International Journal of Pharmaceutics, 37 (1987) 211–218
Elsevier

IJP 01260

Evaluation of acrylic-based modified-release film coatings

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(Received 29 April 1986)
(Modified version received 13 January 1987)
(Accepted 14 January 1987)

Key words: Acrylic polymer; Eudragit E 30 D; Aqueous dispersion; Insoluble excipient; Modified release; Mechanism of release; Film coating; Overcoat

Summary

Although insoluble pharmaceutical additives have been generally incorporated into film-coating formulations to impart a particular color to a solid dosage form or to reduce tackiness during the coating process, the inclusion of insoluble excipients in Eudragit E 30 D formulations, instead of the commonly used hydrophilic polymers, generated predictable modified-release reservoir systems. Dissolution studies of Eudragit E 30 D-coated pellets indicated that the release profiles depended not only on the physicochemical properties of the drug, particularly solubility, but also on the coating levels and the ratio of the additive to Eudragit resin in the dry film. Moreover, the integrity of the coating material and hence the release rates were found to be independent of the pH of the dissolution medium. Storing the coated pellets below the softening temperature of the Eudragit film for an extended period of time did not lead to a significant change in the release profiles. The predominant mechanism of drug release appears to be diffusion through water-filled pores in the film coat. The pellets were overcoated with a water-soluble hydrophilic polymer to prevent aggregation and enhance flowability. The overcoat did not affect the rate or extent of drug release.

Introduction

Solvent-based acrylic polymers have been used in the pharmaceutical industry for coating purposes for over 20 years (Lehmann, 1982). Recently, however, the toxicity and environmental concerns associated with the use of organic solvents coupled with the long-term projected rise of the cost of solvents have forced the pharmaceutical industry to explore alternative procedures. Hot melts (fluid-bed coating) which have had extensive application in the food industry are still in their infancy in the pharmaceutical area (Pondell, 1984) and will, therefore, require some time before they are fully developed and used for routine application. The other alternative is the development of water-based polymeric coating systems that have potential applications for modified release dosage forms. In an effort to adjust to the new trends and enhance the versatility of its polymers, Röhm Pharma has developed new aqueous polymeric dispersions and dispersible colloidal particles under the trade names of Eudragit L 30 D, Eudragit E 30 D and Eudragit L 100-55. Eudragit E 30 D is made by emulsion polymerization and consists of neutral copolymers of ethylacrylate–methylmethacrylate esters that are insoluble in the entire physiological pH range (Lehmann and Dreher, 1973). It is thus suitable for the manufacture of oral dosage forms that

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release the bioactive agents independent of pH at any given site in the gastrointestinal tract. Generally, the polymeric dispersion has been combined with hydrophilic substances, such as polyethylene glycol, sugar and polyvinylpyrrolidone, to provide sustained-release preparations as well as various excipients such as talc, to reduce tackiness during the coating process (Lehmann, 1982). Recent studies, however, indicated that the dispersion can be blended with insoluble pharmaceutical additives to generate film-coated modified-release products (Ghebre-Sellassie et al., 1986). The rate and extent of drug release from these preparations depend upon a number of product variables and are the subject of this paper. The surface morphology, film integrity and homogeneity of these coatings were evaluated using dissolution and microanalytical techniques and are discussed elsewhere (Ghebre-Sellassie et al., 1986).

Materials and Methods

Materials

Eudragit E 30 D [1], kaolin [2], magnesium trisilicate [3], talc [4], non-pareil seeds [5], hydroxypropyl cellulose [6], antifoam [7] and hydroxypropylmethyl cellulose [8] were used as received. Theophylline [9], diphenhydramine hydrochloride [10] and pseudoephedrine hydrochloride [11] were screened through a 60-mesh screen [12] prior to making the respective pellets.

