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Effect of Simulated Gastrointestinal Conditions on Drug Release from Pectin/Ethylcellulose as Film Coating for Drug Delivery to the Colon

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ABSTRACT The aim of this work was to investigate the effect of acidic pH representative of gastric fluid on the release of 5-aminosalicylic acid from beads coated with pectin/ethylcellulose as film coating intended for drug delivery to the colon, in media mimicking the lower gastrointestinal (GI) tract and representative of colonic conditions. In this work, the in vitro incubation of the beads in acid medium was found to influence the hydration and the swelling characteristics of pectin after transfer into simulated intestinal fluid and simulated cecal fluid containing pectinolytic enzymes. Moreover, the drug release profiles from the beads in simulated intestinal fluid after incubation for 2 h or 30 min in simulated gastric fluid vs. no acid incubation were found to be very different. The in vitro degradation of pectin in the coat by pectinolytic enzymes in simulated cecal fluid depended on whether the beads were placed in simulated gastric fluid prior to testing in simulated intestinal fluid. The percentage drug release also depended on the ratio of pectin to ethylcellulose in the coat.

INTRODUCTION

Pectin is a naturally occurring polymer that has been widely reported to act as a material for selective colonic targeting because it is degraded by colonic bacteria (Ashford et al., 1993, 1994). However, because of its water solubility, several approaches have been tried to inhibit pectin solubility in simulated upper gastrointestinal (GI) conditions. In some of these approaches, pectin was applied as a very thick compression coat to drug-containing tablets (Fernandez-Hervas & Fell, 1998) or added in large amounts in powder form to pectin matrix tablets (Ahrabi et al., 2000). In other studies, pectin was applied as a film coat to drug-containing tablets or beads after being mixed with other

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synthetic or naturally occurring polymers such as ethylcellulose and hydroxypropyl methylcellulose (HPMC) to improve film-forming properties and protect against premature release in the small intestine (Macleod et al., 1999; Wakerly et al., 1996a, 1997). Chitosan was also used to form a polyelectrolyte complex (PEC) with pectin that controlled the leaching of pectin from mixed films containing pectin, chitosan, and HPMC (Ofori-Kwakye & Fell, 2002). In this study, the rate of pectin leaching was found to be a function of the film-casting solvent, the pH of the incubation medium, and the HPMC content of the films.

From the aforementioned applications, film coating has been especially useful when preparing multiple-unit systems. Multiple-unit systems have many advantages over single-unit dosage forms such as decreased variability in gastric emptying time (Hardy et al., 1985), reduced risk of high local concentrations of released drugs, stagnation at the ileo-cecal junction is less likely to occur than with larger single units (Feely et al., 1985) and slower transit of small particles through the colon which prolongs contact between the formulation and the absorptive surface, resulting in a greater proportion of drug being absorbed (Adkin et al., 1993).

Pectin is an anionic polysaccharide, and therefore, its gelling ability and solubility depends strongly on the pH of the surrounding media. This article reports the design of a multiparticulate colonic delivery system and investigates the effect of acid conditions in the upper GI tract on the rate of drug release from film coats containing different ratios of pectin and ethylcellulose when incubated in higher pH mimicking lower GI conditions with and without added pectinolytic enzymes. This article also highlights the importance of exposing pectin-containing colonic drug delivery systems to pH conditions mimicking mouth to colon conditions when studying in vitro drug release from such systems. 5-Aminosalicylic acid was used as the model drug.

MATERIALS

5-Aminosalicylic acid (5-ASA; Sigma Chemicals, St. Louis, MO), ethylcellulose in the form of Surelease® (Colorcon Ltd, West Point, PA), pectin USP from apple (Sigma Chemicals, St. Louis, MO), microcrystalline cellulose (Avicel® PH101, FMC Corp., Newark, DE), polyethylene oxide, mol wt 200,000 (Polyox N-80, Union Carbide Corp., Danburg, CT), pectinolytic enzymes (Pectinex Ultra SP-L, Novo Nordisk Biochem., North America, Inc., Franklinton, NC) were obtained from the indicated sources. All other materials used in the dissolution studies were of analytical grade. The abbreviations or names in parentheses are used throughout the article.

METHODS

Bead Preparation

Beads (1–1.5 mm in diameter) containing 60% 5-ASA, 35% Avicel PH101, and 5% polyox N-80 were prepared by extrusion and spheronization using a bench top laboratory extruder model 20/25 and spheronizer model 120 (Caleva Process LTD, England). A wet mass was prepared from the powder mixture before extrusion by using alcohol and sucrose solution. The beads were left to dry overnight in an oven at 50°C.

