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Placebo granules as cores for timed release drug delivery systems

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A drug delivery system is proposed constituted of spherical placebo granules as cores with polymeric surface films containing drug. This timed release dosage form has been prepared by means of a fluidized bed coating technique using ethyl cellulose as the polymeric film and caffeine and salicylic acid as model drugs. The release of the drugs from the dosage form (a) at different drug concentrations and (b) into solutions of different pH showed that drug release was linearly related to the square root of time. Good agreement was found between the theoretical release rate of caffeine, calculated according to Higuchi's equation for a homogenous matrix using membrane permeation parameters measured on linear films, and the experimental results in the case of low drug concentrations. Deviation of the release rate from the homogenous model at high drug concentrations could be explained by crystallization of the drug from the film.

In a previous study, cast ethyl cellulose film was conceived as a potential matrix containing dispersed drug for an oral timed release dosage form (Donbrow & Friedman 1975a). Possible application of polymeric films as a drug delivery system for external use (Sciarra & Gidwani 1972) or for implantation into the body (Tatum et al 1969) have already been reported. However, there is no literature on the oral use of polymeric films as drug carriers for prolonged or sustained release dosage forms. In this work placebo granules were used as a carrier for caffeine and salicylic acid embedded in an ethyl cellulose polymeric film. This new long-acting dosage form was made by using a fluidized-bed coating technique.

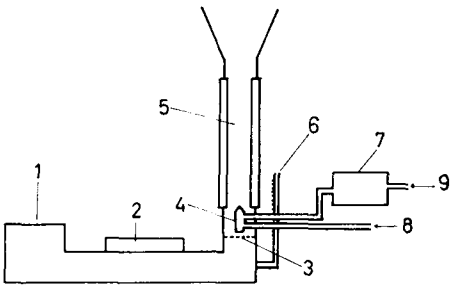

FIG. 1. The general construction of the coating apparatus. Key: 1 air pump, 2 heating unit, 3 sieve, 4 atomizer, 5 coating area, 6 pressure gauge, 7 pump, 8 compressed air, 9 coating solution.

MATERIALS AND METHODS

Materials

Ethyl cellulose, N Type, had an ethoxyl content of 47·5 to 49·0% (Hercules Incorporated, Delaware, U.S.A.). Salicylic acid and caffeine (Merck, Darmstadt, Germany) were B.P. grade.

Coating procedure

Placebo lactose granules (Hans G. Wagner, Dragee-fabrik, Tornesch, W. Germany) were fluidized and coated in the apparatus shown in Fig. 1. The determination of the optimum parameters for use of this equipment in coating has been reported recently (Friedman & Donbrow 1978). The mean granule radius was 0·065 cm and the mean weight 0·2 mg.

Before use, the placebo granules were subjected to the following survival weight test: 100 g was fluidized under the conditions used in the coating process except for omission of coating solution. After 30 min fluidization, the surviving granules were collected and the loss of weight measured.

Batches of 100 g of placebo granules were coated in each experiment using 200 ml quantities of polymer-drug solution. Solution compositions 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 occurred was 8–11 units (Manostat Corp. Tri Flat Fischer & Porter Co.). Coating solutions were pumped (Fluid Metering, Inc., Oyster Bay, N.Y.) at a flow rate of 10 ml min^{-1} to the atomizer, which was operated at a spray pressure of 3 atm. On completion of coating, the granules were fluidized for a further 10 min to remove residual solvent.

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Table 1. Composition of coated granules.

Coating solution[a]		Drug concentration after coating		
Ethyl cellulose % w/v	Drug[b] % w/v	% w/w in dry coat	Caffeine mg cm^{-3} coat[c]	Salicylic acid mg cm^{-3} coat[c]
1·96	0·04	2	27·1	—
1·90	0·10	5	57·1	58·0
1·80	0·20	10	110·0	112·1
1·70	0·30	15	180·7	179·4

a. The solvent was chloroform.
b. Caffeine or salicylic acid.
c. The volume of the coat was obtained by dividing its weight by its specific gravity, 1·14 and 1·16 for caffeine and salicylic acid, respectively. The specific gravity of the films was measured pycnometrically.

Release of caffeine and salicylic acid from coated placebo granules

The initial drug concentration in the granules was measured spectrophotometrically in chloroform after extraction in the same solvent.

Release was studied using 3 g granule samples shaken with 100 ml of extraction fluid in banana-shaped vessels secured in a reciprocal shaking bath at 37 °C. The extraction liquids were water, and U.S.P. aqueous buffer solutions of pH 2 (KCl-HCl) and pH 9·6 (borate, alkaline). Samples were removed and replaced by fresh liquid at suitable intervals, diluted appropriately and the drug content was measured spectrophotometrically (Unicam SP 1805 Pye-Unicam Ltd., Cambridge, England) at 273 and 296 nm for caffeine and salicylic acid respectively.

