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EVALUATION OF HYDROXYPROPYL METHYLCELLULOSE PHTHALATE 50 AS FILM FORMING POLYMER FROM AQUEOUS DISPERSION SYSTEMS.

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ABSTRACT

Hydroxypropyl methylcelluose phthalate 50 (HPMCP 50) was evaluated as a film forming polymer from aqueous dispersion systems. The influence of plasticizer type and level on the elasticity of HPMCP 50 free films prepared by the casting method was studied by measuring Young's modulus using an Instron Material Testing System. The release of a water soluble drug in various dissolution media from pellets coated with HPMCP 50 with 30% plasticizer containing various levels of hydroxypropyl cellulose (HPC) or hydroxypropyl methylcellulose (HPMC) was also studied. The influence of coating level on drug release from pellets was also investigated. Results showed that HPMCP 50 alone without a plasticizer does not form a film. However, when a plasticizer was added HPMCP 50 did form a film. Also, as the concentration of the plasticizer triethyl citrate was increased the elasticity of HPMCP 50 films was increased. Similar results were obtained with the plasticizer diethyl phthalate. For pellets a high coating level was required to achieve adequate protection in 0.06 N HCl. Drug release from coated pellets was found to be dependent upon the type and the level of the water soluble polymer incorporated with HPMCP 50. Drug release was increased as the percentage of HPC was increased. Higher release rates were obtained with HPMC compared to HPC. Coating level significantly influenced drug release in 0.06 N HCl; however, less of an effect was observed at pH 5.5.

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INTRODUCTION

Enteric solid dosage forms can be prepared by film coating a solid formulation with a pH sensitive polymer in which case drug will be released after the dissolution of the film. The polymers which are used for enteric coating are essentially polyacids with carboxyl ionizable groups. Hydroxypropyl methylcellulose phthalate 50 (HPMCP 50) is a polymer which is used to prepare enteric coated solid formulations and is usually delivered from organic based solvent systems. In the pharmaceutical industry the recent trend is to substitute organic based solvent systems with aqueous based systems due to flammability, toxicity and environmental concerns with using the former. Stafford (1) showed that enteric properties of films obtained from neutralized HPMCP solutions were comparable to those obtained from organic solutions of the polymer. Bloor et al., (2) however, reported that an enteric formulation produced from neutralized HPMCP failed in vivo and did not show any enteric properties even though it passed the in vitro USP test for enteric formulations. Chang (3) showed, in vitro, that pellets coated with neutralized HPMCP had less enteric properties than those coated with HPMCP organic solution. The objectives of this work were to evaluate the elasticity of HPMCP 50 films prepared from aqueous dispersion systems and to study the release properties of pellets coated with HPMCP 50 films.

EXPERIMENTAL

Materials:

The active substance is a water soluble drug with pH-dependent solubility ;Hydroxypropyl Methylcellulose Phthalate 50 NF (Shin-Etsu Chemical Co., Japan); Hydroxypropyl Methylcellulose, 5 cps, NF (Aqualon Co., Hopewell, VA); Hydroxypropyl Cellulose, type EF, NF (Aqualon Co., Hopewell, VA); Triethyl Citrate NF (Morflex Chemical Co., Inc., Greenboro, NC); Diethyl Phthalate NF; Antifoam (Ashland Oil Inc., Newark, NJ); Polysorbate 80 NF (Ruger Chemical Co., Irvington, NJ); Colloidal Silicon Dioxide NF (Cabot Chemical Co., Tuscola, IL); Sugar Spheres 20-25 mesh size NF (Ozone Confect. & Bakers Supply, Elmond Park, NJ)

Methods:

Free Film Preparation:

Five hundred grams of HPMCP 50 aqueous dispersions were prepared as follows: The antifoam was added to water and mixed using a dispersator,

then polysorbate 80 was added and mixing was continued for 10 minutes (a). The plasticizer was added to (a) and mixed until dissolved (b). Hydroxypropyl cellulose (HPC) or hydroxypropyl methylcellulose (HPMC) was then added to (b) and mixed until dissolved (c). Finally hydroxypropyl methylcellulose phthalate 50 (HPMCP 50) was added to (c) slowly with mixing. After the addition of HPMCP 50 was completed, the aqueous dispersion was stirred for at least another 45 minutes using a magnetic stirring bar.