Coat Preparation

Two coat formulations containing different amounts of pectin and Surelease® were prepared. Coat formulation one (F1) was prepared by simple mixing of aqueous dispersion of pectin (P) and Surelease® (S) in the ratio (P:S) 1:10 by weight. This ratio corresponds to total solid content of the aqueous dispersion. Coat formulation two (F2) was prepared by mixing aqueous dispersion of pectin (P) and Surelease® (S) in the ratio (P:S) 1:5 by weight. The two coat formulations were chosen because pectin-containing film coats of closely similar ratios have been reported to be successful for colonic delivery in vitro (Milojevic et al., 1996; Wakerly et al., 1997).

Coating Process

Coating was performed by using a laboratory Aromatic Strea-1 fluidized bed coater (Niro-Aeromatic, Columbia, MD). Coating was performed at 50°C inlet temperature, and coating solution was applied through a 1.0-mm spray nozzle at a spray rate of 2 mL/min by using a rabbit peristaltic pump (Rainin Instrument Co. Inc., Woburn, MA) and 25 psi atomizing air pressure. Coating solutions were stirred gently and continuously during the coating process to ensure a uniform coat. Coating solutions were coated onto drug beads to result in 15% coat thickness for

both F1 and F2 formulations. The film thickness is expressed as the theoretical percentage of the weight gained (TWG) used relative to the weight of the uncoated beads. A similar coat thickness was decided for both formulations for comparison purposes. Coated beads were cured for 30 min at 50°C.

Dissolution Testing

Drug release from coated beads was determined in a dissolution tester (VK 7000 Dissolution Testing Station, Vankel Industries, Inc., NJ), following the USP paddle method. All tests were conducted in 900 mL of dissolution medium maintained at 37±0.5°C with a paddle rotation speed at 50 rpm. Dissolution studies were carried out under conditions simulating pH and times likely to be encountered during transit in the GI tract. Testing was carried out by using the following:

1. Simulated gastric fluid (SGF) for 2 h at pH 1.4, followed by simulated small intestinal fluid (SSIF) for 4 h at pH 7.4, followed by simulated cecal fluid (SCF) at pH 6 for 6 h with or without the addition of 3 mL of enzymes. Pectinex Ultra SP-L product was used to mimic pectinolytic enzymes in vivo because a close correlation between its pectinolytic activity and the pectinolytic activity of pure bacteroides ovatus (the main producer of pectinolytic enzymes in the colon) was demonstrated in one study (Wakerly et al., 1996b). Pectinex Ultra SP-L (3 mL) also was reported to be representative of colonic conditions (Wakerly et al., 1997). The buffer pH 6 was used to compromise between the mean pH of the cecum and the optimum pH for the activity of the added enzymes.
2. SSIF for 4 h followed by SCF for 6 h with or without enzymes.

Concentrations of 5-ASA were determined at 302 nm for pH 1.2, at 331 nm for pH 7.4, and at 329 nm for pH 6 by using a Beckman DU 640 Spectrophotometer (Beckman Instruments, Inc., CA).

RESULTS AND DISCUSSION

Release from F1 Coat

Figure 1 shows the percentage of 5-ASA released as a function of time from beads coated with 15% F1 coat formulation during conditions mimicking mouth to colon transit (2 h in SGF at pH 1.4, followed by 4 h in SSIF at pH 7.4, followed by 6 h in SCF at pH 6 with and without enzymes).

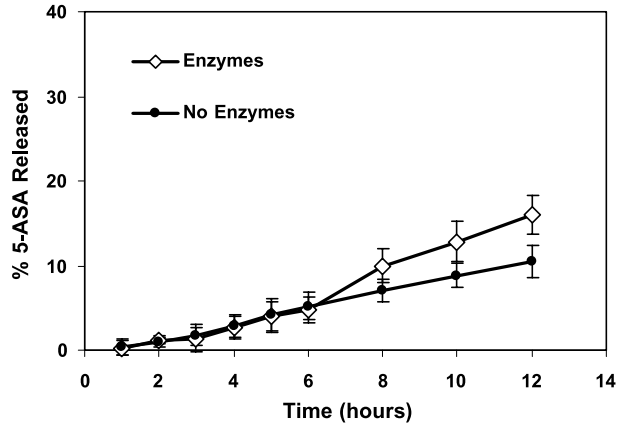

FIGURE 1 **The Release of 5-ASA from Beads Coated with 15% F1 Coat After 2 h in SGF, 4 h in SSIF, and 6 h in SCF with and without Enzymes. N=3 with SD.**

