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In vitro release characteristics of a membrane-coated pellet formulation – influence of drug solubility and particle size

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Summary

The impact of drug solubility and particle size on the in vitro release characteristics of membrane-coated pellets has been investigated for the metoprolol salts, sorbate, benzoate, succinate and fumarate. Three well-defined size fractions of small spherical pellets were prepared for each salt and coated with a membrane of ethylcellulose and hydroxypropyl methylcellulose (proportion 3 : 1). The particle diameter, surface area, volume and apparent density were determined for each fraction of coated pellets and their drug release properties were characterized by an initial lag-time, a constant release rate phase and a final declining release rate phase. Both the particle size and drug solubility were shown to be important for the release properties of the pellets. Thus, the constant release rate was approximately proportional to the surface area of the pellets over the entire solubility range (~ 20–500 mg/ml). All three phases of the drug release curve were strongly influenced by the drug solubility. This was explained on the basis of the different concentration gradients over the membrane as well as by osmotic effects. Although the release rate was shown to be markedly affected by the osmotic pressure, evaluation of the release kinetics did not reveal osmotic pumping to be the major mechanism for the release. Also, diffusion appears to be important for the drug release from the investigated formulations.

Introduction

The formulation of a drug substance into small discrete units (pellets) and subsequent coating with a polymeric membrane is a common way of obtaining pharmaceutical preparations with modified drug release. The principle of film coating offers great flexibility in regulating the delivery of drug from the formulation and is therefore suitable for many types of systems (Rowe, 1985). In particular, the possibility to release a significant part of the dose at a constant (zero-order) rate has gained much attention.

In the development of such formulations, it is important to investigate the influence of different formulation factors on the drug release properties. Thereby critical factors and steps in the design as well as the manufacture of the product might be identified and potential scaling-up and production problems avoided. For example, formulation aspects such as the solubility of the drug substance, the type and amount of the inactive ingredients and the nature of the polymeric membrane have been discussed for two different types

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of membrane-coated systems of the β-blocker metoprolol when evaluating factors of importance for the drug release and biopharmaceutical properties (Theeuwes et al., 1985; Ragnarsson et al., 1987).

In the present study, the in vitro release characteristics of membrane-coated pellets of four metoprolol salts were evaluated. The objective was to investigate the impact of drug solubility and pellet size on the different phases of the drug release process, i.e. the initial lag-time, the constant release rate phase and the final declining rate phase. It was also our intention to gain further knowledge about the drug release mechanism for this type of drug delivery system.

Materials and Methods

Drug substances

The four metoprolol salts listed in Table 1 were synthesized from metoprolol base by crystallization in acetone (Astra Pharmaceutical Production AB, Södertälje, Sweden). The solubility of each salt was determined in distilled water at 37°C after dispersing excessive amounts and stirring for 24 h. The undissolved drug was removed by filtration (Millipore type FG, 0.2 μm) and the filtrate was analysed by UV spectrometry (LKB Ultrospec II).

Preparation of pellets

The metoprolol salts were applied on three separate size fractions of technical grade glass beads according to a previously described crystallization method (Ragnarsson and Johansson, 1988). The obtained drug pellets were sieved to remove aggregates and separated into the fractions 0.315–0.355, 0.40–0.45 and 0.50–0.56 mm. The three size fractions were remixed and coated by top-spraying in a laboratory scale (0.5 kg) fluid-bed apparatus (Hässle workshop). The polymeric solution consisted of ethylcellulose 10 cps (Hercules Inc., Wilmington, U.S.A.) and hydroxypropyl methylcellulose 6 cps (HPMC) (Dow Chemicals Co., Midland, U.S.A.) in a 3 : 1 proportion and using a mixture of equal amounts of isopropyl alcohol and methylene chloride (USP grades) as solvent. By this procedure three distinct size fractions of drug pellets were obtained, all being reproducibly coated with a polymeric membrane of the same thickness and quality. The thickness of the polymeric film was approx. 20 μm.

