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PREPARATION AND PRELIMINARY EVALUATION OF EUDRAGIT RL AND RS PSEUDOLATICES FOR CONTROLLED DRUG RELEASE

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ABSTRACT

Eudragit RL and RS pseudolatices were prepared by the solvent change technique, which consisted of dissolving the polymer in a water miscible organic solvent or in a mixed water miscible organic solvent system, followed by dispersian in deionized water under mild agitation. The organic solvent(s) was removed from the aqueous organic solution to leave a stable Eudragit latex.

Eudragit pseudolatex coated theophylline pellets were prepared in a fluidized-bed coating machine. The effects of polymer type and coating level, plasticizer concentration, and pH of the dissolution medium on drug release were investigated. The higher

content of quaternary ammonium groups attached to the polymer backbone make the coatings produced from Eudragit RL too water sensitive; and hence unsuitable for controlling theophylline release. On the other hand, Eudragit RS films retarded theophylline release over a wide pH range. Release of the drug was found to be a function of the polymer coating level, plasticizer concentration and dependent on pH of the dissolution medium.

INTRODUCTION

Because the use of organic solvents is a serious concern to different federal agencies and to the pharmaceutical industry, several water based pharmaceutical coating systems have been introduced. Some commercially available latices are produced by emulsion polymerization and contain residual monomer, initiators or catalysts, surfactants and other chemicals used in the emulsion polymerization process. These undesirable substances can be of concern for a uniformity of coating, coat stability and, perhaps toxicity. Also available is a 30% w/w ethyl cellulose pseudolatex prepared by an emulsion-solvent evaporation technique. This preparation contains sodium lauryl sulfate and cetyl alcohol as stablizers which may have adverse effect on film formation and cause instability to heat, mechanical shear and organic solvents. Substantial quantities of plasticizer are commonly required when this system is used for sustained release purpose (1,2).

This report concerns a changing solvent technique for preparing Eudragit RL and RS pseudolatices and an examination of some of the formulation factors that can influence the release of theophylline across Eudragit RL and RS films.

EXPERIMENTAL

Preparation of Eudragit RL and RS coating dispersions and solutions

The Eudragit[1] polymer was dissolved in a water miscible organic solvent or in a mixed water miscible organic solvent system.

The polymer solution was then dispersed in deionized water under mild agitation. The organic solvent(s) was subsequently eliminated from the aqueous-organic solution to leave a stable Eudragit RL/RS latex.

Various levels of dibutyl sebacate[2] or triacetin[3] were added as plasticizers to 15% w/v Eudragit latex preparations, and the mixtures were stirred for 30 minutes prior to use for coating.

Acetone solutions of the Eudragit polymers were prepared by dissolving the polymer at a 10% w/v level. Dibutyl sebacate was mixed into the polymer solutions at a concentration of 10% of the polymer.

Preparation of Coated Pellets

Batches of 500 grams of theophylline pellets were coated by using a fluidized bed coating technique[4]. The inlet air temperature was 55°C-60°C and coating dispersions or solutions were pumped to the atomizer at a rate of 8-10 ml/min, operating at a spray pressure of 0.8 bar with a spray nozzle orifice of 0.8 mm. After the coating process, the pellets were dried in the coating chamber for another 15 minutes at the same temperature and air flow.

Dissolution Testing

The theophylline release characteristics were determined by dissolution testing using an apparatus designed by Schering's Method Development Laboratory in Miami. The method uses a modified rotating paddle dissolution apparatus to avoid problems normally encountered with pelletized or microencapsulated formulation, such as pellet flotation and adhesion to the walls of the flask or shaft of the paddle.

A stationary stainless steel, 40 mesh basket is suspended in an appropriate dissolution media, positioned in close proximity to the paddle, and the pellets are inside the basket. A schematic representation of the apparatus is shown in scheme 1. Serial sampling of the fluid at appropriate times, with subsequent HPLC analysis for theophylline content, were performed to generate a cumulative percent released-time profile.