The films were prepared by pouring 40 mL of the aqueous dispersion into weighing boats (4 inches i.d.) lined with teflon and placed in an oven at 60°C for several hours (5-7 hours). The films were then removed from the boats and placed between parafilm and stored at room temperature until analyzed.

Measurement of Young's Modulus of Free Films:

HPMCP 50 free films prepared by the casting method were evaluated for their elasticity by measuring Young's modulus. Young's modulus or modulus of elasticity is a measure of hardness, stiffness or rigidity of the material and is equal to stress (tensile stress)/strain (elongation). Tensile stress is equal to force per unit area of cross section (F/A) and elongation is equal to change in length with respect to original length ($L-L_o/L_o$). Stress, strain and subsequently Young's modulus were determined by using Instron series IX material testing system which is a combination of an Instron test instrument (Instron model 4201) and series IX software and computer.

Preparation of Drug Cores:

Drug cores were prepared by the powder layering technique utilizing sugar spheres as starter seeds. The CF-360 Granulator (Freund Industrial Co., Tokyo, Japan) was used for this purpose. The drug (1 kg) was passed through a Fitzmill® fitted with a screen (0.5 mm round opening) run at a high speed with impact forward. The milled drug was then blended with Cab-O-Sil® (1 g) which was passed through a 100 mesh screen. This blend was layered onto sugar spheres using an 8% hydroxypropyl cellulose solution as the binder. The following conditions were used to prepare the drug loaded cores: rotor was set at 160 rpm; powder feed at 14 g/minute; spray rate at 12 mL/minute; inlet temperature of 40°C to maintain the product temperature at 25°C. The cores were then sieved and those with a mesh size fraction in the range of 12/20 were used.

Preparation of Coated Pellets:

The basic composition of the coating system employed is described below.

	Ingredient	Percent W/W
1-	HPMCP 50	7.0
2-	Triethyl citrate	3.0
3-	Polysorbate 80	0.03
4-	Antifoam	0.1
5-	Water q.s.	100.0

HPC or HPMC were incorporated at various ratios in this formulation. The coating system was prepared as follows: (a) Components 3 & 4 were added to component 5 and mixed using a dispersator. (b) Component 2 was then added to (a) and mixed for 10 minutes using a dispersator. (c) Component 1 was then added to (b) slowly and the suspension was mixed for 45 minutes. When HPC or HPMC were incorporated in the coating system, they were first dissolved in 25% of the water and then mixed with the dispersion described above. The coating was carried out in the Glatt GPCG3 (Glatt Air Techniques, Inc., Ramsey, NJ) machine with rotor insert. 600 g of pellets were coated and the following conditions were employed: spray rate of 10 mL/minute; rotor at 250 rpm; flap 24%; inlet temperature of 42°C; product temperature of 24°C and atomization air pressure of 1 bar. After completion of the coating process the pellets were cured in forced air oven overnight at 60°C.

Dissolution Studies:

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. 0.06 N HCl and 0.05 M phthalate buffer (pH 5.5) were used as the media.

RESULTS AND DISCUSSION

The results obtained for the HPMCP 50 free films are presented in Figures 1-3. The results showed that HPMCP 50 alone without a plasticizer did not form an intact film. However, when a plasticizer was added, HPMCP 50 did form a film. The elasticity of the film formed was dependent upon

