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A Novel pH- and Time-Dependent System for Colonic Drug Delivery

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ABSTRACT

A novel pH- and time-dependent delivery system was developed for delivering drugs to the colon. In vitro studies showed that this novel system could release the drug at a predetermined time, which was mainly controlled by the coating layers of the system. The delayed time of the press-coating layer was controlled by its erosion rate, which followed Hixson-Crowell equation. A proper selection of such factors as the viscosity grade of HPMC and tablet hardness, etc., can help reproduce the drug release profile as expected. The transit profiles in two healthy volunteers by gamma scintigraphy demonstrated that the tablets were able to pass through the stomach and small intestine intact and could safely reach the distal end of the small intestine, where the system began to release the drug contained in the core tablet. For both of the volunteers, disintegration of the tablets occurred in the ascending colon, which had highlighted the potential of this system for colonic drug delivery.

Key Words: Colonic drug delivery; Film coating; Press coating; Tablets; Gamma scintigraphy.

INTRODUCTION

Recently, colonic drug delivery systems (CDDS) have attracted a great deal of interest for the local treatment of a variety of bowel diseases and for improving systemic absorption of drugs susceptible to enzymatic digestion in the upper gastrointestinal (GI) tract.[1–7] Most of the reported approaches for delivering drugs to the colon were mainly based on one of three principles: time-dependent systems, pH-dependent systems, and enzyme-dependent systems.[8–15]

It is known that the transit time of dosage forms through the GI tract is highly variable and depends on many factors, but the small intestine transit time is fairly constant at 3–4 h independent of the size and

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forms of the releasing units as well as the fasted or unfasted state, which constitute the bases of time-dependent systems for colonic drug delivery.

pH-dependent systems could be a simple approach for colonic drug delivery, but lack sufficient site specificity because of the greatly changed pH of the GI tract and the pH drop of the colon (5.5–7.0) from pH 7–8 of terminal ileum.[16] Time-controlled release systems have been used for colonic delivery but are limited due to the large variation of the gastric emptying time of dosage forms from 15 min to more than 3 h,[17] resulting in poor time prediction and site specificity. Based on the physiological characteristics of the GI tract and the features of pH-dependent and time-dependent systems, it could be predicted that the integration of acid resistance and timed-release functions into one formulation seems to be desirable to achieve the site-specificity of drug release in the colon.

The objective of this study was to develop a pH- and time-dependent system for delivering drugs into the colon and to demonstrate its site specificity in the colon. The developed system, using tinidazole as the model drug, consisted of three parts, i.e., a core tablet and two layers of coating (the outer enteric film-coating layer and the inner press-coating layer), which could achieve the minimum influence of gastric emptying time on drug release and guarantee the tablet to reach the colon safely and release the drug in the colon. This article presents the results concerning preparation, in vitro drug release, drug release mechanism, and in vivo tests on drug release in two healthy volunteers by employing the technique of gamma scintigraphy, which has become the most useful and practicable method to investigate the GI performance of pharmaceutical dosage forms.[4,18–20]

EXPERIMENTAL

Materials

Hydroxylpropylmethylcellulose (Methocel™ K4-M) and enteric-type Opadry™ were kindly supplied by Shanghai Colorcon® Coating Technique Co., Ltd. Other excipients used to prepare the tablets were of standard pharmaceutical grade and all chemical reagents used were of analytical grade. Tinidazole normal tablets (500 mg/tab) were purchased from Gruangzhou Huaguang Factory of Pharmaceuticals, China.

Methods

Preparation of Core Tablets

Tinidazole and carboxyl methyl starch sodium mixture was granulated with an 8% starch plaster and then screened through a 20-mesh sieve and dried at 40°C for about 1 hr. The granules were lubricated with 0.5% of magnesium stearate and tabletted on a rotary tabletting machine. Tablets were tested for weight (about 110 mg) and hardness (40 N–60 N).

Coating of the Core Tablets

The inner coating layer was made on the core tablet by press-coating using an excipient mixture, which was made by mixing HPMC, lactose, and microcrystalline cellulose together. One-half of the mixture for each tablet was placed into the die, the core tablet was then placed in the center of the die, and the remaining half of the mixture was placed into the die, and the tablet was press-coated on a rotary tabletting machine at pressure 40–60 N. In this way, the press-coated tablets were made.

