Controlled Permeability Films for Programmable Drug Release

ABSTRACT SUMMARY

This study investigates the influence of sodium alginate or hypromellose (HPMC) as pore formers in a delayed release film coating to achieve controlled and programmable drug release.

Keywords: ibuprofen, hypromellose, sodium alginate, Acryl-EZE®, METHOCEL™, Opadry®, film coating, pore former.

INTRODUCTION

Methacrylic acid copolymers are commonly used as protective membranes for achieving enteric protection for acid labile or irritant drugs. These delayed release films prevent drug release in acid media and provide complete release above the solubilization pH of the polymer used. Controlling the permeability of such films may allow for programmable drug delivery at pH below the solubilization of the polymer system. This will allow a controlled portion of the dose to be delivered in the stomach/ duodenum, while the remainder is released in the intestine. This study will characterize the effect of HPMC or sodium alginate as pore formers in a delayed release film coating to achieve controlled and programmable drug release.

EXPERIMENTAL METHODS

Ibuprofen 200 mg tablets purchased from LNK International (Hauppauge, NY) were used in this study. The ibuprofen core tablets were evaluated for their physical properties using an Erweka Multicheck tester. Seal coating: Opadry®, high performance film coting system, 03K19229 was applied to 3% weight gain (WG) as a seal coat to improve the mechanical strength of the tablets. The tablets (15 kg charge) were seal coated using a dispersion (10% solids) of Opadry in an O'Hara Labcoat II using a 24-inch pan insert. Samples were collected at 1 and 2% WG and evaluated for tablet properties. The process parameters are shown in Table 1.

Table 1: Processing Parameters for Coating Parameters

Paremeters	Opadry	Acryl-EZE
Inlet Air Temp. (ºC)	69.0 ± 3.8	50 ± 2.0
Product Temp. (ºC)	38.6 ± 2.4	35 ± 3.0
Exhaust Air Temp (ºC)	41.9 ± 2.4	39 ± 2.0
Spray Rate (g/min)	61.0 ± 1.4	11 ± 1.0
Atomizing Air (psi)	20	20
Pattern Air Pres. (psi)	25	25
Inlet Air Volume (cfm)	250	175
Pan Rotation (rpm)	13	18

Functional Coating with Acryl-EZE:

Acryl-EZE, aqueous acrylic enteric system, 93F19255 was used as the delayed release coating system with either hypromellose (METHOCEL™ E5) or sodium alginate as the pore former. For each batch, the tablets (1 kg charge) were coated using a Thomas Compu-Lab using a 15-inch pan insert. Batches were coated as per the design of experiments outlined below. The processing parameters are shown in Table 1.

Design of Experiments (DOE):

A full-factorial DOE was generated using JMP software and evaluated for its main effects. The type of pore former (METHOCEL™ or sodium alginate), level of pore former (METHOCEL™E5 at 2.5, 5, and 10%; sodium alginate at 1 and 2.5%), percent weight gain (4 levels; 6, 8, 12, and 16%), and type of testing media, i.e., pH 1.2 media (0.1N HCl) and pH 4.5 acetate buffer, were used as independent variables in the model.

Acid Uptake Testing:

Accurately weighed tablets (n=6) were exposed to pH 1.2 media and pH 4.5 acetate buffer for 2 hours at 37oC in a disintegration apparatus. The tablets, if intact, were patted dry to remove surface moisture and re-weighed. Difference in weight was reported in terms of percent acid uptake.

Dissolution:

Dissolution testing was performed in a Vankel Total Solutions dissolution bath with paddles (apparatus II) at 100 rpm, 37oC. The dissolution testing was performed in 900ml of pH 4.5 acetate buffer containing 10% ethanol for two hours. Ibuprofen absorbance was measured using a Cary50 spectrophotometer at 224nm.

