (0.12M) was added dropwise to this mixture at 0°c-5°c for one hour. The mixture was stirred at room temperature overnight to complete the reaction. The mixture was poured over crushed ice to precipitate the formed 4 methyl 7 oxy coumarine methacrylate. It was filtered off and recrystallized from ethanol (Yield 88 %).

3.3.0 Polymer synthesis:

Synthesis of P(HEMA-MOCM) and P(HPMA-MOCM) :

Bulk polymerization was carried out in test tubes using 0.6% t-butyl hydroperoxide. Use of this initiator avoided the formation of bubbles during polymerization. Polymerization was carried out at 60°c for the first six hours and then at 70°c for the next 12 hours under nitrogen atmosphere. The polymer was isolated in the form of transparent cylinder by breaking the test-tubes. Discs were cut from the cylinder, and were 1.6 cm diameter and 0.09-0.11 cm thickness. These were postpolymerized at 50°c overnight and stored in a desicator over fused calcium chloride to prevent the moisture absorption during storage. Completion of polymerization was confirmed by following the UV spectrum of aqueous extract of the postpolymerized discs. The polymer slabs for release studies were soaked in 4 % theophylline solution in aqueous 0.05 N sodium hydroxide solution.

3.4.0 Dynamic swelling studies

Sorption measurements were performed by weighing the disc samples repeatedly on a Mettler analytical balance, following immersion in water placed in a jacketed vessel maintained at 37°C. The above procedure was repeated for swelling studies in the alkaline medium (0.05N NaOH). The summary of systems investigated appears in Table 3.1 .

3.5.0 Penetration velocity measurements

The penetration velocity for each polymer was determined by the weight gain method in water as described by Peppas and coworkers (1983). The penetration velocity was calculated from the slope of the initial portion of the penetrant uptake curve from the equation

$$v = (dW_g / dt) \; \sigma (1 / 2 A) \qquad 3.1$$

where v denotes the penetration velocity, dW_g/dt denotes the slope of the weight gain vs time curve, σ denotes the density of the water at 37°C. A denotes the area of one face of the disc and factor 2 accounts for the fact that penetration takes place through both faces.

Diffusion coefficient measurements

Diffusion coefficients of theophylline from swollen P(HEMA-MOCM) and P(HPMA-MOCM) matrices were determined experimentally by the desorption technique reported by Yasuda et al (1968). For diffusivity measurements in water, polymer discs were soaked in aqueous solution containing 1% theophylline until equilibrium was reached. For diffusivity measurements in alkaline medium, polymer discs were soaked in 0.05 N NaOH solution containing 1% theophylline until equilibrium swelling was reached. After equilibrium swelling was reached, the discs were removed from the solution, immersed in distilled water for few seconds and blotted with tissue paper to remove the solute adhering on the surface and were used for desorption experiment.

The desorption runs were carried out in pure water at 37° c. The concentration of the diffusant released at the interval of two minutes was determined by monitoring the ab-

sorbance of the dissolution medium. A graph of M_t/M_∞ versus the square root of time was plotted. Diffusion coefficient was calculated from the equation

$$D = \frac{\pi}{16}(L^2) \quad \text{where } L = \frac{d(M_t/M_\infty)}{d(\sqrt{t}/\delta)} \qquad 3.2$$

M_t and M_∞ denote active ingredient released at time t and at infinite time respectively, δ denotes the thickness of the disk and t denotes the time .

3.6.0 In vitro Release Studies

Discs of 1.6 cm diameter and 0.090 to 0.11 cm thickness were coated on one side by silicone grease so that release could take place from one side alone. In case of the discs which were swollen in base and treated with acid to form a barrier layer on the surface, the release was carried out in water from both sides. The release studies were carried out in a jacketted vessel. The polymer disc was suspended by means of a chrome wire into a vessel containing dissolution medium maintained at 37°c which was stirred magnetically . The dissolution medium was changed at appropriate intervals so as to maintain sink conditions. The concentration of theophylline was monitored on a Shimadzu 240 UV-VIS spectrophotometer at 272 nm. The total amount of drug released at time t, viz (M_t) was determined from the appropriate calibration curve. The amount of solute released from the disc after keeping it in solution for prolonged periods were taken as M_∞.Fraction of solute release was expressed as (M_t/M_∞). Kinetic exponent of release (n) was calculated from equation

$$\frac{M_t}{M_\infty} = K t^n \qquad 3.3$$

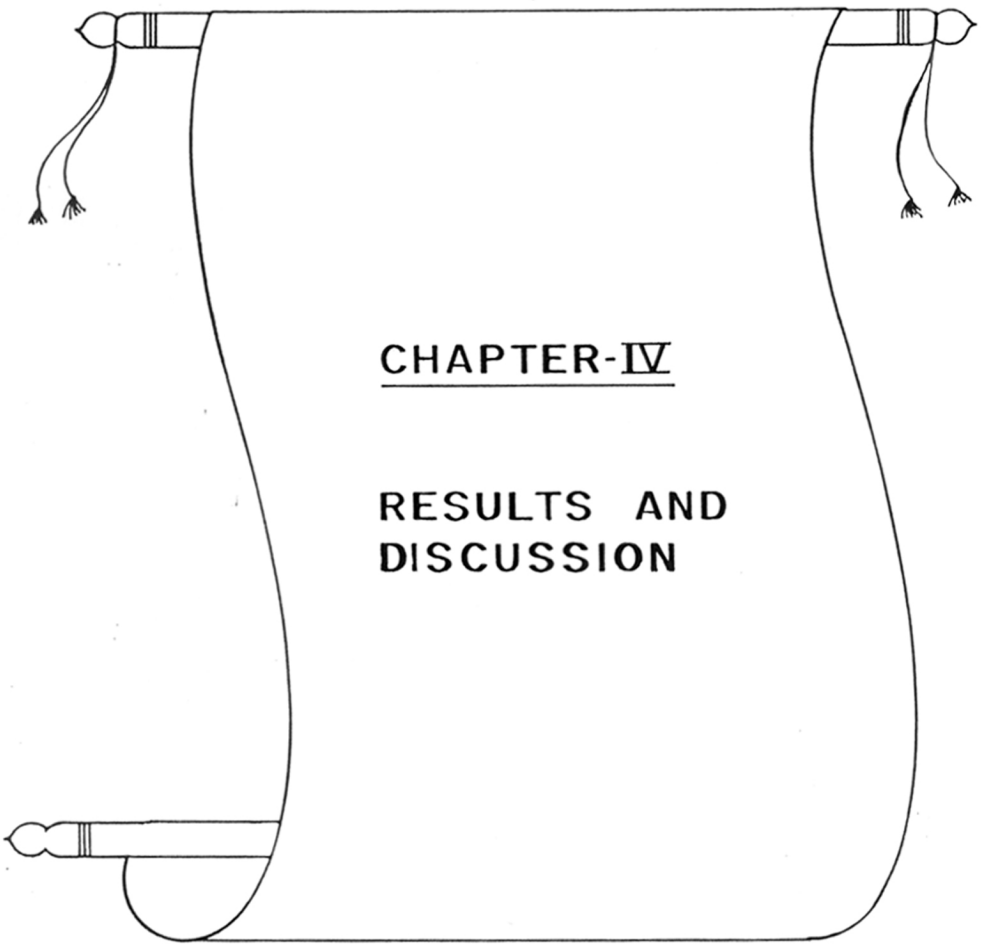
from the slope of the logarithmic plot of (M_t/M_∞) vs t where t denotes the time k is a constant.

The details of the systems studied and the dissolution medium are summarized in Table 3.1.

Table 3.1

Summary of systems investigated

Copolymers	State	Active ingredient	Release medium
HEMA/MOCM	Glassy/Swollen	Theophylline	Water & 0.05N NaOH
HPMA/MOCM	Glassy/Swollen	Theophylline	Water & 0.05N NaOH
HPMA/MOCM	Swollen (with surface barrier)	Theophylline	Water



CHAPTER-IV

RESULTS AND DISCUSSION

4.0.0 Results and Discussion

4.1.0 Hydrogel matrices for drug delivery systems

Amongst various approaches explained in the past for designing matrix systems which would release the active ingredient at constant rates, swelling controlled delivery systems based on glassy/swollen hydrogels appear most promising. A number of attempts have been made to analyze the problem mathematically and establish criteria for the release of the active ingredients at a constant rate from such systems (Hopfenberg and Hsu 1978, Peppas and Franson 1983, Korsemeyer 1986[a], Vyavahare et al 1990[a]). Vyavahare et al (1990)[a] have shown that low molecular weight solutes such as benzoic acid can be released at constant rate from glassy P(HEMA) hydrogels. On the contrary, the release of a bulkier molecule such as theophylline follows anomalous kinetics, since the swelling of the glassy hydrogel due to the penetration of the medium is inadequate to ensure rapid diffusion of theophylline from the swollen hydrogel.

In order to enhance the diffusivity of theophylline, equilibrium degree of swelling of the matrix needs to be enhanced. Siegel (1988) demonstrated that caffeine, a structural analog of theophylline was released at constant rates at pH 3 and 5 from the glassy Poly (methyl methacrylate - Dimethyl aminoethyl methacrylate) viz., P(MMA-DMA) hydrogels as a result of the enhanced swelling in the penetrant layer due to the protonation of DMA. Vyavahare et al (1990)[b] demonstrated that structural changes in the bulk of the polymer which lead to continuous increase in the swelling of the polymer, enhance the diffusivity of the active ingredient from the swollen matrix during the course of release. This leads to the release of the active ingredient at constant rate. The structural changes which can bring about the enhancement in swelling could be (1) hydrolysis of the pendant chain in the polymer ,(2) ionization of the functional groups in the polymer and (3) scission of the labile crosslinks incorporated in the polymer.

In addition to the above mentioned efforts aimed at the delivery of the drugs at constant rate, self regulated stimuli responsive drug delivery systems are being investigated extensively. The stimuli responsive systems have been recently reviewed by Heller

(1988). The basic premise in all such systems is to incorporate in the polymer structure, a monomer which would undergo a reversible structural change in response to the changes in the environment.

This work reports the release of theophylline from the glassy as well as swollen hydrogels comprising copolymers of 4-methyl 7-oxy methyl coumarine methacrylate (MOCM) with hydroxy ethyl methacrylate (HEMA) and hydroxy propyl methacrylate (HPMA). The coumarine rings undergo reversible opening in the alkaline medium leading to reversible swelling and deswelling of the polymer matrix. The results of observed release kinetics have been discussed in terms of the criteria for zero order release.

4.2.0 Release of theophylline in aqueous media

4.2.1 Glassy hydrogels

The kinetics of release of an active ingredient from a glassy hydrogel depends on the relative contributions of the velocity of penetration of the surrounding medium (v), and the diffusivity of the active ingredient (D) from the swollen hydrogel. Zero order release can be achieved from a polymer device which swells at a constant rate , if the counter diffusion of the active ingredient from the swollen layer is rapid as compared to the rate of swelling. In order that the polymer swells at a constant rate , it is necessary that the sorption of the penetrant medium follows Case II transport. It has been shown in the past by Hopfenberg and Hsu (1978), that the release of Sudan Red dye from polystyrene film followed zero order kinetics as a result of constant rate of sorption of n-hexane. The criteria developed in the literature for zero order release from glassy hydrogels include the swelling interface number Swe, (Peppas and Franson 1983) the Deborah number D_D, and the dimensionless parameter $(\sqrt{Dt})/vt$. Also, Lee(1987) has developed the concept of time dependent diffusivity to model zero order release from glassy hydrogels.