The outer coating layer was made on the above press-coated tablets by film coating with enteric-type Opadry in a conventional coating pan. The parameters of film coating process follow: pan rotating speed 20 rpm, atomizing air pressure 2 bar, inlet air temperature 70°C, outlet air temperature 40°C, and tablet bed temperature 38°C. The film-coated tablets were not removed from the pan until complete weight gain was achieved.

Dissolution Tests

Dissolution study of the tablets was performed according to the paddle method described in USP 23 with 900 mL of pH 6.8 phosphate buffer and 100 rpm of rotation speed at 37°C. Aliquots of the dissolution medium were removed at specified time intervals and assayed for the released amount of tinidazole by an ultraviolet-visible spectrophotometer (UV-260, Shimadzu, Tokyo, Japan) at 318 nm. The effects of viscosity grades of HPMC and hardness of the press-coated tablets on the drug release profoles were studied.

Mechanism of Drug Release

Aliquots of the dissolution solution were withdrawn separately at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, and 4.0 hr and absorption values were determined by UV spectrophotometer at 318 nm. At the same time, the tablets were taken out at 0.5, 1.0, 1.5, 2.0, and 2.5 hr, respectively, and placed into weighing bottles and dried until constant weight was achieved. As a result, the percentage of drug release (Yt) and the tablet weight loss, i.e., the erosion amount (Δw), at the given time could be obtained.

In Vivo Release Test

This test was made using the tablets, each containing 2 mg of samarium oxide in its core tablet. The tablets were irradiated for 30 min in a flux of 4×10^{11} neutrons $cm^{-2}s^{-1}$. Each tablet contained about 1.0 MBq of the gamma-emitting isotope, ^{153}Sm, at the time of administration (DxS SPECT, Sophy, France). After an overnight fast, each subject was administered one tablet together with 200 mL of water containing a lower amount of $^{99}Tc^{m}$-DTPA to outline the anatomy of the gastrointestinal tract. Gamma camera (HPGe-4096, Ortec, Greenville, SC, USA) images were recorded at frequent intervals throughout the test. Subjects had a standard meal after the tablet emptied from the stomach. Two healthy male subjects, aged 22–24 years old and weighing between 60 and 65 kg, took part in this test after providing written informed consent. Both were briefed about the nature of the study and the product studied. The subjects were not taking any medications before and during the study and had no history of GI disorders.

RESULTS AND DISCUSSION

Dissolution Profiles of the Presented System

Dissolution tests were performed under the same conditions as mentioned previously with colonic delivery tablets and commercially available normal tablets. The release profiles of both tablets are shown in Fig. 1. Drug release from CDDS tablets began at about 3 hr after the test started and was completed in 4–4.5 hr, while drug release from normal tablets occurred immediately and completely within 5 min. The significantly delayed release effect of CDDS tablets was greatly due to the compression coating layer, in which some polymers such as HPMC help control the beginning time of drug release at about 3 h. In this system, the enteric-film layer was designed to minimize the influence of stomach-emptying time on drug release and to guarantee the tablet could enter the small intestine intact; the compression-coating layer was adopted to delay the drug release for about 3 to 4 h and to allow the tablet to pass through the small intestine to the ileo-caecal junction (ICJ) or proximal colon.

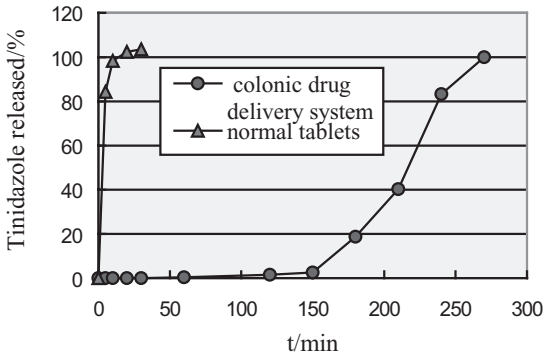

Figure 1. Dissolution profiles of normal tablets (▲) and colonic delivery tablets (●) in 900 mL of pH 6.8 phosphate buffer by paddle method at 100 rpm. Each point represents the mean of six determinations.

