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EUDRAGIT RL AND RS PSEUDOLATICES: PROPERTIES AND PERFORMANCE IN PHARMACEUTICAL COATING AS A CONTROLLED RELEASE MEMBRANE FOR THEOPHYLLINE PELLETS

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ABSTRACT

Theophylline Active pellets were coated with Eudragit RL and RS pseudolatices in a fluidized bed. The effects of polymer ratio, additional oven drying, addition of dispersed solids, and addition of water miscible organic solvents on sustained drug release through the latex film were determined by using a modified U.S.P. paddle dissolution method.

The release rate of theophylline can be varied by changing the polymer ratio. Permeability to the drug increases with an increase in the content of Eudragit RL. Additional oven drying at 60°C for 10 hours caused no significant change in the dissolution profiles. The addition of dispersed solids such as talcum and silica resulted in an increase in drug release rate. There is no significant change in dissolution profiles when 50% methanol or acetone was added to the Eudragit RS pseudolatex.

INTRODUCTION

Limited aqueous coating systems are available for controlled release formulations. Eudragit RL and RS pseudolatices are very

much a part of an increasing trend toward water-based coatings (1-7). Eudragit pseudolatex systems offer an economical alternative to increasingly expensive solvents for solvent-based systems and expensive solvent recovery or incineration equipment for environmental and safety considerations. The present study was undertaken to demonstrate the feasibility of using mixtures of Eudragit RS and RL pseudolatices to control drug release and to study the effects of added solvents and dispersed solids on the release rate of drug.

EXPERIMENTAL

Preparation of Eudragit RL and RS coating dispersions

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] were added as a plasticizer to 15% w/v Eudragit latex preparations, and the mixtures were stirred for 30 minutes prior to use for coating. Dispersions of talc USP and silica[3] in 50 ml water were prepared by mortar and pestle and then added to 15% w/v Eudragit pseudolatex. Each dispersion was added at 25% w/w level based on Eudragit solids. Methanol or acetone (half the volume of Eudragit RS pseudolatex used) was mixed into the pseudolatex. Dibutyl sebacate was then added to the mixtures, and the mixtures stirred for 30 minutes prior to use for coating.

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. 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.

TABLE I
In-batch and between-batch Reproducibility of 18%* Eudragit RS Pseudolatex Coated Theophylline Pellets

Cumulative Percent Released

Time (hour)	Run #1 S.I.F.**	Run #1 S.G.F.***	Run #2 S.I.F.	Run #2 S.G.F.
1	11.7 ± 4.3	1.0 ± 0.0	18.7 ± 3.1	2.9 ± 0.6
2	25.6 ± 5.5	1.7 ± 0.5	34.0 ± 3.9	4.3 ± 0.7
4	50.6 ± 6.8	2.3 ± 0.6	53.5 ± 3.9	6.8 ± 1.2
6	68.1 ± 5.8	3.3 ± 0.6	67.0 ± 3.4	7.6 ± 1.5
8	79.5 ± 4.3	3.7 ± 0.6	75.9 ± 2.7	9.9 ± 1.6

* Eudragit RS coating levels, based on the weight of theophylline active pellets. 10% Dibutyl Sebacate was used to plasticize Eudragit RS pseudolatex.
** Simulated intestinal fluid without enzyme.
*** Simulated gastric fluid without enzyme

NOTE: Data represents the mean ± standard deviation of observations for two batches.

Dissolution Testing

Theophylline release characteristics were determined by dissolution testing using an apparatus designed by Schering's Methods Development Laboratory in Miami (6,8). Serial sampling of the fluid at appropriate times, with subsequent analysis for theophylline content were performed to generate a cumulative percent released-time profile.

Results and Discussion

The reproducibility of Eudragit RS pseudolatex coated theophylline pellet batches prepared under the same conditions was examined with respect to the dissolution profiles. In-batch and between batch variation were found to be within an acceptable range (Table I).

Gradual coalescence, which occurs upon aging of the latex film, was accelerated through post-coating drying at 60°C for 10