RESULTS AND DISCUSSION

The physical characteristics of ibuprofen tablets are shown in Table 2

Table 2: Tablet Properties for Ibuprofen 200 mg Core Tablets and Tablets Seal Coated with Opadry 03K19229

Parameter	Core Tablets (Mean ± S.D.)	Seal Coated* Tablets (Mean ± S.D.)
Weight (mg)	320.4 ± 3.8	328.3 ± 2.6
Hardness (kP)	10.5 ± 1.4	15.2 ± 1.5
Thickness (mm)	5.26 ± 0.04	5.34 ± 0.05
Diameter (mm)	9.57 ± 0.03	9.63 ± 0.06
Friability (%)	0.2	< 0.1
Disintegration time (min)	< 1 min	< 1 min

* 3% WG Opadry 03K19229

Film coating of the ibuprofen cores significantly improved the tablet hardness and friability ($p < 0.01$). Additionally, film coating did not change the disintegration time of the tablets. The increase in mechanical strength accompanied by the reduced friability makes the tablets suitable for application of the delayed release coat. The physical characteristics of seal coated ibuprofen tablets are shown in Table 2. The acid uptakes for seal coated tablets, coated with 12% WG total solids and exposed to 0.1N HCl and acetate buffer (pH 4.5) are shown in Figures 1 and 2, respectively.

Figure 1. Acid Uptake for Ibuprofen Tablets Seal Coated with 3% WG Opadry 03K19229 and 12% total WG of Acryl-EZE and HPMC E5

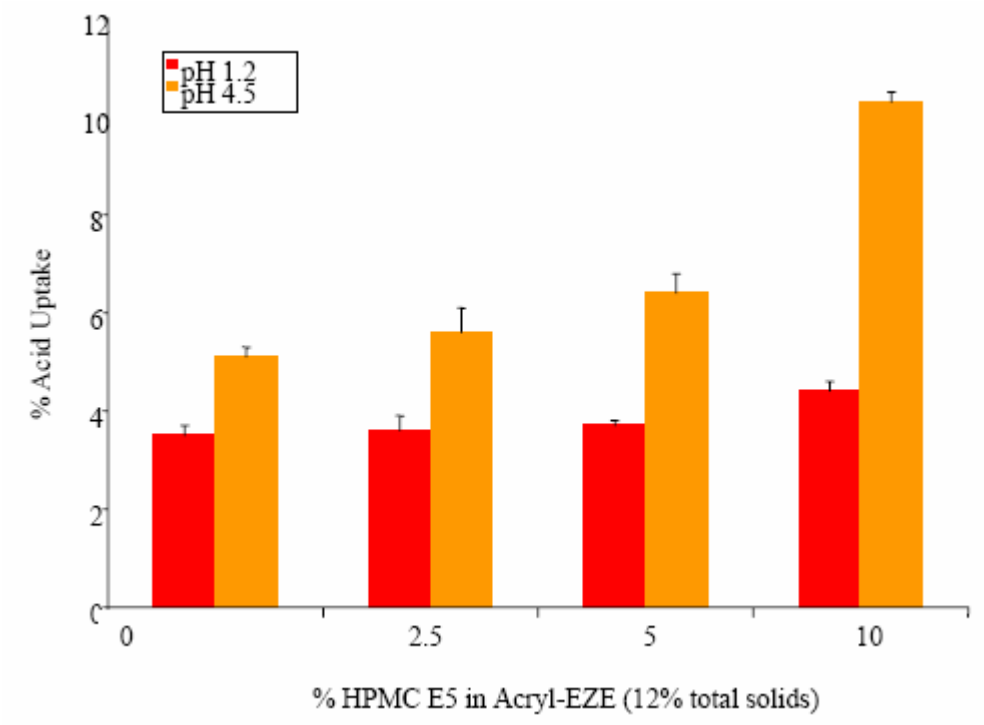
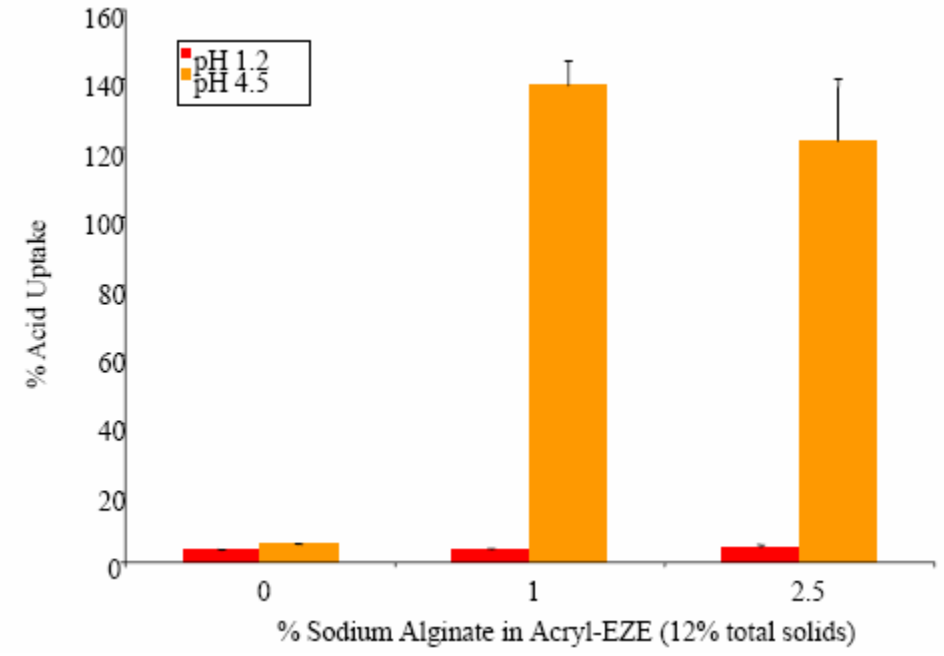


