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FACTORS AFFECTING THE RELEASE OF PROPRANOLOL HYDROCHLORIDE FROM BEADS COATED WITH AQUEOUS POLYMERIC DISPERSIONS

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ABSTRACT

The main objective of this study was to investigate the release kinetics and mechanism involved in the transport of an ionizable drug through polymeric films applied to drug-loaded beads. The influence of factors such as drug loading and membrane thickness on release kinetics were also investigated. Beads containing propranolol hydrochloride were coated with either of two commercially available aqueous polymeric dispersions, Aquacoat® or Surelease®, using the Wurster-Process. Analysis of the drug release data suggest that the drug release followed zero-order release kinetics. The plots of drug release constants versus the reciprocal of membrane thickness were found to be linear for both polymeric dispersions. Increasing the osmotic pressure of the dissolution medium was found to decrease the mass of drug released at any given time for both Aquacoat® and Surelease® coated beads. Hence, drug release from these spherical membrane reservoir systems appeared to be diffusion controlled accompanied by osmotic effects. Thickness-corrected, zero-order release rate constants were found to be independent of the drug loading only for the Surelease® coated beads. Scanning electron micrographs (SEM) and examination of drug solubility in urea solutions, were used to confirm and further elucidate the mechanism of drug release. Finally, the effect of storage of coated beads at room temperature on drug release rate was also investigated.

INTRODUCTION

The earliest work in the area of sustained drug delivery dosage forms can be traced back to a patent issued to Lipowski (1). This work involved coated pellets of drug and was presumably responsible for the development of the SKF - Spansule that was introduced in the early 1950's.

Formulation methods to obtain the desired drug release rate from sustained action dosage forms have been described in the literature (2). As a result of the desire to maximize reproducibility and minimize the risk of dose-dumping, the use of pellets in the development of reservoir-type modified release products has predominated (3). Various methods of producing sustained release products from coated small particles have been reported in the literature (4). Until recently, only polymer/organic solvent coating systems were available. The successful introduction of a wide variety of aqueous based polymeric dispersions has stimulated a great deal of research and has, consequently, resulted in the reformulation of many existing products. These aqueous dispersions which eliminate problems associated with the use of solvent-based systems include: Aquacoat® and Surelease®, each consisting of ethylcellulose as the film coating polymer and Eudragit NE 30D, RL 30D, RS 30D, consisting of copolymers of ethyl acrylate-methyl methacrylate esters.

Aquacoat® a 30% w/w, dispersion is prepared by direct emulsification-solvent evaporation method and contains sodium lauryl sulfate and cetyl alcohol as stabilizers. Surelease®, on the other hand, is a 25% w/w, dispersion prepared by a phase inversion in-situ emulsification technique containing ammonium oleate as stabilizer and dibutyl sebacate as plasticizer (5).

The main objective of this study was to investigate the release kinetics and mechanism involved in the transport of an ionizable drug through polymeric films applied to drug-loaded beads, using Aquacoat® and Surelease®, as the aqueous coating dispersions and propranolol hydrochloride as a water soluble model drug. The influence of formulation factors such as drug loading and membrane thickness on release kinetics were also studied. Additionally, the effect of aging of the polymer coated beads on drug release rate was also investigated.

MATERIALS AND METHODS

Preparation of Coated Beads

Propranolol hydrochloride (Cosma S.p.A. Italy) was applied to Nu-Pareils®, 18/20 mesh (Ingredient Technology Corp., Pennsauken, NJ) using the Wurster-Process (Uni-Glatt Laboratory Unit, Glatt Air Techniques, Inc., Ramsey, NJ) as previously described (4).

Effect of Polymeric Dispersions

In this study, the performance of Aquacoat® (FMC Corporation, Philadelphia, PA) and Surelease® (Colorcon, West Point, PA), as aqueous controlled-release film-coating materials was compared. Once the appropriate quantities of the coating materials were applied, the dried 16 mesh fraction of the drug coated beads were used for the release study. The coating equipment and conditions have been reported in an earlier study (4) and are summarized in Table 1. Size determinations of the coated beads were done by sieve analysis as described by Parrott (6).

Effect of Membrane Thickness

Aquacoat® (used undiluted) was mixed with dibutyl sebacate (DBS) (Union Camp Corp., Jacksonville, FL), a plasticizer that has been recommended for this coating system, for 30 minutes using a propeller-type mixer. The level of DBS used was 24% w/w based on the Aquacoat® solids content. This plasticized coating dispersion was applied at levels of 5, 6, and 7% of the drug bead weight.

Surelease®, which comes ready-plasticized (with DBS), on the other hand, was used as received. The coating levels used were 6, 8, and 10% of the drug bead weight. An overcoat of Opadry® YS-1-7006 (Colorcon, West Point, PA), 10% w/w in distilled water was applied to prevent "blocking" (beads loosely adhering to one another) following the coating process. The quantity of overcoat used was 1% (by wt.) for all Surelease® batches.

In the case of Aquacoat®, the coating process was concluded by gently fluidizing the final coated beads for an hour at 50-60°C to ensure complete coalescence of the film (7). However, for beads coated with Surelease® no such fluidizing was required (8).

