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MODIFYING THE RELEASE PROPERTIES OF EUDRAGIT® L30D

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ABSTRACT

The influence of various additives, namely, PEG, mannitol, and HPMCP 50 incorporated with Eudragit® L30D on drug release from pellets was investigated. Cores of a water soluble drug were prepared by the powder layering technique using the CF Granulator (CF 360) and coating was accomplished utilizing the Glatt GPCG3 machine. Drug release from pellets coated with Eudragit® L30D was found to be influenced by the type and the level of the additive incorporated with the copolymer. At pH 1.5, PEG, regardless of the molecular weight, did not have any significant effect on drug release. At pH 5.5, however, PEG significantly decreased drug release from coated pellets, and the decrease was more pronounced as the molecular weight of PEG was increased. Release of the drug from pellets coated with Eudragit® L30D containing mannitol was found to be dependent on mannitol concentration at pH 1.5, 3.5 and 4.5 but independent of mannitol concentration at pH 5.5.
The release of drug through Eudragit® L30D:HPMCP 50 films was found to be dependent on the ratio of the polymers.

INTRODUCTION

One way of preparing an enteric dosage form is by film coating with a pH sensitive polymer in which case the drug will be released after the dissolution of the film. The polymers which

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are used for enteric coating are essentially polyacids with carboxyl ionizable groups. These polymers dissolve at a pH higher than that encountered in the stomach. Usually films formed from these polymers are sprayed from organic based solvent systems. Dosage forms may be designed to release the drug at pH levels lower than where the polymer is soluble by incorporating other water soluble polymers or small leachables molecules whose solubility is independent of pH. Numerous examples are discussed in the literature where additives and particularly water soluble substances have been incorporated with film forming polymers to modify their release properties (1-3). Eudragit® L30D is an aqueous solid dispersion which is used to prepare enteric coated solid formulations. The objective of this investigation was to study the influence of various additives on the release properties of Eudragit® L30D films.

EXPERIMENTAL

Materials:

The active substance is a water soluble drug with pH-dependent solubility; Hydroxypropyl Cellulose, type EF, NF (Aqualon Company, Hopewell, VA); Triethyl Citrate NF (Morflex Chemical Co.,Inc, Greensboro, NC) ; Colloidal Silicon Dioxide NF (Cabot Chemical Co., Tuscola,IL); Sugar Spheres NF 20-25 mesh size (Ozone Confec. & Bakers Supply, Elmwood Park, NJ); Eudragit® L30D (Rhom Tech., West Germany); Kaolin USP (Whittaker, Clarks & Dasniels, Inc., South Plainfield,NJ; Mannitol USP (ICI, Wilmington, Delware); Hydroxypropylmethyl Cellulose Phthalate 50 NF (Shin-Estu Chemical Co., Japan)

Methods:

Development of the Core Utilizing Nonpareils (sugar spheres) as Starter Seeds :

The core formulation was prepared by the powder layering technique utilizing Sugar Spheres NF as starter seeds. The CF-360 Granulator (Freund Industrial Co., Ltd., Tokyo, Japan) was used for this purpose. The drug (1kg) was passed through a Fitzmill®, set at high speed with impact forward, fitted with a screen with 0.05 mm round openings.

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The milled drug was blended with Cab-O-Sil® (1g) which was passed through a 100 mesh screen. This blend was layered onto sugar spheres seeds in the CF-360 Granulator using an 8% hydroxypropyl cellulose solution as the binder.

Core composition is as follows:

Ingredient	% W/W
1- Drug	65.2
2- HPC(EF)	2.1
3- Cab-O-Sil	0.1
4- Sugar Spheres 20-25 mesh	32.6

The following conditions were used to prepare the drug loaded cores: rotor was set at 160 rpm; powder feed at 14 gm/minute; spray rate at 12 mL/minute; inlet temperature of 40°C to maintain the product temperature at 25°C. The cores were dried on trays in an oven overnight at 45°C. The cores were then sieved and those with a mesh size fraction in the range of -12 to +20 were used.

Coating of Cores

The composition of the coating system employed is described below:

Ingredient	%W/W
1- Eudragit® L30D	41.0
2- Triethyl citrate	1.3
3- Kaolin	2.4
4- Water	55.3

The system is prepared by adding 3 to 4 and mixing for at least 20 minutes to allow for hydration. Then 2 is added and the suspension is mixed for another 10 minutes. Finally, 1 is added and mixed for 30 minutes; the suspension is passed through # 40 mesh screen. When PEG or mannitol are incorporated in the coating system, they are first dissolved in water and the same procedure

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described above is followed. When HPMCP 50 is used, it is added after kaolin has been added.