Figure 2. Acid Uptake f or Ibuprofen Tablets Seal Coated with 3% WG Opadry 03K19229 and 12% total WG of Acryl-EZE and Sodium Alginate



Core and seal coated (3%w/w) ibuprofen tablets disintegrated during the acid uptake testing within 1 minute. Non-seal coated tablets coated with Acryl-EZE 93F19255 (up to 16% w/w) also disintegrated within 30 minutes in acid media. However, tablets that were seal coated and then coated with Acryl-EZE 93F (6% w/w and above) were able to withstand acid for 2 hours, as shown by the acid uptake values. An increase in the HPMC or sodium alginate level in the enteric film led to higher acid uptake values. These values increased as a function of pH where tablets in pH 4.5 media had significantly greater acid uptake than that seen in pH

1.2. The effect of media pH was greater when sodium alginate – a cationic polymer – was used as a pore former. Sodium alginate being soluble above pH 3.0 caused tablets to absorb acid in greater proportions. Although these tablets bloated with acid uptake, they remained intact.

Drug dissolution was also dependent on the type and level of pore former used. With tablets coated with Acryl-EZE no release was seen in pH 4.5 media. Inclusion of low level (2.5% w/w) of pore former did not change the permeability of the delayed release film, while drug release was seen when HPMC was included at levels of 5% w/w and above (Figure 3). In the case of sodium alginate, the drug release was directly proportional to the level of pore former used, and inversely proportional to the total weight gain of the delayed release film (Figure 4).

Figure 3.