The kinetics of release of theophylline from glassy P(HEMA-MOCM) is depicted in Fig 4.1. The release kinetics follows anomalous kinetics (n=0.635). Vyavahare et al

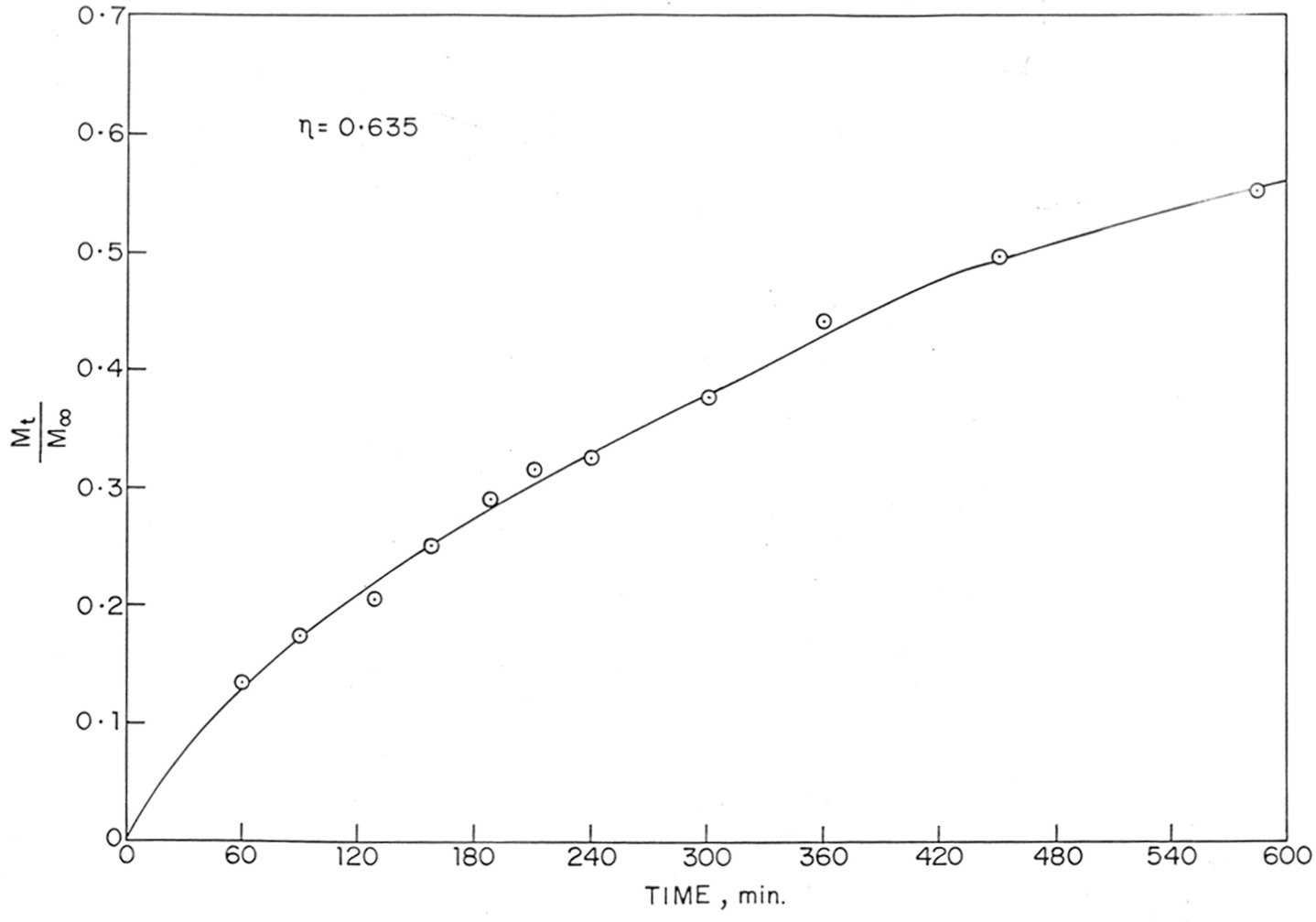


FIG. 41 : RELEASE OF THEOPHYLLINE IN WATER FROM GLASSY P [HEMA (98) MOCM (2)]

(1990)[a] have shown that the release of benzoic acid from glassy P-HEMA hydrogels follows zero order kinetics, whereas that of theophylline follows anomalous kinetics. This has been attributed to the lower diffusivity of theophylline ($1.2 * 10^{-7} cm^2/sec$) as compared to that of benzoic acid ($3.45 * 10^{-7} cm^2/sec$), from the swollen matrix. The incorporation of a small amount of MOCM has practically no effect on the equilibrium swelling of the P(HEMA-MOCM) hydrogel in aqueous medium. The diffusivity of theophylline in the polymer matrix swollen to equilibrium in water was found to be 9.2×10^{-8} cm^2/sec. The anomalous release kinetics of theophylline is thus, not surprising.

In the case of release of theophylline from glassy P(HPMA-MOCM) (Fig 4.2) the diffusivity of theophylline from the swollen matrix drops further. Due to the hydrophobic nature of the P(HPMA-MOCM) matrix, the equilibrium degree of swelling is low (15%). This results in diffusion-relaxation controlled anomalous kinetics (n=0.630).

4.2.2 Swollen hydrogels

The kinetics of release of theophylline from swollen P(HEMA-MOCM) is depicted in Fig 4.3. Since the matrix is already swollen to its equilibrium value and there is no enhancement in the degree of swelling during the course of release , the release pattern is consistent with the diffusion controlled release from a matrix device (n=0.51).

Similarly, the release of theophylline from swollen P(HPMA-MOCM) (Fig 4.4), in water is also diffusion controlled. As already mentioned, the diffusivity of theophylline from the P(HPMA-MOCM) matrix is lower than that from the P(HEMA-MOCM) matrix. The release rate of theophylline from the P(HPMA-MOCM) matrix is therefore lower.

4.3.0 Release of theophylline in alkaline medium

4.3.1 Mechanism of swelling

In the presence of alkali, the hydroxy coumarine ring opens up and hydrophilic sites are formed (COO^-Na^+) along the polymer chain (Fig 4.5). As a result, the polymer swells extensively. Similar systems have been reported earlier, wherein a hydrogel matrix undergoes hydrolysis either in the acidic medium or in the alkaline medium, leading to enhanced degree of swelling (Shah et al 1991, Vyavahare et al 1990[b]).

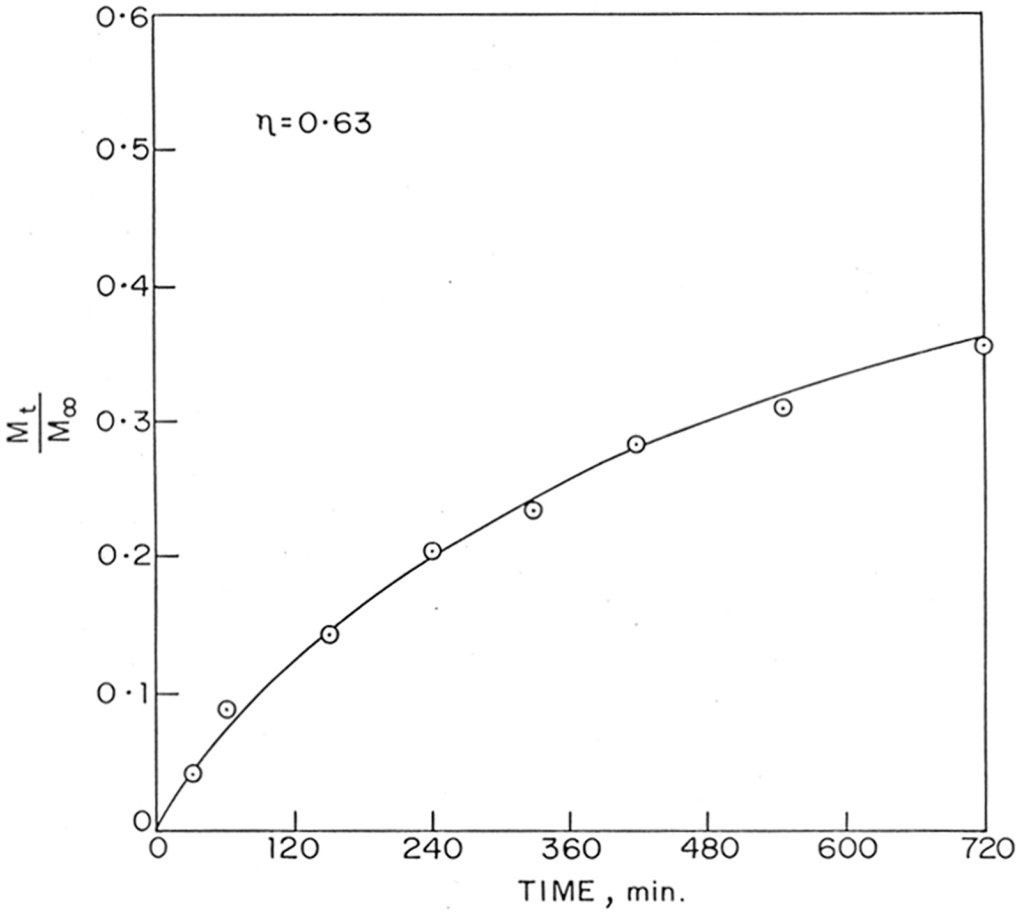


FIG. 4·2: RELEASE OF THEOPHYLLINE IN WATER FROM GLASSY P [HPMA (98) MOCM (2)]

