Zero-Order Drug Release from Hydrocolloid Matrices

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Matrices are manufactured by direct compression of a powder mixture of a polymer, e.g., methylhydroxypropyl cellulose (MHPC) or polyvinylalcohol (PVAI), and a drug. The following factors that can influence the drug release mode were investigated at constant surface: (i) polymer solution viscosity, glass transition temperature, and swelling; (ii) drug concentration in the matrix and solubility; and (iii) conditions of release experiment (hydrodynamics). In the case of zero-order release profiles (hydrocolloids with low viscosities), only the dissolution of the polymer appears to control the drug release rate. Factors accelerating polymer dissolution resulted in higher release rates. Comparison of swollen and dry hydrocolloid matrices shows that the duration and kinetics of drug release were not controlled by the swelling front moving into the dry polymer, and water penetration and relaxation were not rate controlling. Therefore, the glass transition temperature had no effect on drug release from these hydrocolloids. The higher the hydrodynamic stress exerted on the eroding hydrocolloid, the faster the resulting drug release as a result of accelerated polymer dissolution. With hydrocolloids of very high viscosity the polymer dissolution is slow, and drug relese from the swollen gel appears to be controlled by diffusion according to kinetics of the Higuchi type.

KEY WORDS: hydrocolloid matrix; zero-order release; erosion; polymer dissolution; relaxation.

INTRODUCTION

Drug release from hydrocolloid matrices normally shows a square root of time dependency as observed in homogeneous matrices (1). By choice of the appropriate composition, linear drug release profiles can be achieved with hydrocolloid matrices as well, if the releasing surface stays constant (2–11). Various phenomena connected with water intake and swelling are under discussion as the rate-limiting step for these zero-order release; (i) water-induced relaxations of the polymer matrix, (ii) erosion of the swollen gel layer, and (iii) diffusion through a swollen layer, the thickness of the layer being constant with respect to time.

Water-Induced Relaxation of the Polymer Matrix. For various systems of cross-linked polymer and organic solvent, the intake of solvent occurs in a purely relaxation controlled manner (e.g., Ref. 12). The phenomena of relaxation occurring during swelling are often cited as the reason for the deviations of the release profile from the square root of time kinetics (4,8,13). Korsmeyer *et al.* (8) and Catellani *et al.* (4) attributed linear release profiles to relaxation mechanisms alone, without providing evidence in support of this hypothesis. The glass transition temperature (T_g) of the polymers should be examined, since the T_g controls relaxation controlled transport in polymeric substances (14).

Erosion of the Swollen Gel Layer. According to Lapidus and Lordi (15), drug release from methylhydroxypropyl cellulose (MHPC) of a lower viscosity shows deviations from square root of time kinetics, since in addition to diffusion, the swollen matrix erodes and thus the release is accelerated. Drug diffusion through the swollen layer and its erosion are generally regarded as the rate-limiting step of drug release (7,11,16,18).

Diffusion Through a Swollen Layer of Constant Thickness. By varying the release area, the release rate of different active substances from PVAI matrices can be chosen irrespective of drug solubility (5). A swelling and an erosion front can be distinguished here, advancing with the same constant velocity (synchronization of velocities of a moving rubbery/glassy front and a dissolution medium/swollen polymer front). If the hydrodynamic stress is increased by raising the speed of revolution in the USP paddle apparatus, the distance between the two fronts is lowered. According to the authors (5) the penetration of water through the gel layer controls the release. In the case of a very high revolution speed, the two fronts can no longer be distinguished, and the advance of the swelling front determines the rate of drug release. However, other investigators propose that the release rate is constant because the drug diffuses through a gel layer of constant thickness with respect to time (3,10,19–21).

Rationale. Drug release from hydrogels (cross-linked hydrophilic polymers) partly proceeds proportional to time, perhaps a consequence of Case II transport (relaxation controlled mechanisms). Hydrocolloid matrices can behave like hydrogels, especially if the matrix is composed of a high molecular weight polymer. We tested here whether not only swelling-induced (swelling as prerequisite), but also swelling-controlled release mechanisms can be found in hydrocolloids, and to which degree these mechanisms are influenced by various parameters. Previous investigations often refer to formulations with a low proportion of polymer. To exclude diffusion through pores and desaggregation, thin tablets with a high fraction of polymer were investigated. The following factors that can influence the release mode were examined: (i) polymer solution viscosity, T_g, and swelling condition, (ii) drug concentration in the matrix and solubility, and (iii) conditions of release experiment (hydrodynamics).