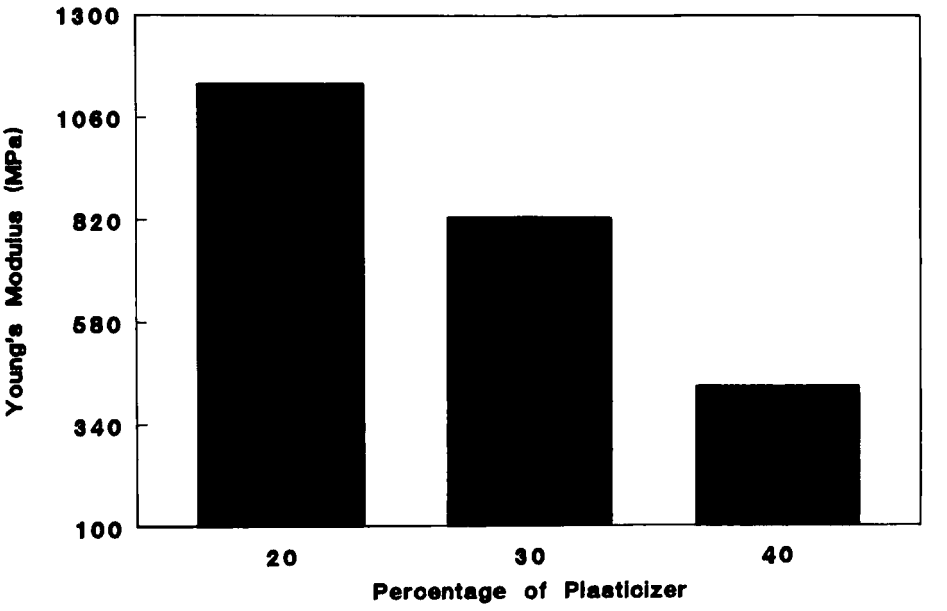

Figure 1

The influence of TEC level on the elasticity of HPMCP 50 free films.

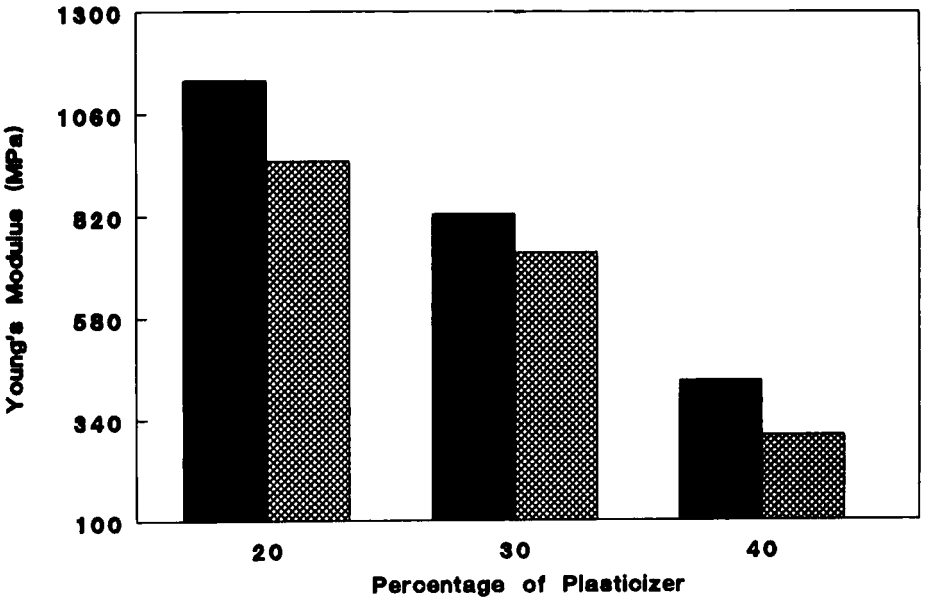

Figure 2

The influence of HPC on the elasticity of HPMCP 50 films. key. HPMCP:TEC (■), HPMCP:TEC:HPC (▨).