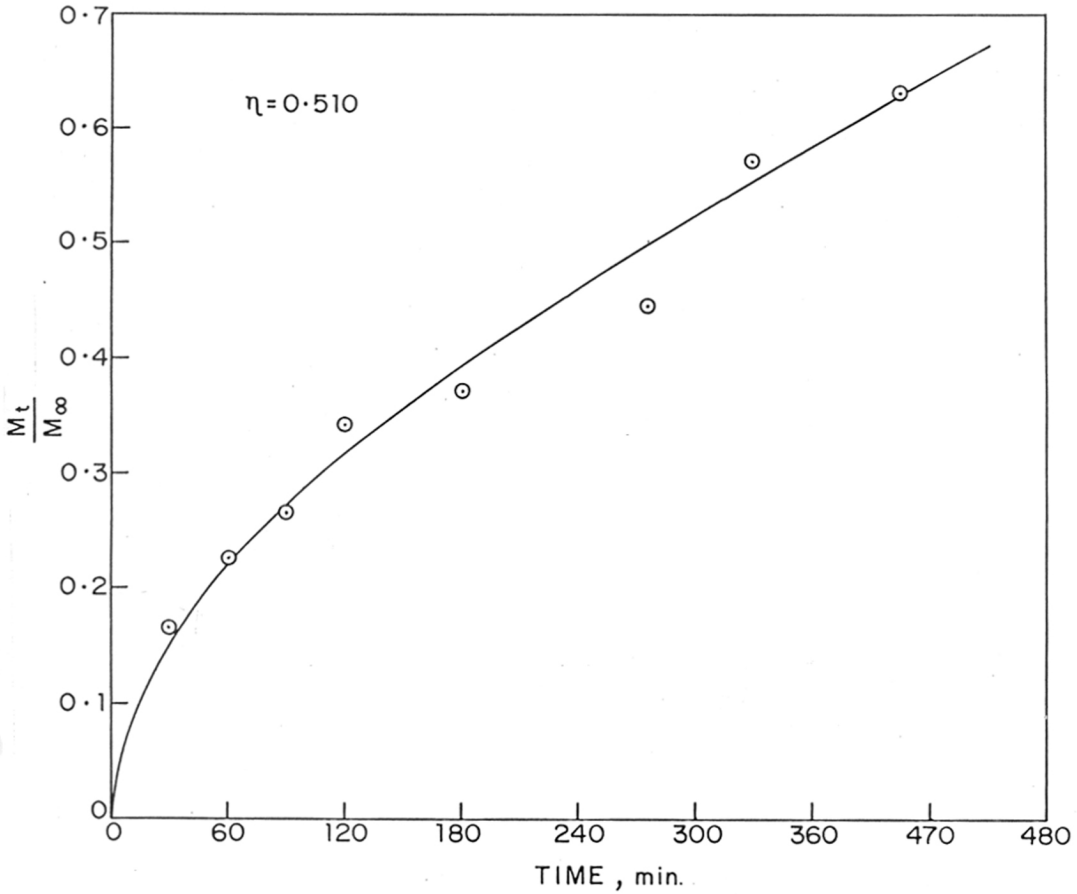


FIG.4·3: RELEASE OF THEOPHYLLINE FROM SWOLLEN P [HEMA (98) MOCM (2)] IN WATER

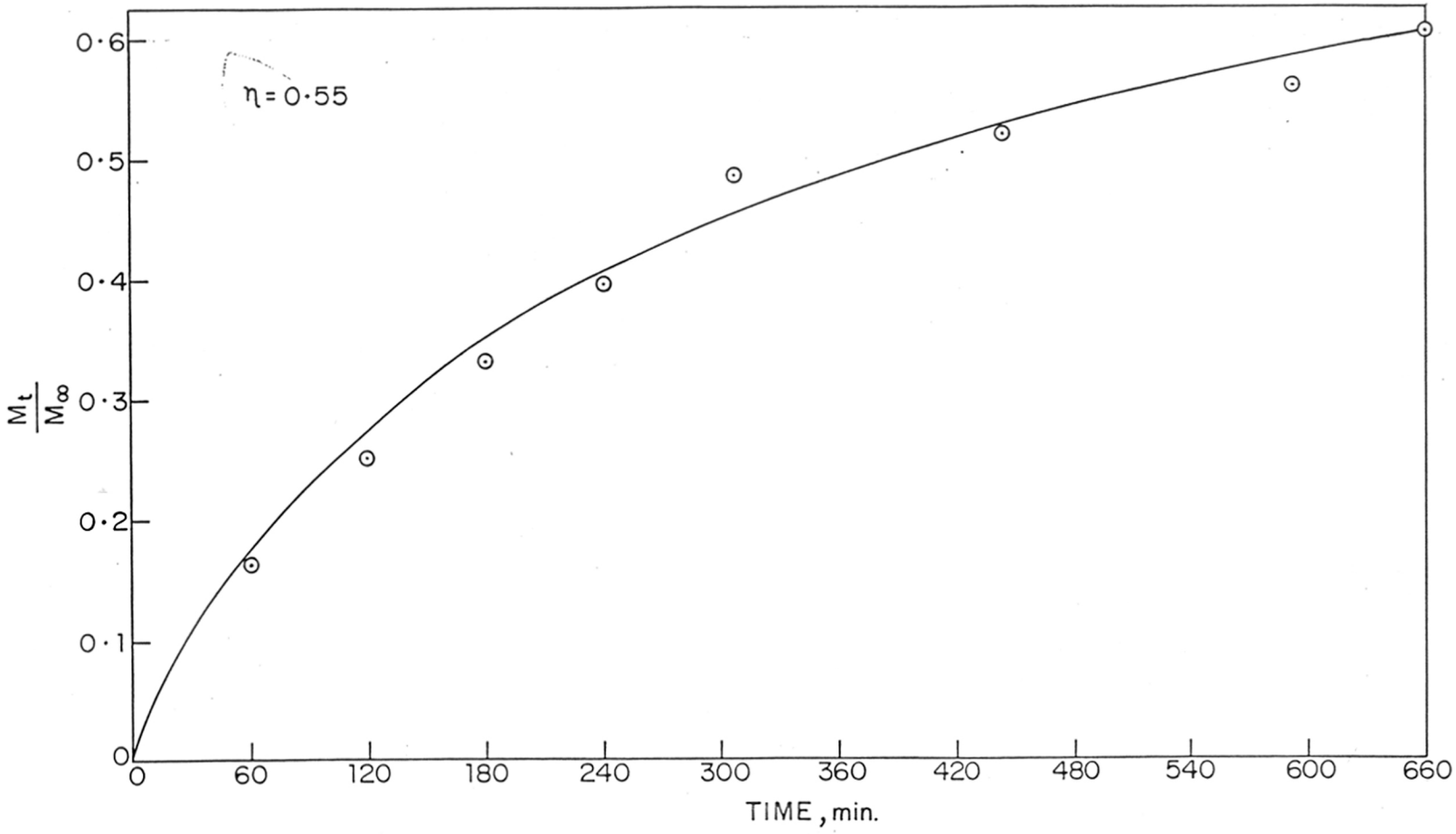


FIG.4·4 : RELEASE OF THEOPHYLLINE IN WATER FROM SWOLLEN P [HPMA (98) MOCM (2)]

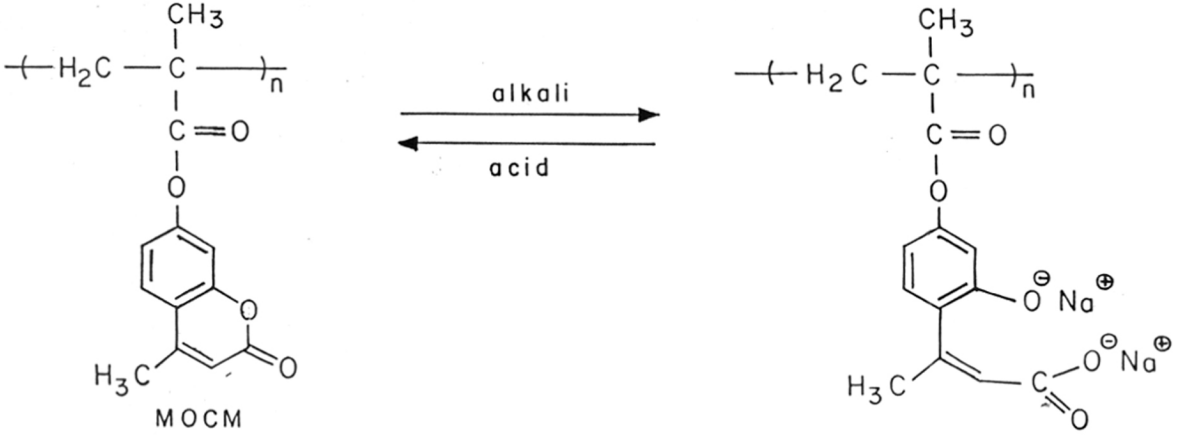


FIG.4·5: REVERSIBLE LACTONIZATION OF MOCM

4.3.2 Glassy hydrogels

The release kinetics of theophylline from glassy P(HEMA-MOCM) hydrogels in water was shown to follow anomalous kinetics, due to its low diffusivity from the P(HEMA-MOCM) matrix. However, if the diffusivity from the matrix can be increased, so that diffusion of theophylline is faster as compared to the rate of swelling, then it should be possible to achieve zero order release. Vyavahare et al (1990)[c] copolymerized HEMA with a crosslinking monomer, which on hydrolysis in alkaline medium enhanced the degree of swelling of the polymer matrix. This increases the diffusivity of theophylline and a constant rate of release was observed. In this work also, the P(HEMA-MOCM) matrices show enhanced swelling behaviour in alkaline medium. The diffusivity of theophylline is sufficiently increased so that the release follows zero order pattern (Fig 4.6).

Another criteria for establishing zero order release from swelling controlled systems is the dimensionless parameter $(\sqrt{Dt})/vt$. It was shown earlier by Vyavahare et al (1990)[a] that for values of this parameter ,which were greater than 1.3, zero order release could be expected from glassy hydrogels. Thus, the value of 2.08 obtained for the P(HEMA-MOCM) system correlates well with the release pattern observed (Table 4.1).

Hopfenberg and Hsu (1978) have demonstrated that if the kinetics of release of an active ingredient from a glassy hydrogel follows zero order release, then the penetration velocity measurements calculated from the dynamic swelling data should match with those calculated from the release data. The value calculated from release data (1.889×10^{-6} cm/sec) for the P(HEMA-MOCM) system is only one third of that calculated from dynamic swelling data (6.26×10^{-6}). This indicates that although the release of theophylline takes place at a constant rate, this is not a consequence of Case II transport controlled penetration of the medium. Similar observations have been reported recently by Shah et al (1991).

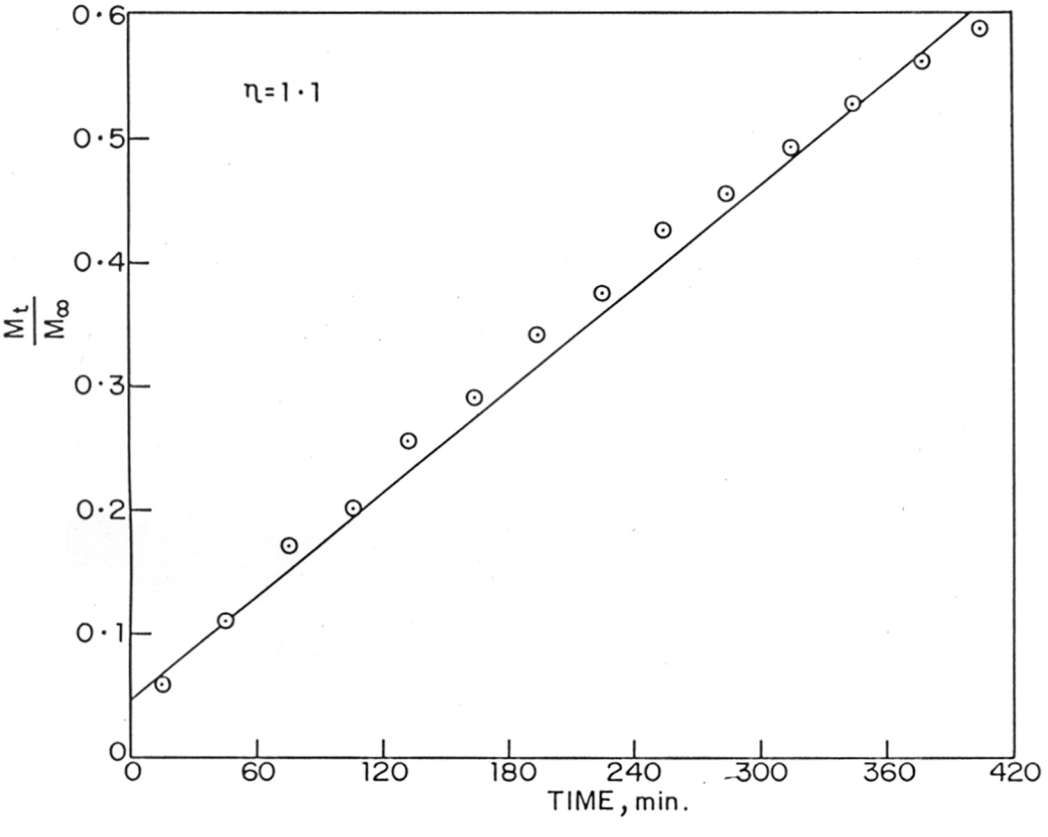


FIG. 4·6: RELEASE OF THEOPHYLLINE IN BASE FROM P [HEMA (98) MOCM (2)]

Table 4.1

Transport and release characteristics for the systems P(HEMA/MOCM) and P(HPMA/MOCM) with Theophylline.

