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EFFECT OF MULTIPLE FILM COVERAGE IN SUSTAINED RELEASE PELLETS

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ABSTRACT

It is shown that in making sustained release pellets, the effect of film laid upon film has a significant effect on the performance (dissolution characteristics) of sustained release pellets, coated with insoluble films. The penetration of liquid and drug substance in and out of the coated pellet is much more rapid than predicted by diffusion coefficients of homogeneous, cast films. General diffusional equations are obeyed.

INTRODUCTION

Many methods are used to produce sustained release products. One of the oldest of these is that of coated beadlets[1]. In this process, drug is coated onto a support beadlet (Fig. 1) until a certain percentage (load) of drug is achieved. The loaded

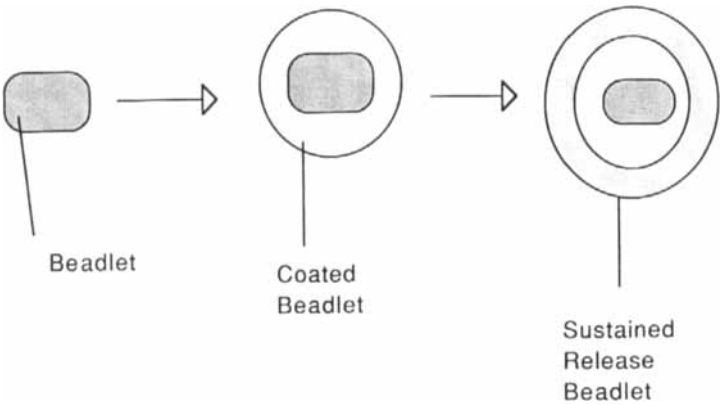


Fig. 1. Coating Schematic

beadlets are then coated with a water-insoluble film. The coating may be carried out either in a coating pan or in a fluid bed.

In general, when a batch is made by this process, the last step is carried out so that different fractions are obtained with each a particular thickness of coating, h (cm). This allows manipulation of the overall rate of release of the final dosage form as has been described in literature[3].

Figure 2 shows the mode by which drug is released when the beadlet is exposed to a liquid. There is first (i) penetration of liquid into the interior of the beadlet, then (ii) dissolution of drug substance to form a saturated solution, and then (iii) diffusion of drug substance through the membrane.

It is obvious that processes (i) and (ii) will occur simultaneously for a short while, but it is assumed in the following

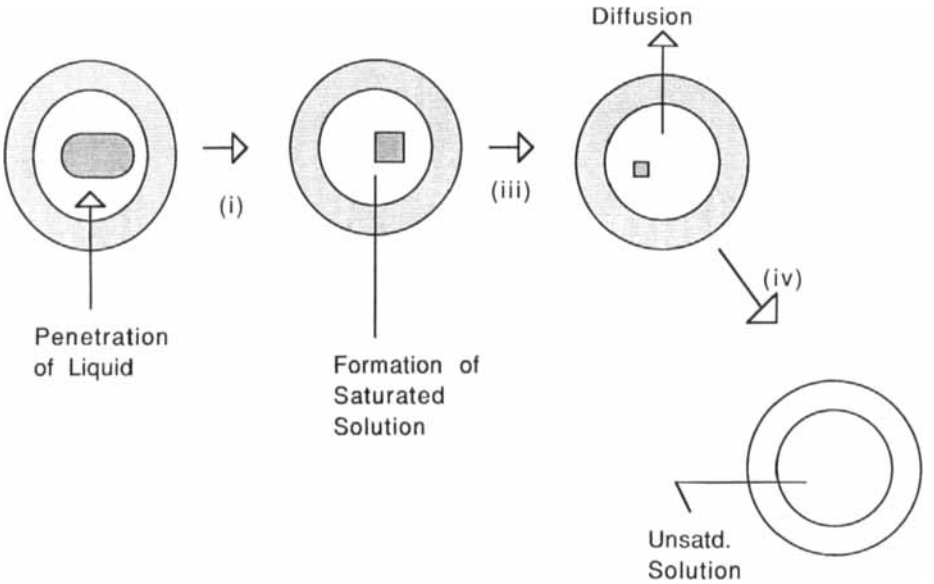


Fig. 2. Dissolution Schematic

that they are consecutive. After a lag time, t_l (sec) the process III will start. The solution inside the pellet will be saturated as long as solid drug is present. The saturation concentration is denoted S (g/cm^3) in the following, and Fick's second law[2-5] which should hold during the steady state period after saturation has been attained, then gives:

$$J = (1/A)dm/dt = (D/h)(S-C) \qquad (1)$$

where J is flux ($g \cdot cm^{-2} sec^{-1}$), A (cm^2) is surface area, m (g) is mass and C (g/cm^3) is the concentration outside the pellet at time

t (sec) and D (cm^2/sec) is the diffusion coefficient of drug through the membrane.

