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A controlled porosity drug delivery system

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Abstract

The relationship between the drug release rate constant (K_o) and the physicochemical properties of porosity modifiers incorporated in the polymer coat of a proposed compression coated drug delivery system was investigated. The effects of particle size, hygroscopicity, solubility, absolute density and powder specific surface area on K_o were related to their influence on the pore structure created. In general, porosity modifiers with larger particle sizes, smaller specific surface areas, greater hygroscopicity coefficients or higher solubilities caused faster drug release, by creating more conducting channels. The porosity modifier particle size and load were related to changes in the coat volume (V_{coat}), coat porosity (ε_{final}) and increased specific surface area (SSA_d). The V_{coat} decreased with an increased loading or particle size, promoting faster release. K_o increased very slowly until ε_{final} and SSA_d reached critical values (approximately 38% and 0.1 $m^2\ g^{-1}$, respectively), after which K_o increased very rapidly. This information allows the selection of a porosity modifier with the appropriate characteristics to provide a delivery system with the desired release rate. Alternatively, one can specify the necessary coat characteristics after porosity modifier release that will yield the desired release rate.

Keywords: Compression coating; Porosity modifier; Release rate; Pore generation; Cluster; Particle size; Surface area; Hygroscopicity; Coat volume

1. Introduction

The focus of research efforts in the drug delivery field has been on developing delivery systems that can deliver drug at a predictable release rate independent of their environment. Core tablets surrounded by a polymeric coat offer a simple but effective approach. The release rate can be altered easily by modifying the coat's physical structure (porosity).

The coat can be applied by compressing the coating material around the core (Mars, 1974; Conte et al., 1983; Verhoeven et al., 1989). The

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release rate from these systems is controlled by several parameters, such as the amount of polymer used, the surface characteristics of the polymer and the compressibility of the polymer (Shivanand and Sprockel, 1993). Because of the stresses encountered during dissolution, the polymer shell must have sufficient physical strength to remain intact during drug release. This means that for a particular polymer the shell will need a minimum thickness and density and changing the release rate through the above mentioned methods is limited. An alternative is to alter the permeability of the shell by dynamically modifying the pore structure of the shell.

Fryklof et al. (1967) incorporated soluble additives (porosity modifiers) in their compressed shell, that upon dissolution increased the release rate. They saw an initial lag time, after which the release rate increased to a constant rate and finally declined to zero. The advantage of using soluble additives in the coat material is that one can design a strong coat with a useful release rate. Källstrand and Ekman (1983) spray coated their core tablet with a suspension of polyvinyl chloride and micronized sucrose in a solvent system using conventional pan technology. They saw an increasing release rate with time followed by the declining rate. Zentner et al. (1985) demonstrated that, with increased loading of sorbitol, the increase in the release rate became smaller. Therefore, increasing the release rate by adding soluble additives had its limitations. Thombre et al. (1989) showed that as sorbitol dissolved out of the coat, the pores generated formed networks through which water entered the system.

The percolation theory, in general, deals with the number and property of pores and pore clusters (Stauffer, 1985). The percolation theory has been used to explain the relationship between pore generation and solute release from films (Siegel, 1988). Dissolution of the porosity modifiers incorporated in the coat creates pores. As the number of pores increase, the pores combine to form a percolating pore cluster or conducting channel, that spans the thickness of the coat. These percolating pore clusters, filled with release media, are the conduits by which drug is released.

It is clear from the literature, that addition of a porosity modifiers to an insoluble polymer coat surrounding a core tablet increases the release rate of the drug. However, the relationship between the physicochemical properties of the additive and the release rate constant have not been studied. In this study we investigated the relationship between the properties of several soluble additives and their effect on the release rate constant of propranolol HCl from a compression coated system, through changes in the coat.

2. Materials and methods

2.1. Materials

The following materials were used as received from the manufacturer without further purification: cellulose acetate butyrate 500-1 (CAB) (a gift from FMC corporation); propranolol HCl (a gift from Knoll Ag.); citric acid (CA); calcium tartrate (CaT), calcium sulfate ($CaSO_4$), mannitol, sodium chloride (Fisher Scientific); and sucrose (Kroger).

2.2. Characterization of powders

2.2.1. Absolute density

The absolute densities of the CAB powder and the porosity modifiers were determined in triplicate using a Micromeritics helium pycnometer. The powders were dried in an oven at 100°C for 12 h prior to analysis.

2.2.2. Particle size analysis

To obtain the desired size fractions, samples of CaT, NaCl and mannitol were placed on top of a standard nest of sieves and shaken until there was no detectable change in the weight of the powder retained on each sieve. CA, CaT and sucrose were used as received. Samples of all the powders were suspended in liquid paraffin and the particle size distributions were determined microscopically. The geometric mean particle size was obtained from log-probability plots.

2.2.3. Intrinsic dissolution rates

The intrinsic dissolution rate of NaCl in 0.02% v/v polyoxyethylene sorbitan monooleate in distilled water was determined. A total of 50 mg of NaCl were compressed at 236 MPa on a hydraulic press (Carver press) using a 6 mm flat faced punch and die set. The NaCl core tablet was placed in a 12 mm die containing the bottom flat faced punch. CAB (300 mg) was carefully poured on top of the core tablet. The powder bed was compressed at 78 MPa. As a result, the NaCl core tablet was coated with the polymer on the annular surface and on one planar surface. This limited dissolution to a single tablet face and maintained a constant surface area. The coated NaCl tablet was affixed to a metal substrate with the exposed surface facing upwards. The tablet on the substrate was placed at the bottom of a dissolution vessel containing 500 ml of the dissolution media at 37°C. Media agitation was achieved with a paddle rotating at 25 rpm. Dissolution fluid (5 ml) were removed at predetermined intervals and analyzed for NaCl content by polarography.