Glassy Copolymer	Eq. Swelling g H_2O/g Poly	Penetration velocity cm/sec	Diffusion Coefficient cm^2/sec	$\frac{\sqrt{Dt}}{vt}$	Release Index, n
HEMA/MOCM* (in water)	0.41	3.30×10^{-6}	9.20×10^{-8}	0.578	0.635
HPMA/MOCM# (in water)	0.15	6.83×10^{-7}	7.78×10^{-8}	-	0.630
HEMA/MOCM (in base)	1.40	6.26×10^{-6}	4.28×10^{-6}	2.08	1.0
HPMA/MOCM (in base)	0.79	1.60×10^{-6}	2.59×10^{-6}	6.81	0.54

* P [HEMA/MOCM (2% w/w)]

\# P [HPMA/MOCM (2% w/w)]

The release profile from P(HPMA-MOCM) is shown in Fig 4.7. In this case, although the value of the dimensionless parameter $(\sqrt{Dt})/vt$ is high (see Table 4.1), the degree of swelling during the course of release is only 28% . Thus, the diffusivity of theophylline from the matrix at 28% swelling is very low, as compared to equilibrium swelling (79%). The release is, therefore, diffusion controlled (n=0.54).

4.3.3 Swollen hydrogels

Release of theophylline in aqueous media from P(HEMA-MOCM) and P(HPMA-MOCM) hydrogels swollen to equilibrium in water was reported to be diffusion controlled (n=0.5) which is to be anticipated.

In contrast, the above hydrogels when immersed in alkaline medium, undergo extensive swelling due to the opening of the coumarine ring. This results in 40 and 33 folds enhancements in the diffusivity of theophylline (Table 4.1). It has been shown earlier that an increase in the diffusivity of the active ingredient accompanying release, leads to the release of the active ingredient at constant rate (Shah et al 1991). It was therefore anticipated that the release of theophylline from the swollen hydrogel matrices into the alkaline medium would follow zero order release. In contrast the release of theophylline from the above matrices is still diffusion controlled (n=0.5). (Figs 4.8 and 4.9)

However, these results are not surprising when one looks at the time scales involved in the swelling process as evidenced by the swelling curves. In fact the swelling process is so slow that the increase in the diffusivity of theophylline by the time 60% of the theophylline is released from the matrix P(HPMA-MOCM) the equilibrium degree of swelling is only 40% and the increase in the diffusivity is from 7.78×10^{-8} to $2.88 \times 10^{-7} cm^2/sec$. As a result, the release of theophylline is still diffusion controlled.

4.4.0 Reservoir devices through volume phase transitions

It is known that hydrogels containing ionizable monomers exhibit pH induced volume phase transitions. The phenomenon of volume phase transitions has been imaginatively exploited for application in the field of controlled release delivery systems. A

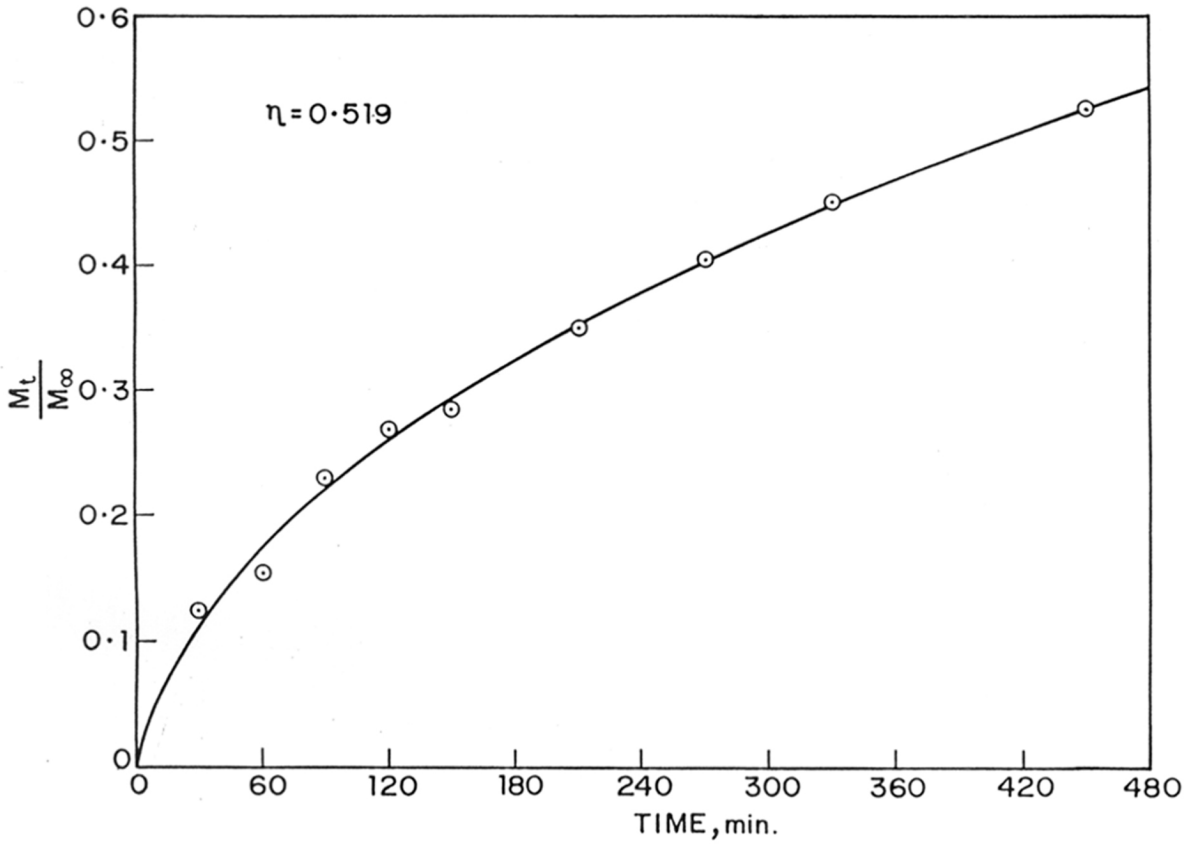


FIG. 4·7: RELEASE OF THEOPHYLLINE IN BASE FROM GLASSY P [HPMA(98) MOCM(2)]

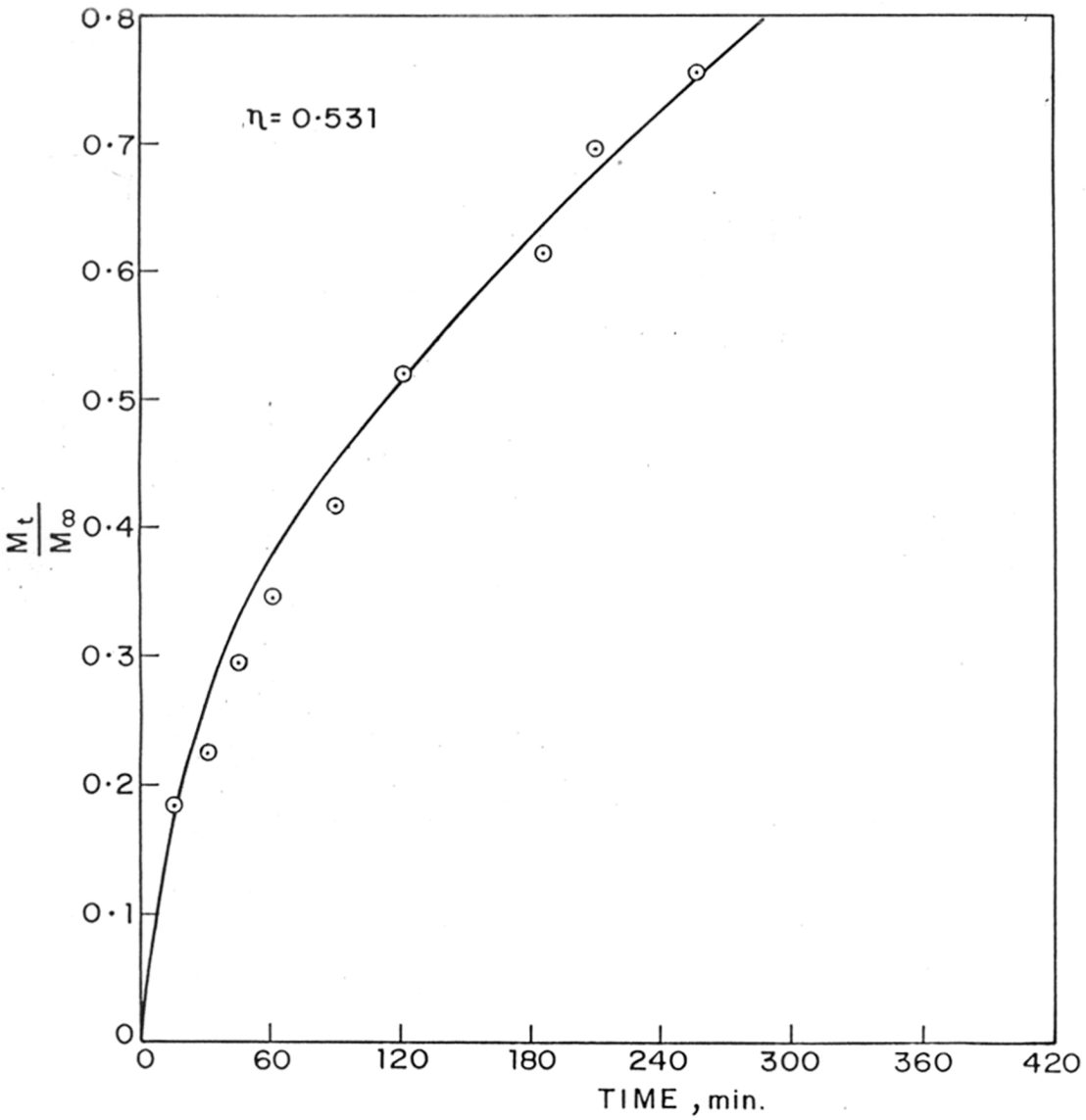


FIG. 4·8 : RELEASE OF THEOPHYLLINE IN BASE FROM SWOLLEN P
[HEMA (98) MOCM (2)]

