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DRUG RELEASE AND SURFACE MORPHOLOGY STUDIES ON SALBUTAMOL CONTROLLED RELEASE PELLETS

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ABSTRACT

The air suspension technique was employed to prepare controlled release pellets of Salbutamol (as the sulphate). The aim of the present study was to determine the influence of various film coating additives on the release characteristics and surface morphology features of salbutamol sulphate pellets coated with Eudragit® RS30D which is the aqueous dispersion of a polymer synthesised from acrylic and methacrylic acid esters. Surface morphology features, which were examined using Scanning Electron Microscopy, revealed that triethyl citrate (plasticiser) was essential for the coalescence of polymeric membranes around the drug-loaded spheres. Higher concentrations (12.5%) of triethyl citrate displayed a more uniform and continuous polymer film resulting in a slower *in vitro* drug release. Micrographs of the cross-sections of pellets with higher concentrations of Eudragit® RS30D indicated the formation of thicker polymer membranes which accounted for the slower drug release rates. Hydroxypropyl methylcellulose (HPMC) inclusion in the polymer film coating increased salbutamol release rates due to its hydrophilic nature which promoted the formation of pores and cracks on the polymer films. A slower *in vitro* release of salbutamol was observed with higher concentrations of the hydrophobic anti-tackiness agent, magnesium stearate. The addition of salbutamol sulphate powder to the polymer dispersion enhanced

drug release rates due to increased film permeability. Polyethylene glycol 200 (PEG 200) resulted in an increased *in vitro* drug release due to both its water soluble nature as well as impairment of film formation attributed to too high a plasticiser content in the coating formulation. As compared to polyethylene glycol 300 (PEG 300) as a plasticiser, triethyl citrate retarded drug release to a greater extent and formed more homogeneous and compact polymer films. The moisture content of PEG 300 plasticised pellets showed a 0.6% increase in moisture content while triethyl citrate plasticised pellets displayed a loss of 0.01% moisture 8 weeks after storage at room temperature.

INTRODUCTION

Controlled release oral dosage forms of many drugs are often preferred over conventional oral dosage forms for a variety of reasons. These include the possible reduction of dosing frequencies thus improving patient compliance. Also, fluctuation of plasma drug levels is minimised which may reduce any drug related side-effects. Several studies (1-4) on controlled release preparations of various drugs have consequently demonstrated superior therapeutic effects over their conventional preparations. Salbutamol, a β_2-adrenergic agonist has a short plasma half life of 2 - 7 hours. This drug therefore requires frequent oral administration of 4 mg immediate release salbutamol tablets to maintain the desired steady state plasma levels. In order to optimise bioavailability and consequently to improve therapeutic efficacy, a controlled release pellets formulation of salbutamol was considered. A multiple unit dosage form instead of a single-unit dosage form was proposed because of various reported advantages (5-7). In recent studies aqueous coating systems have been shown to have various benefits over organic coating systems (8-9). As a result, Eudragit® RS30D, a methacrylate aqueous colloidal polymer dispersion was used as the film coating agent. The Wurster air suspension technique was selected for the preparation of the controlled release pellets due to advantages in efficiency, applicability and versatility (10-11).

The present study was undertaken to determine the influence of various formulation additives on the drug release profiles of controlled release salbutamol pellets.

MATERIALS AND METHODS

Materials

The following materials (laboratory grade) were obtained from commercial suppliers and were used as received :
Non-pareils (Size 853, Average diameter = 1.09 mm) (Adcock-Ingram, S.A.); salbutamol sulphate (Lennon, S.A.); povidone (BDH Chemicals, U.K.); Eudragit® RS30D (Rohm Pharma, Germany); triethyl citrate (Merck, S.A.); magnesium stearate (Protea, S.A.); hydroxypropyl methylcellulose (Protea, S.A.); ethyl alcohol (Protea, S.A.); polyethylene glycol 200 (BDH Chemicals, U.K.) and polyethylene glycol 300 (Merck, S.A.).

Methods

Preparation of pellets:

A prewarmed (60°C) solution of 5.75 g salbutamol and 0.55 g povidone in 200 ml ethanol / water (85:15 $^{v}/_{v}$) was sprayed onto the non-pareils (Aeromatic AG Muttenz Model Strea-1 fluid bed coating apparatus, 200 g charge, atomisation pressure : 0.6 bars, inlet temperature : 60°C, outlet temperature : 40°C, spray rate : 3.3 ml/min) to obtain drug-coated beads. Thereafter, several batches of drug-coated beads were sprayed with prewarmed coating liquid (40°C) of various combinations of Eudragit® RS30D and formulation additives (200 g charge, atomisation pressure : 0.6 bars, inlet temperature : 37°C, outlet temperature : 30°C, spray rate : 1.5 ml/min). The coated pellets were subsequently transferred to a paper-lined tray and cured at 38 ± 0.5°C for 24 hours in an air-heated Gallenkamp Model OV 160 oven.

Dissolution studies:

No compendial method for the dissolution testing of salbutamol oral drug products was available at the time of the study. The rotating basket method (USP XXII, 1990; apparatus 1; 900 ml deionised water; 37 ± 0.5°C; 100 rpm) was used to determine the *in vitro* drug release profiles of the controlled release pellets. In all studies, the Hanson Model SR2 dissolution test apparatus was used. At suitable time intervals, 5 ml samples were withdrawn from each

dissolution flask and replaced with equal volumes of fresh deionised water. The drug content in each sample was analysed by ultra-violet spectrophotometry at 274 nm using a Beckman DU64 spectrophotometer. Readings were corrected for any dilution by sample replacement. All experiments were performed in quadruplicate and each data point on the graphs reflects the mean of the calculated values.