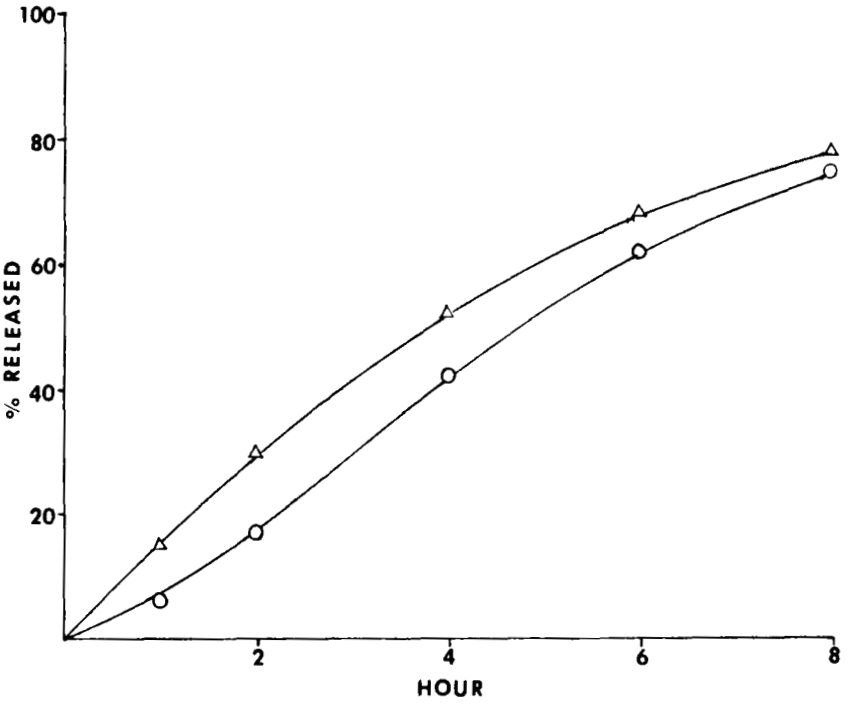

FIGURE 1

Effect of Post-coating drying on the Release of Theophylline in Simulated Intestinal Fluid from 18% Eudragit RS Pseudolatex coated pellets.

KEY: △ Without additional oven drying.
○ With additional oven drying for 10 hours at 60°C.

NOTE: Dibutyl subacate was used at a level of 10% to plasticize Eudragit RS pseudolatex.

hours. Figure 1 shows the effect of post-coating drying on the release of theophylline in simulated intestinal fluid from 18% Eudragit RS pseudolatex coated pellets. However, theophylline release is not significantly altered by additional oven drying at 60°C for 10 hours, indicating that the "gradual" coalescence is apparently completed within the coating time under the present coating conditions.

TABLE II

The Effect of Different Ratio of Eudragit RS and RL on the Release Rates of Theophylline in Simulated Intestinal Fluid from 9% Eudragit Pseudolatex Coated Pellets

Time (hour)	Cumulative Percent Released					
	50:50*	20:80	10:90	7.5:92.5	5:95	0:100
1	99.6 ± 0.8	87.2 ± 1.0	44.3 ± 0.5	46.3 ± 1.2	30.3 ± 6.9	16.8 ± 1.9
2		101.6 ± 0.3	73.9 ± 0.5	60.8 ± 1.3	42.4 ± 5.1	24.4 ± 2.6
4			100.9 ± 0.3	78.8 ± 1.0	57.3 ± 3.6	35.3 ± 2.7
6				89.6 ± 0.9	66.5 ± 3.1	43.9 ± 3.0
8				96.5 ± 0.8	73.7 ± 2.5	50.1 ± 3.8
10				100.6 ± 1.0	78.8 ± 2.9	55.7 ± 4.1

* Eudragit RL pseudolatex : Eudragit RS pseudolatex.
20% Dibutyl Sebacate was used to plasticize Eudragit pseudolatex.