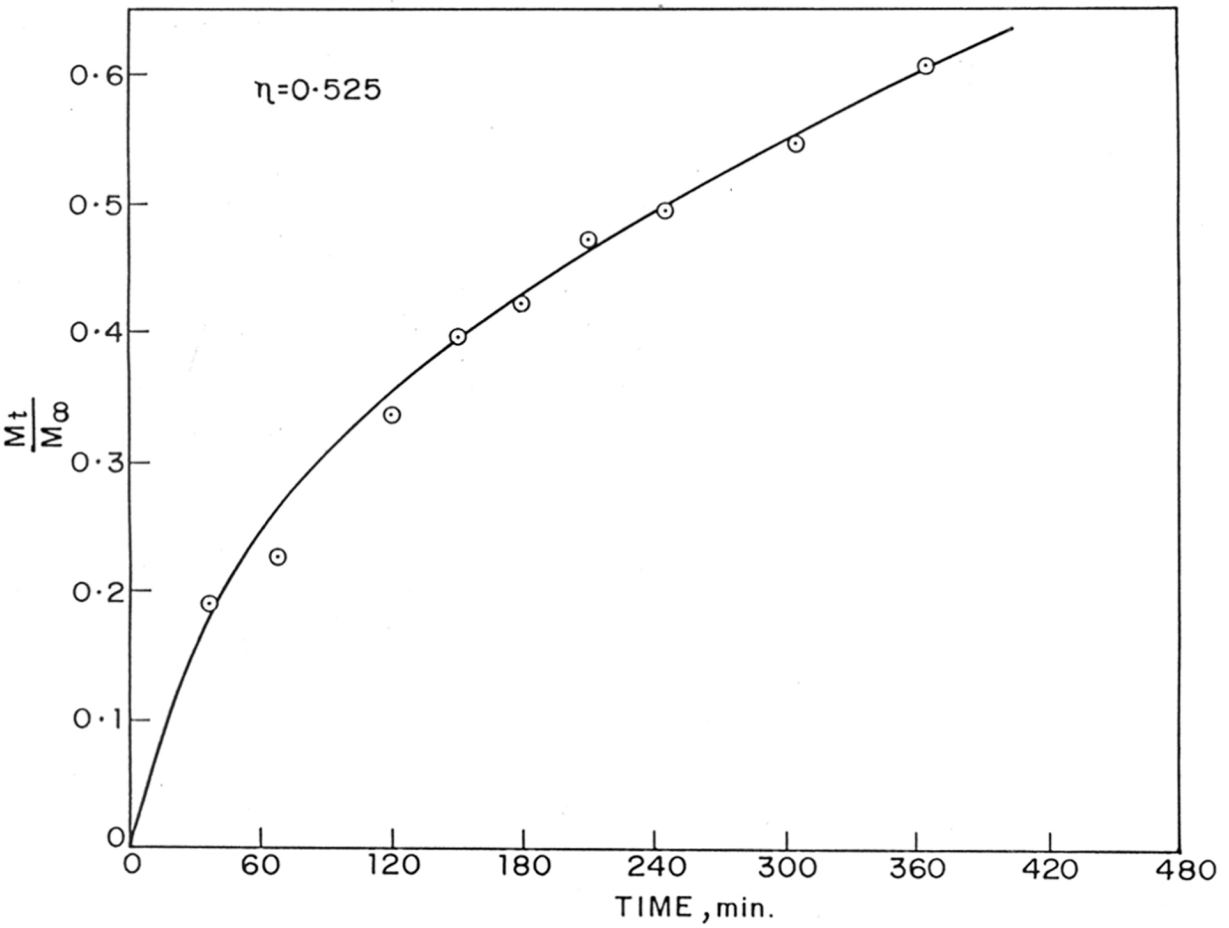


FIG. 4·9 : RELEASE OF THEOPHYLLINE IN BASE FROM SWOLLEN P [HPMA (98) MOCM (2)]

brief overview of the past efforts in this area has been given in Chapter I. If it is possible to restrict the volume phase transitions to the surface of a polymer, causing a collapse of the gel at the surface only, the surface will have a lower permeability than the inner core matrix. The surface then serves as a rate limiting barrier. Although the concept of converting a matrix device into a reservoir device, by imposition of a barrier layer has been used by researchers in the past (Lee 1981), the fabrication of such devices is not amenable to mass production. There is thus a need for a simple procedure to accomplish this. Also, it is desirable that the volume phase transitions take place in the physiological environment of the body.

4.4.1 Volume phase transitions

As has been mentioned in Chapter I, volume phase transitions in gels can be brought about by variation in solvent composition, pH, salt concentration and temperature. Although, extensive studies on the effect of above parameters on the volume phase transitions have been done, very few efforts have been made to investigate the kinetics of swelling and deswelling. Gehrke and Cussler (1989) have studied the kinetics of pH dependent swelling and deswelling of hydrogels based on poly (acrylamide -sodium methacrylate), which swell in base and collapse in the acidic medium. It was shown that the collapse of the hydrogel in the acidic medium was several times faster than the swelling in basic medium. During the collapse of the gel in acidic medium from its initially swollen state, the ionic gel is converted into its nonionic form. The carboxylate ions of the swollen gel are neutralized by the H+ ions which diffuse into the gel. A moving front, separating a nonionic outer shell from the ionized inner core was developed. Further, the collapse was found to follow Fickian behaviour and the thickness of collapsed layer could be estimated from the diffusion coefficient.

In the present work, pH induced volume phase transitions were studied for the system P(HPMA-MOCM). Coumarines undergo ring opening in the presence of alkali to form sodium coumarinate, which is hydrophilic in nature. Acidification leads to relacto-

nization to the ring structure. Thus the ring opening in coumarines is reversible. The polymers are first swollen to equilibrium in alkali, and then immersed in acidic medium for a short time, to form a barrier layer on the surface. The criteria for zero order release of active ingredient from barrier systems is that the inequality condition in equation (1.18) must be satisfied.

The systems which undergo pH induced volume phase transitions offer a significant advantage over the polymers which undergo temperature induced transition. As mentioned earlier the swelling process is much slower than the deswelling process , and hence in an environment having pH close to neutral and containing low sodium ion concentration, the barrier would be expected to remain intact. Therefore. the release in such a medium would be expected to follow zero order kinetics. Since such variations actually take place in the GI tract , the phase transition could be brought about under conditions of physiological significance.

4.4.2 Release of theophylline from P(HPMA-MOCM) hydrogels : A reservoir system

The reversible lactonization of MOCM is shown in Fig. (4.5). The release of theophylline from equilibrium swollen P(HPMA-MOCM) (ESW = 79%) is shown in Fig. (4.9) . The release is diffusion controlled (n = 0.5) . Similarly, release from the completely collapsed gel (ESW = 16%) follows the same pattern, but at a slower rate due to the lower diffusivity of theophylline from the deswollen matrix. When the P(HPMA-MOCM) polymer is immersed in alkali, it swells to equilibrium value of 79% . It is then treated with 0.5N H_2SO_4 for a limited time period, to form a barrier layer of the collapsed gel around the swollen inner core. The release pattern from such a system is shown in Fig. 4.10 which demonstrated that theophylline is indeed released at a constant rate (Vyavahare 1992).

The diffusional characteristics of the core and barrier layer are constant and are governed by the equilibrium degree of swelling. However, the thickness of the barrier layer will increase with the time of immersion in the acidic layer. In order to study the

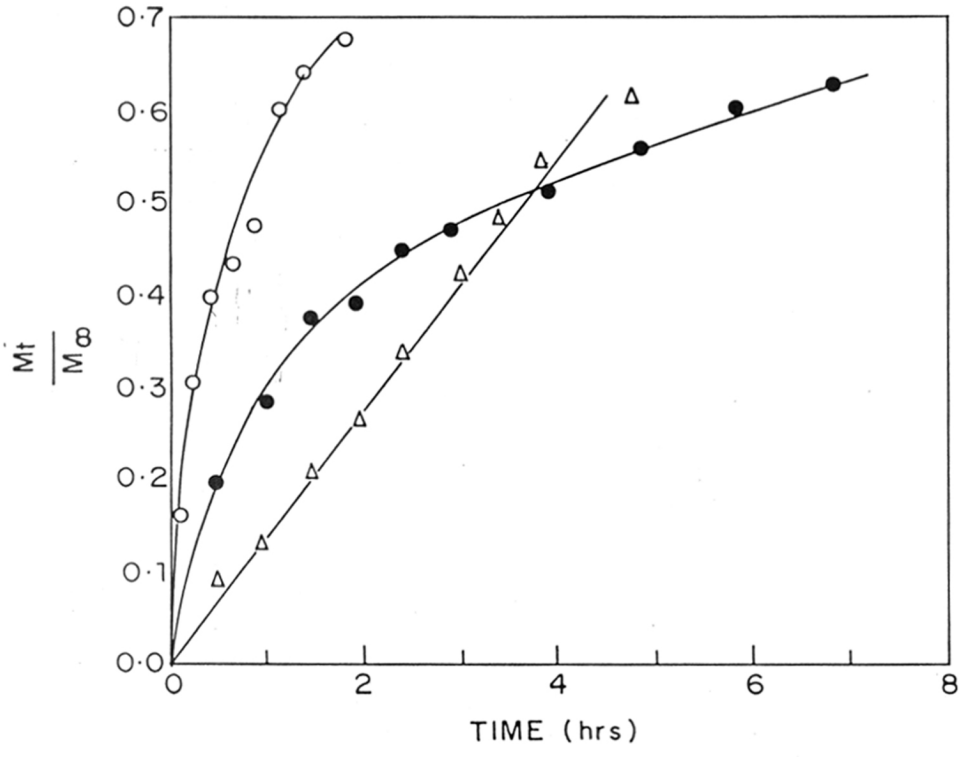


FIG. 4·10 : RELEASE OF THEOPHYLLINE FROM (o) P (HPMA-MOCM) (EWC 79 %), (●) P (HPMA-MOCM) (EWC 16 %) (Δ) P (HPMA-MOCM) TREATED WITH ACID, IN WATER.

effect of acid treatment on the barrier layer thickness and hence the release characteristics of theophylline, the P(HPMA-MOCM) (97/3) hydrogels, swollen to equilibrium swelling in alkaline medium were immersed in 0.5 N H_2SO_4 for different time intervals. The importance of forming a barrier layer of desired thickness is seen from the fact that the release index increases from 0.52 to 1.0 as the immersion time increases (Fig. 4.11). Recently Vyavahare et al (1992) prepared hydrogels based on hydroxypropylmethacrylate and sodium carboxy styrene. The copolymer in the ionized state had an equilibrium swelling of 74%, when immersed in acidic medium (0.1 N H_2SO_4) the hydrogel collapsed to form a barrier layer on the surface. The thickness of the barrier layer was proportional to square root of time (see figure 4.12), which confirms that the deswelling of the hydrogel is a Fickian process.