[1] Rohm Pharma GmbH, Darmstadt, F.R.G.
[2] Georgia Kaolin, Elizabeth, NJ, U.S.A.
[3] Whittaker Clark and Daniels, South Plainfield, NJ, U.S.A.
[4] Cyprus Industrial Materials Co., Englewood, CO, U.S.A.
[5] Beaver Food Products, Pennsauken, NJ, U.S.A.
[6] Hercules, Inc., Wilmington, DE, U.S.A.
[7] Dow Chemical, Midland, MI, U.S.A.
[8] Dow Chemical, Midland, MI, U.S.A.
[9] Knoll Fine Chemicals, Div. of Knoll Pharma. Co., New York, NY, U.S.A.
[10] Warner-Lambert, Holland, MI, U.S.A.
[11] Ganes Chemicals, Inc., Carlstadt, NJ, U.S.A.
[12] U.S. Standard Sieves, E.H. Sargent & Co., Chicago, IL, U.S.A.

TABLE 1

Processing conditions for Eudragit E 30 D-coated drug pellets (Strea I, Aeromatic)

Parameter	Setting
Inlet temperature	30–35 °C
Outlet temperature	20–25 °C
Fluidization air volume (fan)	10–15
Flow rate	1–2 ml/min
Atomization air pressure	0.2–0.6 bar
Nozzle width	1.2 mm

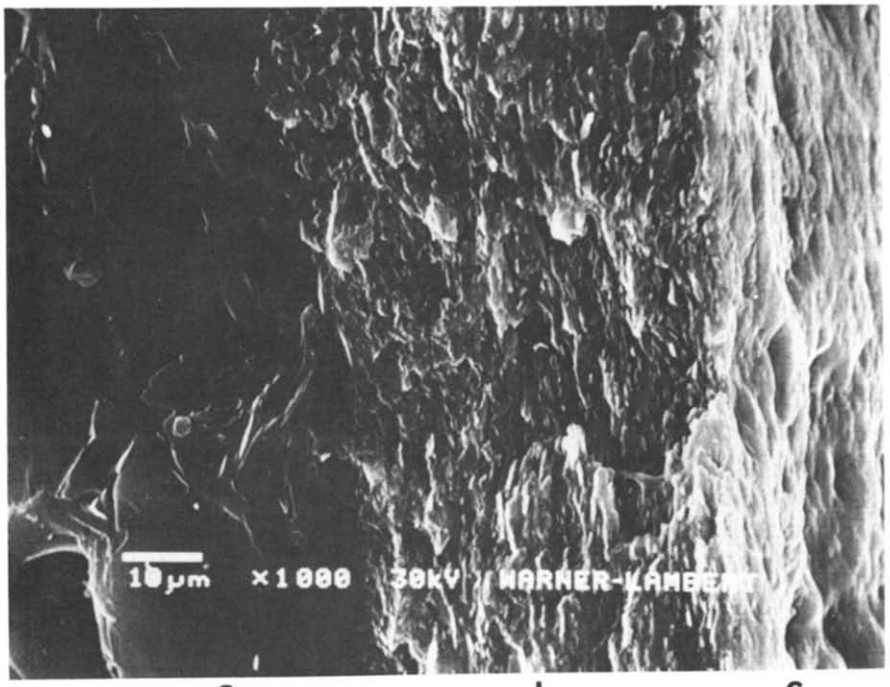
Pellet preparation

Hydroxypropyl cellulose, which was employed as a binder, was dissolved in purified water immediately before use to provide an 8% solution. 900 g of non-pareil seeds were placed in the prewarmed chamber of a centrifugal granulator [13] and allowed to tumble for a maximum of 3 min. The rotor speed was set at 200 rpm. Spraying of the binder solution was then initiated. When the seeds became moist, drug powder was fed at an appropriate rate. After a sufficient quantity of powder was added to build the pellets to the desired size, spraying of the binder solution was terminated. The pellets were partially dried while still in the chamber using fluidizing air. They were then transferred to a paper-lined tray and stored at 45 °C for thorough drying. The dried pellets were screened and the 12–18-mesh fraction collected.