The mass transfer of drug from the solid surface of the undissolved material to the solution is described by the Noyes–Whitney equation (Carstensen, 1974):

$$\frac{dC}{dt} = AK_d(C_s - C) \quad (1)$$

where V is the volume of the dissolution media (cm^3), C is the concentration of NaCl in the solution (g^{-1} cm^3), t is time (h), A is the exposed surface area of the NaCl core tablet (cm^2), C_s is the solubility of NaCl (g^{-1} cm^3) and K_d, the intrinsic dissolution rate (cm h^{-1}), is:

$$K_d = \frac{D}{Vh} \quad (2)$$

where D is the diffusion coefficient of the solute in the dissolution medium (or solvent), V is the volume of the dissolution medium (cm^3) and h is the thickness of the boundary layer (cm).

The dissolution of 70% of the core tablet was linear with time ($r^2 = 0.997$). K_d was calculated from the slopes from these lines, which were determined using least squares regression. The average slope of these lines was 0.054 ± 0.008 g^{-1} $cm^2 \cdot$ per h. The solubility of NaCl was determined to be 0.352 ± 0.007 g^{-1} cm^3. Therefore, K_d for NaCl under these conditions was 0.153 ± 0.024 cm h^{-1}. This indicates that the release of NaCl from the polymer coat was not dissolution rate limited.

2.2.4. Hygroscopicity

The hygroscopicity coefficient for the porosity modifiers was determined at 89% relative humidity using saturated solutions of $ZnSO_4$. The powders were dried at 100°C for 24 h. Samples (1 g) of the porosity modifiers were placed in glass petri dishes of known weights. A saturated solution of $ZnSO_4$ was placed at the bottom of the desiccator and the system was allowed to stand for 24 h. The petri dishes containing the powder samples were placed in the desiccator. At predetermined intervals, the petri dishes were removed, weighed, and replaced. The increase in weight was ascribed to moisture uptake by the powder. The absorption of moisture can be described by the following equation (van Campen et al., 1980):

$$\frac{M_t}{M_\infty} = (1 - e^{-K_h t}) \quad (3)$$

where M_t and M_∞ are the amounts (g) of moisture absorbed at time t and at time infinity, respectively, and K_h is the hygroscopicity coefficient (h^{-1}). The K_h for the porosity modifiers were calculated using linear least squares regression analysis.

2.2.5. Specific surface area

The powder samples were dried in an oven at 100°C for 24 h. The specific surface area of the powders was determined in triplicate by the BET method using a krypton/helium mixture with a Micromeritics Flowsorb 2300 instrument.

2.2.6. Solubility

The solubilities of the porosity modifiers were determined. Excess solid was placed in 10 ml test tubes. A volume of 5 ml of 0.02% v/v polyoxyethylene sorbitan monooleate in distilled water was added. The caps were screwed on and sealed with parafilm. The test tubes were agitated in a shaker bath at 37°C for 3 days. The suspended

Table 1
Characteristics of the porosity modifiers

Porosity modifier	Size (μm)	K_h^a(h^{-1})	SSA[b] (m^2 g^{-1})	ρ_{abs}^c (g ml^{-1})	C_s^d (g ml^{-1})
NaCl	7	0.457	0.209	1.852	0.352
	98		0.054	2.033	
	256		0.018	1.957	
Calcium tartrate	18	0.004	0.504	2.037	0.030
	22		0.437		
	98		0.402		
Mannitol	40		0.227		
	83	0.012	0.186	1.554	0.269
	98		0.167		
Sucrose	21	0.016	0.454	1.593	0.701
Citric acid	270	0.603	0.186		0.844
$CaSO_4$	33	0.207	4.080	2.711	0.002

[a] Hygroscopicity coefficient.
[b] Specific surface area.
[c] Absolute density.
[d] Solubility.

solids were allowed to settle and 3 ml of the clear supernatant were removed. The samples of solutions containing CaT or NaCl were filtered and the first 1 ml of the filtrate was discarded. The solute concentrations were determined by polarography after appropriate dilutions. The solubilities of CA, $CaSO_4$, mannitol and sucrose were determined gravimetrically. A volume of 2 ml of the filtered solutions were pipetted into weighing pans of known weights. The pans containing the solutions were dried in an oven at 50°C to constant weight.

2.3. Preparation of the coated tablet

To make the core tablets, 50 mg of propranolol HCl were compressed at 78 MPa on a hydraulic press (Carver Press) using a 6 mm flat faced punch and die set. The punch faces and the die wall were lightly dusted with magnesium stearate before each compression. After ejection, the core tablets were carefully wiped clean to remove the magnesium stearate. The core tablets were stored in closed HDPE bottles at 24°C for 1 day before coating.

A total of 50% (150 mg) of the coating material was placed in a 12 mm die containing the bottom flat faced punch. The core tablet was carefully centered on the powder bed. The rest of the coating material was poured on top of the core tablets and the system was compressed at 31 MPa on the hydraulic press. The coating material comprised CAB only or mixtures of CAB and porosity modifiers. CAB was used as the insoluble polymer in the coating material. Several water soluble materials were mixed with CAB in varying proportions by geometric dilution using a spatula; these materials acted as porosity modifiers (Table 1). The compression coated tablets were stored at 24°C in closed HDPE containers for at least 1 day before any testing occurred. This was done to allow post-compression elastic recovery of the tablets to occur.

2.4. Characterization of the coated tablet

2.4.1. Tablet dimensions

One day after compression the thickness and the diameter of the core tablet and of the compression coated tablet were measured with a digital micrometer.

2.4.2. Drug release

The release of propranolol HCl from the compression coated tablets was determined in an aqueous solution of 0.02% v/v poyoxyethylene sorbitan monooleate at 37°C. Agitation was maintained at 100 rpm with a paddle (Hanson). Samples of volume 4 ml were withdrawn periodically and analyzed by spectrophotometry at 290 nm for the propranolol HCl concentration. The lost volume was replaced with fresh release media.

2.4.3. Porosity modifier release

In the NaCl release studies, the propranolol HCl core tablet was replaced with a CAB core tablet to facilitate the polarographic analysis of NaCl. The release of NaCl from the coat of the compression coated system was determined similar to the propranolol HCl release studies, except that 5 ml of the media were removed periodically and analyzed by polarography. The effective diffusion coefficient for NaCl release was calculated from Eq. (14) using non-linear least squares regression analysis.