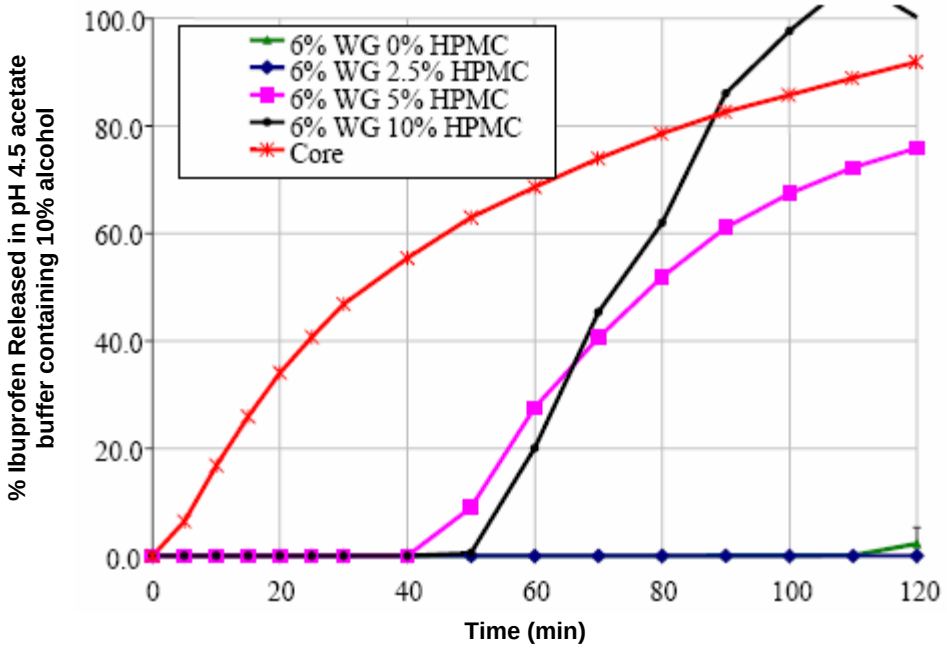
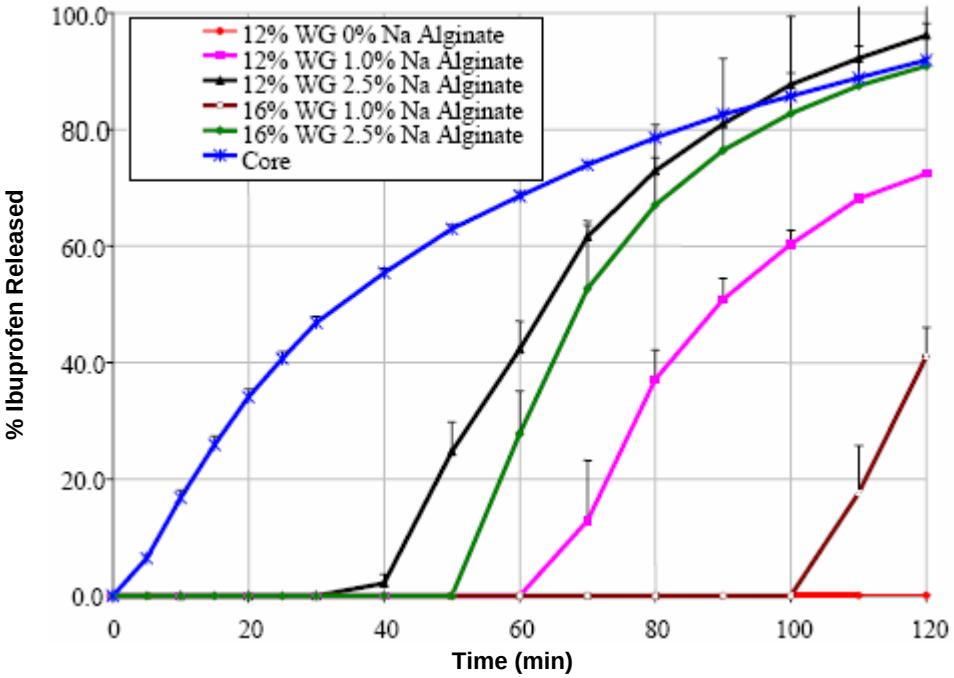


Figure 4.



CONCLUSIONS

An increase in the HPMC or sodium alginate level in the delayed release film increased the acid uptake. Acid uptake values increased as a function of pH where acid uptake in pH 4.5 media was greater than that seen in pH 1.2. Acryl-EZE provided enteric protection in pH 4.5 media however drug release was noted when HPMC or sodium alginate was included as a pore former. Drug release was directly proportional to the level of pore former used, and inversely proportional to the total weight gain of the delayed release film. These data would indicate the usefulness of pore formers in delayed release films to achieve controlled and programmable drug release.

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