Release Study

Drug release was determined by using beads containing the equivalent of 40, 60 or 80 mg of propranolol hydrochloride respectively. In all studies, the USP dissolution apparatus 1 (basket) (Hanson Research Co., Northridge, CA) was employed using 900 ml of distilled water (37 ± 0.5°C) with an agitation speed of 100 rpm. Samples were collected at suitable time intervals, filtered through a Millex®-HA 0.45 μm filter (Millipore Corp., Bedford, MA) and assayed spectrophotometrically (Bausch & Lomb, Rochester, NY) at 289 nm for the drug content. At the conclusion of each release study, the beads were removed, ground and assayed to determine the residual drug content. The cumulative mass of drug released was computed at any time (t). The total amount of drug present in the beads was calculated as the sum of the cumulative mass of drug released at the last sample and the mass of drug remaining (residue) in the beads.

Drug Release Mechanism/Kinetics

The experimentally obtained values of the mass of drug released against time for different formulations and in various dissolution media, were fitted by a

TABLE 1

COATING EQUIPMENT AND PROCESS CONDITIONS

Drug-Coating Formulation		
Propranolol hydrochloride, USP		4.00% w/v
Hydroxypropyl methylcellulose, NF[a]		0.05% w/v
Polyethylene glycol 3350, NF		0.05% w/v
Alcohol (95%), USP 60)		
)→		to 100 mL
Distilled water, USP 40)		
Process Conditions		
Spray Process	-	6" Wurster
Partition	-	3/8"
Atomizing Air Pressure	-	1 bar
Inlet Air Temperature	-	55°C (50-60°C set-point)
Exhaust Air Temperature	-	38-42°C
Fluidizing Air Volume	-	25 cfm
Material Charge	-	1.0 Kg

a a 50:50 mixture of Methocel® E5 Premium and Methocel® E15 LV Premium

multiple linear regression program following the necessary mathematical transformation for each factor investigated (LOTUS® 123). The goodness of fit and the best estimate of slope and intercept for the plots were obtained.

Very often diffusion through porous membranes is accompanied by osmotic effects (9, 10). To investigate if such is the case and further elucidate the mechanism involved in the solute transport, drug release was also determined in 4, 8, and 12 molal urea (Ruger Chemical Co.,Irvington, NJ) solutions.

Effect of Drug Loading

The influence of drug loading was studied by preparing separate batches, each containing 8, 12, and 16% drug dry weight per 500 mg of the core (equivalent to 40, 60, and 80 mg, respectively, of propranolol hydrochloride). The amount of fixing agent (HPMC) and plasticizer, however, remained unchanged at 2 and 0.2% dry weight, respectively. The levels of Aquacoat® and Surelease® were 6 and 8%, respectively.

Equilibrium Solubilities

Equilibrium solubility determinations were made at 37±0.5°C in the urea solutions (4,8,12 molal) and in distilled water. In each determination, the tubes were rotated using a rotating bottle apparatus (Ernest D. Menold Co., Lester,PA). Samples were collected, diluted, filtered through a 0.45 μm filter and assayed at appropriate time intervals until identical concentrations were obtained for two consecutive determinations.

RESULTS AND DISCUSSIONS

Total Assay

Processing efficiency with respect to application of the drug-fixative formulations can be examined by determining the drug content uniformity and coating efficiency. The results of these evaluations in the present study are presented in Table 2. The small individual variation from the mean values for the drug content indicates that the drug distribution was uniform. Similar results were reported in an earlier study (4).

Drug Release Mechanism/Kinetics

DIFFUSION

The release of drug from a spherical membrane reservoir system, Figure 1, (11), based on Fick's Law, is given by

$$m_t = \frac{4\Pi DK\Delta C}{l} * t \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

where,

m_t = amount of drug released at time t

ΔC = difference in concentration between the solutions on either side of the membrane

K = partition coefficient of drug between the membrane and core

D = diffusion coefficient of drug in membrane

$l = \frac{(r_0 - r_1)}{(r_0 r_1)}$

Π = constant

Plots of mass of drug released (mg) versus time are shown in Figures 2-5. The release rate constants were calculated from a linear regression ($r^2 > 0.98$) fit of all points in the zero-order region. Accordingly, zero-order drug release was maintained up to about 70-80% of drug release, after which the release rate declined. Presumably, the decline in release rate was due to the decrease in the drug concentration in the cores below the saturation level resulting in a loss of the constant release rate.

TABLE 2

SUMMARY OF TOTAL ASSAY RESULTS

BATCH #	DRUG LOADING (mg)	TOTAL ASSAY[a,b] (mg)	RSD (%)	COATING EFFICIENCY[c] (%)
A	40	21.015 ± 0.029	0.138	86.69
B	40	21.579 ± 0.092	0.426	95.45
C	60	31.779 ± 0.204	0.642	98.43
D	80	40.219 ± 0.413	1.030	96.53

a mean ± SD of 3 determinations
b amount present in 300 mg of coated beads
c calculated on the basis of amount used