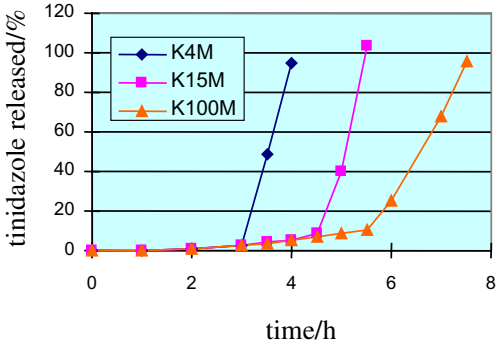

Figure 2. Effect of viscosity grades of HPMC on tinidazole release from the colonic drug delivery system.

Effect of the Viscosity Grade of HPMC

The effect of the viscosity grade of HPMC on the drug release profile of the system was tested by using different viscosity grades of HPMC (K4M, K15M, K100M) to make the press-coating layer of the tablets. The results are presented in Fig. 2,

indicating that the viscosity grade of HPMC had a significant effect on the beginning time and drug release rate. The beginning time of drug release was greatly delayed with the increase of the viscosity grade of HPMC, and the release rate was also obviously reduced and sustained. For the system presented, it was designed to release the drug at the scheduled time and then release most of the drug within a short time period. Higher viscosity grades of HPMC were not suitable for this purpose.

Effect of Hardness of the Press-Coated Tablets

The effect of hardness of the press-coated tablets on drug release is shown in Fig. 3. Within the range of 40–60 N, drug release profiles remained relatively unchanged, but obvious differences occurred in the beginning time of drug release with the tablets of the different ranges of hardness. The higher tablet hardness made the drug release begin at a later time than the lower one. Therefore, tablet hardness had to be maintained within as small a range as possible in order to make the release profiles of different batches of tablets repeatable and reproducible.

Mechanism of Drug Release

The weight loss (Δw) of the tablet and its fraction ($\Delta w/w_i$) at 0.5, 1.0, 1.5, 2.0, and 2.5 hr were obtained from the original weight (w_i) and tablet weight (w_d) after dissolution. The release fractions ranging from 0.5 hr to 4.0 hr were also obtained.

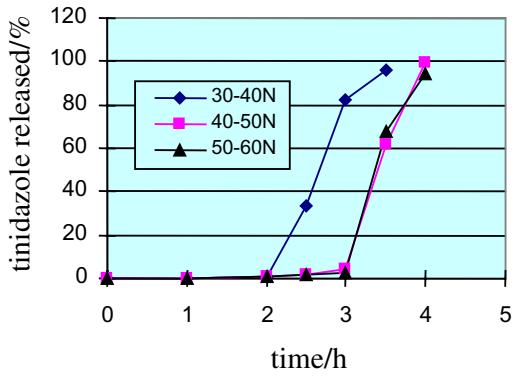

Figure 3. Effect of tablet hardness on tinidazole release from the colonic drug delivery system.

Figure 4 shows the relationship of $\Delta w/w_i$ and y_t with time. It can be seen that $\Delta w/w_i$ increased with time until the tablet coating broke. The profile of y_t with time can be divided into two phases, before and after 3 hr. Before 3 hr, almost no drug release occurred ($y_t < 0.1$), but after that time, most of the drug released rapidly. This can help explain the process of drug release from the tablet. During the early hours of the release test, the medium penetrated only into the outer part of the coat layer, causing the gradual erosion of the coat and resulting in a thinner and thinner coat until the medium entered into the core tablet and caused the disintegrating agent to expand rapidly and break the coat layer and release most of the drug contained in the core.

Figure 5 gives a description of the relation between cubic root of erosion fraction (Wd/Wi) and time. A linear relation between $(Wd/Wi)^{1/3}$ and time

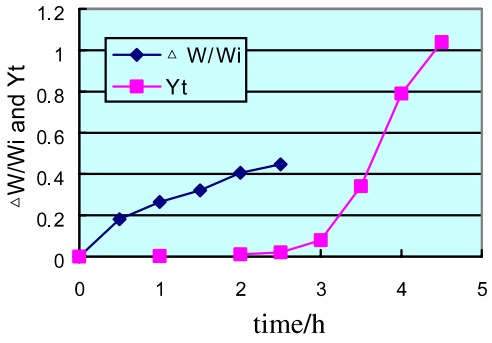

Figure 4. In vitro erosion fraction profile (♦) and tinidazole release profile (■) of the colonic drug delivery tablets in 900 mL of pH 6.8 phosphate buffer by paddle method at 100 rpm.