MATERIALS AND METHODS

Materials

Materials were as follows: diprophylline, c_s in pH 4.4 buffer ($g \cdot 100\ mL^{-1}$), 17.68; etofylline, 8.14; proxyphylline, 25; theophylline, 1.12 (22) (Knoll, D-Ludwigshafen); riboflavine-5′-phosphate sodium dihydrate, 7.6 (22) (Hoffmann-LaRoche, CH-Base); lactose (Meggle, D-Reitmehring); methylhydroxypropyl cellulose (MHPC) (Syntapharm, D-Mülheim-Ruhr, and Shin-Etsu Chemical, Jpn-Tokio), different viscosities of the 2% solutions (see text); polyvinyl alcohol

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(PVAI) (Hoechst, D-Frankfurt/M, and Wacker Chemie, D-Burghausen); 88% degree of hydrolysis of the corresponding polyvinyl acetate, different viscosities of the 4% solutions (see text and figures).

Methods

Biplanar, cylindrical tablets were manufactured by compression of materials with particle size 25–80 μm, applying a pressure of about $9 \cdot 10^2$ MPa in an hydraulic KBr press. The tablets (250 mg; thickness approx. 1.6 mm) are given into a tight-fitting die, leaving one side of the tablet uncovered, so that the release can occur from one tablet surface only (F = 1.3 cm^2), and the size of the releasing area stays constant throughout the experiment. In general, the die was positioned on the bottom of the beaker of the USP paddle apparatus for release experiments, if not otherwise stated, with distilled water, 37°C, 100 min^{-1}. In some cases the die is turned by 180° and immersed by a mounting 20 mm beneath the surface of the release medium. The tablets usually contained 5% of a drug, in most cases proxyphylline (PROX) or riboflavine-5′-phosphate sodium dihydrate (RIBO). No other excipients were included. For better comparison the release profiles are plotted as percentage ($Q \cdot 100\%/Q_\infty$) vs time. The released amounts of drug Q were determined by UV absorption via a flow through cuvette (Lambda 2 UV/VIS spectralphotometer, Perkin-Elmer, D-Überlingen).

Characterization of the Release Profile

To describe the curvature of the release profile, the exponent n of the common exponential equation [Eq. (1)] is calculated from experimental data for $Q/Q_\infty < 0.8$:

$$\frac{Q}{Q_\infty} = kt^n \tag{1}$$

were Q is the amount released at time t, Q_∞ is the overall released amount, k is a release constant of nth order, and n is a dimensionless number.

The exponent n describes the release kinetics, with n = 0.5 for square root of time kinetics and n = 1.0 for zero-order kinetics. Zero-order kinetics prevails if $n > 0.66$ (22,23). The constant k gives a measure of the velocity of drug release. Since k has the dimension $time^{-n}$, release constants of different kinetics cannot be compared directly. To characterize the drug release rate, the mean (dissolution) time MT [24] is applied. MT is the sum of the different periods of time the drug molecules or fractions of the dose stay in the polymer before release, divided by the total number of molecules or the total dose respectively. MT is calculated according to Eq. (2) (22,23):

$$\mathrm{MT} = \frac{n}{n+1} k^{-1/n} \tag{2}$$

RESULTS AND DISCUSSION

Drug release from the hydrocolloids occurred largely during dissolution of the polymer material. At the end of the release process the polymer material is completely dissolved in the case of zero-order release. If the release proceeds according to $\sqrt{t}$ kinetics or with an exponent n at least near 0.5, a part of the polymer matrix can still be seen after 100% release. During the release experiments the tablets changed from opaque to translucent, beginning from the surface.

Drug release slows down with increasing degree of viscosity of the gel-forming polymer, as can be shown, for instance, with PVAI tablets (Fig. 1). The exponent n decreases with increasing solution viscosity from 1 to approx. 0.5 (Fig. 1), i.e., the release from polymers with a lower degree of viscosity proceeds according to zero-order kinetics, whereas a higher viscosity results in drug release showing an approximately square root of time dependency.