Characterization of pellets

A representative sample from each fraction was obtained using a Retsch Spinning Riffler (Retsch, Germany). The particle diameter (d) and projected surface area of approx. 100 individual particles were determined with an image-analyzing system. The system consists of a microscope (Wild, type 376788), a video camera, a monitor and a computer with the software Microscale RT (Epoc, Sweden). The surface area (πd^2) and the volume ($\pi d^3/6$) were determined from the projected area assuming that the particles can be described as perfect spheres. In a

TABLE 1

Physico-chemical characteristics of the metoprolol salts used in the study

Parameter	Sorbate	Benzoate	Succinate	Fumarate
Molecular weight	379	389	652	650
Base : acid relation	1 : 1	1 : 1	2 : 1	2 : 1
Melting point (°C)	135–136	111–112	136–137	147–148
Solubility in water 37°C,				
(mg/ml)	23	86	276	472
(mol metoprolol/l)	0.061	0.221	0.847	1.452
Solubility in octanol				
(mg/ml)	7	45	1.7	1.0
Density (g/cm^3)	1.17	1.18	1.27	1.20

second measurement, the projected area of a sample of pellets (about 1000) with a known weight was determined. Knowing the total volume and weight of the sample the apparent density of each fraction could be calculated. In addition, the densities of the pure drug substances and the glass beads were measured by a Beckman air pycnometer (model 930). These values were used to estimate the porosity of the drug layer.

The in vitro release of metoprolol was measured from three samples of each fraction using USP dissolution apparatus No. 2, at 100 rpm using 500 ml distilled water at 37°C. Metoprolol was measured by UV spectrometry at 274 nm (Hitachi, UV-spectrophotometer 100-60).

The initial lag-time and the rate during the constant (zero-order) release phase were determined by linear regression of the cumulative release vs time curve with extrapolation of the linear phase to the time axis. This is exemplified in Fig. 1 for the succinate salt. A plot of release rate vs time was used to determine the shift from a constant release rate to a declining phase as illustrated in Fig. 2. The data points in the latter phase were fitted to the exponential function: $dm/dt = a \cdot (\text{time})^b$, where dm/dt is the rate and a and b are constants. The intercept between this curve and the linear phase was defined as the start of the last phase. The proportion of drug released during this phase was calculated by integration.

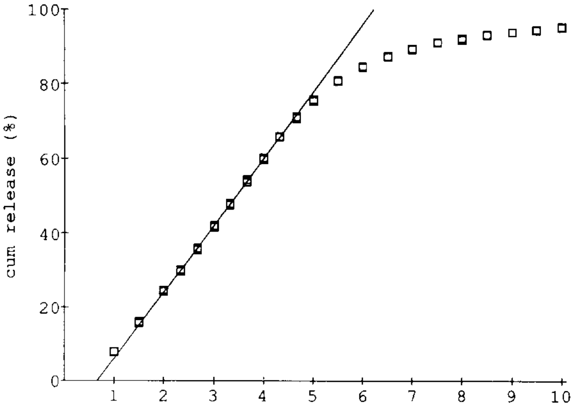

Fig. 1. Cumulative plot of percent drug released vs time for the metoprolol succinate pellets (fraction II). The regression line was obtained from the mean results of three different samples to determine the lag-time (intercept) and the constant release rate (slope).

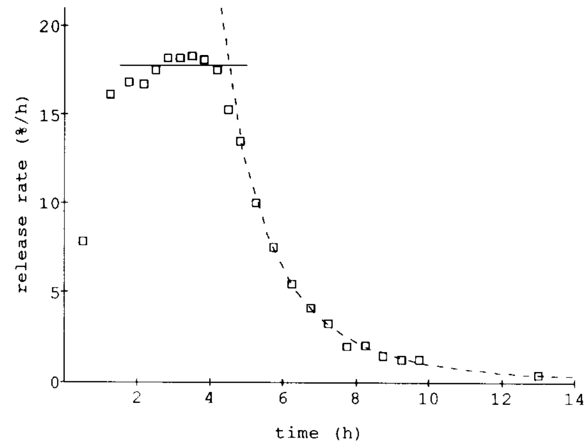

Fig. 2. Release rate vs time curve for the metoprolol succinate pellets (fraction II), illustrating the shift from the constant rate phase to the declining rate phase. The dashed line represents the exponential function $y = a \cdot \text{time}^b$.