Coating procedure

The various coating formulations were prepared by simply mixing suspensions of kaolin, talc or magnesium trisilicate in purified water with the required quantities of Eudragit E 30 D dispersion. A small amount of antifoam was added to prevent foaming during mixing. Known weights of pellets were then transferred to the fluidized bed coating apparatus [14] and coated with the formulations until the desired weight of film was deposited. The coating formulations were stirred throughout the coating process. The coating conditions are given in Table 1.

[13] CF-Granulator, Freund Industrial Co., Ltd., Tokyo, Japan
[14] Strea I, Aeromatic, Towaco, NJ, U.S.A.



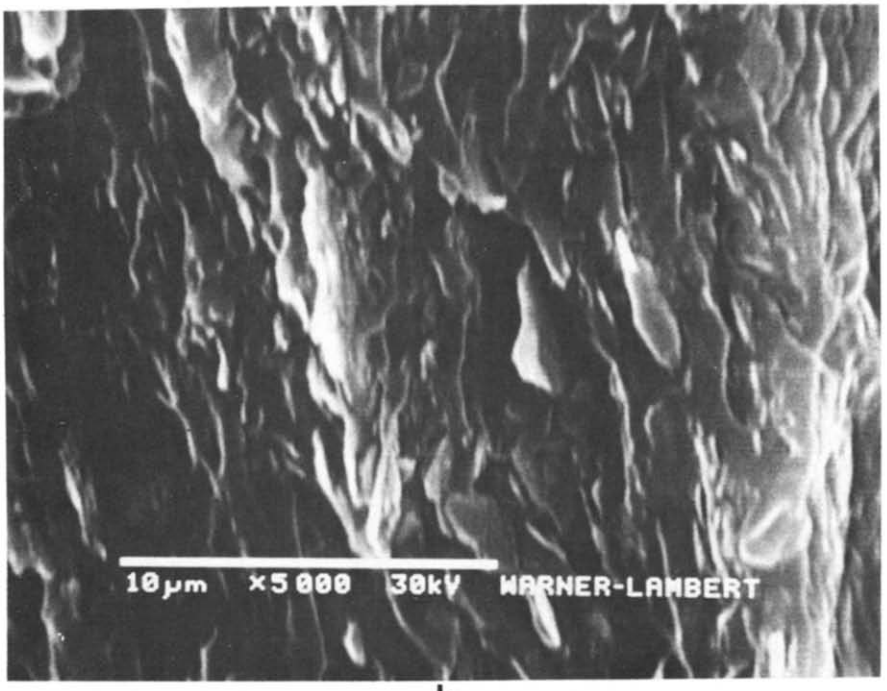


Fig. 1. Scanning electron micrograph of a cross-section of an Eudragit E 30 D-coated drug pellet; a, drug layer; b, cross-section of the film coat; c, surface.

Dissolution

In vitro dissolution studies were carried out using the USP dissolution apparatus II (Paddle) [15] at 37 °C and 75 rpm. The dissolution media were water, simulated gastric and/or intestinal fluid (without enzymes). Samples were withdrawn from the dissolution vessels and an equivalent volume of fresh dissolution medium was replaced automatically at preselected time intervals. Assay of the released drug was conducted spectrophotometrically [16] at 258 nm.

Results and Discussion

Dissolution studies of pseudoephedrine hydrochloride, theophilline and diphenhydramine hydrochloride pellets that were coated with various mixtures of kaolin and Eudragit E 30 D dispersion indicated that the release profiles of the drugs are influenced by a number of factors. In addition to the physicochemical properties of the drugs, the coating levels as well as the amount of insoluble additives in the dry film played a major role in determining the release rates of the bioactive agents from the coated pellets. Other factors which may influence the nature of the film coat and hence the release profiles of the pellets include aging, dissolution medium pH and overcoat.