Using the Glatt GPCG3 machine, the following conditions were employed: spray rate of 6 mL/min; rotor at 250 rpm; flap 24%; inlet temperature of 28°C, product temperature of 24°C and atomization of 1 bar. Upon completion of the coating step, the pellets were dried in the machine for 45 minutes with an inlet temperature of 45°C.

Dissolution System

Dissolution studies were carried out using the USP basket method (USP Apparatus 1). The volume of the dissolution medium was 900 ml and stirring rate of 50 rpm was used. 0.06N HCl (pH 1.5), pH 3.5, pH 4.5 and pH 5.5 phthalate buffers, 0.05 M, were used.

RESULTS AND DISCUSSION

Release of the Drug From Pellets Coated with Eudragit® L30D Aqueous Solid Dispersion Containing PEG

Figure 1 shows the release of the drug from pellets coated with Eudragit® L30D alone, and Eudragit® L30D containing PEG (17% w/w of the film) at pH 1.5. As was expected no drug release was observed from Eudragit® L30D alone at this pH. No release was noted when PEG, regardless of the molecular weight, was incorporated with Eudragit® L30D. Although PEG is used as a platicizer for acrylic polymers, one would expect PEG to increase the permeability of the polymeric film and create water channels or pores through which drug will be released (4); apparently this did not occur. Figure 2 shows the results obtained at pH 5.5. As expected drug was released from pellets coated with Eudragit® L30D alone. For Eudragit® L30D containing PEG, no drug release was observed when PEG 8000 was used, however, some release was observed with PEG 600, and 1450. The release rate of the drug increased as the molecular weight decreased (Figure 2). The effect observed with PEG 8000 could be due to the formation of a film which is not permeable or soluble at pH conditions where

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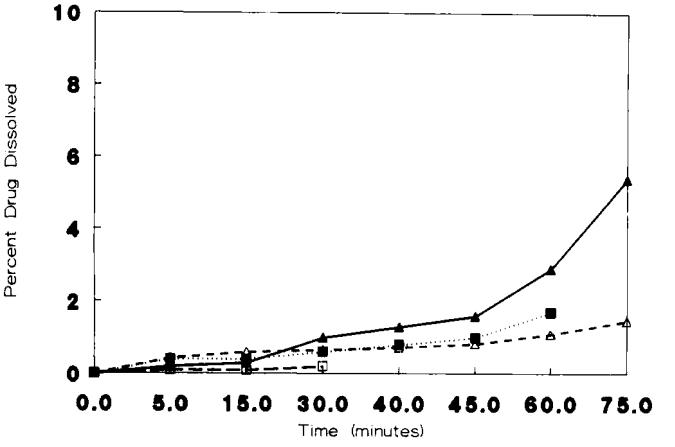

Figure 1. The influence of the molecular weight of PEG on drug release from pellets coated (10% w/w) with Eudragit® L30D containing 17% w/w PEG in 0.06 N HCl. key. no PEG (△), PEG 600 (▲), PEG 1450 (■), PEG 8000 (□).

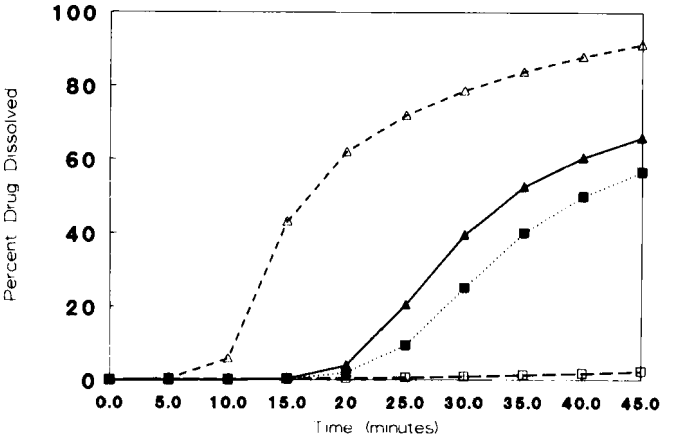

Figure 2. The influence of molecular weight of PEG on drug release from pellets coated (10% w/w) with Eudragit® L30D containing 17% w/w PEG in pH 5.5. key as in Figure 1.

