Drug Development and Industrial Pharmacy, 24(1), 1-9 (1998)

REVIEW PAPER

Oral Controlled Release Dosage Forms. II. Glassy Polymers in Hydrophilic Matrices

F. Veiga, T. Salsa, and M. E. Pina*

Laboratory of Galenic and Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra, P-3049, Coimbra, Portugal

ABSTRACT

Part I of this article reported general considerations of oral controlled release dosage forms and the applications of cellulose ether polymers in hydrophilic matrices. Part II of this study describes the advantages and disadvantages of limited swelling hydrophilic matrices, their preparation, mechanism, and parameters affecting drug release from these systems.

INTRODUCTION

Part I of this study summarized the advantages of drug controlled-delivery therapy and briefly outlined relevant physicochemical and biological properties of a drug that affect controlled-release performance. In order to define "matrix" systems, every parameter required to characterize them was discussed and a classification was proposed. Finally, polymer factors affecting matrix dissolution were presented (1).

The present study reviews glassy polymers and evaluates the drug delivery from their hydrophilic matrices.

Hydrophilic matrices have some likeness to classic matrices, since in both cases, the drug is included into a polymer that has a great water affinity. However, several characteristics differentiate these two systems; the main difference is evidenced by the drug delivery mechanism. Drug diffusion is controlled by the penetration rate of solvent in the matrix. This system belongs to the class of solvent-activated, polymer matrix (2).

In a dry state, the polymer must be glassy with drug essentially immobilized under ambient conditions. In the presence of water, however, hydrogels can absorb a significant amount of water, then macromolecular relaxations occur to form an elastic gel, and at the same time the incorporated drug is released by diffusion through the swollen region.

These devices present slow hydration-limited swelling and are insoluble in water. These properties are explained by the existence of physical and/or chemical bonds among the polymer (2-4).

*To whom correspondence should be addressed.

ADVANTAGES AND DISADVANTAGES OF LIMITED SWELLING HYDROPHILIC MATRICES

In addition to the advantages and disadvantages of oral controlled release dosage forms, the positive aspects of these systems are the following (5): zero-order release kinetics; easy preparation; feasibility of conventional manufacture processes application; possibility of incorporating some drugs with faster degradation; and ability of introduce monomers with adhesive properties in their composition, which can be useful in determined situations.

However, these matrices have presented some disadvantages: zero-order release kinetics is not evidenced when the drug is in a higher concentration; drug can chemically react with the monomers or reticulation agents; and relative high temperature in determined preparation process (such as reticulation and drying reactions) can promote degradation of the drug.

Materials

The polymers used in preparation of limited swelling hydrophilic matrices must present the following requisites (6): glassy state at corporeal temperature; insoluble and limited swellable in aqueous mediums and biological fluids; and without toxicity, essentially when in contact with biological fluids, because these can extract some additives used during the preparation process.

Table 1 (6,7) summarizes the principal limited swelling polymers. Relative to biocompatibility, the most interesting polymers have in their composition hydroxyl groups [poly(vinyl alcohol), PVA; poly(2-hydroxyethylmethacrylate), PHEMA] or bonds of oxygen [poly(ethylene oxide), PEO] (8,9).

Polymers have in their composition monomers linked on linear, branched chain, or under tridimensional net. The linear chains can only permit one type of monomer, whereas the polymers with more than one type of monomer, designated by copolymers, evidence a structure in which the monomers are divided under alternative or sequential aleatory mode (10–13).

The release of previously dissolved drugs from linear hydrophilic polymers is relatively quick, because the continuous swelling can promote its solubilization. If this situation occurs, the drug-controlled release is not achieved, which justifies the necessity of a three-dimensional polymeric net formation.

This structure is attained because links are established between polymeric chains; these can be covalent ionic and hydrogen links described by Doelker (6) as chemical crosslinking, or due to the links between amorphous areas of polymer designated by the referred author as physical crosslinking (crystalline area formation).

