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Review Articles

Swelling controlled-release systems: recent developments and applications

K.V. Ranga Rao and K. Padmalatha Devi

Department of Pharmaceutical Sciences, Panjab University, Chandigarh (India)

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Introduction

During the last two decades, polymers which swell in an aqueous medium have often been used for the preparation of controlled-release dosage forms. Swellable polymers that are water-insoluble are commonly called hydrogels and water-soluble types are called hydrophilic polymers. In these swelling controlled-release systems, the release of a solute (e.g., drug, dye, etc.) is controlled by one or more of the following processes: namely, the transport of the solvent into the polymer matrix, swelling of the associated polymer, diffusion of the solute through the swollen polymer, erosion of the swollen polymer, etc. This article briefly reviews the studies that have used swellable synthetic polymers in drug delivery. Synthetic polymers which are relatively well known for this purpose are poly(hydroxyalkyl-methacrylate), poly(vinyl alcohol), ethylene vinyl alcohol, and their copolymers, poly(ethylene oxide), and cellulose ethers such as hydroxypropylcellulose (HPC), methylcellulose (MC), hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (Na CMC).

Correspondence: K.V. Ranga Rao. *Present address*: Université de Genève, Faculté des Sciences–Section de Pharmacie, 30 Quai Ernest-Ansermet, CH 1211, Genève 4, Switzerland.

Mechanism of release of the drug through the swelling controlled-release system

When a glassy (or dry) polymer comes into contact with water or any other medium with which it is thermodynamically compatible, the solvent penetrates into the free spaces on the surface between the macromolecular chains. When enough water has entered into the matrix, the glass transition temperature (T_g) of the polymer drops to the level of the experimental temperature (which is usually 37 °C for release studies) except for poly(ethylene oxide) whose T_g is approximately −60 °C. Therefore polymers with a T_g greater than 37 °C in their dry (glassy) state can be used to prepare swelling controlled-release dosage forms. The presence of solvent in the glassy polymer causes stresses which are then accommodated by an increase in the radius of gyration and end-to-end distance of the polymer molecules, i.e., the polymer chains get solvated. The increase in the radius of gyration of the polymer molecules is seen macroscopically as swelling. The solvent molecules move into the glassy polymer matrix with a well-defined front at a particular velocity and, simultaneously, the thickness of the swollen or rubbery region increases with time in the opposite direction. The time taken for the increase in radius of gyration of the polymer molecules, which

is a relaxational phenomenon, is a characteristic for that particular polymer/solvent system.

Several investigators have proposed models describing the transport of the solvent or penetrant (Petropoulos and Roussis, 1978; Gostoli and Sarti, 1982; Thomas and Windle, 1982; Korsmeyer and Peppas, 1984a), the solute (Lee, 1980; Amidon et al., 1985; Kou and Amidon, 1987), and both solute and penetrant (Good, 1976; Bamba et al., 1979; Peppas et al., 1980; Korsmeyer et al., 1986; Singh and Fan, 1986; Lee, 1987) in swellable systems and they have been reviewed from time to time by several workers (Korsmeyer and Peppas, 1983; Lee, 1985a; Gander et al., 1986a and b; Davidson and Peppas, 1986; Peppas and Korsmeyer, 1987). No single model successfully predicts all the experimental conditions but they collectively contribute towards an elucidation of the mechanism involved.

For characterising the mode of drug release or penetration of the solvent through the swelling controlled-release system, certain dimensionless numbers such as the Deborah number *De* (Vrentas et al., 1975), α of Hopfenberg et al. (1981), the swelling interface number *Sw* (Peppas and Franson, 1983) and the release exponent, *n* (Korsmeyer and Peppas, 1983; Ritger and Peppas, 1987) were proposed. Their limiting values for various types of release behaviour are given in Table 1. By determining these values experimentally, one can predict whether a particular drug–polymer combination can give zero-order release or not.

TABLE 1

General dependence of release behaviour on Deborah number (D_e); swelling interface number, (Sw); α and release exponent, (n).

Mode of release	D_e [a]	Sw [b]	α [c]	n *,[d]
Fickian	$\ll 1$ or $\gg 1$	$\gg 1$	$\ll 1$	0.45
Zero-order	–	$\ll 1$	~ 1	0.89
Non-Fickian	~ 1	~ 1	> 1	> 0.45 and < 0.89

For details, see: [a] Vrentas et al. (1975); [b] Korsmeyer and Peppas (1983); [c] Hopfenberg et al. (1981) and [d] Ritzer and Peppas (1987). * values for a cylinder.

Use of synthetic swellable polymers in drug delivery

The application of hydrogels in drug delivery has been reviewed from time to time (Kim et al., 1980a; Pedley et al., 1980; Kim, 1985; Roorda et al., 1986a; Mack et al., 1987;). Recent studies using the swellable synthetic polymers in formulating controlled-release dosage forms are reviewed in this article.

2-Hydroxyethyl methacrylate (HEMA)

Among the various hydrogels, the hydroxyalkyl methacrylates have been extensively studied, especially HEMA, which is a monomer of this group. The unique biocompatibility, swelling and diffusion properties of HEMA copolymers have also been reviewed (Ratner, 1981; Mack et al., 1987; Roorda et al., 1986a; Peppas and Moynihan, 1987). Copolymerisation of HEMA with monomers of varying hydrophilicity such as methyl methacrylate (MMA), ethyl methacrylate (EMA), methoxyethyl methacrylate (MEMA), methoxyethoxylethyl methacrylate (MEEMA) etc., using different crosslinking agents like ethylene glycol dimethacrylate (EGDMA), hexanediol diacrylate (HDDA), pentaerythritol triacrylate (PETA), tetraethyleneglycol dimethacrylate (TEGDMA), etc., will give gels with water content ranging from almost zero to over 90% (Schacht & Van Bos, 1987). A pouch prepared from a sheet of HEMA, when filled with neonatal rat or rabbit pancreatic cells, led to prolonged release of insulin (Klomp et al., 1979). This device was found to be biocompatible. Prostaglandin $PGF_{2\alpha}$ (Mack et al., 1983) was loaded into polymerised HEMA (pHEMA) gels by soaking them in 70% ethanolic solution of the drug. In vitro release studies showed that $PGF_{2\alpha}$ release was dependent on drug loading levels as well as on hydrogel swelling. A mixture of low molecular weight prostaglandin PGE_1 and a macromolecule, heparin, was dispersed in the pHEMA matrices and evaluated for their in vitro release. When released, both the agents were found to be biologically active (Ebert et al., 1980).

Hydrogel devices of various types (e.g., monolithic, reservoir, combined monolithic–reservoir, and monolithic with rate-controlling barriers) were prepared for release of progesterone using pHEMA

and pHEMA with the cross-linker EGDMA, in an attempt to produce implantable contraceptive hydrogels. Release of this drug from the monoliths showed two regions of linearity when the data were fitted to the square root of the time relationship. Release rates from the reservoir and the combined reservoir-monolithic systems were fairly constant after the initial 20 days (Cardinal et al., 1981). Monolithic devices with the rate-controlling barrier were first soaked in an ethanolic solution of EGDMA and then exposed to UV light for 30 min. Constant release rates were obtained from these devices. The soaking time in EGDMA, its concentration, and the UV exposure time were found to control the release rate (Lee et al., 1980). pHEMA gels cross-linked with 0.5% glycol dimethacrylate (GDMA) were loaded with procainamide and hydrogels containing 100 mg of the drug were administered to rabbits. For comparison, the equivalent dose was administered orally, as hard gelatin capsules and also i.v. The bioavailability of the hydrogel formulation (63%) was significantly higher than that of the capsule dosage form (38%) (Gyselinck et al., 1983). In vitro release of theophylline from copolymers of HEMA-*N*-vinyl-pyrrolidone indicated quasi zero-order release pattern (Korsmeyer and Peppas, 1984b). pH-sensitive hydrogels were prepared by introducing acidic and basic monomers into the polymerisation mixture. When an anthelmintic, levamisole, was incorporated into these hydrogels, they were found to be superior to the pure drug when tested in nematode-infested animals (Schacht, 1984).