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Eudragit® L30D normally dissolves. No drug release was noted from a silicone elastomer system containing 10% PEG 8000 (4). Although the PEG's were not used in this work as the main plasticizers (triethyl citrate was used as the plasticizer), they are widely employed as plasticizers with film forming polymers. The presence of PEG systems (especially the liquid grades) in films tends to increase their water permeability and reduce protection against low pH in enteric film coatings (5). The results obtained in this study indicate that PEG incorporated with Eudragit® L30D does not only act as a plasticizer but also changes the release properties of Eudragit® L30D films. For a given concentration of PEG, the extent of these changes is dependent upon the molecular weight of PEG incorporated with the polymer. The dissolution results in both pH 1.5 and pH 5.5 media suggest that diffusion through the membrane, osmotic pumping, is perhaps the predominant mechanism that controls drug release in this system rather than diffusion through the pores (6).

Release of the Drug From Pellets Coated with Eudragit® L30D Aqueous Solid Dispersion Containing Mannitol.

Figure 3 shows the release of the drug from pellets coated with Eudragit® L30D containing various levels of mannitol at pH 1.5. As the concentration of mannitol was increased drug release increased. These data demonstrate the dramatic effect of the inclusion of mannitol in the Eudragit® L30D film and suggest that drug release from these pellets occurs through pores (dissolution medium filled) in the film formed by the dissolution of mannitol. The number of pores formed appears to be dependent upon the concentration of mannitol in the film coating. Figure 4 shows that the time required for 50% drug release is directly related to the concentration of mannitol in the film. It was found, however, that at concentrations greater than 10% w/w, this relationship deviated slightly from linearity.

At pH 3.5, drug release was significantly decreased compared to that observed at pH 1.5, Figure 5. The decrease in release is consistent with the decrease in the solubility of the drug at this pH. The results obtained at pH 1.5 and 3.5 suggest that drug release is predominantly through pores formed in the film and that the Eudragit® L30D film without mannitol is not significantly permeable to the drug in this pH range (i.e., pH 1.5-3.5).

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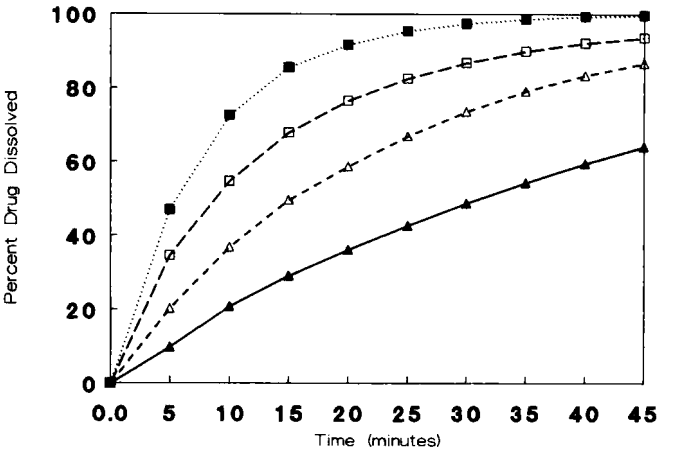

Figure 3. The influence of level of mannitol on drug release from pellets coated (6% w/w coat) with Eudragit® L30D in 0.06 N HCL. Key. 5.9% w/w (▲), 8.5% w/w (△), 11% w/w (□), 20% w/w (■).

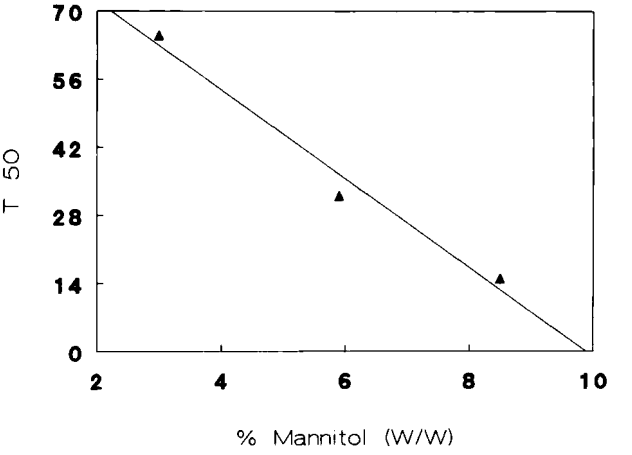

Figure 4. The relationship between the Time for 50% drug release (T50) from pellets and mannitol concentration in the film.

