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THE DEVELOPMENT OF AN ORAL CONTROLLED RELEASE PELLETS FORMULATION OF DIETHYLPROPION HYDROCHLORIDE

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ABSTRACT

In the present study, controlled release pellets of the anorexigenic, diethylpropion hydrochloride were formulated. Selected polymeric film coatings were applied to the drug-loaded non pareils and their effect on in vitro drug release from the multiple-units dosage form was examined. It was found that a combination of Eudragit^{R} RS, polyethylene glycol 200 and magnesium stearate produced a stable film coat that controlled drug release as desired. Dissolution data demonstrated that this formulation displayed predictable and reproducible drug release characteristics.

INTRODUCTION

The choice of an appropriate formulation for a selected drug may play a significant role in successful drug therapy. While several different types of oral controlled release products have been designed to release drug at various rates, all controlled release products are designed so that

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the systemic rate of drug absorption is limited by the rate of drug release from the delivery system[1].

Physiological factors influence both gastrointestinal transit time and the release of drug from a controlled release dosage form, thus also influencing the uptake of drug into the systemic circulation[2]. Gastric emptying of a single unit dosage form may be characterised by an essentially random process with an inherently large inter-subject variablity. The application of the multiple units dosage principle eliminates the dependency of the depot on gastric emptying, since the sub-units are sufficiently small (i.e less than 2 mm diameter) to pass the human pylorus even when the sphincter is closed[3]. It has been suggested that the greatest advantage of the controlled release pellets formulation lies in the reproducible gastrointestinal transport of this multiple units preparation[4]. In addition it has been suggested[5] that the multiple particulate systems that are coated with a non-biodegradable diffusion membrane will allow reproducible, pH-independent zero-order drug release.

The model drug chosen for this study was diethylpropion hydrochloride which is a phenylethylamine derivative that has been used as an anorexigenic in humans. Diethylpropion hydrochloride is readily absorbed from the gastrointestinal tract after oral administration. Its quantitative absorption ability and short half-life (1.5 to 3 hours) make it an ideal candidate for controlled release[6,7,8]. Banci et al.[9] have found that diethylpropion, administered in a controlled release manner, allows a more regular absorption rate and reduced the "peaking effect" encountered after normal administration.

MATERIALS AND METHODS

Materials

The following materials were used : diethylpropion hydrochloride (Temmler-Werke, Marburg, Germany); polyvinylpyrrolidone, M.W. 4400 (BDH Chemicals, Poole,

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England); ethylcellulose (EC), 48.5% ethoxy content, 2.42-2.53 degree of substitution (BDH chemicals, Poole, England); hydroxypropyl methylcellulose (HPMC), viscosity (2% aqueous solution) 4 000 cps (Protea Industrial Chemicals, South Africa); Eudragit RS 100 (Rohm Pharma, Darmstadt, Germany); polyethylene glycol 200 (BDH Chemical, Poole, England) dibutyl phthalate (BDH Chemicals, Poole, England) and magnesium stearate (BDH Chemicals, Poole, England). All other chemicals and solvents were reagent grade and were used as received. Tenuate Dospan (Mer National) is a commercially available preparation containing 75 mg diethylpropion hydrochloride embedded in a controlled release hydrophilic matrix. The release pattern of this preparation was used as a reference standard.

Coating of pellets

All coating procedures were performed in an Aeromatic AG Muttenz Model Strea-1 laboratory scale fluid bed apparatus. The only modification to the system was the placing of a 40 mesh (420 microns) sieve plate onto the perforated bottom of the fluid-bed drier to prevent the small non-pareils/pellets from falling through. The fluid-bed apparatus was bottom-fitted with a 0.8 mm binary nozzle and was coupled to a Fiac gmn 50 air compressor which produced the compressed air necessary for the atomisation of the spray solution. The size of the droplets in the spray solution was regulated by the size of the nozzle and the atomising pressure[10,11]

Coating technique

All batches of pellets were prepared by coating a layer of drug onto non-pareils (1.00-1.18 mm) and then coating a polymer membrane around the drug-loaded beads. This method is convenient, simple and suitable for preparation and analysis of potent drugs. The formulation for the drug-coated beads consisted of 75 mg of diethylpropion

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TABLE 1

Operating Conditions for Drug Coating

OPERATING CONDITION	SETTING
Atomising air pressure	0.6 bars
Fluidised air velocity	120m³/h
Inlet temperature	60°C
Outlet temperature	50°C
Solution temperature	60°C
Flow rate of coating solution	4.7 ml/min
Drying time	60 min

hydrochloride (per capsule) coated onto non-pareils (328 mg) with the aid of povidone (2%) as binder and ethyl alcohol (96%) as the coating solvent.

