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Effect of different polymer-plasticizer combinations on 'in vitro' release of theophylline from coated pellets

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Abstract

Plasticizers are added to the polymer coating of sustained-release granules to improve the mechanical properties of the coating shell. The present investigation evaluated the influence of different plasticizer/polymer combinations on theophylline (TH) release from pellets coated with latex aqueous dispersions of ethylcellulose (EC) or acrylic polymers (ACR). The plasticizers, present in the coating films in amounts ranging from 8 to 30%, were acetylated monoglycerides (AMG), diethyl phthalate (DEP), dibutyl phthalate (DBP) and dibutyl sebacate (DBS).

The release profiles of TH from the coated pellets were influenced by the type and amount of plasticizer and of coating material, and by the ratio polymer-plasticizer. For both types of coating, the drug release rate decreased with increasing plasticizer content. A correlation was found between the permeability coefficients (P_{wv}) to water vapour of free films, having the same composition as those used for coating, and drug release.

Keywords: Theophylline; Coated pellets; Ethylcellulose; Acrylic polymers; Latex aqueous dispersions; Acetylated monoglycerides; Diethyl phthalate; Dibutyl phthalate; Dibutyl sebacate; Release in vitro; Sustained release

1. Introduction

A standard technique for manufacturing oral sustained-release dosage forms consists of coating drug-containing granules or beads with aqueous, colloidal latex or pseudolatex polymeric dispersions (Lordi, 1986). A certain amount of plasticizer is always added to the polymers in order to improve the mechanical properties of the coating shell. Extensive investigation has been dedicated to the many, interrelated factors involved in optimal particle coating, e.g. type and amount of polymers, polymer/plasticizer combinations and ratios, operative conditions etc. (Lee and Robinson, 1978).

In the present study, the influence of type and amount of plasticizer on theophylline (TH) release

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'in vitro' from pellets coated with colloidal aqueous dispersions of ethylcellulose (EC) or acrylic polymers (ACR) was investigated, in the attempt to bring a further contribution to the understanding of this complex topic. The tested plasticizers were acetylated monoglycerides (AMG), diethyl phthalate (DEP), dibutyl phthalate (DBP) and dibutyl sebacate (DBS).

To assess the relevance of water permeability of the coating films to TH release, the permeability coefficients (P_{wv}) to water vapour of free films, having the same composition of those coating the pellets, were also determined.

2. Materials and methods

2.1. Materials

The following materials were all used as received: anhydrous theophylline, TH, U.S.P. grade, (Merck, D-Darmstadt); magnesium stearate, purified talc, rice starch and sucrose, all Ph. Eur. grade (Carlo Erba, I-Milano); isopropyl alcohol, analytical grade (Carlo Erba); a 30% aqueous dispersion of acrylic copolymers, ACR, (90% v/v Eudragit® RS 30D and 10% v/v Eudragit® RL 30D, Röhm Pharma, D-Darmstadt); a 30% aqueous dispersion of ethyl-cellulose, EC (Aquacoat® ECD-30, FMC Corporation, U.S.A.-Philadelphia); acetylated monoglycerides, AMG, (Myvacet® 9:40, Eastman Kodak Co., USA-New York); diethyl phthalate, DEP, dibutyl phtalate, DBP and dibutyl sebacate, DBS (Fluka Chemie, CH-Buchs). Theo-Dur®-200 tablets were kindly given by Recordati S.p.A., I-Milano.

2.2. Preparation of pellets

Spherical pellets were formed by wet granulation in a vertical high-speed mixer-granulator (maximum capacity = 10 l) equipped with a large impeller at the base of the bowl and with a side-mounted chopper (Roto Junior Granulator, Zanchetta and C., I-Lucca). Both blades had variable speed controls and current monitor. The machine was also equipped with a device for spraying binding solutions (Spraying Systems, USA) and with a heating jacket.The powder mixture had the following composition (% w/w):

TH	50.0
Sucrose	37.5
Rice starch	9.5
Talc	2.0
Magnesium stearate	1.0

In a typical granulation process, a homogeneous mixture was obtained by stirring (300 rpm) in the machine for 5 min 1.00 Kg TH, 0.75 Kg sucrose, 190 g rice starch, 40 g talc and 20 g magnesium stearate. Isopropyl alcohol (460 ml) was then sprayed (70 ml/min) over the powder mixture using the spraying device of the granulator. The process was completed in about 10 min.

