CONTROLLED RELEASE DELIVERY SYSTEMS BASED ON THERMALLY REVERSIBLE HYDROGELS

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DECLARATION

Certified that the work incorporated in the thesis " STUDIES IN CONTROLLED RELEASE DELIVERY SYSTEMS BASED ON THERMALLY REVERSIBLE HYDROGELS " submitted by Miss. P.P.Notani 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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LITERATURE SURVEY

1.0.0 Introduction

Controlled release technology evolved as an active discipline for pesticide delivery in early seventies. Since then the technology has found applications in diverse fields in the delivery of a wide range of bioactive molecules such as pharmaceuticals, pesticides, fertilizers, pheromones, and plant growth regulators. The advantages of controlled release delivery systems include a) more efficient use of bioactive materials b) better environmental management c) ease of handling the toxic materials etc. As a result of the extensive research over the past two decades, a large number of products based on this technology have been commercialized (see Table I). There has been a distinct trend over the past few years to elucidate the mechanism of release from the various types of release devices. As a result, it is now possible to design a release device based on scientific principles from the knowledge of the relevant physicochemical data for the polymer and the bioactive molecule.

1.1.1 Controlled Release Delivery Systems

Some of the bioactive molecules initially delivered by the controlled release mechanism were molluscides, pesticides and insecticides. However, it was soon realized that the technology can have a major impact in the area of pharmaceuticals. As a result, research in the controlled release of pharmaceuticals has received a major impetus over the last two decades. Fertility control has been one of the most extensively investigated area. [Zaffaroni (1974), Scommenga (1975)].

TABLE I

CONTROLLED RELEASE DELIVERY SYSTEMS

COMMERCIAL APPLICATIONS

Product	Description	System	Controlling Mechanism
Brocon CR	Nasal decongestant in HPC matrix	Erodible matrix	1
Toxhid	Warfarin	Erodible matrix	1
Ocusert	Pilocarpine in EVA copolymer	Laminated reservoir	2
No pest strip	DDVP in PVC	Monolithic device	2
Penncap^{M}	Methylparathion in polyamide	Reservoir device	2
Conrel	Gossyplure in polyamide	Hollow fibre	2
Hercon tape	Baygon in PVC - polyester laminate	Laminated reservoir	2
Incracide E - 51	Copper sulphate in rubber	Monolithic device	2
Dursban 10 CR	Chlorpyrifos in chlorinated polyethylene	Monolithic device	2
No foul	Marine antifoulant in neoprene rubber	Monolithic device	2
Altoside - SR 10	Methoprene in polyamide	Microcapsule	2
Zodiac	Baygon in PVC	Monolithic device	2
Progestasert	Progesterone in EVA copolymer	Reservoir device	2

1 = Chemically controlled, 2 = Diffusion controlled release.

Controlled release formulations have been developed to deliver narcotic antagonists, fluoride for dental treatment and drugs to combat cancer. For long term delivery, implants are the most desirable choice. Silicone and high density Polyethylene have been widely used in the manufacture of intrauterine devices because of their physiological inertness and biocompatibility. One of the earliest successes of the technology was the development of the device " Occusert " for the treatment of glaucoma to reduce the occular pressure. A low, constant therapeutic level of pilocarpine is maintained in the eye. In the conventional therapy the drug had to be administered as eye drops every six hours.(Ness 1971). The first successful transdermal therapeutic system delivered scopolamine , a powerful antiemetic drug for the control of motion sickness.(Chandrasekaran et. al. 1978). A membrane moderated controlled release device developed was Rose - Nelson pump (Rose and Nelson 1955) to deliver medication to the rumen of the sheep. An osmotic pump for the controlled release of insulin was also introduced for the treatment of diabetes. (Tamborlane et. al. 1979).

1.1.2 Rationale for Controlled Release Drug Delivery Systems

In the conventional treatment, drugs are administered at periodic intervals by ingestion of pills and liquids, or by injection. These are then distributed throughout the body. In such cases the concentration of the drug in the blood initially rises to the " therapeutic range ", which is the range in which the blood concentration of the drug is sufficient to produce the desired therapeutic effect. Above a certain level,

the drug is toxic and can cause side effects such as headache, nausea, variations in blood pressure, or mental depression. Subsequently, the drug concentration in the blood returns to the therapeutic range and remains within the therapeutic range for quite some time. Finally, the drug concentration drops below the therapeutic level. The drug is then ineffective. (see Fig.1). (Robinson 1978).

A more desirable regimen would be to release the bioactive molecule in such a way that its concentration is maintained within the therapeutic limits for extended time. It would be even more desirable if this active agent is released directly to the target. A controlled release drug delivery system is capable of achieving one or more of the following (Lee and Good 1986).

1. Maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuations.
2. Predictable and reproducible release rates for extended time duration.
3. Enhancement of activity in the case of drugs which have short half life.
4. Elimination of side effects, frequency of dosing, and waste of drug.
5. Optimized therapy and better patient compliance.

1.1.3 Controlled Release Delivery Systems: Kinetics of Release

The controlled release delivery systems can be broadly classified as follows according to the rate controlling mechanism.

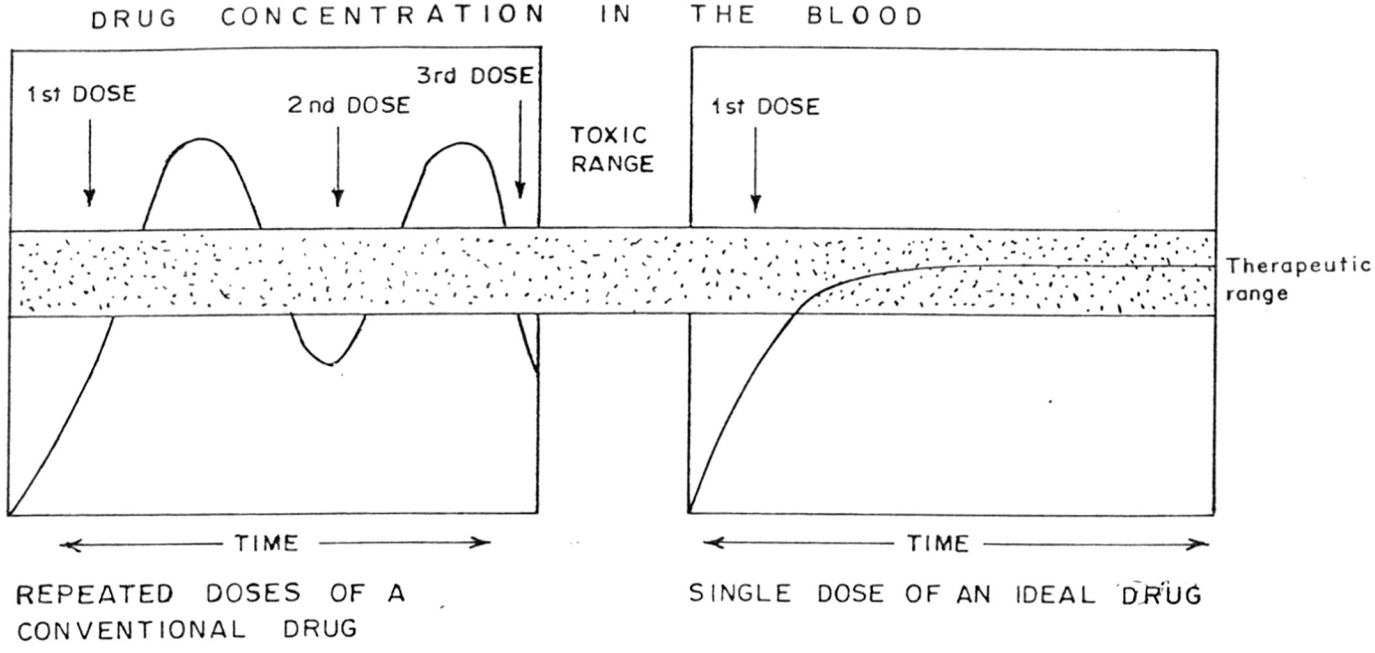


FIG. 1.

DRUG CONCENTRATION AS A FUNCTION OF TIME FOLLOWING ADMINISTRATION

I Diffusion controlled systems

a] Reservoir systems

b] Matrix systems

II Chemically controlled systems

a] Bioerodible systems

b] Pendant chain systems

III Swelling controlled systems

A brief outline of the release characteristics of each type of device is given below.

I. **Diffusion controlled systems**

a) Reservoir systems

A number of products based on reservoir systems have been commercialized. These include devices such as progestasert, occusert, Hercon dispensers and transdermal delivery systems. One of the merits of the system is that it offers a strictly zero order release. Basically a reservoir system consists of a polymer membrane which controls the release rate of the bioactive molecule contained in it. A zero order release kinetics results if the activity within the reservoir is maintained constant during the life span of the device. Chien and Lambert (1976) developed the following relationship for the release of progesterone from a silicone capsule into an infinite medium (i.e. perfect sink condition).

$$\frac{Q}{t} = \frac{C_p k D_s D_m}{K D_s \delta_D + D_m \delta_m} \qquad (1)$$

where Q denotes the amount of active ingredient released per unit surface area of the device, C_p is the solubility of the active

ingredient in the membrane, and δ_D and δ_m denote the thickness of the reservoir membrane and the hydrodynamic boundary layer in its immediate neighborhood. Zero order release results when a matrix device is laminated between the two rate controlling membranes. e.g. Olanoff et.al. (1979) demonstrated that the release of tetracycline and glutamate from 2 - hydroxyethyl methacrylate - methylmethacrylate copolymers as rate controlling membranes followed zero order kinetics. In both the cases the release rates were matrix controlled. Kinetics of release from laminated reservoirs containing an erodible matrix has been recently investigated by Thombre and Himmelstein (1984).

b) Matrix systems

The system consists of a bioactive molecule dispersed in a polymeric matrix. The greatest merit of the matrix device is the ease of fabrication. Based on a pseudo steady state assumption and absence of boundary layer effects, Higuchi (1960) first attempted to model the release rate from a matrix device containing an active ingredient in excess of its solubility. Chien et al (1976) derived the following expression for the release from a matrix device.

$$\delta_m^2 + \frac{2(A-C_p)D_m\delta_m\delta_D}{(A-\frac{C_p}{2})D_s\bar{k}K} = \frac{2C_pD_m}{(A-\frac{C_p}{2})}t \qquad (2)$$

where A denotes the loading of the active ingredient , $C_p$denotes the solubility in the polymer phase, δ_D denotes the thickness of the hydrodynamic layer in the vicinity of the device and δ_m denotes the thickness of depletion zone, D_m and D_s denote the

diffusivities of the diffusing molecule in the matrix and the surrounding medium respectively. A more refined model based on the unsteady state analysis was recently given by Paul and McSpadden (1976). The amount of active ingredient released from an element of thickness δ_m is given by

$$Q = (A - C_p/2)\,\delta_m \qquad (3)$$

and is governed by the relative contributions of the hydrodynamic layer and diffusion from the depletion zone. When the partition coefficient from polymer to solution phase is too low, we have

$$\frac{Q}{t} = \frac{\bar{k}\, D_s K\, C_p}{\delta_D} \qquad (4)$$

Thus, a zero order release results from the matrix device when partition controls the release kinetics. Also when the partition coefficient of the active ingredient is high, we have,

$$Q = \left[(2A - C_p)\, C_p D_m t\right]^{1/2} \qquad (5)$$

The release rate under such conditions is proportional to the square root of time. The release kinetics is thus governed by the environmental conditions. e.g. Roseman and Yolkowski (1976) observed that " in vivo" release rates of a series of p - amino benzoic acid esters followed a zero order kinetics. On the contrary, "in vitro " release rates were proportional to the

square root of time. One of the limitations of the matrix systems is that the release rate decreases with time.

II. **Chemically controlled systems**

a) **Bioerodible system**

The bioerodible polymer for use as implants has to be essentially biocompatible and yield nontoxic products on degradation. Yolles et. al. (1970) were the first to demonstrate the utility of poly (lactic acid) as a synthetic biodegradable polymer in the release of cyclocine. Characteristics of an ideal polymer for use in implants have been summarized by Langer and Peppas (1983). A summary of the various polymers used is given by Yolles and Sartori (1980). Bioerodible polymers have been utilized in the controlled release of bioactive molecules in various forms. The types of devices based on bioerodible polymers are summarized in Fig. 2.

Reservoir devices

The release rate from reservoir devices based on biodegradable polymers as the rate controlling membranes is identical to that of the conventional systems and equation (1) is still valid. The rate controlling membrane maintains its integrity over the effective life of the device. The membrane degrades later.

Matrix devices

In the case of diffusion controlled devices, the rate of biodegradation of the polymer over the period of treatment is almost negligible e.g. Schindler et. al. (1977) observed that the release of progesterone from poly (ϵ caprolactone) was

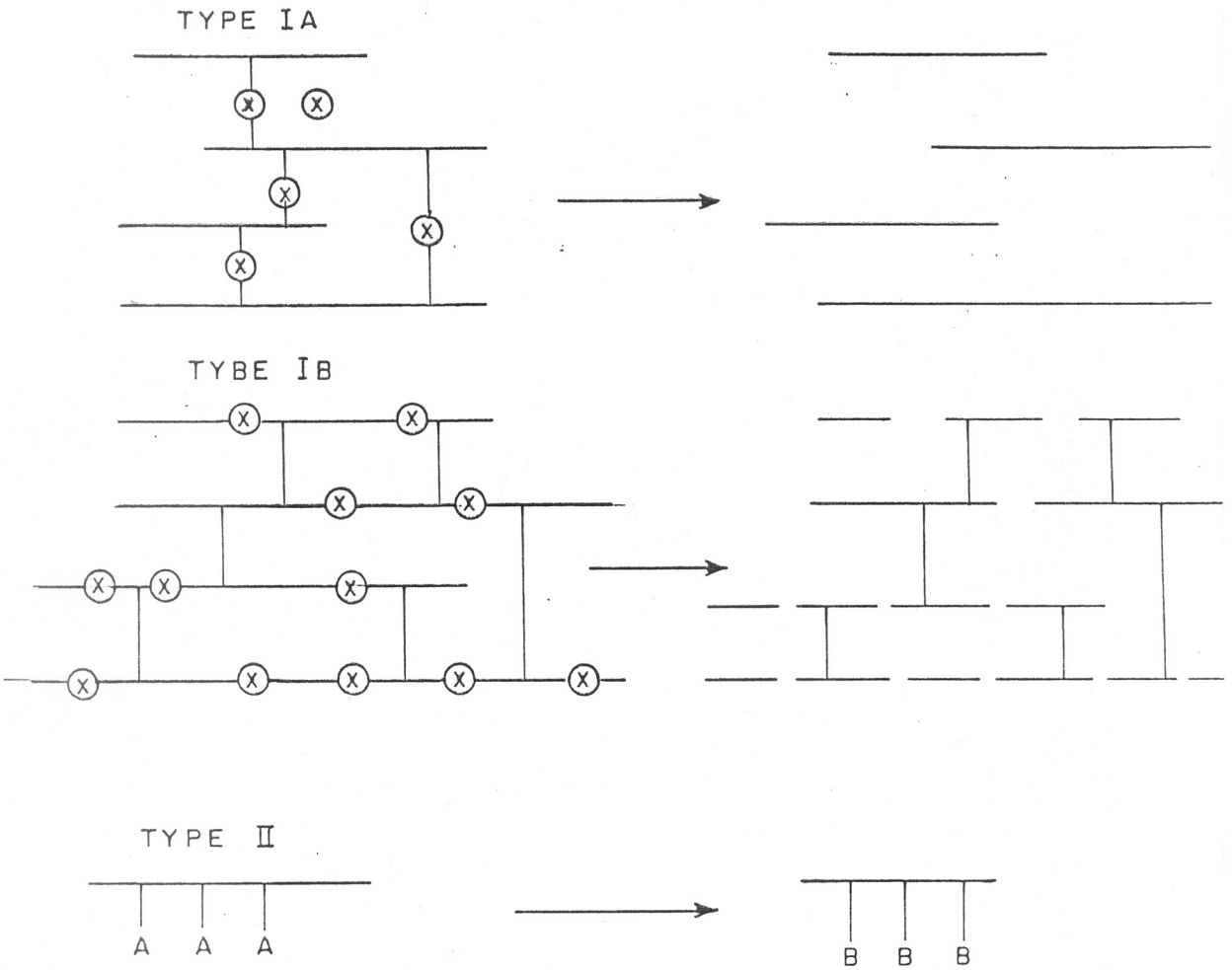


FIG. 2.