Another way to reduce the swelling polymer and retard the drug delivery consists of the substitution of some hydrophilic monomer by hydrophobic monomer. This is verified with PEO, in which some monomers of ethylene oxide are changed by propylene oxide into poloxamers (14).

The chemical crosslinking reactions can be chemically induced or irradiation-induced when the polymers are dissolved. The method of reaction consists of the addition of a small amount of a substance (reticulation agent) that induces the crosslinking to the polymer (7,15–17).

Figure 1 (7) shows crosslinking reactions of two very commonly used polymers: PVA, crosslinked by glutaraldehyde and PHEMA, crosslinked by ethylene glycol dimethacrylate (EGDMA).

It is important to note that some polymers can be crosslinked by gamma irradiation. The chemical reticulation of PVA uses around 0.5% crosslinking reagent; relative to PHEMA it is usually necessary to apply 1% of crosslinking reagent (EGDMA) (10).

The amount of crosslinking reagent used in polymer crosslinking is directly related to the diffusion coefficient, because when the reticulation degree is higher, the diffusion coefficient is lower, which means that the crosslinking degree plays an important part in delivery control of a drug, mainly when the drug has a high molecular weight.

More recently, the use of interpenetrating and crosslinking techniques has provided an interesting way of modifying the equilibrium water content in PHEMA. The incorporation of PVA into a PHEMA/PVA interpenetrating polymer network hydrogel system shows extensive swelling and slow water desorption (18).

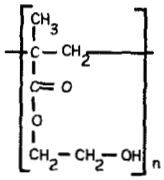
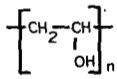
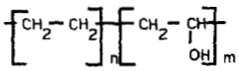
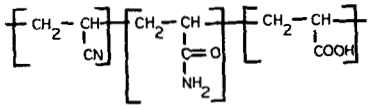
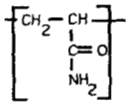
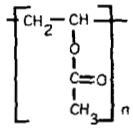
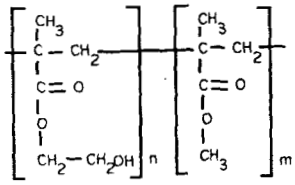
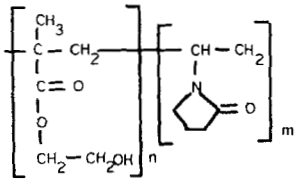
The physical reticulation reactions that carry out crystalline area formation are achieved by submission of polymer to heat during or after its preparation. The formed crystalline areas show a high density of macromolecular chains compared to other areas, explaining the impermeability to solvents evidenced by crystalline areas (10).

The Preparation Process

The limited swelling matrices are prepared in two steps: first drug is incorporated in the polymer structure, and then the matrix form is achieved.

Table 1

Main Limited Swelling Polymers

Polymer	Abbreviation	Constitutive Monomer
Poly(2-hydroxyethylmethacrylate)	PHEMA	
Poly(vinyl alcohol)	PVA	
Poly(ethylene oxide) or Poly(ethylene glycol)	PEO PEG	$H(OCH_2CH_2)nOH$
Poly(vinyl alcohol-*co*-ethylene)	EVA	
Poly(acrylonitrile)	PAN	
Polyacrylamide	PAA	
Poly(vinyl acetate)	PVAc	
Poly(2-hydroxyethyl methacrylate-*co*-methylmethacrylate)	P(HEMA-*co*-MMA)	
Poly(2-hydroxyethyl methacrylate-*co*-vinylpyrrolidone-N)	P(HEMA-*co*-NVP)	