Amidon et al. (1985) synthesized pHEMA-methacrylic acid gels cross-linked with TEGDMA and studied their swelling in 0.1 M HCl and 0.1 M phosphate buffer (pH 7). At pH 7, the swelling was affected by the cross-linking density. Release of phenylpropanolamine followed the square-root of the time relationship. When propranolol HCl (D'Emanuele and Staniforth, 1987) and chlorhexidine (Plaut et al., 1981) were allowed to pass through the pHEMA films cross-linked to different degrees, some interaction was reported between the cationic drug and the negatively-charged binding sites within pHEMA.

The permeabilities of hydrophilic and hydrophobic solutes in pHEMA films were studied ex-

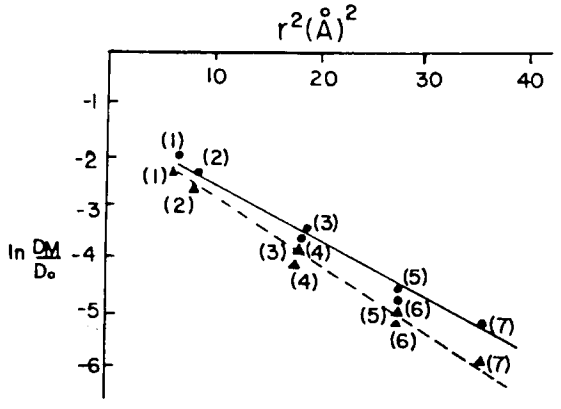

Fig. 1. Dependence of diffusion coefficients of hydrophilic solutes on molecular size in (———) pHEMA and (- - - - -) pHEMA cross-linked with 1 mol% EGDMA: (1) urea; (2) thiourea; (3) glucose; (4) inositol; (5) sucrose; (6) lactose; (7) raffinose. D_m/D_0 is the ratio of the diffusion coefficient of the solute in the hydrated membrane to that in water (Kim et al., 1980b).

tensively by Kim and his coworkers. Hydrophilic solutes pass through the pore mechanism and their diffusion coefficients were inversely proportional to the molecular size as shown in Fig. 1. Hydrophilic solutes have low diffusion coefficients and penetrate via either pore or partition mechanisms. Steroids were found to pass through highly cross-linked pHEMA films owing to the partition mechanism, whereas the hydrophilic solutes failed to pass through the highly cross-linked hydrogels (Kim et al., 1980b).

Similar studies with hydrophilic non-electrolytes and inorganic chloride salts (mol. wt. range: 20–500 Da) revealed that the membrane diffusion coefficient in pHEMA and cross-linked pHEMA decreased exponentially with increasing molecular size (Wisniewski and Kim, 1980). Sato and Kim (1984) studied the macromolecular diffusion through various synthetic porous and dense membranes including cellulose (cellulose acetate and regenerated cellulose), hydrogels (copolymers of pHEMA + MEMA and pHEMA + MEEMA) and biodegradable polymers (copolymers of lactic and glycolic acids). The results showed that the macromolecules diffuse through the membranes by a bulk water channel and through the polymer matrix depending on the method of membrane fabri-

cation. Membranes of HEMA, HEMA-styrene and HEMA-*N*-vinyl pyrrolidone were prepared by a free radical polymerisation procedure. The permeability of the antiviral drug, Ara-A, through these membranes revealed that the tracer diffused through the water-filled pores existing in the membrane. Swelling of the membrane was reported to be temperature-dependent (Miyajima et al., 1987). Using these membranes and the same drug, transdermal patches were prepared and filled over the azone-pretreated abdomen of hairless mice. Plasma profiles were found to be related to the in vitro permeabilities of the membranes (Komada et al., 1986). Hydrophilic-hydrophobic balanced copolymer membranes of HEMA-styrene and propylene oxide-polyethylene oxide were found to allow the drugs to pass through by both partition and pore mechanisms. The membrane of cross-linked poly(*N*-isopropylacrylamide-butylmethacrylate) copolymers demonstrated excellent thermosensitive release behaviour. When the temperature was decreased from 30 °C to 20 °C, the release rate increased immediately and when the temperature was raised to 30 °C, no noticeable lag time was observed as shown in Fig. 2. Such pulsatile release demonstrated the feasibility of obtaining thermoregulatory dosage forms (Kim et al., 1987).

When thiamine HCl was loaded into cross-linked pHEMA beads, the in vitro release was zero-order at low loadings and disappeared as the amount loaded was more than 18.7% w/w. The swelling rate was also fastest with the beads having the highest drug content (Lee, 1983). The initial burst effect observed was eliminated by Lee (1984a and b, 1985a and b) in a novel manner by stirring the oxprenolol HCl-loaded HEMA spheres in water at 23 °C for 5–30 min during which the penetrating solvent fronts did not meet. Then the beads were immediately freeze-dried. In this way, sigmoidal type of drug concentration distribution in the matrix was obtained. Upon drying, these systems gave zero-order release kinetics up to about 3 h. The effect of this concept on the release kinetics was examined theoretically for both the diffusion-controlled and surface erosion-controlled matrices in planar, cylindrical and spherical geometries. Concentration profiles capable of generating zero-order release were identified (Lee, 1986). This model assumes a constant diffusion coefficient of the drug and a constant volume of the controlled-release device.

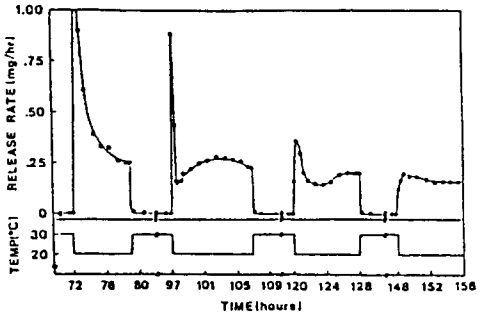

Fig. 2. Pulsatile release rate of indomethacin from a copoly(*N*-isopropyl acrylamide-butylmethacrylate) monolithic device in response to a step-wise temperature change in phosphate-buffered saline solution (pH 7.4) (Kim et al., 1987).

When a pHEMA matrix was covered with a porous and non-permeable membrane (waterproof 'Band-Aid' of Johnson & Johnson Ltd.), salicylic and benzoic acids were released at a zero-order rate (Pywell et al., 1986). Release of a drug from pHEMA gels was found to cause ruptures in the gel due to the latter's deswelling. As a result, the release rate was more than expected from a simple matrix device. By controlling these variables, oxprenolol HCl was released at a nearly zero-order rate for about 9 h (Roorda et al., 1986b and 1987). Collagen-pHEMA gels were found to be biocompatible for up to 6 months when implanted in rats (Rao & Jeyanthi, 1987). A kinetic model for prediction of the structural characteristics of pHEMA microparticles cross-linked with EGDMA was proposed. The gel point, number of effective cross-links per linear chain etc., were calculated (Mikos & Peppas, 1987).