The most significant finding of this study is that the barrier formation can take place *"in-situ"* conditions. Thus Vyavahare et al (1992) have simulated the release of metrodinazole under physiological conditions. The HPMA based hydrogel was immersed in simulated gastric juice for different time periods, which are typical residence times in the stomach. The release was simulated in intestinal fluid and was found to take place at a constant rate.

4.5.0 Stimuli Responsive Delivery Systems

The polymeric hydrogels which undergo reversible swelling and deswelling as a result of structural changes are being increasingly investigated for stimuli sensitive "on-off" type delivery systems . The stimulus could be temperature pH or electrical potential. It was suggested that the hydrogels which undergo temperature induced deswelling so as to form surface regulated systems lead to "on-off" release, while the hydrogels which lead to matrix pumping systems offer very little control over release.

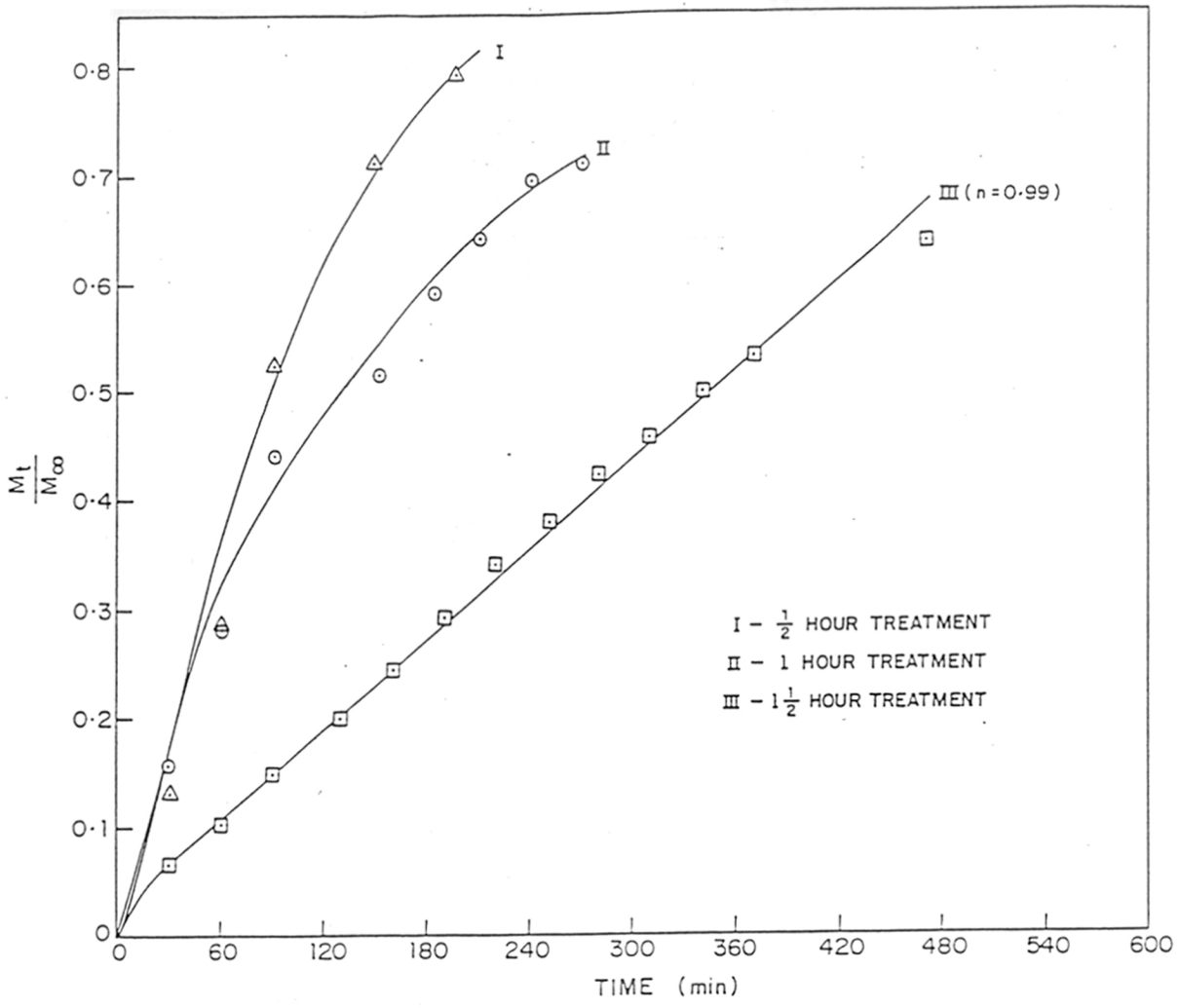


FIG. 4·11 : RELEASE OF THEOPHYLLINE IN WATER FROM SWOLLEN P-HPMA(98) MOCM(2) TREATED WITH 0·5N H_2SO_4

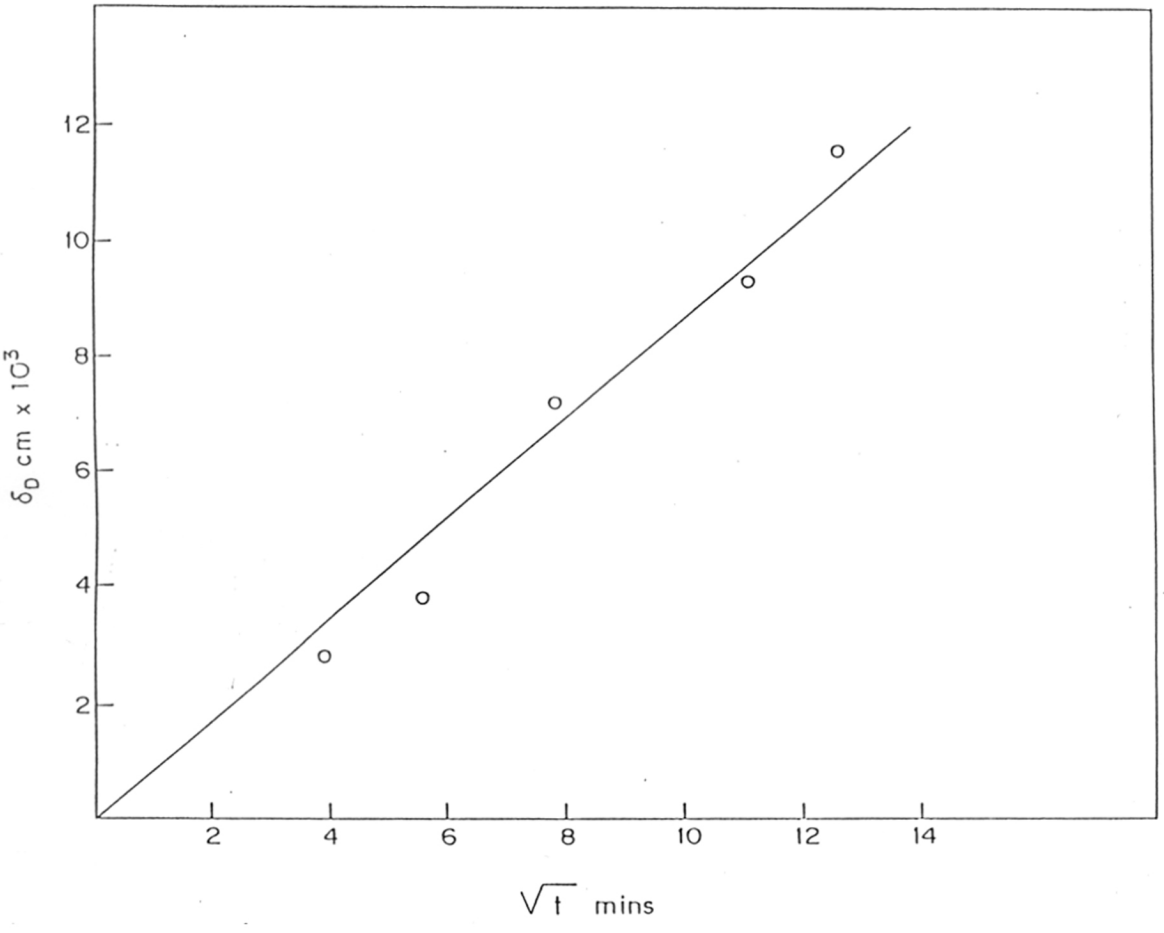


FIG.4·12:PLOT OF BARRIER THICKNESS vs $\sqrt{t}$

We have already shown that P(HPMA-MOCM) and P(HEMA-MOCM) matrices swell in the alkaline medium due to the reversible opening of the coumarine ring and collapse in the acidic medium as a result of the closure of the coumarine rings. (Figs 4.13 and 4.14). It is seen from the figures that collapse occurs more rapidly than swelling. In order to investigate the potentials of the hydrogels synthesized in this work for stimuli sensitive delivery systems, P(HPMA-MOCM) hydrogels were swollen to equilibrium in water and then exposed to acid and alkali at time intervals specified in Fig. 4.15. It is evident from the release profile of theophylline that the release is triggered in the alkaline medium and significantly suppressed in the acidic medium. On the other hand, the release profile of theophylline from P(HEMA-MOCM) hydrogel shown in Fig. 4.16 indicates that the release rate is not significantly influenced whether the release medium is acidic or alkaline.

Release properties of both types have been reported in the past. Yoshida et al (1991) reported release of testosterone from thermoresponsive hydrogels based on Poly (Methacryloyl-L-proline-co-2-hydroxy propyl methacrylate) and Poly (Methacryloyl-L-proline-co-polythyleneglycol(600) dimethacrylate) . In the former case the fraction of testosterone released at 0°C increased linearly with time, while at 40°C the release was suppressed. In contrast, the release rate of testosterone from Poly-(Methacryloyl-L-proline-co-polythyleneglycol(600) dimethacrylate) was slightly enhanced as temperature was increased from 0°C to 40°C. An investigation of the morphology of the hydrogels revealed that the deswelling in the former case led to the formation of a rigid barrier on the surface. Hydrogels of this type were termed surface regulated systems. On the other hand the collapse of the hydrogels of the latter type did not reveal the formation of barrier layer as examined by scanning electron microscopy. It was argued that as the deswelling occurred without affecting the porosity of the surface layer, water was squeezed out of the matrix. Hydrogels of this kind were termed as matrix pumping systems.