Scanning electron microscopy:

Whole and cross-sectioned pellets were mounted on brass stubs using double-backed adhesive tape. Mounted samples were sputter-coated for 5 - 10 minutes at 1.1 kV under an argon atmosphere with gold-palladium (Polaron SEM Coating Unit E5000) before examination under the Philips SEM 500 scanning electron microscope. The images obtained were captured on Ilford Pan-F black and white 35 mm film.

Moisture content determination:

0.36 g of pellets (equivalent to 8 mg salbutamol) from 2 batches, one plasticised with triethyl citrate and the other with polyethylene glycol 300 (PEG 300), were placed in Size 0 clear hard gelatin capsules. The capsules together with 2.00 g of activated silica gel (as a dessicant) were then placed in each of 2 rectangular, amber glass bottles which were closed with bakelite screw top lids and placed in a cupboard at room temperature (20 ± 2°C). The moisture content of the pellets were determined immediately after curing and 8 weeks after storage at room temperature.The analysis was performed using a Karl Fischer Automat E547 coupled to a Multi-Dosimat E415 and Multi Burette E485. In all studies three replicates, each using 0.2 g of coated pellets, were performed.

RESULTS AND DISCUSSION

Effect of Triethyl Citrate

Plasticisers promote polymeric deformation thereby enhancing film coalescence and are therefore an indispensable component of a coating formulation.

The results of the dissolution tests (Figure 1) emphasise the importance of triethyl citrate as a

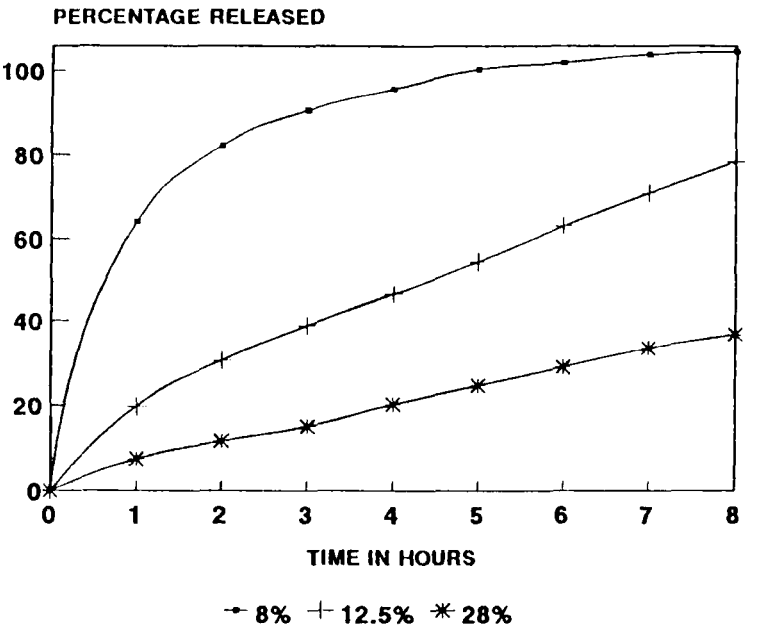

FIGURE 1
Effect of triethyl citrate on the drug release profiles of salbutamol sulphate coated pellets.

plasticiser for Eudragit® RS30D. As the quantity of triethyl citrate increased from 8% to 28%, the coated pellets displayed a slower *in vitro* release of salbutamol.

Scanning electron micrographs of the surfaces of pellets including 8% and 12.5% triethyl citrate in the formulation were compared in an attempt to explain the observed drug release characteristics. At a low plasticiser concentration of 8%, the latex particles were insufficiently plasticised. This therefore interfered with the coalescence or fusion of the latex particles, hence resulting in the discontinuous polymer film observed (Figure 2A). Increasing the plasticiser concentration to 12.5% enhanced the deformation and coalescence of the polymer spheres. Consequently, the surfaces of these pellets showed an improvement in the smoothness and continuity of the polymer film (Figure 2B) which resulted in the slower *in vitro* drug release observed.