The non-pareils were charged into the pre-warmed chamber of the fluid-bed drier and then fluidised at 60°C for 30 minutes (spray rate : 4.7 ml/min).

The general operating conditions of the fluid-bed apparatus are given in Table 1.

Application of the polymer coats

Ethylcellulose : Drug-loaded non pareils were coated with known concentrations (5% and 10%) of ethyl cellulose which is a known film-former. Hydroxypropyl methylcellulose was included as a channelling agent in selected batches. Ethyl alcohol was selected as the coating solvent.

The coating solution was introduced as an atomised spray at a rate of 2 - 5 ml/min. The coating fluid was applied as rapidly as possible without causing agglomeration of pellets. Coating was intermittent with application (5 minute intervals) and drying (30 minute intervals) being alternated until the coating was completed. Operating conditions were the same as those for drug coating (Table 1).

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Methacrylates (Eudragit® RS) : The advantages and applicability co-polymers (Eudragit®) have been well documented[13]. Eudragit® RS was chosen as a suitable polymer as it is known to be non-biodegradable and only slightly water-permeable, and that it allows pH-independent diffusion-controlled release of drug.

Acetone and isopropyl alcohol (isopropanol) were combined in equal parts to from a rapidly drying co-solvent. Eudragit® RS films were applied at 3%, 4% and 5% concentrations onto drug-coated non-pareils.

The polymer solution was applied in an uninterrupted manner to the pellets at a rate of about 5 ml/min. This process was an improvement on the ethylcellulose process as the former could be completed in one hour whereas the latter (ethylcellulose) usually required twenty hours for completion.

The prepared pellets were cured overnight at 37°C before initiating any further dissolution studies. Six samples were tested for each batch.

Room temperature storage of the pellets coated with Eudragit® RS indicated the necessity of including a plasticiser and a lubricant in the coating membrane.

Further batches of pellets were therefore coated with known concentrations (2%, 3%, 4% and 5%) of Eudragit® RS using 0,5% polyethylene glycol 200 as plasticiser and 0.5% magnesium stearate as lubricant. Operating conditions for the polymer coating were similar to those for drug coating (Table 1); the only difference being that the coating temperature was 45°C and the solution temperature was 50°C for the polymer coating.

For all batches coated with Eudragit® RS, plasticiser and lubricant , the drug-loaded non-pareils were prepared as described earlier (Coating Technique). After being oven-dried at 37°C overnight, these beads were fluidised for 30 minutes in the prewarmed fluid-bed apparatus.

The coating mixture was then introduced as an atomised spray at the rate of 2.5 - 3.0 ml/min. Intermittent periods

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of coating (5 min.) and drying (10 min.) were repeated until coating was complete.

The pellets were then dried at 50°C for a further 60 minutes in the fluid-bed apparatus. The newly prepared batch was cured overnight in an oven with an air-circulating fan at 37°C. Six samples each of about 0.45 g of pellets (equivalent to 75 mg of diethylpropion hydrochloride), accurately weighed, were then subjected to dissolution studies.

Dissolution studies

Dissolution studies were performed using the paddle method (USP XXII, Apparatus 2) at 50 rpm rotation. In all experiments a six station dissolution apparatus (Caleva Model 7ST) was used. Deionised water (900 ml) at 37 ± 0.5°C constituted the dissolution medium.

Aliquots (10-20 ml) were removed at 0.5, 1, 2, 4, 6 and 8 hours and were filtered through 0.8 µm AA Millipore filters before they were analysed by spectrophotometry at 254 nm (Beckman DU30 Spectrophotometer).

RESULTS AND DISCUSSION

Ethylcellulose as film-former

Release rates of diethylpropion hydrochloride from ethylcellulose-coated pellets were measured in relation to wall thickness and membrane permeability. Hydroxypropyl methylcellulose (HPMC) combined with ethylcellulose has previously been used to form transport channels for drug penetration through the polymer membrane to the dissolution medium[14].