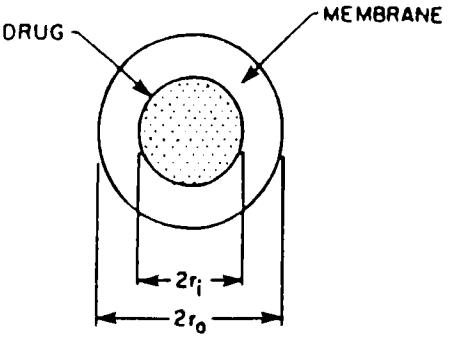

FIGURE 1

GEOMETRY OF A RESERVOIR DEVICE

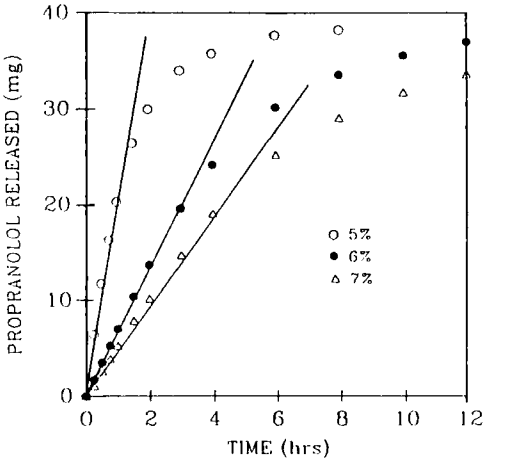

FIGURE 2

EFFECT OF MEMBRANE THICKNESS
AQUACOAT

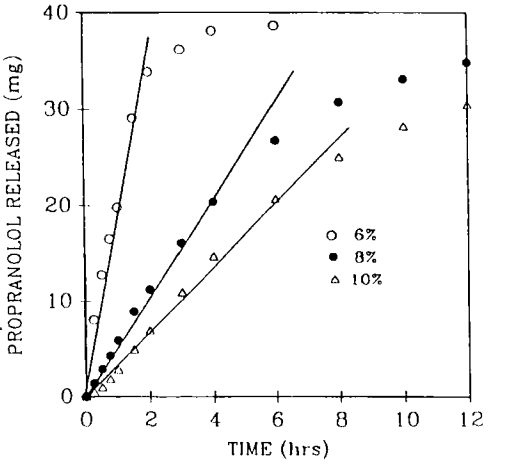

FIGURE 3

EFFECT OF MEMBRANE THICKNESS
SURELEASE

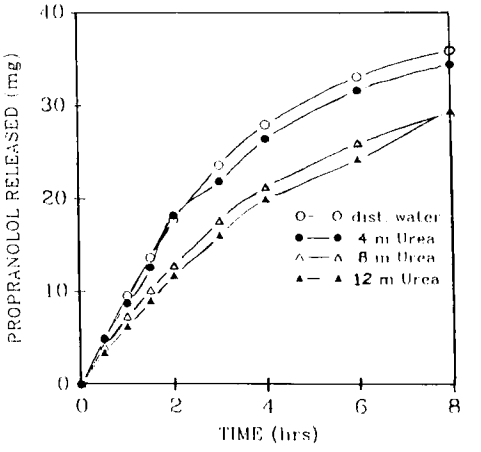

FIGURE 4

EFFECT OF OSMOTIC PRESSURE
AQUACOAT 6%

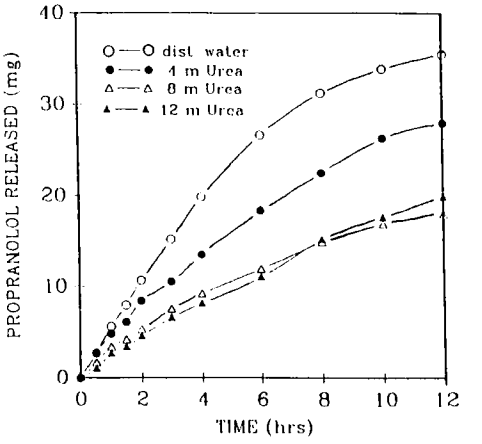

FIGURE 5

EFFECT OF OSMOTIC PRESSURE
SURELEASE 8%

OSMOTIC PRESSURE

The release rate from an osmotic pump is given by Theeuwes (12),

$$m_t = \frac{AL_p\sigma S\Delta\pi}{l} * t \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

where,

m_t = amount of drug released at time t
A = membrane area
L_p = mechanical permeability
σ = reflection coefficient
S = solubility of the core mass
$\Delta\pi$ = osmotic pressure difference between the osmotic salt in the core and the external solution $\pi_c - \pi_e$
l = membrane thickness

The release of propranolol hydrochloride from coated beads was also studied at 37°C in media differing in osmotic pressure. The computation of osmotic pressure was performed by using equations discussed by Zentner et al. (13). Plots of drug released versus time in various urea solutions are shown in Figures 4 and 5. The release rates decreased as the osmotic pressures of the dissolution fluid increased. No drug was released from these coated beads as the osmotic pressure developed in the dissolution media was equal to or greater than the one in the core, i.e. $\pi_c - \pi_e < 0$.

The osmotic pressure may be due to the core, i.e. from the drug itself and excipients i.e. sugar spheres. This in addition to the solubility of the drug, may be a drug release rate regulating factor. Measurements of propranolol hydrochloride solubility in various urea solutions indicated an increase in solubility with an increase in osmotic pressure of the urea solutions (Table 3). This may be due to urea acting as a complexing agent increasing the solubility of propranolol hydrochloride (14).

Furthermore, the release rates were plotted against the osmotic pressure difference (Figure 6), a linear dependence was found. The positive ordinate indicates a contribution of the other release due to diffusion. Therefore, it is concluded that the transfer of drug not only takes place by a classical diffusion process but was also modulated by osmotic pressure. Similar approaches to confirm osmotic release have been reported in the literature (9,13,15).

Effect of Membrane Thickness

Figures 2 and 3 illustrate the drug released versus time plots for Aquacoat® and Surelease®, respectively. Figure 7 shows SEM's for beads coated at various coating levels for the polymeric dispersions. As anticipated, the release rate decreased with an increase in membrane thickness for both coating dispersions as predicted by equation 1.