2.4.4. Surface area changes

To determine the changes in the surface area of the coat at specified time points during NaCl release, 30 compression coated tablets containing NaCl were made. The propranolol HCl core tablet was replaced with a CAB core tablet to facilitate data analysis. Three tablets were used as control and did not undergo any release study. The remaining 27 tablets were subjected to a release study similar to that for propranolol HCl. At 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6 and 12 h, three tablets were removed from the appropriate dissolution vessels and dried in an oven at 100°C for at least 24 h. The surface area of the dried tablets were then determined using the BET method. A krypton/helium mixture was used with a Micromeritics Flowsorb 2300 instrument. The surface area of each tablet was determined at least three times. The three control tablets were subjected to the same procedures. The surface area of the control tablets served as a reference point for the other tablets.

The specific surface area of the control tablets is defined as the SSA_i (specific surface area initial). The specific surface area of the tablets after dissolution of the NaCl is defined as the SSA_f (specific surface area final). The difference between SSA_i and SSA_f is defined as SSA_d (specific surface area difference).

2.4.5. Porosity changes

For tablets containing NaCl as the porosity modifier, the increase in the coat's porosity during NaCl release was calculated. The coat's porosity at time t (ε_t) is:

$$\varepsilon_t = \varepsilon_0 + \varepsilon_{NaCl} \tag{4}$$

where the tablet's initial porosity (ε_0) is:

$$\varepsilon_0 = \frac{\rho_{app}(coat)}{\rho_{app}(coat)} \tag{5}$$

and the porosity due to the release of NaCl from the coat (ε_{NaCl}) is:

$$\varepsilon_{NaCl} = \frac{M_{NaCl} V_{coat}}{\rho_{NaCl}} \tag{6}$$

where M_{NaCl} is the amount of NaCl released and ρ_{NaCl} is the absolute density of NaCl.

The volume of the coat (V_{coat}) is:

$$V_{coat} = \pi r_t^2 h_t - \pi_c^2 h_c \tag{7}$$

where r_t is the radius of the tablet, h_t is the thickness of the tablet, r_c is the radius of the core and h_c is the thickness of the core. The overall apparent density of the coat (ρ_{app}(coat)) (g ml^{-1}) is:

$$\rho_{app}(coat) = (\rho_{cab} X_{cab}) - (\rho_{NaCl} X_{NaCl}) \tag{8}$$

where ρ_{cab} is the absolute density of CAB and X_{cab} and X_{NaCl} are the weight fractions of CAB and NaCl, respectively. For simplicity, we assume that there is no density gradient in the coat; such a density gradient may exist since the pressure transfer through the coat upon compression is not uniform. The absolute density of the coat (ρ_{abs}(coat)) (g ml^{-1}) is:

$$\rho_{abs}(coat) = \frac{M_{tab} - M_{core} - M_{NaCl}}{V_{coat}} \tag{9}$$

where M_{tab} is the mass of the tablet and M_{core} is the mass of the core (g).

2.5. Analysis

Propranolol HCl was analyzed by spectrophotometry at 290 nm. The standard curve was linear in the range of 1–50 mg l^{-1} ($r^2 = 0.999$). Sodium chloride was analyzed by differential pulse polarography. A static mercury drop electrode was used with a polarographic analyzer in the differential pulse polarography mode (EG&G, Princeton, NJ). The analysis was carried out under a nitrogen blanket (99.999% nitrogen). The NaCl aqueous (deionized water) solutions contained 0.02% polyoxyethylene sorbitan monooleate and 0.01 M tetraethyl ammonium hydroxide as the supporting electrolyte. The following settings were used: a scan range of 1.9–2.7 V; a scan rate of 5 mV s^{-1}; a current of 100 μA; a pulse height of 50 mV; a drop time of 1 s; and a purge time of 4 min.

2.6. Statistical analysis

A linear least squares method was used to determine the release rate constant (K_o) for propranolol HCl and the dissolution rate constant for NaCl. A non-linear least squares method was used to determine the effective diffusion coefficient for NaCl. One-way and two-way analysis of variance were used to detect any significant differences between treatment means using the Minitab statistical software. Tukey's procedure for multiple means comparison was used with $\alpha = 0.05$. A multiple linear regression method was used to study the relationship between K_o and the powder properties.

3. Results and discussion

3.1. Drug release

The release profile from the compression coated system was typically sigmoidal with a linear segment (Fig. 1). After penetrating the coat, the release media dissolved the porosity modifier and created a saturated propranolol HCl solution in the core. Propranolol HCl then diffused outward through the media filled channels in the coat. While the solution concentration in the pores was maintained constant by the solid drug present, a constant release rate was seen. Upon depletion of the solid drug source, the internal concentration declined causing a decrease in the release rate. Similar profiles were seen by other investigators (Fryklof et al., 1967; Conte et al., 1983; Källstrand and Ekman, 1983). Thus, the release of propranolol HCl from this system required several rate processes to occur in parallel or in series.

The constant release of propranolol HCl across the compressed polymer barrier is described by Eq. (10) (Shivanand and Sprockel, 1993):

$$\frac{dM}{dt} = \frac{D_e A}{h}(C_i - C_o) \tag{10}$$

where M is the amount of propranolol HCl released (mg); t is time (h); D_e is the effective diffusion coefficient ($cm^2\ h^{-1}$); A is the effective surface area (cm^2); h is the coat thickness (cm); C_i is the drug concentration inside the tablet (mg cm^3); and C_o is the drug concentration outside the tablet (mg cm^3). Zentner et al. (1985) pointed out that mass transfer from coated tablets is by

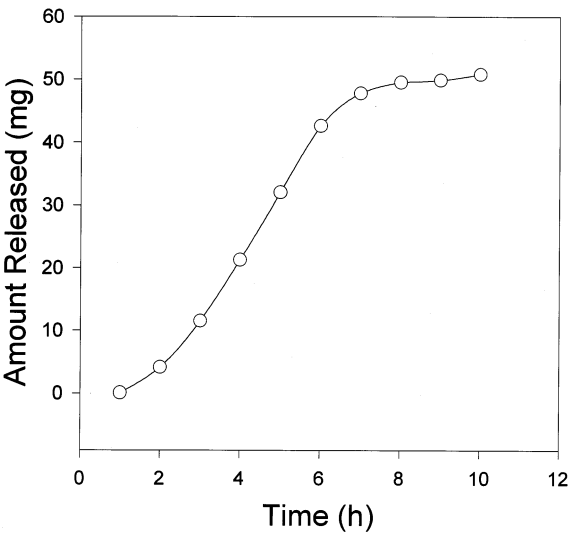

Fig. 1. A typical release profile for propranolol HCl from the compression coated drug delivery system with mannitol as the porosity modifier.