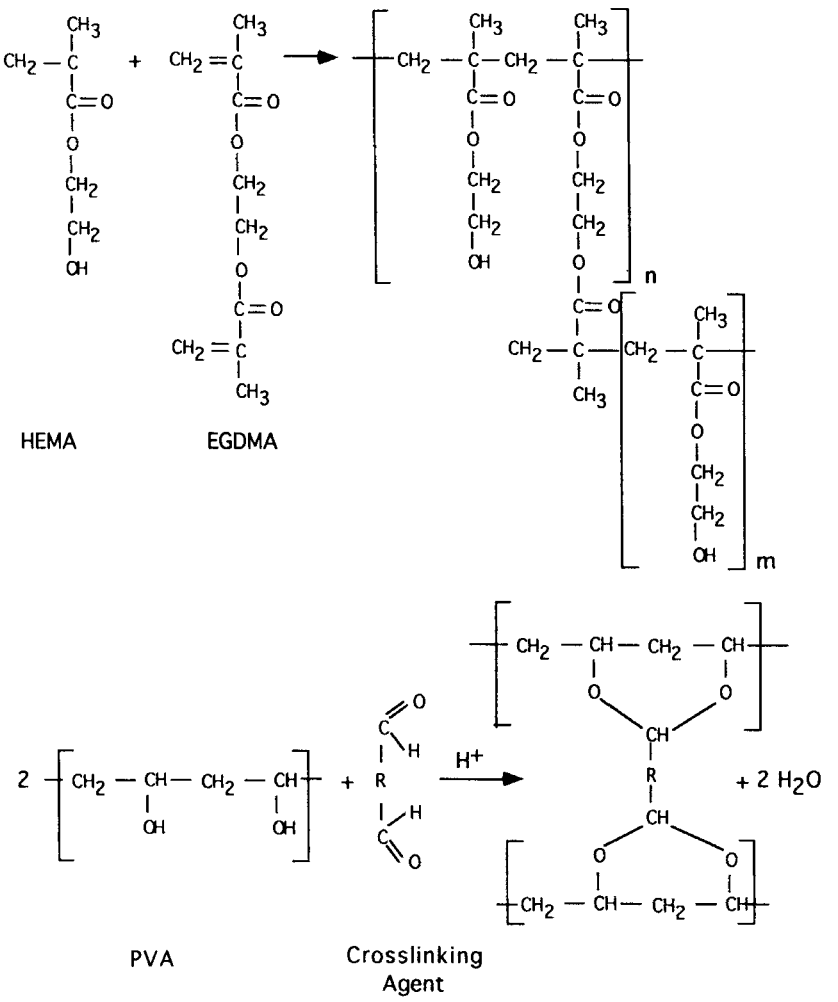


Figure 1. Crosslinking reactions (taken from ref. 7).

Gander et al. (6) have presented three methods for drug incorporation:

1. The drug is dissolved or dispersed into monomer, sometimes under solution or in formed polymer solution; the incorporation of drug is directly obtained by polymerization and reticulation. This process imposes the stability of drug in reaction conditions. The monomers and/or the residual reagents are not removed from the final product, once its extraction is carried out to important drug wastes.
2. The final polymer is impregnated by a drug solution. The advantage of this method is to improve a previous purification of the polymer. However the impregnation is limited many times by drug solubility in the appropriate solvent to the swelling polymer, and it is kept from reaching the free spaces in macromolecular net.
3. In the case of thermoplastic polymers the drug can be mixed with powder polymer. The incorporation of drug (dispersed or dissolved) into macromolecular net occurs during heat preparation. This method can only be used with drugs with good thermal stability.

The shape of limited swelling hydrophilic matrix tablets is usually obtained by compression of granulated particles from the mass formed by polymer and drug.

Other preparation methods exist, such as the Colombo et al. technique (19), in which the drug is mixed with a polymer (PVA) and with a diluent followed by wet granulation with polyvinylpirrolidone (PVP) 5% in alcohol solution. The obtained granulated mixture is

lubricated with magnesium stearate and finally compressed.