Results and Discussion

Metoprolol salts

All four salts showed good crystallization properties, forming large and relatively free-flowing crystals with planar symmetry. As shown in Table 1, the water solubility differed substantially between the four salts, approximately covering the range 20–500 mg/ml.

Particle size and surface area

Each fraction showed a narrow particle size distribution and a good reproducibility with a small variation for the different measurements. The mean values for the four salts were within the following ranges for fractions I, II and III, respectively; 0.43–0.46, 0.47–0.49 and 0.57–0.59 mm. A more detailed presentation of the results has previously been given (Ragnarsson et al., 1989). The mean values of the particle surface area and the density for each fraction of pellets are listed in Table 2.

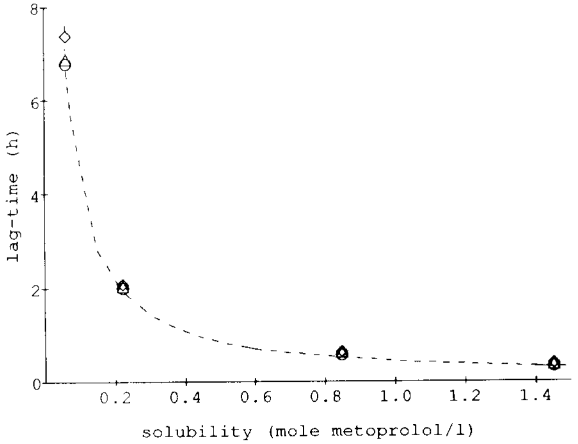

Fig. 3. Relationship between lag-time and drug solubility (mol metoprolol/l) for each fraction of pellets. The dashed line represents the best fit to the function $f(x) = k/x$ including all data. Fraction I (○), fraction II (△); fraction III (◇).

In vitro release

The three release phases and their evaluation are exemplified in Figs 1 and 2 for the succinate salt. The same release pattern was obtained for all four salts and all three fractions. A similar approach to the evaluation of release curves has previously been described (Vidmar and Jalsenjak, 1982).

Lag-time The pellet size had no significant influence on the lag-time as seen in Fig. 3 for the three size fractions. On the other hand the effect of drug solubility was very marked, the relationship between the lag-time and the solubility appearing to be hyperbolic in nature. This is probably explained by the different osmotic effects depending on the solubility of the drug salt. Thus, the more soluble salts are expected to induce a higher osmotic influx rate of water into the pellet and at the same time generate a more rapid expansion of the surrounding membrane. Another effect which may contribute to the different lag-times is that tensile stresses in a membrane of the present type have been shown to increase the permeability of dissolved drug molecules (Hjärtstam et al., 1990).

Constant release phase During this phase, the release rate follows zero-order kinetics as long as the drug solution inside the membrane remains saturated (i.e. provided that there is solid drug in the core) and the membrane permeability for water and the drug salt remains unchanged. Such a zero-order phase was achieved for all salts and fractions in this study.

It has earlier been demonstrated that drug solubility may be used to govern the release properties of membrane-coated formulations (Theeuwes, 1975; Golomb et al., 1987). The influence of drug solubility on the constant release rate in the present study is shown in Table 3. The

TABLE 2

Characteristics of coated pellets determined from the projected area measurements in the image-analyzing system

Parameter	Fraction	Sorbate	Benzoate	Succinate	Fumarate
Particle surface area (cm^2/g)	I	126.6	125.4	116.9	119.8
	II	107.4	105.6	101.2	105.3
	III	79.3	77.0	73.5	75.1
Density (g/cm^3)	I	1.1	1.1	1.2	1.1
	II	1.2	1.2	1.2	1.2
	III	1.3	1.3	1.4	1.3
Porosity [a] (%)	I	26	11	12	14
	II	17	13	9	6
	III	19	12	– [b]	3

[a] Porosity of the metoprolol salt layer.