The solubility of the drug under investigation does not influence duration or linearity of the release from tablets of polymers with a low degree of viscosity (Figs. 2 and 3) as proposed earlier for the case of synchronization of front velocities (3,5,10,20,21). Diffusion of drug through the gel layer (boundary layer control) can therefore be excluded as the rate-limiting step in this case. On the other hand, the release expressed as a percentage speeds up with a higher content of active substance in the matrix (drug loading), and the duration of release (MT) decreases (Fig. 4), whereas the release exponent n remains nearly unchanged around 0.9, denoting linear release profiles (Fig. 5).

The reason for the latter might be seen in drug particles, dissolving from the swollen layer, leaving an increased surface area and thereby accelerating the dissolution of the gel. This probably indicates that the rate-limiting step is connected with polymer dissolution. The strong influence of hydrodynamic stress (Fig. 6) suggests the analogy to dissolution processes according to Noyes–Whitney and Nernst–Brunner.

To examine whether relaxation has any significance as the rate-limiting factor, the release from dry and preswollen hydrocolloids is compared. Preswelling was performed at 85.1% relative humidity, inducing water uptake of 19.4% at equilibrium. As can be seen from Fig. 7 as an example, preswollen PVAI tablets, already translucent, release the drug within the experimental error practically linearly and at the same rate as the dry samples. This means that the release behavior is completely independent of the glass transition

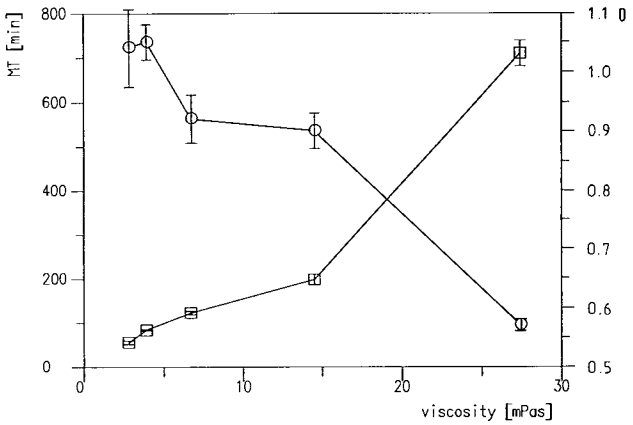

Fig. 1. Dependence of the mean time of release MT (left) and release exponent n (right) on the degree of viscosity of the polymer. RIBO, 5% (mean ± SD; n = 5). PVAI, 88% degree of hydrolysis; Viscosity, 4% solution. (□) MT; (○) n.

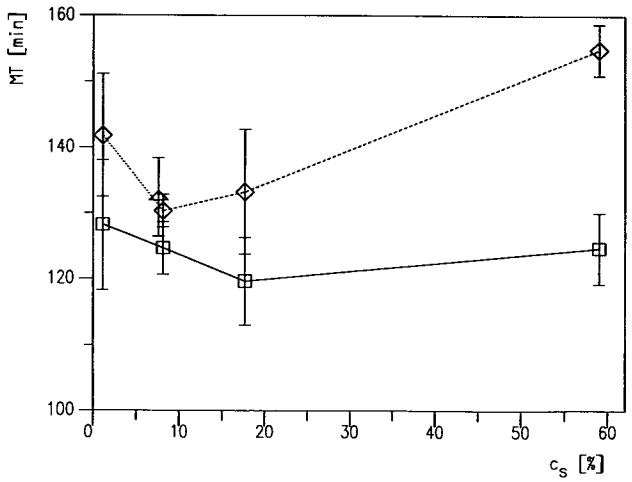

Fig. 2. Dependence of the mean time MT on the solubility c_s of the drug under investigation; tablets of polymers with a low degree of viscosity (mean ± SD; n = 5). Drug content, 5%; dissolution in buffer, pH 4.4. (□) PVAI 8-88, xanthin derivatives. (◇) MHPC 6, xanthin derivatives. (△) PVAI 8-88, RIBO.