Lai et al. (20) obtained matrices by the following method: a mixture of glycerin and water was heated to 70°C, the polymer (PVA) added, and the temperature increased to 90°C until complete dissolution of all components. Continuing the process, the drug was added and the water evaporated until a semi-solid mass was obtained and transferred to the appropriate moldings.

With the aim of obtaining zero-order release kinetics, some work was carried out to evaluate the influence of shape matrices on the drug release kinetics (21,22).

From the described methods for molding the matrix tablets, it is necessary to differentiate those that can be easily transposed to industrial scale, such as Colombo et al. technique (19), and those for which execution is a laboratory scale, like the method proposed by Hsieh et al. (23). In spite of present limitations of this last process, it is important, because it is possible to obtain model matrices with good biopharmaceutical characteristics (for example, zero-order release kinetics).

Many times, it is difficult to carry an appropriate technology to its industrial-scale transposition.

DRUG RELEASE MECHANISM

The drug delivery from limited swelling hydrophilic matrices implies non-Fickian transport or anomalous transport.

In these matrices the drug is incorporated initially into glassy polymers and its diffusion is not possible because it has a lower diffusion coefficient in these polymers. However, after the penetration of dissolution medium, the drug can diffuse from the gel area to outside; thus the front advance of the dissolution medium penetration is the phenomenon responsible for the delivery mechanism (5).

Alfrey et al. (24) contributed to the understanding of non-Fickian transport mechanism when they proposed a second diffusion type, designated case II transport. The characteristics of this transport are the following: A well defined penetration front of dissolution medium, separating the glassy polymer from exterior swollen area, where any real gradient of solvent concentration doesn't exist; the penetration front advances with a constant velocity, v; and the sample weight increase is constant with the time.

Figure 2 (25) shows the schematic comparison of some essential characteristics of Fickian diffusion and case II transport. Between these two situations, the anomalous transport is placed.

In glassy polymers the transport phenomena have been analyzed by several authors (24,26-29). Because the swelling process shows evidence of mechanical resistance on the interface level, defined by the transition of polymer from glassy state to hydrated state, those authors considered that the penetrating agent transport could happen by Fickian diffusion (where those resistances are not important) or contrarily by non-Fickian diffusion, on which the mechanical resistances acquire greater expression, known as transport by "super case II" type (the drug delivery rate increases with the time).

For a better understanding of the molecular aspects of this phenomenon, Thomas et al. (30,31) and Gostoli et al. (32) developed theoretical and experimental studies, and concluded that non-Fickian diffusion is explained by macromolecular chain relaxation, in accordance with the advance of penetration of the front solvent.

Figure 3 (25) represents a glassy polymer film in contact with a solvent that promotes its swelling: initially only the exterior film layer is reached by solvent molecules that pass into the macromolecular polymer net, promoting its passage from glassy state to hydrated state.

The polymer swelling is strongly limited because the mechanical resistances of adjacent glassy material are not easily deformed, making the surface between glassy zone and the exterior film layer inalterable. The increase of polymer volume is possible because of exterior film layer deformation, which is associated on the molecular level to a relaxation and a reorientation of macromolecular chains. The increase of volume in which the solvent diffusion is possible gradually occurs, contrary to Fickian diffusion, during which the macromolecular rearrangement (swelling of small chains) is almost immediate.

For a well defined solvent front, the time of exterior film layer swelling must be shorter than the necessary time to equilibrium between the polymer and the solvent on the following elements. After this initial swelling phase, the solvent front advances with a constant rate into the film (25).

The study of limited swelling hydrophilic matrices concentrates on the following aspects (6): penetration of dissolution medium into the matrix containing the drug; diffusivity of the solute in hydrated polymer; and drug delivery during the swelling.