Table 2
The zero order release rate constants (K_o) and lag times (T_{lag}) from the various delivery systems

Modifier	Load (%)	Size (μm)	K_o (mg h^{-1})	T_{lag} (h)
None	30		0.999 ± 0.145	29.648 ± 5.871
NaCl	10	7	1.038 ± 0.735	2.447 ± 0.482
	30	7	5.407 ± 0.735	2.573 ± 0.244
	30	98	4.403 ± 0.534	3.462 ± 0.741
	30	256	15.900 ± 3.139	4.204 ± 0.405
	50	7	18.560 ± 6.789	1.087 ± 0.220
CaT	30	18	1.333 ± 0.128	-0.334 ± 0.299
	30	22	1.337 ± 0.147	0.652 ± 0.341
	30	98	1.710 ± 0.096	-0.931 ± 0.602
	50	22	2.007 ± 0.041	0.869 ± 0.340
Mannitol	10	83	1.701 ± 0.305	2.976 ± 1.123
	30	40	8.383 ± 0.532	2.949 ± 0.240
	30	83	7.972 ± 0.615	2.876 ± 0.123
	30	98	10.410 ± 0.993	2.911 ± 0.223
	50	40	49.851 ± 7.313	1.453 ± 0.088
	50	83	39.479 ± 5.455	0.847 ± 0.192
Sucrose	10	21	0.800 ± 0.0158	4.883 ± 0.864
	30	21	5.775 ± 0.541	2.862 ± 0.404
	50	21	84.968 ± 12.353	0.888 ± 0.200
Citric acid	30	270	8.969 ± 1.345	
$CaSO_4$	30	33	2.106 ± 0.149	1.058 ± 0.417

diffusion and by osmotic pumping. The overall release rate constant (K_o) is defined as:

$$K_o = \frac{D_e A C_i}{h} \tag{11}$$

The release rate constants (K_o) and lag times (T_{lag}) were calculated from the slopes of the linear segments (see Table 2). The macroporous cellulose acetate butyrate membrane surrounding the propranolol HCl core tablet was 2.73 ± 0.03 mm thick. Because of the low porosity of the coat ($\varepsilon_o = 0.231$), K_o was limited to 1.00 ± 0.15 mg h^{-1}, with a lag time of 29.65 ± 5.87 h. Addition of porosity modifiers to the coating material increased K_o tremendously. For example, at a 30% level of porosity modifiers in the coat, K_o ranged from 1.33 ± 0.13 mg h^{-1} to 15.90 ± 3.14 mg h^{-1}. The relative increase in K_o between the various porosity modifiers is due to their physicochemical properties. The characteristics of the porosity modifiers used in this study are listed in Table 1.

3.2. Powder properties

A stepwise multiple regression method was used to relate the physicochemical properties of the porosity modifiers listed in Table 1 to K_o. We found that a second degree polynomial adequately approximated the underlying relationship between K_o and the properties (Fig. 2; $r^2 = 0.996$; slope $= 0.998$):

$$K_o = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_4 x_4 + \beta_5 x_5 + \beta_{11} x^2 + \beta_{24} x_2 x_4 + \beta_{25} x_2 x_5 + \beta_{34} x_3 x_4 + \beta_{35} x_3 x_5 \tag{12}$$

where β_o is the intercept of the regression equation; β_n are the coefficients of the regression equation; and x_n are the properties. The coefficients of the polynomial with their P-values are listed in Table 3. We pooled all the non-significant ($P \geq 0.1$) higher order terms with the error term. All the remaining terms in the statistical model are significant ($P < 0.1$), except the intercept ($P =$

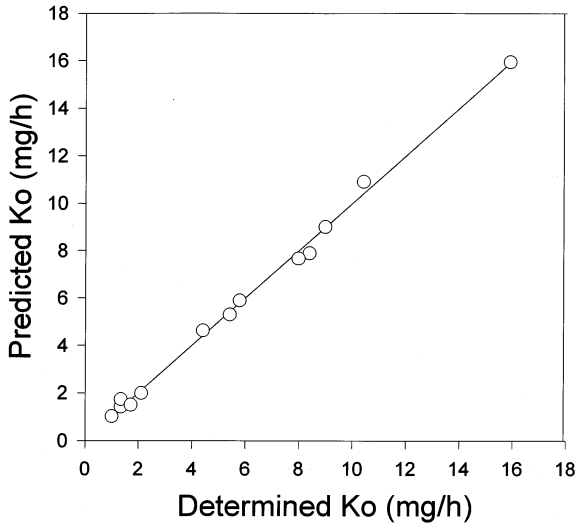

Fig. 2. Regression of the release rate constant (K_o) fitted from Eq. (12) on K_o determined experimentally.

0.265), particle size ($P = 0.270$) and absolute density (ρ_{abs}; $\rho = 0.811$). Particle size and absolute density were left in the model because the higher order terms Size^2, $K_h \cdot \rho_{abs}$, and SSA $\cdot \rho_{abs}$ were significant ($P = 0.086$, $P = 0.035$ and $P = 0.048$, respectively). That ρ_{abs} by itself was not significant may be surprising, except that the range of values was relatively narrow (1.554–2.711 g ml^{-1}).