[b] Estimation uncertain due to micro-cracks in the drug layer.

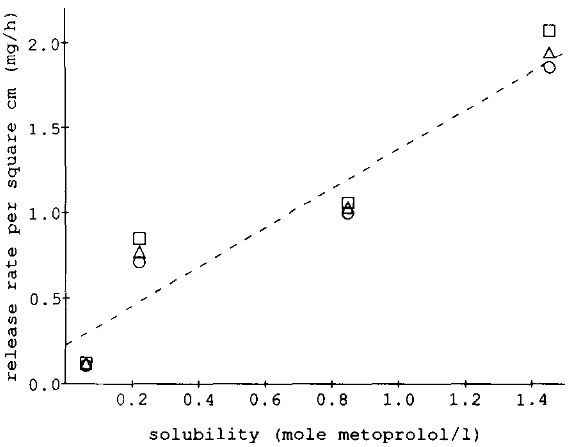

Fig. 4. Plot of release rate per surface area vs drug solubility for each fraction: I (○); II (△); III (◇). The dashed line represents the average linear regression for the three size fractions ($r^2 = 0.91$).

higher release rate achieved for the more soluble salts can be explained as being due to steeper concentration gradient and an increased osmotic pressure difference over the membrane. The latter effect may also induce tensile stresses in the film leading to greater permeability (Hjärtstam et al., 1990). Since these factors act in the same direction the drug solubility should have a considerable influence on the release rate from this type of formulation.

In accordance with results reported by Ragnarsson and Johansson (1988), the release rate from the pellets was approximately proportional to their surface area (Fig. 4). However, there was a consistent tendency of the coarsest fraction to give a somewhat faster release rate per unit surface area than the finer fractions. The opposite behaviour was shown by results reported in a recent paper where the release rate per unit surface area was lower for larger particles (Wesdyk et al., 1990). This was due to a thicker film coat on the coarser fractions as a result of segregation of the pellets in the Wurster coating column. Although this explanation cannot be excluded in the present study, the top spray coating procedure used has been shown to give reproducible and consistent film properties when applied on pellets within the investigated size range (Ragnarsson and Johansson, 1988). The small effect of the pellet size on the release rate may also be due to differences in hydrostatic pressure, resulting in a faster pumping rate for the larger particles (Hjärtstam et al., 1990).

Declining rate phase When no more solid drug remains in the pellet the drug solution will gradually become diluted and the release rate will decrease. Obviously, the percentage of total drug being released during this phase was highly dependent on the solubility of the drug substance whereas the particle size was of no importance in this respect (Table 3).

Another factor that may influence the shift from a zero-order release rate to a declining rate is the volume of the solution inside the membrane. This volume is determined by the density of the salt, the porosity of the pellet core and the possible expansion of the film during the release process. In the ideal case when the porosity is zero and no expansion of the film occurs, the fraction of drug remaining in the core as a saturated drug solution when all solid drug has been dissolved is given by the ratio between the solubility and density of the drug substance (C_s/ρ)

TABLE 3

Constant release rate per surface area and percentage of total drug released in the declining rate phase for each fraction and salt

Parameter	Fraction	Sorbate	Benzoate	Succinate	Fumarate
Constant drug release rate (mg/h per cm^2)	I	0.11	0.71	1.00	1.86
	II	0.12	0.77	1.03	1.94
	III	0.12	0.85	1.06	2.07
% drug released in declining rate phase	I	9	14	30	50
	II	6	14	30	49
	III	10	16	32	51