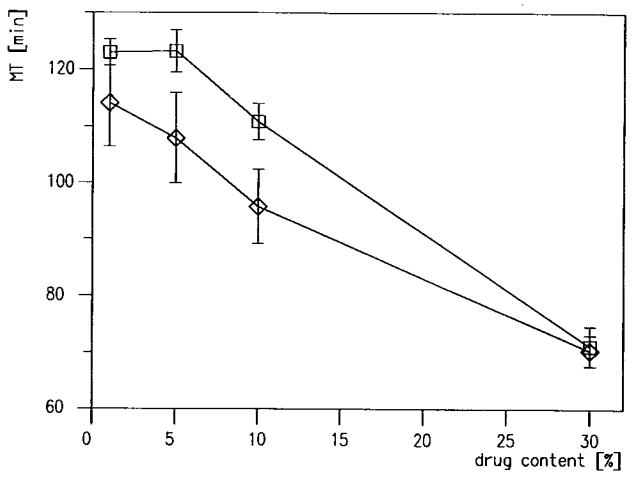

Fig. 4. Dependence of the mean time MT on drug content; tablets of polymers with a low degree of viscosity (mean ± SD; n = 5). (□) PVAI 8-88, RIBO. (◇) MHPC 6, PROX.

temperature of the polymeric hydrocolloid-forming agent [$T_{g\ dry}$ = 55 to 61°C, $T_{g\ preswollen}$ = −5 to −12°C (22)]. Preswollen MHPC tablets also release like dry ones (MHPC 6 and MHPC 30,000) (22). For that reason also water penetration cannot be considered as the rate-limiting parameter. Furthermore, synchronization of the velocities of the rubbery/glassy front and the dissolution medium/swollen polymer front as proposed by several authors (3,5,10,20,21) does not seem to be a prerequisite for zero-order release.

The constant release of the drugs which are dispersed in the hydrocolloid matrices might be described as a process that is controlled solely by dissolution of the polymer (25–27): Drug substance which lies free at the surface of the matrix will dissolve on first contact with the dissolution medium. The polymer starts to take up water at the surface and to dissolve subsequently. Water penetrates the matrix in the form of a sharply defined swelling front, with a concentration gradient of water building up between the dry core and the swollen surface layer. Only the outer swelling layers should be in a state allowing the delivery of drug to the dissolution medium. Drug dispersed in the hydrocolloid matrices will either dissolve from the outer swollen layer and diffuse together with the polymer from the surface or dissolve after it has been delivered to the surrounding medium in the form of small particles which will dissolve afterwards (especially a drug substance of low solubility). The more drug dissolves from the outer swollen layer together with the polymer, the larger will be the volume free of polymer left behind, and the faster the polymer dissolution is to be expected. Because of the higher dissolution rate of the polymer, the drug delivery as a percentage is increased if a higher amount of active ingredient is incorporated in the matrix as illustrated in Fig. 6.

The rate of polymer dissolution increases with hydrodynamic stress (26), since thereby the diffusion of hydrated polymer from the outer swelling layer will be facilitated.

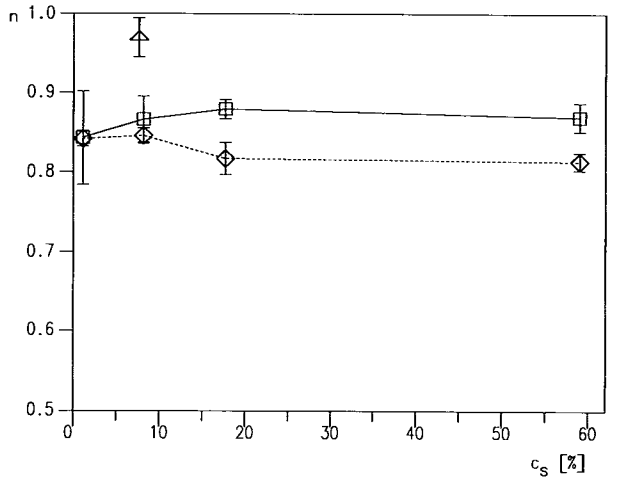

Fig. 3. Dependence of the exponent n on the drug solubility c_s; tablets of polymers with a low degree of viscosity (mean ± SD; n = 5). Drug content, 5%; dissolution in buffer, pH 4.4. (□) PVAI 8-88, xanthin derivatives. (◇) MHPC 6, xanthin derivatives. (△) PVAI 8-88, RIBO.