Ethylene-vinyl alcohol (EVA) and its copolymers

EVA and its copolymers are glassy, water-swellable as well as water-insoluble. These polymers can easily be processed by the conventional extrusion and injection moulding techniques. The safety and biocompatibility of this polymer are reflected in its use as a haemodialysis membrane. Hopfenberg et al. (1981), studied the release of sodium chloride and malachite green at 4, 15 and 25 °C

and observed in some cases non-Fickian release of the drug through the polymer. The same workers (Gaeta et al., 1982) studied the absorption and desorption equilibria and kinetics for lithium chloride (Li Cl) and water at 25 °C. Drug loading was dependent on the concentration of the external drug solution. The drug release rate was independent of the concentration of the drug present in the film. Using two grades of EVA with different percentages of vinyl alcohol and different degrees of crystallinity, films containing theophylline were prepared by compression and dissolution-compression techniques (Ségot-Chiq and Peppas, 1986). Release studies revealed that both the porosity and the degree of crystallinity were important in the release process. Release kinetics were dependent on the square root of time. Miyazaki et al. studied the permeability of steroids, prednisolone and prednisone (1981), and the anticancer agents, 5-fluorouracil (5-FU) and ftorafur (1983), through EVA membranes having different mol% of ethylene and different thicknesses for 8 days using a dialysis cell. The rate of permeability was found to be dependent upon the monomer composition. These workers (Miyazaki et al., 1985a) reported that by implanting EVA matrices containing 5-FU, the life-span of mice with Ehrlich ascites carcinoma was prolonged significantly. The results obtained are given in Table 2.

TABLE 2

Effect of EVA copolymer matrices containing 5-FU and free 5-FU on survival time of mice bearing Ehrlich ascites carcinoma

Ehrlich ascites carcinoma (2×10^6 cells) was inoculated i.p. into ddY mice. Chemotherapy was given with intraperitoneal single injection (free 5-FU) or implantation (EVA matrices). (Miyazaki et al., 1985a)

Compound	Dose (mg per mouse)	Mean survival time (days)	T/C [a] (%)	Survivors at 60 days
Control	–	18.2(1.3)	100.0	0/6
Free 5-Fu	3.9 [b]	22.2(1.6)	122.0	0/6
	7.2 [c]	20.5(0.9)	112.6	0/6
EVA matrix without 5-FU	– [c]	20.7(0.7)	113.7	0/6
EVA matrix containing 5-FU	3.9 [b]	43.8(3.7) *	240.7	1/6
	7.2 [c]	41.7(5.4) **	229.1	0/6

[a] Calculated as the ratio of the mean survival time of the treated group divided by that of the control group.
[b] Chemotherapy was given at 2 days after inoculation.
[c] Chemotherapy was given at 3 days after inoculation.
* Significantly different ($P < 0.001$) from the control.
** Significantly different ($P < 0.005$) from the control.

Similar but slightly less effective results, compared to those with 5-FU, were obtained with EVA matrices containing adriamycin against *E. ascites* and P388 leukaemia in mice (Miyazaki et al., 1985b). The release rate of 5-FU from the EVA matrix was increased by external ultrasound irradiation and this was attributed to the increase in temperature in the matrix (Miyazaki et al., 1985c). Hou et al. (1985) reported prolonged miotic activity when an EVA bead of 2.2 mm diameter containing 2 mg of pilocarpine HCl was inserted into the lower cul-de-sac of albino rabbits. Restoration of normal pupil diameter occurred 30 h after inserting the bead. The latter neither caused any inflammation to the treated eyes nor constricted the pupil of the control eyes.

Poly(vinyl alcohol), PVA

Several of the properties and synthesis of PVA and its copolymers were reviewed recently by Peppas (1987). Release of theophylline through the slabs of PVA cross-linked to different degrees with glutaraldehyde was studied by Korsmeyer and Peppas (1981). Cross-linking impeded the release rate significantly and the release behaviour was predominantly Fickian. Predrying of the cross-linked systems decreased the release rate and anomalous diffusion was seen in some cases. Influence of the molecular size of the solute through PVA disks was studied by taking KCl, phenylpropanolamine and bovine serum albumin as the model drugs. An increase in the size of the solute decreased the release rate and the release profiles were closer to Fickian type. The addition of water-soluble polymer (*N*-vinyl pyrrolidone) increased the release rate due to its removal from the disks by dissolution along with the solute (Korsmeyer et al., 1983). Mini matrices of PVA and diprophylline were prepared by compression. Their surface was cross-linked by soaking them in

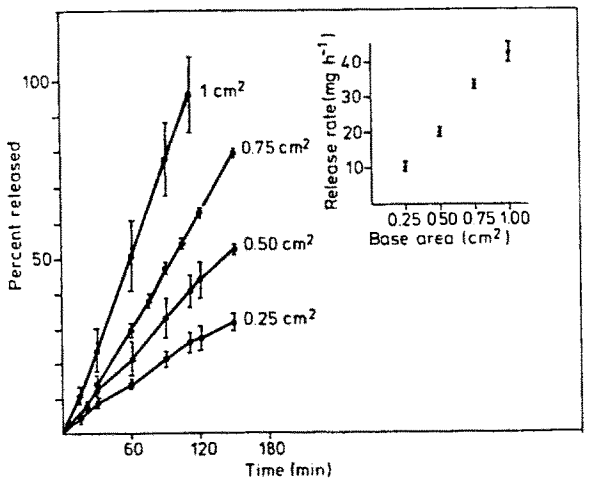

Fig. 3. Release of diclofenac sodium (cumulative percent) as a function of time from one surface of the tablets having different surface areas. The tablets contain drug (50%), PVA (30%), and mannitol (20%). Inset is the relationship between the release rate and the base area of the tablet (Colombo et al., 1987).

an acidic formalin solution and subsequent exposure of the dried matrices to UV light or to heat in an oven. In vitro studies showed that by optimizing the cross-linking conditions zero-order release could be obtained (Colombo et al., 1985). Diclofenac sodium and diprophylline with solubilities of 3% and 30%, respectively, were mixed with Mowiol 40-88 (a soluble PVA) and mannitol in different ratios, granulated with soluble polyvinyl pyrrolidone, and compressed into tablets of different diameters. The tablets were covered on all surfaces, except one, with a water-insoluble grade of cellulose acetate propionate. In vitro studies indicated that there was a linear relationship between the release rate and the base area of the tablets as shown in Fig. 3. Significant differences were also noted in vivo, when the tablets with different diffusion areas were administered to humans (Colombo et al., 1987).

Lai et al. (1987) incorporated indomethacin at 1%, 2% and 4% w/w levels into molten PVA and 10 cm disks were prepared using moulds. The release profiles followed the classical square root of the time relationship. Increase in the drug content from 1% to 4% w/w increased the amount released in one day from 12 mg to 25 mg. By taking lithium carbonate as a model drug, Süss reported (1983) that, by increasing the drug concentration or the porosity of the PVA mouldings, the release rate could be increased. However, when a less soluble drug like aspirin was incorporated into tablets of PVA, an increase in the drug content decreased the release rate owing to poor wetting and slow swelling of the tablet (Süss & Bruder, 1987). The rate of swelling and thus the release rate could be controlled by the addition of magnesium stearate or potato starch (Süss, 1983). Release kinetics of nalidixic acid from the matrices prepared with different PVA/veegum ratios at two compression levels were studied in four different dissolution media. The porosity of the matrix did not affect the release rate significantly in any medium (Forni et al., 1986). Wang (1986) studied the release of methylene blue from disks prepared by direct compression and containing maleic anhydride and PVA or polycaprolactone (PCL). By changing the ratio between PVA and PCL, the dye could be released at a zero-order rate. Increase in the temperature and concentration of the anhydride increased the release rate. Wang observed that PVA also diffused through the matrix along with the dye. Mixtures of poly(styrene-co-maleic anhydride) and PVA were found to sustain the release of some drugs. The sustaining capacity of the hydrogel was reported to depend on the percentage of drug present in the tablet (Laughlin et al., 1987). Rectal administration of PVA hydrogel preparations of indomethacin to rats and dogs produced sustained plasma levels for 24 h and 9 h, respectively, although the plasma levels were higher in the rat and lower in the dog. Propranolol HCl-containing hydrogels did not show a sustaining effect (Morisaka et al., 1987). When another PVA hydrogel preparation containing bunitrolol HCl was applied on rat abdominal skins under occlusion, constant plasma levels were maintained for about 48 h. The in vitro release profile was similar to that of the matrices and 100% of the drug was released within 6 h. This shows that PVA can be used for preparing transdermal preparations (Nagayasu et al., 1987).