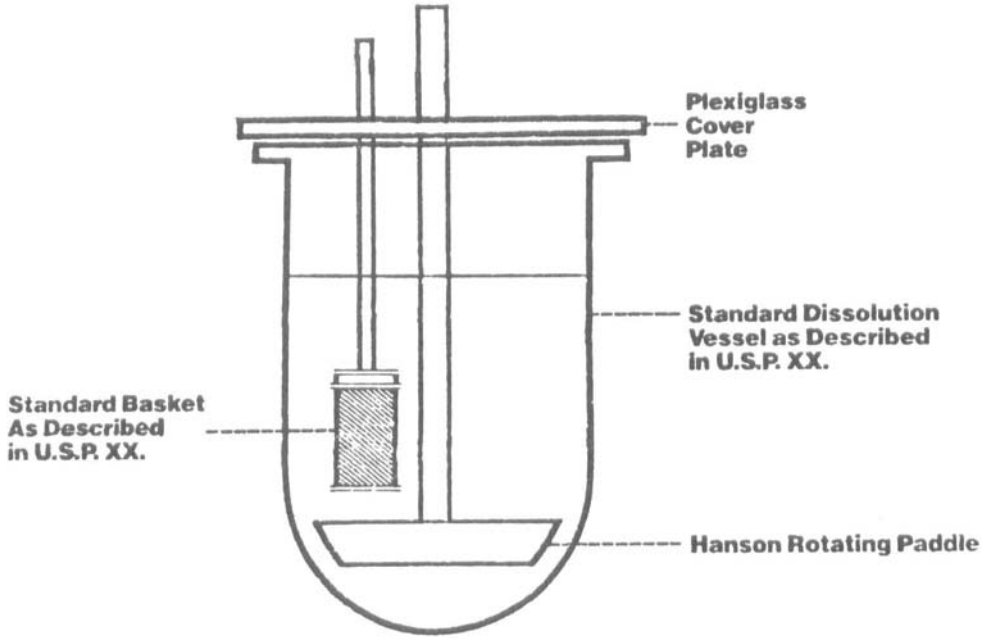

Diagram of the Fixed Basket Dissolution Apparatus

RESULTS AND DISCUSSION

Preparation and Physical Characteristics of Eudragit RL and RS Pseudolatices

Eudragit RL/RS are copolymers synthesized from acrylic and methacrylic acid esters with quaternary ammonium groups. Despite their ionic character, these polymers are insoluble in water because of the low concentrations (2.5 - 5 percent) of ammonium groups. However, they are soluble in semi-polar solvents and they are easily dispersed in water to give latices. Eudragit RL and RS Pseudolatices prepared by the solvent change technique do not contain any emulsifier or stabilizer but are inherently stable. The major stabilizing factor in these pseudolatices is the positive charge on the particles arising from quaternary groups on the polymers. Various deflocculating agents can be added to the latex systems in order to further extend the shelf life. However, the

TABLE I

Theophylline Release from Eudragit RL coated pellets in Simulated Intestinal Fluid

	Cumulative Percent Release		
Time (min)	9% Eudragit RL Latex Coated Theophylline Pellets*	18% Eudragit RL Latex Coated Theophylline Pellets*	9% Eudragit RL Solution Coated Theophylline Pellets
15	-	82.3 ± 6.1	82.6 ± 2.7
30	-	95.8 ± 1.4	100.7 ± 2.3
45	-	99.0 ± 0.9	
60	101.7 ± 0.4	99.5 ± 0.7	

* Eudragit RL Pseudolatex plus 10% dibutyl sebacate was used to coat theophylline pellets

** Eudragit RL acetone solution was used to coat theophylline pellets

permeability of Eudragit films may be altered by the addition of deflocculating agents. The absence of emulsifiers has several interesting consequences. The latex spheres are not enveloped by a specific surfactant layer. Consequently the surface is less sensitive to mechanical shearing as well as to organic solvents, and therefore the latex can be heated or stirred or even diluted with solvents, without causing precipitation. Films formed from the latex without surfactants are also less easily broken up by aqueous solutions.

The solvent change preparation method is known to yield smaller latex spheres than either direct emulsification or inversion emulsification(3). The particle size and particle size distribution of the latex are important characteristics which affect shelf life, stability, rheological properties and film properties. As a result of the smaller latex particles and the absence of sur-