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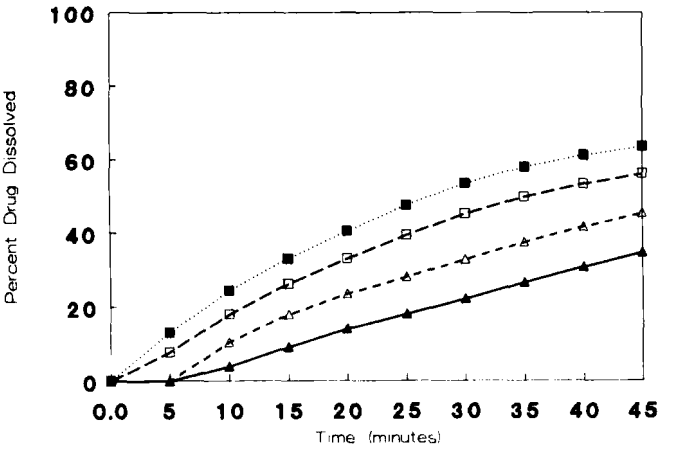

Figure 5. The influence of the level of mannitol on drug release from pellets coated (6% w/w coat) with Eudragit® L30D in pH 3.5. key as in Figure 3.

At pH 4.5, drug solubility does not increase, however, the release of the drug was significantly increased (Figures 6-7). Although the acrylic polymer is not completely soluble at this pH, some of the carboxylic acid groups may begin to ionize and cause softening and swelling of the film. This can cause formation of media filled channels or pores which facilitate drug diffusion. Therefore, drug release at this pH could be attributed to both diffusion through the media filled channels created as a result of the polymer swelling and the pores formed as result of mannitol dissolution.

At pH 5.5, release of the drug was independent of mannitol concentration in the coating film since Eudragit® L30D dissolves at this pH (Figure 8).

Figure 9 shows the influence of film thickness (coating level) on drug release from pellets coated with Eudragit® L30D-mannitol system. At pH 1.5, coating level had a dramatic effect on the release of drug from pellets. At pH 5.5, however, the effect of coating level on drug release is less pronounced. This is due to dissolution of the polymer and decreased drug solubility.

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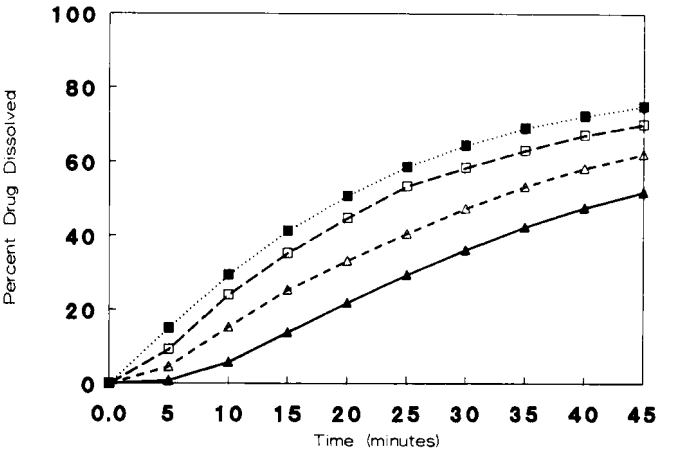

Figure 6. The influence of the level of mannitol on drug release from pellets coated (6% w/w coat) with Eudragit® L30D in pH 4.5. key as in Figure 3.

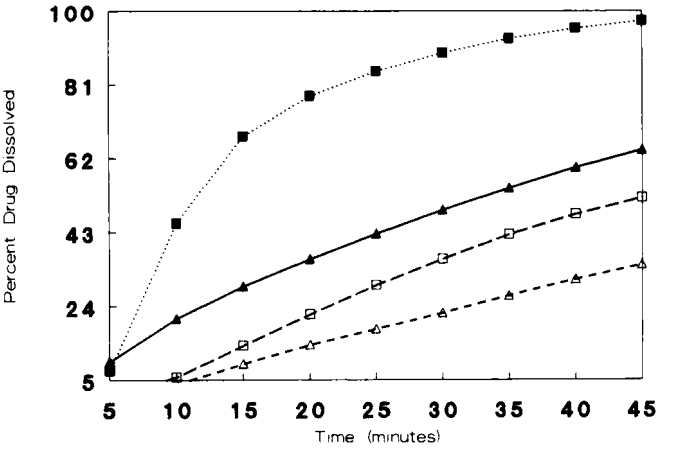

Figure 7. Release of drug from pellets coated (6 %w/w coat) with Eudragit® L30D containing 5.9% w/w mannitol as a function of pH. key. pH 1.5 (▲), pH 3.5 (△), pH 4.5 (□), pH 5.5 (■).