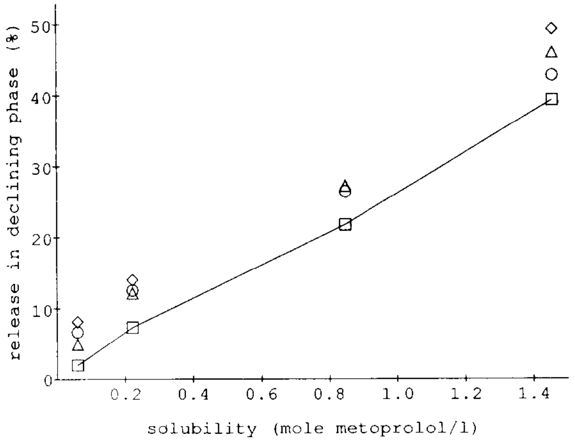

Fig. 5. Percentage of the drug dose released in the declining rate phase vs drug solubility. The squares connected with a line are theoretical values assuming a porosity of zero. The other symbols represent the actual release for each fraction [I (○); II (△); III (◇)] after adjustment for the measured porosity.

(Theeuwes, 1975). Consequently, this fraction will be delivered at a non-constant rate. At a given porosity (P) of the pellet, a more general expression for the total fraction released during the declining rate phase is then given by the expression: $C_s/\rho \cdot 1/(1-P)$.

An application of the discussion above is illustrated in Fig. 5 showing a plot of percentage drug released after the shift from a zero-order release rate to the declining rate phase vs the drug solubility. The theoretical values assuming a porosity of zero were compared with those obtained from the release curves after adjustment for the estimated porosity (Table 2), i.e. by multiplying the values in Table 3 by ($1-P$). As shown in Fig. 5, there was a discrepancy between the theoretical line and the experimental data despite this compensation. Although there was some difficulty in determining the porosity for the largest fractions of the succinate and fumarate salts due to inconsistencies in the drug layer, the major cause of this effect is probably an expansion of the polymeric membrane caused by hydrostatic forces. An expansion in the apparent pellet size of only a few (5–10) micrometres during the release process, would be sufficient to compensate for the deviation between the theoretical and experimental data.

Drug release mechanism

The major mechanisms for the release of drug from reservoir systems are diffusion and osmotic pumping. The latter has been demonstrated to be a major mechanism for the drug release from various types of membrane-coated formulations (Theeuwes, 1975; Zentner et al., 1985; Lindstedt et al., 1989; Ozturk et al., 1990). The basic differences between these two release principles are schematically illustrated in Fig. 6.

The polymeric membrane used in the present investigation is a mixture of ethylcellulose (76%) and HPMC (24%). Membranes composed of these two polymers have been thoroughly investigated using both free films and coated tablets (Lindstedt et al., 1989, 1991; Hjärtstam et al., 1990). These studies showed that increasing the proportion of HPMC in the composition decreased the reflectivity and increased the permeability of the membrane. It also lowered the tensile stress required to induce convective permeability. Furthermore, it was shown that HPMC can be leached from the membrane leaving water-filled pores (channels) in the film when the content exceeded 20% of the film composition.

When Lindstedt and co-workers (1989) studied the release from coated potassium chloride tablets, they found osmotic pumping to be the predominant mechanism for film compositions containing up to 24% HPMC. In a similar experiment, the release rate of metoprolol fumarate, succinate and benzoate from fraction III of the present pellets was measured in saccharose solutions of varying osmotic pressure. The result showed that the osmotic pressure difference ($\Delta\Pi$) over the membrane had a strong effect on the release rate for all three salts. This is illustrated in Fig. 7, which depicts the release curves for the succinate and fumarate salts in water and after reducing $\Delta\Pi$ by about 50%. However, there was no clear-cut relationship between $\Delta\Pi$ and the release rate for the different salts, which indicates that processes other than osmotic pumping are also involved. Moreover, the different lipophilicities of the salts, as indicated by their solubility in octanol (Table 1), may also have an impact on their ability to diffuse through the membrane.