Poly(ethylene oxide), PEO

This is another water-soluble crystalline linear polymer prepared by the polymerisation of ethyl-

ene oxide. PEO of mol. wt. ranging from 10 to 20,000 Da is used in pharmacy. To make this polymer swellable and water-insoluble, the polymer chains are cross-linked. Different methods of cross-linking, various properties and applications of the cross-linked polymers were described by Graham (1986, 1987). Graham and his coworkers are at the forefront in formulating PEO-based dosage forms releasing the drug at a zero-order rate. Some such formulations developed by these workers are being tried successfully in patients. To induce labour and abortion, stable vaginal pessaries containing cross-linked PEO and prostaglandin E_2 were prepared. Their use led to a significant reduction in the need for caesarian section, oxytocin drip and epidural anaesthetic. Similarly, to induce postoperative analgesia, suppositories of morphine containing an immediate dose and a maintenance dose for 12 h were also formulated. By administering another suppository containing only the maintenance dose, the required analgesia could be prolonged for 24 h. Relevant literature describing in vitro and clinical results was cited in the reviews of Graham (1986, 1987) and are therefore omitted in this article. In order to optimize the release rate, several factors affecting it such as degree and rate of swelling of the hydrogel, device geometry, concentration of the drug solution, swelling periods etc., were studied by McNeill and Graham (1987). Graham et al. (1988) studied the release of caffeine from cross-linked PEO slabs of different thicknesses. The release profiles followed the square root of the time relationship. A linear relationship existed between the half-life of caffeine in the swollen hydrogel and the slab thickness. Both bound and free-water were identified in the hydrogel with the DSC scans. Micromatrices (400–600 μm) of cross-linked poly(alkylene oxides) were prepared and loaded with proxyphylline, theophylline and methylcatechine. Various preparation parameters such as mol. wt. of the initial PEO, copolymer composition, interlinking degree etc., and the drug's characteristics influenced the release rate (Gander et al., 1986c, 1988). Van Bos and Schacht (1987) prepared polyurethanes from A-B-A type block copolymers. The equilibrium water content of these gels was found to depend largely on the ethylene oxide content. The gels were loaded with propranolol hydrochloride. Diffusion coefficients for the drug in different hydrogels were determined. Cross-linked hydrogels of poloxamers (A-B-A type copolymers) were prepared by irradiating the aqueous solutions with γ-irradiations for several hours (Al-Saden et al., 1980). The spherulite growth, the gel structure, swelling characteristics and the drug release properties were studied. Poloxamers released the drug slowly compared to the solutions (Law et al., 1984).

Cellulose polymers

Cellulose ethers are also becoming popular as matrices since they are easy to prepare, they can accommodate a large percentage of the drug, and the release is less influenced by the processing variables. Among the cellulose ethers, MC, HPC, HPMC and Na CMC are the most popular. Many factors affecting the release of drugs from cellulose matrices have been reviewed (Doelker, 1987; Padmalatha Devi, 1987). Relevant literature about cellulose matrices has been cited in our earlier publication (Ranga Rao et al., 1988). The release profiles of freely soluble drugs normally follow the classical square root of the time relationship, i.e., the release rate decreases with time. Baveja & Ranga Rao (1986) were the first to suggest the use of both anionic and non-ionic cellulose ethers as a solution to this formulation problem. The initial burst effect seen for very soluble drugs when incorporated into HPMC matrices was minimized by incorporating Na CMC into the matrix. Later, by using a mixture of anionic Na CMC and non-ionic HPMC in an optimum ratio, Baveja et al. (1987) prepared nearly zero-order release tablets of very soluble β-blockers, namely, propranolol hydrochloride (PH), metoprolol tartrate (MT) and alprenolol hydrochloride (AH). These workers indicated that besides the ratio of drug to total polymer, the ratio between the anionic and non-ionic polymers was important to obtain zero-order release till the entire drug was released from the tablets. Release of PH from such a system is shown in Fig. 4.

Ranga Rao et al. (1988) formulated zero-order release tablets of MT and AH, using a mixture of HPC + Na CMC and MC + Na CMC. These

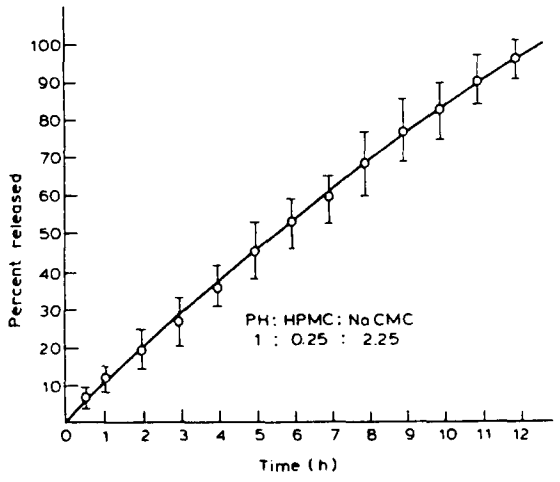

Fig. 4. Release of propranolol hydrochloride (cumulative percent) as a function of time from tablets of different batches ($n = 10$) containing HPMC and Na CMC in an optimum ratio. Vertical bars indicate ± S.D. (Baveja et al., 1987).

workers reported that the erosion rate of the matrix releasing the drug at a zero-order rate and containing AH, HPC and Na CMC was fairly constant and was about 2.5 times higher compared to a matrix containing the same ratio of AH and polymer but only HPC. The authors' group (Baveja et al., 1987 and Ranga Rao et al., 1988) were of the opinion that by optimizing the ratio between the drug and the total polymer and also the ratio between the anionic and non-ionic gums, the rates of advancement of the swelling front into the glassy polymer and the attrition of the rubbery-state polymer were made equal so that the diffusional path length for the drug and hence the zero-order release remained nearly constant. When the release data were fitted to the empirical equation of Korsmeyer and Peppas (1983); Ritger and Peppas (1987), the values of n were found to be closer to that needed for zero-order release, i.e., 0.89.

This hypothesis may not account for the constant release rate observed when the size of the matrix is much smaller than the original size (due to the constant erosion rate, the matrix size decreases with time). The authors therefore propose that since (a) the rate of penetration of solvent into the tablet decreases with time (Hopfenberg, 1976) and (b) the erosion rate of the matrix is nearly constant (Ranga Rao et al., 1988), the diffusional path length for the drug changes with time. Therefore the drug release rate per unit area of the matrix changes with time as the size of the matrix changes with time. The net effect is that the plot of the cumulative amount released from the dosage form vs time is linear till the entire drug is released from the tablet.

