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RELEASE RATE OF DRUGS FROM ETHYL CELLULOSE COATED GRANULES CONTAINING CAFFEINE AND SALICYLIC ACID.

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ABSTRACT

Fluidized bed coating with ethyl cellulose - polyethylene glycol mixtures has been utilized for prolongation of drug release from granules containing salicylic acid and caffeine as model drugs. Drug release from the coated granules followed first order kinetics.

Particle size of the active material, granule composition and extraction medium pH did not affect the rate and kinetics of drug release. Increase in coat thickness decreased the release rate whereas elevation of the ratio of polyethylene glycol to ethyl cellulose enhanced the release rate to a degree related to the polyethylene glycol concentration. The permea-

bility constants of salicylic acid and caffeine for the ethyl cellulose-polyethylene glycol coatings were of a similar order to those measured previously using solutions of the drugs with planar barrier films.

INTRODUCTION

Film coating is one of the accepted methods of prolongation of drug release from granules (1, 2). The coating material may be soluble or insoluble in the fluids of the digestive system. In the case of soluble coating materials, the dosage form may include a variety of granules or cores having different coat thicknesses (3). The release rate in such a system may be controlled by the solution of the coat or the diffusion of the drug through the coat or both these processes. However, with insoluble coating materials, the release process will be controlled solely by the diffusion through the film coat. These considerations are applicable on condition that the process is not controlled by drug dissolution rate and the rate-limiting process is penetration of the coating layer.

Soluble coating materials in use include waxes and lipids whereas the insoluble type is comprised mainly of hydrophobic film-forming polymers (4).

A number of factors determine the extent to which a polymer is suitable for use in a prolonged action dosage form. The most important are: the extent of its penetrability by medicinal

agents, its toxicity, its stability, and its physical-mechanical properties (5, 6).

The hydrophobic polymer ethyl cellulose is accepted as a non-toxic pharmaceutical agent, having proved to be useful as a binder in tabletting. It is insoluble in water and digestive fluids (7).

In previous work, ethyl cellulose alone or mixed with polyethylene glycol was used for formation of planar and spherical film matrices containing dispersed drugs designed to give prolonged action and the mechanism and kinetics of release from such films were studied (8, 9). These polymers were also used to form a new type of delivery system in which placebo cores were coated with films which contained the drugs (10). In the present study, granules containing salicylic acid and caffeine as model drugs were coated with ethyl cellulose and ethyl cellulose-polyethylene glycol films. The influence of granule and coating composition, granule diameter, coat thickness and external pH on drug release was investigated.

EXPERIMENTAL

Materials.

Ethyl cellulose, N type, had an ethoxyl content of 47.5 to 49.0% and the viscosity of a 5% w/w solution in toluene-ethanol 80:20 w/w was 100 c.p.s. (Hercules Incorporated, Delaware, U.S.A.). Calcium (ortho) phosphate (Precipitated),

and polyethylene glycol 4000, BDH Ltd., Poole, U.K. Lactose, caffeine and salicylic acid, Merck, Darmstadt, Germany. All of the materials were B.P., U.S.P. or reagent grade.

Granulation.

Granules were prepared containing 3% $^{w}/_{w}$ of salicylic acid or caffeine. The fractions of the drugs and diluents passing through a 60 mesh sieve or, in one case, the micronized drug were wet-granulated using aqueous polyvinyl pyrrolidone solution as a binder with lactose or calcium phosphate diluents. The wet powder mixture was passed through 10 or 20 mesh sieves and the granules were sphericized and smoothed by pan-rotation for half an hour. They were then oven-dried at 40°C. The granules were finally sieved using 10/40 and 20/40 mesh sieves for the 10 and 20 mesh batches, respectively, to remove aggregates and fine particles, and used in the coating experiments.

Coating experiments.

The fluidized bed coating technique was used; the procedure is presented in detail elsewhere (11).

Batches at 100 g of granules were coated in each experiment using chloroformic polymer drug solutions. The compositions of the coating solutions and the granules are shown in Table 1.

Flotation of the granules and spraying were commenced after the temperature in the coating region of the apparatus had reached

30-40°C. The pressure at which satisfactory fluidization occured was 8-11 units (Monostat Corp. Tri Flat U.S. pat. 2731830 Fisher and Porter Corp.). Coating solutions were pumped (Fluid Metering Inc., Oyster Bay, N.Y.) at a flow rate of 10 ml/min to the atomizer, which was operated at a spray pressure of 3 Atm. On completion of coating the granules were fluidized for a further 5 min to ensure complete removal of chloroform and drying.

Measurement of coat thickness.

Dry coated granules were sliced into hemispheres and the coat thickness measured microscopically. Thicknesses reported were based upon 100 measurements and ranged within ± 12% of the mean.

Release rate studies.