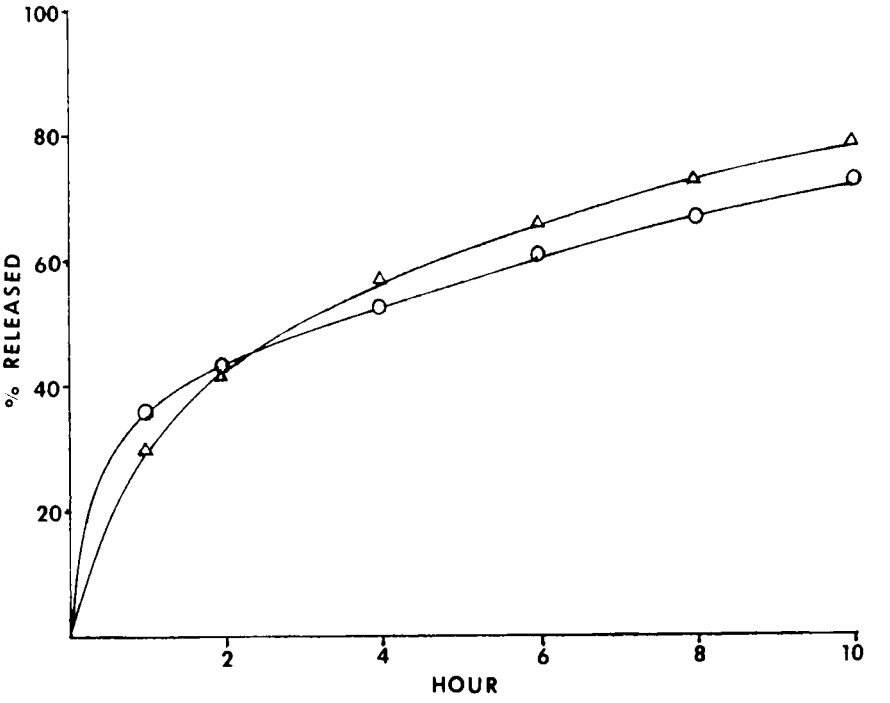

FIGURE 2

Comparison of the Release Rates of Theophylline in Simulated Intestinal Fluid from Pellets coated with mixture of Eudragit RS Pseudolatex:Eudragit RL Pseudolatex (95:5) and Eudragit RS plus RL (95:5) Pseudolatex.

KEY: △ Mixture of Eudragit RS Pseudolatex:Eudragit RL Pseudolatex (95:5)
○ Eudragit RS plus RL (95:5) pseudolatex.

NOTE: Dibutyl Sebacate was used at a level of 20% to plasticize Eudragit Pseudolatex.

Eudragit RS/RL pseudolatices can be mixed in any proportion one with the other, which means the permeability of Eudragit pseudolatex film can be controlled by mixing the two latices. Table II shows the effect of different ratios of Eudragit RS and RL on the release rates of theophylline from 9% Eudragit Pseudolatex coated pellets. A wide range of release rates for theophylline can be obtained by simply changing the ratios of Eudragit RS

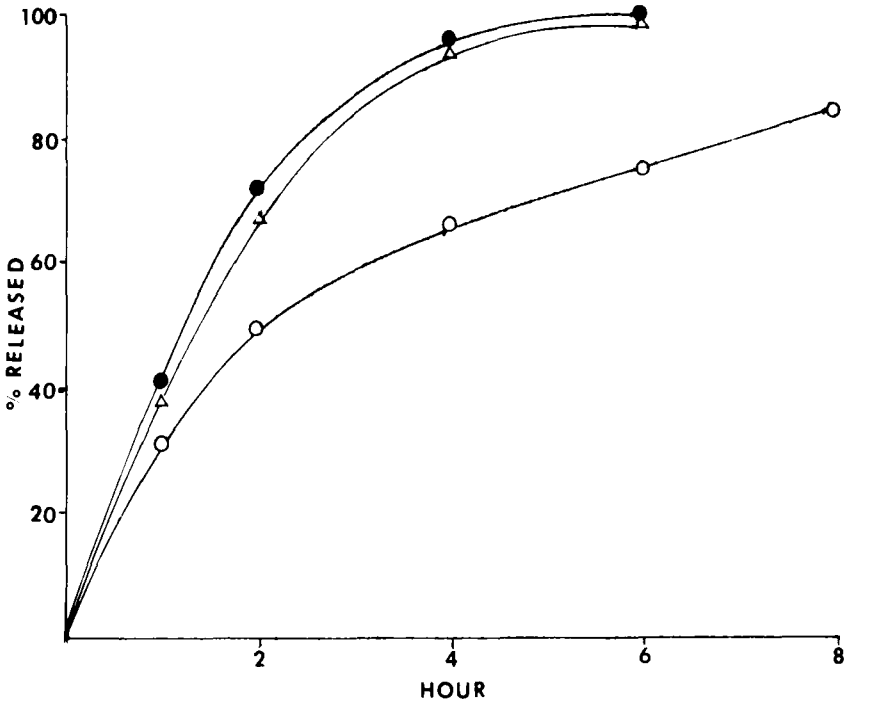

FIGURE 3

Effect of addition of dispersed solids on the dissolution rates of Theophylline in Simulated Intestinal Fluid from 9% Eudragit RS Pseudolatex coated pellets

KEY: ○ No Solids Added
△ 25% Talcum Added
● 25% Syloid Added

NOTE: Dibutyl Sebacate was used at a level of 10% to plasticize Eudragit RS Pseudolatex

and RL. Eudragit RL latex film was readily permeable to water and theophylline and therefore released all the drug within 30 minutes Eudragit RS latex film was slightly permeable to water and theophylline and gave only 55.7% release of the payload at the end of a 10 hour dissolution test. As expected dissolution profiles for theophylline pellets coated with mixtures of Eudragit RS and RL pseudolatices fit between these two extremes. Drug release from the latex coated pellets appeared to follow first order kinetics.