Assuming that the film properties were the same after application on all drug cores irrespective of the salt, a further indication of the release mechanism could be obtained by establishing the relationship between the release rate and drug solubility. Thus, if osmotic pumping is the predominant mechanism, the zero-order release rate should be proportional to the square of the solubility. This is clearly evident when replacing Π in the formula in Fig. 6 by $C \cdot R \cdot T \cdot \Phi$ (Φ: molal osmotic coefficient) (Zentner et al., 1985). On the other hand, if drug diffusion is the major release mechanism, the release rate should be directly proportional to the solubility (Fig. 4). The results from the regression analysis of the two relationships were comparable (Table 4), however, the correlation was somewhat better for the diffusion-related equation.

Calculations based on the release rate in the declining rate phase could be performed only for the fumarate and succinate, since the fraction released in this phase was too small for the other salts. The following equations were used assuming osmotic pumping (Eqn 1) and drug diffusion (Eqn 2) to be the mechanism, respectively:

$$\mathrm{d}m/\mathrm{d}t = \frac{(\mathrm{d}m/\mathrm{d}t)_z}{\left(1 + \frac{(\mathrm{d}m/\mathrm{d}t)_z}{C_s \cdot V} \cdot (t - t_z)\right)^2} \tag{1}$$

$$\mathrm{d}m/\mathrm{d}t = (\mathrm{d}m/\mathrm{d}t)_z \cdot e^{-\left(\frac{(\mathrm{d}m/\mathrm{d}t)_z}{C_s \cdot V} \cdot (t - t_z)\right)} \tag{2}$$