TABLE 3

EQUILIBRIUM SOLUBILITIES OF PROPRANOLOL HYDROCHLORIDE AT 37°C IN VARIOUS UREA SOLUTIONS

DISSOLUTION FLUID	SOLUBILITY (mg/mL)[a]	π_e (atm)[b]	$\Delta\pi^c$ $\pi_c - \pi_e$
Dist. water	251.523 ± 1.278	0	191.38
4 m Urea	307.223 ± 5.346	77.37	114.01
8 m Urea	332.050 ± 13.778	128.24	63.14
12 m Urea	354.877 ± 4.219	161.15	30.23

a mean ± SD of 3 determinations
b calculated using $\pi^{ideal} = \pi\ \phi$
π^{ideal} = CRT and ϕ = molal osmotic coefficient
c π_c = 191.38 (see appendix)

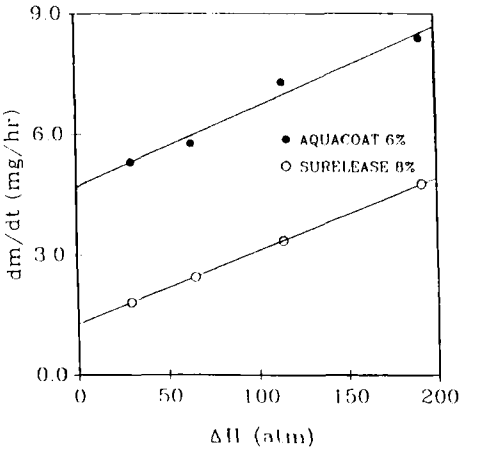

FIGURE 6

EFFECT OF OSMOTIC PRESSURE

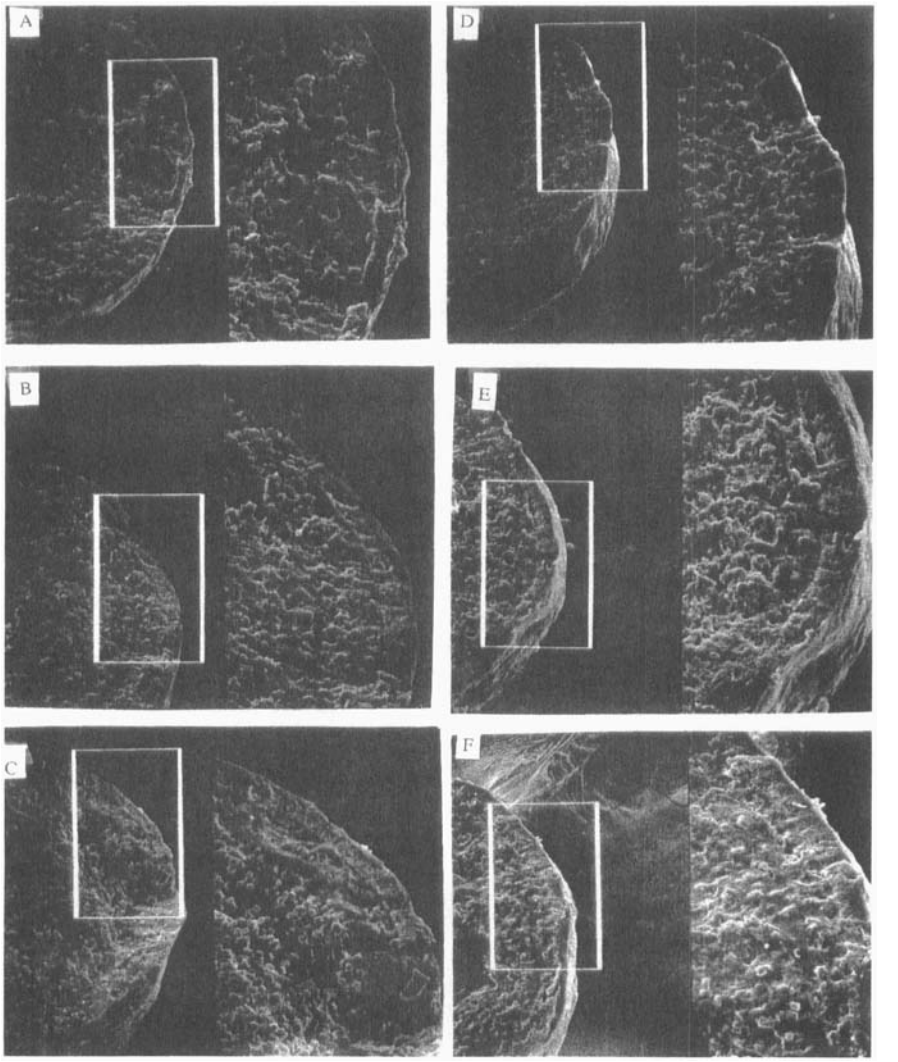

FIGURE 7

SCANNING ELECTRON MICROGRAPHS AT VARIOUS COATING LEVELS

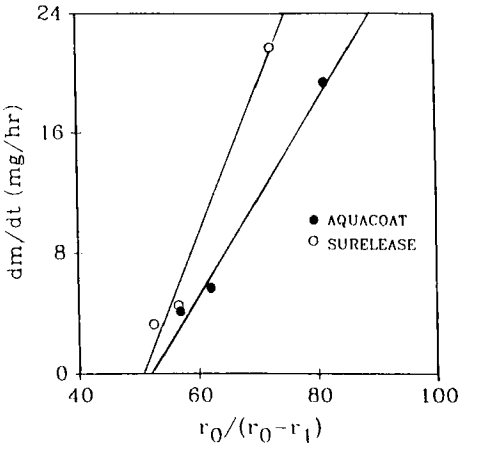

FIGURE 8

EFFECT OF MEMBRANE THICKNESS

If r_1 (radius of drug coated bead) is a constant, then equation 1 becomes

$$\frac{dm_t}{dt} = K_1 \frac{r_0}{(r_0-r_1)} \quad \text{.....(3)}$$

where, $K_1 = 4\Pi DK_A Cr_1$

Equation 3 indicates the release rate should be inversely proportional to $(r_0-r_1)/r_0$ or directly proportional to $r_0/(r_0-r_1)$. In this study, the relationship between the release rate constant and the reciprocal of the membrane thickness was also found to be in agreement with equation 2. Figure 8 shows the plot of this relationship for both the polymeric dispersions studied. Similar results have been reported by Steuernagel (16).