CLASSIFICATION OF BIOERODIBLE POLYMERS FOR CONTROLLED RELEASE

proportional to the square root of time upto eighty percent exhaustion. The release kinetics in this case follows Higuchi model (Higuchi 1961). On the contrary, if the rate of degradation of the polymer is much faster than the diffusion of the active ingredient from the matrix, the release kinetics is governed by the matrix erosion rate. The erosion of the polymer matrix could occur by a) cleavage of the crosslinks which have insolubilized a soluble polymer, b) conversion of an initially insoluble polymer into a soluble polymer and c) conversion of an insoluble polymer into soluble oligomers. The merits and limitations of devices undergoing degradation by each of the mechanisms discussed above have been reviewed by Heller (1984).

b) **Pendant chain systems**

In these systems, the bioactive molecule is chemically linked to the polymer matrix. It is released by a chemical scission step which is generally hydrolysis. The technique is most commonly used in controlled release of pesticides and drugs. The literature on the synthesis and release of pendant chain systems has been reviewed by Harris and Arah (1980) and Kim et. al. (1980). A series of organotin polymers were synthesized and the release rates of tributyl tin chloride from the matrix were studied by Somasekharan and Subramanian (1980). The hydrolysis of the pendant chain and subsequent reaction of the molecule with sodium chloride were extremely rapid compared to the diffusion of the tributyl tin species through the matrix. The release characteristics conformed to a diffusion controlled mechanism, although the system has been classified as chemically controlled system.

III Swelling controlled systems

Hopfenberg et.al. (1981) proposed that if a glassy polymer containing an entrapped solute be exposed to a medium which would rapidly diffuse into the matrix, and also swell it considerably, then the release of the solute is governed by the velocity of the moving boundary separating the swollen and the unswollen polymer. Swelling of the matrix polymer by the penetrating medium can thus be considered as phase erosion. Since the phase erosion follows a zero order kinetics, the release of the entrapped molecule would follow zero order kinetics. This was shown to be the case for the release of Sudan Red 1V dye from polystyrene films immersed in n - Hexane.(Hopfenberg and Hsu 1978).

Peppas and Franson (1983) introduced the concept of swelling interface number to predict the mechanism of release from a swollen polymer. The equilibrium swelling interface number was defined as

$$\left(Sw_e = \frac{V \cdot \delta_{max}}{D_s} \right) \qquad (6)$$

where v denotes the velocity of the advancing penetrant front, δ_{max} denotes the equilibrium thickness of the swollen phase and D_s denotes the diffusion coefficient of the bioactive molecule in the swollen polymer. A zero order release kinetics was predicted for $Sw_e \simeq 0.01$. From the definition of the swelling interface number it is easy to realize that swelling controlled release depends upon a) a constant velocity of the penetrant swollen

front b) high penetrant activity and c) high diffusion coefficient of the bioactive molecule in the swollen polymer. The knowledge of diffusional Deborah number and of diffusion coefficient of the bioactive molecule in the swollen polymer is an essential prerequisite for the design of a swelling controlled release device. For a given polymer-penetrant system, the release of a small molecule would show zero order release rate, whereas a large molecule such as theophylline would still be released by a diffusion controlled mechanism. However, no devices exploiting this methodology have been as yet commercialized.

1.1.4 Importance of Zero Order Release in Pharmaceutical Applications.

As has been shown earlier, a wide range of release patterns are exhibited by different controlled release devices. Zero order release pattern is widely 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. 3. The drug concentration in the plasma can be given by the equation

$$C_{Plasma} = \frac{(Dose)_a}{V_d} \frac{K_a}{K_a - K_e} \left(e^{-K_e t} - e^{-K_a t} \right) \qquad (7)$$

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 a formulation related variable whereas all the other terms are characteristics of the drug.

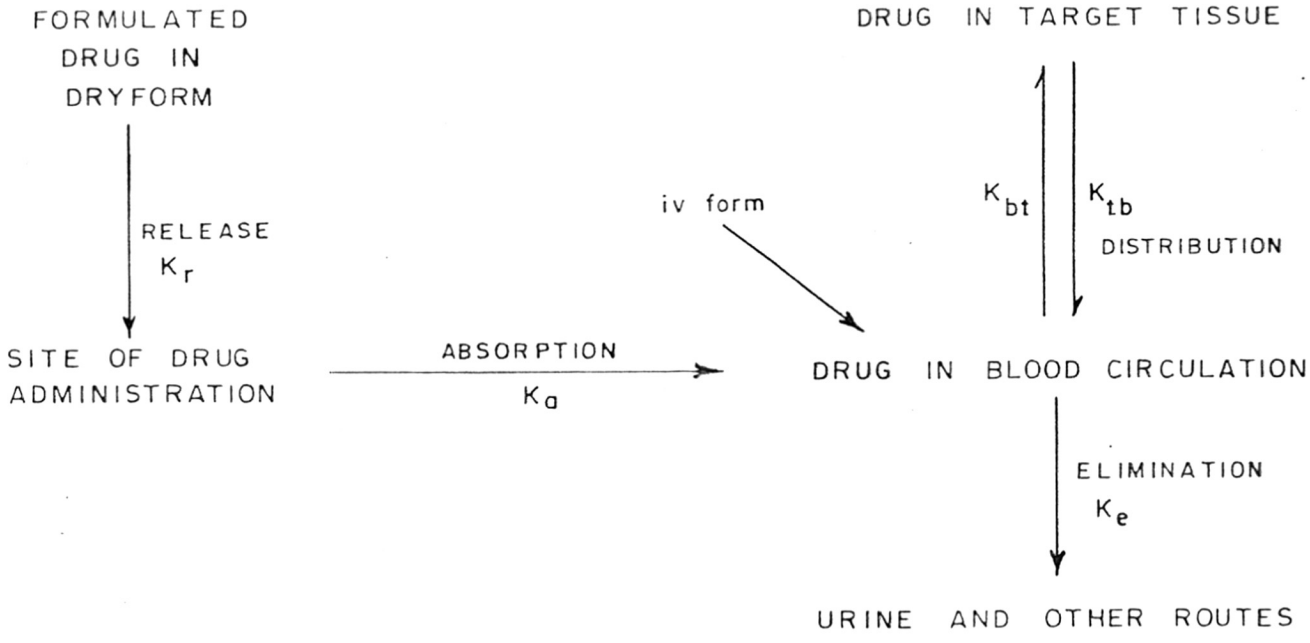


FIG. 3.

PHARMACOKINETIC PROCESSES IN DRUG ADMINISTRATION

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

$$C_{plasma} = \frac{K_o}{K_e V_d} \left(1 - e^{-K_e t}\right) \qquad (8)$$

where, K_o denotes the rate constant for the zero order release. At some time after the administration of the drug, the $e^{-K_e t}$ term approaches zero and a steady state drug concentration given by

$$(C_{plasma})_{ss} = \frac{K_o}{K_e V_d} \qquad (9)$$

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

$$(C_{plasma})_{ss} = \frac{K_o}{\beta V_d} \qquad (10)$$

where β is the composite rate constant for drug elimination estimated by a plot of terminal elimination phase of a plot of ln (C_{plasma}) vs. t. 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 a first order kinetics, the concentration of the drug in the plasma is given by

$$C_{plasma} = \frac{K_1 (dose)}{(K_1 - K_e) V_d} \left(e^{-K_e t} - e^{-K_1 t}\right) \qquad (11)$$

equation 11 is a transformed form of equation 7 since release of drug from CRD system becomes the rate controlling step i.e., $K_1 << K_a$.

For a multicomponent system

$$C_{plasma} = \frac{K_1 (dose)}{(K_1 - \beta) V_d} \left(e^{-\beta t} - e^{-K_1 t} \right) \qquad (12)$$

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

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

1.1.5 Approaches to Zero Order Release from Matrix Systems

The matrix systems are generally preferred because of the ease of fabrication and low cost. However,these devices cannot give a constant release rate from classical geometries such as slabs, cylinders or spheres. This is a result of the increasing diffusional resistance and decreasing area as the penetrating front proceeds inward.

Consider diffusion from a slab of thickness L, in which the initial drug concentration is C_o and the concentration at the

surface is maintained at C (for C = 0 , this corresponds to perfect sink conditions). Fick's second law, along with the proper initial boundary conditions, may be written as

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \qquad (13)$$

where, $t=0 \qquad -L/2 < x < L/2 \qquad C = C_o$

$t \neq 0 \qquad x = +L/2 \qquad C = C_1$ (14)

solutions of Fick's law using a trigonometric series solution under these conditions gives equation (15)

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp \left[\frac{-D(2n+1)^2 \pi^2}{L^2} t \right] \qquad (15)$$

where, M_t is the amount of drug released at any time, and M_∞ is the amount of drug released at infinite time. The quantity M_t / M_∞ is known as fractional release. Solution of equation (15) using a series of error functions gives equation (16).

$$\frac{M_t}{M_\infty} = 4 \left[\frac{Dt}{L^2} \right]^{1/2} \left[\pi^{-1/2} + 2 \sum_{n=1}^{\infty} (-1)^n \text{ ierfc } \frac{nL}{2\sqrt{Dt}} \right] \qquad (16)$$

where , ierfc (x) represents the integrated complimentary error function. For values of fractional release less than 0.60 (i.e. at short times) equation (16) may be approximated by equation (17).

$$\frac{M_t}{M_\infty} = 4 \left(\frac{Dt}{\pi L^2} \right)^{1/2} \qquad (17)$$

The fractional release is proportional to the square root of time. Similar results may be obtained for spheres and cylinders. The approaches adopted in the past to attain a constant rate of the active ingredient include the following.

Geometric modifications

Brooke and Washkuhn (1977) suggested earliest of the geometric modifications to achieve zero order release from matrix systems. Drug was filled in a hollow cylinder with an impermeable wall outside. The drug is released from the inner core of a cylinder. When exposed to an aqueous medium, because of the geometric shape, as the drug is lost from the device, the interfacial area increases leading to a relatively constant rate of release. The release data display linearity with time following an initial burst.

In another study Langer et. al. (1980) demonstrated the utility of geometric modifications to achieve near zero order release kinetics. Nelson et. al. (1986) fabricated a device that incorporated the idea of geometric modification. In a poly carbonate sheet, many frustum shaped cells were drilled using a specially fabricated kit as shown in Fig. 4. Ethyl p - amino benzoate was dispersed in a silicone elastomer base. This was added to the drilled cells and cured. A non permeable backing was provided on the upper surface. When exposed to an aqueous medium, the drug diffuses out from the small openings at the bottom surface. As the drug is lost from the device, interfacial area increases because of the peculiar geometric shape. The release data display linearity with time following an initial burst.

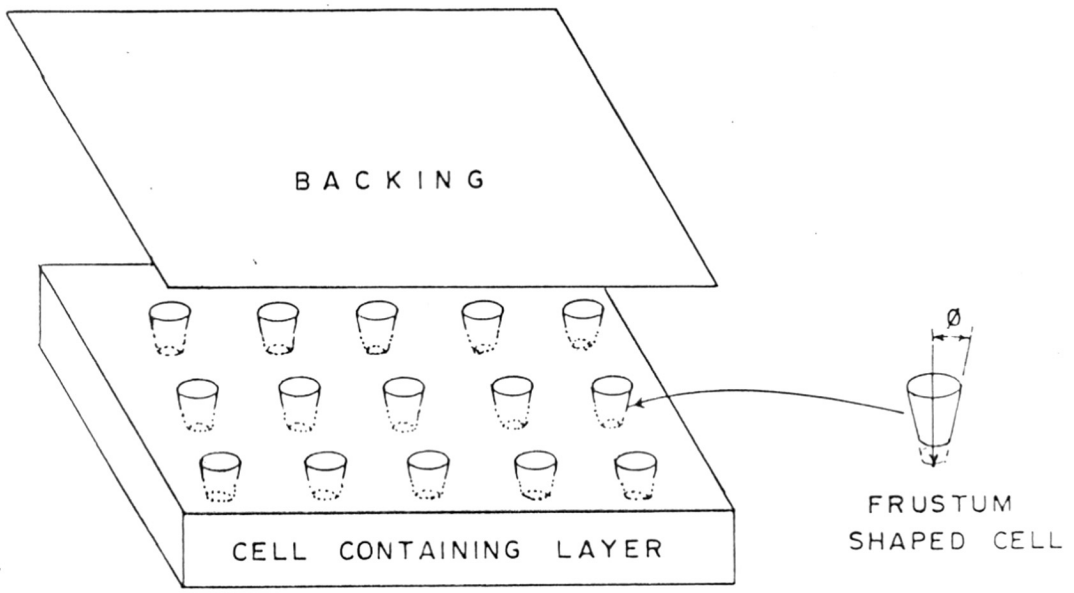


FIG. 4

FRUSTUM – ARRAY DEVICE

Laminated reservoirs

Cardinal et. al. (1980) studied the release of progesterone from reservoir - monolithic type hydrogel devices. A matrix device based on PMEEMA or Poly (HEMA - MEEMA) containing progesterone was prepared. PHEMA served as the barrier membrane. It was shown that so long as the permeability of the barrier material was lower than that of the matrix, a constant release rate could be achieved upto twenty days.

Anderson et. al. (1979) studied tetracycline release from trilaminated discs. Drug dispersed in the appropriate matrix formed the core. A hydrophobic polymer which served as the rate limiting membrane formed the outer layer. Matrix maintained a constant activity of the drug at the interface between the core and the outer membrane, thus resulting in constant release rate. Similar results are obtained by Borodkin and Tucker (1975).

Nonuniform concentration profiles

A constant rate of drug release can be achieved by establishing a special sigmoidal drug concentration profile across the matrix. Lee (1983) explored the effect of nonuniform concentration distribution as an approach to achieve zero order release from matrix systems. Hydrogel beads containing HEMA and a polymeric crosslinking agent (PX) were prepared. These beads were subjected to a controlled extraction process in water. The extraction time was shorter than the time required for penetrating solvent front to meet at the center. This treatment resulted in a sigmoidal drug distribution, which was immobilized by freeze drying. Zero order release was observed in some cases

upto 60 % of total release.

Polymer blend matrices

By using a mixture of Sodium carboxy methyl cellulose (Na CMC) and hydroxyproyl methyl cellulose (HPMC) or hydroxy propyl cellulose or methyl cellulose as matrices, nearly zero order release of several very soluble drugs was achieved. Baveja et. al. (1985,1987), Ranga Rao et. al. (1988). It was found that in addition to the molecular size and aqueous solubility of the drug, other factors like erosion of the matrix, interaction between the drug and the polymer(s) might govern the release of the drugs. Ranga Rao (1987, 1988) showed that an increase in the solubility of the active ingredient increased the release rate in a nonlinear manner from both the matrices. (Figs. 5 and 6). Presence of drug increases the erosion rate (ER) of the pure polymer to different degrees depending on the nature of the drug (Figs 7 and 8). Erosion rate in alkaline medium was much lower compared to that in acidic medium, which in turn is slightly lower than that in water (Fig. 9).

1.1.6 Swelling Controlled Delivery Systems: Mechanistic Aspects

Diffusional Transport in Polymers

Swelling controlled delivery systems consist of glassy polymer matrices. The penetration of the surrounding medium into the matrix follows case II kinetics. The diffusivity of the active ingredient in the swollen matrix is high. The kinetics of release is therefore controlled by the velocity of the penetrating medium. For the design of the swelling controlled systems a knowledge of the diffusional transport in both glassy and rubbery polymers is essential.