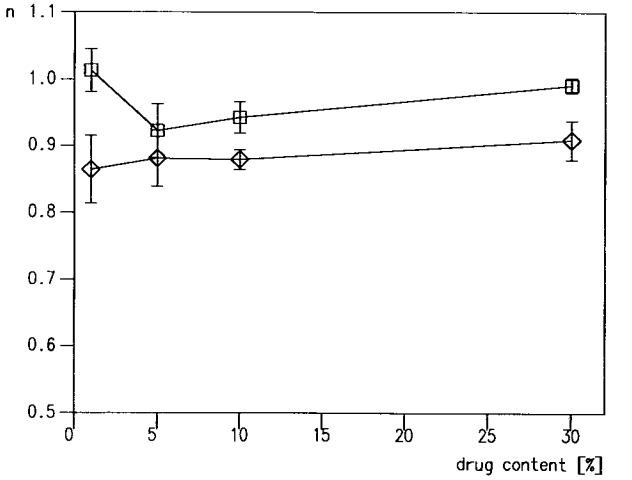

Fig. 5. Dependence of exponent n on drug content; tablets of polymers with a low degree of viscosity (mean ± SD; n = 5). (□) PVAI 8-88, RIBO. (△) MHPC 6, PROX.

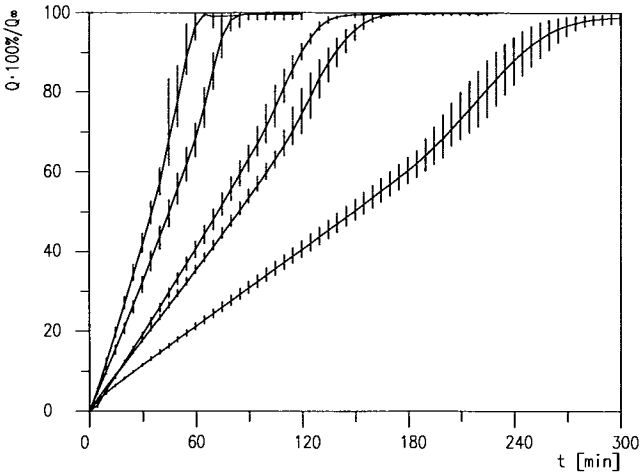

Fig. 6. Influence of hydrodynamics on the release of 5% PROX from PVAI 8-88 (median and variability; $n = 5$). Speed of revolution (from left to right): 300, 200, 100, 75, and 35 min^{-1}. Mounting turned by 180° (for explanation see Materials and Methods).

Since the rate of drug delivery increases with hydrodynamic stress as well, the reason for faster release in case of higher speeds of revolution appears to lie in the increased polymer dissolution.

For polymers with the same chemical structure, the dissolution rate decreases with rising molecular weight (26–30), which can be accounted for by the increase in the thickness of the swollen layer (26,27). In the case of a very high molecular weight, the dissolution of the polymer is impeded dramatically, since the thickness of the swollen layer greatly expands (27). The dependence of polymer dissolution on molecular weight also explains the simultaneous decelaration of drug delivery from hydrocolloids of a high solution viscosity. Linear drug release is achieved mainly with gel-forming agents of lower molecular weight. If the molecular weight reaches a certain value, polymer dissolution seems to be slowed down to such an extent that diffusion of drug through the swollen layer may contribute markedly to the overall release. At this point the release profile gradually turns from zero-order to square root of time kinetics. When the molecular weight is very high, the contribution of polymer dissolution should be marginal, and the diffusion of drug through the swollen gel alone appears to control release, which then shows square root of time dependence (15,22).

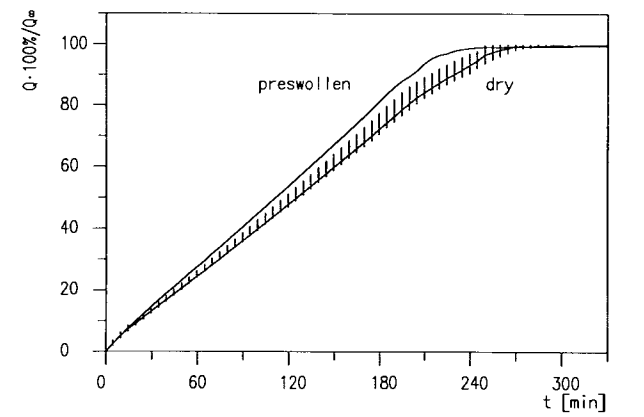

Fig. 7. Release of RIBO from dry and preswollen hydrocolloid matrices (medians, variability for one typical example, $n = 5$ to 6). PVAI 8-88, 5% RIBO, dry tablets and tablets with a previous water uptake of 19.4% (at 85.1% RH).

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