Quantities of about 100 mg, accurately weighed, of crushed coated granules were shaken with 150 ml water in 200 ml volumetric flasks for 10 minutes after which they were diluted to volume. Samples of the solution were filtered and their drug content determined spectrophotometrically (Unicam SP 1800 U.V. Spectrophotometer, Pye-Unicam Ltd., England) at 273 nm and 296 nm, the maxima for caffeine and salicylic acid respectively in water, using appropriate standard solutions.

Release rates from coated granules were measured in banana-shaped extractors designed to enable the granules to be shaken continuously in a reciprocal shaker at 37°C during the release

Table 1.

Composition of coated granules and release rate constants.

(Except when otherwise stated lactose was used as filler,

granule radius was 0.074 cm and drug powder diameter was 240 μ).

	Expt.	PEG (% w/w)[a]	Coating Soln. vol. (ml)	Release rate constant (k) $10^3(min^{-1})$	s.d.	c.v.
Salicylic acid	1	10	600	9.5	0.21	2.2
	2	20	600	16.2	0.28	4.7
	3	20	1200	10.7	0.27	6.1
	4	20	1800	5.6	0.34	6.7
	5	40	600	33.0	0.08	3.0
	6	50	600	44.4	0.06	1.3
	7[b]	50	600	42.8	0.11	2.6

Caffeine	8	10	600	1.6	0.10	6.2
	9	20	600	1.9	0.21	1.1
	10	40	600	3.1	0.10	3.2
	11[c]	40	600	3.0	0.08	2.6
	12	40	400	5.5	0.11	2.5
	13	40	1000	2.5	0.14	2.6
	14	50	600	3.4	0.11	4.4
	15[b]	50	600	3.5	0.15	4.7
	16[d]	50	600	9.6	0.11	1.0

and sampling. The extracting fluid (100 ml water or buffer solution) prewarmed to 37°C was added to about 3 g of accurately weighed coated granules and at suitable intervals 2 ml samples were removed, diluted as required and the concentration of drug released was determined spectrophotometrically.

pH effect.

Release rates of salicylic acid and caffeine from coated granules were measured in USP buffers of pH 2 and pH 9. Absorption maxima were the same as in water except for that of salicylic acid at pH 9, which shifted to 298 nm, with accompanying change in extinction coefficient.

RESULTS and DISCUSSION

The rate of release R of active material from coated granules is a function of the following factors:

$$R = f(P_s, S, T, P_f)$$

where P_s is the rate of penetration of the extracting fluid into the granule, S is the dissolution rate and T the internal transport rate of the active substance inside the granule, and P_f is the rate of penetration of the film wall by the active substance.

The release rate may be influenced by any of these variables but may be dependent on one of them if it becomes the slowest process and rate-determining under particular circumstances.

For the formulations and coating prepared in this work, treatment of the drug release data by plotting logarithm of the fraction undissolved versus time gave linearity in all the systems in accordance with the first order equation:

$$\log(Co - C) / Co = - kt/2.303 \quad \text{..... (Eq. 1)}$$

where C_o, C, are the drug concentrations at zero time and time t respectively, $(C_o-C)/C_o$ is the fraction of drug remaining in the granules at time t, while k is the specific release rate constant of the process. The release rate constants presented in Table 1 were calculated by graphic solution of equation 1.

Effect of granule composition.

After solution in the water permeating the film and granule, the drug diffuses within the granule to the inner wall, penetrates it and passes into the external solution. The factors determining the internal transport rate of the drug are the porosity and tortuosity of the granule matrix and the viscosity of the liquid medium formed in the granule.

Calcium phosphate and lactose matrices represent opposite tendencies in granule structure, the former yielding an insoluble matrix the diluent particles of which remain largely intact within the polymeric binder while the latter, partially dissolving during granulation, gives interconnected particles owing to crystallization of lactose during drying. Moreover

partial solution of lactose in the permeating solvent would lead to change in granule structure, tending towards formation of a more porous and fluid matrix. On account of this, differences might be expected to occur in the rates of internal diffusion of caffeine and salicylic acid in lactose and calcium phosphate matrices. Release of salicylic acid and caffeine from these contrasting types of granule matrix is compared in Experiments 6 and 7, and 14 and 15 (Table 1). Rate constants are based on measurements covering about 90% drug release. They show that there is no significant difference in the release rates of either drug from the two matrices, hence it is assumed that the internal transport rate of these drugs has no influence on their release rate from the coated granules tested. As the coating selected for these comparisons were amongst those of highest permeability in which there might have been a mixed rate control mechanism, the same conclusions hold for the slower release systems, which would be increasingly membrane-controlled.

Influence of caffeine particle size.