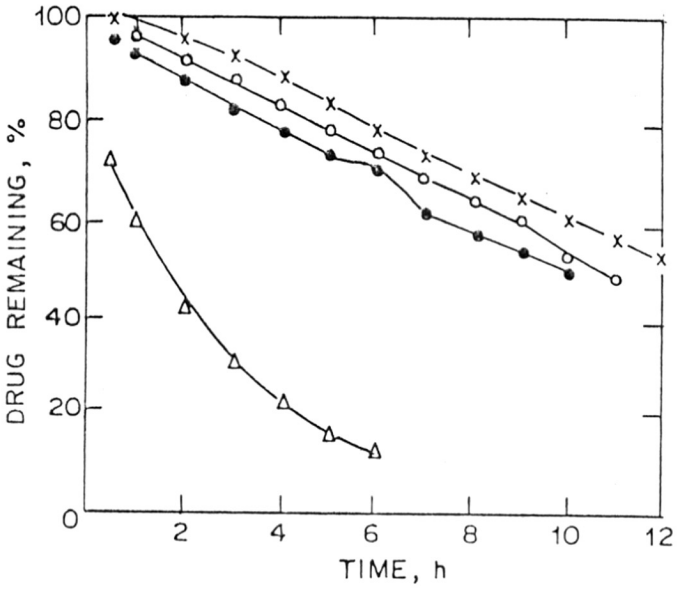


FIG. 5.

INCREASE IN RELEASE RATE OF ACTIVE INGREDIENT FROM HPMC MATRICES AS A FUNCTION OF ITS SOLUBILITY

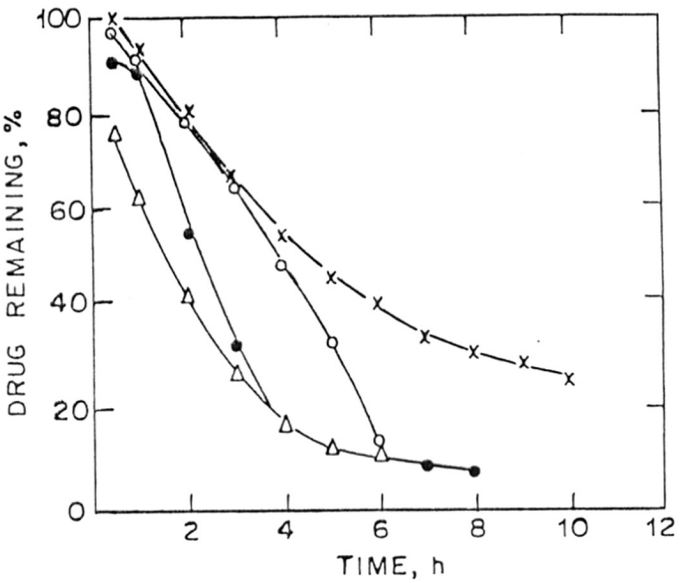


FIG. 6.

INCREASE IN RELEASE RATE OF ACTIVE INGREDIENT FROM HPMC + NaCMC MATRICES AS A FUNCTION OF ITS SOLUBILITY

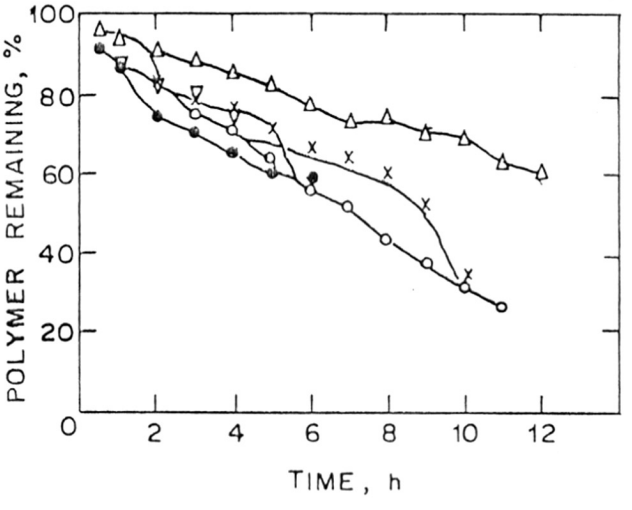
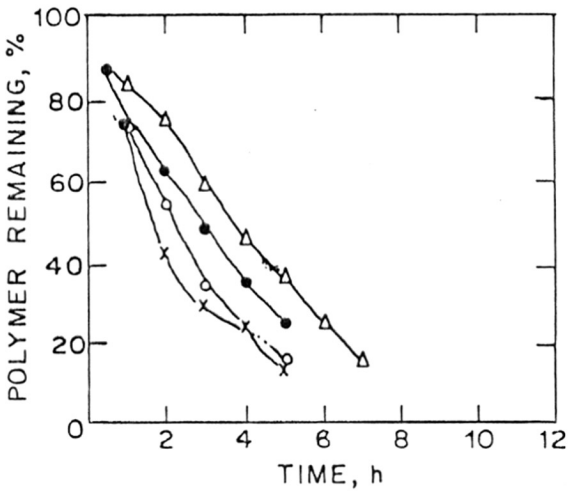


FIG. 7.

EROSION RATE (ER) OF HPMC DEPENDING ON THE NATURE OF THE DRUG



Δ NO DRUG

x PINDOLOL

o ALLOPURINOL

• Na SALLCYLATE

FIG. 8.

EROSION RATE OF HPMC + NaCMC DEPENDING ON THE NATURE OF THE DRUG

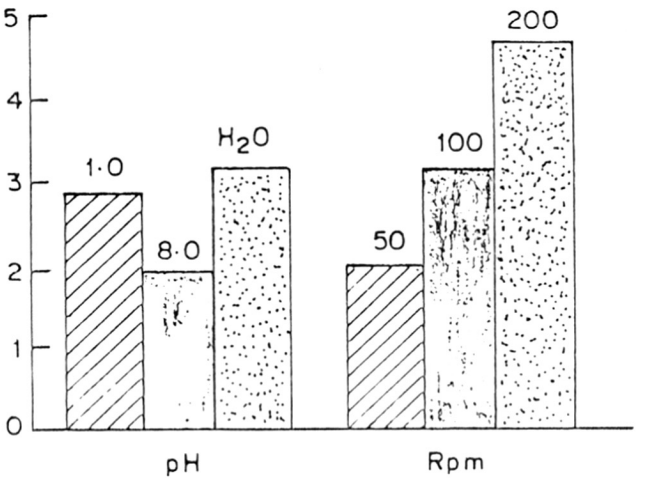


FIG. 9.

DEPENDENCE ON EROSION RATE OF THE HPMC MATRICES ON THE rpm OF THE PADDLE

Diffusional transport plays a critical role in polymers. The rate of free radical polymerizations is significantly influenced by the diffusitivity of the initiators, monomers, growing chain radicals, whereas that of polycondensation reactions is governed by the diffusivity of the low molecular weight product liberated in the polycondensation step. Diffusion of low molecular weight solutes in polymer melts plays a crucial role in the devolatilization of the polymers to maintain regulatory standards. Diffusional transport also plays a crucial role in the applications of the polymers as barrier resins for packaging, membranes for gas separations and matrices for controlled release delivery systems.

While during synthesis the polymer is either in the solution or in molten state, it is a rubbery or glassy solid during applications. It is therefore obvious that the diffusional transport in polymers would be governed by the phase state of the polymer and the nature of the diffusant.

In the classical diffusion theory it is assumed that the diffusion field exists in the equilibrium state and remains so during the diffusion experiment. However, in the case of the polymers the assumption is not necessarily always valid. (Vrentas et. al. 1975).

The diffusional transport in the various polymer - diffusant systems described above can be classified into three regimes of diffusional transport. The regimes are defined by the ratio of the time scales associated with the diffusion and relaxation in polymers. This dimensionless parameter called the

diffusion Deborah number is defined as

$$D_{(DEB)} = \left(\frac{\lambda_m}{\theta_D}\right) \tag{18}$$

where λ_m denotes the characteristic relaxation time for polymer - diffusant system and θ_D denotes the characteristic time associated with the diffusion process. For unidirectional diffusion of a penetrant into the polymer, the diffusion time is given by

$$\theta_D = \left(\frac{L^2}{D}\right) \tag{19}$$

where L denotes the thickness of the film and D denotes the diffusivity of the penetrant molecule in the polymer. The regimes of diffusion are defined by the penetrant concentration and the phase state of the polymer and are shown in Fig. 10.

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 molecule is diffusing 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 very 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 penetrant system is at a temperature higher than its glass transition temperature, the molecular motions are very rapid, the changes in the polymer structure can be considered to

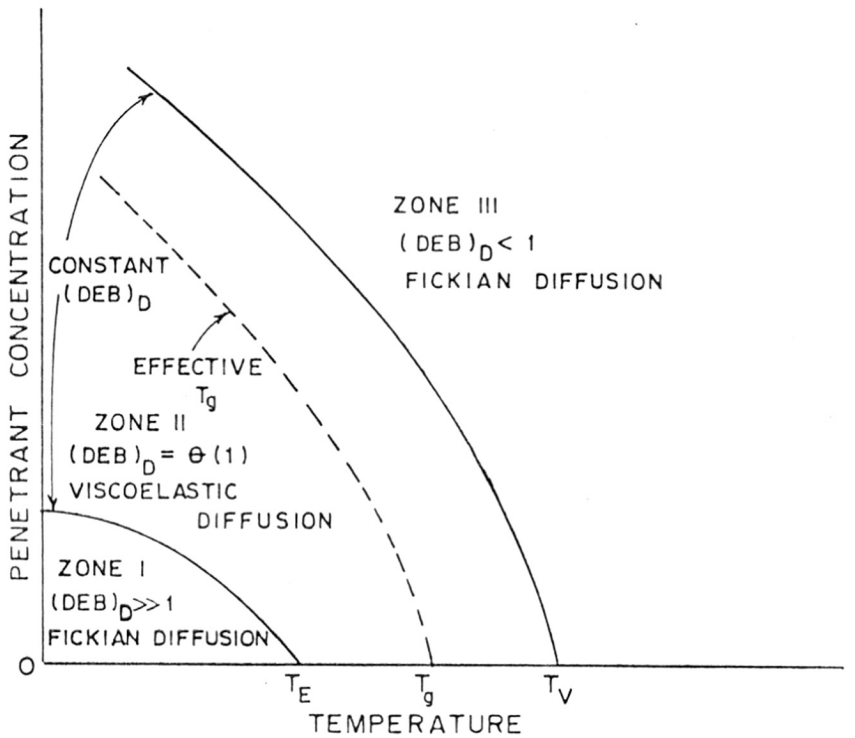


FIG. 10.

REGIMES OF DIFFUSIONAL TRANSPORT

take place almost 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.

In the intermediate range wherein the penetrant activity is reasonably high and the polymer penetrant 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 amorphous polymers in terms of the phase states of the polymer and the critical temperature of the penetrant are summarized in Table II. Thus, when the penetrant diffuses into 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 from the Fickian behaviour are observed depending on the penetrant activity. Typical amongst these are a) two stage sorption and b) case II transport of organic vapours in polymers at temperatures close to glass transition temperatures e.g. sorption of acetone in cellulose acetate and desorption of vinyl chloride monomer from PVC. Two stage sorption could be considered to be made up of 1) a fickian term and 2) a relaxation controlled term . The phenomenon is considered to result from bulk scale structural changes in the polymer and has been recently reviewed by Joshi (1985).

TABLE II

TRANSPORT IN AMORPHOUS POLYMERS

$T > T_c$	$T < T_c$
Fickian diffusion, single mode sorption	
Ideal Fickian diffusion concentration independent diffusion coefficient.	Concentration dependence 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 anamolous diffusion. Case II and super case II transport.

An intersting case results when the transport process is relaxation controlled. The phenomenon was called case II transport by Alfrey et.al. (1966). The most distinctive feature of the case II transport is the linear weight gain of the polymer with respect to time. Other features of case II transport depend upon a) the choice of the penetrant b) its shape and size c) structural features of the polymer matrix and d) experimental conditions and are summarized below :

1) The rate of sorption is linear with respect to time and not square root of time as is the case in Fickian sorption.
2) As the penetrant is sorbed, a sharp boundary separating the glassy polymer and the swollen rubbery polymer moves into the interior leaving the swollen rubbery 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.
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. e.g. during sorption of methanol - acetone mixture in polystyrene, a Fickian diffusion front of methanol is followed by an acetone front moving at constant velocity.

Following approaches have been proposed in the literature to elucidate the case II transport in polymers

1) Diffusion - convection model (Frisch et.al. 1969).

2) Diffusion in glassy polymers with discontinous swelling (Peterlin 1965).

3) Case II transport as a solution of the diffusion equation (Peterlin 1977).

4) Models of case II transport as a solution of the diffusion equation (Peterlin 1980).

5) Deformation model of case II transport. (Thomas and Windle (1984).

1.1.7 Criteria for Swelling Controlled Release

The swelling controlled systems depend upon the differences in the diffusivity of the active ingredients in the glassy and the rubbery polymers and also on the velocity of the penetration of surrounding medium into the glassy hydrogel matrices. In swelling controlled polymeric systems, the drug is originally dissolved or dispersed in polymer solution. Upon solvent evaporation, a solvent free, glassy, polymeric matrix is obtained in which the drug is uniformly dispersed. As the penetrant enters the matrix, the polymer is lowered below the temperature of the release experiment, and the swollen polymer allows the drug to diffuse out.

Relaxation controlled (case II) transport of vapors and liquids in glassy polymers has been reported for a number of polymer diluent systems (Kwei and Zupko 1969, Hopfenberg et.al. 1978) and a mechanistic interpretation of the phenomena has been offered (Windle 1985). Hopfenberg and Hsu (1978) demonstrated that the release of Sudan Red IV from polystyrene film followed zero order kinetics as a result of constant rate of sorption of n

- hexane. Hopfenberg et.al. (1981) also reported zero order release of sodium chloride from ethylene - vinyl acetate polymer films and proposed the concept of diffusional conductance as a measure of the relative magnitude of the penetrant velocity and the diffusionsl transport of the active ingredient.

Peppas and Franson (1983) analyzed the kinetics of release of theophylline from poly (2 - hydroxyethyl methacrylate - methyl methacrylate), copolymers and proposed that the swelling interface number (Sw) could be used to correlate the release kinetics. The swelling interface number is defined as

$$Sw = \frac{V \cdot \delta(t)}{D_s} \qquad (20)$$

where v denotes the velocity of the penetrating front, D_s, the diffusion coefficient of the active ingredient from the swollen matrix, and $\delta(t)$ denotes the thickness of the swollen part of the device. In fact Sw is essentially the reciprocal of the diffusional conductance defined by Hopfenberg et.al. (1981). Peppas and Franson (1983) proposed a conservative criterion for the zero order release in terms of the equilibrium swelling interface number (Sw_e) defined as

$$Swe = \frac{V_{max} \cdot \delta_{max}}{D_s} \qquad (21)$$

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 denotes the index of release, Peppas and Franson (1983) predicted that zero order release will result for $Sw_e << 1.0$. However, subsequently Davidson and Peppas (1986) observed that

the release of theophylline from these matrices approached zero order (n = 0.931), even for $Sw_e \simeq 1.0$. It was further concluded that there was no unique value for n for each value of Sw_e and that the release index cannot be predicted on the basis of the equilibrium swelling interface number alone. (Davidson and Peppas 1986).

Lee (1986) analyzed the kinetics of release from swellable polymers by assuming the diffusion coefficient of the active ingredient to be a function of time.

$$D(t) = D_i + (D_\infty - D_i)\left[1-\exp(-kt)\right] \qquad (22)$$

where D_i denotes the instantaneous component of the diffusion coefficient of the active ingredient from the polymer matrix, D_∞ denotes the diffusivity of the active ingredient from the polymer at equilibrium degree of swelling and k denotes the reciprocal of the relaxation time. The release behaviour of an active ingredient from the swellable matrix can be correlated with the Deborah number for release.

$$DER = \frac{D}{k\ell^2} \qquad (23)$$

Although the parameter is analogous to the diffusional Deborah number $D_{[DEB]}$, it needs to be borne in mind that by its very definition, the Deborah number for release for a given system will vary only due to k, since D would be constant. Thus in analogy with the diffusional Deborah number $D_{[DEB]}$, the release kinetics would follow Fickian characteristics for

$$\frac{D}{k\ell^2} \gg 1$$

and (24)

$$\frac{D}{k\ell^2} \ll 1$$

whereas the release behaviour would be anomalous i.e. the release index would deviate from n = 0.5, for

$$\frac{D}{kl^2} \geqslant 1$$

and (25)

$$\frac{D}{kl^2} \leqslant 1$$

zero order release (wherein n = 1.0) would be a more specific case of anomalous behaviour. However, the parameter does not explicitly define a criterion for zero order release.