Effect of Drug Loading

Figures 9 and 10 show SEM's for beads coated at various drug loading levels for Aquacoat® and Surelease® respectively. According to equation 1, the release rate should be independent of drug loading if the ratio of r_0/r_1 is accounted for. Figure 11 illustrates the plot of dm_t'/dt versus drug loading.

$$\frac{dm_t'}{dt} = \frac{dm_t}{dt} * \frac{r_0 r_1}{(r_0-r_1)} \quad \text{.....(4)}$$

where, $\frac{dm_t'}{dt}$ = normalized rate constant

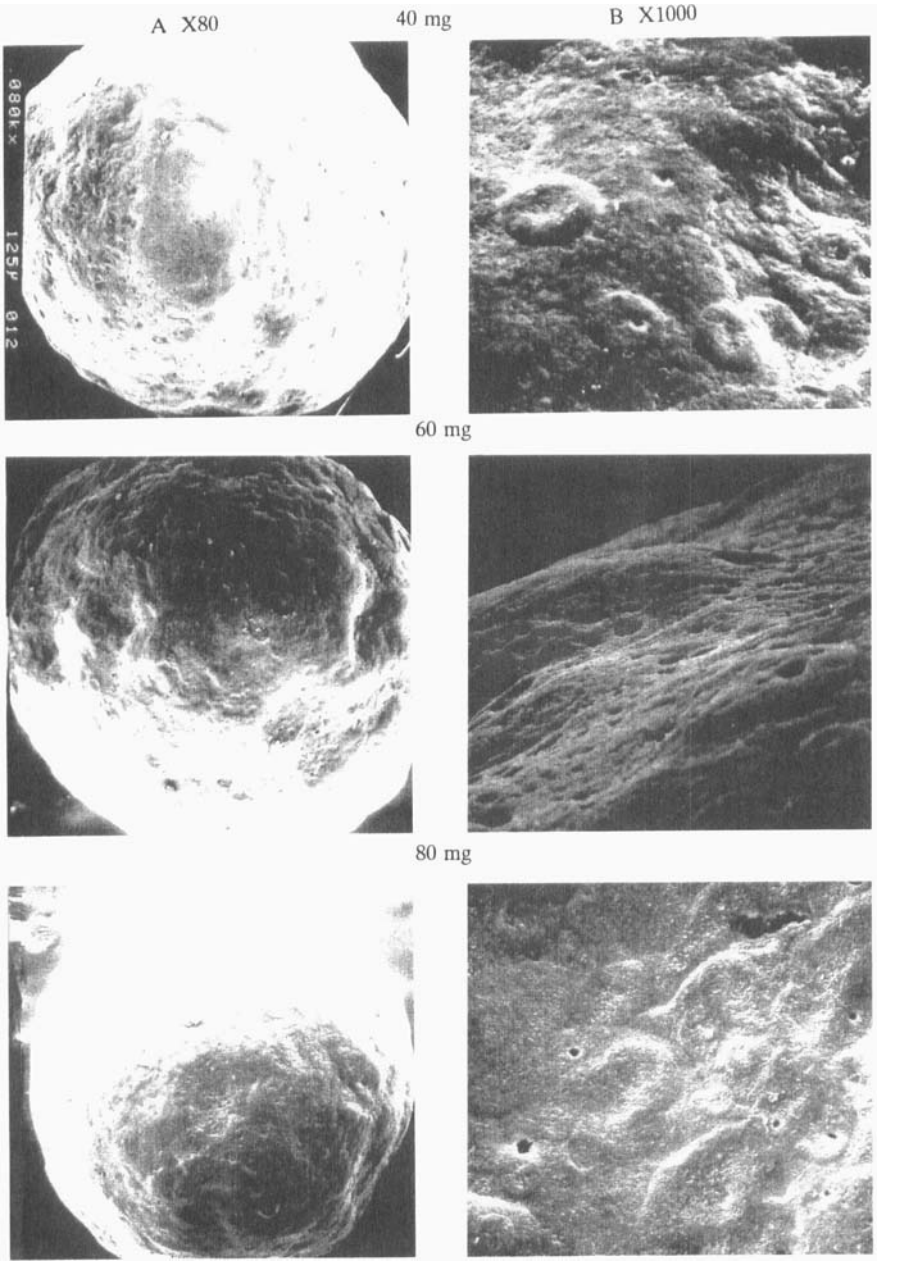

FIGURE 9

SCANNING ELECTRON MICROGRAPHS AT VARIOUS DRUG LOADING FOR AQUACOAT 6% COATED BEADS

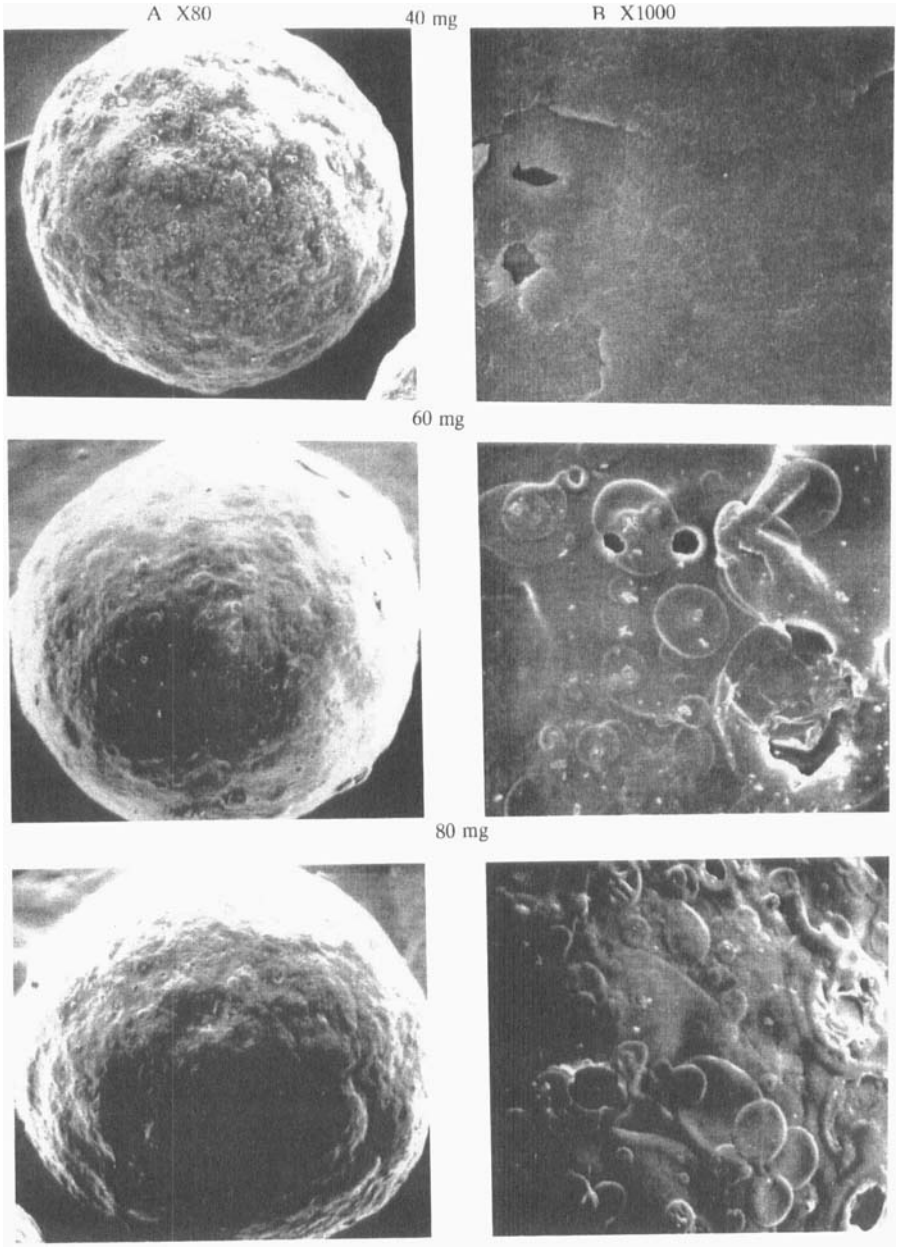

FIGURE 10

SCANNING ELECTRON MICROGRAPHS AT VARIOUS DRUG LOADING FOR SURELEASE 8% COATED BEADS

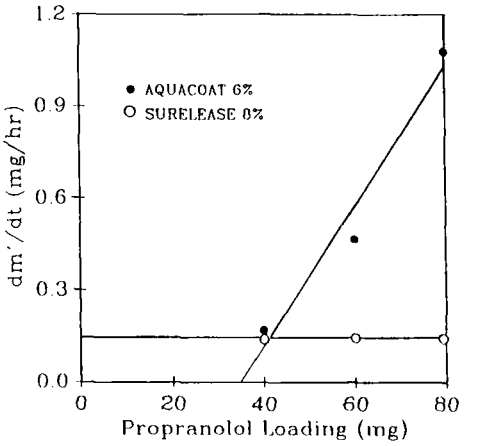

FIGURE 11

EFFECT OF DRUG LOADING

As seen from the Figure 11 drug release from Surelease® coated beads was found to be virtually independent of drug loading; conversely, Aquacoat® coated beads showed an increase in release rate with an increase in drug loading. This increase may be attributed to the greater migration of the drug during the application of Aquacoat® which resulted in the formation of a microporous membrane.

Furthermore, as seen from Figure 12 it appears that more drug (as represented by dots) has migrated into the coating layer for Aquacoat®, whereas for Surelease® (Figure 13) migration has occurred to lesser extent. Propranolol has a pKa of about 9.45, whereas the pH of Surelease® and Aquacoat® are approximately 12 and 7, respectively (7,8). Therefore, propranolol will be ionized and very soluble in the Aquacoat® aqueous phase. This could potentially allow more drug to be solubilized and distributed throughout the polymer film during coating.

