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Preparation and In-Vitro Evaluation of A Controlled Release Drug Delivery System of Theophylline Using An Aqueous Acrylic Resin Dispersion.

SHUN POR LI[1], RAMESH JHAWAR[1], GUNVANT N. MEHTA[2], RICHARD J. HARWOOD[3] and WAYNE M. GRIM[1].

[1]Pharmaceutical Research and Development Division, Rorer Central Research, Rorer Group, Inc., Fort Washington, PA 19034

[2]Pharmaceutical Development Department, Rorer Pharmaceutical Corporation, Fort Washington, PA 19034

[3]Squibb United States, Princeton, NJ 08543

Abstract

Eudragit® E30D was utilized in conjunction with talc and xanthan gum to coat theophylline granules via a Wurster-type air suspension column. Since the resin is extremely tacky and cannot be used alone as a coating formulation, different amounts of talc and xanthan gum were incorporated into the Eudragit® E30D suspension to allow for coating of theophylline granules. The release profile of theophylline from the coated granules was found to be dependent on the ratio of the additives to the resin used in the coating suspension as well as on the coating level applied to the final product. A sample of theophylline granules coated with a film-coating suspension containing 1.5:1.0::Talc:Eudragit® E30D resin (calculated on dry basis) exhibited a zero order release profile. However, the in-vitro release rates of this formulation decreased on storage. As the ratio of talc and Eudragit® E30D was changed to 1:1, the coated theophylline granules showed a release profile that remained unchanged even after exposure at room temperature, 30°C and 40°C for three months. A stable theophylline formulation was achieved by curing the coated product at 40°C for 24 hours.

INTRODUCTION

The pharmaceutical industry has been shifting very rapidly from solvent-based film coating systems to aqueous film coating methods due to: (1) the high cost of solvent and solvent recovery systems; (2) ever increasing environmental concerns; (3) explosion hazards; and (4) toxicity associated with the exposure of operators to organic solvents during the film coating processes.[1,2] The availability of new aqueous polymeric dispersions provides more opportunities for formulators to accomplish this task. Several controlled release formulations were successfully prepared using these aqueous polymeric disperions.[3-7] One of these polymeric colloidal dispersions, Eudragit® E30D, has been recommended for sustained release formulations becasue it is insoluble in the entire physiological pH range.[8] Indeed, this polymer has been reported to have been successfully utilized for the preparation of controlled release products.[9-11]

A simple and convenient method to prepare sustained release theophylline formulations was reported.[9,12] Theophylline granules were coated with an aqueous Aquacoat® dispersion *via* an air suspension apparatus to yield a sustained release product. Recently, a method was developed for coating non-uniform granular particles in a uniform and controlled manner.[13] The method described a way to minimize the variability of the release profile of the finished product by applying the coating based on surface area rather than weight.

This report describes the method of coating theophylline granules with a combination of Eudragit® E30D, talc and xanthan gum *via* a Wurster column process to yield a sustained release formulation. The stability of these formulations is also reported.

EXPERIMENTAL

Materials

Theophylline anhydrous granules[a] USP grade were used. Eudragit® E30D[b], an aqueous dispersion of an acrylic resin of 30% total solids, was used as received. Xanthan gum[c] and talc[d] were used as received. All reagents were analytical grade or better.

Equipment

The coating experiments were conducted using a Wurster air suspension coating column.[e]

Dissolution Test

The dissolution tests were conducted using apparatus II, USP XXI/NF XVI with a paddle. The equivalent of three hundred milligrams of theophylline was tested as coated granules in 900 mL of dissolution medium; pH 3.0 phosphate buffer was used from zero to 3.5 hours and then the pH was changed to 7.4 by addition of sodium hydroxide solution. An agitation speed of 50 rpm was used in this study. Samples were removed at suitable time intervals. The collected samples were assayed spectrophotometrically using a Beckman DU®-6 spectrophotometer[f] at 271 nm for theophylline content.

Preparation of Coating Dispersion

Talc was added to the distilled water and the mixture was stirred for five minutes using a propeller type mixer. Xanthan gum (equivalent to 1% (w/w)) solution was added to the mixture and mixed for five minutes. Eudragit® E30D dispersion was then introduced to the mixture and the dispersion was stirred for ten minutes and was used immediately for coating.

Preparation of the Coated Theophylline Granules

An air suspension coating column was utilized for coating each batch of 600 grams of theophylline granules. Three different formulations of Eudragit® E30D dispersion were prepared for evaluation (Table 1). Once the predetermined amount of coating dispersion was sprayed, the coated granules were dried for five minutes in the column using the fluidizing air. The dried granules were further dried in a 40°C oven for 24 hours. The general operating conditions of the Wurster column are given in Table 2.