RESULTS AND DISCUSSION

An advantage of the coating apparatus developed for these studies is its suitability for work on the laboratory scale with batches of 50 to 300 g of granules or tablets, commercially available equipment being unsatisfactory for coating such small batches. The friability properties of the placebo granules were found to be satisfactory under the conditions used for fluidization, the loss in weight of 100 g of granules during 1 h fluidization being in the range 1–1·5%.

Equations for drug release from planar and spherical homogeneous and heterogeneous matrixes were developed by Higuchi (1963). He also showed that up to 50% release there is no significant difference between the amounts released predicted by the two equations. Roseman (1972) considered that the same relation held for planar and cylindrical matrices. For prediction of the amount of caffeine and salicylic acid released from the granules in the present study, the equation for the planar case (eqn 1) was used and compared with experimental data measured to less than 50% release, viz.:

$$Q = [D(2A - c_s)c_s t]^{1/2} \quad .. \quad (1)$$

$$\text{or } Q = Kt^{1/2} \quad .. \quad .. \quad (1a)$$

where Q is the amount of drug released per unit exposed area (mg cm^{-2}), D is its diffusion coefficient (cm^2 s^{-1}) in the matrix, A its concentration in the matrix (mg cm^{-3}), c_s its solubility in the matrix (mg cm^{-3}) and t is the time (s).

Two important assumptions made in the application of this equation are:

(1) the rate-limiting step is the diffusion of the drug from the matrix

(2) the matrix is homogeneous and the drug is released directly from the matrix and not through interconnected pores or channels.

It was confirmed experimentally for caffeine that variation of the shaking rate failed to cause any alteration in the kinetics of release from the film, i.e. there are no diffusion layer effects in the system under the conditions used. Figs 2 and 3 present the

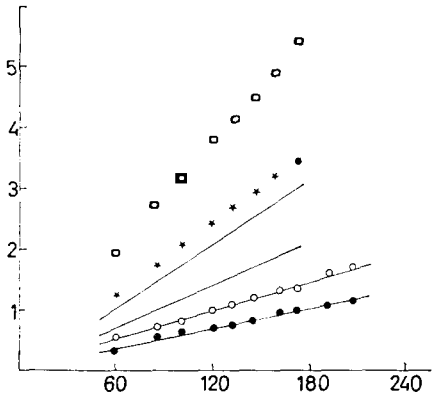

FIG. 2. Release of caffeine from coated placebo granules. Key (caffeine concentration in coating): ● 2; ○ 5; * 10 and □ 15%. Full lines represent predicted values.

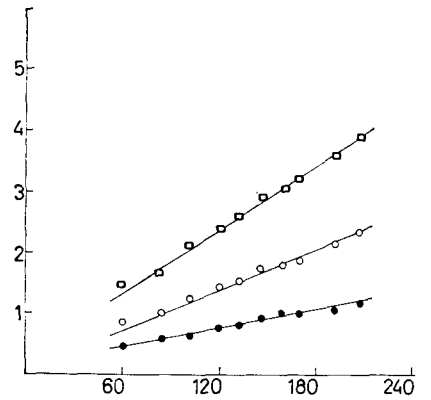

FIG. 3. Release of salicylic acid from coated placebo granules. Key (salicylic acid concentration in coating): ● 5, ○ 10 and □ 15%.

relationships between the quantity of caffeine and salicylic acid released and (time)$^{1/2}$ and show that in both systems the dependence is linear.

Data required for prediction of drug release kinetics according to equation (1) were measured earlier by permeation of caffeine and salicylic acid from aqueous solutions through linear ethyl cellulose films cast from chloroform solutions (Donbrow & Friedman 1975b). The diffusion coefficients obtained by using the time lag method (Barrer 1939) were $2{\cdot}26 \times 10^{-11}$ and $1{\cdot}96 \times 10^{-11}$ cm^2 s^{-1} for caffeine and salicylic acid, respectively. From the measured permeability coefficient for caffeine in ethyl cellulose of $4{\cdot}4 \times 10^{-11}$ cm^2 s^{-1}, the partition coefficient of caffeine between the film and water obtained using the partition—diffusion relation $P = DK_p$ was found to be 1·94. Henry's law observance was demonstrated for salicylic acid in sorption experiments and as the solubility of caffeine in ethyl cellulose films is much lower, observance of the law is assumed. This permits the use of the simple relation between partition coefficient and solubility for calculating the solubility of caffeine in ethyl cellulose film (C_m) by using the equation (Roseman & Higuchi 1970)

$$C_m = K_p C_w$$

where C_w is the water solubility of the drug. For a caffeine solubility of 25 mg ml^{-1} in water (Desai et al 1966), the corresponding film concentration of caffeine will be 48·5 mg ml^{-1}. Using equation (1) with the measured or calculated parameters for caffeine, together with the surface area calculated from the granule core dimensions, the drug concentration in the coating and the weights used, release rates have been predicted for the coated granules prepared in this work. These are shown in Fig. 2, together with the experimentally measured amounts of caffeine released. It can be seen that there is good agreement between the experimental and theoretical values at 2 and 5% concentration of the drug in the film. However, above this concentration level there is a positive deviation from the predicted values.