One of the factors determining the dissolution rate of a solid is its surface area; in most substances, there is a direct relation between the surface area and dissolution rate. Experiments 10 and 11 (Table 1) compare release rates of caffeine from two batches of coated granules, differing only in the particle diameter of the drug, which was 36 μ in the one case and 240 in the other. No difference is evident in the release rates of these two

batches, hence the degree of comminution of the drug is not of influence. Assuming that the large difference in initial particle size of the active material is retained during granulation, dissolution rate is not the rate-determining step in the release from the coated granules. This conclusion would also be applicable to the slower release batches for the reasons stated earlier.

Effect of film thickness.

The release constants of experiments 2, 3, 4 and 10 , 12, 13 (Table 1) show the effect on drug release of change in the quantity of the coating material applied. There is a rank inverse relationship between weight of film coating and release rate as in planar rate-controlling films (12).

Effect of granule radius.

For a given sample weight, reduction of the granule radius increases total surface area. Consequently application of identical volumes of coating solution to granules of different radii should yield coatings of different thicknesses, the thickness diminishing with decrease in radius.

Assuming cores and coated granules to be spherical, the film thickness Δr is directly related to the core radius r, while the total surface area A is inversely related to the core radius, i.e. $\Delta r \alpha {}^{1}/_{r}$. For release through a rate-controlling film, the rate R is given by

$$R = dq/dt = Af(P_f, C) /\Delta r \quad \text{..... (Eq. 2)}$$

Under the conditions defined in this experiment, for two granule sizes the relative release rates are given by:

$$R_1/R_2 = A_1\Delta r_2/A_2\Delta r_1 = r_2^2/ r_1^2 \qquad \ldots\ldots\ldots\ldots \text{(Eq. 3)}$$

assuming the other factors to remain constant.

Experiments 14 and 16 (Table 1) compare release from granules of radii 0.46 and 0.74 mm. Release is more rapid from the smaller granules, the ratio of the rate constants being 2.82. As the ratio of the mean radii of the large and small granules is 1.61, the predicted ratio of the rates is, from equation 3, 1.61^2 or 2.59, i.e. about 8% below the experimental ratio, which we consider to be good agreement bearing in mind the approximations of sphericity, linearity, and quasi-steady state.

Change of granule size is clearly an effective method of controlling release rates of film-coated products, subject to the limitations of manufacture of uniform graded cores and of the use of adequate quantities of polymer to ensure uniform coating.

Effect of pH.

Table 2 shows the release rates of caffeine and salicylic acid into water and buffer solutions of pH 2 and 9. There is no evidence from these results that the pH of the extraction medium has any significant effect on the release rate of these drugs from ethyl cellulose-polyethylene glycol film-coated granules. Although caffeine is unionised at both pH values, salicylic acid

Table 2. Effect of pH on the release rates.

Granules	Extracting medium		
	Water $10^3(min^{-1})$	Buffer pH 2 $10^3(min^{-1})$	Buffer pH 9 $10^3(min^{-1})$
Salicylic acid[e]	33.0	33.1	33.2
Caffeine[e]	3.1	3.1	3.0

(pK_a 2.98) would be present mainly in the unionised form at pH 2.00 and as the anion at pH 9. the solubilities and permeabilities of which differ greatly (13), hence the constancy of release rate shows that the film coating retains its barrier properties to the passage of buffer salt ions into the cores. The results confirm those obtained on drug penetration through linear films (12) in which pH was found not to affect drug permeation rates through ethyl cellulose-polyethylene glycol films.

Effect of film composition.

It was found previously that penetration of certain compounds through planar ethyl cellulose films was increased by the addition of polyethylene glycol (12). The film-coated granules behave

similarly, the release rates of caffeine and salicylic acid increasing with polyethylene glycol content in the coating solution and hence in the film (Fig.1 and expts. 1, 2, 5, 6 and 8, 9, 10, 14 from Table 1). There is in fact a linear releation between

