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RESEARCH PAPER

A pH-Dependent Colon-Targeted Oral Drug Delivery System Using Methacrylic Acid Copolymers. II. Manipulation of Drug Release Using Eudragit® L100 and Eudragit S100 Combinations

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ABSTRACT

Tablets containing mesalazine as a model drug were coated using various combinations of two methacrylic acid copolymers, (Eudragit® L100 and Eudragit S100) by spraying from aqueous systems. The Eudragit L100–Eudragit S100 (w/w) combinations studied were 1:0, 4:1, 3:2, 1:1, 2:3, 1:4, 1:5, and 0:1. The coated tablets were tested in vitro for their suitability for pH-dependent colon-targeted oral drug delivery. The dissolution profiles of the drug obtained from the studied tablets demonstrate that the release of the drug could be manipulated by changing the Eudragit L100–Eudragit S100 ratios in the combinations within the pH range between 6.0 and 7.0 in which the individual polymers are soluble, and a coating formulation consisting of a combination of the two polymers can overcome the issue of high gastrointestinal (GI) pH variability among individuals. The results also demonstrate the feasibility of using aqueous dispersions of Eudragit L100–Eudragit S100 combinations for coating tablets for colon-targeted delivery of drugs, and that the formulation can be adjusted to deliver drug(s) at any other desirable site of the intestinal region of the GI tract in which pH of the fluid is within the range 6.0 to 7.0. For

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colon-targeted delivery of drugs, the proposed combination system is superior to tablets coated with either Eudragit L100 or Eudragit S100 alone.
Key Words: *5-Amino salicylic acid; Aqueous film coating; Colon-targeted drug delivery; Extended-release tablet; Mesalazine; pH-Dependent delivery system.*

INTRODUCTION

The colon has been the target for delivery of many drugs because it is a site for some specific diseases, such as ulcerative colitis, Crohn's disease, bowel cancer, some infections, and constipation, and is also considered a suitable site for delivery of both conventional and labile molecules (1,2). The colon-targeted oral delivery systems require the drug to be protected during gastrointestinal (GI) transit until the dosage form reaches the colon. To overcome such difficulties, various novel delivery systems, such as time-dependent delivery (3,4), pH-dependent systems (5), and delivery systems based on utilization of bacteria (or enzymes produced by these bacteria) that colonialize the colon specifically (6,7), have been developed.

Despite widespread use of pH-dependent systems for colon-targeted delivery of drugs, there has always been controversy about their usefulness for the intended purpose (2), mainly because of (*a*) high GI pH variability among individuals and (*b*) lack of proper coating material that would dissolve at the desired pH of the colon, thus bypassing the effect of the stomach and the small intestine on the dosage form. Although methacrylic acid copolymers such as Eudragit® L100-55, Eudragit L100, and Eudragit S100 have commonly been used as pH-dependent polymers for coating solid dosage forms (because of their solubilities at pH of 5.5 or higher, 6.0 or higher, and 7.0 or higher, respectively), none of them is suitable for use alone for coating of dosage forms that would start releasing the drug specifically at pH 6.5, which is generally considered as the suitable pH for colon-targeted delivery. In vitro studies performed by Ashford et al. (8) demonstrated the possible failure of mesalazine tablets coated with Eudragit S100 in colon-targeted delivery. A similar view was also expressed by Rijk et al. (9) as a result of a study with a few brands of commercially available pH-dependent mesalazine tablets in humans.

In a previous paper (10), we hypothesized that it would be possible to combine Eudragit S100 with either Eudragit L100-55 or Eudragit L100 in various ratios to coat tablets to manipulate the drug release within the pH range 5.5 to 7.0 or 6.0 to 7.0, respectively; in the same report, we also demonstrated the usefulness of Eudragit L100-55–Eudragit S100 combinations for manipulation of drug release within the pH range 5.5 to 7.0. In this paper, we report the results obtained for Eudragit L100–Eudragit S100 combinations.