Very little drug release (1%) was observed in SGF for 2 h. Pectin USP, which is a high-methoxy (HM) pectin, is known to form strong gels at pH 1–3.5. Under simulated gastric pH conditions, the available acid groups in the polysaccharide chains are not dissociated and are, therefore, capable of forming hydrogen bonding to acid or hydroxyl groups on adjacent chains resulting in the formation of what is known as junction zones, which are rigid networks of hydrogen bonding. Thus, it can be suggested that pectin in F1 coat did not dissolve during 2 h in SGF because of gel formation. Although pectin is ionized and soluble at pH 7.4, the percentage drug released after 4 h in SSIF was only about 5%. This could be attributed to very slow drug release through the gelled pectin and ethylcellulose in the coat. It can also be suggested that ethylcellulose, which is a hydrophobic sustained-release material known to form nonporous films, controlled the hydration and dissolution of pectin at higher pH to a large extent by inhibiting the penetration of dissolution medium into the coat. When the beads were transferred to SCF containing pectinolytic enzymes, the percentage drug release after 6 h was higher (16%) than drug release in SCF with no added enzymes (10%). It was observed that the percentage drug released in SCF with or without pectinolytic enzymes for 6 h was very small. Although F1 coat was successful in preventing drug release in SGF and SSIF, the percentage drug release in SCF, even in the presence of enzymes, was very small,

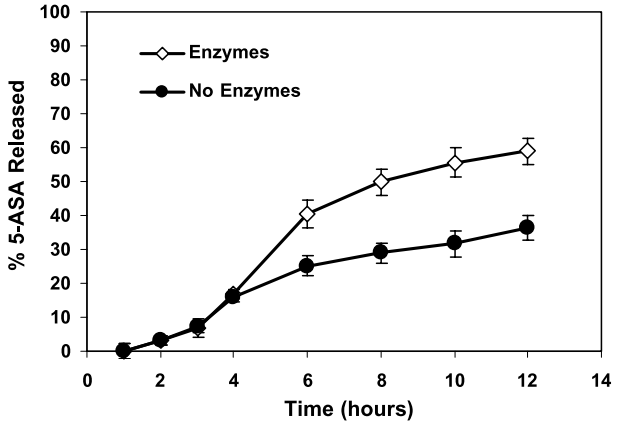

FIGURE 2 **The Release of 5-ASA from Beads Coated with 15% F1 Coat After 4 h in SSIF and 6 h in SCF with and without Enzymes (No Acid Incubation). N = 3 with SD.**

suggesting that the pectin in the coat was not succeptible to enzymatic attack.

Figure 2 shows the percentage of 5-ASA released as a function of time from beads coated with 15% F1 after 4 h in SSIF (no acid exposure) and 8 h in SCF with and without added pectinolytic enzymes.

The drug release profiles from coated beads incubated for 2 h in SGF vs. no acid incubation were found to be very different. In vitro release experiments in SSIF and SCF with no acid incubation showed higher and faster drug release. The beads exhibited 17% and 59% drug release over 4 h in SSIF and 6 h in SCF with pectinolytic enzymes, whereas the same beads incubated first for 2 h in SGF exhibited 5% and 16% drug release, respectively. The higher percentage of drug release observed when the beads were placed directly in SSIF could be due to ionization of pectin at higher pH, resulting in a weak gel formation that rapidly dissolves. The high level of ethylcellulose in the coat, however, was successful in controlling the percentage drug release to only 17%. These results are consistent with those obtained with Semdé et al. (1998) in which isolated films made of HM pectin and ethylcellulose were unable to prevent the leaching of pectin in the absence of pectinolytic enzymes in 0.05 M acetate-phosphate buffer at pH 4.5 (no acid incubation), even when the pectin content was low. It was even suggested that mixed films made of pectin/ethylcellulose are unsuitable for colonic drug delivery. In this study, it was reported that the release of pectin from Surelease films appears to be highly dependent on the level of HM pectin in the mixed films.