1.2.0 Thermally Reversible Hydrogels

The concept of gel was first proposed in the nineteenth century. Gel denoted a two phase system in which the dispersed phase, although constituted a very small volume fraction, formed a three dimensional network, swollen by a large quantity of the dispersion medium. Although both amorphous and crystalline inorganic compounds were known to form gels, it was realized at an early stage that this was a characteristic feature of the high molecular weight organic compounds. It is interesting to note that a precise definition of "gel" has been eluding the scientists for almost a century and this has to a certain extent led to an abuse of the word "gel". A recent review on gels has tried to bring about the most acceptable definition of gels and a scheme for the classification of gels (Russo 1987).

Gels can in principle be classified into two categories. Type one includes gels which contain a network structure formed by secondary intermolecular forces. The gels in

this category include soaps, phospholipids, reticular networks such as vanadium pentoxide gels and gels resulting from the aggregation in natural polymers such as gelatin, alginates etc. Gels in the second category consist of a three dimensional network structure formed by the covalent linkages. This category includes vulcanized rubbers, tanned gelatin, condensation polymers synthesized from multifunctional monomers and vinyl polymers containing small amounts of divinyl monomers.

The most significant property of the gels relevant to the scope of this work is the volume phase transition. Imagine a crosslinked polyacrylamide gel imbibed in water to the equilibrium degree of swelling. When such a gel is immersed in acetone/water mixtures of increasing acetone concentration, the gel shrinks progressively. A plot of swelling ratio (v_f/v_i) vs solvent composition appears as shown in Fig. 11. The swelling behaviour with increasing degree of hydrolysis is also shown in Fig. 11. As the degree of hydrolysis increases, the swelling curve, initially continuous, shows a point of inflection at about 40% acetone concentration. At this stage, swelling ratio 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.

Phase transitions of the type described above can also be realized when a hydrolyzed polyacrylamide gel swollen in 50% acetone solution is subjected to an electric field of 500 mV / cm (Tanaka et. al. 1982). The phenomena described are not only restricted to the vinyl polymers or to the synthetic polymers

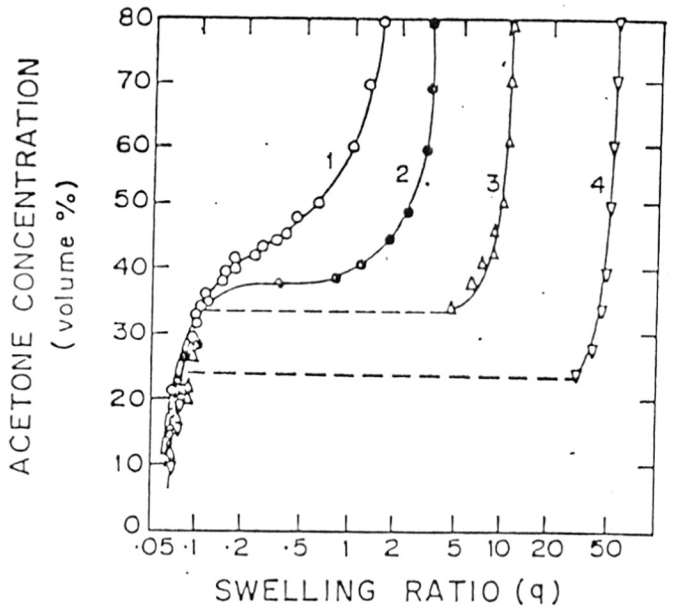


FIG. 11

A CONTINUOUS-DISCRETE TRANSITION WITH INCREASING DEGREE OF HYDROLYSIS FOR PAM GELS

alone, but are also exhibited by natural polymers such as gelatin, agarose and DNA. The volume phase transition in gels is a universal phenomena exhibited by both natural and synthetic, non-ionic as well as anionic and cationic polymers and these transitions can be brought about by variation in solvent composition, temperature or by the application of the electric field.

The swelling behaviour of Poly (N - isopropylacrylamide) gels in water as a function of temperature is shown in Fig. 12. A discontinuous phase transition is observed at 33.2°c. It is interesting to note here that while the swelling ratio of hydrolyzed polyacrylamide gels increases with increasing temperature, the swelling ratio of Poly (N - isopropylacrylamide) gels decreases with increasing temperature. The volume phase transition in Poly (N - isopropylacrylamide) has been discussed in details in subsequent sections.

1.2.1 Solution Behaviour and Phase Equilibria in Polymers

When an amorphous polymer is mixed with a suitable solvent, it disperses in the solvent and then dissolves to form a solution. In a good solvent, chain dimensions are far greater than the unperturbed dimensions as a result of the favoured polymer solvent interactions. On the other hand, in a poor solvent such interactions are limited and the chain dimensions are restricted. The thermodynamics of solutions can be described by

$$G = H - TS \qquad (26)$$

where G is the Gibbs free energy function, H is the enthalpy and

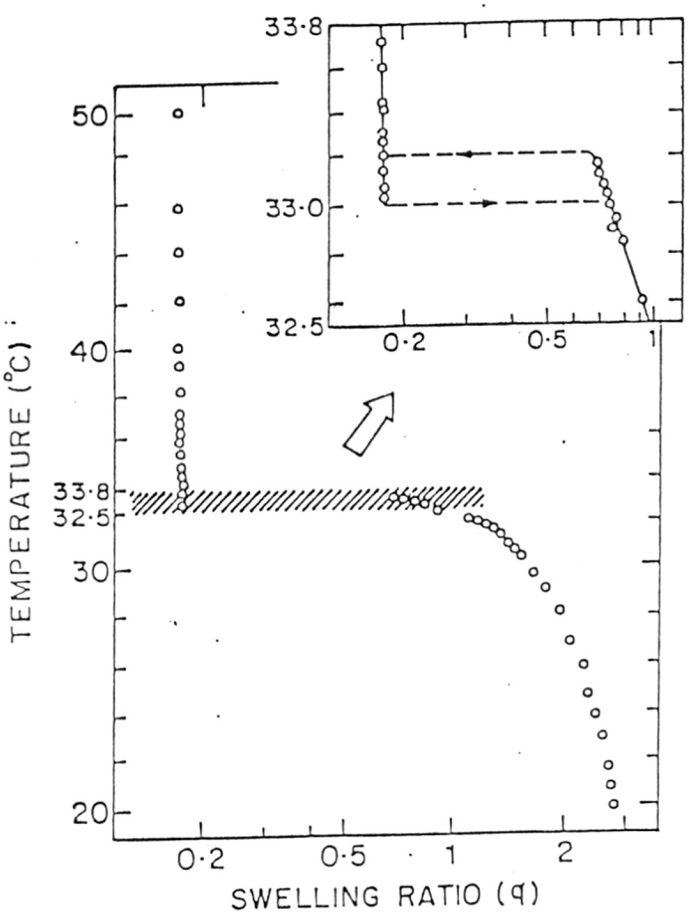


FIG. 12

TEMPERATURE INDUCED VOLUME-PHASE TRANSITION OF POLY. N-ISOPROPYL ACRYLAMIDE GEL IN WATER

S is the entropy. When the Gibbs free energy of mixing $\Delta G^m \leqslant 0$, a homogeneous solution results and

$$\Delta G^m = G_{12} - (G_1 + G_2) \qquad (27)$$

where G_{12} is the Gibbs free energy of the solution, and G_1 and G_2 denote the corresponding values for the components of the mixture. The thermodynamic characteristics of the nonpolar polymer solutions can be expressed in terms of the partial molar quantities

$$\Delta H_1 \geqslant 0 , \quad \Delta S_1 \geqslant -R \ln x_1 \qquad (28)$$

which deviate markedly from those for the ideal solution

$$(\Delta H_1 = 0 \quad \text{and} \quad \Delta S_1 = -R \ln x_1) \qquad (29)$$

The subscript 1 denotes the solvent and x its mole fraction. For a good solvent these deviations are large and ΔG^m is negative, whereas for a poor solvent these deviations decrease until the "theta" condition is attained i.e.

$$\Delta H_1 = \Delta S_1 \qquad (30)$$

Deviations from ideality in the case of ΔH^m are caused by the need to break solvent - solvent contacts and the polymer - polymer contacts to form new polymer - solvent contacts. This can be expressed as

$$\Delta H^m = z \Delta e N_1 \phi_2 \qquad (31)$$

where N_1 is the number of solvent molecules, z is the lattice coordination number, ϕ_2 is the volume fraction of the polymer and Δe is the energy of formation of a polymer - solvent contact. The large deviations in ΔS^m can be attributed to the differences in size between the polymer and the solvent molecules. Flory and

Huggins chose a simple lattice representation for the polymer solution and calculated the entropy change on a statistical basis estimating the total number of ways in which the polymer and solvent molecules could be arranged on the lattice (Flory 1953). It was assumed that the size of a polymer segment was comparable to that of a solvent molecule. The partial molar free energy of dilution is given by

$$\left(\partial \Delta G^{m} / \partial n_1\right) = \Delta G_1 = RT \left\{ \ln(1-\phi_2) + (1-1/x_n)\phi_2 + X_1 \phi_2^2 \right\} \qquad (32)$$

Here, $X_1 = z\Delta_e / RT$ and is known as the Flory - Huggins interaction parameter, n_1 denotes the number of moles of the solvent, and $x_n = (v_2 / v_1)$ is the number average degree of polymerization for the polymer. The first two terms in the brackets represent the entropic contributions and the final term the enthalpic contribution. However, it must be noted that the approach suffers from the following limitations

(1) a uniform density of lattice site occupation is assumed, which holds only for concentrated solutions

(2) the segment locating process is assumed to be purely statistical, which would be true only if Δe was zero and

(3) the treatment assumed that the flexibility of a chain is unaltered on passing into solution from the solid state.

Attempts to modify this theory, have been made by Huggins, Miller, and Guggenheim. It was recognized that X_1 is actually a free energy parameter composed of entropic (X_S), and enthalpic (X_H), contributions.

The expression for X then becomes

$$X_1 = X_H + X_S \qquad (33)$$

where

$$X_H = -T(\partial X_1/\partial T) \text{ and} \qquad (34)$$

$$X_S = \partial(TX_1)/\partial T \qquad (35)$$

Phase Equilibria In Polymer Solutions

The Flory - Huggins theory can be used to predict the equilibrium behaviour of two liquid phases when both contain amorphous polymer and one or two solvents. Consider a two component system consisting of a liquid (1) which is a poor solvent for the polymer, (2) Complete miscibility occurs when the Gibbs free energy of mixing is less than the Gibbs free energies of the components, and the solution maintains its homogeneity only as long as ΔG^m remains less than the Gibbs free energy of any two possible coexisting phases. The situation is represented by curve T_4 in the Fig. 13. The miscibility of this type is strongly temperature dependent, and as T decreases, the solution separates into two phases. At any temperature, say T_1 , the Gibbs free energy of a mixture corresponding to the composition x_2''' is higher than either of the two coexisting phases whose compositions are x_2' and x_2'' and phase separation takes place. As the temperature is increased, the limits of this two phase coexistence contract until eventually they coalesce to produce a homogeneous one phase mixture at T_c , the critical solution temperature. At the critical solution temperature the first, second and third derivatives of the Gibbs free energy with

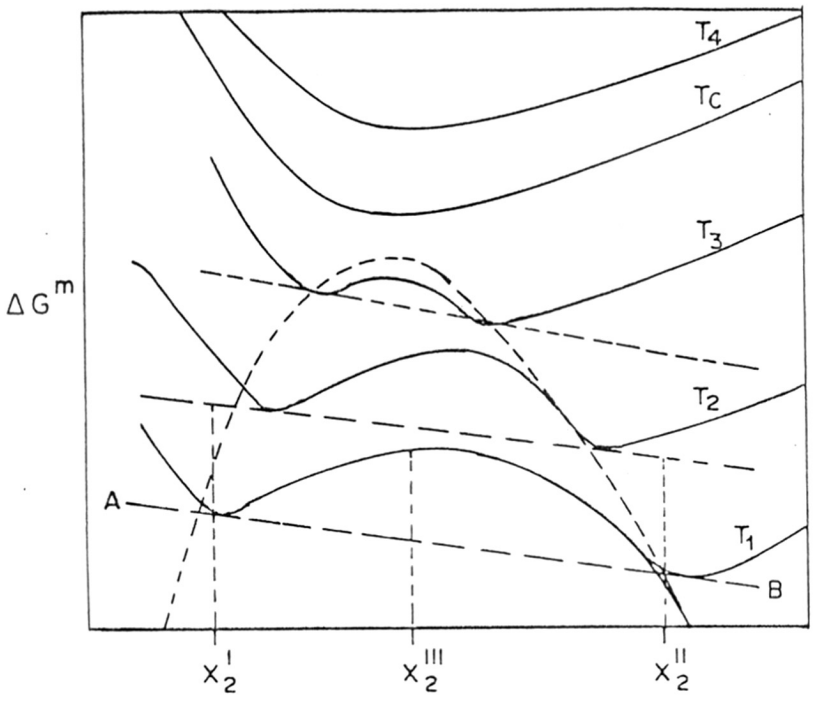


FIG. 13.

DEPENDENCE OF GIBB'S FREE ENERGY OF MIXING (ΔG^m) ON THE SOLUTION COMPOSITION

(SCHEMATIC)

respect to the mole fraction are zero.

$$\partial(\Delta G^m)/\partial x_2 = \partial^2(\Delta G^m)/\partial x_2^2 \qquad (36)$$

$$= \partial^3(\Delta G^m)/\partial x_2^3 = 0 \qquad (37)$$

The partial molar Gibbs free energies of each component are equal at this point. The conditions for incipient phase separation are

$$\partial\mu_1/\partial\phi_2 = \partial^2\mu_1/\partial\phi_2^2 = \partial^3\mu_1/\partial\phi_2^3 = 0 \qquad (38)$$

The critical composition for phase separation is given by

$$\phi_2, C = 1/(1 + x_n^{1/2}) \quad 1/x_n^{1/2} \qquad (39)$$

and $$x_1, C = 1/2 + 1/x_n^{1/2} + 1/2\ x_n \qquad (40)$$

which indicates that $X_{1,c} = 0.5$ at infinitely large chain length. A linear temperature dependence is also predicted for X_1

$$X_1 = a + b/T \qquad (41)$$

Systems which show phase separation or precipitate on heating are said to have a lower critical solution temperature (LCST). In an LCST system, the right hand branch of the curve is characterized by a positive slope, indicating that the polymer will swell less as the temperature increases. (see Fig.14).The phase diagram for systems when the solution is poor is depicted by area A as shown in the Fig. 15. The critical temperature, T_c occurs near the maximum of the cloud point curve and is often referred to as the UCST.

For nonpolar systems ΔS^m is normally positive but weighted heavily by T. Solubility then depends mainly on the magnitude of ΔH^m, which is normally endothermic and hence positive. Consequently as T decreases ΔG^m eventually becomes positive and phase separation takes place. Table III lists the various systems that exhibit LCST and UCST.