In order to identify whether the solubility or the molecular size of the solute is primarily influencing the release through cellulose matrices, the release of 27 drugs with various solubilities and molecular weights through matrices of HPMC and HPMC + Na CMC was studied by Ranga Rao et al. (1987). They concluded that the release rates were higher when Na CMC was present in the matrix except for very soluble drugs owing to faster erosion of the swollen gel. Several less-soluble drugs were released at a nearly zero-order rate through HPMC matrices indicating that the solubility of the drug plays an important role in the release behaviour. Similar observations were reported by Ford et al. (1987) by studying the release of 7 soluble and insoluble drugs through HPMC matrices. The molecular weight of the drugs (an approximate indicator of molecular size) could not be related to their release rates, indicating that molecular geometry might be playing a role. This aspect was studied by the author's group (Baveja et al., 1988a) by taking 6 structurally related water-soluble bronchodilators as model drugs. Their release rates through HPMC matrices of 3 different viscosity grades were found to be highly correlated ($r > 0.95$) with the accessible surface area (ASA) of the drugs. ASA is a parameter which quantifies the molecular size and shape based on the 3-dimensional geometry of the molecule (Pearlman, 1980). Using those correlations, the release rate of another drug was predicted by calculating its ASA. The predicted release rate was in close agreement (± 5%) with the experimentally obtained release rate. Ford et al. reported a linear relationship between (i) the Higuchian release rate and reciprocal of the weight of HPMC present in the tablet (1985a) and (ii) the log Higuchian release rate and the log of HPMC content in the tablet (1985b). The authors' group found that when HPMC alone or a mixture of HPMC and

Na CMC in a constant ratio were present in the matrix, a linear relationship was seen between the in vitro half-life of the matrix (time to release 50% of the drug present in the matrix) and the ratio of total polymer to drug present in the matrix (Baveja et al., 1988b). Feely and Davis (1988) studied the effect of surfactants in retarding the drug release from HPMC matrices and reported that the hydrocarbon chain length of the surfactant did not mainly influence the release of the drug. They found that the surfactant was effective only when the latter and the drug were ionised and when they had opposite charges. These workers reported an inverse linear relationship between the Higuchian release rate and the number of molecules of the surfactant (sodium alkylsulfates) present in the HPMC matrix.

The ability of cellulose matrices to exhibit zero-order release in vivo was proved by administering the tablets of AH, PH, MT and oxprenolol HCl to fed mongrel dogs. For comparison, the equivalent doses of rapid-releasing formulations were also administered to the same dogs after a wash-out period of 1 week. Pharmacokinetic profiles indicated that nearly constant blood levels were maintained by the cellulose matrix tablets of all the drugs for about 12 h. Plasma concentrations at the end of 24 h were significantly higher with the matrix tablets compared to the conventional formulations (Padmalatha Devi, 1987 and Padmalatha Devi et al., 1987). Sam et al., (1987) administered matrices containing ORG 6370 and HPMC alone or HPMC + Na CMC to human volunteers and reported that the sustaining ability of cellulose matrices in vivo was better when Na CMC was present in the matrix.

A double-layer floating tablet, consisting of a carbon dioxide-generating blend ($CaCO_3$, $NaHCO_3$, citric acid, excipients and HPMC) in one layer and sodium riboflavine 5′-phosphate, HPMC and excipients in the second layer, was prepared by Ingani et al. (1987). This tablet, when ingested, liberated carbon dioxide which was entrapped in the HPMC gel and hence the tablet remained floating in the stomach. This floating tablet, a classical hydrodynamically balanced capsule and a non-floating sustained-release hydrophilic matrix tablet were administered to humans in fasted and fed conditions. The floating dosage forms significantly increased the gastric residence time compared to the non-floating preparation. In fasted subjects, higher drug excretion rates were observed with the floating tablet. Hashim and Li Wan Po (1987) also mixed a carbon dioxide-generating blend with KCl and HPMC, and reported that, by using an optimum amount of the gas-generating mixture, zero-order release could be achieved. Machida et al. (1987) prepared floating film and tablets for cinnarazine and 5-FU. When these formulations were administered to beagle dogs, the 5-FU did not show such prolonged profiles. Venkatesh et al. (1987) reported strong intermolecular interaction between HPMC and ibuprofen by conducting differential scanning calorimetric (DSC) studies.

Vinyl groups were introduced into human albumin and using the product formed as a cross-linker, hydrogels of polyacrylamide, polyacrylamide-co-*N*, *N*-dimethyl-aminoethyl methacrylate were prepared. These hydrogels remained in the stomach until they were digested by the enzymes (Park and Park, 1987). Certain swellable polymers like polyacrylic acid (carbomer), loosely cross-linked polyacrylic acid (polycarbophil), high mol. wt. celluloses such as Na CMC and HPC etc., were found to adhere strongly to the glycoproteins of the mucus. Several mucoadhesive dosage forms have been prepared for drug delivery through various routes, but this subject is not included in this review.

A short review like this cannot be comprehensive. Many polymers such as poly(*N*-vinyl pyrrolidone), polymethacrylamide, polyacrylamide, HPC etc., had to be omitted or are dealt with only briefly. However, this review has described the potential of swellable polymers for delivering drugs at the desired rate through various routes.

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References

Al-Saden A.A., Florence, A.T. and Whateley, T.L., Cross-linked hydrophilic gels from ABA block copolymeric surfactants, *Int. J. Pharm.*, 5 (1980) 317–327.

Amidon, G.L., Kou, J.H. and Lee, P.I., Swelling and drug release from p-HEMA-MAA-hydrogel system. *Proc. Int. Symp. Controlled Release Bioact. Mat.*, 12 (1985) 21–22.

Bamba, M., Puisieux, F., Marty, J.P. and Carstensen, J.T., Physical model for release of drug from gel forming sustained release preparations. *Int. J. Pharm.*, 3 (1979) 87–92.

Baveja S.K. and Ranga Rao, K.V., Sustained release tablet formulation of centperazine. *Int. J. Pharm.*, 31 (1986) 169–174.

Baveja, S.K., Ranga Rao, K.V. and Padmalatha Devi, K., Zero-order release hydrophilic matrix tablets of β-adrenergic blockers. *Int. J. Pharm.*, 39 (1987) 39–45.

Baveja, S.K., Ranga Rao, K.V., Singh, A. and Gombar, V.K., Release characteristics of some bronchodilators from compressed hydrophilic polymeric matrices and their correlation with molecular geometry. *Int. J. Pharm.*, 41 (1988a) 55–62.

Baveja, S.K., Ranga Rao, K.V. and Padmalatha Devi, K., Relationship between gum content and half-life of soluble β-blockers from hydrophilic matrix tablets. *Int. J. Pharm.*, 47 (1988b) 133–139.

Cardinal, J.R., Kim, S.W., Song, S., Lee, E.S. and Kim, S.H., Controlled release drug delivery systems from hydrogels: Progesterone release from monolithic, reservoir, combined reservoir monolithic and monolithic devices with rate controlling barriers. *AIChE Symp. Series*, 77 (1981) 52–61.

Colombo, P., Conte, U., Caramella, C., Gazzaniga, A., and La Manna, A., Compressed polymeric minimatrices for drug release control. *J. Controlled Release*, 1 (1985) 283–289.

Colombo, P., Gazzaniga, A., Caramella, C., Conte, U. and La Manna, A., In vitro programmable zero-order release drug delivery system. *Acta Pharm. Technol.*, 33 (1987) 15–20.

Davidson III, G.W.R. and Peppas, N.A., Solute and penetrant diffusion in swellable polymers V. Relaxation-controlled transport in p (HEMA-co-MMA) copolymers. *J. Controlled Release*, 3 (1986) 243–258.