Mechanism of release

During the coating process in fluidized bed equipment, each pellet is sprayed with only a small portion of the coating formulation in a random fashion each time it traverses the spray path. The intermittent layering of the droplets on the substrate eventually generates a film coat characterized by channels with tortuous paths. A cross-section of a coated drug pellet indicates that imperfections are present throughout the film coat (Fig. 1). This observation is consistent with a previous report in which scanning electron microscope pictures of spray-coated tablets or pellets were shown having a very heterogenous film structure, often containing many artifacts (Porter, 1982). Mercury porosimetry was used to further examine the nature of the coating material which was composed of 3 parts of Eudragit resin and two parts of kaolin. An increase in the applied pressure was accompanied by corresponding increase in the amount of mercury intruded, thereby indicating the porous nature of the film coat (Fig. 2). This phenomenon was observed with all levels of insoluble additives. Moreover, film porosity is related to the amount of insoluble excipients incorporated in the coating formulation (Ghebre-Sellassie et al., 1986). During dissolution, the predominant mechanism of drug release is expected to be diffusion through the water-filled pores, as opposed to drug diffusion through the insoluble polymeric film. Such systems, therefore, should release the drug, provided its solubility and pK_a are favorable, independent of both the pH of the gastrointestinal fluids and gastric motility. The structure of the pores in the film coat is incorporated into the diffusion coefficient of the solute in pure water, D_w, by means of the porosity, ϵ, and the tortuosity, τ, of the coating material to define the effective diffusion coefficient, D_{eff} as

$$D_{eff} = D_w \, \epsilon/\tau \qquad (1)$$

If the solute partitions into the polymeric membrane, which probably is negligible in the present case, and the size of diffusing molecule is less than the diameter of the pores, a pore/wall partition

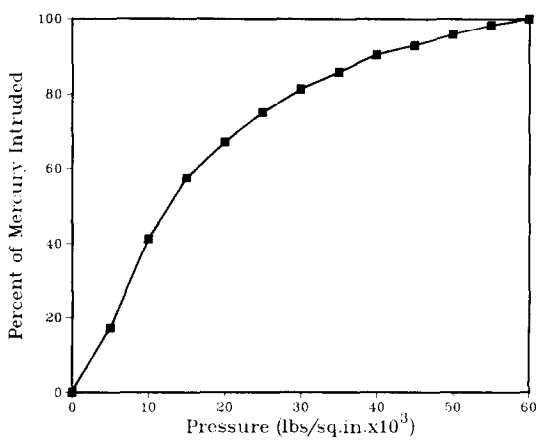


Fig. 2. Percent of mercury intruded as a function of pressure.

[15] Hansen Research, Northridge, CA, U.S.A.

[16] DU-7 Spectrophotometer, Beckman Instruments, Inc., Somerset, NJ, U.S.A.

coefficient, K_p, can be incorporated into the diffusion coefficient as shown (Peppas and Meadows, 1983).

$$D_{eff} = D_w(\epsilon/\tau)K_p \quad (2)$$

In addition to diffusion, however, osmotic and convective forces are expected to play a significant role in the rate and amount of drug release. Therefore, the cumulative percent released is a composite function of drug solubility, osmotic activity of the components of the drug pellet and the size of the pores in the film coat.

Effect of the relative ratio of Eudragit E 30 D resin to additive in the final film on release profile

As shown in Fig. 3, the rate of drug release and the lag time are proportional to the ratio of kaolin to resin. As the amount of kaolin in the coating formulation is increased, the percent drug released per unit time is correspondingly increased until a point is reached where the integrity of the film is no longer maintained and immediate release is achieved. In contrast, the length of time required for the initiation of release increases as the ratio of kaolin to resin in the formulation decreases. If the curves in Fig. 1 were compensated for the differences in lag times, it would appear that the rates of release are not markedly different. However, a first order plot of the data showed otherwise (Fig. 4). In general, satisfactory modified-release products may be obtained with additions of 5–50% kaolin to Eudragit E 30 D resin calculated on the basis of the dry film. The ratio of additive to resin required to generate the desired release properties is determined by the physicochemical properties of the substrate. For a given rate of drug release and a specific coating level, extremely water-soluble drugs require a lower ratio of kaolin to resin in the final film than poorly water-soluble active ingredients. Therefore, the composition of the wall material is a very important factor which needs to be considered during the development of a modified-release dosage form.