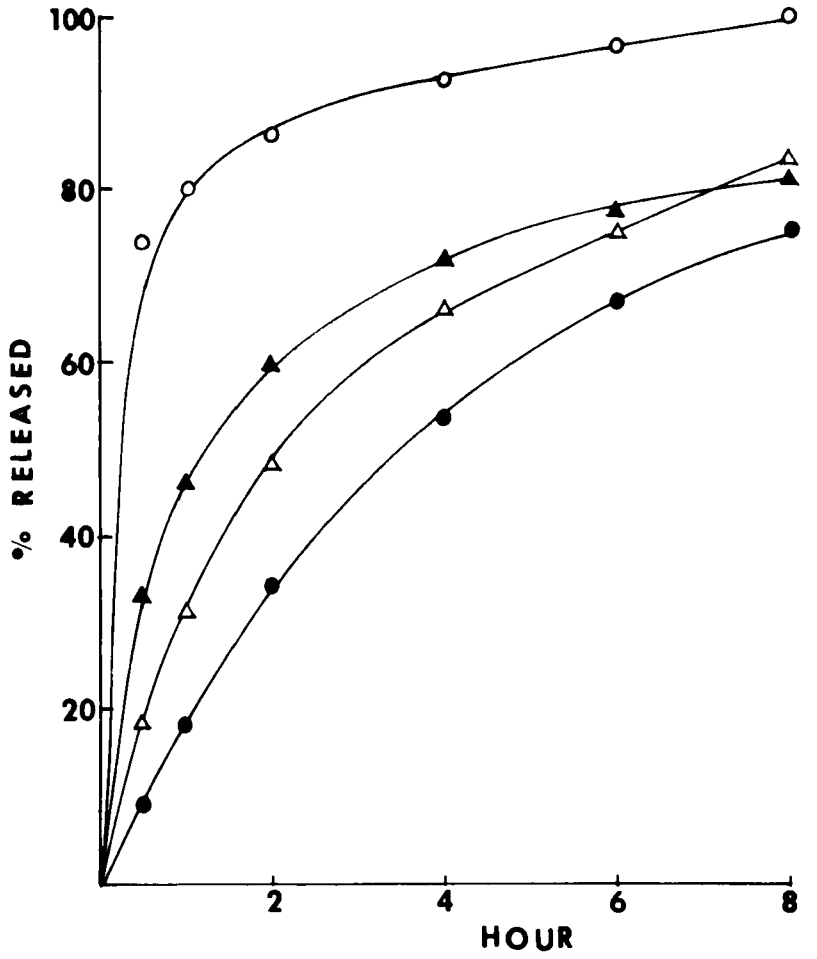

FIGURE 1

Theophylline Release from Eudragit RS Pseudolatex coate pellets in simulated intestinal fluid as a function of coating thickness

Key: ○ 3% Coating Level
▲ 6% Coating Level
△ 9% Coating Level
● 18% Coating Level

NOTE: 10% Dibutyl Sebacate was used to plasticize Eudragit RS Pseudolatex.

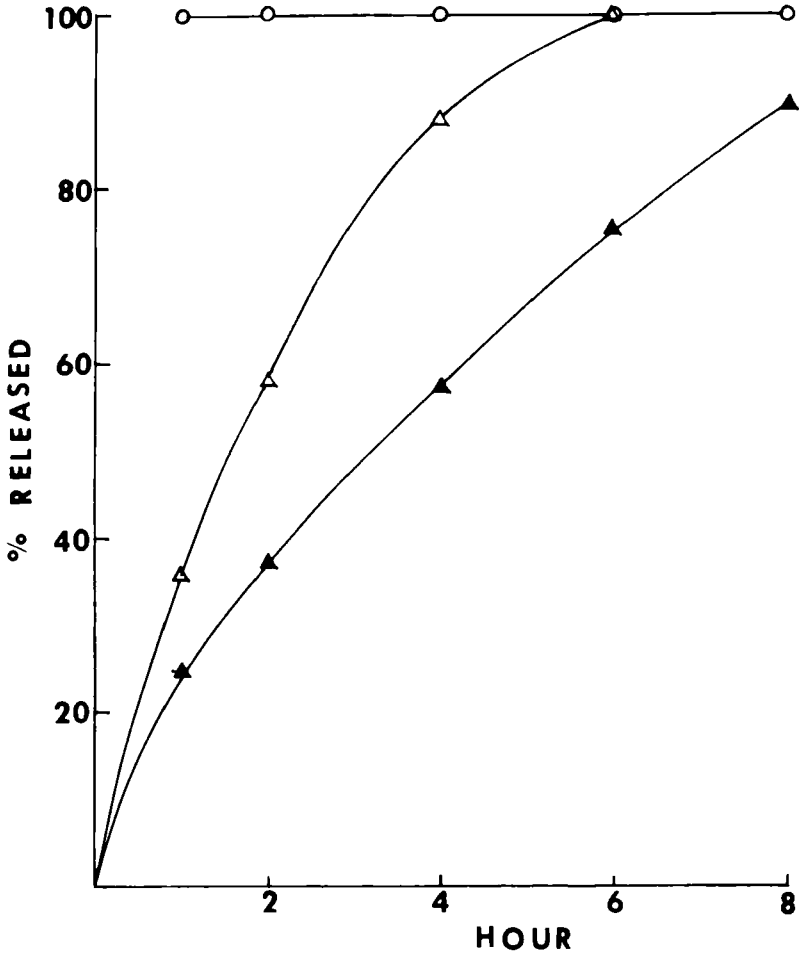

FIGURE 2

Effect of various Dibutyl Sebacate levels with 9% Eudragit RS Pseudolatex coating on Theophylline Release from pellets in Simulated Intestinal Fluid