Doelker, E., Water-swollen cellulose derivatives in pharmacy, In Peppas, N.A. (Ed.), *Hydrogels in Medicine and Pharmacy, Vol. II, Polymers*, CRC, Boca Raton, 1987, pp. 115–160.

D'Emanuele, A.J. and Staniforth, J.N., The anomalous diffusion of propranolol hydrochloride through cross-linked poly HEMA films. *J. Pharm. Pharmacol., Proc. Br. Pharm. Conf.*, 39 (1987) 28p.

Ebert, C.D., McRea, J.C. and Kim, S.W., Controlled release of antithrombotic agents from polymeric matrices. In Baker, R.W. (Ed.), *Controlled Release of Bioactive Agents*, Academic, New York, 1980, pp. 107–122.

Feely, L.C. and Davis, S.S., Influence of surfactants on drug release from hydroxypropylmethylcellulose matrices. *Int. J. Pharm.*, 41 (1988) 83–90.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E., Formulation of sustained release promethazine hydrochloride tablets using hydroxypropylmethylcellulose matrices. *Int. J. Pharm.*, 24 (1985a) 327–338.

Ford, J.L., Rubinstein, M.H. and Hogan, J.E., Propranolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose. *Int. J. Pharm.*, 24 (1985b) 339–350.

Ford, J.L., Rubinstein, M.H., McCaul, F., Hogan, J.E. and Edgar, P.J., Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. *Int. J. Pharm.*, 40 (1987) 223–234.

Forni, F., Iannuccelli, V., Cameroni, R., Coppi, G. and Bernabei, M.T., Matrici eterogenee di tiposwelling: proprieta fisiche e meccanismo di cessione. *Farmaco Ed. Prat.*, 16 (1986) 155–164.

Gaeta, S., Apicella, A. and Hopfenberg, H.B., Kinetics and equilibria associated with the absorption and desorption of water and lithium chloride in an ethylene-vinyl alcohol copolymer, *J. Membrane Sci.*, 12 (1982) 195–205.

Gander, B., Gurny, R. and Doelker, E., Matrices à libération contrôlée par le gonflement du polymère. Partie I: Mécanismes de pénétration des solvants dans les polymères. *Pharm. Acta Helv.*, 61 (1986a) 130–134.

Gander, B., Gurny, R. and Doelker, E., Matrices à libération contrôlée par le gonflement du polymère. Partie II: Préparation des systèmes médicamenteux et analyse de la cinétique de libération. *Pharm. Acta Helv.*, 61 (1986b) 178–184.

Gander, B., Gurny, R. and Doelker, E., Crosslinked polaxomers as a versatile drug delivery system, *Drug Dev. Ind. Pharm.*, 12 (1986c) 1613–1623.

Gander, B., Gurny, R., Doelker, E. and Peppas, N.A., Crosslinked poly(alkylene oxides) for the preparation of controlled release formulations, *J. Controlled Release*, 5 (1988) 271–283.

Good, W.R., Diffusion of water soluble drugs from initially dry hydrogels. In Kostelnik, R. (Ed.), *Polymeric Delivery Systems*, Gordon and Breach, New York, NY, 1976, pp. 139–153.

Gostoli, C. and Sarti, G.C., Diffusion and localised swelling resistances in glassy polymers. *Polym. Eng. Sci.*, 22 (1982) 1018–1026.

Graham, N.B., Hydrogels in controlled drug delivery. In Piskin, E. and Hoffman, A.S. (Eds.), *Polymeric Biomaterials NATO ASi Series E: Applied Sci., No. 106*, 1986, pp. 170–194.

Graham N.B., Poly(ethylene oxide) and related hydrogels, In Peppas, N.A. (Ed.), *Hydrogels in Medicine and Pharmacy. Vol. II. Polymers*, CRC, Boca Raton, 1987 pp. 95–113.

Graham, N.B., Zulfiqar, M., MacDonald, B.B. and McNeill, M.E., Caffeine release from fully swollen poly(ethylene oxide) hydrogels. *J. Controlled Release*, 5 (1988) 243–252.

Gyselinck, P., Schacht, E., Severen, R.V. and Braeckman, P., Preparation and characterisation of therapeutic hydrogels as oral dosage forms. *Acta Pharm. Technol.*, 29 (1983) 9–12.

Hashim, H. and Li Wan Po, A., Improving the release characteristics of water-soluble drugs from hydrophilic sustained release matrices by in situ gas generation. *Int. J. Pharm.*, 35 (1987) 201–209.

Hopfenberg, H.B., Controlled release from erodible slabs, cylinders and spheres, In Paul, D.R. and Harris, F.W. (Eds.), *Controlled Release Polymeric Formulations, ACS Symposium Series No. 33*, American Chemical Society, Washington D.C., 1976, pp. 26–32.

Hopfenberg, H.B., Apicella, A. and Saleeby, D.E., Factors affecting water sorption and solute release from glassy ethylene-vinyl alcohol copolymers. *J. Membrane Sci.*, 8 (1981) 273–282.

Hou, W.M., Miyazaki, S. and Takada, M., Controlled release of pilocarpine hydrochloride from ethylene-vinyl alcohol copolymer matrices. *Chem. Pharm. Bull.*, 33 (1985) 1242–1248.

Ingani, H.M., Timmermans, J. and Moes, A.J., Conception and in vivo investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. *Int. J. Pharm.*, 35 (1987) 157–164.

Kim, S.W., Hydrogels for controlled drug release. In Gebelein, C.G. and Carraher Jr., C.E. (Eds.) *Bioactive Polymeric Systems, An Overview*, Plenum, New York, 1985, pp. 143–150.

Kim, S.W., Cardinal, J.R., Wisniewski, S. and Zentner, G.M., Solute permeation through hydrogel membranes, Hydrophilic vs. hydrophobic solutes. In Rowland, S.P. (Ed.), *Water in Polymers, ACS Symposium Series* No. 127, American Chemical Society, Washington D.C., 1980b, pp. 347–359.

Kim, S.W., Okano, T., Bae, Y.H., Hsu, R. and Lee, S.J., Hydrophilic-hydrophobic balanced polymers for controlled delivery of drugs. *Proc. Int. symp. Controlled Release Bioact. Mat.*, 14 (1987) 37–38.

Kim, S.W., Peterson, R.V. and Feijen, J., Polymeric drug delivery systems. In Ariens, E.J. (Ed.), *Drug Design Vol. 10*, Academic, New York, 1980a, pp. 193–250.

Klomp, G.F., Ronel, S.H., Hashiguchi, H., D'Andrea, M., Dobelle, W.H., Hydrogels for encapsulations of pancreatic islet cells. *Trans. Am. Soc. Artif. Intern. Organs.* 25 (1979) 74–76.

Komada, F., Miyajama, M., Okano, T., Durrani, M., Kim, S.W., Higuchi, W.I., Shannon, W.M. and Baker, D.C., Design of an ARA-A transdermal delivery system for animal studies: Regulation of drug concentration in vivo. *Proc. Int. Symp. Controlled Release Bioact. Mat.*, 13 (1986) 93–94.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A., Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.*, 15 (1983) 25–35.

Korsmeyer, R.W., Lustig, S.R. and Peppas, N.A., Solute and penetrant diffusion in swellable polymers. I. Mathematical modelling. *J. Polym. Sci. Polym. Phys. Ed.*, 24 (1986) 395–408.

Korsmeyer, R.W. and Peppas, N.A., Effect of the morphology of hydrophilic polymeric matrices on the diffusion and release of water soluble drugs. *J. Membrane Sci.*, 9 (1981) 211–227.