TABLE III

CRITICAL SOLUTION TEMPERATURES FOR VARIOUS POLYMERS

Polymer	Solvent	LCST(^{o}c)	UCST(^{o}c)
1)Poly iso - butylene	Ethane	< 0	36
2)Poly iso - butylene	Propane	85	103
3)Poly iso - butylene	Iso Butane	114	142
4)Poly propylene	n - pentane	152	202
5)Poly propylene (isotactic)	n - pentane	136	201
6)Poly iso - butylene	n - pentane	75	199
7)Rubber	n - pentane	130	201
8)Silicone	n - pentane	----misicible-----	
9)Poly iso - butylene	Isopentane	54	189
10)Poly iso - butylene	Cyclopentane	71	-
11)Poly iso - butylene	Benzene	150 -170	-
12)Poly styrene	Benzene	----misicible-----	
13)Poly iso - butylene	n - hexane	128	-
14)Poly iso - butylene	n - heptane	168	-
15)Poly iso - butylene	n - octane	180	-
16)Poly N - isopropyl acrylamide	Water	31 - 33	

17) Poly N,N, Diethyl acrylamide	Water	29 - 30

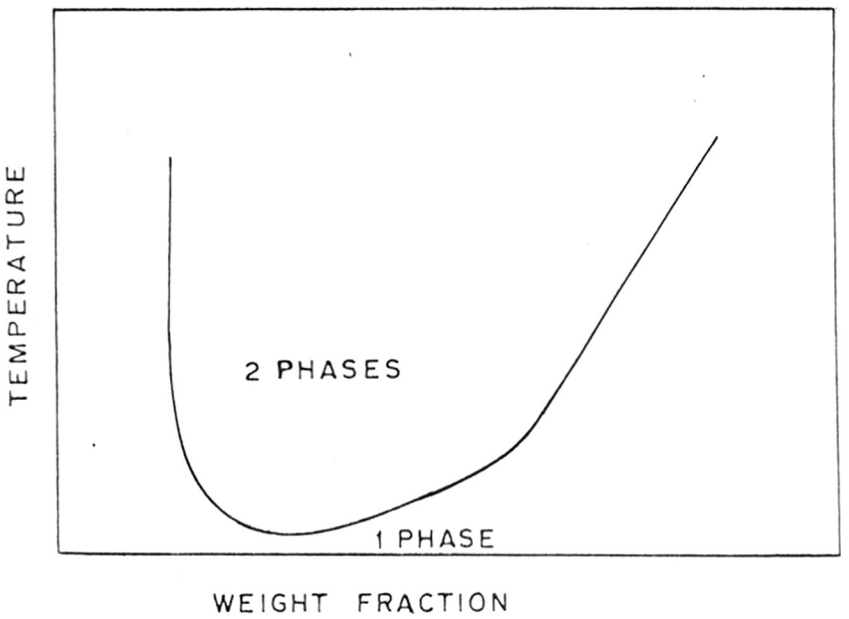


FIG. 14.

STYLIZED PHASE DIAGRAM OF A SYSTEM
LOWER CONSOLUTE BEHAVIOR

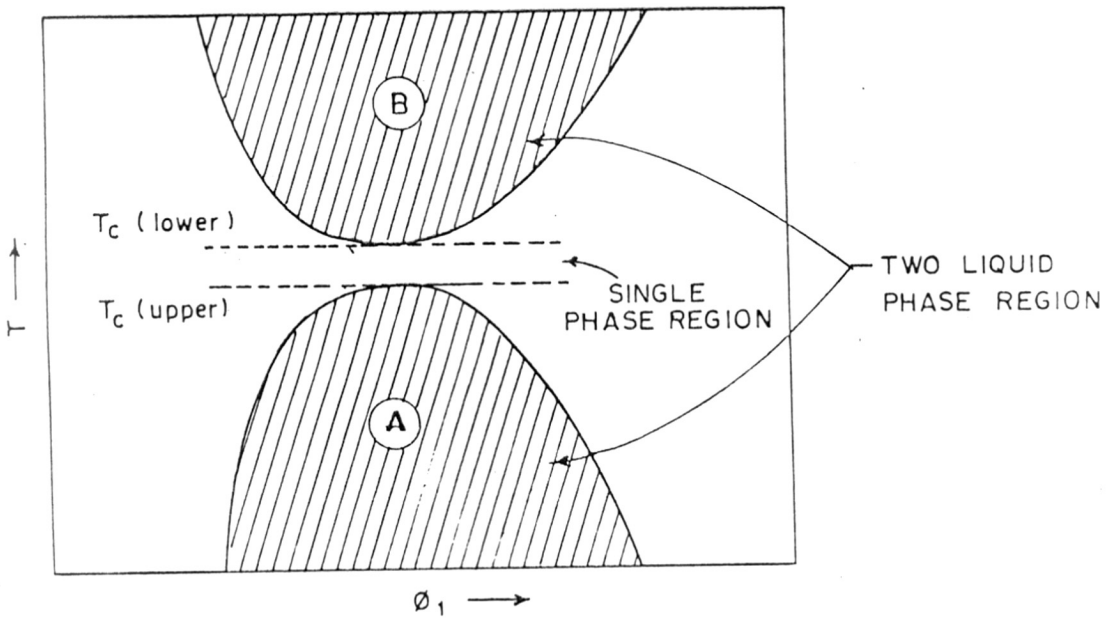


FIG. 15.

SCHEMATIC DIAGRAM OF THE THE TWO TYPES OF PHASE DIAGRAM ENCOUNTERED IN POLYMER SOLUTIONS

A - THE TWO-PHASE REGION YIELDING THE UCST

B - THE TWO-PHASE REGION GIVING THE LCST

Solubility Rules For LCST Systems

Phase separation which results with increasing temperature is essentially entropic in contrast to the conjugate phenomenon of an UCST which is enthalpic. The general solubility rule states that as a polymer which is soluble in water at all temperatures is made increasingly hydrophobic, before complete water insolubility is reached, a range of compositions will be found which will have inverse temperature solubility and the more hydrophobic the polymer the lower the LCST. (Taylor et. al. 1975) The free energy G per mole of a binary mixture is given as

$$G = \left(X_1 \mu_1^{\circ} + RTX_1 \ln X_1 + X_2 \mu_2^{\circ} + RTX_2 \ln X_2\right) + G^{EX} \qquad (42)$$

The terms in parentheses represent the ideal free energy of mixing of components 1 and 2 at mole fractions x_1 and x_2 with the components having the value μ°_1 as standard chemical potentials. G^{EX} is the excess free energy per mole of mixture. For a stable mixture, a plot of G vs. X_2 must be concave upward. If the curve develops a bulge and becomes convex upward, then there are two compositions which are more stable, and the system will undergo phase separation.

At the critical point,

$$\left(\frac{\partial^2 G}{\partial X_2^2}\right)_{T.P} = 0 = \frac{RT}{X_1 X_2} + \left(\frac{\partial^2 G^{EX}}{\partial X_2^2}\right)_{T.P} \qquad (43)$$

It can be concluded that mixtures formed with positive deviations from Raoult's law exothermally and with large losses in entropy on formation, would exhibit LCST. There are three different

modes by which LCST systems can be formulated,

(1) a monomer which may be insoluble in water is copolymerized with a more soluble one, with varying mole ratios and the LCST is examined. e.g. the copolymerization of diacetoneacrylamide (DAA) and acrylamide. (2) to build hydrophobicity into the monomer unit and then homopolymerize or copolymerize it. (3) the third option is to decrease the hydrophobic exclusion moieties of a polymer system, or conversely, to increase them. e.g. the fractionation of poly (vinyl alcohol - vinyl acetate) . (Nord et, al. 1951) Details of the three methods have been discussed by Taylor (1975).

Effect of Polymer Composition on LCST

Poly (N - isopropyl acrylamide) is positioned at the threshold of the highly soluble and highly insoluble polymers. The polymer exhibits a LCST in water at 31-33^{o}c.(Heskins and Gulliet 1968, Haas et. al. 1970, Taylor et. al. 1975). Below the LCST, a 20% solution of PNIPAAm can be prepared. Above the LCST its solubility is less than 10 %. This solubility difference above and below the LCST serves a number of purposes like, delivery or separation of biomolecules to or from aqueous solutions. (Hoffman et.al. 1987) and in an immunoassay (Cole et.al. 1987, Jones et.al. 1986).

Copolymers of NIPAAm can be prepared with various monomers like Acrylamide (Am), N Methyl Acrylamide (NMAAm),N Ethyl Acrylamide (NEAAm), N N Butyl Acrylamide (NNBAAm) and N T Butyl Acrylamide (NTBAAm). (Priest et.al.1987). This helps in either raising or lowering the LCST of the copolymer formed. Am

was the most effective at raising the LCST of the copolymer formed and NEAAm was more efficient than NMAAm. NTBAAm lowered the LCST of the copolymer formed in direct and apparently linear proportions to the amount of NTBAAm added.

Effect of Third Component

It could be shown thermodynamically that the LCST of a system would be raised by a third component whose activity is about the same in both the phases. The greater the hydrophilic / hydrophobic ratio, the more susceptible the molecules are to the third component effects. Prigogine and Defay (1954) showed the effect of third component on the consolute point. It was shown that for an upper consolute system, if the third component has a large discrepancy in its solubilities in the two separating phases, then the UCST will be raised. If, however, the third component is about equally soluble in both separating phases, then the UCST will be lowered and the systems become more compatible. The results of some experiments with the cloud points of the copolymers of Diacetone acrylamide and Acrylamide have been shown by Taylor et.al.(1975). The addition of 1 % Sodium dodecyl sulfate causes a strong increase (from 55 - 225 cc / g) in the intrinsic viscosity [η] of Poly (N - isopropylacrylamide). In the presence of 1 % Sodium dodecyl sulfate, PNIPAAm remains in solution even on boiling. Other polymers which interact with SDS are Poly Methacrylic acid, Poly Acrylic acid, Poly Vinyl alcohol, Poly Vinyl Pyrrolidone and Poly ethylene oxide. This interaction with SDS is attributed to hydrophobic bonding. (Murai et.al. 1972).

The hydrogen bond breaking agents such as LiCl (6M)

and urea (5M), which cause a large increase in the [η] of Poly methacrylamide but do not affect that of Poly acrylamide, cause the precipitation of Poly (N - isopropylacrylamide) from dilute solutions at 30°c. Sodium dodecyl sulfate interacts with the polymer, causing the elongation of the polymer molecules. (Murai et.al. 1972).The behaviour is similar to that of a polyelectrolyte and this feature suggests that the binding of Sodium dodecyl sulfate on polymer is due to the contact between the hydrophobic parts of polymer and of Sodium dodecyl sulfate. Poly vinyl formal (PVF) and Poly vinylbutyral, which are insoluble in water and in the common organic solvents, may be dissolved in highly concentrated surfactant solutions.(Isemura and Kimura 1955).

1.2.2 Thermally Reversible Hydrogels : Synthesis and Characterization

Poly N - substituted acrylamides and methacrylamides were suggested for medical uses because of their suitable properties (Sprinel et.al. 1971, Kopecek et.al. 1973). The application of such gels swollen in water is however restricted due to their poor mechanical properties such as low tensile strength, low elongation at break etc. These properties can be improved by copolymerizing strongly hydrophilic monomers with hydrophobic monomers of the same type e.g. the copolymer of N,N Diethyl acrylamide and t - butyl acrylamide, crosslinked with methylene bisacrylamide (Ulbrich and Kopecek 1979). The improvement in the mechanical properties of the copolymers of N,N Diethyl acrylamide is not only due to the effect of the lower

equilibrium degree of swelling but also because of the influence of hydrophobic interactions between the individual segments of the polymeric network. Interactions of the methyl groups of the t - butyl substituent seem to participate in these reactions to some extent. The mechanical properties of various copolymers of N,N - diethyl acrylamide are listed in Table IV.

Polyacrylamide swells faster than Poly (N - isopropyl acrylamide) but there is no apparent correlation between the swelling behaviour and the copolymer composition. Polymerization variables which can influence its swelling behaviour have been reviewed. (Heskins and Gulliet 1968). Depending on the degree of ionization and molecular structure, both anionic and cationic hydrogels exhibit pH dependent abrupt changes in their equilibrium degree of swelling. When an ionic network is placed in a swelling agent, there are three contributions to the free energy of the system 1) mixing, 2) elastic - retractive, and 3) ionic terms expressed by ΔG_{mix}, ΔG_{el} and ΔG_{ion}, respectively. Drugs incorporated into the hydrogel structure at one temperature can be released abruptly at another temperature by the collapse of the network structure (Peppas and Brannon 1988). Hoffman and his associates have reported the possibility of using poly acrylamides to release various drugs. (Dong and Hoffman 1986). The structural parameter defining the overall crosslinked structure of the network is the number average mol. wt. between crosslinks $\overline{M}_c$, or the equivalent number average degree of polymerization between crosslinks, N_c . The last parameter is defined by the equation

$$\Delta G = \Delta G_{mix} + \Delta G_{el} + \Delta G_{ion} \qquad (44)$$

TABLE IV

MECHANICAL PROPERTIES OF VARIOUS COPOLYMERS OF N,N - DIETHYLACRYLAMIDE

Comonomer	[MBAA] = 0.5 %			[MBAA] = 1.5 %		
	λ_B	σ_B ($kg \cdot cm^{-2}$)	σ_S ($kg \cdot cm^{-2}$)	λ_B	σ_B ($kg\ cm^{-2}$)	σ_S ($kg\ cm^{-2}$)
-	1.54	0.96	2.75	1.31	1.38	3.05
N - Butyl acrylamide	2.22	1.11	1.70	1.45	1.62	2.32
Butyl acrylate	2.50	2.89	3.66	-	-	-
N - tert Butyl acrylamide	2.10	1.36	2.35	1.80	3.20	4.84
tert - Butyl methacrylate	1.70	6.50	10.00	1.44	8.54	11.3
N - tert Butyl acrylamide	5.14	5.86	8.95	2.72	6.20	8.30

[AIBN] = 1×10^{-2} mole / l; 23 vol % DMSO, 13 mole % of comonomer.

λ_B = elongation at break, σ_B = cross section of the swollen sample, σ_S = cross section of the dry sample.

$$\bar{N}_c = \frac{\bar{M}_c}{M_r} \qquad (45)$$

where M_r is the molecular weight of the polymer repeating unit. The actual size of a macromolecular chain between two consecutive junctions (crosslinks) of the network, r, when placed in a swelling agent is given by the equation

$$r = l \bar{N}_c^{v} \qquad (46)$$

where l is the effective segment length, and v is a characteristic exponent for the system. The thermodynamic dependence of v is related to the temperature at which the swelling occurs. In good solvents (Flory interaction parameter , $x < 0.5$), the value of v is 3/5 and the interactions between repeating units of the crosslinked chains are repulsive which results in swelling.

1.2.3 Applications of Thermally Reversible Hydrogels

Significant advances have been made in the area of biotechnology. Just as petroleum refining, the biotechnological processes yield a large number of products. The diversity of products call for a wide range of separation processes for the recovery of the products. Another characteristic of these separation processes is the need to deal with very dilute solutions and consequently very large volumes of solutions handled and produce highly purified dry products such as microorganisms, fragmented micelle etc. As a result the purification processes are extremely elaborate and expensive. The investments involved in separation and isolation of the products tend to be higher than the production costs.

Most bioseparations involve the following steps 1) removal of the insolubles, 2) isolation, 3) purification and 4) polishing. While the concentration enhancement is achieved in the isolation step, the quality is enhanced during the purification step and one of the endeavors has been to combine one or more of these steps.(Belter et.al. 1988).

The use of hydrogels for the concentration and separation of macromolecules has been reported in the past (Vartak 1983). Badiger (1988) discussed the strategies for the 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). In a recent communication these authors also reported the use of plate and frame devices making use of flat sheets comprising Poly (N - isopropylacrylamide) for the concentration and separation of the solutes such as blue dextran.

Immunoassay for Biologically Active Processes

Affinity bioseparation processes in which the molecule to be separated / concentrated is bound to the polymer backbone by suitable ligands have been reported. Cole et. al. (1987) reported the conjugation of immunoglobulin (Ig) with the Poly (N - isopropyl acrylamide). The polymer and polymer - Ig conjugate was precipitated and the precipitate was recovered by centrifugation. From the mixture, the bound conjugate was isolated by elution over hydroxylapatite column. The conjugate

was then incubated with the reagent, (a fluoroscein thiocyanate labeled monoclonal antibody which specifically binds the chain of the immunoglobulin Ig G.) and isolated by precipitation above the LCST. The dissolution and precipitation was repeated to remove the adsorbed reagent which would give a signal. The isolated polymer was then redissolved and the fluorescence signal intensity measured to estimate the human Ig G. The technique offers advantage over other heterogeneous immunoassays in that the (1) binding takes place in solution rather than in the solid phase, (2) non specific binding is minimal and (3) concentration levels in the final assay can be easily manipulated to get satisfactory signal intensities.