If the volume of the dissolution cell is V (cm^3) then the concentration at time t is given by

$$C = m/V \tag{2}$$

or

$$dC = (1/V)\cdot dm \tag{3}$$

which, inserted in Eq. 1 gives:

$$dC/[S-C] = (A\cdot D/\{h\cdot V\})\cdot dt \tag{4}$$

where

$$k = AD/\{hV\} \tag{5}$$

so

$$C = C'[1-E^{-k(t-t_i)}] \tag{6}$$

where C' is the concentration at infinite time, i.e.,

$$C' = m_o/V \tag{7}$$

where m_o (g) is the initial amount of drug per particle, and t_i has been introduced as an initial condition. The above holds for both one pellet particle or a population of N pellet particles.

All the drug will have dissolved at a point in time, t* (sec) and Eq. 1 then becomes:

$$J = k \cdot [C^* - C] \quad (8)$$

where C^* is the inside concentration at time t^*.

In treating data, Eq. 6 is best written:

$$\ln[C' - C] = -k(t - t_i) + \ln C' \quad (9)$$

C' as mentioned, is the concentration at infinite time and should, theoretically, be given by Eq. 7. Often, however, this is not quite the case, and hence the logical treatment is by iteration. t_i, of course, can be found as the x-intercept of a plot of Eq. 9.

When films are applied, it is doubtful they are done so in form of a continuous film. In a coating pan (or a fluid bed device), it is more likely that the film consists of segments that overlap (Fig. 3). This is akin to the model for sugar-coated tablets, suggested by Carstensen et al.[6] If this is the case then

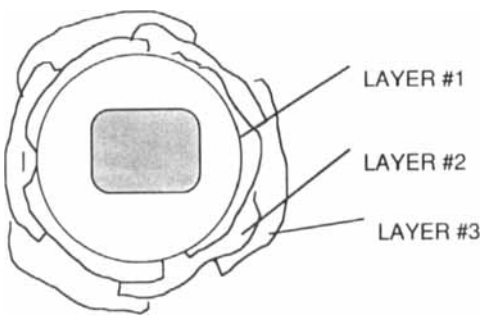


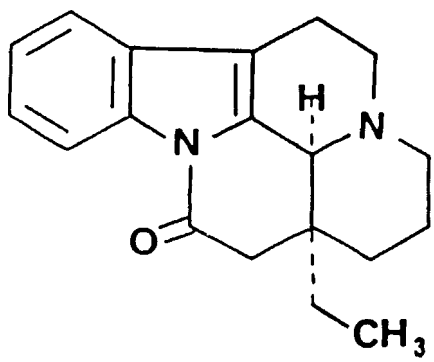
Fig. 3. Schematic of layering in placing a film on a pellet.

Eq. 5 and 6 would still apply, but the interpretation of D would be different.

It is the intent of this article to demonstrate that this latter holds true in the case of a polyacrylic polymer (Eudragit E30D).

MATERIALS AND METHODS

The support pellets used to make the sustained release pellets were spherical granules[7-9] of a diameter of 1 mm of the following composition: 73% saccharose and 27% corn starch. The drug substance used was I-eburnamonine ($C_{19}H_{23}N_2O$, MW = 294.4)



The solubility of the hydrochloride salt is 625 mg/ml. The film former[10-12] used was a 30% aqueous suspension of acrylic polymer (Eudragit E30D):

$$[-CH_2CHCOOC_2H_5]_{n1}\cdots\cdots\cdots[-CH_2C(CH_3)COOCH_3]_{n2}$$

where n1/n2 = 1/2. The density is 1.04 g/cm^3, hence the density of the dried film is 1.12 g/cm^3.

The pellets were placed in a coating pan, and wetted by spray-addition of an 8% aqueous Pharmacoat solution. A conspergent mixture of 2 parts of drug and one part of talc was added, and the resulting product then hand-screened and dried. The dry pellets were returned to the coating pan, and the cycle continued until the drug content was 2.5%.

The pellets were assayed by adding an accurately weighed amount of about 100 mg of pellets to 50 ml of N/10 hydrochloric acid in a 200 ml volumetric flask. After dissolution was complete, it was filtered and brought to volume and the optical density determined at 240 nm. The pellets were then coated with the aqueous polymer solution, diluted 1:4.