RESULTS AND DISCUSSION

Insoluble pharmaceutical additives, such as talc, have been incorporated into film-coating formulations to reduce tackiness of Eudragit® E30D polymer during the coating process.[10, 11, 13, 14] To reduce tackiness, the amount of talc added in relation to Eudragit® E30D ranges from 0.5 to 1.5 parts talc to each part of Eudragit® E30D.

From the data generated, it was found fewer agglomerates of coated granules when greater amount of talc were used. The coating process using Formulation 1 (Eudragit® E30D:Talc::1.0:1.5)

Table 1

Composition of Eudragit® E30D Mixture Film*

Material	Formulation (dry basis) 1	2	3
Eudragit® E30D	39.8%	49.8%	76.9%
Talc	59.7%	49.8%	23.1%
Xanthan Gum	0.5%	0.4%	---

*Formulations were coated with the same amount of Eudragit® E30D but different amount of talc and xanthan gum.

Table 2

General Operating Parameters of the 4"/6" Wurster Column and the Settings During the Manufacturing of Coated Theophylline Granules.

Operating Parameters	Setting
Atomizing air pressure	12-16 psi
Fluidizing air velocity	0.02 - 0.04 inch of water
Partition height	3/8 inch
Pump/Drive	Masterflex• 16 Pump Head[g]
Nozzle	Spraying System 1/4 J Series, 40/100/120[h]
Filter	2 X 24 inch
Plate	W-6-3
Inlet temperature	65 - 73°C
Outlet temperature	30 - 37°C
Flow rate of coating solution	6 - 10 mL/min.

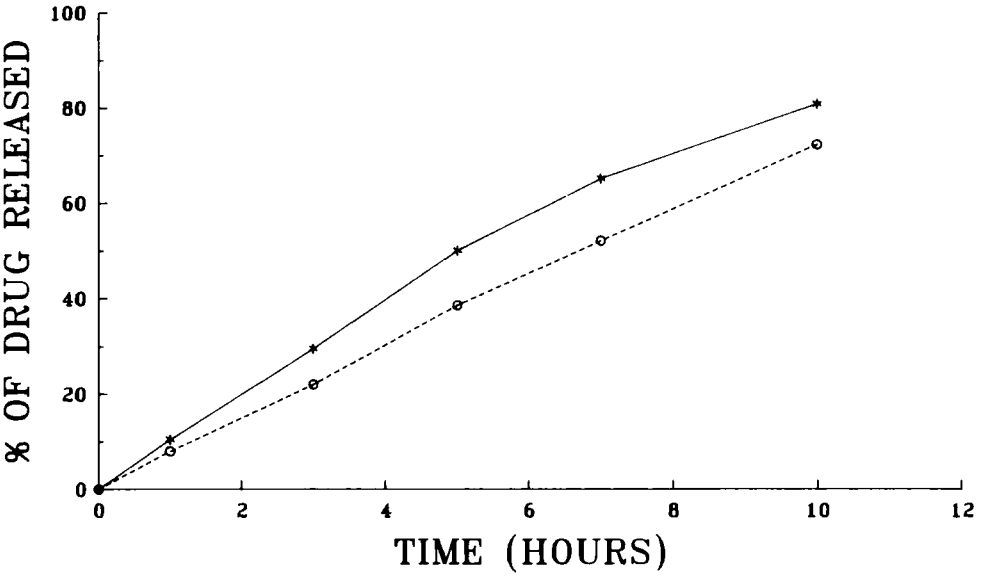

FIGURE 1: Effect of talc on the release profile of coated theophylline granules (Samples were stored at 40°C for two weeks).

Key: × —— Formulation 2 (E30D:Talc::1:1; lower amount of talc)
o —— Formulation 1 (E30D:Talc::1:1.5; higher amount of talc)

was trouble free. There were not any agglomerates of granules, as compared to the Formulation 2 (Eudragit® E30D:Talc::1:1). As the amount of talc to Eudragit® E30D resin was reduced to 30% by weight of dry lacquer resin (Formulation 3), the coating process was very difficult to control. With Formulation 3, an intermittent spraying cycle of the coating dispersion was required to complete the coating process. However, many more agglomerates were found in the finished product as compared to the other two formulations. The incorporation of xanthan gum into the Eudragit® E30D/talc dispersion was needed to make the coating process possible. The incorporation of small amounts of xanthan gum (1% w/w aqueous solution) into the dispersion of Eudragit® E30D and talc successfully eliminated the problem of talc sedimentation found in Formulation 3. A much larger amount of coating (up to 25 to 30% of coating) could then be applied onto the theophylline granules without causing any agglomeration of the coated product. In addition, xanthan gum, being a good suspending agent, was used to keep talc suspended in the dispersion. Xanthan gum, unlike many suspending agents, is compatible with Eudragit® E30D dispersion. It is non-ionic and therefore did not coagulate the resin dispersion.