Mathematically, it has been demonstrated that to carry out a zero-order release or near zero-order release, two conditions are necessary (4): the transport of sol-

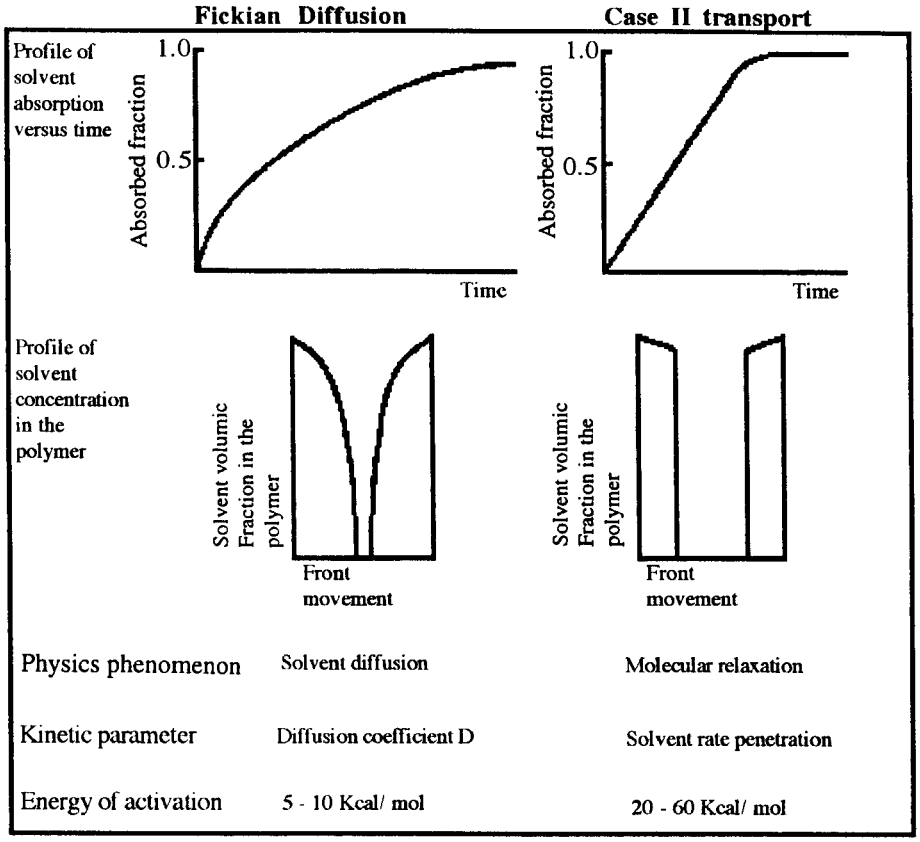


Figure 2. Schematic comparison of some essential characteristics of Fickian diffusion and case II transport (taken from ref. 25).

vent into polymer must be anomalous or case II transport; and the solution diffusivity in hydrated layer must be higher than solvent mobility in the system.

These two criteria were characterized by a two-dimensional number, the Deborah diffusion number and the maximum number of swelling interface (S_{max}).

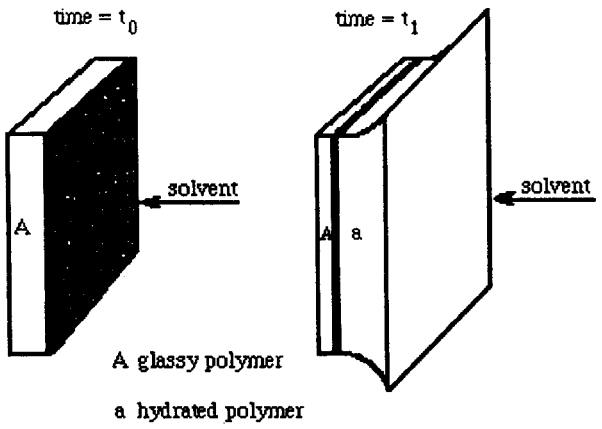


Figure 3. Schematic representation of case II transport of a solvent into a glassy polymer (taken from ref. 25).