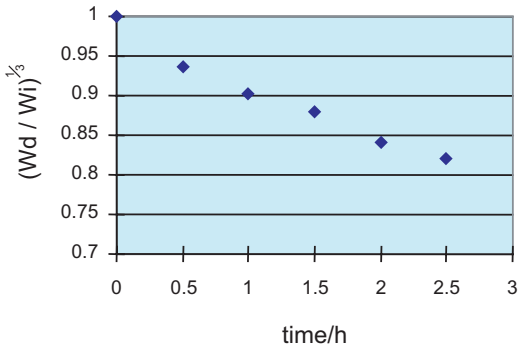

Figure 5. Cubic root plot of erosion fraction as a function of time from the Hixson-Crowell equation $(Wd/Wi)^{1/3} = 1 - kt$), Wd is the dry weight of tablets at time t, Wi is the initial dry weight of tablets.

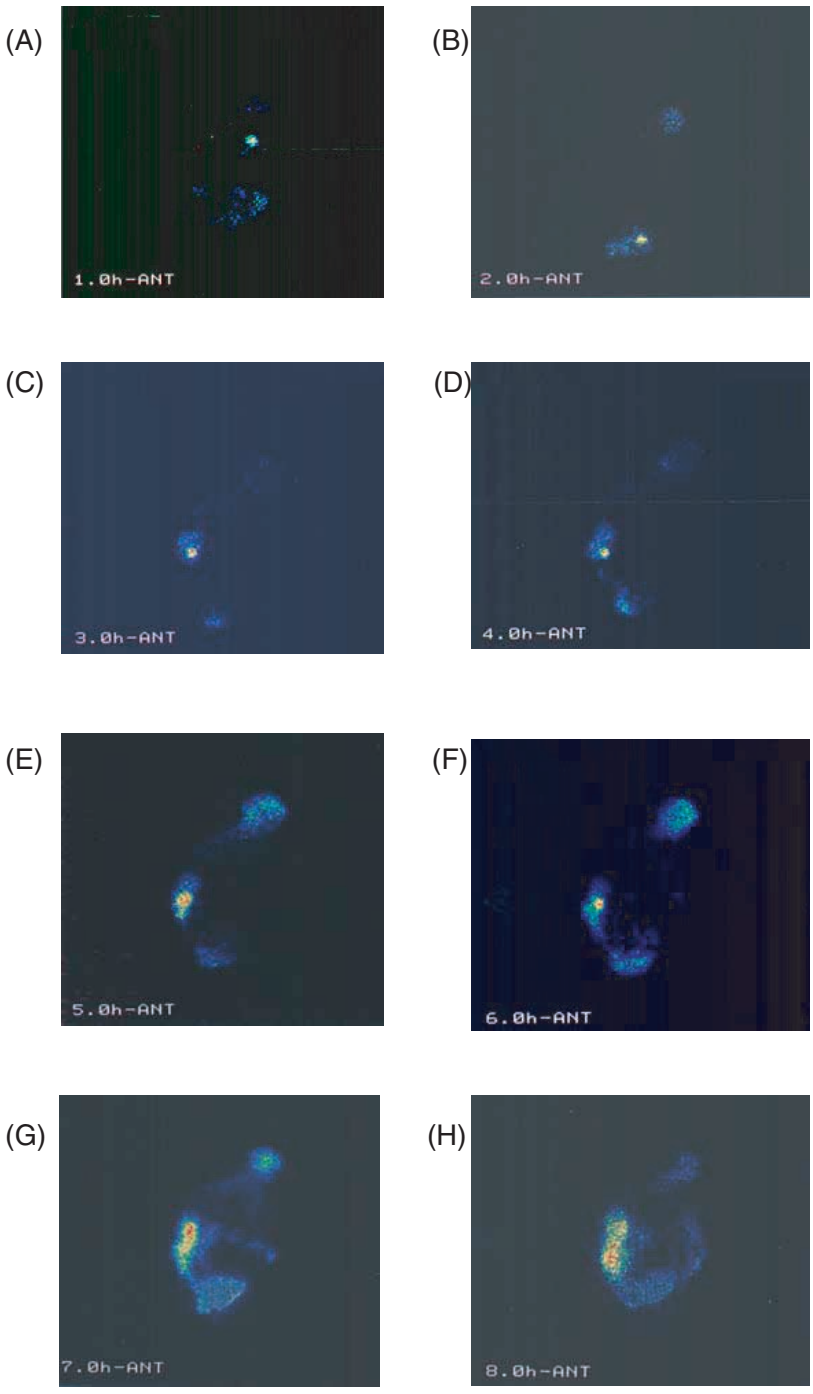

Figure 6. Gastrointestinal transit and disintegration of the developed colonic release tablet in volunteer 1. (A) 1 h, intact tablet. (B) 2 h, intact tablet. (C) 3 h, intact tablet in the ICJ. (D) 4 h, intact tablet in the ICJ. (E) 5 h, intact tablet in the ascending colon. (F) 6 h, intact tablet in the ascending colon. (G) 7 h, disintegrated tablet in the ascending colon. (H) 8 h, disintegrated tablet in the ascending colon.

was observed over the early time period (0.5–2.5 h). The obtained equation was

$$(Wd/Wi)^{1/3} = 0.9632 - 0.0583t (R = -0.9965, n = 5)$$

which indicated that the change of the tablet weight followed the Hixson-Crowell cubic root equation, $(Wd/Wi)^{1/3} = 1 - kt$ (k is the erosion rate constant for the tablet). This further suggests that the tablet weight loss was probably due to the erosion of the tablet. The starting time of drug release of the system was controlled by the erosion rate mentioned previously.

In Vivo Release Test

The in vivo release test in two healthy volunteers covered the time period over 8 hr following the administration of the tablet. A reasonable amount of $^{99}TC^{m}$-DTPA helps make the GI tract clearer and also make it possible to locate the tablet in the GI tract. It is easy to tell the image difference between $^{99}TC^{m}$-DTPA and ^{153}Sm. Since $^{99}TC^{m}$-DTPA is dissolved in water, after administration it flows and disperses through the entire GI tract and therefore outlines the GI tract. $^{99}TC^{m}$-DTPA displays as a fairly dim blue color while ^{153}Sm shows as a bright yellow color. The time of tablet disintegration was judged by visually observing the change of the tablet image. Before disintegration, on the background of blue color there was a small but intensely yellow round spot existing in the images because the isotope ^{153}Sm was present only in the core. But when disintegration took place, the spot image changed into a dispersed one, for the isotope originally in the core came out and distributed in a relatively larger area.