Korsmeyer, R.W. and Peppas, N.A., Macromolecular and modelling aspects of swelling-controlled systems. In Roseman, T.J. and Mansdorf, S.Z. (Eds.), *Controlled Release Delivery Systems*, Marcel Dekker, New York, 1983, pp. 77–90.

Korsmeyer, R.W. and Peppas, N.A., Transport phenomena in polymers. Diffusion and anomalous transport in glassy polymers. *Polym. News*, 9 (1984a) 359–361.

Korsmeyer, R.W. and Peppas, N.A., Solute and penetrant diffusion in swellable polymers. III. Drug release from glassy poly(HEMA-co-NVP) copolymers. *J. Controlled Release*, 1 (1984b) 89–98.

Kou, J.H. and Amidon, G.L., Mechanism of drug release from a dynamically swelling hydrogel matrix. *Proc. Int. Symp. Controlled Release Bioact. Mat.*, 14 (1987) 79–80.

Lai, J.S., Chiang, C.H. and Wu, T.H., Release kinetics of indomethacin from polymeric matrices. *Drug Dev. Ind. Pharm.*, 13 (1987) 1399–1408.

Laughlin, T.J., Adair, T.R., Perkins, B.H. and Dunn, R.L., Hydrogel delivery systems based on polymer alloys. *Proc. Int. symp. Controlled Release Bioact. Mat.*, 14 (1987) 39–40.

Law, T.K., Whateley, T.L. and Florence, A.T., Some chemically modified polaxomer hydrogels: preparation, morphology and swelling properties, *Int. J. Pharm.*, 21 (1984) 277–287.

Lee, E.S., Kim, S.W., Kim, S.H., Cardinal J.R. and Jacobs, H., Drug release from hydrogel devices with rate-controlling barriers. *J. Membrane Sci.*, 7 (1980) 293–303.

Lee, P.I., Diffusional release of a solute from a polymeric matrix—approximate analytical solutions. *J. Membrane Sci.*, 7 (1980) 255–275.

Lee, P.I., Dimensional changes during drug release from a glassy hydrogel matrix. *Polym. Commun.*, 24 (1983) 45–47.

Lee, P.I., Novel approach to zero-order drug delivery via immobilized nonuniform drug distribution in glassy hydrogels. *J. Pharm. Sci.*, 73 (1984a) 1344–1347.

Lee, P.I., Effect of non-uniform initial drug concentration on the kinetics of drug release from glassy hydrogel matrices. *Polymer*, 25 (1984b) 973–978.

Lee, P.I., Kinetics of drug release from hydrogel matrices. *J. Controlled Release*, 2 (1985a) 277–288.

Lee, P.I., Kinetics of drug-release from glassy polymers: effect of initially nonuniform drug distribution. In Gebelein, C.G. and Carraher, Jr., C. E. (Eds.), *Polymeric Materials in Medication*, Plenum, New York 1985b, pp. 79–85.

Lee, P.I., Initial concentration distribution as a mechanism for

regulating drug release from diffusion controlled and surface erosion controlled matrix systems. *J. Controlled Release*, 4 (1986) 1–7.

Lee, P.I., Interpretation of drug-release kinetics from hydrogel matrices in terms of time-dependent diffusion coefficients. In Lee, P.I. and Good, W.R. (Eds.), *Controlled Release Technology: Pharmaceutical Applications, ACS Symposium series No. 348*, American Chemical Society, Washington D.C., 1987, pp. 71–83.

Machida, Y., Iwata, M. and Nagai, T., Preparation and evalulation of intragastric floating preparations, *Proc. Int. Cong. Pharm. Sci. F.I.P.*, 47 (1987), Abstract No. 22.

Mack, E.J., Sharma, K. and Kim, S.W., Hydrogel diffusion and drug delivery systems. In D.D. Breimer and P. Speiser (Eds.), *Topics in Pharmaceutical Sciences 1983*, Elsevier, Amsterdam, 1983, pp. 265–275.

Mack, E.J., Okano, T. and Kim, S.W., Biomedical applications of poly(2-hydroxyethyl methacrylate) and its copolymers. In Peppas, N.A. (Ed.), *Hydrogels in Medicine and Pharmacy, Vol. II, Polymers*, CRC, Boca Raton, 1987, pp. 65–93.

McNeill, M.E. and Graham, N.B., Morphine hydrogel suppositories: device design, scale-up and evaluation. In Lee, P.I. and Good, W.R. (Eds.), *Controlled Release Technology: Pharmaceutical Applications, ACS Symposium series No. 348*, American Chemical Society, Washington, DC 1987, pp. 158–170.

Mikos, A.G. and Peppas, N.A., A model for prediction of EGDMA-crosslinked pHEMA microparticles produced by suspension/copolymerisation/cross-linking. *J. Controlled Release*, 5 (1987) 53–62.

Miyajima, M., Okano, T., Kim, S.W. and Higuchi, W.I., Preformulation of an Ara-A transdermal delivery system: membrane fabrication and characterisation. *J. Controlled Release*, 5 (1987) 179–186.

Miyazaki, S., Hou, W.M. and Takada, M., Controlled drug release by ultrasound irradiation. *Chem. Pharm. Bull.*, 33 (1985c) 428–431.

Miyazaki, S., Ishii, K. and Nadai, T., Drug permeability of ethylene-vinyl alcohol copolymer membranes, *Membrane*, 6 (1981) 279–280.

Miyazaki, S., Takeuchi, S., Hou, W.M., Hashiguchi, N., Yokouchi, C., Takada, M., Hosokawa, M., Koga, Y. and Kobayashi, H., Antitumor effect of implanted ethylene-vinyl alcohol copolymer matrices containing anticancer agents on Ehrlich ascites carcinoma and P388 leukemia in mice. *Chem. Pharm. Bull.*, 33 (1985b) 2490–2498.

Miyazaki, S., Takeuchi, S., Sakamoto, M. and Takada, M., Controlled release of anticancer agents through hydrophilic ethylene-vinyl alcohol copolymer membranes, *Membrane*, 8 (1983) 241–242.

Miyazaki, S., Takeuchi, S., Sugiyama, M., Takada, M., Hosokawa, M., Koga, Y. and Kobayashi, H., Effect of implanted ethylene-vinyl alcohol copolymer matrices containing 5-fluorouracil on Ehrlich ascites carcinoma, *J. Pharm. Pharmacol.*, 37 (1985a) 64–66.

Morisaka, K., Morimoto, K., Fukanoki, S., Hyon, S.H. and Ikada, Y., Rate-controlled rectal drug delivery system using PVA hydrogel. *J. Pharm. Sci.*, 76 (1987) S282.

Nagayasu, A., Morimoto, K., Morisaka, K., Hyon, S.H. and Ikada, Y., Evaluation of bunitrolol transdermal system using PVA hydrogel. *J. Pharm. Sci., 76 (1987) S283.*

Padmalatha Devi, K., *Studies on Formulation of Sustained Release Dosage Forms of Some Beta Adrenergic Blockers*, Ph.D. thesis, Panjab University, Chandigarh (India), 1987.

Padmalatha Devi, K., Ranga Rao, K.V., Shankarnarayan, A., Garg, S.K., Sharma, P.L., Buri, P. and Baveja, S.K., Comparison of pharmacokinetics of conventional and sustained release formulations of propranolol in fasted and fed dogs. In Aiache, J.M. and Hirtz, J. (Eds.), *Proc. 3rd Eur. Cong. Biopharm. Pharmacokinet., Vol. II, Experimental Pharmacokinetics*, Imprimerie de l'Université de Clermont-Ferrand, France, 1987, pp. 126–135.