The on-off release of P(HPMA-MOCM) hydrogels can thus be explained. However, since the release rate of theophylline for the system P(HEMA-MOCM)

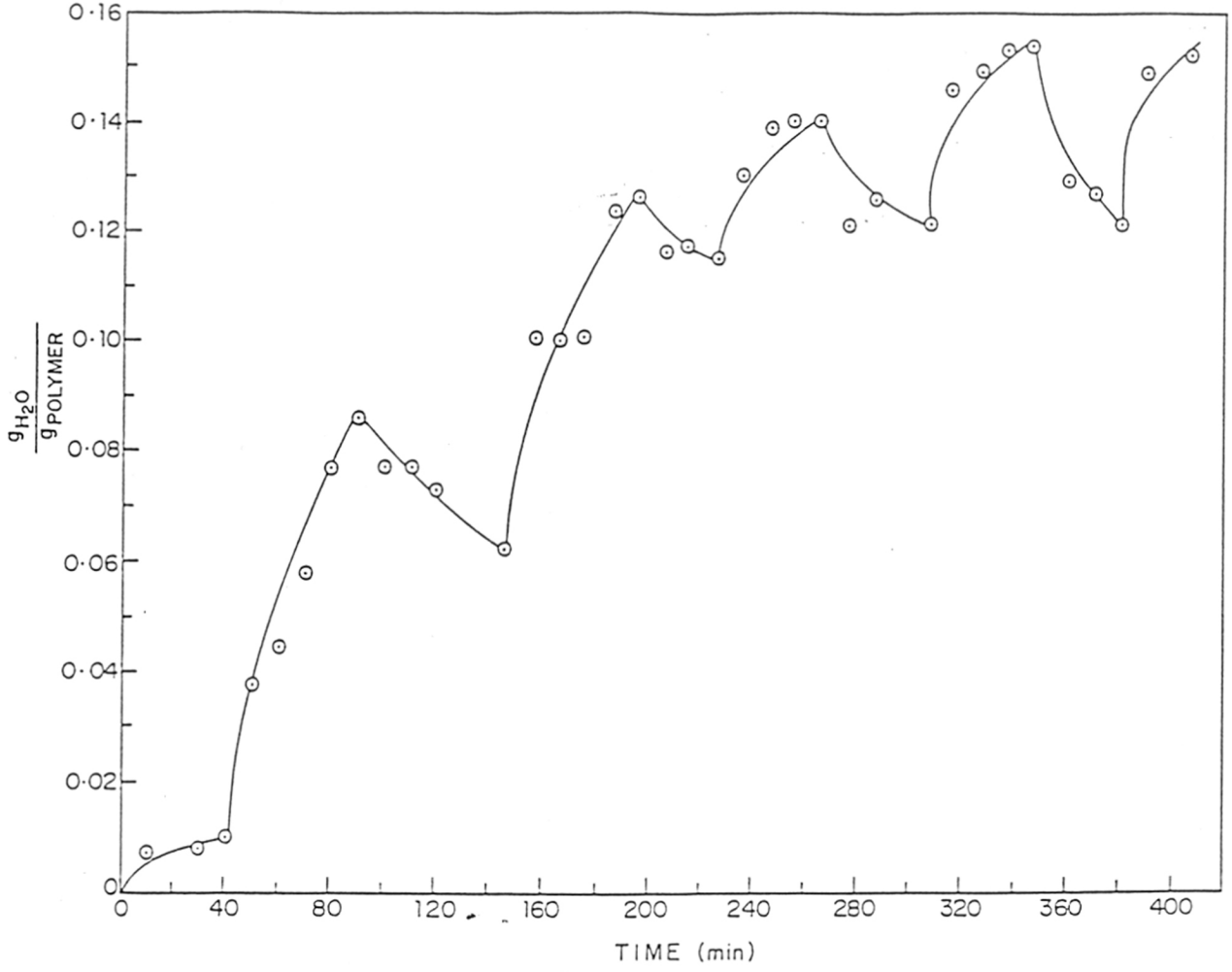


FIG. 4·13 : WEIGHT GAIN/LOSS STUDIES OF P-HPMA(98) MOCM(2) IN 0·05 N NaOH/ 0·05 N H_2SO_4

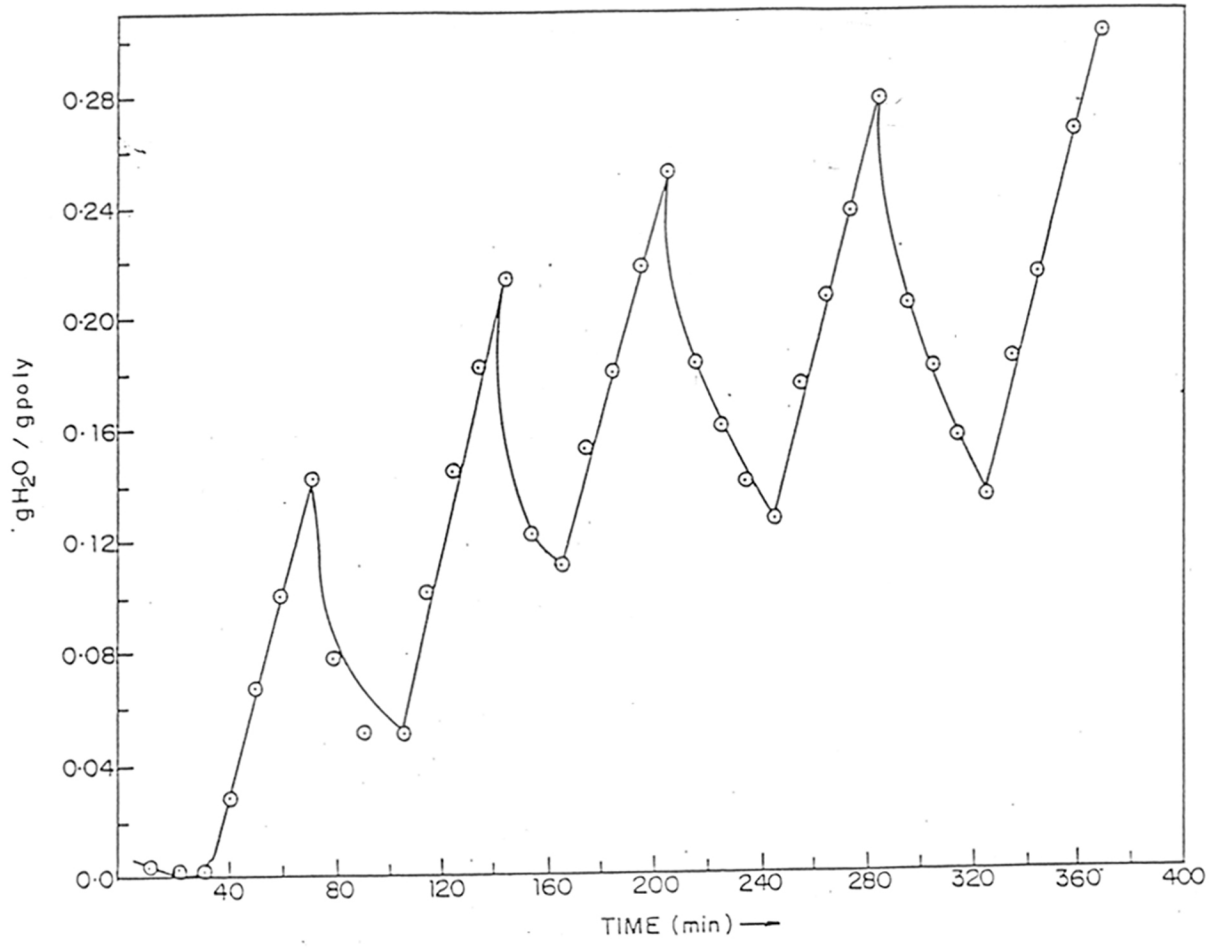


FIG. 4·14: WEIGHT GAIN/LOSS STUDIES OF P(HEMA)(98) MOCM(2) IN 0·05N NaOH / 0·05N H_2SO_4.

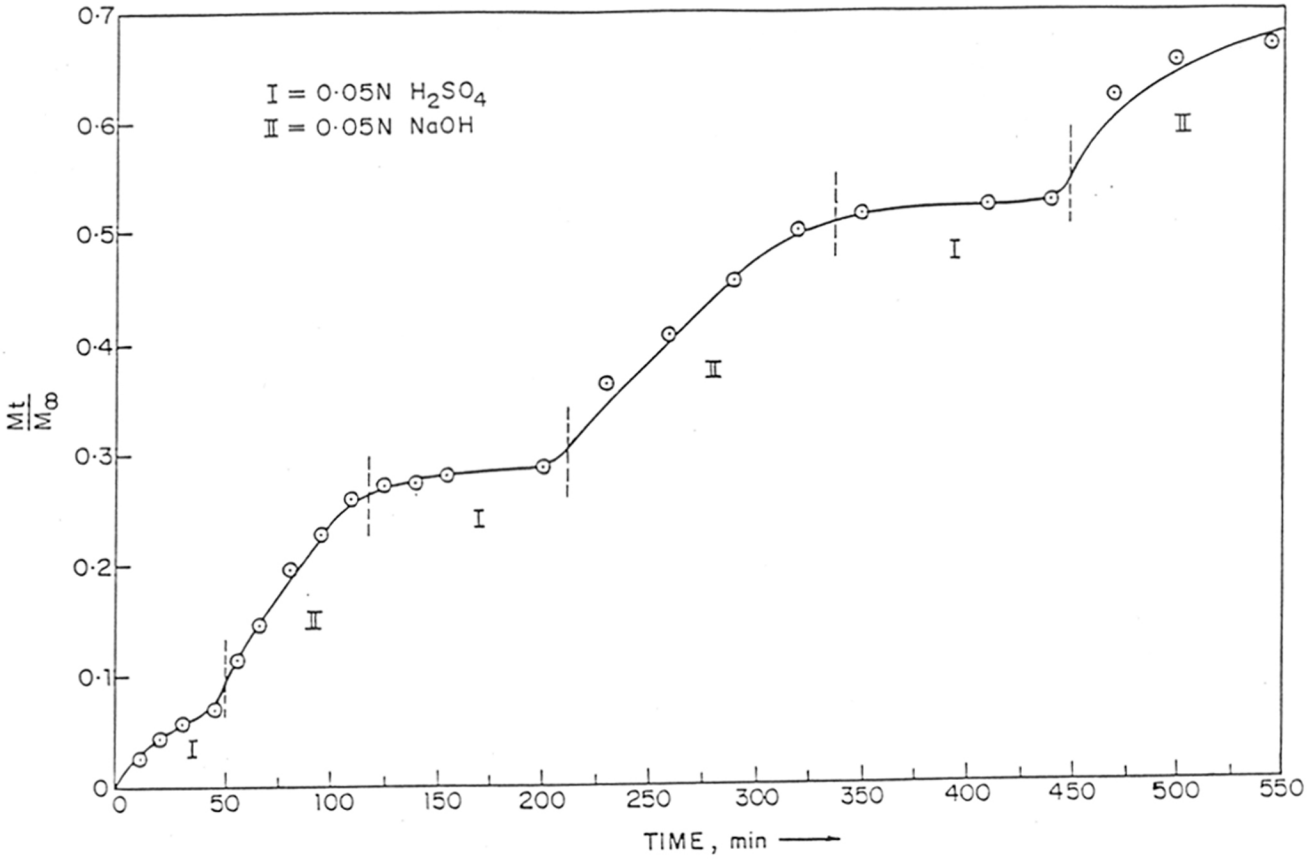


FIG.4.15 : RELEASE OF THEOPHYLLINE IN ACID / BASE - P(HPMA)(98) MOCM(2).

