A Simple and Rapid Method for the Quantification of Eudragit RS100 and RL100 Poly(methacrylates) in Sustained-Release Dosage Forms

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A colorimetric ion-pair complexation method has been developed which provides a simple and rapid way of quantifying Eudragit RS100 and RL100 in pharmaceutical dosage forms. The quaternary ammonium groupings in these polymers appear to form an ion-pair complex with the dye tropaeolin OOO. When extracted into an organic phase, the optical density at 484 nm is linearly related to polymer concentration. Control of pH is important, and it should be maintained within the range 4.5 to 9.0. A wide range of pharmaceutical excipients commonly used in tablet, pellet, and film-coating formulations did not interfere with formation of the complex, but certain drugs were found to significantly enhance or decrease the assay response. Good reproducibility, precision, and accuracy were demonstrated when the method was applied to a film-coated pellet formulation containing an interfering drug (promethazine hydrochloride). However, removal of interfering substances must be optimized. The method was sufficiently sensitive for the determination of polymer on a single dose unit of encapsulated beads.

KEY WORDS: Eudragit; poly(methacrylate); film coating; controlled release; quantitative analysis.

INTRODUCTION

The Eudragit family of poly(methacrylate) copolymers are utilized as release-controlling agents in pharmaceutical dosage forms (1), either in matrix systems or, more commonly, as external film coats to form release-controlling membranes around tablets, pellets, or drug particles (2,3). Eudragit RS100 and RL100, utilized widely in sustained release, are insoluble in water but permeable to an extent dependent on the frequency of trimethylammonioethyl ester (TMAE) substitution. Hence RS100 is less permeable and confers greater sustaining of release than RL100, and mixed RS/RL films show intermediate water permeability and drug release rates (4,5).

The rate of drug release from dosage forms coated with these polymers is critically dependent on the amount of polymer applied during the film-coating process (6). The amount required to achieve a given sustained-release profile depends on factors such as drug solubility and surface area of the dosage form, but such is the potency of these materials as sustained-release modulators, the polymer may often comprise only a few percent by weight of the dosage form (7). Very precise control of the amount of polymer applied during film coating is therefore essential to ensure interbatch uniformity of drug release rate.

Unfortunately, there is at present no easy routine assay method for these polymers in the small quantities that may be present in dosage forms. As a consequence, indirect methods such as measurements of weight gain, spray rate, spray time, or volume of coating solution are often used to control the film coating process. Considerable inaccuracies arise with these methods through spray losses, friability, or changes in moisture content, and these parameters vary with batch size and the equipment used. A simple and precise method of quantifying the exact amount of these polymers applied to a dose form would therefore directly aid product development, scale-up of film-coating processes, and quality control of the final product.

The chemical structure of these polymers renders them difficult to quantify spectroscopically. Electrochemical titration in water-free solution in the presence of mercury acetate has been suggested (8), but the TMAE groups within these polymers also offer the opportunity for development of a more simple and sensitive colourimetric assay method based on ion-pair complexation. For many years, photometric determination by complexation with anionic dyes was a standard pharmacopoeial assay for water-soluble quaternary ammonium compounds (9,10), but the success of ion-pair complexation assays in quantifying water-insoluble polymeric materials is less well documented.

MATERIALS AND METHODS

Materials. Eudragit RS100 and RL100 were from Rohm Pharma GmbH, Darmstadt, Germany. Tropaeolin OOO (reagent grade) and sodium chloride (Analar) were from BDH Chemicals, Poole, UK. Promethazine hydrochloride was from Rhone-Poulanc plc, Dagenham, UK. Other pharmaceutical materials were a gift of the Boots Company and were of European or British Pharmacopoeial quality. Solvents were reagent grade.

Preparation of Promethazine Sustained-Release Pellets. A model sustained-release pellet dosage form was prepared containing 7% promethazine HCl, 43% lactose USP, and 50% (w/w) microcrystalline cellulose (Avicel PH-101). A 5-kg powder blend was wet-massed with 2.3 L distilled water, extruded (Alexanderwerk G100/160S, Orthos Engineering, Market Harborough, UK), spheronized (Caleva Model 15, Newcastle, Staffs, UK), and dried at 60°C for 1 hr in a fluid bed drier (Aeromatic, ACM, Tadley, Hants, UK) to 5% moisture content. The sieve fraction 0.85- to 1.4-mm pellets were used in this study. Film coating was carried out using a Manesty Accelacota 10 (Manesty Machines, Speke, UK).