In line with our previous report (10), the main objective of this study was to develop a single aqueous coating system that would allow the dosage form to pass the jejunum intact and to start releasing the drug either at the small intestine or to the colon, depending on the pH profile of the GI tract of particular individuals. This study was also designed to see the impact of individual variability in pH profile of the GI tract and prolonged residence time of the dosage form on the release profile of the drug. Mesalazine was used as a model drug, and the studied formulations were designated as Eudragit L100–Eudragit S100 ratios (w/w) throughout the text.

EXPERIMENTAL

Materials

Mesalazine (5-amino salicylic acid) was obtained in house (PLIVA d.d.). Methacrylic acid copolymers (Eudragit L100 and Eudragit S100) were supplied as gifts by Röhm GmbH Chemische Fabrik (Darmstadt, Germany). The coloring agents tartrazine and titanium dioxide and the plasticizer triethyl citrate (TEC), used for coating, were also obtained as gifts from Warner Jenkinson Europa Limited (Norfolk, UK) and Reilly Chemicals (Brussels, Belgium), respectively. Other excipients used to prepare the tablets were standard pharmaceutical grade, and all chemical reagents used were analytical grade.

Methods

Preparation of Core Tablets

Core tablets containing 125 mg of mesalazine as a model drug were prepared with lactose monohydrate as the main filler/constituent using wet granulation technology (high-shear mixing) as described previously (10). The tablets were evaluated for appearance, uniformity of weight, hardness, friability, and disintegration time to meet predetermined criteria suitable for coating.

Coating of the Tablets

Spraying dispersions for coating were prepared as described in the previous report for coating with Eudragit

L100-55–Eudragit S100 combinations (10), except that Eudragit L100 was treated exactly in the same way as Eudragit S100 because of similar film-forming properties of both the polymers, in contrast to Eudragit L100-55, which has different film-forming properties from Eudragit S100 and required a different combination of coating aid materials than Eudragit S100. Briefly, aqueous dispersions were prepared from each polymer separately and then combined at various proportions to obtain the desired Eudragit L100–Eudragit S100 ratios. The plasticizer TEC was added directly to the polymer dispersion(s), and a dispersion of the other coating aid materials (including tartrazine and titanium dioxide as coloring agents) was prepared separately and then combined and mixed with the polymer dispersion. Trials were conducted using Eudragit L100–Eudragit S100 ratios (w/w) of 1:0, 4:1, 3:2, 1:1, 2:3, 1:4, 1:5, and 0:1.

The core tablets were coated at the 18% level (w/w, total solid applied) using a fluid bed coating apparatus as described previously (10). The required level of coating was determined on the basis of our previous experience (10) and results obtained from preliminary disintegration experiments performed according to British Pharmacopoeia (BP) when all tested formulations passed the enteric performance test for 2 hr in 0.1 N HCl.

Dissolution Test

Experiments were performed to study the effect of (*a*) coating formulations, (*b*) pH of the dissolution media, and (*c*) GI pH variability among individuals on drug release profiles of the tablets.

The experiments were carried out as described in the previous report (10) (USP basket method, 100 rpm, 37°C), and the most promising formulation (4:1) was tested under extreme conditions of the GI tract to account for individual variability, as proposed by Ashford et al. (8), by subjecting the formulation to prolonged dissolution studies based on generally accepted GI transit times (i.e., 2, 1, 2, and 2 hr for the stomach, duodenum, lower small intestine, and colon, respectively) using Sorensen's phosphate buffer of two pH profiles, the so-called low and high profiles. For the low-profile test, the pH was adjusted to 6.1, 7.0, and 6.5 to mimic the duodenum, lower small intestine, and colon, respectively; and for the high profile, pH 7.2 was used to mimic the duodenum condition, while pH 7.8 was used for both the intestine and the colon.

A statistical comparison of the dissolution data obtained for the 4:1 formulation under both the low- and high-profile pH conditions was made with those reported for the 1:5 (Eudragit L100-55–Eudragit S100) formulation in our previous paper (10) using a software package known as JMP® (version 2.0.5) (SAS Institute, Cary, NC). An analysis of variance (ANOVA) of the dissolution data demonstrated suitability ($p < .05$) of the linear regression model for comparing both formulations; hence, linear regression lines obtained for the two formulations under both the low and high pH profile conditions were compared using the Student *t* test.

