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Release of propranolol HCl from a tablet coated with a macroporous membrane

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Summary

The release of propranolol HCl from core tablets coated by compression with ethyl cellulose (EC) or cellulose acetate butyrate (CAB 381 or CAB 500) was studied. The release profile was typically sigmoidal, with a constant release segment. The zero-order release rate constant (K_0) for EC was 6.63 ± 0.45 mg/h compared to 1.98 ± 0.16 mg/h for CAB 381 and 2.56 ± 0.27 mg/h for CAB 500. The media transfer coefficient into the EC disks also was much faster ($64.50 \pm 4.94 \times 10^{-5}$ cm^2/h) than that for CAB 381 ($7.57 \pm 0.39 \times 10^{-5}$ cm^2/h) or CAB 500 ($8.09 \pm 1.31 \times 10^{-5}$ cm^2/h). The propranolol HCl dissolution rate constant at 25 rpm was not significantly affected by the pressure used to make the core tablet ($p = 0.712$). The decline in K_0 with increasing amounts of polymer used in the coat was accurately modelled by an exponential function ($r^2 = 0.971$). The extrapolated value for the intrinsic dissolution rate with no polymer coating (206.10 mg/cm^2 per h) was close to the determined intrinsic dissolution rate (210.47 mg/cm^2 per h). Increasing the compression pressure resulted in an initial decline in the normalized mass transfer coefficient, K_n, followed by an increase in K_n; the influence of pressure on K_n diminished with increasing polymer amount. Since K_n incorporates the reduction in coat thickness and the radial expansion of the core tablet (due to the applied pressure), the increase in K_n is probably due to microscopic stress fractures in the coat.

Introduction

Constant release of drug from a delivery system is desirable in many instances. Compression of a polymer powder around the core tablet is one way of applying a porous coat to control the release rate. Even though the process of preparing this delivery system is simple, the release rate has a complex relationship with many process parameters.

Several approaches exist in the literature to accomplish constant drug output (Fryklof et al., 1956; Lipper and Higuchi, 1977; Kuu and Yalkowski, 1985; Bechard and McCullen, 1988; Hansson et al., 1988). Frykolf et al. (1956) showed that by simply compressing a polymer powder on top of the two planar surfaces of a core tablet containing drug, a fairly constant drug release rate was obtained. In their method the core tablet consisted of polymer and drug. The duration of the constant output depended on the thickness of the coat, on the annular surface area left ex-

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posed, and on the amount of drug incorporated in the core tablet.

Mars (1974) extended this principle to completely cover a core tablet containing drug with a polymer. The release from these systems was biphasic, with a significant constant release segment. The constant release rate was inversely related to the amount of polymer used in the coat. Increasing the pressure used to apply the polymer coat resulted in an exponential decline of the release rate to a constant value. The pressure and the amount of polymer used were varied independently, so that their separate effects could be identified, but not their combined effect. The particle size distribution of the polymer powder had little influence on the release rate, unless a very coarse powder was used. With the coarser polymer powder a slight increase in the release rate was seen. The external fluid dynamics did not influence the rate of release under the conditions studied.

Conte et al. (1983, 1984) used a hydrophilic polymer which swelled in water to press coat a core tablet. They attributed the lag time seen to hydration of the coat. After the lag time a significant portion of the drug was delivered at constant rate. After depletion of the solid drug, the rate declined exponentially. Increasing the amount of polymer used resulted in slower release rates and longer lag times. They reported that the pressure used to apply the coat had no effect on the release rate. This is plausible since the rate controlling property of the polymer was swelling, which was not sensitive to pressure. The pressure and the amounts of polymer used were varied simultaneously, but their independent effects were not identified. They showed that the release rate depended on the solubility of the drug enclosed in the porous barrier, and that the pH inside the tablet was rate controlling not the external pH of the media. They also found that the hydrodynamic conditions did not affect the release rate.

Verhoeven et al. (1989) compressed a polymer-drug powder mixture into a matrix tablet, which was then 'dry-coated' with a layer of polymer-drug powder mixture. The layer contained less drug than did the core matrix tablet. The pH of the dissolution media influenced the release of oxprenolol HCl from their delivery system. They also showed that the release rate could be increased by adsorbing a hydrophilic molecule (sodium lauryl sulfate) on the surface of the polymer. The surfactant facilitated the penetration of the polymer coat by the dissolution media. The effects of the polymer amount and pressure were not studied.