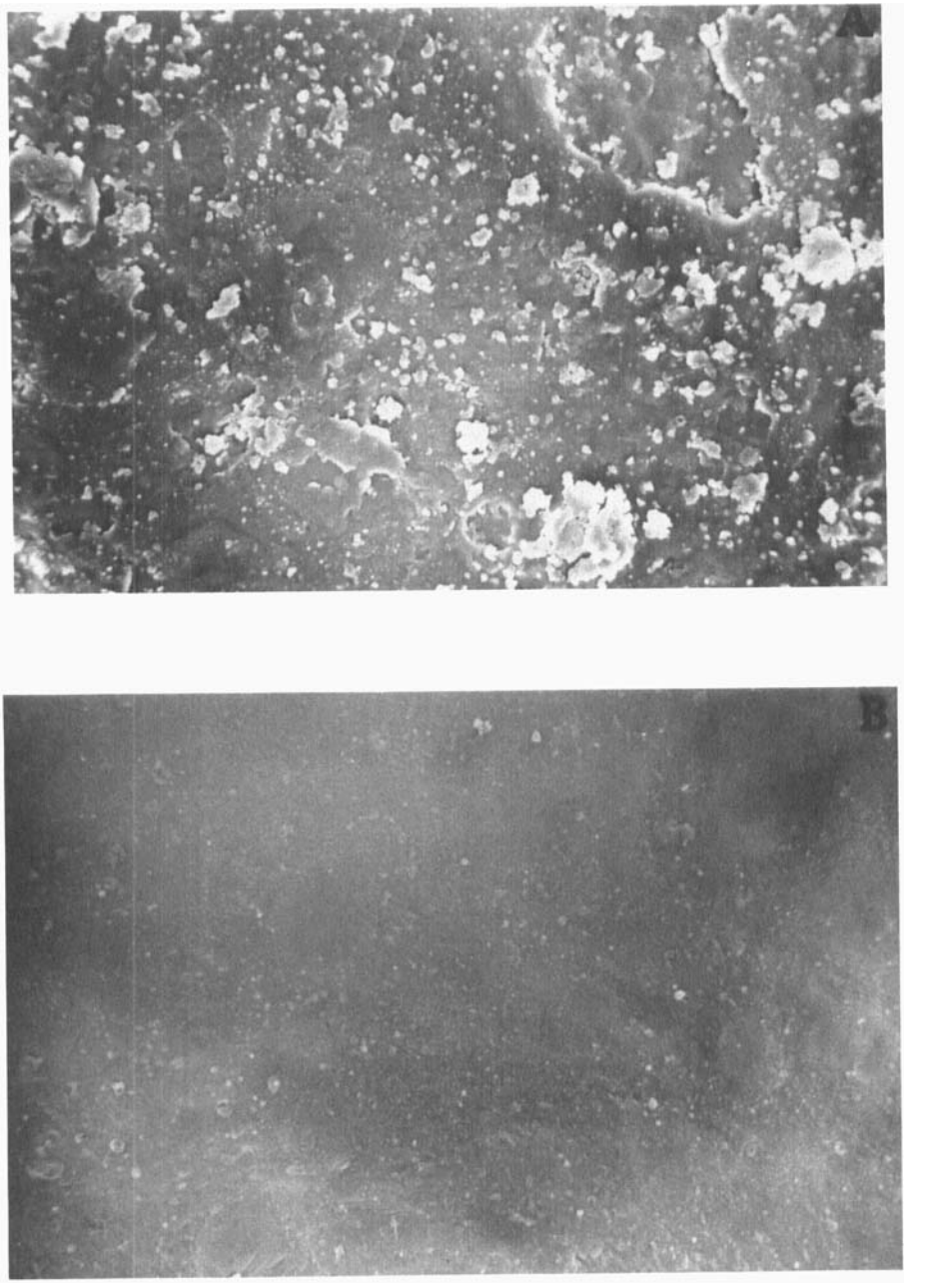

FIGURE 2
Surface morphology of controlled release pellets plasticised with various quantities of triethyl citrate. A)8% B)12.5%
(Magnification: X640)

Effect of Eudragit® RS30D

By maintaining the plasticiser (triethyl citrate) quantity constant at 16.67% relative to the polymer content it was shown that drug release rates were inversely proportional to the quantity of polymer coated onto the non-pareils (Figure 3). The drug release data from each batch were fitted to first-order kinetic equations. Linear regression analyses were performed and the computed drug release rate constants were correlated to the polymer membrane thickness of the pellets from these batches (Table 1). The polymer membrane thickness of pellets was measured using a scanning electron microscope.

The data in Table 1 clearly shows that an increase in the polymer quantity resulted in a thicker polymer membrane. Hence, the increase in polymer membrane thickness retarded the migration of salbutamol through the polymer wall material into the dissolution medium. This, therefore, explains the slower *in vitro* drug release observed with increased quantities of polymer content. In support of the findings of this study, a similar inverse relationship between polymer membrane thickness and the drug release rate constant was reported by Jambhekar *et al.* (12).

In another investigation, when the quantity of triethyl citrate in the formulation was kept constant relative to the quantity of non-pareils (0.75%) as with all other excipients, the *in vitro* release of salbutamol increased with increased quantity of polymer (Figure 4). Based on the findings exploring the influence of triethyl citrate on drug release (Figure 1 and Figure 2), the results obtained in this study could be attributed to the decrease in the ratio of plasticiser:Eudragit® RS30D combination as the quantity of polymeric material increases. Hence, this results in insufficient deformation of the colloidal polymeric spheres resulting in poor film formation and faster drug release rates.

Effect of Hydroxypropyl Methylcellulose

The ability of HPMC to modify the release characteristics of salbutamol is illustrated (Figure 5). The percentage of salbutamol released per unit time increased dramatically with the incorporation of HPMC into the coating liquid.

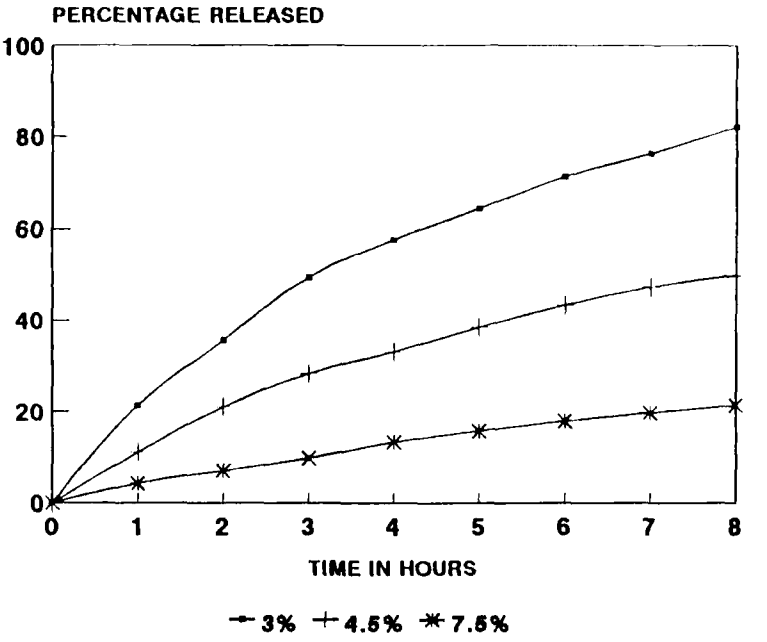

FIGURE 3
Effect of Eudragit^{R} RS30D on the drug release profiles of salbutamol sulphate coated pellets (Plasticiser quantity constant relative to mass of polymer).