The resulting pellets were dried for 40 min at 70°C under reduced pressure inside the granulator, while stirring at the same speed. The dried product was sieved using a vibrating screen (Analysette 3, A. Fritsch and Co., D-6580 Idar Oberstein): the main fraction (mean diameter 797.5 mm, about 80% yield) was used for the study.

2.3. Coating procedure

The pellets were coated using an experimental, specially designed air-suspension apparatus which will be the object of a separate communication. Coating was effected by spraying over the beads one aqueous polymeric dispersion (ACR or EC), to which different percentages of plasticizer (AMG, DBP, DBS or DEP) had been added. Prior to spraying, the coating dispersions were vigorously stirred in order to assist dispersion of the plasticizer into the polymeric acqueous blend. The amounts of plasticizers (in percent w/w, calculated on the dry lacquer substances) added to the coating dispersions are indicated in Table 1. The applied (dry) coating ranged from 9.5 to 10% of the pellets' weight.

2.4. Release tests '*in vitro*'

The dissolution studies were carried out using the USP XXI rotating paddle method (37°C, 75

rpm). Release tests were run at least in triplicate, on amounts of pellets whose overall TH content corresponded to 200 mg. Single Theo-Dur®-200 tablets were also tested for comparison. The dissolution media (500 ml) were simulated gastric fluid (pH1.2) for 2 h and simulated intestinal fluid (pH7.2) for 6 h, both without enzymes. Samples were withdrawn from the dissolution vessel at preselected time intervals, and replaced with an equivalent volume of pre-warmed dissolution medium. The samples were assayed spectrophotometrically (272 nm) as such or after suitable dilution. The release rates were calculated from the initial (0–3 h) portions of curves, obtained by plotting the cumulative amount of drug released vs. time.

2.5. Water vapour transmission tests

The polymeric free films for this study were prepared as follows: samples (8.0 g) of the coating mixtures, poured in teflon® Petri dishes (diameter, 9.0 cm), were allowed to evaporate at 30°C for 24 h. The resulting homogeneous films had average thickness 0.46 mm. Circular matrices (diameter, 2.0 cm) were cut from the films with a punch. The permeability studies were carried out by a gravimetric method (Sciarra and Gidwani, 1972; Guo et al., 1993). Briefly, this consisted of determining the rate of evaporation of water, at constant temperature, from glass jars, to whose opening the polymeric film was firmly sealed.

Table 1
Amount of plasticizers added to the coating polymeric dispersions

Plasticizer, % w/w[a]	EC	ACR
AMG	8, 16, 23	— — —
EP	16, 23, 30	8, 16, 23
DBP	— — —	16, 23, 30
DBS	16, 23, 30	16, 23, 30

[a]Calculated on dry lacquer substance.

Table 2
Apparent zero-order release rates[a] of TH from the coated pellets, calculated from the initial (0-3 h) portions of the 'in vitro' release profiles

Coating	Plasticizer, % w/w			
	8	16	23	30
EC/AMG	12.37	10.10	8.52	
EC/DEP		19.41	10.28	8.86
EC/DBS		15.73[b]	14.47[b]	10.35[b]
ACR/DBP		10.03	5.97	3.35
ACR/DEP	*	4.81	3.21	
ACR/DBS		*	25.22	25.26

[a]Expressed as % w/w TH released vs. time (h). The rate calculated for Theo-Dur 200 was 9.81% h^{-1}. All correlation coefficients of the linear plots were in the range 0.890–0.990.
[b]The release rates were calculated from the post-lag-time (3–4 h) linear portions of release plots.
*Fast and non-linear release kinetics.

3. Results and discussion

3.1. Release tests

The results of release tests carried out on the pellets coated with the two different latex aqueous dispersions (EC and ACR), each of which contained different proportions of a plasticizer (AMG, DEP, DBP or DBS), are summarized in Table 2. The release profiles of some of the composition which offered the best results, and of the

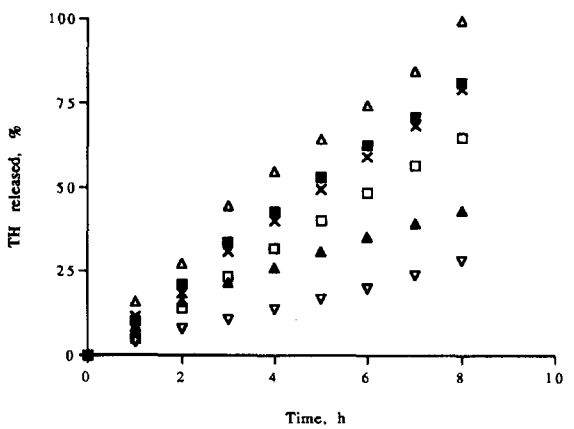

Fig. 1. Release of TH from selected preparations. Key: X, Theo-Dur® 200; △, ACR/DBP 16%; ▽, ACR/DBP 30%; ▲, ACR/DEP 16%; □, EC/AMG 23%; ■, EC/DEP 23%.