Table 3
Coefficients for the regression of the powder properties on K_o

Variable	Property	Coefficient	P-value
Constant	Inherent K_o (mg h^{-1})[a]	1.03 ± 0.672	0.265
X_1	Size (μm)	-0.031 ± 0.021	0.270
X_2	K_h (h^{-1})[b]	192.11 ± 38.43	0.038
X_3	SSA (m^2 g^{-1})[c]	-99.10 ± 21.38	0.044
X_4	ρ_{abs} (g ml^{-1})[d]	0.93 ± 3.42	0.811
X_5	Solubility (g ml^{-1})	67.18 ± 14.91	0.046
X_1^b	Size[b]	0.00021 ± 0.000066	0.086
X_2X_4	$K_h \cdot \rho_{abs}$	-93.19 ± 17.97	0.035
X_2X_5	$K_h \cdot$ solubility	-124.70 ± 23.10	0.033
X_3X_4	SSA $\cdot \rho_{abs}$	47.18 ± 4.38	0.048
X_3X_5	SSA $\cdot$ solubility	-99.23 ± 32.71	0.094

[a] Release rate constant.
[b] Hygroscopicity coefficient.
[c] Specific surface area.
[d] Absolute density.

The intercept of the regression equation (β_o) represents K_o in the absence of any porosity modifier. The predicted K_o with out porosity modifier (1.03 ± 0.05 mg h^{-1}) is very close to the determined value (1.00 ± 0.145 mg h^{-1}). If one looks at the main effects, the following conclusion can be made. In general, porosity modifiers with larger particle sizes, greater hygroscopicity coefficients, smaller specific surface areas or higher solubilities caused a faster drug release.

The effect of porosity modifier particle size on K_o is related to the ability of the pores created after the dissolution of the solute particles to form percolating pore clusters or conducting channels. We assume that diffusion through the polymer particles was negligible and that the release of propranolol HCl occurred through media filled channels in the coat. The number and topology of such channels directly affect the rate of drug release from polymer matrices (Siegel and Langer, 1990) and the pore topology is influenced by the particle size (Desai et al., 1965).

To study the effect of pore topology further, three particle sizes each of calcium tartrate (CaT), mannitol and NaCl were studied at the 30% loading. The 30% loading was selected because it is close to the percolation threshold and would, therefore, accentuate the effect of particle size on K_o. The change in K_o with size was modest, unless a relatively large particle size was used. For example, increasing the NaCl particle size from 7 to 98 μm had a small impact on K_o (5.41 ± 0.735 mg h^{-1} compared to 4.40 ± 0.534 mg h^{-1}) (Table 2). The NaCl 256 μm particle size increased K_o approximately three fold to 15.90 ± 3.139 mg h^{-1}. Increasing the CaT and mannitol particle sizes, from 18 to 98 μm and 40 to 98 μm, resulted in equally small increases in K_o.

The effect of particle size on transmembrane transport is related to the formation of conducting channels across the membrane. In membranes with relatively large pores transmembrane diffusion may occur through clusters of only a few pores, well below the percolation threshold (Siegel, 1988). In other words, the larger the re-

sulting pores the smaller the number needed to form a conducting cluster. From our data, it is apparent that below 100 μm, particle size has a minor effect on K_o. Using a simple cubic lattice in a computer simulation, Siegel et al. (1989) studied the effect of solute particle size on the available solute fraction (ASF). They reported that, below the critical porosity, smaller particles had a smaller ASF. With smaller particles there are more layers per unit thickness. As the network of pores required to connect an interior particle becomes longer and less probable, that particle is less likely to be connected to the surface. Therefore, formation of a conducting channel is more probable with the NaCl 256 μm particle than with the 7 μm particle at equal loading.

There is a general increase in K_o with a decrease in porosity modifier specific surface area (SSA). To understand the inverse relationship between SSA and K_o, one must envision the pores generated after disssoution of the modifier particles. A porosity modifier with a smaller SSA would generate pores with smaller surface areas, on an equivalent weight basis. To account for the smaller surface area there would have to be fewer and larger pores. These larger pores could easier connect to form a conducting channel, which would explain the faster drug release.

There is a general decline in K_o with an increase in ρ_{abs}. An increase in ρ_{abs} means a decrease in the modifier volume based on equal weight. Hence, modifiers with a larger ρ_{abs} will generate pores with smaller volumes upon dissolution. This means that there will be fewer conducting channels available for the diffusing propranolol HCl and hence, the slower release with a larger ρ_{abs}.

A larger hygroscopicity coefficient (K_h) indicates a greater affinity for water, and presumably signify a faster dissolution of the modifier. The dissolution rate controls the rate of pore generation. At very low K_h values ($\leq 0.1\ h^{-1}$), K_o is independent of K_h. For example, the large differences in K_o between tablets containing CaT, mannitol and sucrose are not reflect in their K_h values. As K_h increases, it becomes a better predictor of K_o. Interestingly, the relationship between K_h and K_o mirrors that between K_h and C_s. Therefore, it can be argued that the effect of K_h on K_o is

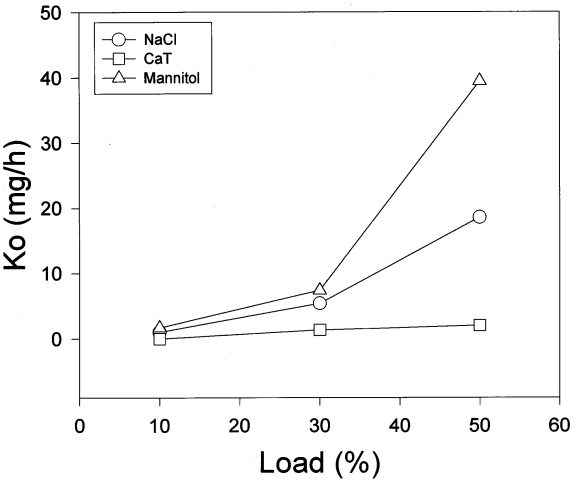

Fig. 3. Effect of mannitol, NaCl and calcium tartrate load on K_o.

artificial and that C_s is the controlling parameter. This is logical since K_o depends on the number of conducting channels rather than on the rate at which the channels are formed.