Dissolution rates were carried out in a Dibbern cell using a Munzel flow-through apparatus[13,14] without recirculation. Microphotographs were taken of the coated pellets to visualize the nature of the surface.

For reasons that will become obvious below[15,16], one coating run was carried out by adding a small bottle which had been placed in the bed of beadlets prior to coating.

The diffusion coefficients of the coats themselves were determined by casting a film on a glass plate and drying it. Next the film was immersed in water at 37°C and stripped off the glass plate. This type of film is denoted "cast" in the following. A

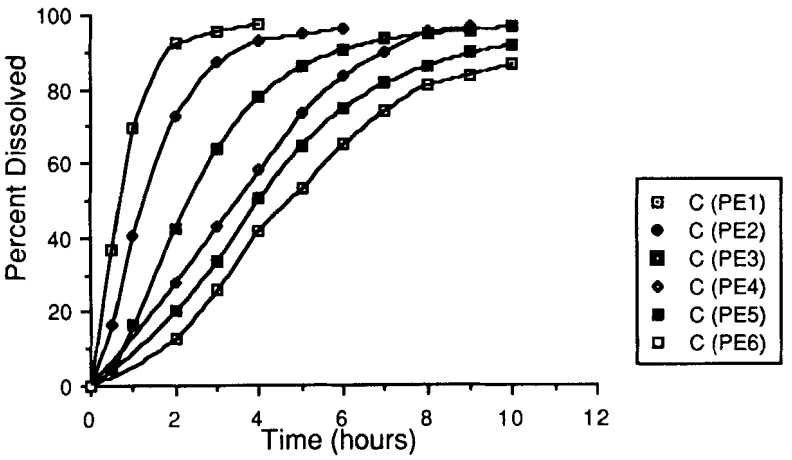


Fig. 4. Release curves of the various formulae

second film was formed by spraying the polymer suspension onto a glass plate and proceeding as above. This is denoted a "sprayed" film in the following. The film deposited on the bottle was also placed in water at 37°C for an hour and then stripped. This is denoted "coated" in the following. The films were placed in a diffusion cell[17-19]. The compartments were each of a volume of 100 ml and the membrane surface area was 12 cm^2. Diffusion experiments were carried out in a constant temperature bath.

RESULTS AND DISCUSSION

The dissolution data are shown in Fig. 4.

These data are treated according to Eq. 9 by iteration. The data are shown graphically in this fashion in Fig. 5. The value of C' is chosen as the one which gives the smallest value of s_{yx},

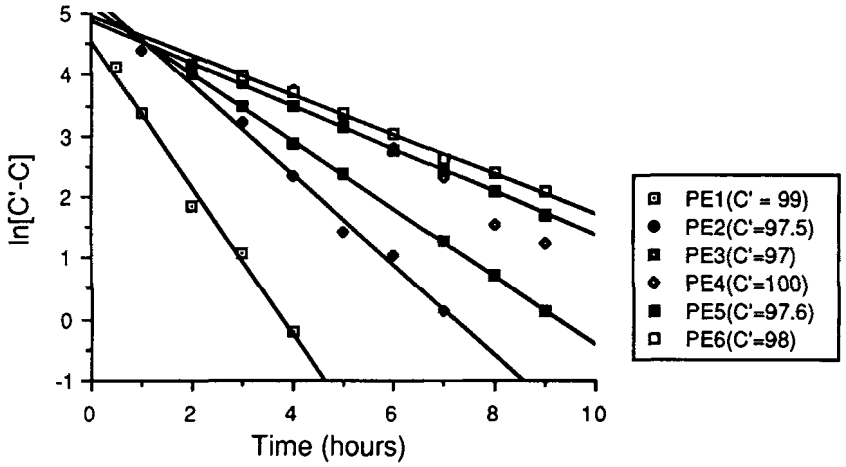


Fig. 5. Data treated according to Eq. 9

TABLE 1

Values of C' for the various runs and least squares fit parameters.

Lot	C' mg/ml	-Slope	Inter-cept	t_i, hr	s_{yx}	N	10^3h (cm)	$1/h_1$ cm^{-1}
PE1	98.5	1.200	4.561	-0.038	0.226	5	2	500
PE2	97.5	0.775	4.775	0.1913	0.128	7	2.5	400
PE3	97	0.544	5.098	0.906	0.025	8	3	333
PE4	100	0.523	5.882	2.441	0.095	6	3.5	286
PE5	100	0.495	5.764	2.159	0.136	6	4	250
PE6	94.5	3.270	5.308	2.149	0.051	7	4.5	220

the square root of the residual sum of squares, when linear regression is performed.