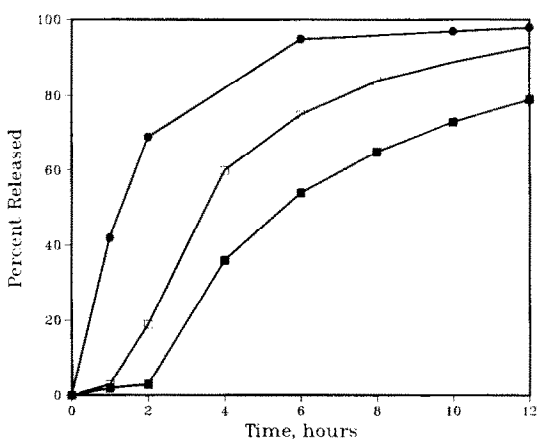


Fig. 3. Effect of the relative ratio of Eudragit E 30 D resin to kaolin in the final film on release profile. Resin:kaolin: ●, 3:3; □, 3:2; ■, 3:1.

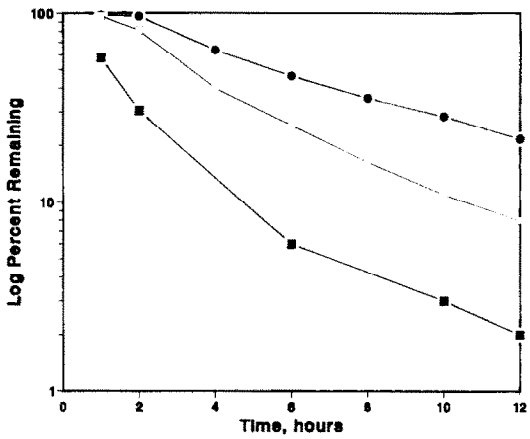


Fig. 4. Log plot of the effect of the relative ratio of Eudragit E 30 D resin to kaolin in the final film on release profile. Resin: kaolin: ■, 3:3; □, 3:2; ●, 3:1.

Effect of film thickness on release profile

The release profiles of drug-loaded pellets depend, to a great extent, on the coating level of the final product. An increase in coating thickness is always accompanied by a decrease in the release rates of the pellets (Figs. 5 and 6). The relationship, however, is not linear and varies significantly with the properties of the active ingredient. Highly water-soluble drugs generally require higher coating levels than poorly soluble compounds. This behavior is partially attributed to the different rates of migration of the species during the coating process. During film deposition, highly water-soluble drugs dissolve in the sprayed droplets and remain embedded in the film after the evaporation

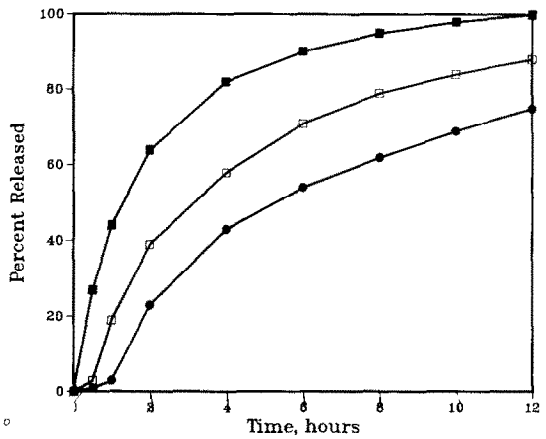


Fig. 5. Effect of film thickness on the release profile of diphenhydramine hydrochloride pellets. Coating: ■, 13%; □, 19%; and ●, 31%.

of water. As more and more layers of film are deposited to constitute the wall material, the migration of drug diminishes until a coating film devoid of drug is produced. Since the presence of the drug in the inner parts of the coating leads to a porous structure during dissolution, a thicker coat is required to generate a specific release profile than would be the case with poorly water-soluble drugs.