Park, K. and Park, H., Enzyme-digestible balloon hydrogels for long-term oral drug delivery: synthesis and characterization. *Proc. Int. symp. Controlled Release Bioact. Mat.*, 14 (1987) 41–42.

Pearlman, R.S., Molecular surface areas and volumes and their use in structure/activity relationships. In Yalkowsky, S.H., Sinkula, A.A. and Valvani, S.C. (Eds.), *Physical Chemical Properties of Drugs*, Dekker, New York, 1980, pp. 321–345.

Pedley, D.G., Skelly, P.J. and Tighe, B.J., Hydrogels in biomedical applications. *Br. Polym. J.*, 12 (1980) 99–110.

Peppas, N.A. and Franson, N.M., The swelling interface number as a criterion for prediction of diffusional solute release mechanisms in swellable polymers. *J. Polym. Sci. Polym. Phys. Ed.*, 21 (1983) 983–997.

Peppas, N.A., Gurny, R., Doelker, E. and Buri, P., Modelling of drug diffusion through swellable polymeric systems. *J. Membrane Sci.*, 7 (1980) 241–253.

Peppas, N.A. and Korsmeyer, R.W., Dynamically swelling hydrogels in controlled release applications. In Peppas, N.A. (Ed.), *Hydrogels in Medicine and Pharmacy, Vol. III, Properties and Applications*, CRC, Boca Raton (1987) pp. 109–135.

Peppas, N.A., Hydrogels of poly(vinyl alcohol) and its copolymers. In Peppas, N.A. (Ed.), *Hydrogels in Medicine and Pharmacy, Vol. II, Polymers*, CRC, Boca Raton (1987) pp. 1–48.

Peppas, N.A. and Moynihan, H.J., Structure and physical properties of poly(2-hydroxyethyl methacrylate) hydrogels. In Peppas, N.A. (Ed.), *Hydrogels in Medicine and Pharmacy, Vol. II, Polymers*, CRC Boca Raton (1987), pp. 49–64.

Petropoulos, J.H. and Roussis, P.P., Influence of transverse differential swelling stress on the kinetics of sorption of penetrants by polymer membranes. *J. Membrane Sci.*, 3 (1978) 343–356.

Plaut, B.S., Davies, D.J.G., Meakin, B.J. and Richardson, N.E., The mechanism of interaction between chlorhexidine digluconate and poly(2-hydroxyethyl methacrylate). *J. Pharm. Pharmacol.*, 33 (1981) 82–88.

Pywell, E.J., Yalkowsky, S.H. and Collett, J.H., Effect of a rate controlling membrane on release from polyHEMA hydrogels. *Drug Dev. Ind. Pharm.*, 12 (1986) 1767–1775.

Ranga Rao, K.V., Padmalatha Devi, K. and Buri, P., Mode of solute release from cellulose matrices, In Aiache, J.M. and Hirtz, J. (Eds.), *Proc. 3rd Eur. Cong. Biopharm. Pharma-*

cokinet., Vol. I, Biopharmaceutics, Imprimerie de l'Université de Clermont-Ferrand, France, 1987, pp. 473–482.

Ranga Rao, K.V., Padmalatha Devi, K. and Buri, P., Cellulose matrices for zero-order release of soluble drugs, *Drug Dev. Ind. Pharm.*, in press.

Rao, K.P.R. and Jeyanthi, R. Collagen-polyhydroxyethylmethacrylate hydrogels: their in vivo biocompatibility. Proc. *Int. symp. Controlled Release Bioact. Mat.*, 14 (1987) 43–44.

Ratner, B.D., Biomedical applications of hydrogels: review a critical appraisal. In William, D.F. (Ed.), *Biocompatibility of Clinical Implant Materials*, Vol. 2, CRC Press, Boca Raton, Florida, 1981, pp. 145–175.

Ritzer, P.L. and Peppas, N.A., A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. *J. Controlled Release*, 5 (1987) 37–42.

Roorda, W.E., Boddé, H.E., De Boer, A.G. and Junginger, H.E., Synthetic hydrogels as drug delivery systems. *Pharm. Weekbl. Sci. Ed.*, 8 (1986a) 165–189.

Roorda, W.E., De Vries, M.A., Kosho, C., De Leede, L.G.J., De Boer, A.G. and Junginger, H.E., Zero-order release of oxprenolol-HCl: a new approach. *Proc. Int. symp. Controlled Release Bioact. Mat.*, 13 (1986b) 206–207.

Roorda, W.E., De Vries, M.A., De Leede, L.G.J., De Boer, A.G. and Junginger, H.E., Zero-order release from hydrogels by controlled rupture formation. *Proc. Int. Cong. Pharm. Sci. F.I.P.*, 47 (1987), Abstract No. 238.

Sam, A.P., Zwinkels, J., Timmer, C.J. and Beach, C.A., In-vitro and In-vivo performance of hydrophilic matrix tablets. *Proc. Int. Cong. Pharm. Sci.* F.I.P., 47 (1987), Abstract No. 253.

Sato, S. and Kim, S.W., Macromolecular diffusion through polymer membranes. *Int. J. Pharm.*, 22 (1984) 229–255.

Schacht, E., Hydrogel drug delivery systems; physical and ionogenic drug carriers. In Anderson, J.M. and Kim, S.W. (Eds.), *Recent Advances in Drug Delivery Systems*, Plenum New York, 1984, pp. 259–278.

Schacht, E. and Van Bos, M., Potential developments in hydrogel gastrointestinal delivery systems. In Breimer, D.D. and Speiser, P. (Eds.), *Topics in Pharmaceutical Sciences*, Elsevier, Amsterdam, 1987, pp. 3–17.

Ségot-Chiq, S. and Peppas, N.A., Solute and penetrant diffusion in swellable polymers. IV. Semicrystalline, swelling-controlled release systems of poly(ethylene-co-vinyl alcohol). *J. Controlled Release*, 3 (1986) 193–204.

Singh, S.K. and Fan, L.T., Mathematical simulation of anomalous transport: a generalised model for swelling controlled release systems. *Proc. Int. symp. Controlled Release Bioact.* Mat., 13 (1986) 116–117.

Süss, W. and Bruder, K., Herstellung von Acetylsalicylsäure Tabletten mit verzögerter Wirkstoffliberation auf der Basis hydrophiler Matrixformen. *Pharmazie*, 42 (1987) 457–458.

Süss, W., Zur Herstellung von retàrd formlingen auf der Basis hydrophiler Matrixformen mit Hilfe von Polyvinylalkohol. *Pharmazie*, 38 (1983) 476–478.

Thomas, N.L. and Windle, A.H., A theory of case II diffusion. *Polymer*, 23 (1982) 529–542.

Van Bos, M. and Schacht, E., Hydrophilic polyurethanes for the preparation of drug delivery systems. *Acta Pharm. Technol.*, 33 (1987) 120–125.

Venkatesh, G., Eichkoff, W.M. and Vishnupad, K., Studies on mechanism of drug release from hydrophilic monolithic delivery devices, *J. Pharm. Sci.*, 76 (1987) S305.

Vrentas, J.S., Jarzebski, C.M. and Duda, J.L., A Deborah number for diffusion in polymer solvent systems. *AIChEJ.*, 21 (1975) 894–901.

Wang, P.Y., Controlled release by a combination chemical matrix. *Proc. Int. symp. Controlled Release Bioact. Mat.*, 13 (1986) 39–40.

Wisniewski, S. and Kim, S.W., Permeation of water-soluble solutes through poly(2-hydroxyethyl methacrylate) and poly(2-hydroxyethyl methacrylate) crosslinked with ethylene glycol dimethacrylate. *J. Membrane Sci.*, 6 (1980) 299–308.