Effect of Aging on Release Profile

One of the concerns in using Aquacoat® dispersions is that it requires a curing stage before drug release is stabilized. This curing stage depends on the formulation (plasticizer used) and coating conditions (16). On the other hand, curing of Surelease® coatings is not always been deemed to be necessary (17). To investigate whether there was, if any, change in the dissolution profiles, coated beads were stored in sealed plastic containers at room temperature for 24 months. As seen from Figures 14 and 15, both Aquacoat® and Surelease® coated

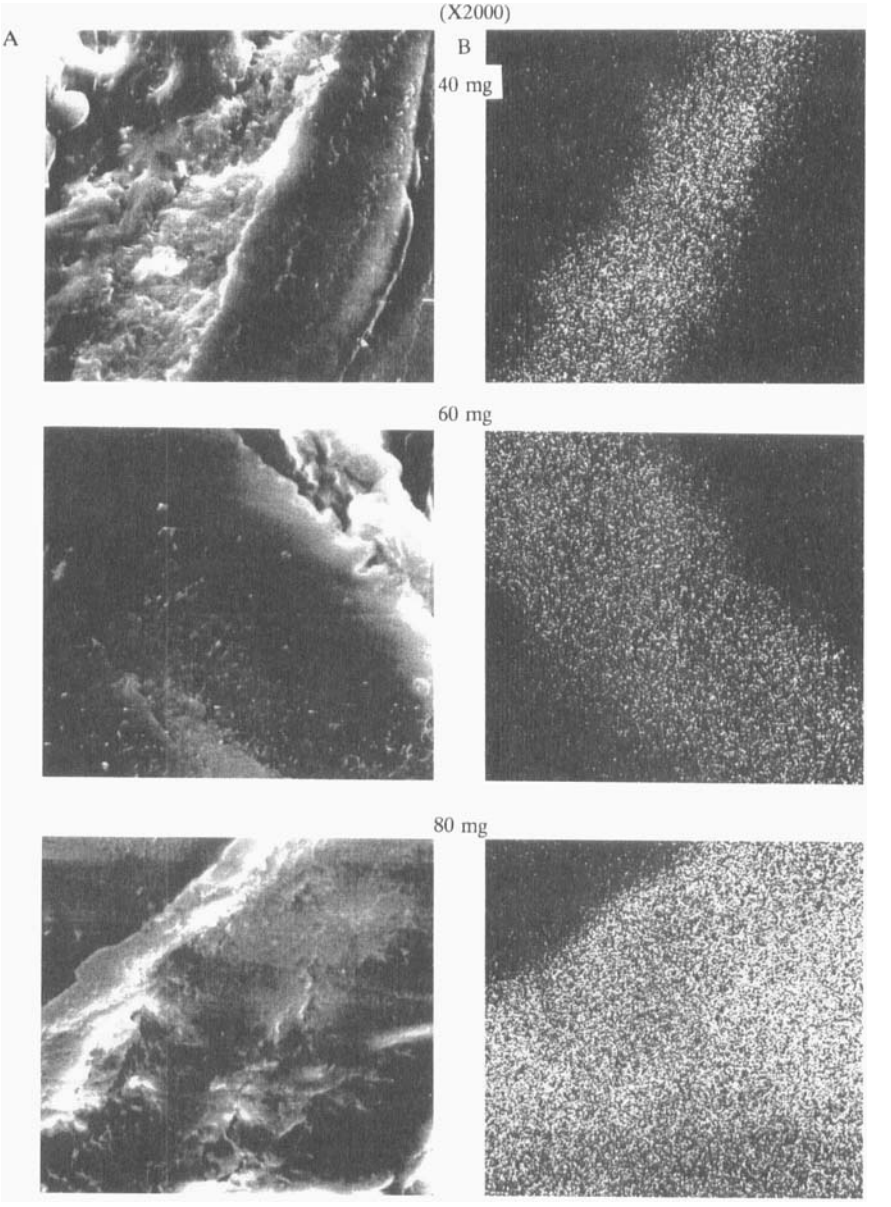

FIGURE 12

SCANNING ELECTRON MICROGRAPHS FOR AQUACOAT 6% COATED BEADS

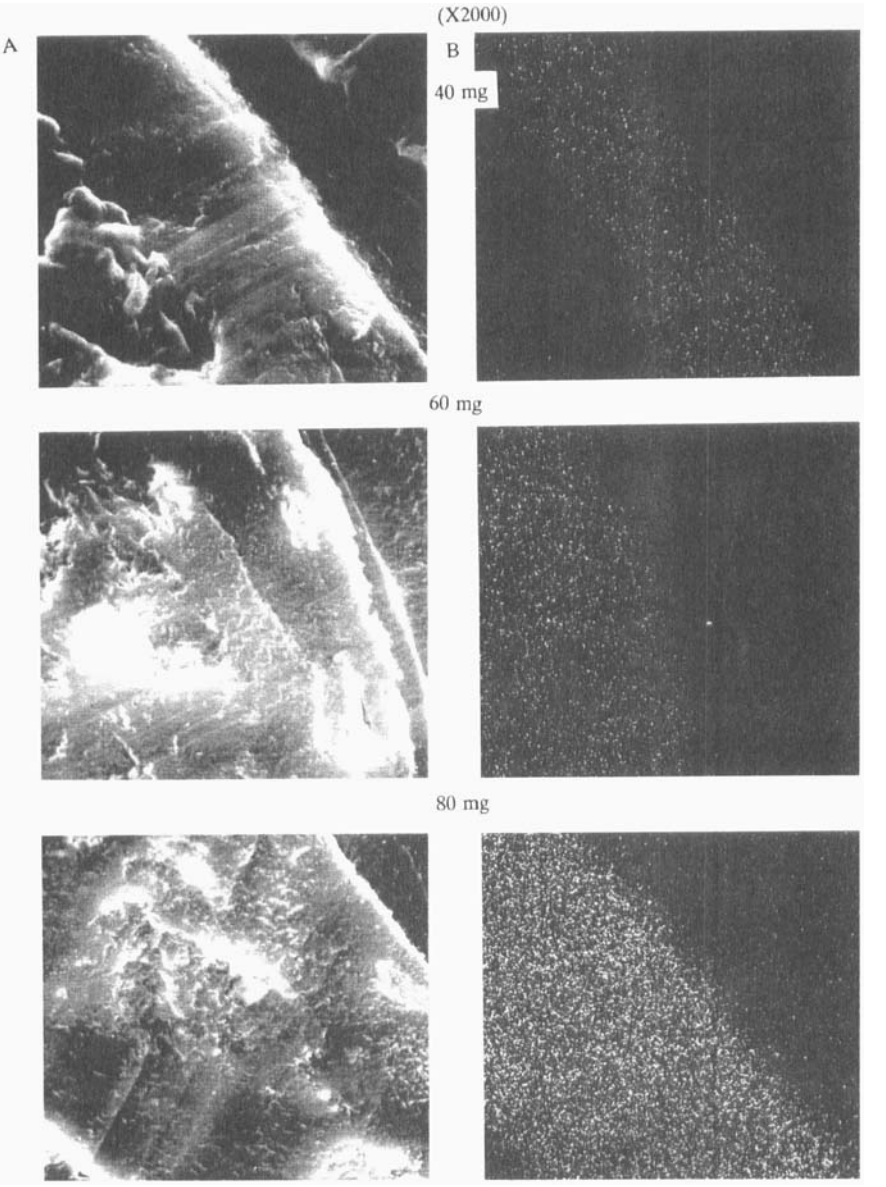

FIGURE 13

SCANNING ELECTRON MICROGRAPHS FOR SURELEASE 8% COATED BEADS

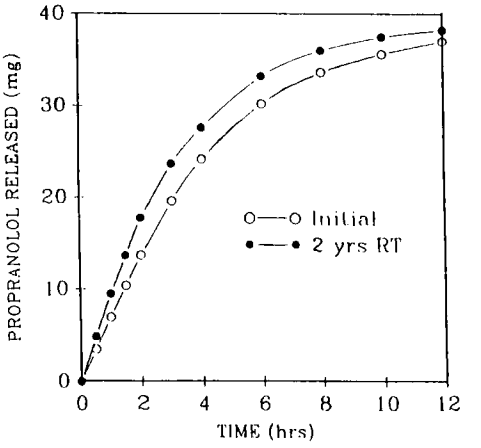

FIGURE 14

STABILITY DATA
AQUACOAT 6%

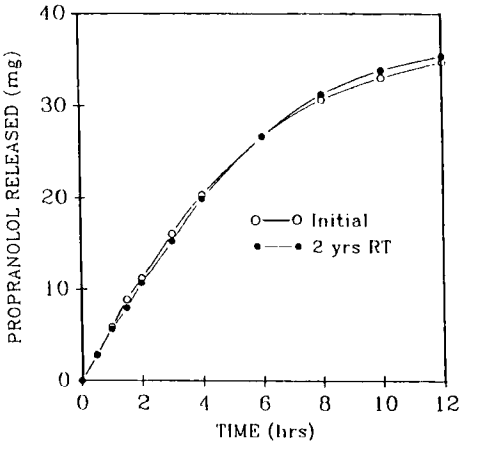

FIGURE 15

STABILITY DATA
SURELEASE 8%

beads showed no difference in release rates on aging ($p < 0.05$). It must be emphasized that film coated beads should not be stored above the softening temperature of the film, since this could lead to unpredictable changes in the release profiles (3). Furthermore, Steuernagel (16) in his study postulated that the increase in release of phenylpropanolamine from beads stored at elevated temperatures was not only due to drug migration into the film, but also a result of the contribution of the butylated plasticizers to a solubility effect.

CONCLUSIONS