RESULTS

All formulations passed the BP criteria for an enteric performance test in 0.1 N HCl when tested for disintegration, and none of the tested formulations released more than 2% of mesalazine in 0.1 N HCl in 2 hr during dissolution testing.

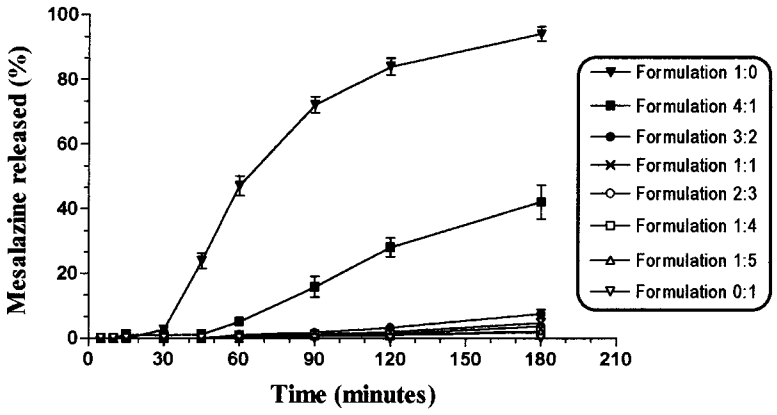

Figure 1. Effect of coating formulations on the release of mesalazine. Dissolution profiles of the tablets in pH 6.5 mixed phosphate buffer. The mesalazine core tablets were coated with various Eudragit L100–Eudragit S100 combinations (w/w) and were tested in 0.1 N HCl for 2 hr prior to the buffer stage. Vertical bars indicate standard errors of the means ($n = 6$).

The dissolution profiles of the tested formulations in pH 6.5 buffer media are presented in Fig. 1. Formulations containing 50% (w/w) or more Eudragit S100 (i.e., formulations with ratios of 1:1, 2:3, 1:4, 1:5, and 0:1) in the combinations virtually did not release any mesalazine at pH 6.5, and none of the studied formulations released 50% of the drug in 180 min when the test was terminated except tablets coated with only Eudragit L100 (the formulation with a 1:0 ratio), which released 50% of the drug in 60–70 min, with about 84% release in 120 min. The rate of release of the drug increased with increase in Eudragit L100 content in the formulations containing less than 50% Eudragit S100 (i.e., formulations with ratios of 1:0, 4:1, and 3:2), but that was not apparent during the first 30 min of the test.

As expected, in pH 7.0 medium, the tested formulations produced significantly faster dissolution profiles than in pH 6.5 medium (Fig. 2). The 1:0 formulation (i.e., tablets coated with only Eudragit L100) released 50% of the drug in 45 min, with about 87% released in 90 min (data not shown). The tablets coated with only Eudragit S100 (formulation with a 0:1 ratio) had the slowest dissolution rate in pH 7.0 among all the formulations tested, with almost no release during the first 90 min of the dissolution run. This 0:1 formulation released about 70% of the drug at 180 min, when the test was terminated. At pH 7.0 as well, the rate of dissolution of the tablets increased with increase in Eudragit L100 content of the tested formulations.

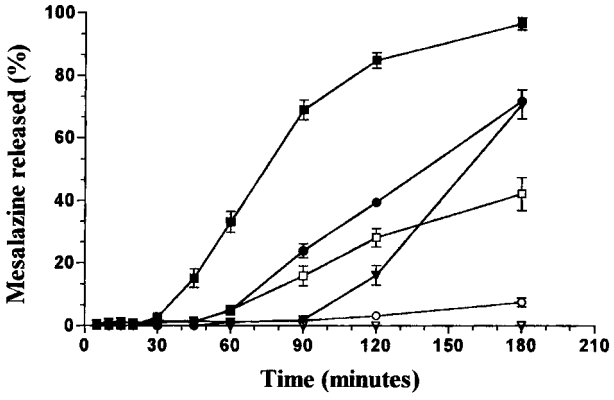

Figure 2. Effect of pH of the dissolution medium on release of mesalazine from the tablets tested in pH 6.5 (open symbols) and 7.0 (closed symbols) mixed phosphate buffers. The mesalazine core tablets were coated with Eudragit L100–Eudragit S100 combinations of: 4:1 (squares), 3:2 (circles), and 0:1 (triangles) and tested in 0.1 N HCl prior to the buffer stage for 2 hr. Vertical bars indicate standard errors of the means ($n = 6$).