Feedback Controlled Systems

Dong and Hoffmann (1986) immobilized asparaginase on the Poly (N - isopropylacrylamide co acrylamide). It was observed that the enzyme activity was lost above the LCST and maintained above LCST reversibly. This ability to switch on and off the catalytic activity of the enzyme can be used to control the rate of the enzyme catalyzed reaction.

1.2.4 Controlled Release Delivery Systems Based On Thermally Reversible Hydrogels :

The critical solution temperature phenomenon in polymers can be exploited for the release of the active ingredients from the polymeric matrices. (Hoffman 1986). Four distinct possibilities can be imagined. 1) When the polymer is swollen at a temperature below the LCST and active ingredient released also at a temperature below the LCST, the polymer matrix would not cross over the LCST and behave as an ordinary polymer

matrix through which a purely diffusion controlled release of the active ingredient would be expected. Since the diffusion would be strictly Fickian, the release would follow first order kinetics. This has been found to be the case for the release of methylene blue and vitamin B_{12} from N - isopropyl acrylamide based polymers. 2) When the polymer is swollen at a temperature lower than the LCST and then exposed to a medium at a temperature greater than the LCST a series of structural changes are triggered. In the first instance there is a thermal gradient across the device. This triggers the collapse of the polymer which is accompanied by the syneresis and the skin formation on the surface of the polymer . One would therefore expect a burst of the active ingredient followed by the conventional Higuchi type of release. Surprisingly the release of Vitamin B_{12} and Methylene blue from such systems has been found to consist of two regions. The release kinetics in each region follows zero order kinetics, although such a simple release profile is not anticipated during the first stage of release. 3) The release of methylene blue from a dry Poly (N - isopropylacrylamide) polymer matrix in a medium maintained at a temperature above the LCST of the polymer follows a zero order kinetics. Further the release rate decreases as the experimental temperature is increased. This could be explained assuming that the penetration of water in a glassy Poly (N - isopropylacrylamide) matrix follows Case II transport. The criteria for zero order release of active ingredients from glassy polymers have been extensively studied. (Vyavahare et.al.1988).

The swelling interface number for a system is defined by

$$Sw_e = \frac{V \cdot \delta_{max}}{D_s} \qquad (47)$$

where v represents the velocity of the penetrant into the glassy matrix and δ denotes the thickness of the disc and D_s denotes the diffusivity of the active ingredient from the swollen matrix. A qualitative analysis of the system on the basis of this criteria has not been reported. In the case of the Poly (N - isopropyl acrylamide) polymers both velocity of the penetrant and the diffusivity of the active ingredient from the swollen polymer would decrease with the increasing temperature as the degree of swelling decreases abruptly above the LCST. 4) It is anticipated that the release of an active ingredient from a glassy Poly (N - isopropylacrylamide) polymer at a temperature below the LCST would also follow a zero order release as in the earlier case. At a temperature below the LCST, the equilibrium swelling would be higher than that at temperature above LCST. Consequently the velocity of penetration of the medium and the release rate of the active ingredient is anticipated to be greater at lower temperatures. These predictions need to be verified.

1.2.5 Unsolved Problems :

The need for zero order release for the delivery of drugs which have short biological half life and low therapeutic index is well established. Various approaches have been explored in the past to achieve zero order release. These include :(a) non uniform concentration profiles, (b) geometric modifications, (c) laminated reservoirs and (d) swelling controlled delivery

systems. There has been a continuing need to seek newer methodologies for zero order release.

Polymers which exhibit lower critical solution temperatures (LCST) have been shown to yield zero order release. Four different mechanisms can be imagined. (Hoffman 1987) :

(1) when the polymer is swollen at a temperature below the LCST and the active ingredient is also released at a temperature below the LCST, the release would follow first order kinetics, since the diffusion would be strictly Fickian.

(2) when the polymer is swollen at a temperature lower than the LCST and then exposed to a medium at a temperature greater than the LCST, then the release pattern would be complex. Initially there is a thermal gradient across the device, the polymer collapses and skin formation takes place on its surface.

(3) the release would follow zero order kinetics when the active ingredient is released from a dry polymer matrix at a temperature above the LCST of the polymer.

(4) the release of an active ingredient from a glassy polymer at a temperature lower than the LCST would also follow zero order release. These mechanisms need to be understood and verified.

Many of the polymers which exhibit LCST behaviour are glassy hydrogels. Normally the degree of swelling of a polymer increases marginally as the temperature is increased. Additionally the rate of diffusion of an active ingredient from the matrix also increases. In the case of the hydrogels exhibiting LCST behaviour, the degree of swelling significantly decreases as the temperature is raised above the LCST. As a

PART – II.

EXPERIMENTAL WORK

result, the diffusivity is expected to decrease. It would be interesting to investigate the release characteristics of hydrogels of this type. Finally there is a need to undertake systematic investigations of the effect of the monomer structure on the equilibrium degree of swelling, penetration velocities, diffusion of active ingredient and interpret the release kinetics of the active ingredients in the context of the criteria for zero order release from the swellable glassy hydrogels, reported in the literature.

2.0.0 Scope of present work :

Polymers which exhibit lower critical solution temperatures are only recently being explored as matrices for the controlled release delivery systems. The release kinetics of Vitamin B_{12} and methylene blue from Poly (N - isoproyl acrylamide) was recently reported by Hoffman et.al.(1986). The dry polymer disc was first incubated at 4^{o}c in the respective solutions and the release kinetics were studied at 50^{o}c. The release kinetics showed two regions : initially there was a rapid release of the active ingredient followed by a slower release. The first region is probably due to the release of the pore water near the surface along with the solute dissolved in it. The surface skin formed represents an increasing resistance to the solute transport from the gel. The gel continues to collapse, which represents an increasing resistance to both diffusion and hydrostatic pressure flow across the thickening skin membrane. This leads to an apparently constant but lower release rate after the first 4 - 5 minutes.

The scope of the present work is limited to the investigation of the role of 1) equilibrium degree of swelling on the penetration velocity 2) the diffusivity of the active ingredient and consequently 3) the kinetics of release of the active ingredient.

This investigation was taken up with the following in mind :

(1) to investigate the effect of the monomer structure on the velocity of penetration and the diffusivity of the active

ingredient through the polymeric hydrogel and to correlate the effect of these parameters on the release kinetics above and below the LCST.

(2) to compare the results of the release kinetics with the criteria for zero order release cited in the literature and the results of the prior investigations in this area.

3.0.0 EXPERIMENTAL WORK

3.1.1 Monomer Synthesis and Characterization:

The monomers synthesised were a series of N - substituted acrylamides. Acryloyl chloride was prepared by the condensation of acrylic acid and benzoyl chloride using hydroquinone as the inhibitor. (Stempel et.al. 1950). All the monomers were synthesised in the laboratory by the condensation of the acid chloride and the respective amine. (Butler et. al. 1960). A typical procedure was as follows :

12.18 gm. (0.21 moles) of n - isopropyl amine and 125 ml. of distilled and dry diethyl ether were added to a round - bottom flask. The temperature was maintained at 0^{o}c. 9.0 gm. (0.1 mole) of acryloyl chloride was diluted with 25 ml. of diethyl ether and added to the reaction mixture from a dropping funnel in a dropwise manner over a period of 45 mins. to 1 hr. The reaction mixture was stirred constantly. After the addition was complete, the reaction mixture was stirred for another 6 hrs. The salt was filtered off and the monomer was recovered by distilling off ether at room temperature under vacuum. The solid monomer was recrystallised from diethyl ether and its purity was confirmed by TLC and NMR.

$CH_2 = CHCOCl + 2\ R_2NH \longrightarrow CH_2 = CHCONR_2 + R_2NH.HCl$

All the monomers were similarly synthesised.

Crude liquid monomers like n - propyl acrylamide, acryloyl pyrrolidone and n - butyl acrylamide were column separated using petroleum ether and ethyl acetate in ratios of 100 : 0, 95 : 5 and 90 : 10. The eluates were checked for their purity by TLC which showed a single spot corresponding to the monomer. The stationary phase used was Silica gel (60 -120 mesh). The monomers were recovered by concentrating the solvents on a rota vapor bath under vacuum. The structures of the monomers were confirmed by NMR.

I. n - propyl acrylamide : $C_6H_{11}O\ N$ (Mol. wt. : 113)

IR (Neat) :

990 and 910 cm^{-1} ($CH_2 = CH$), 1650 cm^{-1} ($\overset{NH}{\underset{|}{C}} = O$),

3300 cm^{-1} (N - H)

NMR ($CDCl_3$) :

1.8 δ t (3H $CH_3 - CH_2$ -), 2.4 δ m (2H $H_2C - CH_2 - CH_3$-)

4.3 δ dd (2H $NH - CH_2 - CH_2$ -), 6.5 δ dd (1H HC = C),

7.2 δ m (2H $CH_2 = CH$)

II. Acryloyl Pyrrolidone : $C_7H_9O_2N$ (Mol. wt. : 139)

IR (Neat) :

910 and 990 cm^{-1} ($CH_2 = CH$), 16650 cm^{-1} ($- \overset{O}{\underset{||}{C}} - NH -$),

1720 cm^{-1} (O = C)

NMR ($CDCl_3$) :

2.4 δ m (2H CH_2), 3.0 δ t (2H CH_2), 4.2 δ t (2H CH_2),

6 - 7 δ m (2H $CH_2 = C$), 7.8 δ dd (1H C = CH)

III.n - Butyl acrylamide : $C_7H_{12}ON$ (Mol.wt. : 126)

IR (Neat) :

910 and 990 cm^{-1} ($CH_2 = CH$), 1650 cm^{-1} ($O = C - NH$),

3300cm^{-1} (NH)

NMR ($CDCl_3$) :

1.8 δ t (3H $CH_3 - CH_2 -$), 2.5 δ m (4H $- CH_2 - CH_2 -$),

4.3 δ dd (2H $HN - CH_2 -$), 6.6 δ dd (1H $HC = C\langle$),

7.2 δ m (2H $C = C\langle^{H}_{H}$)

IV. N - isopropyl acrylamide : $C_6H_{11}ON$ (Mol.wt. : 113)

IR (Neat) :

910 and 990 cm^{-1} ($CH_2 = CH$), 1650 cm^{-1} ($O = C - NH$),

3300 cm^{-1} (NH)

NMR ($CDCl_3$) :

1.6 δ d (6H $H_3C\diagdown\diagup H_3C$ $CH -$), 4.8 δ m (1H $H_3C\diagdown\diagup H_3C$ $CH -$),

6.6 δ dd (1H $HC = C$), 7.3 δ m (2H $H_2C = C$)

V. N,N, diethyl acrylamide : $C_7H_{13}ON$ (Mol.wt. : 127)

IR (Neat) :

910 and 990 cm^{-1} ($CH_2 = CH$), 1640 cm^{-1} ($O = C - NH$),

3500 cm^{-1} ($- N\langle$)

NMR ($CDCl_3$) :

1.2 δ t (6H ($CH_3 - CH_2 -$) 2),

3.5 δ q (4H ($- CH_2 - CH_3$)2), 5.8 δ dd (1H $CH = C$),

6 - 7 δ m (2H $CH_2 = C -$)

VI. t - Butyl acrylamide : $C_7H_{14}ON$ (Mol.wt. : 128).

IR (Nujol):

910 and 990 cm^{-1} ($CH_2 = CH$), 1640 cm^{-1} (O = C - NH)

NMR ($CDCl_3$) :

1.5 δ s (9H - C(CH_3)$_3$), 4.0 δ dd (1H HC = C),

5.6 δm (2H H_2C = C).

Details of the synthesis are summarized in Table V.

3.2.1 **Polymer Synthesis and Characterization :**

All the monomers except n - isopropyl acrylamide were bulk polymerized. A typical procedure was as follows :

0.0815 gm. (0.05 moles) of methylene bis acrylamide were dissolved in 10.0 gm. (0.0793 moles) of n - butyl acrylamide [[Monomer] / [Crosslinker] $\simeq$ 150]. 0.08 gm. (0.8%) of tert - butyl hydroperoxide was then added and the mixture was stirred in a test tube. Nitrogen gas was bubbled. The test tube was then sealed and kept in a water bath maintained at 60°c for 1 hr. and then at 65 - 75°c. The polymerization was complete within 2 - 3 hrs. It was then maintained at this temperature overnight. The test tube was then broken to recover the polymer in the form of a cylinder. The cylinder was then cut on a lathe into discs having thickness in the range 0.1 to 0.12 cm. The polymer discs were post polymerized at 60°c for 6 - 8 hrs. After post polymerization the discs were extracted in acetone to remove the unreacted monomer. The absence of monomer was confirmed by spectrophotometeric analysis. The discs were then soaked in saturated aqueous solutions of the active ingredient to be

TABLE V

DETAILS OF MONOMER SYNTHESIS

Amine	TEA (moles)	Amine (moles)	Acid chloride (moles)	Solvent
Pyrrolidone	-	2.1	1.0	Benzene
n - Butyl	1.1	1.1	1.0	Benzene
t - Butyl	-	2.1	1.0	Ether
n - Propyl	1.1	1.1	1.0	Benzene
iso - Propyl	-	2.1	1.0	Ether
N,N,Diethyl	-	2.1	1.0	Ether

TEA = Triethyl amine.

Acid chloride = Acryloyl chloride.

loaded till equilibrium swelling was reached. The discs were then freeze dried and stored in a dessicator.

All the other monomers were bulk polymerized as per the details summarized in Table VI.

n - isopropyl acrylamide was polymerized by the solution polymerization technique at room temperature using water as the solvent.

n - isopropyl acrylamide : 2.0 gm. (0.01769 moles) was dissolved in 5 ml. of double distilled water. 0.0180 gm. of methylene bis acrylamide [Monomer] / [Crosslinker] $\simeq$ 150, was then added to the monomer solution and dissloved. 0.003 gm. (0.0000258 moles) N,N,N',N', tetramethyl ethylene diamine was added, followed by 0.006 gm. (0.000023 moles) of potassium persulfate. Nitrogen gas was bubbled through the mixture which was then poured in a petridish at room temperature. Polymerization was complete in half - an hour. The polymer sheet was kept at room temperature overnight. The polymer discs were obtained by punching the sheet. These were then extracted in water to remove all the unreacted monomer, which was confirmed by spectrophotometeric analysis of the extract. The discs were then stored in a dessicator.

Swelling Studies :

Swelling experiments were performed for the various polymers both below and above their lower critical solution temperatures. The LCST values for these polymers are given in Table VII.

The dry polymer disc was weighed and immersed in double distilled water maintained at the temperature of the experiment.

TABLE VI

CONDITIONS FOR BULK POLYMERIZATION

Monomer	Temp (^{o}c)	Initiator
Acryloyl Pyrrolidone	25 - 26*	A
n - Propyl acrylamide	40 - 42	A
n - isopropyl acrylamide	25 - 26	B
n - Butyl acrylamide	60 - 65	A
N,N Diethyl acrylamide	25 - 26	A

Crosslinker used was Methylene bis acrylamide :

[Monomer] / [X - linker] $\simeq$ 150.

A = Tert - butyl hydroperoxide.

B = Potassium persulfate and N,N,N',N' Tertramethyl ethylene diamine.

* = for initial six hours and 50^{o}c overnight.

TABLE VII

LOWER CRITICAL SOLUTION TEMPERATURES

Polymer	LCST (^{o}c)
Acryloyl Pyrrolidone	55
n - Butyl acrylamide	<0
n - isopropyl acrylamide	31
n - Propyl acrylamide	22
N,N, Diethyl acrylamide - t - butyl acrylamide	29 - 30

Heskins and Guillet (1968).

The weight of the slab was checked by removing it from water and after blotting it with a tissue paper. This procedure was repeated every 30 mins. till there was no further weight gain.

Equilibrium swelling was calculated from the equation :

$$\% \text{ swelling} = (w_s - w_d) / w_s \times 100 \qquad (48)$$

where w_s denotes the weight of the swollen polymer and w_d denotes the weight of the dry polymer. The equilibrium swelling values for all the polymers (above and below LCST) are listed in Table VIII.