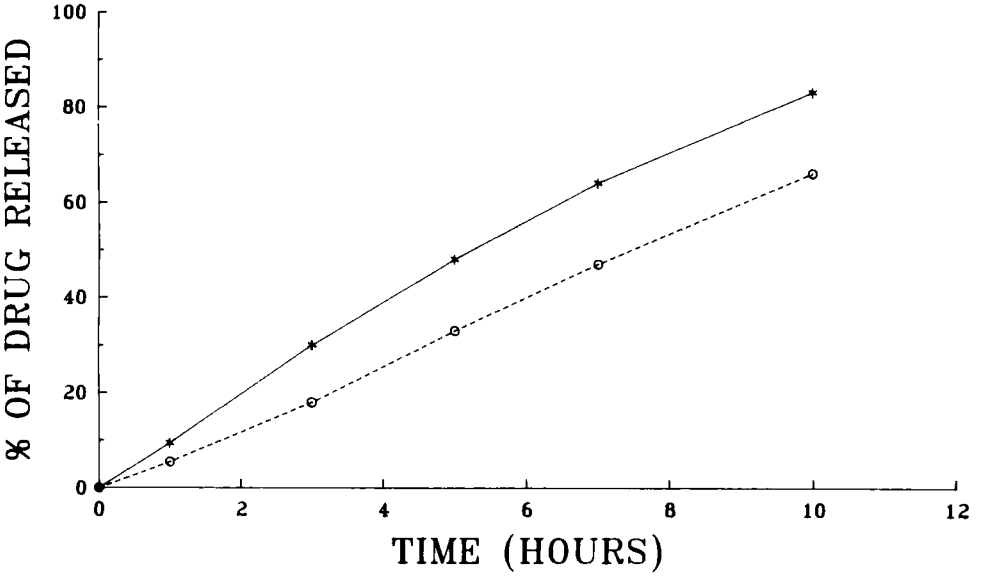

FIGURE 2: Effect of xanthan gum on the release profile of coated theophylline granules (Samples were coated with the same amount of Eudragit® E30D and talc film).

Key: × —— 0.17% xanthan gum
o —— 0.12% xanthan gum

Effect of Processing Aids on the In-Vitro Release Profile of Eudragit® E30D Coated Theophylline Granules

As shown in Figure 1, the rate of drug release is affected by the ratio of talc to resin. As the amount of talc in the coating formulation is increased, the percent theophylline released per unit time is correspondingly decreased. The incorporation of larger amounts of talc, which is hydrophobic in nature, resulted in a thicker layer of coating. The diffusion of the drug through a thicker coating gives rise to a slower theophylline release profile of the coated granules. Figure 2 shows the effect of the amount of xanthan gum incorporated into the film on the release profile of the coated granules. The increase in Eudragit® E30D film permeability resulted from the increase in film porosity when the xanthan gum in the film dissolved. The incorporation of a higher amount of xanthan gum, a hydrophilic polymer, modifies the permeability characteristics of the polymeric network by creating more pores through which the drug can diffuse. Therefore, a faster in-vitro dissolution profile was observed as the amount of xanthan gum increased in the film.

Table 3

pH Profiles of Eudragit® E30D Coated Theophylline Granules*
(Formulation 1)

	pH of Dissolution Media				
Time (Hours)	1.2	3.0	5.0	6.5	7.5
1	29%	25%	22%	28%	27%
2	50%	41%	41%	47%	46%
3	58%	51%	51%	57%	58%
4	71%	64%	64%	70%	71%
5	78%	71%	73%	77%	79%
7	87%	81%	85%	87%	89%
10	98%	93%	95%	97%	98%
24	101%	101%	102%	101%	101%

* Samples were stored at 40°C for two weeks.