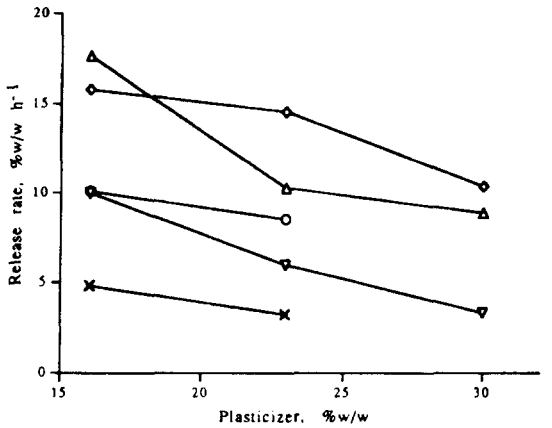

Fig. 2. Effect of plasticizer content on release rate of TH from the coated pellets. Key: X, ACR/DEP; ▽, ACR/DBP; ○, EC/AMG; △, EC/DEP; ◇, EC/DBS.

reference formulation, Theo-Dur®-200 tablets, are illustrated in Fig. 1. Some plots (EC/AMG 8 and 16%, EC/DEP 16 and 30%, ACR/DBP 23%, and ACR/DEP 23%) were omitted from the figure for clarity. The apparent release rates of the preparations reported in the figure, and of the omitted ones, were reasonably constant: in some cases, there was a slight decline after the initial 0–3 h period, in correspondence with the pH change of the dissolution medium, was observed. The apparent zero-order release rates reported in Table 2 were calculated from the initial (0–3 h) portions of the release plots. Of the 18 different batches tested, two (ACR/DEP 8% and ACR/DBS 16%) showed a fast and uncontrolled release. Increasing the percentage of DBS in ACR, as in ACR/DBS 23 and 30%, while still providing apparent initial zero-order kinetics, resulted in exceedingly fast release. Release from all EC/DBS batches (16, 23 and 30%) was characterized by high (3–4 h) lag times. The batches whose release profiles approximated most that of the reference formulation were EC/AMG 16% and EC/DEP 23% (release rates = 10.10 and 10.28% h^{-1}, respectively, vs. an observed release rate for Theo-Dur® = 9.81% h^{-1}).

The effect of the plasticizer content on release is illustrated in Fig. 2, where the rates of the preparations showing apparent (initial, or post lag-time) zero-order kinetics are plotted vs. the corresponding plasticizer contents. A trend towards a reduction of the release rate with increasing plasticizer content is clearly apparent. An influence on drug release from coated granules of amount and type of plasticizer in the polymeric shell has been observed by several authors: the trend, however, was not always in the same direction as that observed in this study. While, for example, Chang et al., 1989 found that increasing DBS (or triacetin) levels from 0 to 30% in ACR-coated pellets resulted in a proportionally reduced TH release, Ho and Suryakusuma, 1988 reported that 20% DEP showed the slowest permeation rate of chlorphenyramine maleate through ACR films, while 25 or 15% DEP gave higher permeation rates. According to Guo et al., 1993, this can be explained on the basis of an optimal coalescence of the coating film, which occurs only at a definite plasticizer concentration.

3.2. Water vapour transmission of free films

These tests were carried out to gather additional information, possibly leading to predictive correlations on the behaviour of the coating shells. As indicated by Singh et al., 1968, drug release from coated granules is controlled by the rate of solvent penetration. Thus, it was reasoned that the permeability to water vapour of the coating films might be correlated with the observed rate of release. All polymer-plasticizer combinations were cast as free, thin films, whose permeability to water vapour was determined by the gravimetric method of Sciarra and Gidwani, 1972. Three polymer-plasticizer mixtures, EC/DBS 16%, EC/AMG 8% and ACR/DEP 8% formed brittle and inconsistent films, which proved unsuitable for the test. The water vapour permeability coefficients of the films, P_{wv}, defined as the milligrams of water permeating at steady state each 24 h per 0.1 mm film thickness per cm^2 per unit pressure drop, are reported in Table 3. Fig. 3 illustrates the relationship existing, for the different films, between water vapour permeability coefficients and plasticizer content.