The results showed that the disintegration site of the tablets in both volunteers was in the ascending colon, and the disintegration time was between 7 and 8 h. For volunteer 1, the tablet reached the ICJ and the ascending colon at about 3 h and 5 h, respectively, and began to disintegrate at about 7 h in the ascending colon. For volunteer 2, the corresponding time was 5 h and 7 h, respectively, which was a little later than that of volunteer 1. The disintegration took place at about 8 hr in nearly the same site as that of volunteer 1. The gastrointestinal transit process of the tablet in volunteer 1 is shown in Fig. 6. The in vivo test demonstrated that the developed system could deliver the drug to the colon successfully and highlighted the potential of this system for colonic drug delivery.

CONCLUSION

A novel pH- and time-dependent delivery system was developed for delivering drugs to the colon, which could carry the drug through the stomach and small intestine intact to the distal end of the small intestine and begin to release the drug in the colon. The in vitro studies showed that this novel system could release the drug at a predetermined time, which was mainly controlled by the coating layers of the system. The delayed time of the press-coating layer was controlled by its erosion rate, which followed the Hixson-Crowell equation. A proper selection of such factors as the viscosity grade of HPMC and tablet hardness, etc., can help reproduce the drug release profile as expected. The in vivo tests in two healthy volunteers by gamma scintigraphy demonstrated that this system could deliver the drug to the colon successfully and highlight the great potential of this system for colonic drug delivery.

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