TABLE 1:
Relationship Between Polymer Quantity, Drug Release Rate Constant and Polymer Membrane Thickness

POLYMER QUANTITY(%)	RELEASE RATE CONSTANT (k)(hr^{-1})	*POLYMER MEMBRANE THICKNESS (μm)
3.0	0.210	22.29±3.29
4.5	0.0875	47.13±4.15
7.5	0.0299	72.50±5.40

*Mean of 4 replicate determinations.

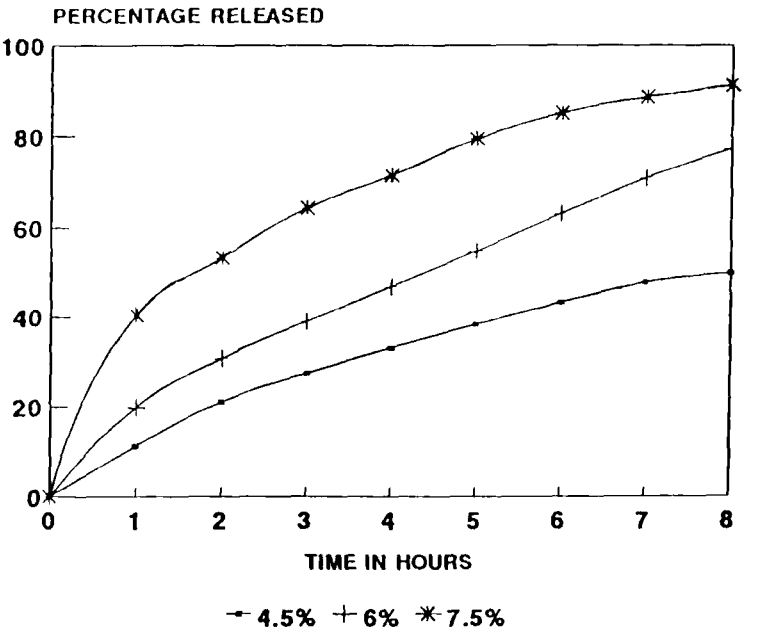

FIGURE 4
Effect of Eudragit® RS30D on the drug release profiles of salbutamol sulphate coated pellets (Plasticiser quantity constant relative to mass of non-pareils).

The formation of pores and cracks/channels on the film coat after dissolution testing is clearly shown (Figures 6A and 6B). The access of dissolution medium to the drug layer is therefore promoted thus enhancing the drug release rates. This effect may be explained by the water-soluble nature of HPMC which increases hydration of the polymer membrane. The subsequent leaching out of HPMC from the film coat during dissolution testing may explain the observed morphological features of the pellets.

Furthermore, during the study, an apparent visual increase in the viscosity and slight adhesiveness of the polymer coating solution was observed with the inclusion of HPMC to the coating formulation. Consequently, agglomeration of the pellets during the coating process was more prevalent than during the

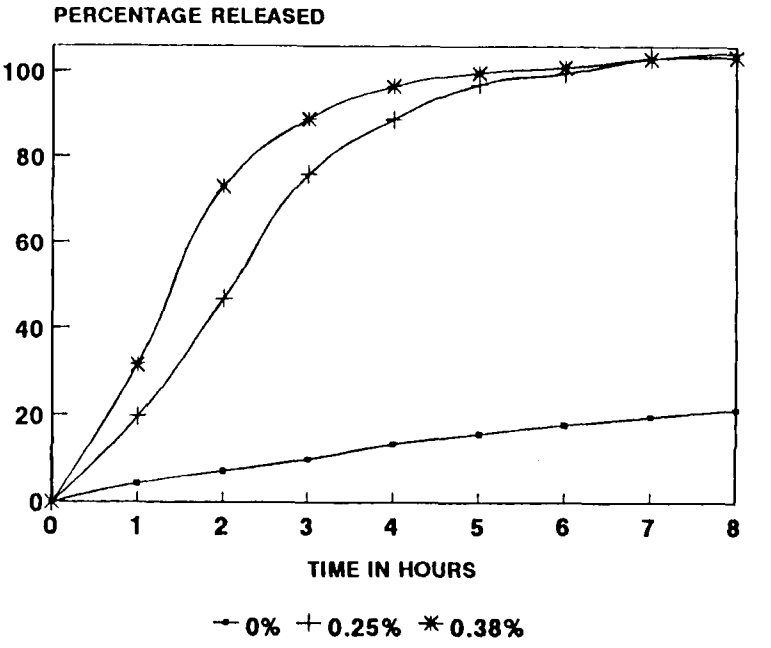

FIGURE 5
Effect of HPMC on the drug release profiles of salbutamol sulphate coated pellets.

study where no HPMC was used. This therefore necessitated an intermittent spray cycle to complete the coating process. Hence, the surface imperfections resulting from agglomeration of the pellets could also be a contributing factor to the increased drug release rates. Non-reproducible drug release rates between different batches could therefore be expected and HPMC was considered an undesirable additive under the operating conditions of this study.

Effect of Magnesium Stearate

Magnesium stearate was incorporated into the formulation (as a lubricant) to reduce the inherent tackiness of Eudragit® RS30D and therefore overcome processing difficulties associated with this polymer. The release of salbutamol decreased with a corresponding increase in the quantity of magnesium stearate (Figure 7). The slower *in vitro* drug release