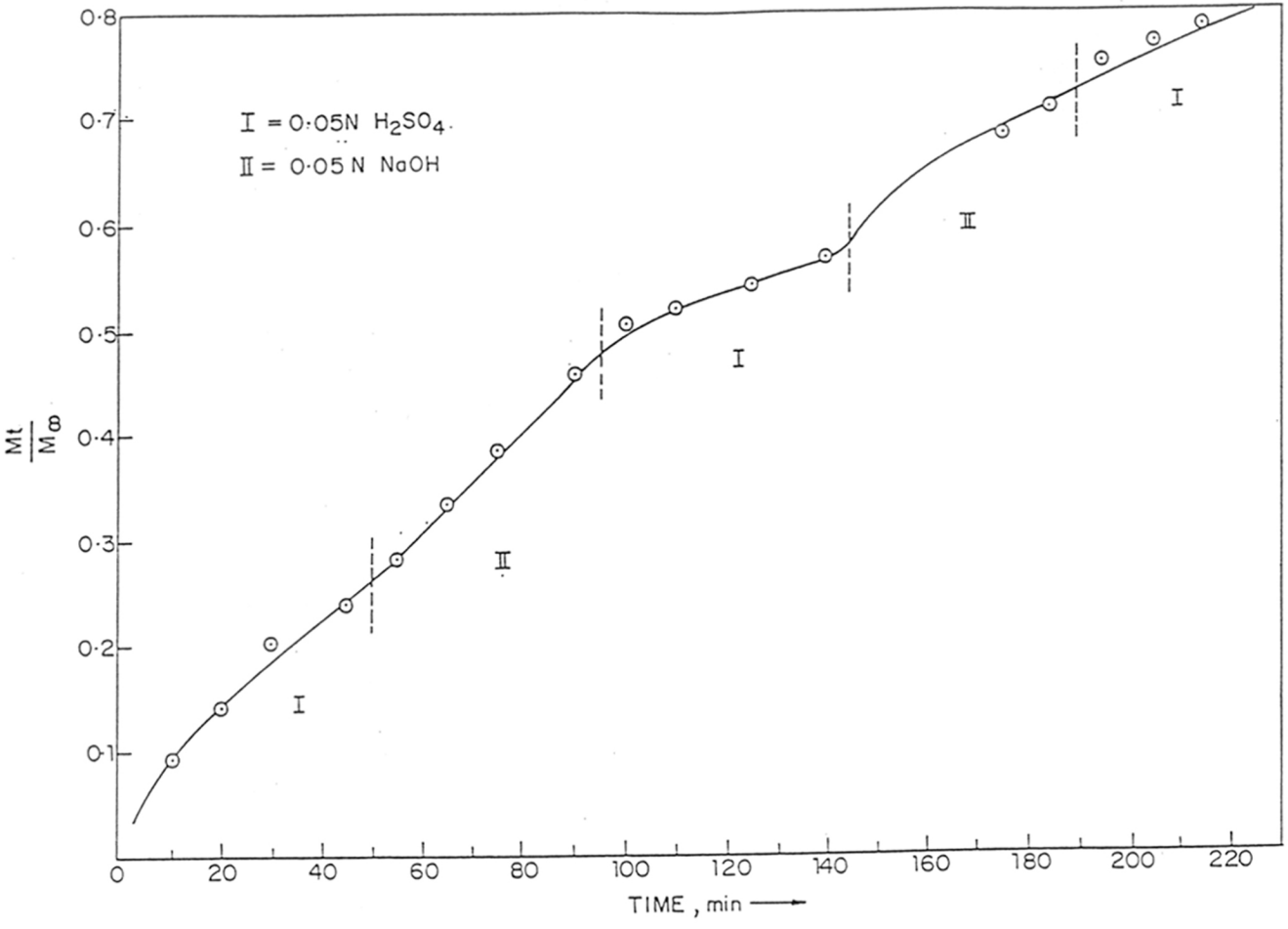


FIG. 4·16: RELEASE OF THEOPHYLLINE IN ACID/BASE -P(HEMA)(98) MOCM (2).

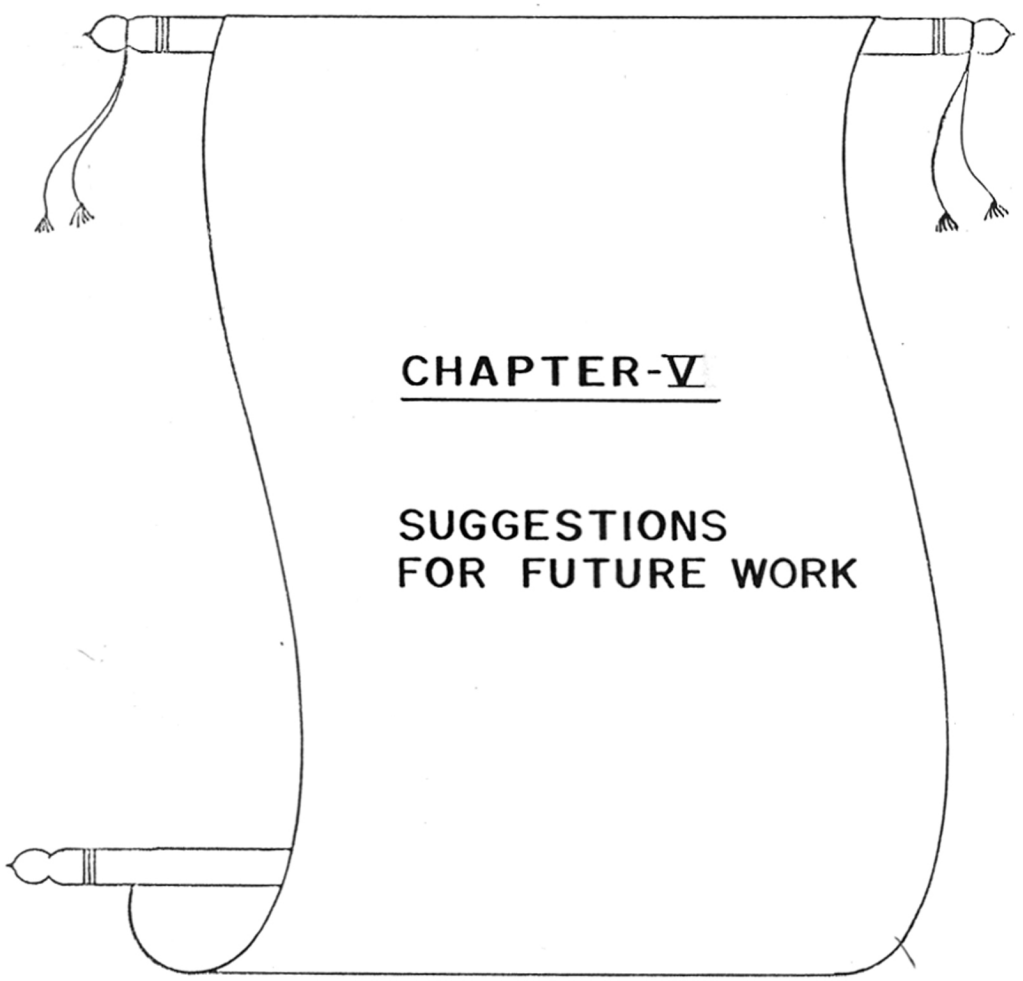
in the acidic medium is slightly lower than that in the alkaline medium, we believe that this system may not be a matrix pumping system. Release at finite rate can be attributed to the fact that even though the deswelling results in the formation of a surface layer, the permeability of the collapsed layer would be high enough as a result of high degree of hydration of the polymer even in acidic medium as compared to that for P(HPMA-MOCM)

At this stage we would like to comment on the differences in the release characteristics of two types of hydrogels. The release of active ingredient from HEMA based hydrogels swollen to equilibrium in alkali and exposed to acid lead to anomalous release profile. Release from the hydrogels swollen to equilibrium in water is not significantly affected when exposed to either acid or alkali. This can be attributed to the fact that the differences in degrees of hydration of the core and the barrier layer are not so significant as to drastically influence the diffusivities. Since HPMA is less hydrophilic, the overall degree of hydration and the diffusivity of the active ingredient is significantly influenced by the state of the comonomer. When the gels are swollen in alkali and the barrier layers are formed in the acid medium, the active ingredient is released at a constant rate under the conditions defined by equation (1.18). The on-off release can be attributed qualitatively to the fact that the equilibrium swelling of the hydrogel in water is considerably much less than that in alkali. When the release is carried out in the acidic medium the thickness of the collapsed layer increases with time and the diffusivity of active ingredient through the collapsed layer is further lowered. As a result, the release of the active ingredient is almost completely suppressed.

4.6.0 Conclusions

This chapter demonstrates the zero order release of theophylline from glassy polymers as a result of the enhanced swelling accompanying solvent penetration. The zero order release from a matrix device is demonstrated by imposing a rate controlling barrier on the surface. The barrier formation takes place by bringing about pH dependent

volume phase transitions on the surface of the matrix. The on/off release of theophylline from swollen matrices in acid/base alternatively is also shown.



CHAPTER-V

SUGGESTIONS FOR FUTURE WORK

SUGGESTIONS FOR FUTURE WORK

Extensive efforts have been carried out in the last two decades to achieve constant rate of release of drugs from drug delivery systems. Efforts have been aimed at designing novel drug delivery systems and establishing criteria for achieving zero order release from such systems. The various approaches utilised in the past include change in geometry of device, non-uniform drug concentration profile, swelling controlled systems and imposition of a rate controlling barrier layer on the surface of the device.

Traditionally, swelling controlled zero order release has been explained on the basis of Case II transport of the solvent medium into the polymer matrix. In many cases, however, no qualititative physicochemical data such as the penetration velocity, swelling kinetics etc. are reported to support the Case II transport controlled release kinetics. Dimensional changes in the device accompanying release can also lead to the release of the active ingradients at constant rates. Theoretical models attempting to explain release kinetics on the basis of such approaches have been reported in the literature (Korsmeyer and Peppas 1986, Petroupolous 1978). These need to be experimentally validated.

In this group, zero order release from swelling controlled systems has been reported in the past. Copolymers based on HEMA (2-hydroxyethyl methyl methacrylate) and HPMA (2-hydroxypropyl methyl methacrylate) have been used to achieve zero order release of theophylline from glassy and swollen matrices, respectively. This work reports the release of theophylline from [HEMA-co-4-methyl-7-hydroxy coumarine methacrylate] and [HPMA-co-4-methyl-7-hydroxy coumarine methacrylate] systems. The work provides the necessary physicochemical data to quantitatively establish the Case II transport controlled release kinetics.

Another approach which has been reported in the past to achieve zero order release is the imposition of a rate controlling barrier layer on the surface of the matrix device. However, in this case also there has been no effort to provide a quantitative explanation as to how zero order release is possible from such systems. Release kinetics have been explained in a qualititative manner, using the terms such as swelling controlled systems and matrix pumping systems (Yoshida et.al. 1989). It is not clear as to what is the mechanism of release and under what conditions zero order release from such systems is possible.

Further work needs to be undertaken to quantify the results based on the criteria for zero order release from barrier systems and compare the results based on these predictions with the qualititative considerations put forth in the literature.

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