Other investigators have shown that the flux across porous polymer barriers decreased with an increase in the thickness, an increase in the pressure used to make them, and a decrease in the mean particle size of the polymer powder (Giordano et al., 1985; Ritschel et al., 1990).

What is lacking is a study which investigates the combined effect of pressure and polymer amount on drug release. The purpose of this study was to investigate the interaction between the effects on release due to pressure and due to polymer amount used to coat propranolol HCl core tablets.

Materials and Methods

Materials

The following materials were used without further purification: propranolol HCl (a gift from Knoll AG); cellulose acetate butyrate 381-2 and cellulose acetate butyrate 500-1 (a gift from FMC Corp.); and ethyl cellulose 10 cps (Scientific Polymer Products).

Propranolol HCl solubility

1 g of propranolol HCl was placed in 5 ml test tubes and 3 ml of distilled water containing 0.02% v/v polyoxyethylene sorbitan monooleate were added. The test tubes were placed in a shaker bath at 37 ± 0.5°C for 1 week. The suspended solid was allowed to settle, and the supernatant was sampled and filtered. The first 1 ml of the filtrate was discarded. The drug concentration was determined spectrophotometrically at 290 nm after appropriate dilution. The concentrations were in the linear range (1–50 mg/ml; $r^2 = 0.9999$). The solubility of propranolol was 0.115 ± 0.024 g/ml.

Core tablet preparation

50 mg of propranolol HCl were compressed on a hydraulic press (Carver Press) at pressures ranging from 78.73 to 236.20 MPa using a 6 mm flat-faced punch and die set. The die wall and punch faces were lightly dusted with magnesium stearate before each compression. The tablets were stored for 12 h at room temperature before coating.

Intrinsic dissolution rate

Core tablets compressed at 78.73, 157.50, or 236.20 MPa were coated with 300 mg of CAB 500 at 31.5 MPa on the annular surface and on one planar face using a 12 mm flat-faced punch and die set. This limited the dissolution to a single tablet face and maintained a constant surface area. The coated core tablet was affixed to a metal substrate, with the exposed surface facing upwards, and placed at the bottom of a dissolution vessel containing 1000 ml of distilled water with 0.02% v/v polyoxyethylene sorbitan monooleate. The medium was maintained at 37 ± 0.5°C. To determine the effect of agitation, the dissolution rates of core tablets compressed at 78.73 MPa were determined at 15, 25, 35, and 50 rpm. To determined the effect of compression pressure, the dissolution rates at 25 rpm also were determined of tablets compressed at 157.50 or 236.20 MPa. Samples (4 ml) were taken at frequent intervals and analyzed spectrophotometrically at 290 nm. The volume withdrawn was replaced with fresh dissolution medium.

Coating of the core tablet

A weighed amount of polymer powder (50% by weight) was placed in a 12 mm die containing the lower flat faced punch. The core tablet was centered on top of this powder bed. The remaining amount of polymer powder (50% by weight) was placed in the die and compressed on the hydraulic press (Carver Press) at pressures ranging from 15.7 to 47.2 MPa.

Drug release studies

The coated tablets were placed in 1000 ml of distilled water, which contained 0.02% v/v polyoxyethylene sorbitan monooleate to improve wetting of the coat. The system was maintained at 37 ± 0.5°C and agitated at 100 rpm with a paddle. Samples (4 ml) were taken at specified intervals and, after completion of the experiment, analyzed spectrophotometrically at 290 nm for propranolol HCl. The volume withdrawn was replaced with fresh dissolution medium.

Dimensions

The diameter and the thickness of the core tablets were measured using a digital micrometer. The same measurements were made for the coated tablets before the drug release studies. After dissolution, the remaining empty polymer shells were carefully removed and air dried for 24 h. Since the thickness of the polymer coat on the annular surface was approx. 10-times that of the coat on the top and bottom of the core tablet, we presumed that very little, if any, release occurred through the annular surface. Therefore, the portion of the coat immediately over the core tablet was painstakingly removed and the thickness of these coats were measured with the micrometer. To estimate the dimensions of the core tablet after the second compression, the core tablet was coated on the annular surface and on one planar surface with 62.5, 75 or 125 mg of CAB 500 at the same pressures used to compress the coated tablet. After 24 h the core tablet was meticulously removed; care was taken not to damage the core tablet. The diameter and thickness of the core tablet were measured with the micrometer.