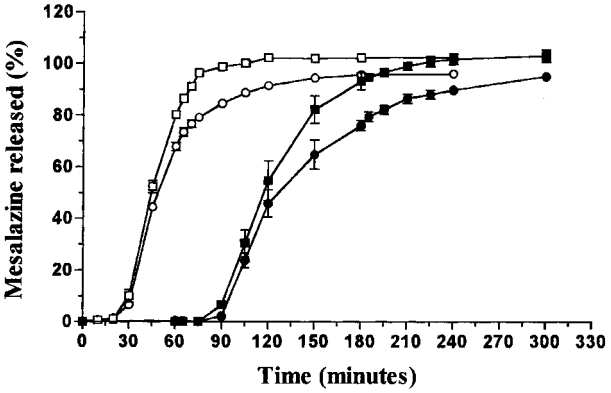

Figure 3. Effect of individual GI pH variability on release profile of the tablets of Eudragit L100–Eudragit S100 4:1 (squares) and Eudragit L100-55–Eudragit S100 1:5 (circles) formulations subjected to prolonged dissolution studies in Sorensen's phosphate buffer with the pH adjusted to 6.1, 7.0, and 6.5 to mimic the low-profile (closed symbols) and to 7.2 and 7.8 for the high-profile (open symbols) individuals as described in the text. In both profiles, the tablets released a negligible amount (or none) of mesalazine in 0.1 N HCl; hence, the profiles are not included in the curves. Vertical bars indicating standard errors of the means ($n = 6$) are within the points if not visible.

The drug release profiles of the tablets (4:1 formulation) subjected to prolonged dissolution studies at low- and high-profile pH media are shown and compared in Fig. 3 with those reported for a 1:5 Eudragit L100-55–Eudragit S100 formulation previously (10). There was no release of mesalazine from the 4:1 formulation under stomach conditions for 2 hr, and the dissolution profiles in 0.1 N HCl are not included in the curves presented in Fig. 3.

The difference in pH profiles significantly influenced the release profiles of the tablets. Under the low pH profile conditions, the release process began after about 30 min at pH 7.0 (lower small intestinal condition, i.e., after 90 min of the duodenal condition), with 93% drug release at the end of the testing period (i.e., after 5 hr of the total test period in various pH media). The release process continued in the pH 6.5 buffer medium, with a cumulative release of 100% of the drug at 45–60 min, that is, after about 6 hr of total dissolution period.

In the case of the high pH profile conditions, the release of mesalazine began after 30 min in the duodenal condition (pH 7.2), and 80% of the drug was released at the end of the dissolution run (i.e., after 60 min). During the follow-up run in the intestinal condition, the drug release was continuous and rapid, with about 100% release

in 30 min (i.e., after 1.5 hr of the emptying from the stomach condition).

Both the intercepts and slopes of the linear regression lines of the dissolution data obtained under both the low and high pH profile conditions for the two tested formulations were not found to differ significantly ($p > .05$) when compared using the Student t test, but the differences were significant ($p < .05$) under both the low- and high-profile conditions when the data obtained according to different GI regional conditions (duodenal, lower small intestinal, and colonic) were compared separately (i.e., on a step-by-step basis).

DISCUSSION

The data presented in Fig. 1 and Fig. 2 demonstrate that the rate of release of the drug could be manipulated to a certain extent by combining the two polymers in various proportions, but for the formulation containing 50% or more Eudragit S100 in the combinations, the effect was not apparent under the lower pH condition (i.e., pH 6.5). This is attributable to the fact that only one (Eudragit L100) of the two polymers is soluble at this pH, making it a less discriminatory medium for the combination formulations enriched with Eudragit S100 than the higher pH medium, in which both polymers are soluble. The dissolution profile obtained for the 0:1 formulation at pH 7.0 also demonstrates that the dissolving process of the film produced by Eudragit S100 is rather slow. The release of the drug began only after 90 min of the dissolution run. Similar results were obtained for tablets coated with only Eudragit L100 at pH 6.0 (data not shown). The slowness of the dissolution process of the films produced by Eudragit S100 at pH 7.0 probably explains why the formulation effect was not apparent in pH 6.5 medium for combinations enriched with Eudragit S100 and suggests that further prolongation of the dissolution test would be appropriate for testing the effectiveness of these formulations.