Penetration Velocity Measurements :

The penetration velocities for the polymers were calculated from the initial weight gain curve. (Peppas and Franson 1983, Davidson 1983). The penetration velocity was calculated from the slope of the initial portion of the penetrant uptake curve from the equation

$$v = (dw_g / dt) \times \rho \times (1 / 2A) \qquad (49)$$

where v denotes the penetration velocity, dw_g / dt denotes the slope of weight gain vs time curve, ρ denotes the density of water, A denotes the area of one face of the disc and factor two accounts for the fact that penetration takes place through both the faces. Fig. 16 shows a plot of weight gain versus time for Poly (n - Butyl acrylamide) at $38^{\circ}c$ (LCST $\simeq 22^{\circ}c$).

The penetration velocities and equilibrium swelling content are listed in Table VIII.

Diffusivity Measurements :

The diffusion coefficients of benzoic acid from the swollen polymers were obtained both below and above their LCST

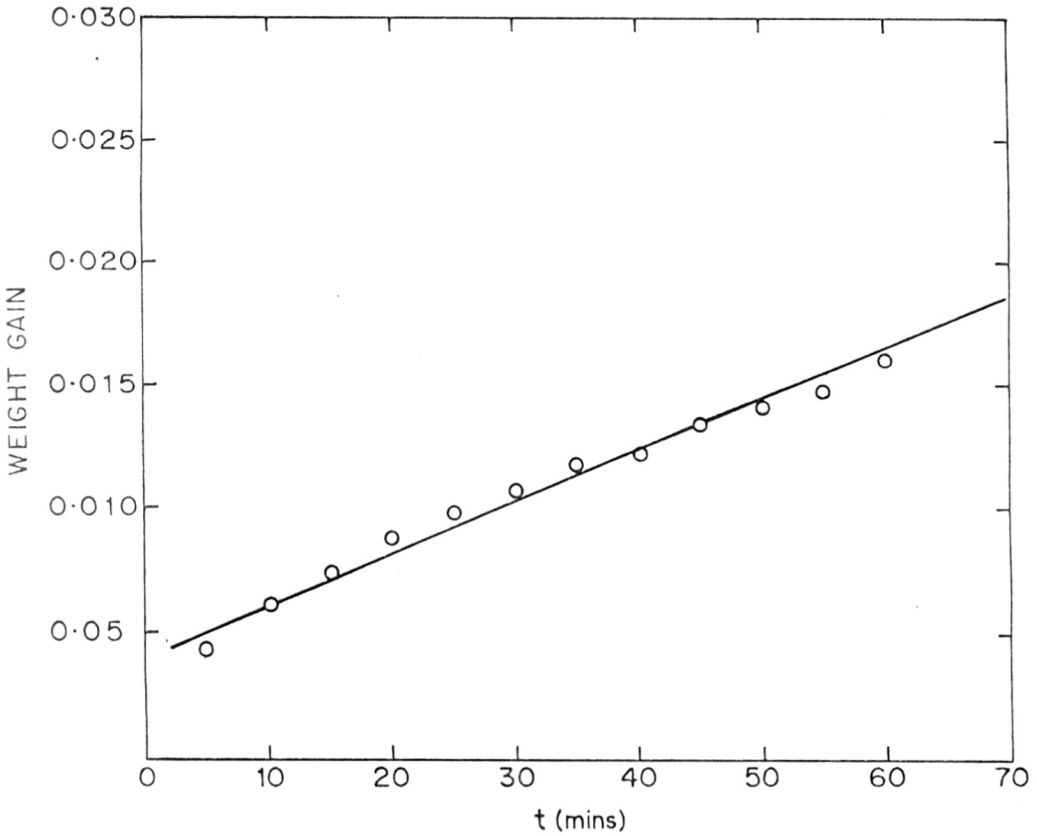


FIG.16

PLOT OF wt.gain vs. TIME, POLY (n-PROPYL ACRYLAMIDE) AT 38°C (LCST ≃ 22°C)

TABLE VIII :

EXPERIMENTAL RESULTS

Polymer	Temp (°C)	% Swelling (s)	Penetration velocity (cm / sec)	Diffusion coefficient (cm^2/sec)	Swelling interface number (Sw_e)	Index of releas (n)
Acryloyl Pyrrolidone	65	16.00	1.39×10^{-6}	2.47×10^{-7}	0.8059	0.6
	38	27.60	2.06×10^{-6}	6.80×10^{-8}	2.8858	0.6
N,N,Diethyl acrylamide - t - butyl acrylamide	38	26.70	7.67×10^{-7}	2.31×10^{-8}	2.6745	0.5
	20	74.24	2.28×10^{-5}	5.08×10^{-8}	40.37	0.8
n - Propyl acrylamide	38	19.28	8.00×10^{-7}	6.53×10^{-8}	1.0042	0.5
	10	88.16	4.85×10^{-6}	6.20×10^{-7}	0.6801	0.6
n - Butyl acrylamide	38	12.19	2.68×10^{-7}	1.83×10^{-8}	1.0932	-

by the desorption technique reported by Yasuda et.al. (1968).

The polymer slab was soaked in an aqueous, saturated solution of benzoic acid at the temperature at which diffusivity measurement was to be conducted. It was soaked till equilibrium swelling was reached. The polymer slab was then removed from the solution and immersed in double distilled water for 2 mins. to remove benzoic acid adhering on the surface.

Diffusion coefficient was calculated from the equation

$$D = (\pi / 16) L^2 \qquad (50)$$

where $L = d (M_t / M_\infty) / d (\sqrt{t} / \delta)$, M_t denotes the amount of diffusant released at time t, M_∞ denotes the amount of diffusant released at infinite time, δ denotes the thickness of the disc and t denotes the time. Fig.17 shows a plot of M_t / M_∞ versus $\sqrt{t}$ for benzoic acid from Poly (Acrylol Pyrrolidone) at $65^\circ c$ (LCST $\simeq 55^\circ c$).

The results for the other polymers investigated are listed in Table VIII.

3.3.1 Release Studies :

The experimental setup for the release studies is shown in Fig. 18. Release experiments were performed for the various polymers both below and above their LCST. Prior to the release studies the polymer slabs were soaked in saturated aqueous solution of benzoic acid at room temperature till the equilibrium degree of swelling was attained. The polymer slabs were then removed from the solution and freeze dried. The weight of the polymer slab and its thickness was checked. Just before starting the release experiment, the slab was immersed in double distilled water for 5 mins. to remove the solute on the surface. It was

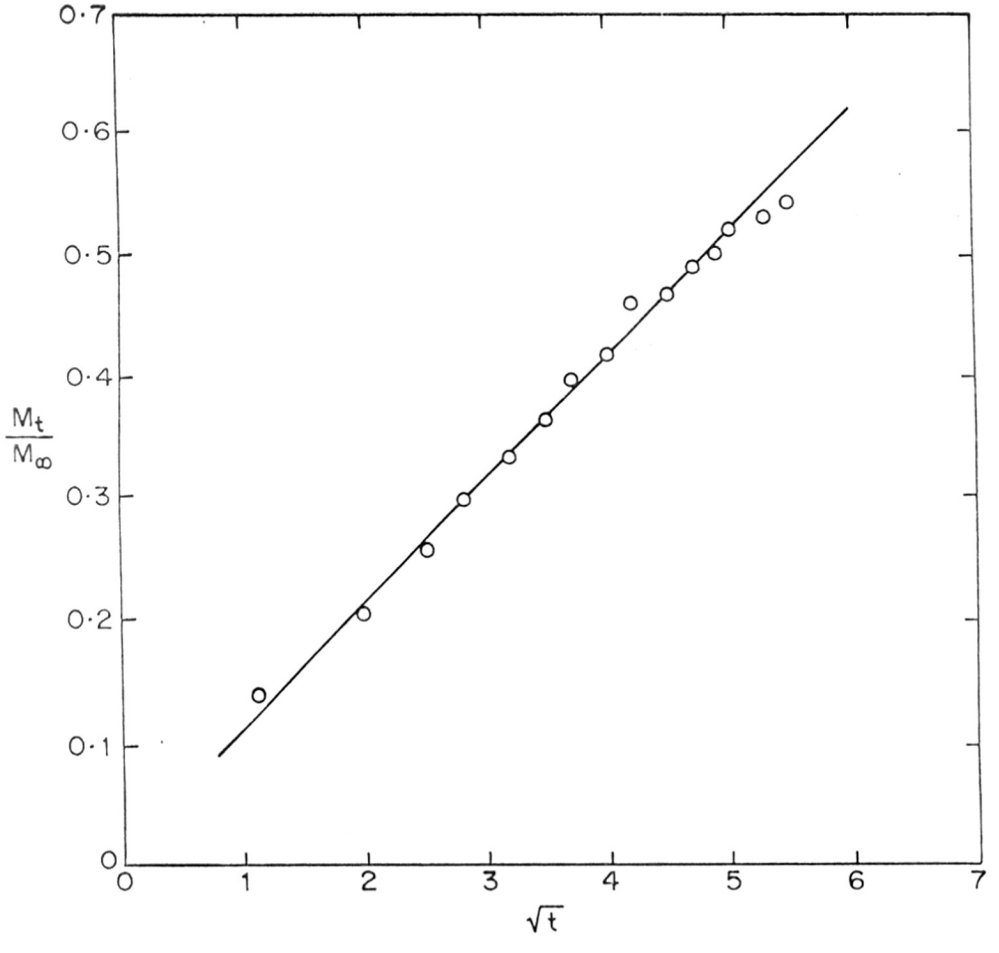


FIG. 17

PLOT OF M_t/M_∞ vs. $\sqrt{t}$ FOR BENZOIC ACID, POLY (ACRYLOYL PYRROLIDONE) AT 65°C (LCST $\simeq$55°C)

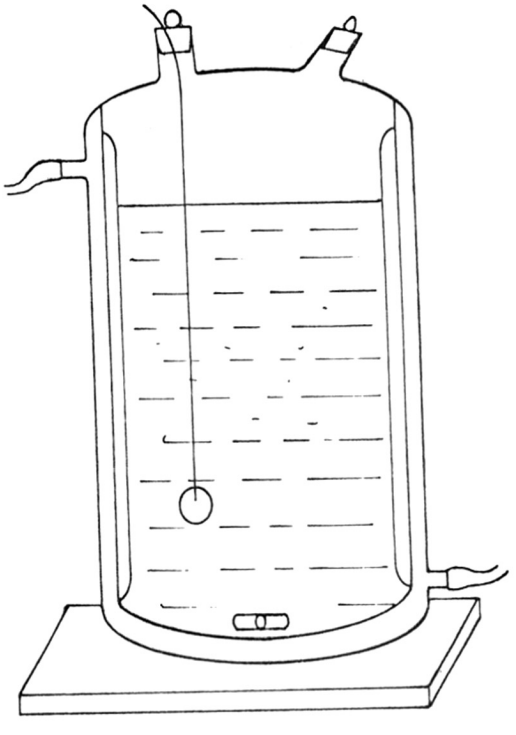


FIG.18

EXPERIMENTAL SETUP FOR RELEASE STUDIES

then suspended by means of a chrome wire into a jacketed reactor containing 200 ml. of double distilled water maintained at the temperature of the experiment. Water was stirred magnetically. 2 ml. aliquots were withdrawn every 30 mins. and replaced by 2 ml. of fresh double distilled water. The aliquots were then checked for their absorbances at λ = 228 nm. (ϵ = 650). The release index was determined from a plot of ln (M_t / M_∞) vs ln t. A typical plot for the release of benzoic acid from Poly (N,N Diethyl acrylamide - t - butyl acrylamide) at 20°c (LCST $\simeq$ 29 - 30°c) is shown in Fig.19.

4.0.0 Results and Discussion

As mentioned in the earlier section, this investigation was undertaken with a view to : (1) investigate the effect of the monomer structure on the velocity of penetration and the diffusivity of the active ingredient through the polymeric hydrogel and (2) to correlate the effect of these parameters on the release kinetics above and below the lower critical solution temperature. The results of the release kinetics with the criteria for zero order release cited in the literature and the results of the prior investigations in this area were then compared.

For this purpose a series of monomeric acrylamide derivatives were synthesized. These were polymerized and obtained in the form of glassy hydrogel discs. The measurements were made at two temperatures above and below the LCST.

Penetration Velocity

The velocity of penetration of the surrounding medium

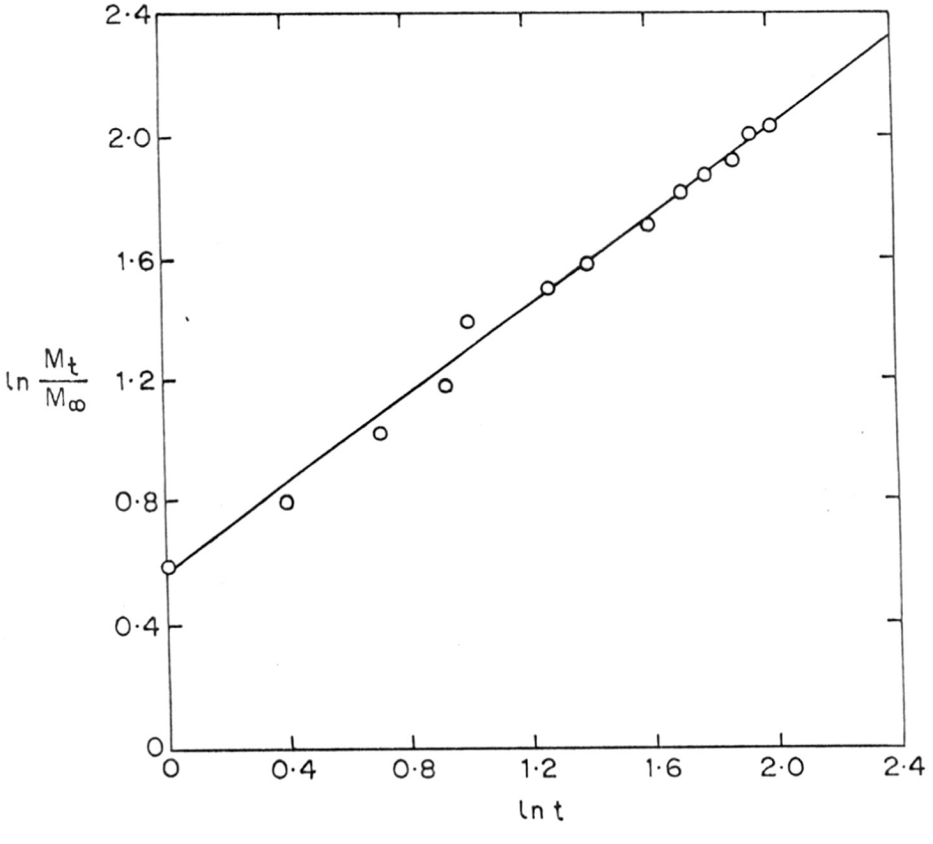


FIG.19

PLOT OF ln M_t/M_∞ vs. ln t FOR THE RELEASE OF BENZOIC ACID, FROM POLY (N,N DIETHYL ACRYLAMIDE t-BUTYL ACRYLAMIDE) AT 20°C (LCST $\simeq$ 30°C)

into the glassy polymer can be, in principle, calculated from the knowledge of the thermophysical data according to the relationship proposed by Peppas and Franson (1983).

$$V_{max} = K' \left[\frac{\rho'_p}{\rho_p} (Q-1) - \frac{T_g - T}{\beta/\alpha_f} \right]^m \qquad (51)$$

where ρ'_p and ρ_p denote the densities of the penetrant and polymer respectively, Q denotes the equilibrium degree of swelling, T_g is the glass transition temperature of the polymer, T is the temperature of experiment, α_f is the coefficient of expansion of free volume, β is the contribution of diluent to the free volume of the polymer - diluent system and K' and m are empirical parameters. The values of α_f and β for the polymer - diluent system are not always known, and even when available the values are not very accurate. The parameters K' and m are purely empirical in nature. The accuracy of m is rather uncertain. It is, therefore, desirable to measure the penetration velocity experimentally. The velocity of penetration of water into the glassy polymer can be measured by a variety of techniques, such as the dynamic swelling measurements and examination of the photomicrograph of the swelling film as a function of time (Hopfenberg and Hsu 1978). Further, if it is assumed that the concentration of the active ingredient is uniform throughout the matrix and that the swollen phase contains no active ingredient, the velocity of penetration can be calculated directly from the release data.