Initial Method. A method for the determination of low concentrations of aqueous cationic detergents (11) was used as a starting point for method development. In the initial experiments 3 ml Eudragit RS100 (ERS), 0.4 g L^{-1} in chloroform, vortex mixed with 5 ml tropaeolin OOO, 8×10^{-4} *M* in 0.1 *M* sodium chloride, was centrifuged at 2300 rpm for 8 min to separate the two phases, and the color intensity in the

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chloroform layer determined spectophotometrically in 5-mm cells.

Final Assay Procedure. This was developed during this work. Pellets containing 2 to 20 mg ERS (1 to 10 mg ERL) were washed with 50 ml chloroform to dissolve the polymer. Three milliliters of the chloroform solution was added to 5 ml tropaeolin OOO, 8×10^{-4} *M* in 0.1 *M* sodium chloride in a stoppered glass tube, vortex mixed for 120 sec, and centrifuged for 8 min at 2300 rpm, and the optical density of the chloroform layer determined at 484 nm in 5-mm quartz cells.

Promethazine HCl Removal Procedure. Pellets were soaked in 500 ml distilled water for 12 hr, washed with 1 L water in a crucible sinter, and dried at 45°C to constant weight.

RESULTS AND DISCUSSION

Complex Formation and Analysis Wavelength

In the presence of polymer, the chloroform layer acquired an orange color on mixing. The absorption maximum (484 nm) was identical to that of the dye in the aqueous layer. In the absence of polymer, the chloroform layer remained uncoloured. This result suggests that a chloroform-soluble polymer:dye complex forms readily at the aqueous:organic interface, enabling transference of the otherwise chloroform-insoluble dye into the organic layer. 484 nm was used as the analysis wavelength in all subsequent work.

Optimization of Assay Parameters

Maximum color intensity in the chloroform layer was attained after 100 sec of vigorous vortex mixing and the color intensity in the chloroform layer remained stable for at least 12 hr. A minimum of 5 ml of 2.67×10^{-4} *M* dye solution was found necessary to maintain an orange color in the aqueous layer after complexation with 3 ml of 0.4 g dm^{-3} ERS; otherwise the response diminished as the dye in the aqueous phase became exhausted. In subsequent experiments mixing time was standardized at 120 sec and 5 ml of 8×10^{-4} *M* dye solution was used to ensure that an excess of dye was present in the aqueous layer.

Absorbance:Concentration Linearity and Method Sensitivity

Absorbance at 484 nm in the chloroform layer was found to be linearly related to polymer concentration over the range 0.05 to 1.2 absorbance units (2.5×10^{-2} to 5×10^{-1} g dm^{-3} ERS concentration, $r = 0.9996$), and in three replicate experiments, the coefficient of variation of the regression line slopes was less than 2%. A polymer concentration of 2.5×10^{-2} g dm^{-3} ERS was taken as the minimum reliable reading, but sensitivity could be doubled if 10-mm-pathlength cells were utilized. The experiment repeated using Eudragit RL100 (ERL) gave a ratio of 2.05:1 (ERL: ERS) between the regression line gradients (Fig. 1). This agrees well with the manufacturer's quoted ratio of 2:1 for the degree of TMAE substitution in these polymers.

The Effect of pH on Assay Response

The dye is a pH indicator and differences in ionization of tropaeolin OOO were expected to cause changes in assay response over some of the pH range. The pH of the aqueous dye phase was adjusted with 0.1 *M* hydrochloric acid or 0.1 *M* sodium hydroxide prior to the assay procedure. The results showed that the assay response was virtually independent of pH over the pH range 4.5–9.0 (Fig. 2). Above pH 9 the assay response was reduced, and the color of the aqueous dye layer changed visibly from orange to red. However, the chloroform solution remained orange at all pH's and there were no detectable wavelength or intensity shifts. In subsequent experiments the pH of the aqueous phase was controlled to between 5 and 7. pH control is important because in developing a method for a particular formulation, it may be necessary to remove interfering compounds by acid or alkali washing.