Effect of substrate solubility on release profile

Although coating levels and composition of coating formulations are critical parameters that must be addressed during the development of a modified release product, the physicochemical properties, particularly solubility, of the substrate determine the coating process that must be adopted. It is these properties that govern the migration rate of drug entities during film deposition. Comparison of Figs. 5 and 6 clearly underscores the importance of solubility on the rate and extent of release. At a given ratio of kaolin to resin, pellets composed of the slightly water-soluble drug, theophylline (8 mg/ml), require much less coating levels than those composed of diphenhydramine hydrochloride (1 g/ml), a freely water-soluble compound, to achieve comparable release profiles.

Effect of type of additive on release profile

Kaolin can be replaced in the formulation by any other water-insoluble substance that is compatible with the polymeric dispersion without any loss of sustaining properties (Fig. 7). Talc and magnesium trisilicate were incorporated in the coating material and generated similar release profiles. In each case, the ratio of additive to Eudragit E 30 D resin was 2 : 3, while the coating level was 15%. Substances chosen to replace kaolin should also be insensitive to pH changes in order to maintain the unique pH independent property of Eudragit E 30 D. Additives that are ionic in character must be avoided since they tend to

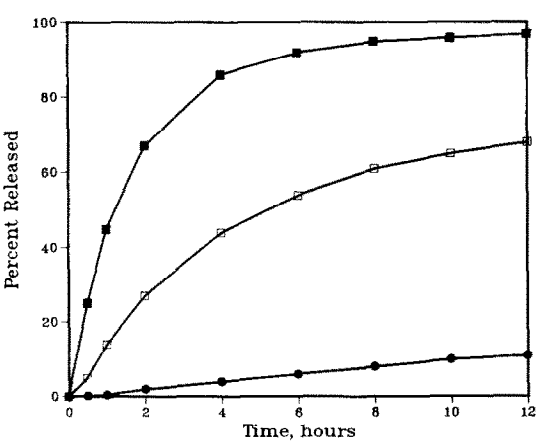


Fig. 6. Effect of film thickness on the release profile of theophylline pellets. Coating: ■, 4%; □, 9%; and ●, 20%.

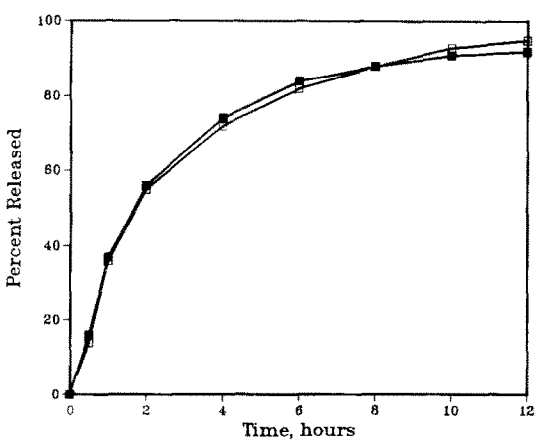


Fig. 7. Effect of type of additive on the release profile of pseudoephedrine hydrochloride pellets. ■, Talc; □ magnesium trisilicate.

coagulate the dispersion, thereby leading to discontinuous and unsatisfactory film coatings.