Figure 1 illustrates the difference in dissolution rates between the pellets coated with 5% ethylcellulose and the pellets coated with 10% ethylcellulose. As might be expected, the release rate decreased as the film thickness increased, suggesting that the drug solution has to diffuse

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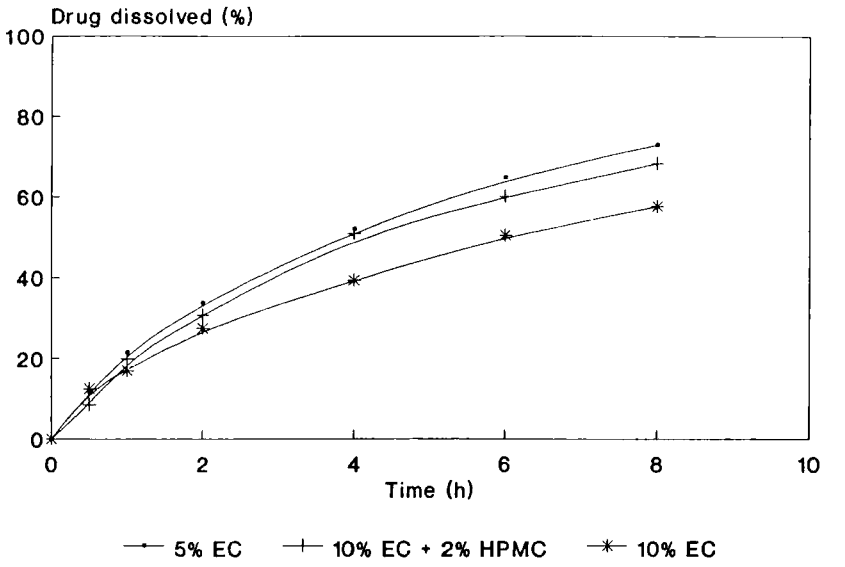

FIGURE 1
Drug dissolution of pellets coated with EC and HPMC as a function of time

through a thicker membrane before dissolution in the surrounding medium occurs.

Figure 1 also shows that the release rate was increased as the HPMC content was increased from 0% to 2% in a 10% ethylcellulose coat. An increase in release rate, which accompanied the increased HPMC level, suggests a large increase in the formation of pores in the ethylcellulose matrix. The pores appear to facilitate diffusion on the drug into the dissolution medium. Hence by six hours the pellets with 2% HPMC had released 70% of the drug while the pellets with no HPMC had released only 50% of the total drug content. It is probable that the permeability mechanism was controlled by diffusion through the film polymer matrix and that the rate of release was a function of wall thickness and composition of the membrane. Donbrow and Samuelov[14] have also shown that the drug release through ethylcellulose films is a function of membrane thickness and composition.

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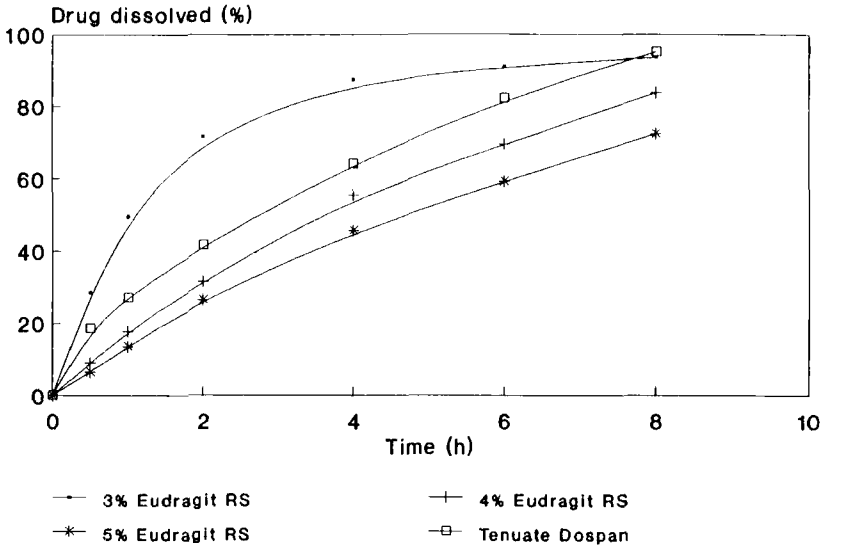

FIGURE 2
Drug dissolution of pellets coated with Eudragit RS as a function of time

During the coating of the batches described it became evident that the high viscosity of the ethylcellulose alcoholic solution caused the agglomeration of pellets in the fluid-bed apparatus. In order to avoid the agglomeration, more dilute solutions were used. Furthermore, pellets were coated for short time periods (5 minutes) and dried for longer periods (30 minutes) at relatively high temperatures (70°C). As a result, the processing times for these batches were very lengthy (up to 20 hours for 1 batch) rendering the procedure impractical. Thus ethylcellulose was considered to be inappropriate for purposes of this investigation.