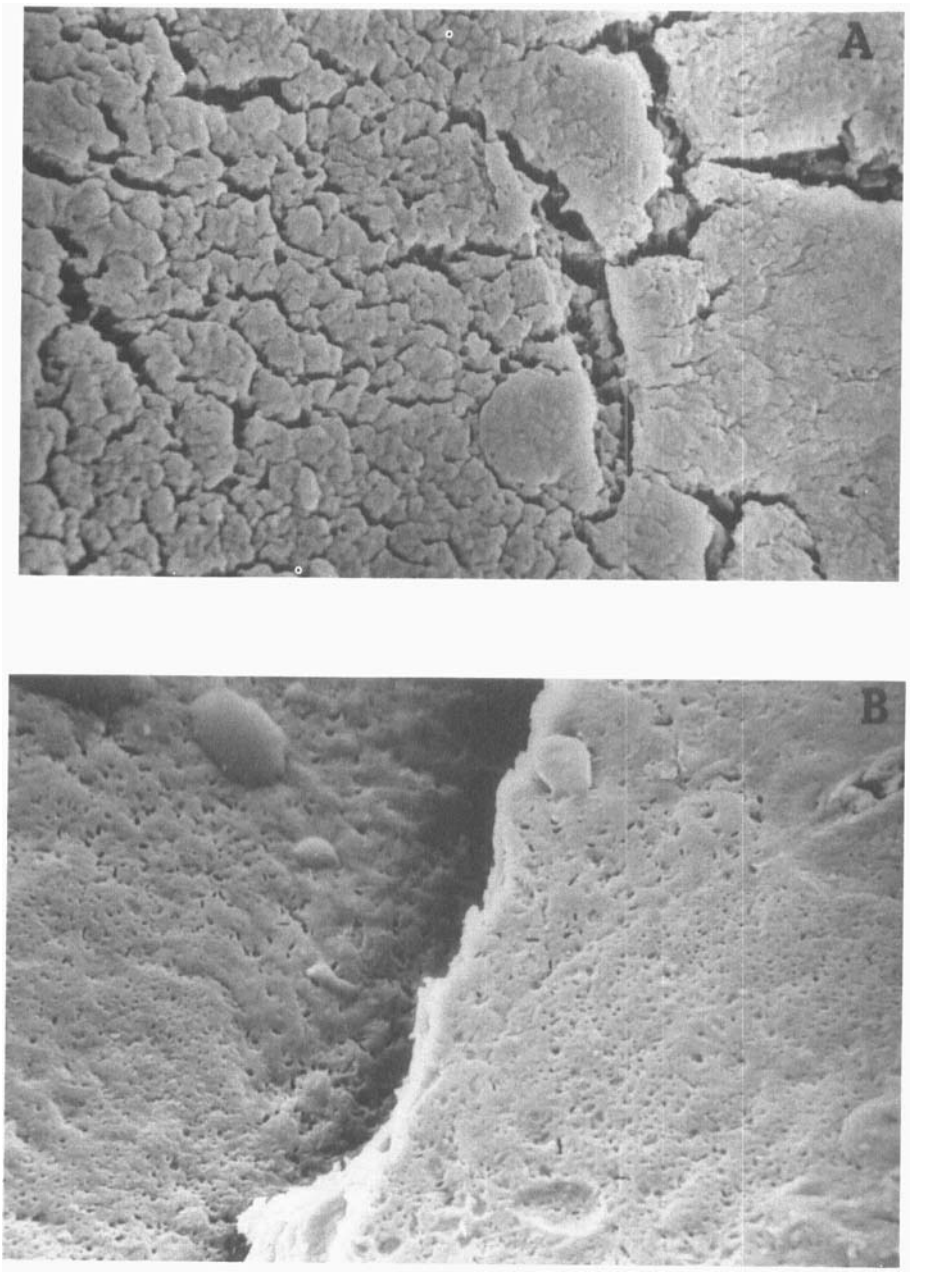

FIGURE 6
Surface morphology of controlled release pellets containing 0.25% HPMC after dissolution testing. (Magnification X2500)

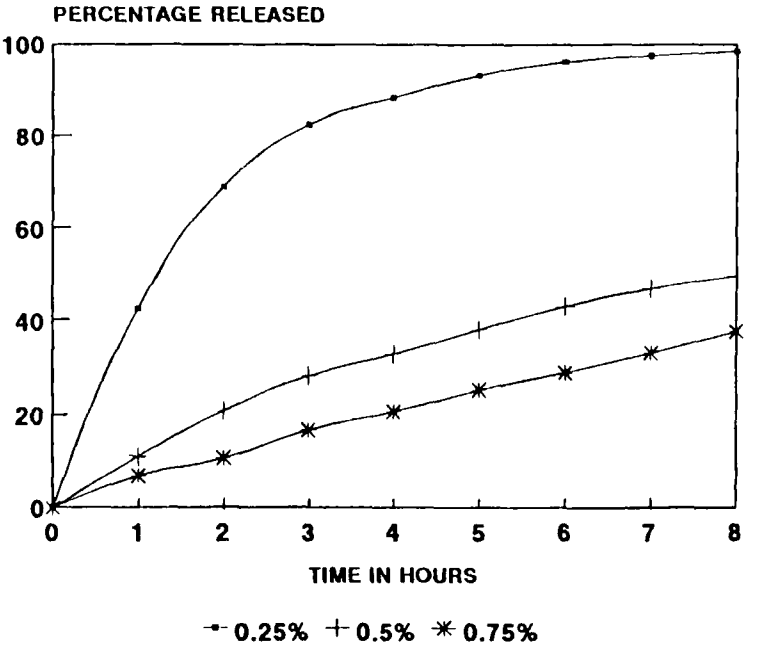

FIGURE 7
Effect of magnesium stearate on the drug release profiles of salbutamol sulphate coated pellets.

with larger quantities of magnesium stearate is possibly due to the hydrophobic nature of magnesium stearate which inhibits hydration of the polymeric membrane and thus retards the release of salbutamol into the dissolution medium.