Compact porosity

To investigate the effect of amount of CAB 500 on the porosity of the disks, we compressed different amounts of CAB 500 (100–300 mg) at 31.5 MPa. The porosity of the disks were calculated by considering the mass-volume balance. The apparent densities of the disks were determined from the mass and the dimensions of the disks. The absolute density of CAB 500 was determined using a helium pycnometer. The porosity and thickness of these compacts are listed in Table 4.

Water penetration

The rate at which the dissolution media penetrated the disks was determined. To ensure suffi-

cient sensitivity, 1 g samples of the polymers were compressed at 31.5 MPa to yield disks 2.284 cm in diameter. After 24 h, the disks were weighed and submerged in a column of dissolution media 9.00 cm high. At preselected intervals the disks were carefully removed, reweighed and replaced. The increase in weight was recorded as the weight of water which had penetrated the disk. The height of the media column was maintained at the same level.

Statistical analysis

One-way and two-way analysis of variance was used to detect significant differences between treatment means using the Minitab statistical software. Tukey's procedure for multiple means comparison was used with $\alpha = 0.05$. A linear least-squares method was used to determine the release rate constant. A non-linear least-squares method was used to fit the effect of polymer amount on the release rate constant.

Results and Discussion

Release mechanism

Fig. 1 depicts a representative profile for the release of propranolol HCl from a core tablet coated with EC. The following mechanism is postulated for the release of propranolol HCl from this delivery system.

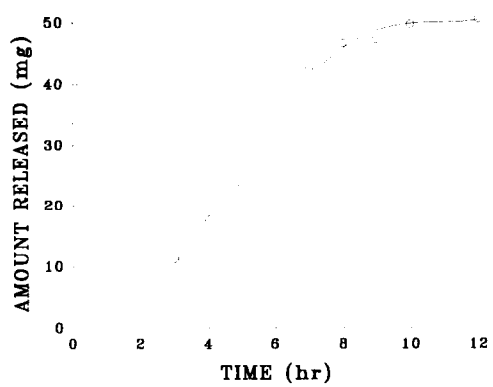

Fig. 1. A representative profile for the release of propranolol HCl from tablets coated with 150 mg of EC at 31.5 MPa.

When the coated propranolol HCl tablet was placed in the dissolution media, the media penetrated the coat. Mass transfer of the media through the polymer particles is assumed minimal, because of the thickness of the coat (300–700 μm). Therefore, penetration through the pore structure is considered the major pathway. We will assume media penetration through a simple capillary to provide a qualitative understanding of the process.

The media penetrated the pores by capillary pressure, which is the difference in pressure across the media-air interface (Moore, 1972). Since the dissolution media wetted the polymer, the pressure difference across the interface was a pressure drop compared to atmospheric pressure. According to the Laplace equation for an ideal capillary (Adamson, 1967), the capillary pressure depends on the contact angle between the media and the polymer surface, and the effective radius of the pore. The volumetric flow rate through an ideal capillary is governed by the Hagen-Poiseuille law (Chaterjee, 1985). The volume flux, which is analogous to the rate of penetration, varies with the pore radius and the capillary pressure.

When media reached the core tablet, a saturated solution was established. Propranolol HCl was then released through the media filled pores. Zentner et al. (1985) studied the release of KCl from tablets which were spray coated with a microporous cellulose acetate membrane. They concluded that the release of KCl was by Fickian diffusion (concentration gradient) and by osmotic pumping (pressure gradient).

The release of propranolol HCl across the compressed polymer membrane is described by Eqn 1:

$$\frac{dQ}{dt} = \frac{K_n \cdot A}{h}(C_i - C_o) \qquad (1)$$

where dQ/dt is the drug release rate (mg/h); K_n (cm^2/h) represents the mass transfer coefficient normalized for coat thickness and surface area, A is the effective surface area (cm^2), h denotes 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). Early on the release rate increased (see Fig. 1). As long as C_i was a saturated solution, maintained by the solid drug source, a constant release was observed. A zero-order rate, K_0, is defined as:

$$K_0 = \frac{K_n \cdot A}{h} \tag{2}$$

Once all the solid drug dissolved, the core solution concentration declined exponentially, resulting in an exponential decline of the drug release.