The modifier solubility determines the extent to which the modifier will dissolve in the medium. This controls the pore structure and, thereby, the rate of propranolol HCl release (K_o). There is an increase in K_o with an increase in solubility. The increase in solubility caused a larger fraction of the modifier to be released, creating more conducting channels. The dissolved solute may lower the local solubility of the drug in the pores (Zentner et al., 1991). The high concentration of dissolved solute also may have increased the viscosity of the fluid in the channels. Both factors could reduce drug diffusion in the channels below a theoretically calculated value.

3.3. Pore cluster size

Three loading levels each of CaT, mannitol, NaCl and sucrose were investigated to study the effect of cluster size on K_o. Fig. 3 shows the effect of loading on K_o. A small increase in K_o was seen at the 10% porosity modifier level compared to no porosity modifier. It was only at loading levels above 30% that the tremendous influence of the porosity modifier on K_o became apparent (Table 2).

The coat of the control tablet (containing no porosity modifiers) had a low porosity (0.231 ± 0.014). The probability of forming a conducting channel across this coat was low, which accounts for the slow release of propranolol HCl from the control tablet. Dissolution of porosity modifier particles created secondary pores, that expanded the pore cluster size and, thereby, increased K_o.

The effect of loading appears fairly straight forward; increasing the modifier load increased K_o by increasing the number of conducting channels. The degree of increase, however, was very small for CaT. We attribute this to the low solubility of CaT ($C_s = 0.030$ g ml^{-1}). A mass balance on the polymer shell after drug release, revealed that a very small fraction of the incorporated CaT had dissolved. The percent of the incorporated CaT released for the 10%, 30% and 50% CaT loadings was 18.8, 11.9 and 14.2%, respectively. Therefore, it is not surprising that the CaT load did not significantly increase K_o. This underscores the importance of the available solute fraction (ASF) rather than the modifier loading as the controlling factor.

To exemplify the relationship between ASF and K_o, NaCl ($C_s = 0.352$ g ml^{-1}) was used. A higher ASF produced a larger K_o (Fig. 4). At a low ASF, the mean cluster size was insufficient to form many conducting channels, which restricted K_o. As the ASF increased the number of conducting channels escalated, increasing K_o.

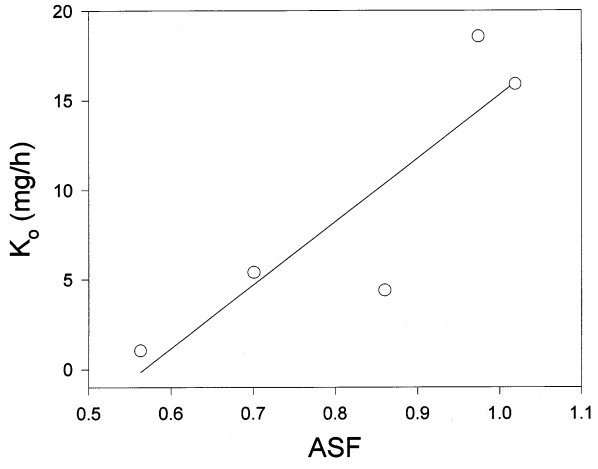

Fig. 4. Effect of available solute fraction (ASF) on K_o.

3.4. Mechanistic analysis

To fully understand how a porosity modifier influences the release rate constant (K_o), we investigated coats containing NaCl as the solute. The changes in the coat before, during and after NaCl dissolution are used to explain the effect on K_o.

A model for the three dimensional release of a solute from a polymer matrix was first developed by Fu et al. (1976). Solute release from a cylinder of radius a and thickness $2l$ follows Fick's second law:

$$\frac{\delta C}{\delta t} = D_e\left[\frac{\delta_2 C}{\delta r^2} + \frac{1}{r}\frac{\delta C}{\delta r} + \frac{\delta^2 C}{\delta^2 z}\right]$$

$$t = 0 \quad -l \le z \le l \quad C = C_o$$

$$0 \le r \le a$$

$$t > 0 \quad z = \pm l \quad C = C_s \tag{13}$$

where C_o is the initial NaCl concentration (g cm^{-3}) in the matrix; C_s is the concentration of NaCl at the exposed surfaces (g cm^{-3}); a is the radius of the disk (cm); and $2l$ is the thickness of the disk (cm). The solution to the diffusion equation with these initial and boundary conditions was obtained by Carslaw and Jaeger (1959). Fu et al. (1976) calculated the total mass transferred across all exposed surfaces and the fraction of solute released (F) at time t:

$$F = \frac{M_t}{M_\infty} = 1 - \frac{8}{l^2 a^2}\hat{X}(2)\,\psi(2) \tag{14}$$

$$\hat{X}(k) = \sum_{m=1}^{m=\infty} \exp(-D_e \alpha_m^2 t)\ (\alpha_m)^{-k} \tag{15}$$

where M_t (g) is the amount of NaCl released at time t; and M_∞ (g) is the amount of NaCl released at finite time.

$$\psi(k) = \sum_{n=o}^{n=\infty} \exp(-D_e \beta_n^2 t)\ (\beta_n)^{-k} \tag{16}$$

where D_e is the effective diffusion coefficient for NaCl. β was calculated as:

$$\beta_n \frac{(2n+1)\pi}{2l} \tag{17}$$

and α was calculated from the positive roots of the zero order bessel function, J_o; i.e. $J_o(a\alpha_n) = 0$.