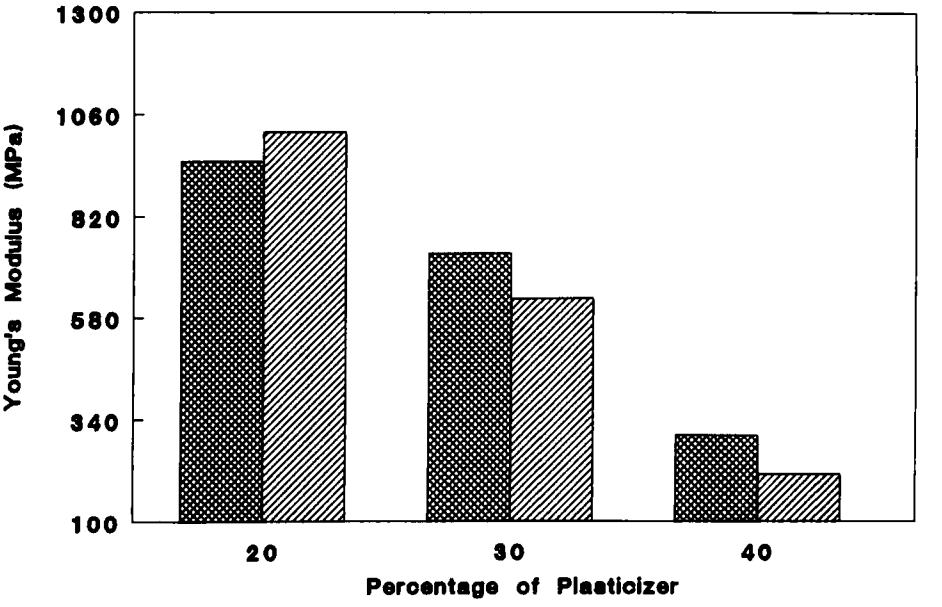

Figure 3

Comparison of elasticity of HPMCP 50 films containing TEC versus those containing DEP as plasticizers. key. HPMCP:TEC:HPC (▨), HPMCP:DEP:HPC (▩).

the type and the level of the plasticizer used. As the concentration of the plasticizer triethyl citrate (TEC) was increased, the elasticity of the film was increased as indicated by a decrease in Young's modulus (Figure 1). An increase in the plasticizer level incorporated with the polymer results in a corresponding decrease in the glass transition temperature (4). At a certain plasticizer level, the extent of the change in glass transition temperature is dependent upon the type of plasticizer and the polymer. Figure 2 shows the results for films comprised of HPMCP 50, HPC and TEC compared to those obtained for films comprised of HPMCP 50 and TEC. As can be seen, in the presence of HPC (5.6 w/w) the elasticity of the films significantly increased. Figure 3 shows the result obtained for films comprised of HPMCP 50, HPC and TEC compared to those obtained for HPMCP 50, HPC and DEP (diethyl phthalate) as a function of TEC and DEP level in the films. As can be seen the elasticity of the films at 20% (w/w) plasticizer level was somewhat higher for films containing TEC than those containing DEP. However, at higher plasticizer levels DEP appears to result in a greater elasticity

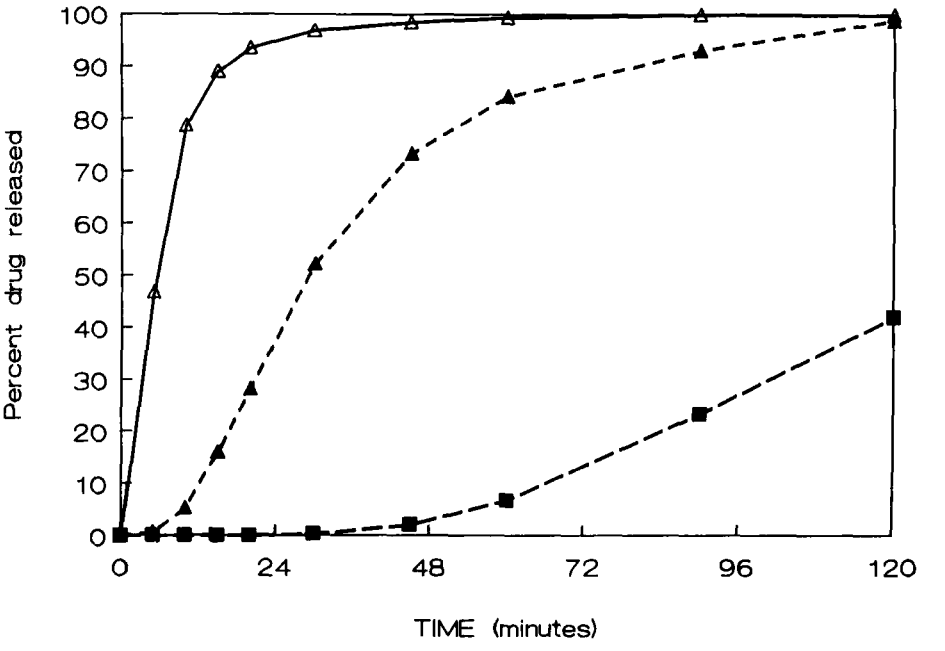

Figure 4

The influence of HPMCP 50 coating level on drug release from pellets in 0.06 N HCl. key. 10% w/w (△), 20% w/w (▲), 30% w/w (■).

for the films. Preliminary experiments were carried out and it was found that for pellets coated with HPMCP 50 containing DEP (30% w/w) as a plasticizer instead of TEC the coating efficiency decreased from about 87% to 62%. These results suggest that TEC is a better plasticizer for HPMCP 50 and the data obtained for free films may not be extrapolated to actual coating processes. Based on these results TEC was chosen as the plasticizer for HPMCP 50.