Water penetration

The absorption of water by the polymer disks was an unsteady state flow of liquid into the pore structure which is not uniformly saturated with the media. This unsteady state flow of liquid into a porous media is analogous to a mass transfer process due to a concentration gradient.

Consider a cylindrical slab with thickness $2L$ much smaller than the radius R. The one-dimensional flow of an incompressible liquid in the x-direction with an idealized constant mass transfer coefficient can be described by:

$$\frac{\delta S}{\delta t} = K_w \frac{\delta^2 S}{\delta x^2} \tag{3}$$

where S is the degree of saturation and K_w denotes the mass transfer coefficient for the liquid in the porous medium. If the disk is originally dry (at $t = 0$, $-L < x < L$, $S = S_0$), and both surfaces of the disk are in contact with the media and are kept 100% saturated (at $t > 0$, $x = \pm L$, $S = S_s$), the solution to Eqn 3 is (Crank, 1975):

$$\frac{S - S_0}{S_s - S_0} = 1 - \frac{4}{\pi} \sum_{n=0}^{n=\infty} \frac{(-1)^n}{2n+1} \times \exp\left(\frac{-K_w (2n+1)^2 \pi^2 t}{4L^2} \right) \times \cos\left(\frac{(2n+1)\pi x}{2L} \right) \tag{4}$$

TABLE 1

The polymer disk media mass transfer coefficients (K_w) and the release rate constants (K_0)

Polymer	K_w (cm^2/h) ($\times 10^{-5}$)	K_0 (mg/h)
EC	64.5 ±4.94	6.63±0.45
CAB 381	7.57±0.39	1.98±0.16
CAB 500	8.09±1.31	2.56±0.27

If M_t is the mass of media which was absorbed at time t and M_∞ is the mass of medium absorbed at infinite time, then the degree of saturation is:

$$S = \frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{n=\infty} \frac{8}{(2n+1)^2 \pi^2} \times \exp\left(\frac{-K_w (2n+1)^2 \pi^2 t}{4L^2} \right) \tag{5}$$

According to Eqn 5 eventually the entire disk will become saturated with the media (as t approaches infinity, S approaches 1).

The mass transfer coefficient for media penetration (K_w) was obtained by fitting the experimentally determined absorption data to Eqn 5 (see Table 1). 10 terms were used in the expansion of the series. The best fit was determined by minimizing the sum of squares residual between the experimental data and the values predicted from the expanded Eqn 5 at each time point. These comparisons are shown in Fig. 2. The K_w for CAB 381 ($7.57 \pm 0.39 \times 10^{-5}$ cm^2/h) and the K_w for CAB 500 ($8.09 \pm 1.31 \times 10^{-5}$ cm^2/h) were not significantly different from each other, but they were significantly different from the K_w for EC ($64.50 \pm 4.94 \times 10^{-5}$ cm^2/h) ($p \leq 0.001$). The sums of squares residuals normalized for the degree of saturation at time t were less than 0.144. This indicates that the absorption data were accurately described by Eqn 5. According to the mass transfer coefficient, the quickest media penetration occurred with EC, but the mass transfers of media into disks made from CAB 381 or CAB 500 were approximately the same. Of the three polymers EC is the least hydrophobic.

Intrinsic dissolution rate

The intrinsic dissolution rate, J, is defined as the mass flux per unit time per unit surface area (mg/h per cm^2), and follows the Noyes-Whitney equation (Carstensen, 1974):

$$J = \frac{dm}{dt}\frac{1}{A} = k_d(C_s - C) \quad (6)$$

where dm/dt is the mass dissolved per unit time (mg/h), k_d denotes the dissolution rate constant (cm/h), A is the surface area available for dissolution (cm^2), C_s represents the solubility of the drug (mg/cm^3), and C is the concentration of the drug in the bulk solution at time t (mg/cm^3). When $C_s \ggg C$,