Effect of Addition of Drug to the Coating Liquid

Small quantities of salbutamol sulphate powder were added to the primary polymer dispersion in an attempt to slightly alter drug release characteristics. However, as shown in Figure 8 even a small percentage of 0.13% drug powder resulted in a profound increase in drug release rates. A 0.75% inclusion of salbutamol sulphate powder resulted in an almost immediate release of drug (81.02% in 1 hour). The obvious increase in the permeability of the polymer membrane could be due to an increase in its porosity upon the drug in the polymer layer dissolving

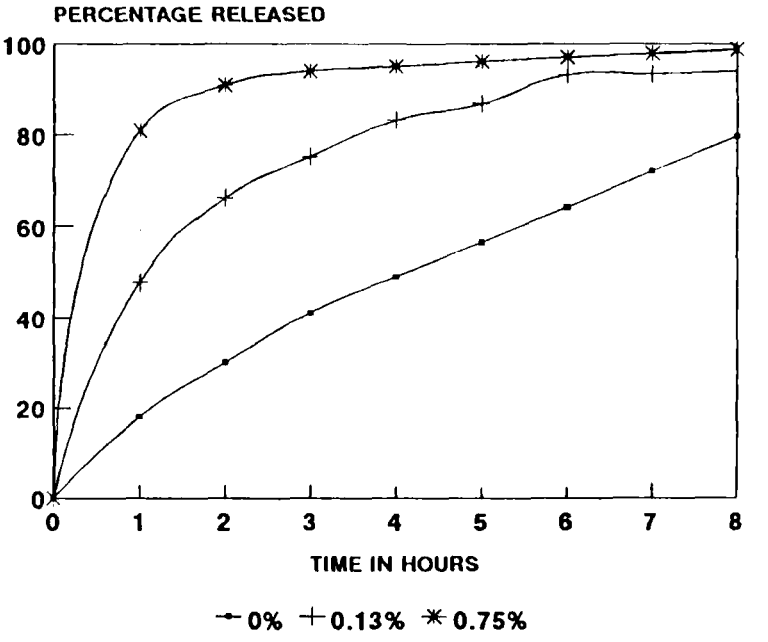

FIGURE 8
Effect of the addition of drug powder to the polymeric liquid on the drug release profiles of salbutamol sulphate coated pellets.

rapidly in the dissolution media. An examination of the polymer membrane surfaces, after 8 hours of dissolution testing, of pellets incorporating 0.13% salbutamol in the polymer layer revealed a myriad of tiny pores throughout the entire surface of the pellets (Figure 9).

In contrast to this study Li *et al.*(13) found that 0.25% of theophylline powder incorporated into an ethylcellulose dispersion resulted in only a slight increase in drug release rates, with rapid release rates only being achieved with a 1% inclusion (±60% in 1 hour). The reason for the above occurrence could be as a direct result of the drugs's solubility that is compared to theophylline which is only slightly soluble in water, salbutamol sulphate is freely soluble in water thus promoting the formation of further numerous pores on the polymeric membrane as

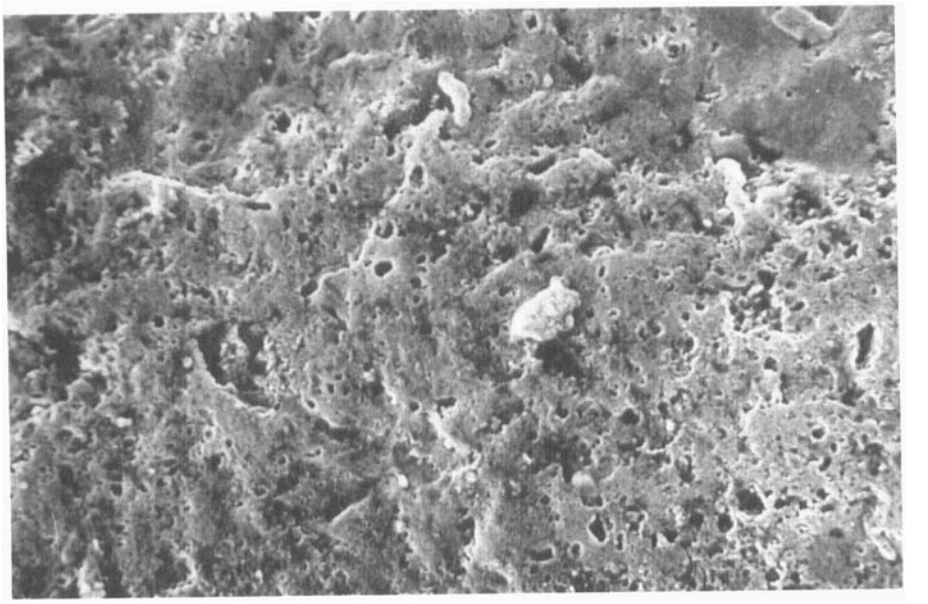

FIGURE 9
Surface morphology of controlled release pellets containing 0.13% drug powder in the polymer dispersion after dissolution testing. (Magnification: X2500)

the drug in the polymer layer initially dissolves easily in the dissolution media. Consequently, this resulted in faster initial drug release rates as compared to theophylline.

Effect of Polyethylene Glycol 200 (PEG 200)

The drug release characteristics as presented in Figure 10 indicate a faster *in vitro* release of salbutamol with the inclusion of 0.5% and 1% PEG 200 to the polymer dispersion. The water soluble nature of PEG 200 resulted in increased film permeability and consequently a faster *in vitro* drug release.