Dissolution results in 0.06 N HCl for pellets coated with HPMCP 50 (using the Strea 1, Aeromatic, Columbia, Maryland, USA) are plotted in Figure 4. These results show that films produced using HPMCP 50 aqueous dispersion system even at about 30% (w/w) coating level did not provide complete inhibition of drug release in acid and a significant drug release can be observed. As can be seen at 10% (w/w) coating level, there was about 99.4% of the drug released in 1 hour. At 20% (w/w) coating level the amount of drug released was about 84.3% which was decreased to 6.34% at 30% (w/w) coating level. This suggests that in order to prepare enteric

coated pellets using HPMCP 50 aqueous dispersion system, a high coating level is required to prevent the drug from being released in the stomach. This could be attributed to film imperfections which occur with aqueous dispersion systems particularly when the polymer particle size is large. In this case the polymer (HPMCP 50) used has an average particle size of 10 μm . The formation of a continuous film is dependent to a great extent upon the polymer particle size used. Smaller polymer particles require less driving force to coalesce than larger particles (5). Imperfections result in the formation of a more porous film which leads to the formation of dissolution medium filled channels or pores through which drug diffusion occurs. With Eudragit® L30D (Rhom Pharma, Germany) which is a latex system used to prepare enteric solid formulations, much lower coating levels were needed to achieve the same drug release under acidic conditions (6). It should also be noted that drug solubility will play an important role in determining the coating level necessary to achieve adequate acid resistance in the stomach. Also, it can be speculated that for HPMCP 50 solvent based systems, lower coating levels will be needed to obtain release rates similar to those obtained with aqueous based systems.

The influence of coating level on drug release from pellets coated with HPMCP 50 containing the water soluble polymer HPC was studied in 0.06 N HCl and in pH 5.5 phthalate buffer. Coating level significantly influenced drug release in 0.06 N HCl. As the coating level increased drug release significantly decreased, Figure 5. However, coating level had little effect on drug release at pH 5.5, Figure 6. This can be attributed to the polymer dissolution at this pH. At low pH conditions, diffusion through the aqueous channels or pores and osmotic pumping are the predominant mechanisms controlling drug release from pellets coated with HPMCP 50 system (7-9).

Drug release from coated pellets was found to be dependent upon the type and level of water soluble polymer incorporated with HPMCP 50. As the concentration of the water soluble polymer hydroxypropyl cellulose increased, drug release increased, Figure 7. As was shown in Figure 2, the elasticity of HPMCP 50 casted films containing 5.6% HPC (w/w) significantly increased relative to those without HPC. Therefore, the increase in drug release observed with the increasing HPC level is consistent with the increase in the elasticity of HPMCP 50 films. Also the enhanced drug release may be due to HPC dissolution and subsequent formation of dissolution medium filled channels or pores. However, due to the large molecular weight of the water soluble polymers used in this study, leaching out of these polymers from the film may not occur. Therefore, the enhanced drug release could be due to hydration and