In agreement with our previous report on tablets coated with Eudragit L100-55–Eudragit S100 combinations (10), the dissolution mechanism of tablets (reported here) coated with Eudragit L100–Eudragit S100 combinations can also be explained as due to pore (and/or weak points) formation in the film as a result of faster solubilization of Eudragit L100 than Eudragit S100 at the studied pH because this polymer is soluble within the entire pH range studied. At a particular pH (within the 6.0–7.0 range), the higher the amount of Eudragit L100 in the formulation, the more weak points or pores should be formed, thus creating channels for the dissolution media to penetrate into the tablets, resulting in faster dissolution of the drug. Formation of channels in pectin/ethylcellulose mixed films due to solubilization of pectin was found to be responsible for dissolution of the drug from tablets coated with these materials in combinations (7).

The dissolution profiles of the tablets of 4:1, 3:2, and 0:1 formulations, presented in Fig. 2, also demonstrate the pH-dependent release mechanism of the formulations and confirm that dissolution occurs due to pore formation, which significantly increases at pH 7.0 due to solubilization of both the polymers at this pH.

The release profiles of the drug obtained for the 4:1 formulation during prolonged dissolution studies under both the low and high pH profile conditions demonstrate the superiority of the combination formulation over tablets coated only with Eudragit S100 since the results do not show any sign of the coating layer being intact up to the end of 5 hr of residence time in the GI tract, thus minimizing the risk of coming out intact with feces, as demonstrated by Ashford et al. (8) for tablets coated with Eudragit S100. On the other hand, the tablets coated with only Eudragit L100 released 87% of the drug in pH 7.0 medium in 1.5 hr, which is too rapid for colon-targeted delivery of drugs considering the average GI transit time of solid dosage forms, particularly for individuals with a relatively high GI pH profile. As was the case for the Eudragit L100-55–Eudragit S100, 1:5 formulation (10), the results suggest that the release process for the 4:1 formulation would start as early as in the duodenum in patients with extremely high pH profiles and would continue for about 1.5 hr of residence time or in the distal region of the small intestine in patients with extremely low profiles prior to reaching the ascending colon of the GI tract, which is the desirable site for colon-targeted delivery of drugs like mesalazine. The release of the drug would continue in the colon for low-profile patients. Although the dissolution rate of the tested combination formulation (4:1) is relatively high under the high pH profile conditions, this eliminates the risk of total failure of the tablets in releasing the drug under low-profile conditions.

Since the tested pH profiles cover both extremes of the highly variable patient groups, a coating formulation with Eudragit L100–Eudragit S100 combination containing about 80% (w/w of the total polymer applied) or less Eudragit L100 seems to be appropriate for colon-targeted delivery systems. Of course, other formulation factors, such as coating thickness, total polymer applied, physicochemical properties of the drug, loading dose, size and shape of the tablets, also deserve consideration.

The statistical indifference of the overall dissolution data between the 4:1 (w/w) Eudragit L100–Eudragit S100 and 1:5 (w/w) Eudragit L100-55–Eudragit S100 formulations demonstrate higher effectiveness (in eliminating the risk of failure in releasing the drug) of Eudragit L100-55 than Eudragit L100 in the combinations due to its relatively higher and faster solubility in the entire pH range ($\geq$5.5) of the intestinal region irrespective of individual pH profiles. But, the significant differences in the regional dissolution profiles between the two formulations suggest that they are not completely interchangeable and would require further proportional adjustments of the two variable polymers, Eudragit L100-55 and Eudragit L100, with Eudragit S100 to obtain interchangeable dissolution profiles throughout the GI tract.

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