Effect of dissolution medium on release profile

Dissolution studies showed that the integrity of the coating material and hence the release rates of the pellets are independent of the pH of the dissolution medium. As depicted in Fig. 8, the release profiles of coated pseudoephedrine hydrochloride pellets in simulated gastric and intestinal fluids (without enzymes) are virtually identical. The same trend will always be observed as long as the bioactive agent is soluble in the dissolution medium. Such pH independence of the film coat ensures the development of modified release products that are not affected by the variable pH that prevails in the gastrointestinal tract. Total GI transit time, irrespective of gastric emptying time, will determine the amount of drug that will be available for absorption.

Effect of aging on release profile

Although Eudragit E 30 D formulations containing hydrophilic film formers as modifiers have been used to generate sustained release products, there has always been concern of film-hardening as a function of time and a corresponding change in release rate. In an effort to test the validity of such a concern with the present formulation, diphenhydramine hydrochloride pellets were coated with a mixture of Eudragit E 30 D and kaolin and stored at room temperature for 18 and 40 months. Dissolution data obtained from these aged pellets indicated no significant difference in release behavior (Table 2). It must be emphasized, however, that the coated pellets should not be stored at temperatures above 40 °C. Otherwise, the film coat will either soften or harden, depending upon the temperatures the coated products are subjected to, and lead to unpredictable release profiles.

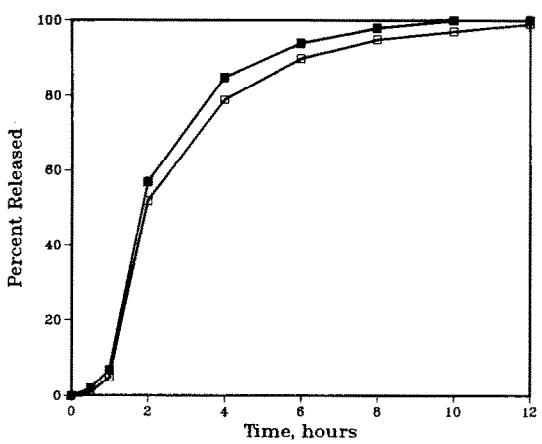


Fig. 8. Effect of dissolution medium on the release profile of pseudoephedrine hydrochloride pellets. ■, Gastric fluid; □ intestinal fluid.

TABLE 2

Release data of coated diphenhydramine hydrochloride pellets aged at room temperature for 18 and 40 months

Time (h)	Percent released	
	18 months	40 months
0.5	2	3
1	5	5
2	14	10
4	55	50
6	72	71
8	83	83
10	89	90
12	94	95

Effect of an overcoat on release profile

Pellets coated with Eudragit formulations stick to one another upon storage at or above room temperature to form soft lumps. Although these lumps are broken easily at lower temperatures and generally appear to have no effect on dissolution

TABLE 3

Release data of diphenhydramine hydrochloride pellets with and without an overcoat

Time (h)	Percent released	
	With overcoat	Without overcoat
0.5	4	3
1	9	8
2	33	33
4	56	56
6	69	69
8	77	77
10	82	82
12	85	85

profiles, their formation can be totally prevented by the application of an overcoat that is composed of a water-soluble, hydrophilic film former with or without an antitackiness agent. The overcoat (about 2%) did not affect the rate or extent of drug release (Table 3). Overcoating agents include cellulosic ethers and polyethylene glycols.

Conclusion

Eudragit E 30 D formulations containing appropriate pharmaceutical additives provided release rates that are independent of the pH of the dissolution medium, exhibited predictable and reproducible drug release characteristics, and generated very stable films whose properties did not change as a function of time. In addition, incorporation of the additives helped alleviate the tackiness problems inherent to Eudragit formulations, and increased the solids content of the coating formulations without raising the viscosity appreciably. The soft lumps that are commonly observed with Eudragit E 30 D-coated pellets upon storage are eliminated by the application of a hydrophilic overcoat without altering the release profiles of the pellets.

Acknowledgements

The authors are grateful to Mrs. Uma Iyer and Dr. Michael Harris for their comments and suggestions and to Mrs. Ruth Cohnstein for typing the manuscript.

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