Methacrylates as coating polymers

Drug release patterns for the batches coated only with Eudragit® RS as a coating polymer are shown in Figure 2. Figure 2 also demonstrated the similarity in the release

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profiles of the batch coated with 5% Eudragit® RS and RS Tenuate Dospan® 75mg Tablets.

As might be expected, the rate of drug release from the prepared pellets was inversely proportional to the thickness of the polymer coat. The thicker the membrane, the longer is the penetration time of the dissolution medium and thus drug release is delayed. It was therefore found that the 3% Eudragit® RS-coated batch released drug most rapidly while the 5% batch released the drug relatively slowly. When the 4% Eudragit®-coated pellets formulation is compared to the reference (Tenuate Dospan®), it is apparent that a degree of similarity exists between the release profiles with a difference of about 10% (percentage dissolved) at each sampling point. Storage of the pellets at room temperature (25 ± 3°C) for 1 month however revealed on visual inspection that the surfaces of the pellets hardened and became brittle during storage and were therefore unsuitable.

The use of Eudragit® RS has also previously been associated with film hardening as a function of time[15]. Clearly, the sole use of Eudragit® RS as a coating polymer with no added excipients failed to provide a product that complied with the stability requirements for a chosen dosage form.

Inclusion of plasticers in the polymer membrane

A plasticiser was included in the coating formulation in order to improve the stability of the film coat by altering the flexibility of the membrane.

The inclusion of suitable plasticers in polymeric films has been studied[16,17,18]. By lowering the glass transition temperature of the polymer[19], the plasticer serves to alter physical properties such as flexibility, hardness, tensile strength and elasticity. Polymer-plasticer systems differ widely and compatibility is specific. Several polymers are compatible for inclusion in Eudragit® RS films, viz. the phthalates (especially, dibutyl phthalate) and the polyethylene glycols.

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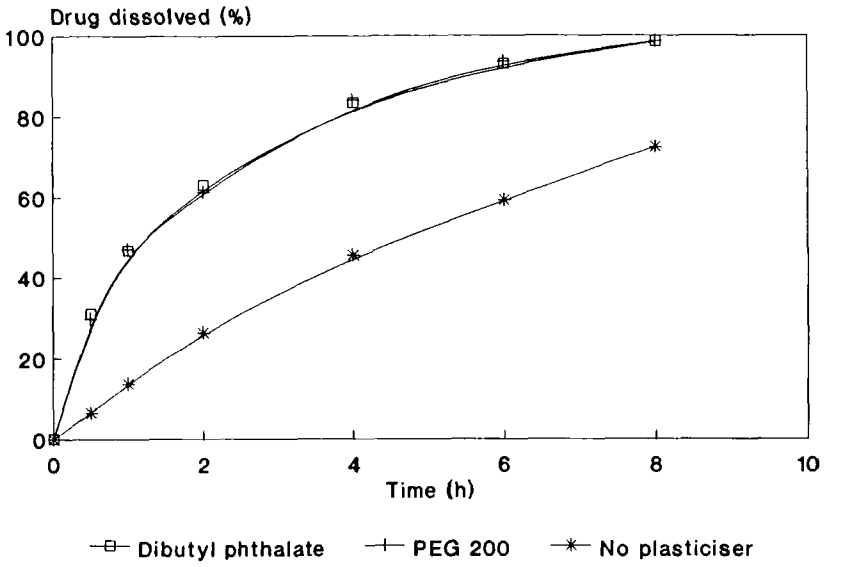

FIGURE 3
Drug dissolution of pellets coated with Eudragit RS (5%) and plasticisers as a function of time

The influence of plasticiser addition was determined by formulating pellets with 0.5% dibutyl phthalate (high viscosity) or 0.5% polyethylene glycol 200 (low viscosity).