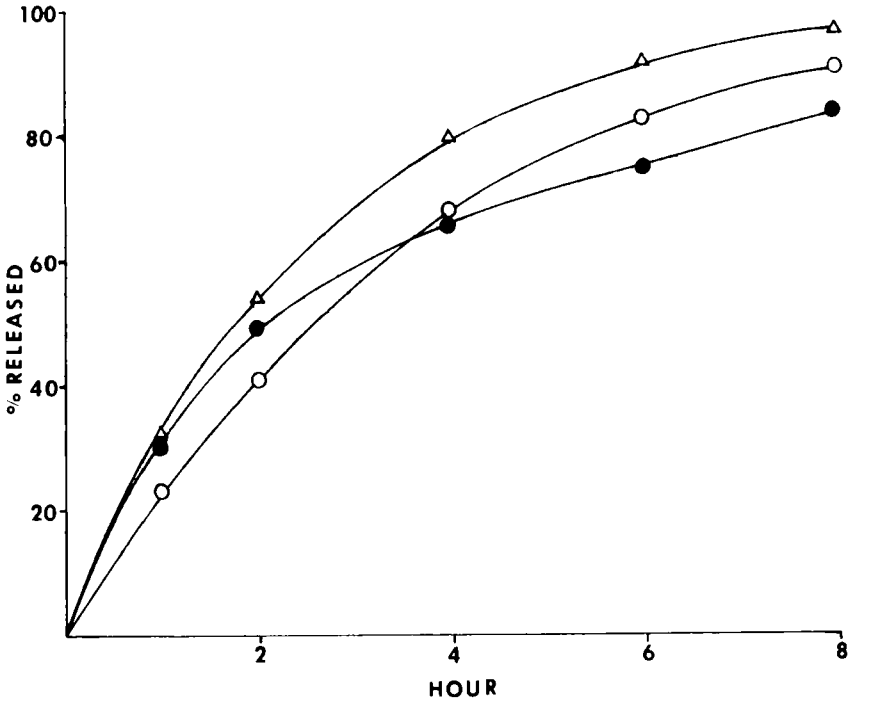

FIGURE 4

Effect of added solvent on the Dissolution Rates of Theophylline in Simulated Intestinal Fluid from 9% Eugragit RS Pseudolatex Coated Pellets.

KEY: ● No Solvent Added
△ 50% Methanol Added
○ 50% Acetone Added

NOTE: Dibutyl Sebacate was used at a level of 10% to plasticize Eudragit RS Pseudolatex

The appearances of Eudragit RS and RL pseudolatices respectively were milky white and translucent white dispersions which indicated that Eudragit RS pseudolatex may have different latex sphere size from the Eudragit RL pseudolatex. When mixtures of Eudragit RS pseudolates and Eudragit RS pseudolatex are to be used for coating, it may result in incomplete coalescence of latex spheres due to the polydisperse nature of the coating systems. An attempt was made to minimize the polydispersity of pseudolatex

systems by mixing Eudragit RS and RL during the pseudolatex preparation process. Comparison of the release rates of theophylline in simulated intestinal fluid from pellets coated with mixtures of Eudragit RS pseudolatex and Eudragit RL pseudolatex (95:5) and Eudragit RS plus RL (95:5) pseudolatex, however, indicates that there is no significant difference in the dissolution profiles. It suggests that the polydisperse mixtures of Eudragit RS and RL pseudolatexes may not have a significantly adverse effect on the film formation (Figure 2).

Dispersed solids were added in order to reduce the tackiness and the permeability of the polymer film. However, these finding cannot be confirmed by the dissolution tests for theophylline pellets coated with 9% Eudragit RS pseudolatex plus 25% talcum or silica (Figure 3). The enhancement of dissolution rate by inclusion of dispersed solids may be due to an increase in porosity and heterogeneity of the membranes (9).

For special application, the Eudragit pseudolatex can also be mixed with water-miscible organic solvents without causing precipitation. The milky white appearance will be retained to a certain dilution point, and then Eudragit latex spheres dissolve out in the excess organic solvent. Figure 4 shows the effect of added solvent on the dissolution rates of theophylline from 9% Eudragit RS pseudolatex coated pellets. There is no drastic change in the dissolution profiles when 50% methanol or acetone was added to the Eudragit RS pseudolatex. However, the pumping speed had been increased to avoid a nozzle clogging problem.

CONCLUSION

Eudragit RS/RL pseudolatices are soap-free latex systems which enjoy several advantages such as stability to heat and mechanical shear, and dilutability with organic solvents. The film forming properties are outstanding, as a result of which controlled release and taste-masking properties can be obtained by using Eudragit RS/RL pseudolatices.

FOOTNOTES

1. Rohm Pharma, Darmstadt, West Germany
2. Union Camp, Jacksonville, Florida
3. Syloid 72, Micron-sized synthetic silica, Grace Davison Chemical, Baltimore, Maryland
4. Glatt Air Techniques, Inc., Ramsey, New Jersey

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