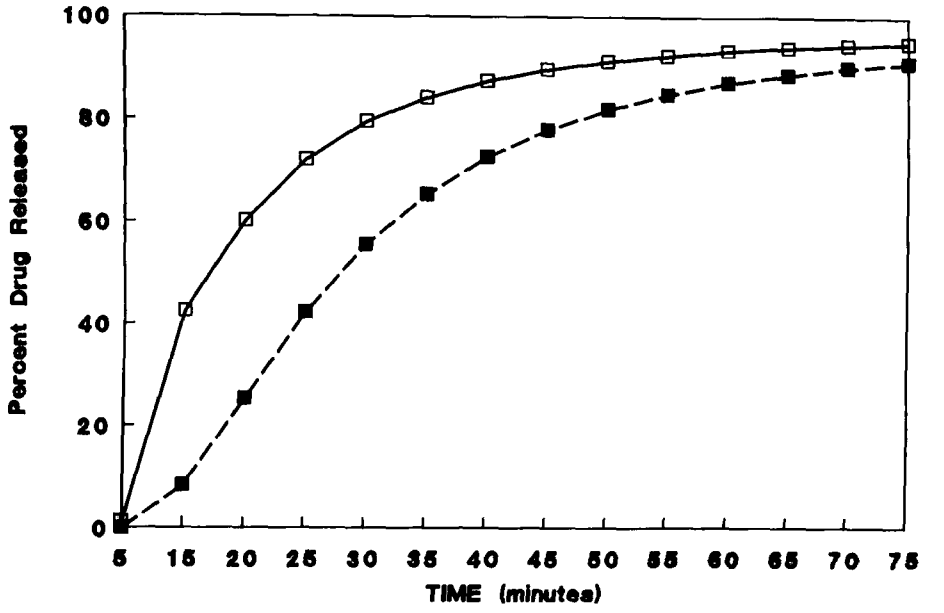

Figure 5

The influence of coating level of HPMCP 50 containing HPC on drug release from pellets in 0.06 N HCl . key. 20% w/w (□), 25% w/w (■).

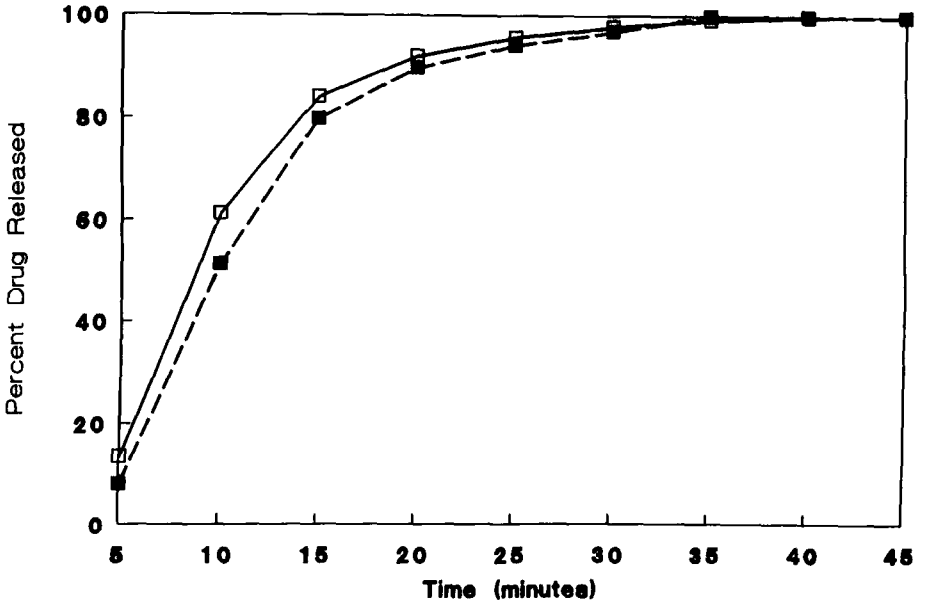

Figure 6

The influence of coating level of HPMCP 50 containing HPC on drug release from pellets in pH 5.5 phthalate buffer. key. 20% w/w (□), 25% w/w (■).