Table 4
Characteristics of compression coated tablets containing NaCl

Size (μm)	7	7	7	98	256
Percent (%)	10	30	50	30	30
K_o (mg h^{-1})	1.038	5.407	18.560	4.403	15.900
De[a] (cm^2 h^{-1})	4.81×10^{-3}	4.68×10^{-3}	13.0×10^{-3}	4.93×10^{-3}	2.06×10^{-3}
ASF[b]	0.563	0.701	0.974	0.860	1.019
V^c_{coat} (cm^3)	0.314	0.290	0.265	0.288	0.279
$\varepsilon^d_{Initial}$	0.251	0.259	0.252	0.252	0.221
ε^e_{Final}	0.328	0.378	0.553	0.384	0.393
ε^f_{Peak}	0.297	0.416	0.526	0.391	0.320
SSA^g_i (m^2 g^{-1})	0.345	0.302	0.197	0.335	0.268
SSA^h_f (m^2 g^{-1})	0.368	0.413	0.348	0.402	0.355
SSA^i_d (m^2 g^{-1})	0.023	0.111	0.151	0.067	0.087

[a] Effective diffusion coefficient for NaCl.
[b] Available solute fraction
[c] Volume of the coat.
[d] Initial coat porosity.
[e] Final coat porosity.
[f] Porosity at peak release rate.
[g] Initial specific surface area.
[h] Final specific surface area.
[i] Difference in specific surface area.

Tukey's multiple means test ($\alpha = 0.05$) revealed no significant difference between the D_e at 10% and 30% NaCl loading, but there was a significant increase in D_e at the 50% NaCl loading. The D_e for NaCl release from these systems reflects the resistance encountered by the diffusing species. The resistance encountered is a function of the number of conducting channels available for diffusion and the tortuosity of those channels. NaCl loading affected the number of channels available for diffusion.

The effect of modifier particle size on pore structure was previously examined. Initially, there is no change in D_e with particle size, with subsequent increases in particle size resulting in a smaller D_e. A similar reduction in release rate with increased particle size was reported previously (Desai et al., 1965; Chandrasekaran and Paul, 1982; Foster and Parrott, 1990). Siegel (1988) proposed a pore structure inwhich solute release is through a central channel to which pores are connected by narrow ducts. Solute transfer from these deadend pores is slow (Balazs et al., 1985), resulting in a small D_e. Larger NaCl particles would be more affected by this phenomenon.

In general, D_e is inversely related to K_o, which may seem counter intuitive. The exception to this is the system containing 50% of 7 μm NaCl particles. A closer examination of the coat dynamics explains this apparent paradox. NaCl release depends on a network of interconnected NaCl particles regardless of the depth. Release of propranolol HCl, however, depends on the number of conducting channels across the coat. A shallow, limited pore cluster would result in a fast release of the accessible NaCl (large D_e), but a slow release of drug (small K_o). Conversely, a deep conducting pore cluster would result in a slow release of NaCl (small D_e), but a fast release of drug (large K_o). An example of the former is the coat containing 10% of 7 μm NaCl particles and of the latter is the coat containing 30% of 256 μm NaCl particles. At a 50% NaCl loading the pore cluster size (number of conducting channels) is so large that the release of NaCl and propranolol HCl are fast.

Addition of NaCl to the coating material modified the compression properties of the coating material. The apparent volume of the coat (V_{coat}) decreased with an increase in NaCl loading or particle size. This is reflected in the differences

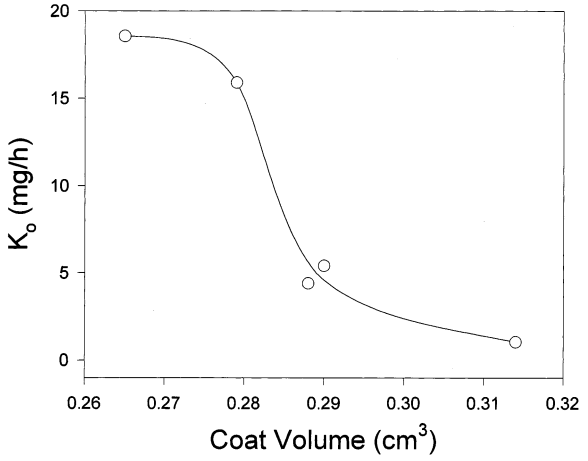

Fig. 5. Effect of porosity (ε_t) on release rate of propanolol HCl (at 30% loading of NaCl of 98 μm particle size).

in V_{coat} between the various formulations (Table 4). A smaller V_{coat} denotes a thinner coat, which promotes faster drug release (Fig. 5). A thinner coat means a shorter conducting channel that requires fewer open pores.

The initial porosity of the coat (ε_0) did not vary much with the NaCl loading, and only slightly with the particle size (Table 4). However, both the load and particle size of NaCl affected K_o (Table 2). We, therefore, conclude that the ε_o did not significantly affect K_o.

The final porosity (ε_{final}) is reached after release of the available solute fraction (ASF). A larger ε_{final} represented a greater number of channels available for the outward diffusion of propranolol HCl. Using a scaling law, Hastedt and Wright (1990) showed that the relative diffusivity of solutes in a compressed matrix increased with porosity. Fig. 6 depicts the relationship between ε_{final} and K_o. K_o increased slowly until ε_{final} reached a critical value ($\approx 38\%$), after which K_o increased very rapidly. Saltzman and Langer (1989), in their study of bovine serum albumin release from thin, solvent casted membranes, determined a percolation threshold of 33%. The ε_{final} increased significantly with the increase in NaCl loading, but only slightly with the increase in particle size (Table 4). The changes in ε_{final} explain the increase in K_o with NaCl loading, but not from tablets containing the 256 μm particles. The same arguments presented previously for the effect of size on K_o apply here.

To further study the interaction between porosity and the release rate, the instantaneous release rate for propranolol HCl (dM/dt) was correlated with the coat's porosity at time t (ε_t). ε_t was calculated using Eqs. (4)–(7). The release data was approximated adequately by a sigmoidal function. To calculate dM/dt, we differentiated the function with respect to time. Fig. 7 depicts a typical relationship between dM/dt and ε_t. Initially, dM/dt increases very slowly with an increase in ε_t. Close to the maximum porosity, dM/dt escalates rapidly to a maximum, after which dM/dt decreases sharply. In all cases, except for the 30% 256 μm (i.e. 30% loading of NaCl of 256 μm particle size), the maximum release rate occurs at a peak porosity, ε_{peak}. The ε_{peak} increases with increased NaCl load (Table 4). This suggests that pore generation progresses as a retreating boundary from the surface of the coat to the core as successive layers of NaCl particles dissolve. Appreciable drug release does not occur until this pore boundary reached the core tablet. As the NaCl particle size increased, ϵ_{peak} decreased (Table 4). This suggests that larger particles can form conducting channels at lower porosities, which we alluded to previously.