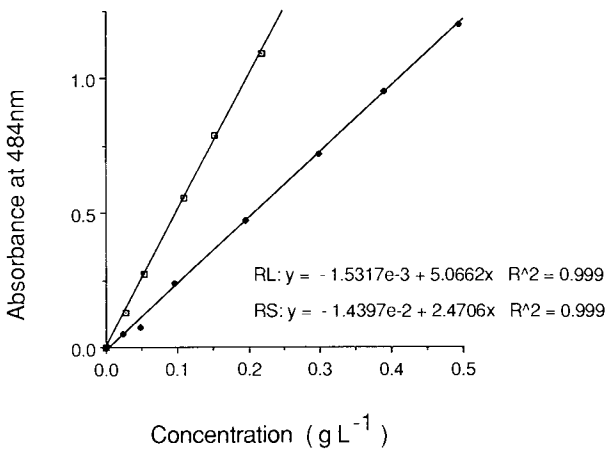

Fig. 1. Concentration:absorbance relationships and linear regression line fits for (♦) Eudragit RS and (□) Eudragit RL.

Interference from Drugs and Common Pharmaceutical Excipients

The influence of a range of pharmaceutical excipients commonly used in tablet, pellet, and film-coating formulations was investigated and several representative drug substances were also included. Chloroform was used for extracting ERS and ERL from dose forms as it dissolves the polymers rapidly and easily, however, other chloroform-

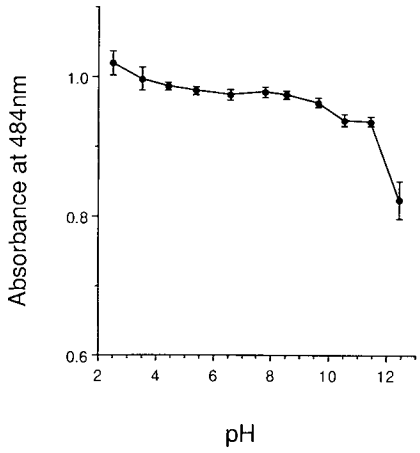

Fig. 2. The effect of pH on assay response (mean ± 1 SD; $n = 3$).

soluble substances which interfere with the assay response may also be extracted. Twenty-five milligrams of material (100 mg in the case of lactose and Avicel) was added to the reaction mixture prior to performing the assay. While none of the excipients tested appeared to interfere significantly, certain drugs were shown to enhance or decrease the color response (Table I).

Promethazine HCl and phenylpropanolamine HCl are cations over the pH range of the assay and these drugs themselves complex with the dye in the absence of polymer, leading to positive readings ("positive" interference). However, other drugs possessing ionized amine groups at these pH's (hydrochlorothiazide, theophylline) did not give this response, and chloroform solubility of the drug or drug/dye complex may also be important in determining if a particular drug interferes. Drugs which reduced the assay response ("negative" interfering species) contained anionic groupings and it is postulated that these drugs may interfere by competing with dye molecules at the phase interface for the cationic binding sites on the polymer.

Table I. The Effect of a Range of Common Pharmaceutical Excipients and Drugs on the Assay Response

Substance added	Result (% mean control reading)	Interference
Controls (no added substance)	Range (n = 4): 98.6 to 101.7	
Excipients		
Calcium sulfate USNF	99.5	None
Calcium carbonate Eur.P	99.0	None
Carboxymethylcellulose	99.2	None
Croscarmellose BP (Ac-Di-Sol)	99.6	None
Hydroxypropylmethylcellulose (Methocel E4M)	103	None
Lactose	101	None
Magnesium stearate.	98.3	None
Microcrystalline cellulose (Avicel PH 101)	99.2	None
Polyvinylpyrrolidone	99.6	None
Polyethylene glycol 6000	101	None
Sodium starch glycollate (Explotab)	101	None
Starch (Maize)	99.9	None
Stearic acid	87.6	Negative
Sucrose	98.2	None
Talc USP	99.5	None
Tricalcium phosphate (Encompress)	100	None
Drug substances		
Ascorbic acid	99.7	None
Diltiazem HCl	99.5	None
Frusemide	104	None
Hydrochlorothiazide	103	None
Nifedipine	97.7	None
Paracetamol	102	None
Theophylline HCl	102	None
Aspirin	94.0	Negative
Diclofenac Na	28.0	Negative
Diazepam	93.7	Negative
Flurbiprofen	83.5	Negative
Ibuprofen	92.8	Negative
Indomethacin	89.3	Negative
Metoclopramide HCl	>200	Positive
Phenylpropanolamine HCl	154	Positive
Promethazine HCl	>200	Positive