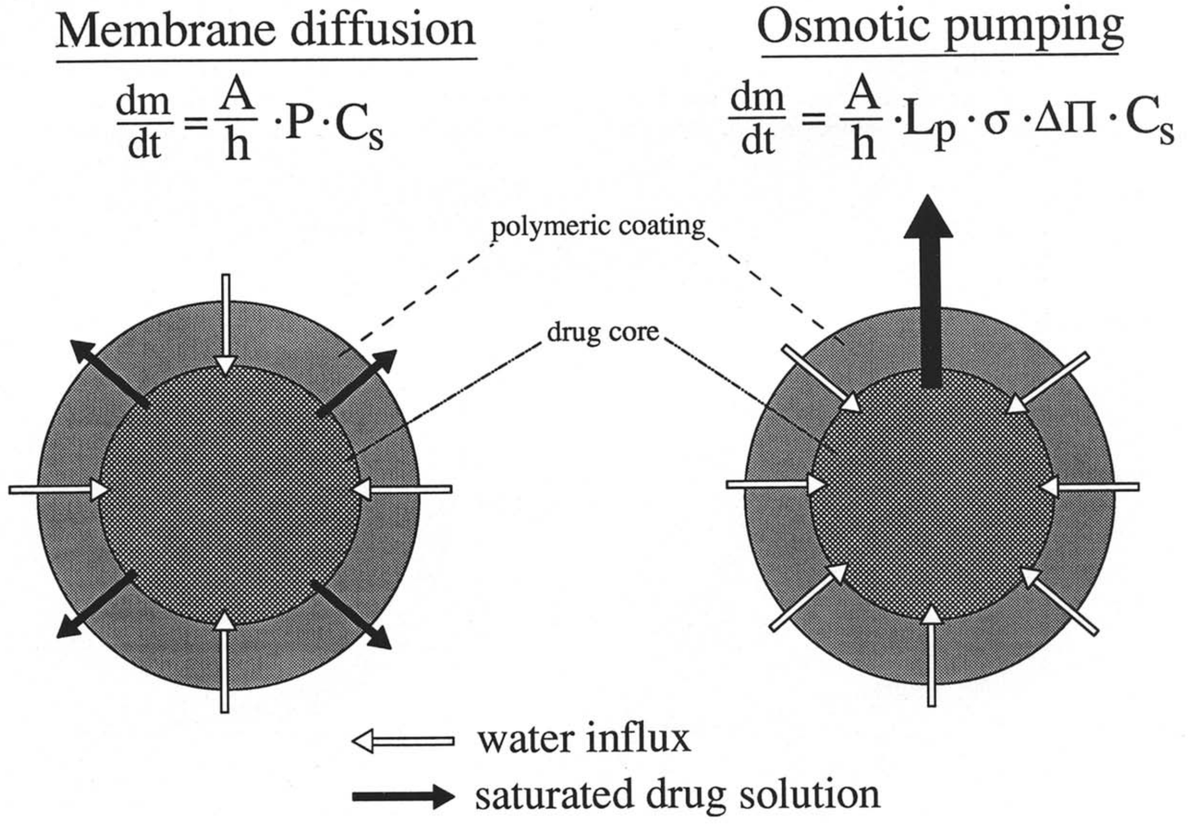

Fig. 6. Schematic illustration of drug release by membrane diffusion and osmotic pumping. The equations represent the release rate ($\mathrm{d}m/\mathrm{d}t$) in the constant release phase for the two mechanisms. A, surface area of the pellet; h, wall thickness; L_p, hydraulic permeability; σ, reflection coefficient; $\Delta\Pi$, osmotic pressure difference across the wall; P, permeability coefficient of the solute; C_s, solubility of the drug core.

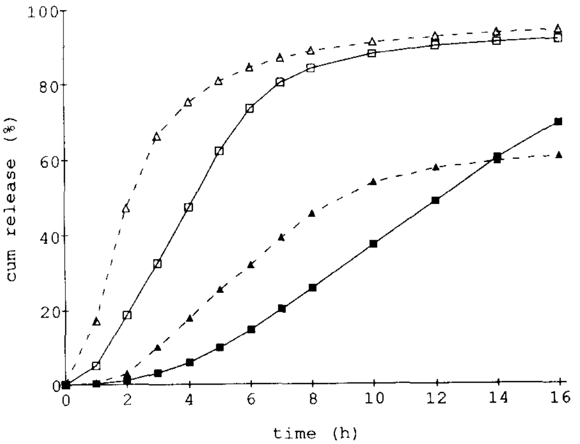

Fig. 7. Cumulative drug release from fraction III of the succinate (□) and fumarate (△) pellets. (Empty symbols) Purified water; $\Delta\Pi \sim 3.0$ MPa (succinate), $\Delta\Pi \sim 6.5$ MPa (fumarate). (Filled symbols) Saccharose solution 170.2 and 288.1 g/l; $\Delta\Pi \sim 1.5$ MPa (succinate), $\Delta\Pi \sim 3.6$ MPa (fumarate).

TABLE 4

Goodness-of-fit characteristics for the relationship between release rate (dm/dt) per unit area and drug solubility (C_s, mol metoprolol / l) in the constant release rate phase

Relationship [a]	Fraction	Equation characteristic	
		p value [b]	r^2
$\mathrm{d}m/\mathrm{d}t = \text{const} \cdot C_s$	I	0.038	0.93
	II	0.044	0.91
	III	0.053	0.90
$\mathrm{d}m/\mathrm{d}t = \text{const} \cdot C_s^2$	I	0.056	0.89
	II	0.060	0.88
	III	0.064	0.88

[a] Explanations of the different constants are provided in Fig. 6.

[b] Significance level for the regression (slope).

where $\mathrm{d}m/\mathrm{d}t$ is the release rate, $(\mathrm{d}m/\mathrm{d}t)_z$ represents the constant release rate, C_s is the drug solubility, V denotes the volume of the core solute and $(t - t_z)$ is the time difference between the total time and the time for the phase shift, i.e. when all solid drug in the core has dissolved. Eqn 1 has previously been described by Theeuwes (1975), whereas Eqn 2 was obtained by combining Fick's law (Fig. 6) and the general expression for