The Deborah diffusion number, which charaterizes the step of the solvent penetration, is defined by (27)

$$(\mathrm{DEB})D = \lambda_m/\Theta D$$

where λ_m = relaxation time of the medium (dependent on rheological parameters) and ΘD = diffusion time of solvent in polymer, defined according to the equation:

$$\Theta D = L^2 D$$

where L = film thickness and D = diffusion coefficient of solvent in polymer.

When the relaxation and the diffusion have the same value, $(\mathrm{DED})D \approx 1$, the transport of solvent is anomalous or case II type (33).

The value of swelling interface number allows the determination of the solution diffusivity relative to solvent mobility. This non-dimensional number was initially proposed by Korsmeyer et al. (34) under the following equation:

$$S_w = v\delta(t)/D_{ip}$$

where v = penetration velocity of solvent into polymer,

$\delta(t)$ = hydrated layer thickness in time t, and D_{ip} = diffusion coefficient of solution into hydrated polymer.

Considering that S_w changes during the swelling, it is necessary to determine the maximum value (S_{wmax}) that allows the calculation of the delivery mechanism (35):

$$S_{wmax} = V_{max}\ \delta_{max}/D_{ip}$$

where V_{max} = highest penetration rate of solvent, δ_{max} = highest thickness of hydrated layer, and D_{ip} = diffusion coefficient into hydrated polymer.

A zero-order release kinetics is observed when S_{wmax} is lower than 0.01, in accordance with the fact that high-diffusivity solute, slow penetration of solvent, and limited swelling of polymer constitute favorable parameters.

Figure 4 (34) represents schematically the two fronts (interfaces) characteristic of this swelling behavior a front separating the glassy rubbery state (swelling interface) which moves toward the glassy state with velocity V; and a front separating the rubbery polymer from the pure dissolution medium (polymer interface). The aqueous medium C penetrates the glassy polymer with velocity V (swelling interface front); diffusion of the solute occurs under countercurrent in hydrated polymer layer B, which thickness δ increases with time; a second interface P separates this solvent layer.

To analyze these experimental results about drug release from this kind of system (limited swelling hydrophilic matrices), they are applied to the following equations (36):

$$M_t/M_\infty = Kt^n$$

$$d\ M_t/S\ dt = nCoKt^{n-1}$$

which represent the amount of released drug in time t and the release velocity by area unit, used in determination of n. Practically, this value can be determined by a graphic representation of drug percentage (M_t/M_∞) versus time.

The relations between n, S_w, and release mechanism of drug from glassy polymer are shown in Table 2 (36).

The importance of matrix dimension to transport type has been experimentally analyzed and it was verified that a case II transport (zero-order release) is only possible until a determined size, from which the transport changes to anomalous or Fickian diffusion. The shape of matrix has an important function and it was been observed that solvent absorption kinetics only stay linear when the transport is unidirectional (film or disk); in case of cylinders and spheres, the absorption velocity decreases because of the reduction of radial penetration surface.

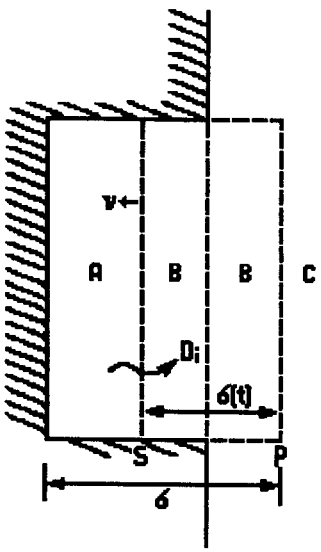


Figure 4. Moving fronts during dynamic swelling of a glassy polymer. A, glassy state; B, rubbery state; C, dissolution medium; S, swelling interface; P, polymer interface (taken from ref. 34).

PARAMETERS AFFECTING DRUG RELEASE

Several factors can change the release kinetics of drug from the matrix.

Shape and Size of Matrix

The experiments carried out revealed that the release grows with a smaller size matrix and that spherical form represents a profile release near zero-order kinetics.