A further explanation for the observed drug release characteristics is also presented as follows. During the coating process of batches including 0.5% and 1% PEG 200, it was observed that the pellets were

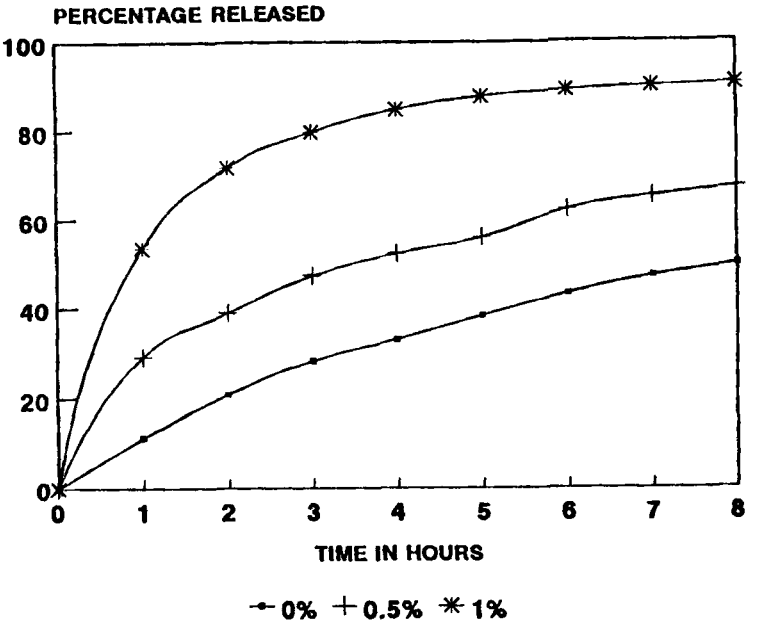

FIGURE 10
Effect of PEG 200 on the drug release profiles of salbutamol sulphate coated pellets.

tacky resulting in agglomeration and poor fluidisation of the product mass. Furthermore upon storage, cured pellets adhered to each other and consequently formed a clump of pellets devoid of free-flowing characteristics. In contrast, pellets from the batch with no PEG 200 in the polymer layer showed no processing difficulties and were also free flowing upon storage. An examination of the polymer coating formulations employed for these batches (Table 2) possibly explains the above phenomenon. PEG 200 can also be used as a plasticiser, thus its combination with triethyl citrate in the formulation resulted in the plasticiser content increasing to 38.9% (based on polymer content). Since the recommended plasticiser quantity for Eudragit® RS30D IS 10 - 20% (14) there was clearly an excess of plasticiser in the formulations containing both triethyl citrate and PEG 200 as coating excipients. The consequent excessive softening of the polymeric spheres during coating could be a reason for the observed tackiness and agglomeration of

TABLE 2:
Comparison of Pellets Formulations Investigating the Influence of PEG 200

CONSTITUENT	BATCH 0% PEG 200	WITH 1% PEG 200
Eudragit® RS30D	4.5% (9 g)	4.5% (9 g)
Magnesium stearate	0.5% (1 g)	0.5% (1 g)
PEG 200	0%	1% (2 g)
Triethyl citrate	16.67% (1.5 g)	16.67% (1.5 g)
Deionised water	qs 100 ml	qs 100 ml

the polymer surfaces. Hence, the resulting impairment of favourable film formation is therefore also a contributory factor to the faster *in vitro* drug release observed with PEG 200.

The quantities of both excipients in a single formulation should therefore be carefully considered in order not to exceed the maximum recommended plasticiser quantity for Eudragit® RS30D formulations.

Comparison of Polyethylene Glycol 300 (PEG 300) and Triethyl Citrate as Plasticising Agents for Eudragit® RS30D

The effectiveness of equivalent amounts of PEG 300 and triethyl citrate as plasticisers in retarding drug release of salbutamol controlled release pellets was compared. Two separate batches of pellets, one plasticised with 12.5% PEG 300 and the other with 12.5% triethyl citrate, and similar in all other excipients, were prepared. As shown in Figure 11 triethyl citrate was capable of retarding drug release to a greater extent than an equivalent quantity of PEG 300. Triethyl citrate is soluble in water while PEG 300 is freely water soluble. Hence PEG 300 is overall a more hydrophilic plasticiser than triethyl citrate and it therefore has the capacity to enhance film

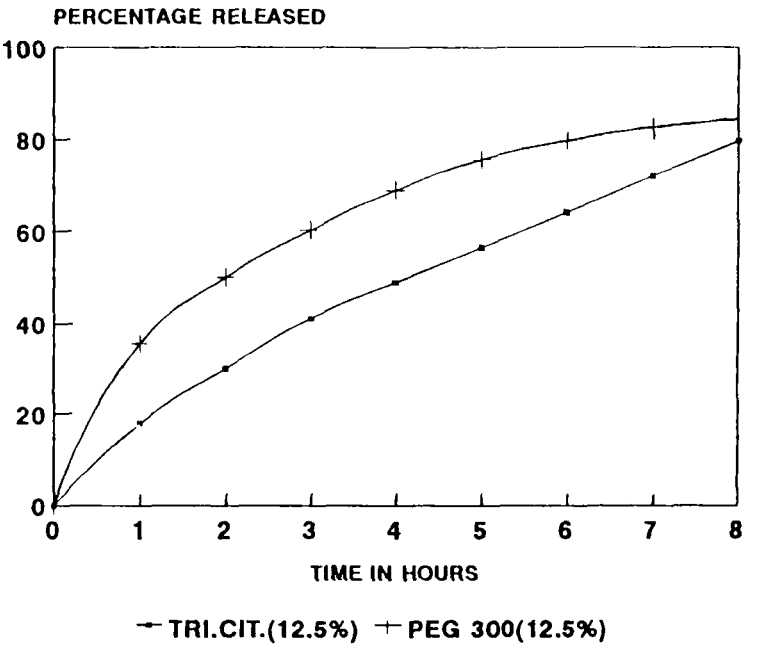

FIGURE 11
Comparison of drug release profiles of pellets coated with different plasticisers.

permeability to a greater extent during dissolution testing.

Furthermore, scanning electron microscopy studies on the surfaces of pellets plasticised with PEG 300 and triethyl citrate indicated clear differences in their morphological features. The polymer film plasticised with triethyl citrate was clearly more uniform (Figure 12A) than PEG 300 plasticised film coats (Figure 12B). This therefore explains the faster drug release observed with PEG 300 as a plasticiser. Hence although PEG 300 generated polymer membranes capable of providing controlled drug release, the discontinuous and imperfect surface features were considered undesirable.