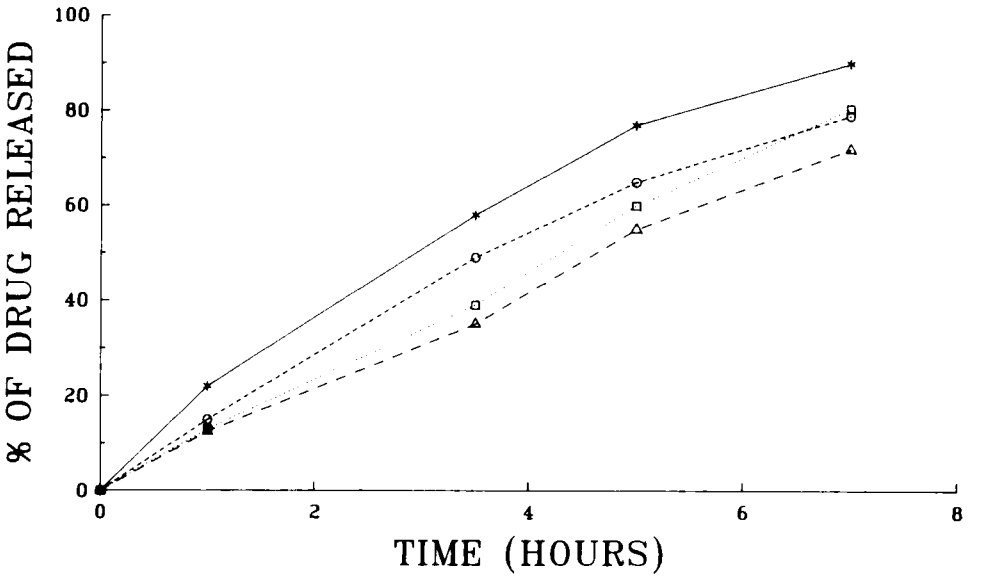

FIGURE 3: Effect of drying on the release profiles of Eudragit® E30D coated theophylline granules (Formulation 1).

Key: × —— Rt for 24 hours
o —— 40°C for 5 hours
□ —— 40°C for 12 hours
△ —— 40°C for 24 hours

Table 4

Stability Study of Eudragit® E30D Coated Theophylline Granules (Formulation 1)

Stability Station	Time (Hours)	Test Periods: Initial	2 Weeks	4 Weeks	12 Weeks
Room Temp	1	13%	11%	12%	11%
	3.5	35%	38%	37%	31%
	5	55%	54%	49%	47%
	7	72%	69%	66%	63%
	10	85%	84%	86%	85%
30°C	1		11%	11%	9%
	3.5		34%	32%	27%
	5		50%	45%	40%
	7		62%	61%	54%
	10		77%	80%	76%
40°C	1		8%	11%	10%
	3.5		26%	30%	24%
	5		39%	42%	36%
	7		52%	57%	50%
	10		67%	77%	72%

As can be seen from Table 3, the release of theophylline from the coated granules coated with Eudragit® E30D, talc and xanthan gum film is pH-independent. These data indicate that the addition of these two additives essentially did not change the inherent pH-independence of an Eudragit® E30D film.

Furthermore, a zero order release profile (up to ten hours) was achieved by balancing the addition of talc and xanthan gum into the Eudragit® E30D film (see Figure 1).

Effect of Drying on the Release Profiles of Eudragit® E30D Coated Theophylline Granules

Film formation of aqueous latex dispersions involves the coalescence of latex spheres.[15] Release characteristics of

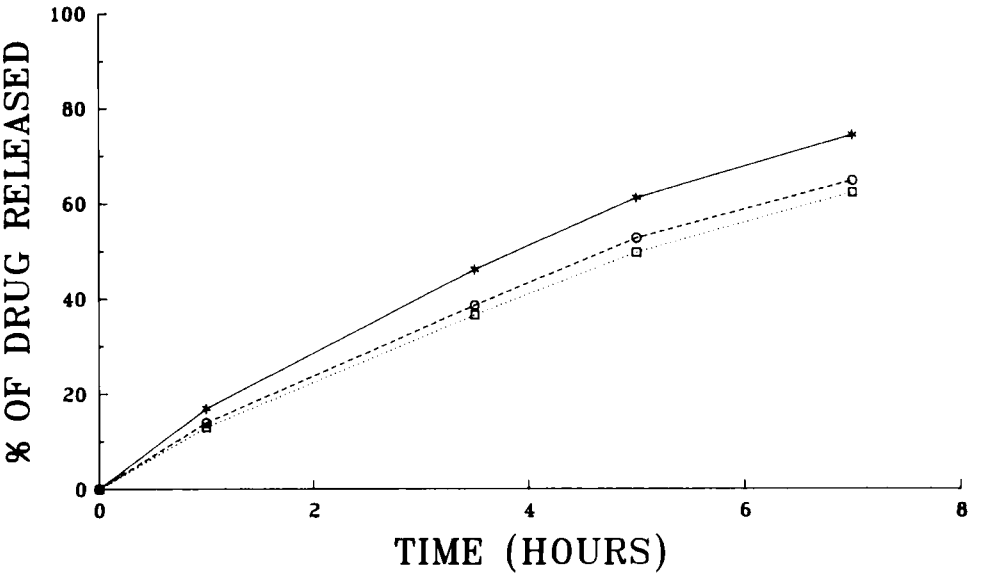

FIGURE 4: Effect of drying on the release profiles of Eudragit® E30D coated theophylline granules (Formulation 2).