$$J = \frac{dm}{dt}\frac{1}{A} = k_d C_s \quad (7)$$

The dissolution of up to 60% of the core tablet was linear with time ($r^2 = 0.999$). The slopes of the lines, determined using least-squares regression, were used to calculate the dissolution rate constants at 15, 25, 35, and 50 rpm. A plot of rpm vs k_d yielded a straight line ($r^2 = 0.998$) (see Fig 3). The y-intercept of that line yields a k_d of 1.83 cm/h. This corresponds to a dissolution rate with no agitation, J_0, of 210.47 mg/h per cm^2. Within the pressure range studied (78.73–236.20 MPa), the pressure used to compress the core tablet had no significant effect on k_d (see Table 2) ($p = 0.712$). This rapid dissolution rate indicates that a saturated solution was established very quickly once water penetrated the coat. Therefore, dissolution can not be considered as a rate-limiting step.

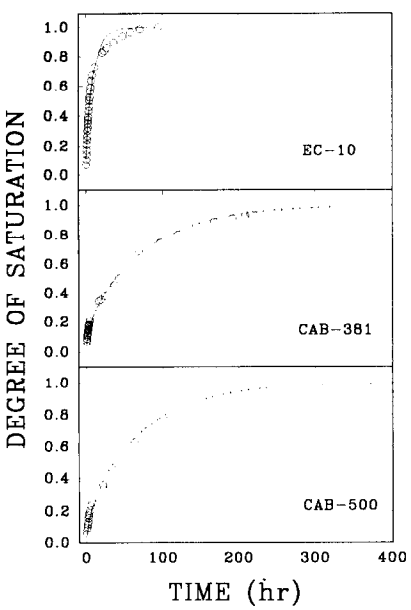

Fig. 2. Media saturation of polymer disks compressed at 31.5 MPa (the maximum S.D. was 0.494×10^{-4}). (○) Experimental data; (–) fit to Eqn 5.

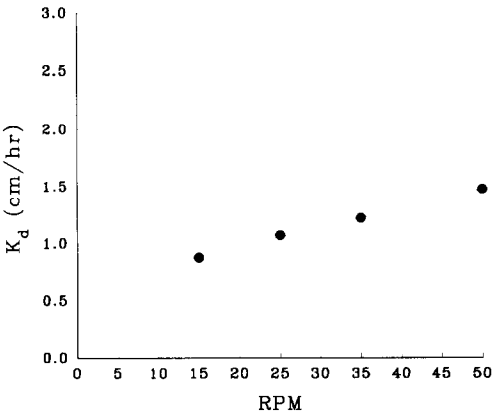

Fig. 3. Effect of media agitation (rpm) on the dissolution rate constant (K_d) from core tablets compressed at 78.73 MPa. (the maximum S.D. was 0.357).

Polymer type

The release of propranolol HCl from core tablets coated with EC CAB 381, or CAB 500 is depicted in Fig. 4. The release rate constants (K_0) for these formulations were calculated from the slopes of the linear segments (see Table 3). The K_0 were significantly different ($p < 0.001$).

TABLE 2

The effect of core compression pressure on the dissolution rate constant (K_d) at 25 rpm

Pressure (MPa)	K_d (cm/h)
78	2.26 ± 0.399
157	2.17 ± 0.433
236	1.99 ± 0.339

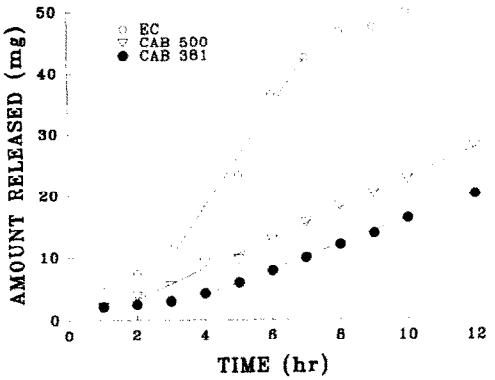

Fig. 4. Effect of polymer type on the amount of propranolol HCl released from core tablets coated with 150 mg of polymer at 31.5 MPa (the maximum S.D. was 0.517).

The polymers have different compression properties (Shivanand and Sprockel, 1992). Particle rearrangement and deformation under pressure affect not only the total compact porosity, but also the pore size distribution. The total porosity only indicates the total void space present; of greater importance to drug release are the number of pores contiguous with both surfaces of the membrane.