The large difference in the percentage drug release in SCF containing pectinolytic enzymes from drug beads incubated first for 2 h in SGF vs. no acid incubation (16% vs. 59%) suggests that gelation and hydration of pectin in the coat are very important for susceptibility to enzymatic attack in vitro. The higher percentage of drug released in the presence of enzymes (59%) compared to no enzymes (36%) also suggests that pectin is more susceptible to enzymatic attack when it is not subjected to SGF.

It is noteworthy that when a thick compression coat made of HM pectin and chitosan in the ratio 10:1 was used to coat minitablets, it was shown that more drug was released from the pectin:chitosan coat when the coat was subjected to 2 h at pH 1.1, followed by 3 h at pH 7.4 and then placed in pH 6 buffer containing pectinolytic enzymes (Fernandez-Hervas & Fell, 1998). No drug was released from these minitablets when they were placed directly in pH 6 buffer containing pectinolytic enzymes for 4 h and was attributed to little pectin hydration under these conditions, which is necessary for enzymatic activity. These results might suggest that pectin behaves differently when used in thick compression coats than when used in thin film coats. It can also be suggested that the rate of gelation of pectin will depend on the coat composition and the rate of penetration of dissolution medium into the coat.

Figure 3 shows the drug release profiles from F1 beads placed for 30 min in SGF, followed by 4 h in SSIF, followed by 8 h in SCF with and without pectinolytic enzymes. The drug release in SSIF and SCF after incubating the beads for 30 min in SGF was found to be very similar compared with drug release from beads incubated for 2 h in SGF. These results indicate that even a short-time exposure of the beads

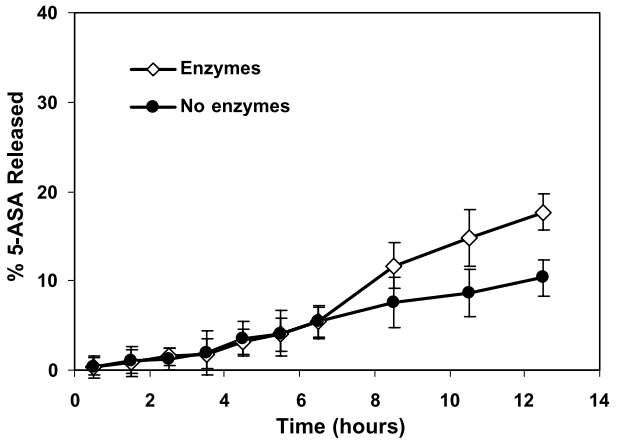

FIGURE 3 **The Release of 5-ASA from Beads Coated with 15% F1 Coat After 30 min in SGF, 4 h in SSIF, and 6 h in SCF with and without Enzymes. N = 3 with SD.**

to SGF resulted in a much slower drug release in SSIF and SCF than expected based on release studies in SSIF only (no acid incubation). Dissolution testing for short time in SGF is especially important for small drug beads because drug pellets less than 2 mm are reported to empty rapidly from the stomach and are not greatly affected by the presence of food in the stomach (Davis et al., 1986).

Release from F2 Coat

Figure 4 shows the drug release profiles from beads coated with F2 formulation in simulated upper and lower GI conditions. Very little drug was released after 2 h in SGF at pH 1.4 (<4%). The percentage drug release after 4 h in SSIF was also small but larger than drug release from beads coated with F1 formulation under the same conditions (10% vs. 5%). This could be due to more pectin and less ethylcellulose in F2 coat (1P:5S) compared to F1 coat (1P:10S). On the other hand, the percentage drug release in SCF in the presence of pectinolytic enzymes was almost three times higher from F2 coat than from F1 coat (46% vs. 16%).

The higher the amount of pectin in the coat, the higher the area covered by pectin, which results in more hydration and more susceptibility to enzymatic attack. When F2 beads were not subjected first to SGF, the release was very fast and complete in almost 8 h. This indicates that the level of ethylcellulose in F2 coat was not able to control the drug release when the beads were not incubated in SGF. These results suggest that the rate of penetration of dissolution medium into the coat depends not only on the ratio of pectin to ethylcellulose in the coat but also on whether the beads were incubated first in SGF before being transferred to simulated intestinal fluids.