In this work, the velocity of the penetrating front v_{max} was calculated from the dynamic swelling experiment. (see

Fig.16). The amount of water sorbed as a function of time was recorded for a period of 1.5 hours. The penetration velocity was then calculated from the equation

$$V_{max} = \left(\frac{dg_w}{dt}\right)\left(\frac{\rho'_p}{\rho_p}\right) 1/2A \qquad (52)$$

where (dg_w / dt) represents the rate of sorption of water, ρ_p and ρ'_p denote the densities of polymer and water at the temperature of the experiment. A denotes the area of cross section of the disc. The factor 2 is introduced since both surfaces of the disc are exposed to the penetrant medium.

The velocity of penetration medium into the glassy hydrogel is given by

$$V_{max} = K' \left[C_{max}(X^*, t) - C^*\right]^m \qquad (53)$$

where K' and m are empirical parameters, $C_{max}(x^*, t)$ is the equilibrium penetrant concentration. In order to correlate the values of penetration velocity, the parameters K' and m must be known and so also the relationship between the penetrant concentration and the glass transition temperature of the penetrant - polymer system. The polymers chosen in this work belong to the family of substituted acrylamides. As a first approximation if we assume that K' and m are same and the term C^* makes a negligible contribution as compared to $C_{max}(x^*, t)$, a plot of ln v vs. ln C_{max} would be expected to be linear. The plot is shown in Fig.20. The linearity justifies the assumptions made. Further the value of the index m was found to be 2.5. This is in good agreement with the values reported by Joshi (1985) for a

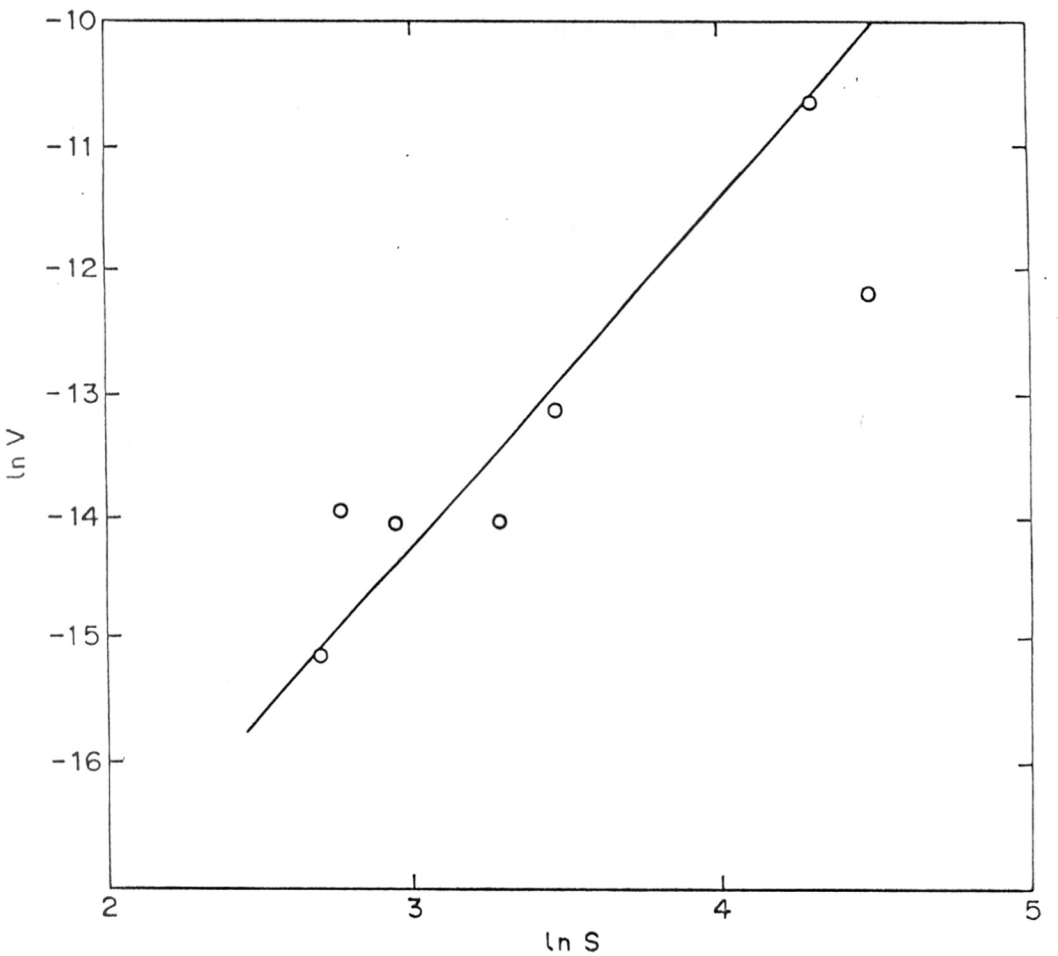


FIG. 20

DEPENDENCE OF PENETRATION VELOCITY ON THE EQUILIBRIUM SWELLING OF HYDROGELS

variety of polymers.

Diffusion Coefficient

Diffusion coefficients of the solutes from the polymers can be estimated from the semiempirical approaches reported in the literature (Yasuda et.al. 1968, Yasuda et.al. 1969, Kulkarni and Mashelkar 1983). A number of techniques are reported in the literature for the measurement of diffusivities (Yasuda et.al.1968, Wood et.al. 1982). In this work diffusivities of benzoic acid were determined by the method reported by Yasuda et.al. (1968). The values are summarized in Table VIII.

Yasuda et.al. (1968) have proposed a correlation with the degree of swelling based on the free volume considerations. Since the polymers belong to the same family of substituted acrylamides the correlation would be expected to be valid if the degree of swelling primarily determines the diffusivity. A plot of ln D vs. 1/s has been shown in Fig.21. It can be seen that the correlation holds fairly good.

Interpretation of the Release Kinetics

In discussing the kinetics of release from the glassy hydrogels which exhibit LCST behaviour, four distinct possibilities were envisaged by Hoffman (1987):

1) when the polymer is swollen at a temperature below the LCST and the active ingredient is also released at a temperature below the LCST, the release would follow first order kinetics, since the diffusion would be strictly Fickian.

2) when the polymer is swollen at a temperature lower than the LCST and then exposed to a medium at a temperature greater than the LCST, then the release pattern would be complex. Initially

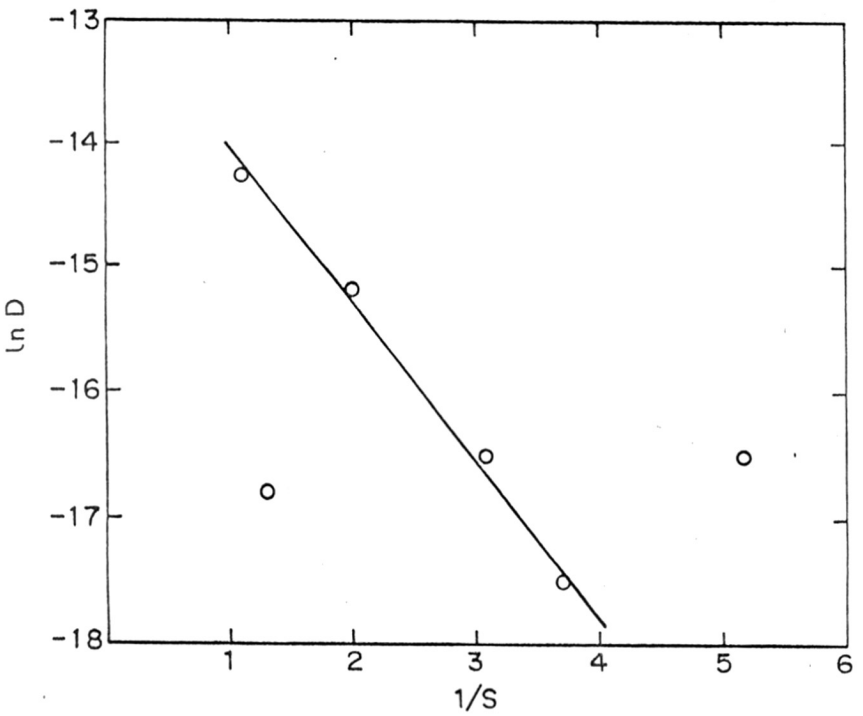


FIG. 21

DEPENDENCE OF DIFFUSION COEFFICIENT ON THE EQUILIBRIUM SWELLING OF HYDROGEL (YASUDA 1968)

there is a thermal gradient across the device, the polymer collapses and skin formation takes place on its surface.

3) the release would follow zero order kinetics when the active ingredient is released from a dry polymer matrix at a temperature above the LCST of the polymer.

4) the release of an active ingredient from a glassy polymer at a temperature lower than the LCST would also follow zero order release.

Since the swelling interface number criterion defines the relative rates of penetration and the diffusive transport of the solute it can be applied to elucidate the kinetics of release from the glassy hydrogels regardless of whether the polymer exhibits LCST behaviour .

The maximum thickness for a glassy hydrogel implant releasing active ingredient in an aqueous medium cannot exceed 0.10 - 0.15 cm. The velocity of penetration of water is governed by the equilibrium swelling of the polymer. Hence, the only parameter which can control the release index as indicated by the value of the swelling interface number is the diffusion coefficient of the active ingredient. The effect of the molecular size of the diffusant on the swelling interface number and the kinetics of release has been discussed by Vyavahare et.al. (1988).

In order to ensure high diffusivity, benzoic acid was chosen as an active ingredient. The index of release was obtained by fitting the data into the equation

$$\frac{M_t}{M_\infty} = Kt^n \qquad (54)$$

where M_t denotes the amount of active ingredient released at time t, M_∞ denotes the amount released at infinite time, K denotes the proportionality constant and n denotes the release index. It is evident from Table VIII that the index of release lies within the range 0.5 - 0.8.

The values of the equilibrium swelling interface number for the hydrogel polymers investigated in this work are summarized in Table VIII. Although the penetration velocity and the diffusivity of benzoic acid through the swollen hydrogels vary over two orders of magnitude, it is observed that an increase in the velocity is always accompanied by an increase in the diffusivity of benzoic acid. As a result, the values of the swelling interface number remain practically unaffected. Besides the values lie in the range which indicates that the release is essentially diffusion controlled. It is therefore not surprising that very minor deviations from the release index for the diffusion controlled release (viz. n = 0.5). It is only in the case of Poly (N,N Diethyl acrylamide) below LCST, the swelling number is in the range where the anomalous release kinetics is to be expected.

Conclusions

This work reports the kinetics of release of a low molecular weight solute viz. benzoic acid from a series of substituted acrylamide polymers which exhibit LCST behaviour. The polymers have been chosen so as to exhibit a wide range of swelling and the LCST. The conclusions of the investigation are summarized below :

The equilibrium swelling varied over a wide range depending upon the choice of the monomer and whether the measurements were made at temperatures below or above LCST.

The penetration velocity increased with increasing equilibrium degree of swelling.

Irrespective of whether the polymer was above or below LCST, the penetration velocity was governed primarily by the equilibrium degree of swelling. The ability of the medium to plasticize the polymer is comparatively less important and can be ignored as the first approximation. This is further substantiated by the fact that the values of the exponent m are in good agreement with those given in the literature for the hydrophobic polymers.

Diffusivity of the solute in the polymer matrix is essentially governed by the degree of swelling.

Regardless of the equilibrium degree of swelling and whether the polymer is above or below the critical temperature, the release of benzoic acid followed diffusion controlled release kinetics.

The release kinetics observed could be satisfactorily explained in terms of the values of the equilibrium swelling interface number calculated for the systems investigated.

Suggestions For Further Work

This work demonstrates that regardless of the equilibrium degree of swelling and whether the polymeric matrix is above or below LCST, the kinetics of release of benzoic acid from a series of substituted acrylamide polymers follows the conventional Higuchi type of kinetics. This has been primarily due to the fact that the penetration velocity as well as the diffusion coefficient are influenced in such a way that the swelling interface number is not significantly altered. Based on this work, following suggestions can be offered for further research.

1) The choice of a hydrophobic polymer which would undergo the transition to a hydrophilic polymer during the course of release.
2) Choice of hydrophobic monomers for copolymerization with the hydrophilic monomer as in the case of the polymer N,N Diethyl acrylamide which shows the release index $\simeq 0.8$.
3) This work shows that within a given family of polymers the penetration velocity is a function of the degree of swelling of the polymer and that the value of the parameter m is in good agreement with the value established in the literature. Further investigations need to be undertaken to ascribe a physical meaning to the parameter m.

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SYNOPSIS

Controlled release technology evolved as an active discipline for pesticide delivery in the early seventies. Since then the technology has found applications in diverse fields in the delivery of a wide range of bioactive molecules such as pharmaceuticals, pesticides, fertilizers, pheromones and plant growth regulators. There has been a distinct trend over the past few years to elucidate the mechanism of release from the various release devices. It is now possible to design a release device based on scientific knowledge of the relevant physico chemical data for the polymer and the bioactive molecule. The types of controlled release delivery systems and their release patterns have been extensively reviewed in the literature (1). Amongst the various types of delivery systems developed only reservoir devices are known to provide zero order release of bioactive molecules.

A number of approaches have been made in the past to achieve zero order release from the matrix systems. These include geometric modifications (2), non - uniform concentration profiles (3), polymer blend matrices (4,5) and swelling controlled delivery systems (6 - 7).

Swelling controlled delivery systems consist of glassy polymer matrices. The penetration of the surrounding medium into the matrix follows case II kinetics. The diffusivity of the active ingredient in the swollen matrix is high. The criteria for the swelling controlled release of physically dispersed bioactive molecules from glassy hydrogels have been reviewed in the literature (6 - 7). However, no systems of pragmatic importance based on swelling controlled release have been

developed as yet.

Acrylamide based polymers exhibit lower critical solution temperature (LCST) behaviour and are also glassy in the dry state.

Following possibilites have been envisaged for the release of an active ingredient from a glassy hydrogel which exhibits the LCST behaviour (8):

(1) when the polymer is swollen at a temperature below the LCST and the active ingredient is also released at a temperature below the LCST, the release would follow first order kinetics, since the diffusion would be strictly Fickian.

(2) when the polymer is swollen at a temperature lower than the LCST and then exposed to a medium at a temperature greater than the LCST, then the release pattern would be complex. Initially there is a thermal gradient across the device, the polymer collapses and skin formation takes place on its surface.

(3) the release would follow zero order kinetics when the active ingredient is released from a dry polymer matrix at a temperature above the LCST of the polymer.

(4) the release of an active ingredient from a glassy polymer at a temperature lower than the LCST would also follow zero order release. These mechanisms need to be understood and verified.

The release kinetics of Vitamin B_{12} and methylene blue from Poly (N - iso propyl acrylamide) was recently reported by Hoffman et.al.(9). The dry polymer disc was first incubated at $4^{\circ}c$ in the respective solution and the release kinetics were studied at $50^{\circ}c$. The release kinetics shows two regions : initially there is a rapid release of the active ingredient

followed by a slower release. The first region is probably due to release of the pore water near the surface along with the solute dissolved in it. The surface skin formed over it represents an increasing resistance to both diffusion and hydrostatic pressure flow across the thickening skin membrane. This leads to an apparently constant but lower release rate after the first 4 - 5 minutes.

The objectives of the present work were :

(1) to investigate the effect of the monomer structure on the velocity of penetration and diffusivity of the active ingredient through the polymeric hydrogel and to correlate the effect of these parameters on the release kinetics above and below the LCST.

(2) to compare the results of the release kinetics with the criteria for zero order release cited in the literature and the results of the prior investigations in this area.

In the present work the release kinetics of benzoic acid for a series of substituted acrylamide derivatives both above and below their LCST was investigated. The equilibrium swelling and penetration velocities as well as the diffusivities of benzoic acid were also determined below and above the LCST. Although the penetration velocity and the diffusivity of benzoic acid varied over a wide range, the variation of the equilibrium swelling interface number was not very significant. As a result, in most cases the release of benzoic acid was found to be linear with respect to the square root of time.

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