In addition to their permeability characteristics, the moisture content of pellets plasticised with PEG 300 and triethyl citrate prior to

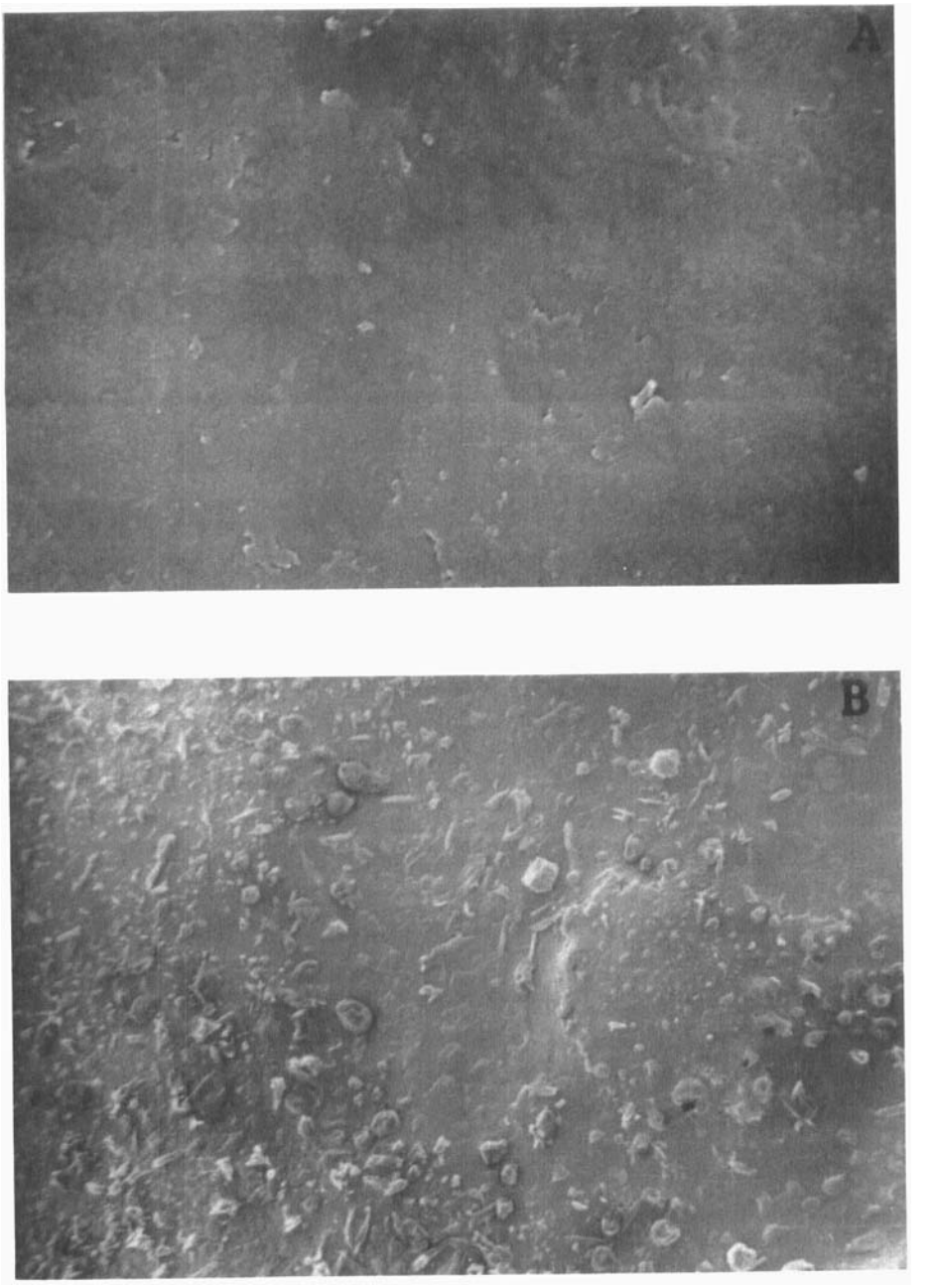

FIGURE 12
Surface morphology of controlled release pellets plasticised with:
A) 12.5% Triethyl citrate
B) 12.5% PEG 300
(Magnification: X640)

TABLE 3:
Moisture Content of Eudragit® RS30D Coated Pellets Incorporating Different Plasticisers

PLASTICISER AND QUANTITY	MOISTURE	CONTENT(%)	
	*Initially	*8 Weeks after storage	% Moisture absorbed\ lost
Triethyl citrate - 12.5%	2.66±0.17	2.65±0.006	-0.01
PEG 300 - 12.5%	3.19±0.060	3.79±0.036	0.60

* Mean of 3 replicates.

and after 8 weeks of storage at room temperature was compared and the mean data are presented in Table 3.

As indicated in Table 3, the pellets with triethyl citrate plasticised films displayed a loss of 0.01% moisture while those with PEG 300 showed a gain of 0.6% moisture after 8 weeks of storage at room temperature (20 ± 2°C). These results indicate a minor change in moisture content of both batches of pellets. Although a 0.6% moisture absorption (based on total mass of pellets) of PEG 300 plasticised Eudragit® RS30D coated pellets was considered minor with regard to this particular study, the results obtained could nevertheless be useful when selecting coating additives where a low dose drug being incorporated into the pellet dosage form is sensitive to moisture degradation. Therefore in such cases the use of triethyl citrate instead of PEG 300 which is slightly hygroscopic could lead to improved stability of moisture sensitive drugs.

CONCLUSIONS

The data generated from the study revealed that the quantity and the physicochemical properties of the coating additives employed influenced the release of

salbutamol through the polymer membrane. This approach can be used to systematically develop a formulation which exhibits a desirable controlled drug release profile.

Scanning electron microscopy studies proved to be effective in explaining the drug release characteristics displayed by the pellets. The morphological features of the pellets clearly influenced their drug release behaviour.

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