Film coating is one of the most frequently employed methods of preparing controlled-release dosage forms. In order to be able to design a desired controlled release drug delivery system based on drug substances with various intrinsic properties (eg. solubility, diffusivity, etc), it is necessary to gain knowledge about the barrier properties of the membrane as well as the drug release mechanisms.

The mechanism of drug release for the spherical membrane reservoir systems prepared in this study appears to be diffusion controlled accompanied by osmotic effects for both polymeric dispersions studied. Equilibrium solubility of the drug increased with an increase in the concentration of the urea solutions, however, this increase in equilibrium solubility was not reflected by an increase in the release rate for the formulations studied. The release rates were found to be inversely proportional to the membrane thickness for both polymeric dispersions. Release rates were found to be independent of drug loading for Surelease®, but not for Aquacoat®. The release profiles for Aquacoat® and Surelease® coated beads showed no difference in release rates, when stored at room temperature for 2 years.

APPENDIX

The approximate osmotic pressure π produced by a saturated solution in an osmotic pump-like device is given by (18)

$$\pi = \frac{\upsilon C_s RT}{M}$$

where,
υ = number of particles into which a molecule ionizes,
C_s = concentration of the drug at saturation
R = 0.082 Litre atm/mole/deg
T = 310°K
M = molecular weight of the drug

	υ	C_s	M	π
Propranolol HCl	2	251.523 g/L	295.81	43.23 atm

For sucrose (Nu-Pareils) is 148.15 atm (9). Hence, the total osmotic pressure π_c is 191.38 atm.

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