Key: ○ 0%
△ 10%
▲ 20%
● 30%

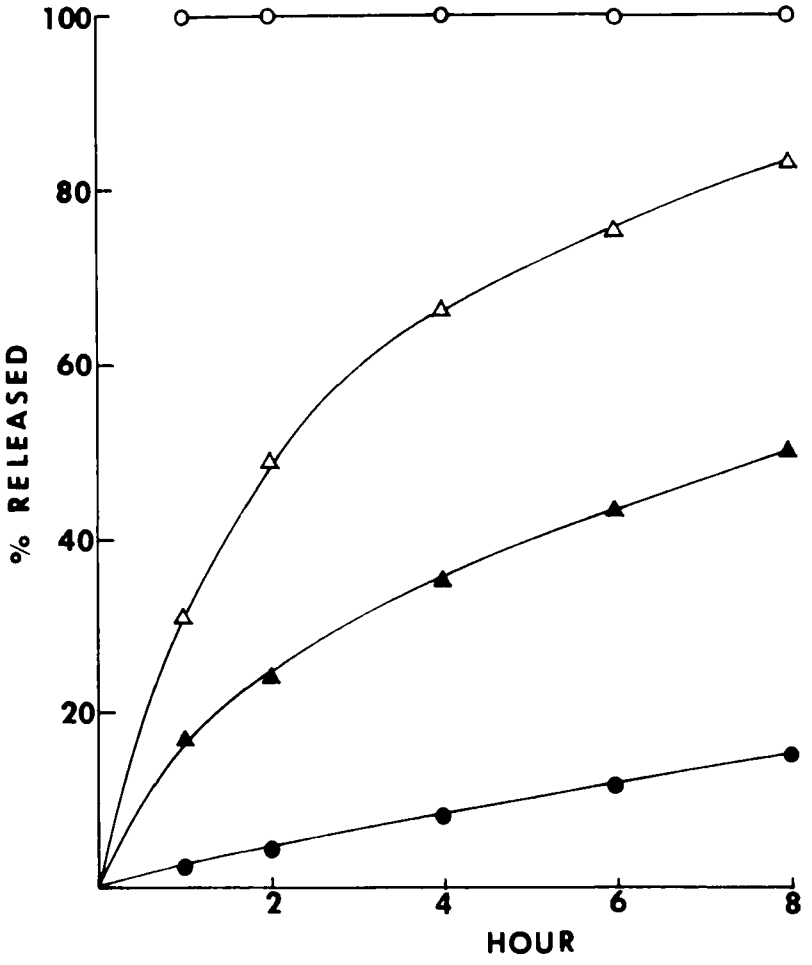

FIGURE 3

Effect of various Triacetin levels with 9% Eudragit RS Pseudolatex coating on Theophylline Release Rate from pellets in Simulated Intestinal Fluid

Key: ○ 0%
△ 10%
▲ 20%

TABLE II

The Effect of Dissolution Media on the Release of Theophylline from Pellets Coated with 18% Eudragit RL/RS Pseudolatices

Time (hours)	Cumulative Percent Release			
	Eudragit RL		Eudragit RS	
	S.I.F.*	S.G.F.**	S.I.F.	S.G.F.
0.25	82.3 ± 6.1	66.3 ± 1.0	-	-
0.5	95.8 ± 1.4	88.9 ± 1.1	9.1 ± 1.8	1.3 ± 0.1
0.75	99.0 ± 0.9	95.0 ± 0.9	-	-
1	99.5 ± 0.7	96.6 ± 0.4	18.7 ± 3.1	2.9 ± 0.6
2			34.0 ± 3.9	4.3 ± 0.7
4			53.5 ± 3.9	6.8 ± 1.2
6			67.0 ± 3.4	7.6 ± 1.5
8			75.9 ± 2.7	9.9 ± 1.6
10			82.5 ± 2.2	11.8 ± 1.9

* Simulated Intestinal Fluid without enzyme

** Simulated Gastric Fluid without enzyme

factants, the film forming properties of Eudragit RL/RS pseudolatexes are excellent.