Polymer Composition

The polymer composition formed by two or more types of monomers (copolymers) defines a swelling velocity and so the drug release kinetics. The studies carried out by Korsmeyer et al. (37), Gaeta et al. (38), and Peppas et al. (35) concluded that higher polymer

Table 2

Correlation Between n, S_w *Values, and Transport Mechanism*

S_w	n Exponent	Transport Mechanism
$>>1$	0.5	Fickian diffusion
$=1$	$0.5 < n < 1$	Anomalous
$<<1$	1.0	Case II

hydrophilic properties promote a higher swelling polymer velocity. These conclusions were verified with the following polymers: poly(2-hydroxymethyl methacoylate-*co*-vinylpyrrolidone-N) [P(HEMA-*co*-NVP) containing 21–71% of HEMA; poly(2-hydroxyethyl methacrylate-*co*-methylmethacrylate) [P(HEMA-*co*-MMA]) containing 0–50% of MMA, and poly(vinyl alcohol-*co*-ethylene) (EVA) containing 28–38% of ethylene groups.

Polymer Crosslinking

An increase in polymer crosslinking (chemical or physical) results in a decrease in both the volume swelling and release. This can be attributed to the decrease in diffusion coefficients of both the drug and the solvent by the reduction of molecular weight between crosslinks and the associated macromolecular mesh size (39–41).

The influence of degree of crosslinking on drug diffusion is important because the molecular weight is high (6). The controlled release from limited swelling hydrophilic matrices requires a high diffusion, which implies a moderate degree of crosslinking.

Molecular Weight and Drug Load

The molecular weight of the drug included in the matrix has a great influence on its diffusion, which means that for polymers with the same crosslinking degree, the diffusivity is lower when the molecular weight is higher. In order to overcome this disadvantage, a polymer with a lower degree of crosslinking, but enough to present its tridimensional structure, is used.

Relative to drug concentration into matrices, some studies carried out (42,43) conclude that higher concentration promotes higher release rate, making it possible change the transport mechanism.

Hopfenberg et al. (42) verified that sudan dye IV release from polystyrene matrices exhibited a zero-order behavior only if the coloring was in concentrations below 4%.

Lee (43), with 2-hydroxyethyl polymethacrylate crosslinked and containing thiamine chlorohydrate, verifed that the release rate of drug was constant when the concentration was low, but this behavior was changed when the concentration was higher than 18.67%.

This review article analyzed the conditions of the development of zero-order release polymeric systems for pharmaceutical applications, by employing the glassy/rubbery transition and dynamic swelling behavior of polymers.

Methods to achieve the requisites for zero-order release kinetics include modification of the swelling behavior of polymer by chemical or physical techniques and changing the drug diffusion coefficient by physical methods.