Key: × —— RT for 24 hours
o --- 40°C for 5 hours
□ —— 40°C for 24 hours

Eudragit® E30D coated theophylline granules usually change with time until full coalescence is achieved.[11] In order to evaluate the effect of aging on the release profiles of these coated theophylline granules, Formulation 1 (Table 1) was made and then stored at room temperature, 30°C and 40°C for twelve weeks. Figure 3 shows that the dissolution rate decreased in relation to time exposed to 40°C. Sample of this batch (dried at 40°C for 24 hours), exposed to 30°C and 40°C for two more weeks showed a further decrease in the dissolution rates. However, the dissolution rates of samples tested at four and twelve weeks at 30°C and 40°C did not exhibit any further decrease (Table 4) and appeared to level off. The decreasing dissolution rates in these samples as a function of time may be attributed to the following scenario: Evaporation of water from the latex spheres, which is an essential step for coalescence process of the latex film, may be prolonged because of the presence of a greater amount of hydrophobic material in the film (talc).

As can be seen from Figure 4, the release profiles of Formulation 2, exposed initially at room temperature for 24 hours

Table 5

Stability Study of Eudragit® E30D Coated Theophylline Granules (Formulation 2)

Stability Station	Time (Hours)	Test Periods: Initial	2 Weeks	4 Weeks	12 Weeks
Room Temp	1	13%	11%	13%	11%
	3.5	36%	37%	36%	34%
	5	49%	53%	48%	47%
	7	61%	70%	62%	62%
	10	78%	84%	82%	76%
30°C	1		11%	13%	11%
	3.5		37%	34%	33%
	5		53%	44%	49%
	7		68%	60%	62%
	10		83%	83%	78%
40°C	1		10%	15%	13%
	3.5		34%	35%	34%
	5		50%	46%	47%
	7		65%	60%	57%
	10		81%	83%	71%

and at 40°C for five and 24 hours, decreased in relation to increase exposure time at elevated temperature. However, samples exposed to 40°C for 5 and 24 hours showed a similar dissolution profile. This data seems to imply that a curing period of 24 hours at 40°C may be enough to stabilize this Eudragit® E30D formulation. The dissolution rates of samples (cured at 40°C for 24 hours) tested at two, four and twelve weeks at room temperatue, 30°C and 40°C stations did not exhibit any major change with respect to the initial dissolution profile (Table 5). These stability data indicate that a relatively stable formulation can be prepared by coating theophylline granules with the Eudragit® E30D/talc (1:1) film followed by a curing period. It was apparent that the coalescence process of latex film was not effected by this combination of Eudragit® E30D and talc. Even though the amount of talc presented in Formulation 2 was much lower than Formulation 1, it was clearly demonstrated that

there was a sufficient amount of talc to counteract the tackiness of Eudragit® E30D resin. Consequently, the agglomerates of the coated theophylline granules were minimized to an acceptable limit and a smooth, trouble-free coating process was established. Furthermore, the proper ratio of Eudragit® E30D, talc and xanthan gum in this formulation yielded a satisfactory and stable theophylline sustained release product.

Conclusion

A stable sustained release theophylline formulation can be prepared by coating theophylline granules with an appropriate amount of Eudragit® E30D resin and the appropriate types and amounts of pharmaceutical additives via a Wurster column process. The incorporaton of talc to Eudragit® E30D resin (in a 1:1 ratio calculated on a dry weight basis) successfully minimized the tackiness problem inherent with the Eudragit® E30D resin. Furthermore, the combination of talc and xanthan gum was used to modify the in-vitro release profile of the coated granules.

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FOOTNOTES

a. Boehringer - Ingelheim, New York, NY.

b. Rohm Tech., Inc., Malden, MA.

c. Keltrol®, Kelco, Inc., Rahway, NJ.

d. Charles B. Chrystal Company, Inc., New York, NY.

e. 4"/6" Wurster Unit, Model 2XP, Lakso Company, Leminster, MA.

f. Smith Kline Beckman Inc., Philadelphia, PA.

g. Cole-Parmer Instructment Co., Chicago, IL.

h. Spraying System and Co., Wheaton, IL.

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