Scanning electron microscopy showed the 10 and 15% caffeine* films to contain microcrystals of the drug, whereas at a lower concentration heterogeneity was not evident. The fact that the release of the undissolved material from the surface of the film at higher drug content is faster may imply that the mechanism of release is different when microcrystals are present.

The large positive deviation in films containing above 5% caffeine points to the possibility that the release mechanism changes from homogeneous to heterogenous transport.

This would assume the formation of a capillary network within the film during drug solution allowing solvent penetration and leaching. In this case, release rate would depend on the solubility and diffusion coefficient of the drug in the leaching solvent according to the equations (Higuchi 1963):

$$Q = \left[\frac{D\epsilon}{\tau}(2A - \epsilon c_s)c_s t\right]^{1/2} \quad .. \quad .. \quad (2)$$

$$\text{or } Q = k\,t^{1/2} .. \quad .. \quad .. \quad .. \quad .. \quad (2a)$$

where the terms are defined as for equation (1) except that D and c_s relate to the values in the leaching medium and ϵ and τ are the porosity and tortuosity of the film. However, in experiments on linear films, in which the caffeine content (15%) was removed by 4 days extraction in water, sodium chloride permeation was checked conductimetrically and no penetration could be detected. Furthermore, the difference between the diffusion coefficient of caffeine in water and the film is of the order of 10^5, whereas its solubility is of the same order in these two media (Donbrow & Friedman 1975b). Assuming that the porosity is approximately 0·05 in the 5% drug film and the tortuosity is in the usual range of 1–3 (Higuchi 1963), their effect on the rate constant (eqn 2a) is much less than that of the diffusion coefficient change and one would expect the release rate of the pure heterogeneous process to be between thirty and one hundred times higher than that of the pure homogeneous process. From Fig. 2, this is evidently not the case in the experimental system. Furthermore, the release rate of salicylic acid is not influenced by change of the pH values of the receiver solutions (see Table 2). It seems therefore that at concentrations above 5%, the mechanism is complex, and involves both heterogeneous and homogeneous mechanisms.

The apparent release rate constants (K′) obtained from the slopes of the Higuchi equation plots, presented in Table 2 indicate that the caffeine is released more rapidly than the salicylic acid at corresponding concentrations. This faster release of caffeine does not accord with the homogeneous model since c_s salicylic acid $\gg$ c_s caffeine in the membrane. However, the possibility of a mixed homogeneous and heterogeneous mechanism would

* These concentrations are above the solubility value for caffeine in ethyl cellulose cited earlier of 48 mg ml^{-1}, which corresponds approximately to the 5% caffeine film.

Table 2. Drug release rate at different pH values of receiving solution.

Drug content % w/w	Apparent release rate constant ($K' \times 10^3 \times 7{\cdot}95$ cm^2) (mg s$^{-1/2}$) Water	pH 2·0	pH 9·6
Salicylic acid			
5	6·31	6·42	6·29
10	7·65	7·60	7·65
15	16·80	16·85	16·70
Caffeine			
2	4·95	5·12	5·18
5	7·65	7·61	7·58
10	20·40	20·71	20·38
15	31·00	31·82	31·21

allow for a greater enhancement of the permeation rate of caffeine than that of salicylic acid with increasing drug concentration. The increased porosity resulting from increased drug content would lead to a higher water content occupying the void space. The solubilities of caffeine in the ethyl cellulose and water regions are 48 and 25 mg ml^{-1} while those of salicylic acid are 300 and 2 mg ml^{-1}, respectively, consequently, the addition of water phase within the membrane would bring a larger quantity of caffeine into solution in the 10 and 15% films, assumed to contain undissolved caffeine, and the resultant increased concentration gradient would cause a pronounced enhancement of rate. However, in the salicylic acid films, the whole of the drug is apparently dissolved in the ethyl cellulose, hence the release mechanism probably follows the model of drug dissolved in the matrix (Jost 1960). There may also be a different membrane structure for the two drugs due to their plasticizing effects.

The dosage form described in this work is different from current drug products in that it consists of a placebo core which is coated with a suspension of the drug in a barrier-film insoluble in the gastrointestinal system, the drug being released by solution in the membrane matrix and diffusion from it. The insolubility of the matrix and the release mechanism ensure that drug release is a function of the design of the product and not of the conditions in the gastrointestinal system. This product would seem to have the further advantage of being relatively independent of the technological variables in production which influence many other forms of sustained-release products, enabling more exact and reproducible dose release.

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