The thicknesses of the coats were calculated by knowing the amount of coating (w g) per cm^2 of pellet surface (A cm^2). If the density of the coating is ϕ' g/cm^3 and its volume is v cm^3 then the amount of per cm^2 is

$$w/A = v \cdot \phi'/A = \phi' \cdot h \qquad (10)$$

Since $\phi' = 1.12$, a weight of solution can be applied to the plate to insure a film thickness of desired magnitude. It follows from Eq. 5 that k should be inversely proportional to h:

$$k = (AD/V)j(1/h) \qquad (11)$$

A plot of k versus (1/h) is shown in Fig. 6. Good linearity is observed. The least squares fit line is:

$$k = [2.9 \cdot 10^{-3}/h] - 0.31 \qquad (12)$$

with a correlation coefficient of 0.97.

The equation differs from Eq. 5 by a significant intercept term (p=0.95). This would imply that above a given thickness, in this case of:

$$h = 2.9 \cdot 10^{-3}/0.31 \approx 0.01 \text{ cm} \qquad (13)$$

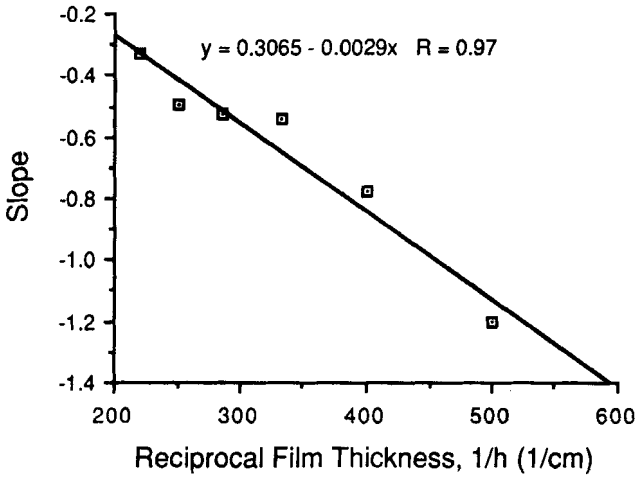


Fig. 6. Data from Fig. 5 plotted according to Eq. 12

the diffusional resistance becomes substantially larger so that the film becomes much more impermeable (within the time span used in an experiment). This raises the question whether the k-values are tied to a diffusion through a homogenous film at all or whether sufficient thickness simply assures that all the "holes" from overlapping fractional films have been covered up.

It should be noted as well, that the lag times should increase with thickness. That this is so, is shown in Fig. 7. This correlation is obviously not as good as that of the slopes, but the uncertainty (lack of precision) for the lag times is considerably larger as well (standard error being about 20% on the individual values, since they are afflicted both by the error in the slope and in the intercepts of the plots in Fig. 5).

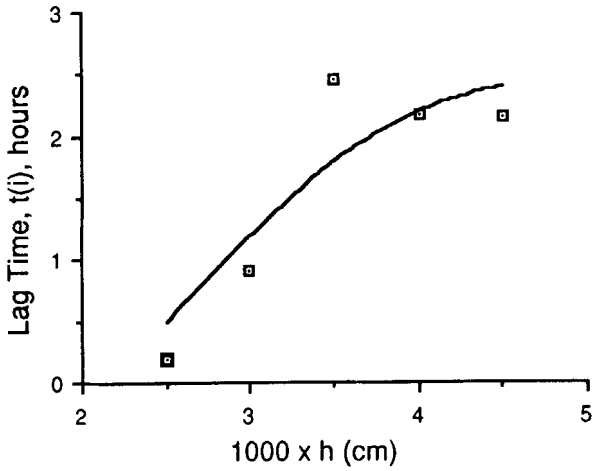


Fig. 7. Lag time increase as a function of film thickness

Hence, the data, as expected, suggest a diffusional process, but there are indications that imperfections in the film from overlap might play a role. It is for this reason that the experiments consisting of coating a small container were carried out. If coating produces a different film that that of casting, then this method provides a means of answering the question directly.