The Removal of Interfering Substances

Simple partitioning after the polymer extraction stage is perhaps the easiest way of the removing interfering species. However, not all such substances can be removed in this way. Repeated acid washings with 50 ml 0.5 M HCl proved ineffective in removing promethazine (0.5 g dm^{-1}) from a solution of ERS in chloroform (10 ml 0.4 g L^{-1}) (measured spectrophotometrically at 248 nm). Table II shows that the partition coefficient in this system heavily favors the organic phase but that reducing the polarity of the solvent would facilitate extraction. Unfortunately as the polarity is decreased, the solubility of the polymer in the organic phase is also reduced. The experiment was repeated with three recommended solvents for ERS: ethylacetate, cyclohexanone, and dichloromethane. The first and second proved too miscible with water, and repeated washings failed to remove the last 10% of drug, which was sufficient drug to interfere significantly with the assay response. Soaking the dosage form in an excess of distilled water prior to chloroform extraction proved the only effective method of removing the drug. Pellets were soaked in 500 ml distilled water for 12 hr, washed with 1 L water in a crucible sinter, and dried at 45°C to constant weight. The polymer was then extracted with 50 ml chloroform. No significant absorbance at 248 nm was detected in the chloroform extract, and in the absence of ERS the extract gave no colorimetric response, suggesting that this procedure had completely removed promethazine.

In conclusion, before this assay method is applied to a new formulation, the drugs and excipients used should be screened for possible interference, and if present, a preassay removal step should be developed.

Accuracy, Precision, and Efficiency of Polymer Recovery of the Method as Applied to a Film-Coated Pellet Dosage Form

A model sustained-release spheronized:extruded pellet dosage form containing 7% (w/w) promethazine HCl was used to test the accuracy and precision of the assay procedure in the presence of an interfering drug. The transfers involved in promethazine removal and the final assay procedure offer several opportunities for polymer losses, and

Table II. Partition Coefficient Data Between 0.5 M HCl and Certain Organic Solvents for Promethazine Hydrochloride (from Ref. 12)

Organic phase	K aqueous/organic
Butan-1-ol	0.07
Chloroform	0.15
Amylacetate	1.14
Ethylacetate	2.70
Benzene	5.25
Ethylether	15.20
Hexane	18.20

spiking experiments were therefore carried out to determine the efficiency of polymer recovery.

The drug removal and final assay procedures were applied to 10 mg Eudragit RS powder dry mixed with 350 mg uncoated pellets (a typical amount that would be filled in a size 0 capsule). The mean result of 97.1% (SD = 2.1%; n = 5) indicated that polymer losses during the assay procedure were small.

In order to ascertain the efficiency of polymer extraction from coated pellets, dry cores were manually coated using a paint brush with a known weight of ERS (approximately 10 mg polymer applied as a 10%, w/v, solution of ERS in 95% isopropyl alcohol) and dried to constant weight at 45°C. After drug removal, the assay method gave a mean result of 99.2% (SD = 2.6%; n = 4) ERS recovery.

The drug removal and final assay procedures were applied to pellets film-coated in an Accelacota with 10% (w/v) ERS in 95% isopropyl alcohol. A 350 mg sample of pellets were analyzed in an identical manner to the manually coated beads, and the assay method gave results of 12.8 mg (SD = 0.12; n = 6) ERS per 350 mg cores. The coefficient of variation of 0.94% perhaps reflects the more even polymer distribution achieved by machine film coating.

Tropaeolin OOO was used in this study, as this dye had previously been successfully utilized in the method from which the present work was derived (11). However, in common with the majority of indicator dyes, the purity of this material as supplied is only 75–85%. The use of an anionic dye of higher purity would allow calculation of the stoichiometry of the complexation reaction and obviate the possible need for standardization of different batches of dye. Likewise if different batches of ERS or ERL vary in their levels of quaternary ammonium substitution, their response may also differ and hence the calibration standard for the assay should be taken from the same batch of polymer as used for film coating. The method provides suitable bench-top assay of these important polymers.

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