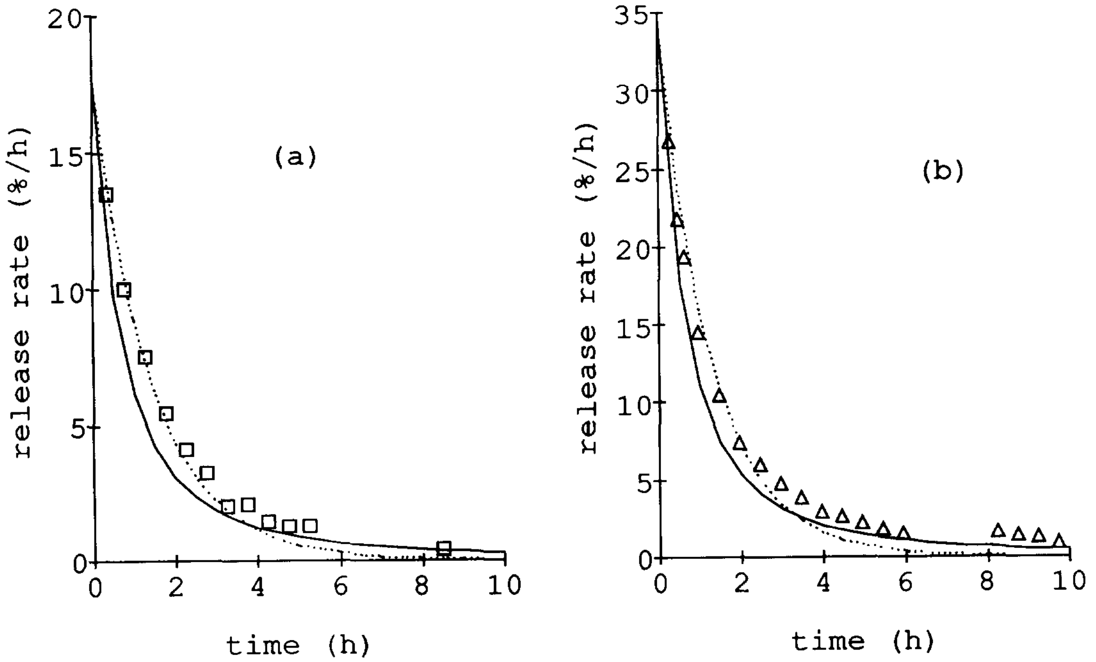

Fig. 8. Release rate vs time in the declining rate phase ($t - t_z$) for fraction II of the succinate (a) and fumarate (b) salt. The continuous and dotted lines represent the expected decline assuming osmotic pumping (Eqn 1) and diffusion (Eqn 2), respectively. (□, △) Experimental data for the two salts.

the delivery rate as a function of the concentration change at a given volume; $dm/dt = -V(dC/dt)$.

As shown in Fig. 8, the actual release rate for both salts corresponds closely with the predicted curves according to the two equations. The fit appeared somewhat better for the diffusion-based equation, however, the differences between the two predictions were too small to allow any definite conclusions regarding the mechanism from these data.

Conclusion

Particle size and drug solubility have been shown to be important for the release characteristics of small spherical pellets coated with a film of ethylcellulose and hydroxypropyl methylcellulose in the proportion 3 : 1.

The particle size had no effect on the initial lag-time and the phase with a declining non-constant release rate. The zero-order release rate was almost proportional to the surface area of the pellets over the entire solubility range studied ($\sim$ 20–500 mg/ml). The small deviations observed for the coarsest fraction are believed to be due to hydrostatic effects that may influence the permeability of the film.

Drug solubility influenced all phases of the release curve. The shorter lag-time seen for the more soluble salts is probably a result of increased osmotic pressure affecting the water influx rate. Furthermore, the more soluble the drug salt the more rapid was the release rate and the lower the fraction of the dose that was released at a constant release rate. This fraction should also be affected by the porosity of the pellet core and by an expansion of the film during the release. Thus, if the major part of the drug dose is to be released at a zero-order rate, the porosity should be low and the water solubility of the drug should not exceed 300–400 mg/ml.

The release mechanism for the investigated formulations appears to be rather complex. The importance of osmotic forces is evident, however diffusion of the drug through the membrane seems as important as osmotic pumping for the release.

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