The data from directly cast films versus a film coated onto a bottle in a coating pan are shown in Fig. 8. In this case it is easiest to obtain the diffusion coefficient under sink conditions, under which Eq. 1 reduces to:

$$dm'/dt = [S \cdot A' \cdot D/h'] \qquad (14)$$

where m' is the mass diffused at time t in the diffusion cell, A'

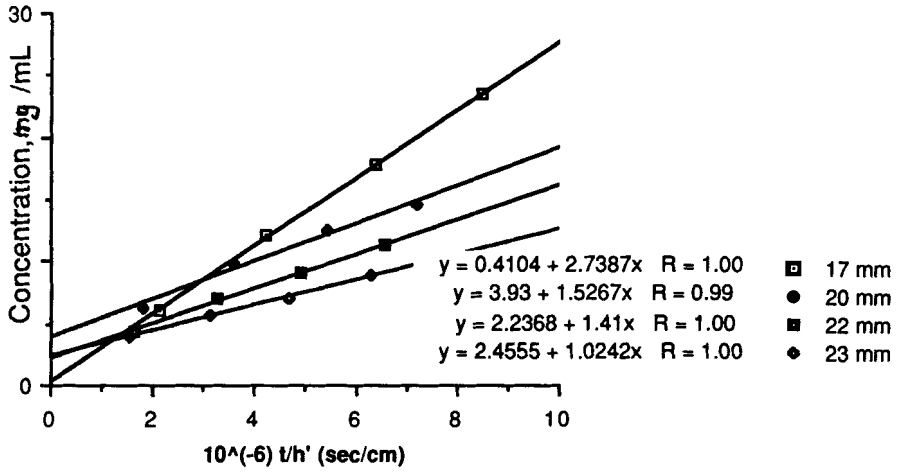


Fig. 8

is the surface area, h' the thickness of the cast or sprayed film, and S is the solubility. The concentration in the receptor compartment is denoted C", i.e.,

$$C' = m'/V' \qquad (15)$$

where V' is the volume of the receptor compartment. Introducing Eq. 15 into Eq. 14 yields

$$C'' = [S \cdot A' \cdot D/V'] \cdot \{t/h'\} \qquad (16)$$

Data treated in this fashion are shown in Fig. 8, using units of $\mu g/cm^3$ as ordinate (C") and sec/mm as abscissa (t/h'). The slopes (converted to units of mg/ml sec/cm) are shown in Table 2.

TABLE 2

Summary of findings from diffusion experiments treated according to Eq. 17

	Thickness ($m\mu$)	Slope (mg/ml)/(sec/cm)	$10^8 D$ (cm^2/sec)
Cast	20	0.176	
	18	0.221	
	25	0.214	
	Average	0.23 + 0.014*	0.31
Sprayed	25	0.919	
	24	0.586	
	27	0.658	
	Average	0.72 ± 0.10	0.96
Coating	17	2.74	
	20	1.53	
	22	1.41	
	23	1.02	
	Average	1.68 ± 0.37	2.24

The solubility of the compound is S = 625 mg/cm^3 and the surface area of the film is 12 cm^2. The volume of the receptor compartment is 100 ml, so according to Eq. 15 the diffusion coefficient in the first case of a film in the coating pan is given by