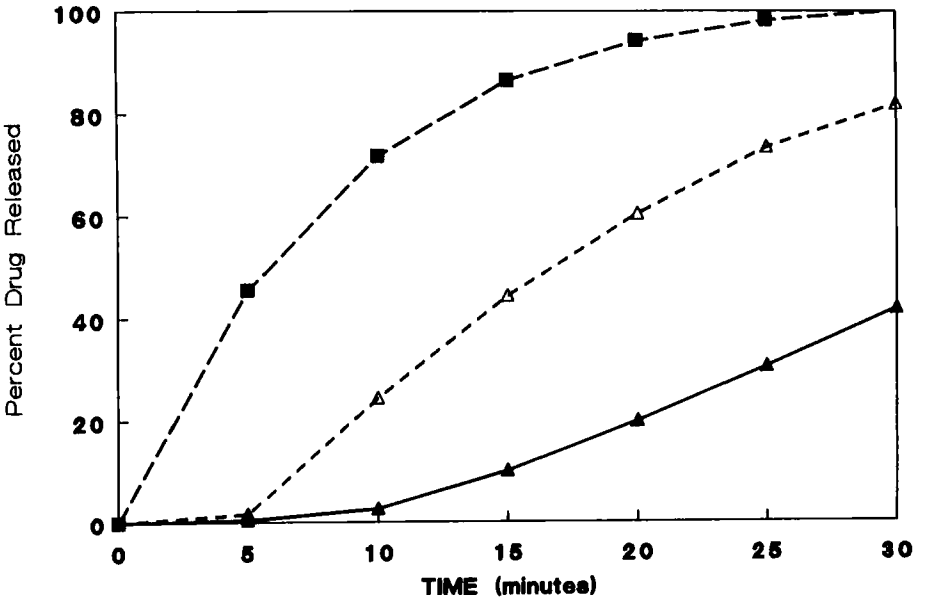

Figure 7

The influence of percentage of water soluble polymer HPC incorporated with HPMCP 50 on drug release from coated pellets in 0.06 N HCl. key. 5.6% w/w (▲), 9% w/w (△), 13% w/w (■).

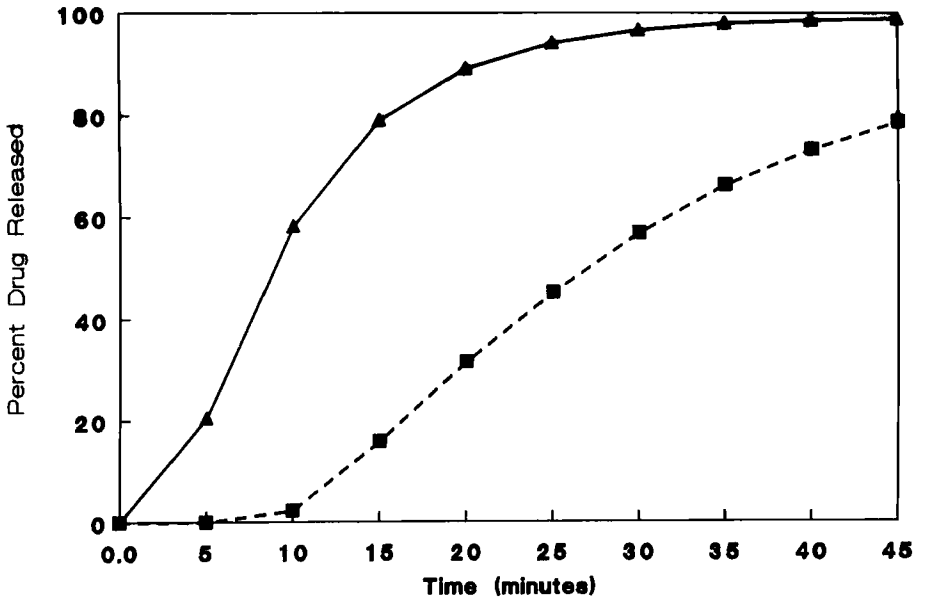

Figure 8

The influence of the type of the water soluble polymer incorporated with HPMCP 50 on drug release from coated pellets in 0.06 N HCl. key. 9% w/w HPMC (▲), 9% HPC (■).

swelling of the films which lead to the formation of dissolution medium filled channels or pores through which drug diffusion occurs. When hydroxypropyl methylcellulose was used at the same level instead of HPC drug release drastically increased, Figure 8. The higher drug release rate observed with pellets coated with HPMCP 50 containing HPMC is consistent with the higher permeability of HPMC compared to HPC (10).

CONCLUSIONS

To prepare enteric formulations using HPMCP 50 aqueous dispersion systems high coating levels are needed in order to achieve adequate acid protection in the stomach. Incorporation of water soluble polymers HPC or HPMC with HPMCP 50 causes an increase in the drug release from coated pellets. As the level of HPC incorporated with HPMCP 50 increased, drug release from coated pellets increased. Pellets coated with HPMCP 50 containing HPMC resulted in faster drug release rate compared to pellets coated with HPMCP 50 containing HPC at the same level.

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