Core compression pressure

The effect of core compression pressure on the release rate of propranolol HCl from CAB 500 coated tablets was significant ($p = 0.017$) and is depicted in Fig. 5. Further statistical analysis on K_0 using Tukey's procedure revealed that significant differences existed only between 78.73, 125.90, and 236.20 MPa. When the 78.73 MPa data point was deleted from consideration, no significant differences were detected between the remaining four pressures ($p = 0.368$). Therefore, below 125.90 MPa the pressure used to make the

TABLE 3

The release rate constants (K_0) and the normalized mass transfer coefficients (K_n) for the various coated tablets

Polymer	Coat Amount (mg)	Coat Pressure (MPa)	Core Pressure (MPa)	K_0 (mg/h)	K_n (cm^2/h) ($\times 10^{-3}$)
EC	150	31.50	78.73	6.63 ± 0.45	–
CAB 381	150	31.50	78.73	1.98 ± 0.16	–
CAB 500	150	31.50	78.73	2.56 ± 0.27	–
CAB 500	100	31.50	78.73	8.08 ± 0.20	–
CAB 500	125	15.74	78.73	17.84 ± 8.79	9.82
CAB 500	125	23.61	78.73	4.71 ± 0.39	1.56
CAB 500	125	31.50	78.73	3.82 ± 0.28	1.37
CAB 500	125	39.35	78.73	10.48 ± 3.16	2.79
CAB 500	125	47.21	78.73	9.62 ± 1.57	2.63
CAB 500	150	15.74	78.73	5.77 ± 1.21	3.17
CAB 500	150	23.61	78.73	3.30 ± 0.65	1.49
CAB 500	150	31.50	78.73	2.56 ± 0.27	1.05
CAB 500	150	39.35	78.73	10.26 ± 1.85	3.39
CAB 500	150	47.21	78.73	9.45 ± 4.23	3.21
CAB 500	200	15.74	78.73	3.03 ± 0.12	2.98
CAB 500	200	23.61	78.73	1.93 ± 0.13	1.56
CAB 500	200	31.50	78.73	1.82 ± 0.38	1.36
CAB 500	200	39.35	78.73	3.03 ± 0.14	2.23
CAB 500	200	47.21	78.73	3.89 ± 0.79	2.30
CAB 500	300	31.50	78.73	0.01 ± 0.01	–
CAB 500	150	31.50	78.73	2.56 ± 0.27	–
CAB 500	150	31.50	125.90	3.48 ± 0.13	–
CAB 500	150	31.50	157.50	3.71 ± 0.44	–
CAB 500	150	31.50	188.90	3.59 ± 0.36	–
CAB 500	150	31.50	236.20	3.16 ± 0.65	–

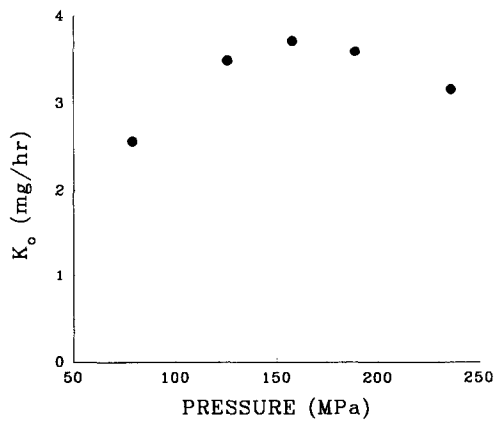

Fig. 5. Effect of core compression pressure on the release rate constant (K_0) from core tablets coated with 150 mg of CAB 500 at 31.5 MPa. (the maximum S.D. was 0.747).

core tablet had a significant impact on the release of propranolol HCl from the delivery system.

Polymer amount

The effect of polymer amount used in the coat on K_0 is depicted in Fig. 6. K_0 declines exponentially with an increase in the amount of polymer used. This decline is empirically described by Eqn 8 ($r^2 = 0.971$):

$$K_0 = j_0 A e^{-(R \cdot M)} \quad (8)$$

where R is a material dependent constant and M is the mass of polymer used. The intrinsic dissolution rate (j_0) calculated from the intercept of Eqn 8 was 206.10 mg/h per cm^2, which is comparable to the intrinsic dissolution rate determined earlier (210.47 mg/h per cm^2). The calculated R value was 203.0 g^{-1}. This profile is different from that reported by Mars et al. (1974) and Conte et al. (1983, 1984). Their data showed an approximately linear dependence of K_0 on the amount of polymer used. However, K_0 only decreased by one half in their studies, but in this study K_0 decreased 8-fold.