$$625 \cdot 12 \cdot D/100 = 2.74 \cdot 10^{-6} \qquad (16)$$

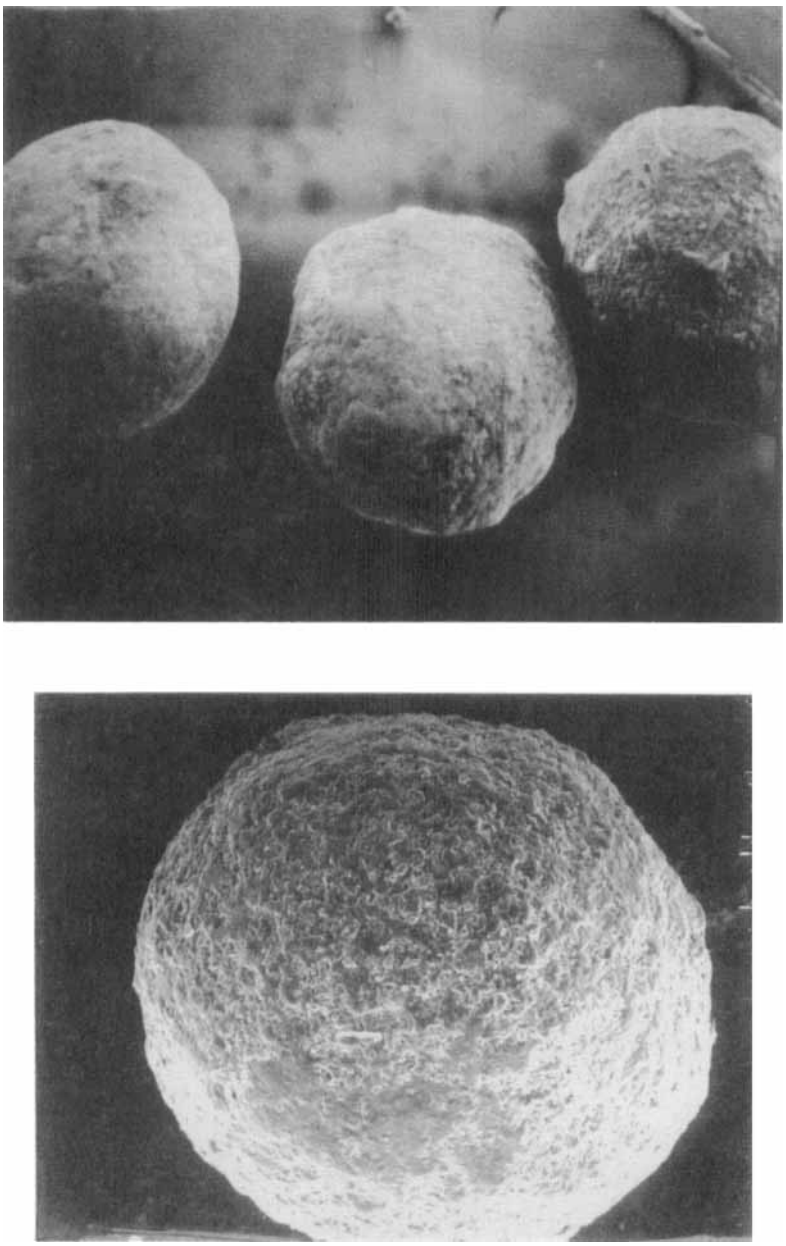


Fig. 9. Electronmicrograph showing onion-skin structure of surface.

(where the units of the slope from Fig. 8 have been converted to $[mg/cm^3)/(sec/cm)]$, i.e., $D = 6 \cdot 10^{-8} cm^2/sec$. The data in Table 2 are shown as a function of film thickness. In the case of the cast and sprayed films there is no dependence of D on thickness (as it should be), but in the last case there is a definite dependence, in that the thicker the film, the smaller the apparent diffusion coefficient. It is obvious, also, that the coating on the pellets exhibit a much higher permeation rate and the value for D calculated in that case (as well as in the case of the sprayed film) is too large because the film is not intact. This is not solely due to the spraying step, because although the diffusion coefficient here is higher than for a cast film, it by no way approaches that of the "coated" film.

Finally, electron microscope presentations of the coated and the uncoated pellets are shown in Fig. 9. It is evident that the coating is attached to the support in an onion-skin fashion.

It should be mentioned in closing that in small scale work the reproducibility of the method is excellent.

SUMMARY

It is shown, in the case of pellets of I-eburnamonine coated with Eudragit E30D, that the coating is an onion-skin like coating. The diffusion of the drug through the coat gives rise to a diffusion coefficient much larger than from cast films, and it is shown that films produced in pan coating consist of discrete films

overlapping one another, thus explaining the more ready penetration of drug substance through the heterogeneous film.

LIST OF SYMBOLS

A (cm^2) = surface area

A' (cm^2) = the surface area of the film in the diffusion cell

C (g/cm^3) = concentration outside the pellet at time

C' (g/cm^3) = the concentration at infinite time

c* (g/cm^3) = the inside concentration at time t* when all drug has dissolved

C" (g/cm^3) = concentration in the receptor compartment in diffusion cell

D (cm^2/sec) = diffusion coefficient of drug through the membrane

h = thickness of film (cm)

h' = the thickness of the cast or sprayed film in the diffusion cell

J = flux ($g \cdot cm^{-2} sec^{-1}$)

k (cm/sec) = dissolution constant

m (g) = mass

m_o (g) is the initial amount of drug per particle

m' (g) = the mass diffused at time t in the diffusion cell

N = number of pellet particles in dissolution sample

S (g/cm^3) = solubility

t (sec) = time

t_i (sec) = lag time

t^* (sec) = time when all drug has dissolved

V (cm^3) = volume of the dissolution cell

v (cm^3) = volume of film

w (g) = the amount of coating per cm^2 of pellet surface

ϕ' (g/cm^3) = density of the coating volume

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