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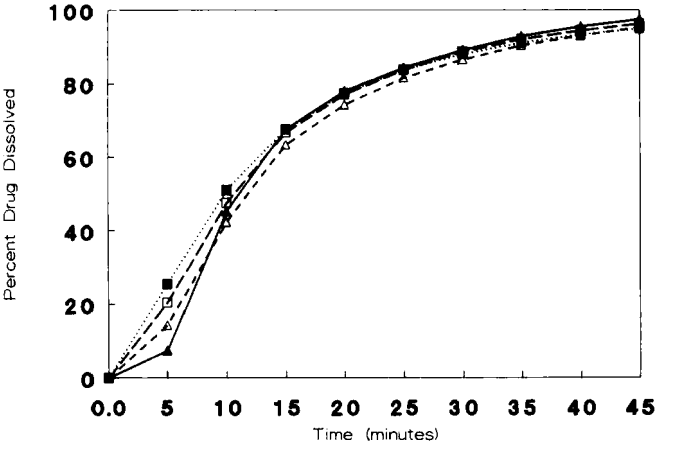

Figure 8. The influence of the level of mannitol on drug release from pellets coated (6% coat) with Eudragit® L30D in pH 5.5. key as in Figure 3.

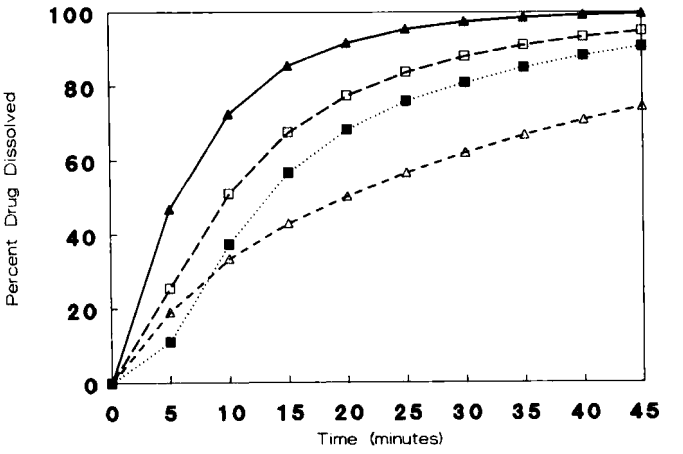

Figure 9. The influence of the coating level on drug release from pellets coated with Eudragit® L30D film containing 20% w/w mannitol at pH 1.5 and pH 5.5. key. 6% w/w coat, pH 1.5 (▲), 10% w/w coat, pH 1.5 (△), 6% w/w coat, pH 5.5 (□), 10% w/w coat, pH 5.5 (■).

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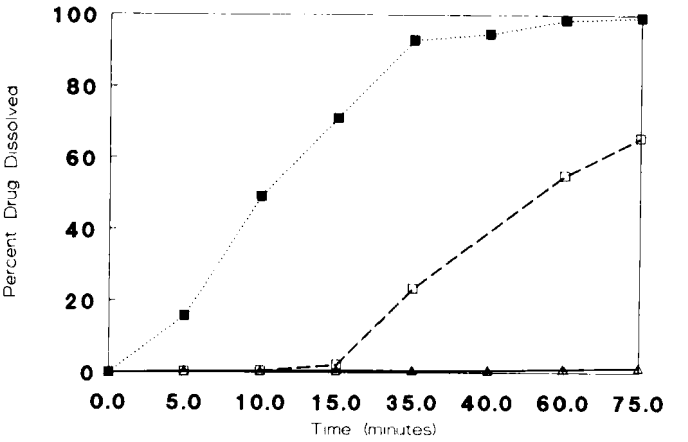

Figure 10. The influence of Eudragit® L30D:HPMCP 50 composition on drug release from pellets (10% w/w coat) in pH 1.5. key. 100% Eudragit® L30D (△), Eudragit® L30D:HPMCP 50; 1.5:1 ratio, (□), Eudragit® L30D:HPMCP 50; 1:10 ratio, (■).