Theophylline Release from Eudragit RL and RS Coated Pellets

Table I shows the cumulative percent of theophylline release from Eudragit RL coated pellets in simulated intestinal fluid. As seen from the data, Eudragit RL was quite permeable to theophylline and water and released all the drug in one hour. The high content of quaternary ammonium groups attached to the polymer backbone make the coatings produced from Eudragit RL too water sensitive; consequently under these conditions Eudragit RL films are probably not suitable as membranes for controlling theophylline release.

Figure 1 shows the cumulative percent of theophylline release from Eudragit RS coated pellets in simulated intestinal

TABLE III

The Effect of the Dissolution Media on the Release of Theophylline from Pellets Coated with 9% Eudragit RL and RS* from Organic Solution

Time (hours)	Cumulative Percent Release Eudragit RL S.I.F.**	Eudragit RL S.G.F.***	Eudragit RS S.I.F.	Eudragit RS S.G.F.
0.25	82.6 ± 2.7	70.7 ± 3.9	-	-
0.5	100.7 ± 0.3	96.7 ± 2.0	-	-
0.75		100.5 ± 1.0	-	-
1			10.2 ± 2.0	6.7 ± 2.3
2			21.9 ± 3.6	10.8 ± 3.5
4			42.1 ± 5.5	18.7 ± 4.7
6			57.3 ± 4.7	24.8 ± 6.0
8			68.7 ± 5.9	27.5 ± 6.3
10			77.2 ± 6.0	-

* Acetone as a solvent for Eudragit RL/RS
** Simulated Intestinal Fluid without enzyme
*** Simulated Gastric Fluid without enzyme

fluid. By virtue of its lower content of quaternary ammonium groups, Eudragit RS films are, in contrast to Eudragit RL, only slightly permeable so that drug release is markedly retarded. As the amount of applied Eudragit RS increases, the rate of theophylline release decreases. At low coating levels, a large portion of the theophylline pellets was not encapsulated properly. The accessible theophylline was released rapidly into the dissolution media, causing a burst effect. After the initial burst, the drug release appeared to follow first order kinetics. Increasing the coating level decreased the initial drug release rate, but had no great effect on the first order release stage.

Figure 2 and 3 show the effect of various plasticizer levels on theophylline release rate from pellets coated with 9% Eudragit

RS. Theophylline release rates were inversely proportional to plasticizer concentration.

The mechanisms involved in the formation of a continuous film from a latex are very different from those involved when films are formed by evaporation from organic solution. Plasticization which aids in overcoming the latex spheres resistance to deformation, is usually critical to formation of a good polymer film from a latex system. When plasticizer was not added, no sustained release of theophylline was observed suggesting that the film was incomplete or discontinuous. On the other hand, a high level of plasticizer resulted in seed agglomeration, sticking, and poor fluidization problems caused by excessive softening of the polymer film.

Table II shows the effect of dissolution media pH on release of theophylline from pellets coated with 18% Eudragit RL and RS pseudolatices. The release rate of theophylline from Eudragit RL and RS coated pellets was faster in simulated intestinal fluid than in simulated gastric fluid. Since non-ionized drug passes through the membrane more readily than the ionized form (4-7), a faster rate of theophylline transport in basic media and a slower rate of theophylline transport in acidic media were expected. In general a pH dependent release is considered a disadvantage. However, it may be utilized as an intestinal delivery system with sustained release properties.

Table III shows the cumulative percent of theophylline release across Eudragit RL and RS films prepared from acetone solutions. Permeability of a Eudragit RS film formed form this solution is somewhat lower than that formed from Eudragit RS Pseudolatex film. However, more extensive development of operating and formulation conditions for aqueous coating systems may result in more resistant films which are comparable to the films formed from solutions.

CONCLUSION

Eudragit RL films were not suitable for controlling theophylline release due to its high permeability to water. Eudragit

RS films retarded theophylline release over a wide pH range. Release rates from Eudragit RS pseudolatex coated pellets are a function of polymer coating level, plasticizer concentration and pH of the dissolution medium.

FOOTNOTES

1. Rohm Pharma, Darmstadt, West Germany
2. Union Camp, Jacksonville, Florida
3. Eastman Chemical Products, Inc., Kingsport, Tennessee
4. Glatt Air Techniques, Inc., Ramsey, New Jersey

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