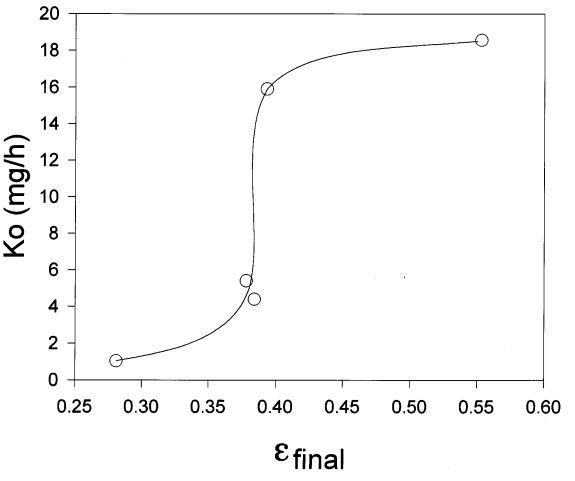

Fig. 6. Effect of final coat porosity (ε_{final}) on K_o.

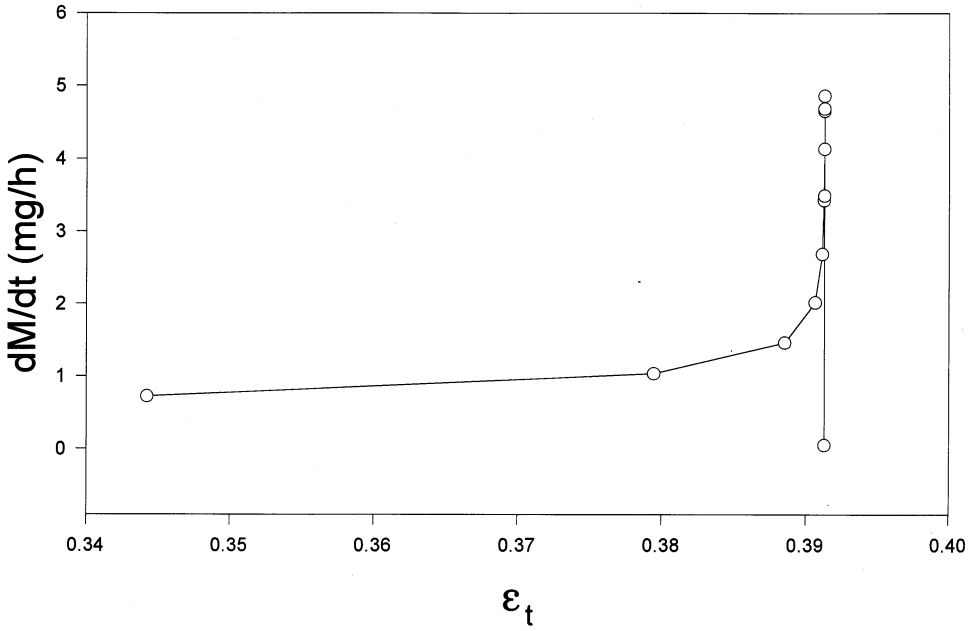

Fig. 7. Effect of coat volume (V_{coat}) on K_o.

The initial specific surface area (SSA_i) of the tablet refers to the void spaces present before dissolution of any NaCl. The SSA increased rapidly on dissolution of the incorporated NaCl, to reach a plateau in approximately 1.5 h (SSA_f, final specific surface area). The effect of including NaCl in the coat on SSA_i is derived from the effect on coat volume (V_{coat}). For example, an increase in NaCl loading causes a reduction in V_{coat}, which in turn decreases the SSA_i. Both SSA_i and SSA_f are inversly related to K_o. The same reasons proposed previously for the inverse relationship between V_{coat} and K_o would explain this inverse relationship. The difference between the specific surface areas ($SSA_d = SSA_f - SSA_i$) correlated well with K_o, with 30% 256 μm (i.e. 30% loading of NaCl of 256 μm particle size) being the exception. SSA_d quantifies the newly created space available for difffusion of propranolol HCl. The increase in K_o with SSA_d was small until SSA_d reached a critical value (approximately 0.1 $m^2\ g^{-1}$) above which K_o increased dramatically (Fig. 8).

4. Conclusion

To accurately control the rate of drug release from the proposed delivery system a suitable porosity modifier must be chosen, based on its physicochemical properties and incorporated at

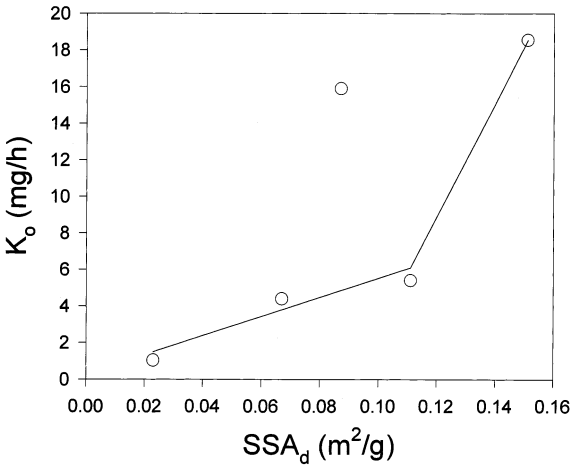

Fig. 8. Effect of increased coat specific surface area (SSA_d) on K_o.

the appropriate loading level. In general, a porosity modifier with a high hygroscopicity coefficient, a moderately high solubility, a low absolute density, a relatively large particle size and a low specific surface area will increase the drug release rate. Alternatively, one can specify the necessary coat characteristics after porosity modifier release that will yield the desired release rate. In general, if the coat provides for a large available solute fraction, a small coat volume, a large final porosity and a large increase in specific surface area, the rate of drug release will increase.

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