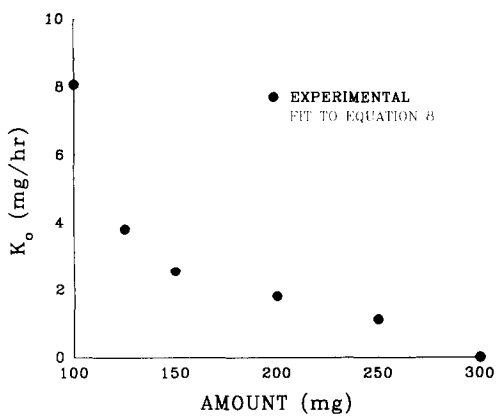

Fig. 6. Effect of amount of CAB 500 used in coating the core tablets at 31.5 MPa on the release rate constant (K_0). (the maximum S.D. was 0.534).

TABLE 4

Characteristics of polymer disks compressed at 31.5 MPa

Polymer	Amount (mg)	Porosity (%)	Thickness (mm)
CAB 500	100	22.2 ± 0.9	0.93 ± 0.02
CAB 500	125	21.9 ± 0.5	1.13 ± 0.01
CAB 500	150	21.1 ± 0.9	1.36 ± 0.02
CAB 500	200	21.0 ± 0.7	1.81 ± 0.02
CAB 500	300	21.4 ± 1.1	2.73 ± 0.03

The decline in K_0 may be attributed to changes in the pore network. The porosities of the CAB 500 compacts of increasing weights were similar, but their thicknesses increased (see Table 4). Presumably this is what occurred in the polymer coat. The increased coat thickness increased the pathlength for mass transfer, effectively retarding the release of propranolol HCl. It is also probable that the increased coat thickness reduced the number of pores contiguous with the core and the outside. This diminished the effective surface area available for mass transfer, and thus decreased the release rate.

Compression pressure and polymer amount

Fig. 7 shows the effects of compression pressure used to apply the coat and of the amount of polymer in the coat on K_0. As expected, K_0 declined initially as compression pressure increased. However, K_0 increased unexpectedly at all three coating levels as the compression pressure increased from 31.5 to 47.21 MPa. As seen from Fig. 7, changes in K_0 with compression pressure were more dramatic for tablets containing smaller amounts of polymer. We hypothesize that the net effect of compression pressure on K_0

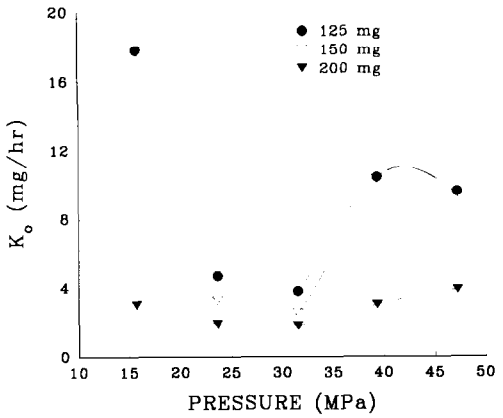

Fig. 7. Effect of the compression pressure used to apply the CAB 500 coat on the release rate constant (K_0). (the maximum S.D. was 1.185).

is due to two opposing forces: the reduction in coat porosity leading to a decline in the coat's permeability and an increase in the core tablet's planar area causing an increased mass transfer. Depending on the applied compression pressure, one of these forces will predominate.

The initial decline in K_0 is attributed to the expected decrease in the coat's permeability with increased compression pressure. The applied compression pressure caused the thickness of the coat to decrease (see Table 5), resulting in a decrease in the porosity of the coat. This increased the resistance to mass transfer and, therefore, decreased K_0.

The increase in K_0 at compression pressures ranging from 31.5 to 47.21 MPa may be due to dimensional changes in the core tablet or to microscopic stress fractures in the coat. The compression pressure used to apply the coat deformed the core tablet, causing the core planar surface area to increase (see Fig. 8). This increased the area available for mass transfer, which would have increased K_0.