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Release of Drug From Pellets Coated with Films Consisting of HPMCP and Eudragit® L30D

This part of the investigation was initiated to evaluate the release properties of a coating system comprised of HPMCP 50 and Eudragit® L30D. Although both systems are used independently to prepare enteric films, they have unique polymer characteristics. For example, Eudragit® L30D dissolves at pH 5.5 and is impermeable to drugs in low pH media. HPMCP 50, on the other hand, dissolves at pH 5.0 and when employed as a suspension from an aqueous based solvent system is somewhat permeable to drugs in lower pH media. Therefore, it was postulated that combining both systems would result in a film which possesses properties of both polymers (sufficient acid resistance at pH 1.5, and fast release at pH 5.5).

Aqueous dispersions of mixtures of both polymers were prepared at various ratios and were used to coat the drug pellets. Dissolution results obtained at pH 1.5 are plotted in Figure 10. As can be seen, no drug release was observed with Eudragit® L30D

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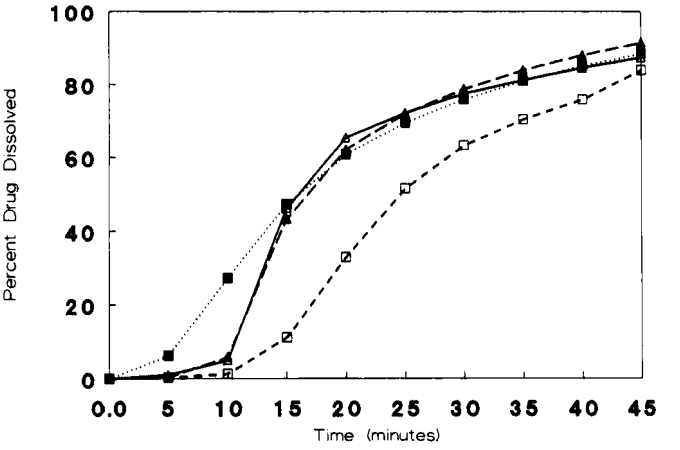

Figure 11. The influence of Eudragit® L30:HPMCP 50 composition on drug release from pellets (10% w/w coat) in pH 5.5. key. 100% Eudragit® L30D (△), Eudragit® L30D:HPMCP 50; 5:1 ratio, (▲), Eudragit® L30D:HPMCP 50; 1.5:1 ratio, (□), Eudragit® L30D:HPMCP 50; 1:10 ratio, (■).

alone, however, it was increased as the ratio of HPMCP 50 increased in the composition. A corresponding decrease in the lag time was obtained with the increase in HPMCP 50 in the composition.

Dissolution results obtained at pH 5.5 are plotted in Figure 11. The release of drug from Eudragit® L30D alone and from Eudragit® L30D:HPMCP 50 at a 5:1 ratio was very similar. The results suggest that Eudragit® L30D is the polymer which controls drug release, and HPMCP 50 at this ratio does not influence the properties of the combined polymer film. Eudragit® L30D:HPMCP 50 at a ratio of 1.5 to 1.0 resulted in a film which is less permeable or soluble than Eudragit® L30D alone. At a ratio of 1:10 (Eudragit® L30D:HPMCP 50), although the initial release rate was increased (no lag time can be seen), the overall drug release did not significantly increase relative to that obtained with Eudragit® L30D alone. Results suggest that incorporation of HPMCP with Eudragit® L30D (at the ratios investigated) does not significantly increase drug release at pH 5.5.

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CONCLUSIONS

Results showed that it was possible to modify the release properties of Eudragit® L30D by incorporating water soluble components. PEG did not influence drug release from Eudragit® L30D coated pellets in pH 1.5, but significantly decreased the release at pH 5.5. The decrease in the release was more pronounced as the molecular weight of PEG increased.

Incorporating mannitol with Eudragit® L30D resulted in more predictable drug release. As the concentration of mannitol increases, drug release increases. Drug release from Eudragit® L30D-mannitol system at pH 1.5 and 3.5 was also related to the solubility of the drug in these two media. However, dependence on drug and polymer solubility was observed at pH 4.5. Drug release at pH 5.5 was controlled by polymer solubility and less dependent on drug solubility.

Incorporation of HPMCP 50 with Eudragit® L30D increased drug release in pH 1.5, but did not significantly increase drug release in pH 5.5 (compared to that obtained with Eudragit® L30D alone). Results suggest that HPMCP 50 incorporation with Eudragit® L30D even at a high ratio (10:1) does not enhance drug release significantly at pH 5.5 which is higher than that of the polymer dissolution (i.e., pH 5).

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