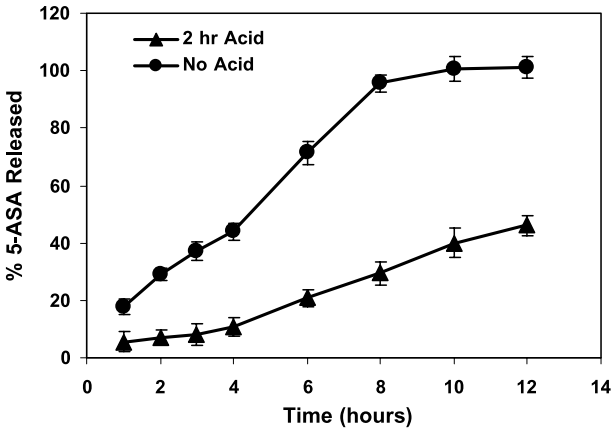

FIGURE 4 The Release of 5-ASA from F2 Beads in SSIF and SCF with Enzymes After 2 h or No Acid Incubation. N=3 with SD.

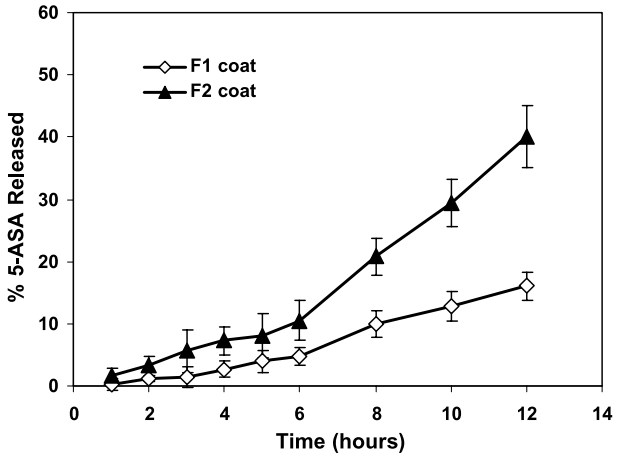

FIGURE 5 Effect of Enzymes on the Release of 5-ASA from Beads Coated with 15% F1 and F2 Coats After 2 h in SGF, 4 h in SSIF, and 6 h in SCF. N=3 with SD.

Figure 5 shows the drug release profiles from beads coated with F1 and F2 formulations after 2 h in SGF, 4 h in SSIF, and 6 h in SCF containing pectinolytic enzymes.

Although F1 coat was successful in minimizing drug release in SGF and SSIF, the overall percentage drug release after 6 h in SCF with pectinolytic enzymes was only 16%. Drug release from F2 coat, on the other hand, was higher after 2 h in SGF and 4 h in SSIF (10%), but the F2 coat was more readily attacked by pectinolytic enzymes, resulting in a much higher release after 6 h in SCF (46%).

These results indicate that F2 coat relative to F1 coat at the same coat thickness substantially enhances drug release in SCF in the presence of pectinolytic enzymes. These results also suggest that pectin hydration necessary for enzymatic attack depends on the ratio of pectin to ethylcellulose in the coat and is greatly inhibited when the pectin in the coats is subjected to simulated acidic gastric conditions. This is especially important with multiple-unit systems because the high surface area of these systems leads to higher area being exposed to bacterial attack in the colon with subsequent rapid drug release.

Controlled-drug release in the colon can also be obtained by carefully selecting the ratio of pectin to ethylcellulose in the coat. Therefore, the design of an effective pectin-ethylcellulose film coat for colonic delivery may require a compromise between the percentage drug released before reaching the colon and

the amount of pectin in the coat to ensure effective enzymatic attack and subsequent drug release.

CONCLUSIONS

The swelling characteristics and hydration of pectin in film coats made of pectin and ethylcellulose on small drug beads for colonic delivery were found to depend on the ratio of pectin to ethylcellulose in the coats and more importantly on whether the beads were incubated first in simulated gastric fluid before testing in vitro release in simulated lower intestinal fluids. The in vitro drug release in simulated upper GI conditions and the degradation of the coats by pectinolytic enzymes in simulated cecal fluid were greatly inhibited when the beads were incubated in acid even for a short time, as indicated by comparing the release in simulated intestinal fluids with or without incubation in acid. This finding was found to be very beneficial in preventing drug release in gastric and small intestinal fluids; thus, no enteric coat would be needed and more drug could reach the colon. The amount of drug released in the colon will depend, however, on the ratio of pectin to ethylcellulose in the coat. The findings in this article show that it is important to expose pectin-containing colonic delivery systems to conditions similar to those found in the upper GI tract prior to testing drug release in media representative of colonic conditions.

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