REFERENCES

1. F. Veiga, T. Salsa, and M. E. Pina, Drug Dev. Ind. Pharm (in press).
2. C. M. Klech and L. Xiaomei, J. Pharm. Sci., 79, 999 (1990).
3. P. I. Lee, Polymer, 25, 973 (1984).
4. E. Doelker, Bull. Gattefossé, 78, 51(1985).
5. N. A. Peppas, and C. Bindschaedler, S. T. P. Pharm., 2, 38 (1986).
6. B. Gander, R. Gurny, and E. Doelker, Pharm. Acta Helv., 61,178 (1986).
7. E. Doelker, S. T. P. Pharm., 3, 207 (1987).
8. H. J. Zhu, L. Xiangzhou, and Y. Shilin, J. Appl. Polym. Sci., 39, 1 (1990).
9. L. Yang, G. Venkatesh and R. Fassihi, J. Pharm. Sci., 85, 1085 (1996).
10. N. A. Peppas, and R. Gurny, Pharm. Acta Helv., 58, 2 (1983).
11. D. Castel, A. Ricard, and R. Audebert, J. Appl. Polym. Sci., 39, 11 (1990).
12. B. G. Cabra, S. H. Gehrke, S. T. Hwang, and W. A. Ritschel, J. Appl. Polym. Sci., 42, 2409 (1991).
13. F. J. Liou, G. C. C. C. Niu, and Y. J. Wang, J. Appl. Polym. Sci., 46,1967 (1992).
14. B. Gander, R. Gurny, and E. Doelker, Drug Dev. Ind. Pharm., 12,1613 (1986).
15. A. Yamasaki, T. Iwatsubo, T. Masuoka, and K. Misoguchi, J. Appl. Polym. Sci., 58, 1657 (1995).
16. C. K. Yeom and K. H. Lee, J. Appl. Polym. Sci., 59,1271 (1996).
17. F. J. Liou and Y. J. Wang, J. Appl. Polym. Sci., 59, 1395 (1996).
18. B. Ramaraj and G. Radhhakirishman, Polymer, 35, 2167 (1994)
19. P. Colombo, A. Gazzaniga, C. Caramela, U. Conte, and La Manna, Acta Pharm. Technol., 33, 15 (1987).
20. J. Lai, C. Chiang, and T. Wu, Drug Dev. Ind. Pharm., 13, 1399 (1987).
21. J. Cobby, M. Mayersohn, and G. C. Walker, J. Pharm. Sci., 63, 725 (1974).
22. J. Cobby, M. Mayersohn, and G. C. Walker, J. Pharm. Sci., 63, 732 (1974).
23. D. S. T. Hsieh, W. D. Rhine, and R. Lander, J. Pharm. Sci., 72, 17 (1983).
24. T. Alfrey, E. F. Gurnee, and W. G. Lloyd, J. Polym. Sci.: part C, 12, 249 (1966).

25. B. Gander, R. Gurny, and E. Doelker, Pharm. Acta Helv., 61, 130 (1986).
26. T. T. Wang, T. K. Kwei, and L. Frish, J. Polym. Sci.,: part A-2, 7, 2019 (1969).
27. J. S. Vrentas and J. L. Duda, J. Polym. Sci.,: Polym. Physics Edition, 15, 441 (1977).
28. G. Astarita and G. C. Sarti, Polym. Eng. Sci., 18, 388 (1978).
29. H. L. Frisch, Polym. Eng. Sci., 20, 2 (1980).
30. N. L. Thomas and A. H. Windle, Polymer, 21, 613 (1980).
31. N. L. Thomas and A. H. Windle, Polymer, 23, 529 (1982).
32. C. Gostoli and G. C. Sarti, Polym. Eng. Sci., 22, 1018 (1982).
33. N. M. Franson and N. A. Peppas, J. Appl. Polym. Sci., 28, 1299 (1983).
34. R. W. Korsmeyer and N. A. Peppas in *Controlled Release Delivery Systems*, Marcel Dekker, New York, 1983, p. 77.
35. N. A. Peppas and N. M. Franson, J. Polym. Sci.,: Polym. Physics, 21, 983 (1983).
36. N. A. Peppas, Pharm. Acta Helv., 60,110 (1985).
37. R. W. Korsmeyer and N. A. Peppas, J. Controlled Release, 1, 89 (1984).
38. S. Gaeta, A. Apicella, and H. B. Hopfenberg, J. Membr. Sci., 12, 195 (1985).
39. N. A. Peppas and S. Ségot-Chicq, S. T. P. Pharm., 1, 121 (1985).
40. R. W. Korsmeyer and N. A. Peppas, J. Membr. Sci., 9, 211 (1981).
41. Cherng- Ju Kim and P. I. Lee, Pharm. Research, 9, 10 (1992).
42. H. B. Hopfenberg and K. C. Hsu, Polym. Eng. Sci., 18, 1186 (1978).
43. P. I. Lee, Polym. Communications, 24, 45 (1983).