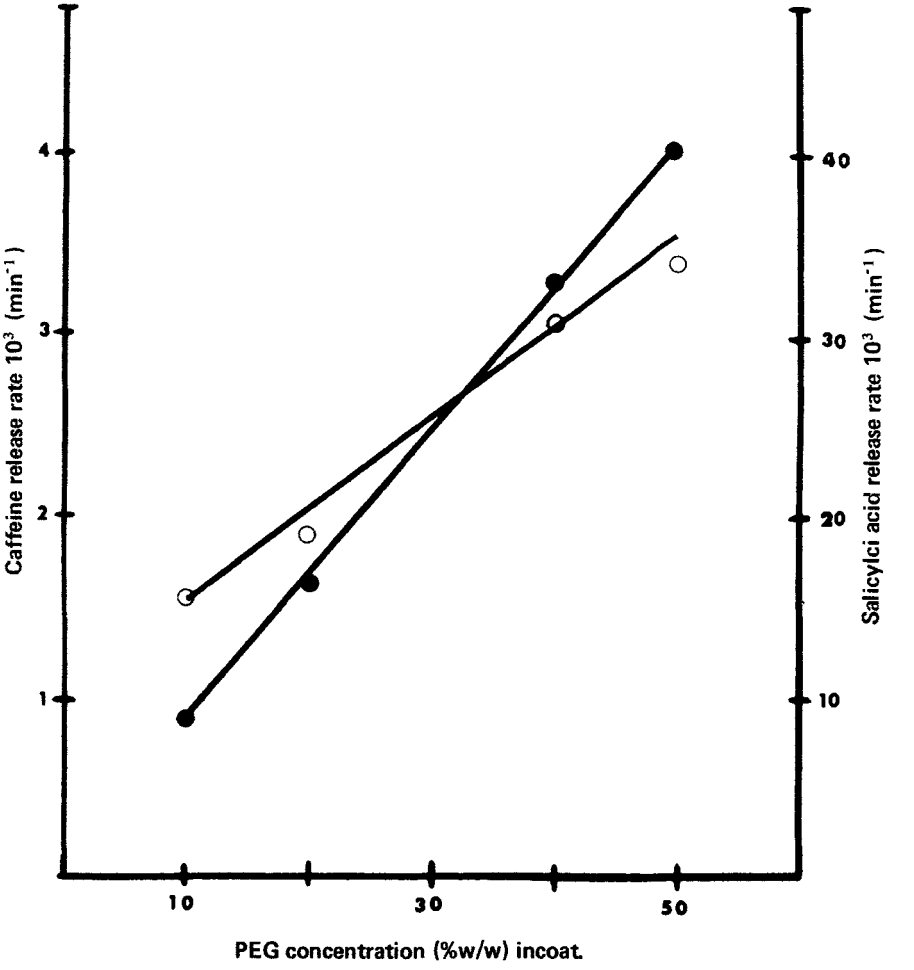

Fig. 1 - Effect of polyethylene glycol content of the coating on release rate. Key: ● salicylic acid, ○ caffeine.

the polyglycol concentration and the release rate in the case of salicylic acid but not in that of caffeine. The mechanism by which the permeability of ethyl cellulose films is raised by polyethylene glycol was discussed earlier (12), the latter being released rapidly from the film on contact with the extracting fluid. Loss of the polyglycol introduces porosity into the film, lowering the effective path length for permeation and raising drug release rates.

The thinness of the coating in comparison with the granule radius enables treatment by linear rather than spherical kinetic equations. Observance of first order kinetics in release of the drugs from the coated granules could be explained by formation of a concentration gradient inside the granule, corresponding to the existence of a quasi-steady state. The release rate constant, under such conditions may be described by the following equation:-

$$K = -PA(V_1 + V_2)/2.303\ h\ V_1\ V_2 \quad \ldots\ldots \text{(Eq. 4)}$$

where V_1 and V_2 are the volumes of the granule core and the extracting fluid, P is the permeability constant of the coating, A is the surface area of the coated granules, and h is the film thickness. From this equation:

$$P = -\ 2.303\ k\ h\ V_1V_2/A(V_1 + V_2) \quad \ldots\ldots\ldots \text{(Eq. 5)}$$

In Table 3 are listed the values of the permeability constants calculated using the above equations compared with those obtained from measurements made on drug penetration of linear films [12]. The values for the granules are lower in salicylic acid and higher in caffeine than those derived from the linear films. However, they increase consistently with polyethylene glycol concentration for each drug and are of the correct order, taking into consideration the difference in the techniques of film preparation in the two cases, the planar films having been formed by a cold casting technique in contrast to the warm spraying technique used for coating. Furthermore, during coating, factors such as the surface area of the granules, cohesion forces,

Table 3.

Permeability constants of salicylic acid and caffeine for ethyl cellulose film-coated granules and for planar films.

PEG ($\%^{w}/_{w}$)[a]	salicylic acid		caffeine	
	planar films	coated granules	planar film	coated granules
	$10^{8}P(cm^{2}/sec)$		$10^{10}p(cm^{2}/sec)$	
10	5.1	1.2	3.8	19.7
20	8.9	2.0	6.7	24.0
40	16.5	4.1	14.3	38.0
50	18.6	5.5	18.6	42.0

temperature and pressure influence the properties of the film formed.

This work shows that by control of the coating thickness, granule size and ratio of polyethylene glycol to ethyl cellulose, designated drug release times may be achieved systematically in the development of film-coated products from drug-granule cores.

FOOTNOTES

a polyethylene glycol concentration in dry coating

b calcium ortophosphate filler

c particle diameter 36 μ

d granule radius 0.046 cm

e 3% w/w of drug, lactose as diluent, 600 ml of coating solution, 40% w/w polyethylene glycol in dry coating.

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