The rate of drug release from both batches was similar (Figure 3). The batch with dibutyl phthalate did, however, tend to agglomerate more easily in the fluidised-bed apparatus during the coating procedure. In order to overcome the tackiness of pellets coated with dibutyl phthalate, longer drying times had to be employed (100 minutes as opposed to 60 minutes for polyethylene glycol-coated pellets). Polyethylene glycol (PEG) was therefore chosen as the plasticiser for the preparation of subsequent batches of Eudragit® RS-coated pellets.

The inclusion of the plasticiser altered drug release characteristics so that drug was released more rapidly from the batch with polyethylene glycol than from the batch with only Eudragit® RS (Figure 3). The batch of pellets

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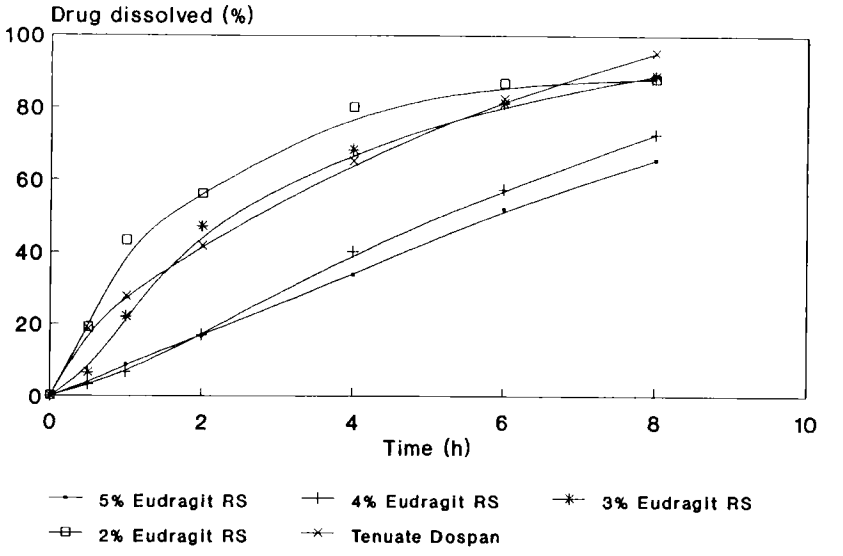

FIGURE 4
Drug dissolution of pellets coated with Eudragit RS, plasticiser and lubricant as a function of time

plasticised with PEG 200 released 47% of its drug content in one hour and a total of 98% after 8 hours, while the batch containing no plasticiser released only 13% in 1 hour and a total of 72% after 8 hours.

Inclusion of lubricants in the polymer membrane

In addition to improving the flexibility and hence the stability of films, the inclusion of a plasticiser into the Eudragit® RS-coating membrane had two effects:

a) Drug release was more rapid in batches where the plasticiser was employed,

b) There was a greater degree of pellet agglomeration in these batches because of the increased tackiness of the coating solutions.

Lubricants or anti-adherents are solid inclusions which decrease the tackiness of coating solutions and which may also have an inhibitory effect on the rate of drug release due to the hydrophobic nature of these substances[18].

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Consequently batches were coated with known concentrations of Eudragit® RS, using 0.5% PEG 200 as plasticiser and 0.5% magnesium stearate as lubricant. Batches containing 2%, 3%, 4% and 5% Eudragit RS were prepared. The results of dissolution studies on these batches are presented graphically (Figure 4).

It was observed that batches coated with 4% and 5% of polymer released drug at a constant rate (zero-order) over an eight hour period (Figure 4). The batch coated with 3% Eudragit® RS displayed release characteristics comparable to the reference preparation, Tenuate Dospan® (Figure 4). The average of the differences at each of the sampling times was 5.7%.

A closer examination of the release rates shows that the drug is initially released more rapidly with about 24% being released in the first hour and a further 24% in the second hour. Thereafter a constant release of about 20% was measured per two hours for the next four hours. In the last 2 hours of the study (6th to 8th hour) a further 10% of drug is released. The total amount of the assayed drug content released was 92.26%.

CONCLUSION

In the present study, drug release characteristics of newly formulated controlled release pellets of the anorexigenic, diethylpropion hydrochloride were evaluated by means of in vitro dissolution tests. The design of this product involved the logical development of a formulation by optimising processing variables until a desirable product was achieved. Further studies, including in vivo bioavailabilty tests need to be considered in order to confirm the suitability of the prepared dosage form.

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