In analyzing the interaction between the compression pressure effect and the polymer amount effect, it is important to consider the interplay between two dimensional changes. The two dimensional changes are the decreased coat thickness and the increased core planar area. The contributions of the dimensional changes to K_0

TABLE 5

Thickness of the CAB 500 coat above the core tablet

Amount (mg)	Pressure (MPa)	Thickness (mm)
100	31.50	0.317 ± 0.060
125	15.74	0.393 ± 0.033
125	23.61	0.303 ± 0.033
125	31.50	0.345 ± 0.019
125	39.35	0.287 ± 0.020
125	47.21	0.301 ± 0.044
150	15.74	0.462 ± 0.053
150	23.61	0.423 ± 0.033
150	31.50	0.398 ± 0.037
150	39.35	0.335 ± 0.025
150	47.21	0.361 ± 0.030
200	15.74	0.704 ± 0.049
200	23.61	0.612 ± 0.072
200	31.50	0.587 ± 0.053
200	39.35	0.600 ± 0.045
200	47.21	0.523 ± 0.034
300	31.50	1.005 ± 0.078

were accounted for by calculating K_n. Assuming that the concentration gradient ($C_i - C_o$) was approximately equal to C_i, K_0 comprised K_n, A, and h (see Eqn 2). The measured dimensions and the drug's solubility were used to calculate K_n. A comparison of Figs 7 and 9 indicates that the dimensional changes after compression account for some of the pressure effects, but not all. Therefore, the presence of stress fractures is probable.

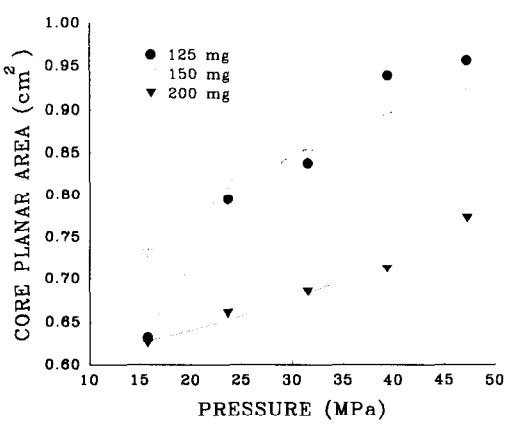

Fig. 8. Effect of the compression pressure on the core planar area of systems coated with CAB 500. (the maximum S.D. was 0.108).

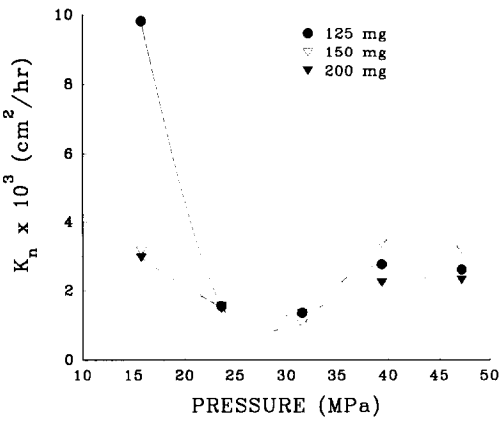

Fig. 9. Effect of the compression pressure on the normalized mass transfer coefficient (K_n) through a CAB 500 coat. (the maximum S.D. was 0.108).

The deformation of the core tablet during compression coating included elastic deformation. The elastic recovery of the core tablet following decompression could have produced microscopic stress fractures in the coat. These fractures would have increased K_0 beyond what was expected based on dimensional changes in the core tablet. Support for this theory comes from the fact that with 200 mg of polymer, K_0 is fairly constant with pressure. The core tablet deformed less and expanded less on decompression. Presumably, there were fewer fracture with the 200 mg coat than with the smaller amounts of polymer.

Conclusion

The release of propranolol HCl from tablets compressed with these polymer was constant after a lag time. An increase in the pressure used during coating caused an initial decrease in the release rate constant (K_0) followed by an increase in K_0. The initial decline in K_0 with pressure was explained by the reduction in the coat's permeability due to a decrease in porosity. The unexpected increase in K_0 with pressure was accounted for, in part, by the radial expansion of the core tablet after compression, which created a larger surface area available for mass transfer. The increase in K_0 not accounted for by the dimensional change, is ascribed to microscopic stress fractures caused by post-compression elastic recovery of the core tablet.

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