As shown in the Figure, in one case (EC/DEP), increasing the plasticizer content reduced significantly the permeability coefficient of the film; in

Table 3
Permeability coefficients (Pwv) to water vapour of the free coating films

Coating	Plasticizer %w/w	Pwv[a]
EC/DEP	16	4.69
EC/DEP	23	2.76
EC/DEP	30	1.10
EC/DBS	16	Not tested
EC/DBS	23	1.61
EC/DBS	30	1.43
EC/AMG	8	Not tested
C/AMG	16	3.50
EC/AMG	23	2.67
ACR/DEP	8	Not tested
ACR/DEP	16	0.92
ACR/DEP	23	0.87
ACR/DBS	16	1.06
ACR/DBS	23	1.01
ACR/DBS	30	0.97
ACR/DBP	16	0.78
ACR/DBP	23	0.46
ACR/DBP	30	0.42

[a]mg water permeating at steady state per cm^2 per 0.1 mm film thickness per 24 h per mm Hg

the case of EC/AMG and EC/DBS, the influence of plasticizer content on P_{wv} was less important. The combinations ACR/DBP, ACR/DEP and ACR/DBS showed low permeabilities, scarcely influenced by an increased content of plasticizer.

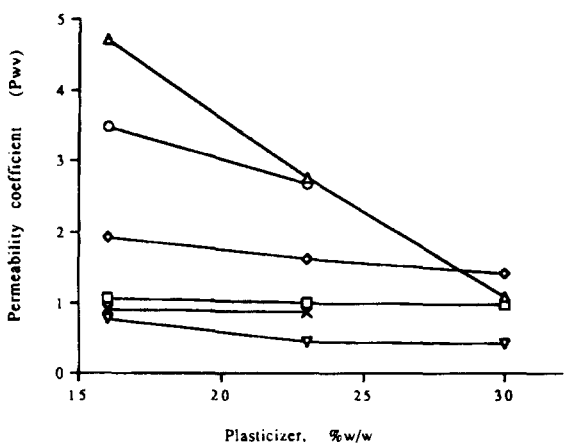

Fig. 3. Influence of the plasticizer content on the permeability to water vapour of the different polymeric free films. Key: △, EC/DEP; ○, EC/AMG; ◇, EC/DBS; X, ACR/DEP; □, ACR/DBS; ▽, ACR/DBP.

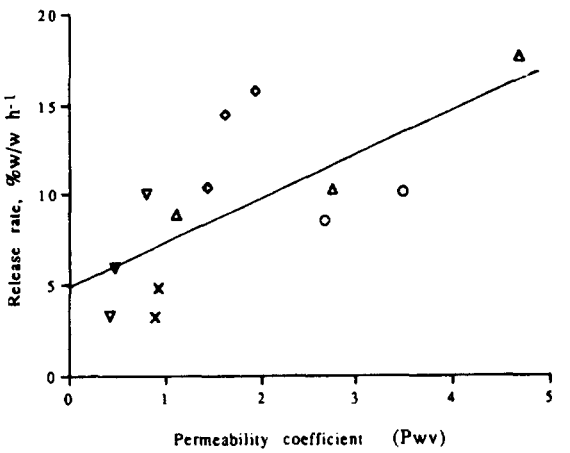

Fig. 4. Plot illustrating the relationship existing between release rate from the coated pellets and permeability coefficient to water of the corresponding free films. Key: ▽, ACR/DBP; X, ACR/DEP; ◇, EC/DBS; ○, EC/AMG; △, EC/DEP.

The relationship existing between the release rates of TH from the coated granules and the water vapour permeability coefficients (P_{wv}) of the corresponding coating films is illustrated in Fig. 4. Even if the data are not indicative of a good linear correlation between rate of release and water permeability of the coating membrane (correlation coefficient of the regression line = 0.731), the reduction of release rate observed in the presence of increasing amounts of plasticizers (Fig. 2) might be attributed to a reduced permebility to water of the polymeric coating.

4. Conclusions

As the present data appear to confirm, the choice of an appropriate plasticizer/polymer combination and the amount of plasticizer present in the polymer coating shell may be critical in determining the performance of sustained-release granules. The type and amount of plasticizer appears to influence the rate of release by altering the water permeability of the polymer coating. The question whether the plasticizer acts, as suggested by Guo et al., 1993, by affecting the coalescence of the latex film-forming particles, or by modifying the hydrophilicity of the final film, or by a combination of both factors, is being further investigated.

Acknowledgements

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