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Oral delayed-release system for colonic specific delivery +

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Abstract

The paper describes a novel oral time-based drug release system for colonic specific delivery. The system, designed to exploit the relatively constant small intestine transit time of dosage forms, consists of drug-containing cores coated with three polymeric layers. The outer layer dissolves at pH > 5, then the intermediate swellable layer, made of high-viscosity HPMC, interacts slowly with aqueous fluids, thus providing the delay phase. The inner film is made of an enteric material. The system provides the expected delayed release pattern, as also indicated by the preliminary in vivo experiments on rats.

Key words: Colonic specific delivery; Oral time-based system; Delayed release; Film coating; High-viscosity HPMC; Small intestine transit time

1. Introduction

Traditionally, extended release dosage forms have been the most fully investigated of modified release systems (Li et al., 1987), and our group has studied this area (Colombo et al., 1990; Gazzaniga et al., 1993; Sangalli et al., 1993).

Currently, the various therapeutic needs for drugs to be delivered to a specific site within the gastrointestinal tract have led to a growing interest in the potential of devices that are able to control time and/or site of delivery.

In particular, systems for delivering drugs into the colon can be used to treat inflammatory bowel diseases locally, to reduce colonic bacterial growth and/or to improve the bioavailability of orally administered polypeptides. A number of oral systems designed for drug release into the colon have recently been reported. Such systems are based on a variety of approaches, including (i) prodrugs, (ii) bioerosion of a polymeric coating which dissolve at specific pH, and (iii) enzymatic degradation of polymeric coatings by colonic bacteria (Peppercorn and Goldman, 1972; Dew et al., 1982; Friend and Chang, 1984; Saffran et al., 1986; Touitou and Rubinstein, 1986; Hardy et al., 1987; Tozer et al., 1991; Ashford et al., 1992,

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1993; Yeh et al., 1992). Limited work has been carried out concerning the possibility of exploiting the relatively constant small intestine transit time (SITT) of dosage forms (Davis, 1985; Chacko et al., 1990; Klokkers-Bethke and Fisher, 1991; Pozzi et al., 1991; Wilding et al., 1992; Gazzaniga and Giordano, 1993). SITT has been demonstrated to be practically independent of the fasted or unfasted state as well as of the size of the releasing units (Davis et al., 1986). On the basis of these considerations, the aim of this work was to prepare a novel oral time-based release system for specific colonic delivery.

2. Drug product design

The drug product design consists of either a single or a multiple unit oral dosage form that is based on core coated with two/three successive layers. The system is composed of the following:

(i) An outer gastroresistant film which 'recognizes' that the system has left the stomach and entered the small intestine;

(ii) An intermediate layer made of a hydrophilic swellable polymer which starts eroding slowly and/or gradually becomes freely permeable when the outer film dissolves following the arrival of the unit into the duodenum: the swellable layer is responsible for the 'lag phase' period and must protect the core for at least 3–4 h (time needed for transit through the small intestine) or more depending on the specific region of the large intestine to be targeted;

(iii) A drug-containing core: the cores (tablets, minitablets, granules, pellets) may have either properties of prompt disintegration or prolonged release patterns.

An additional enteric film can optionally be placed between the hydrophilic swellable layer and the core. This film would act as a further control element to guarantee that no drug release occurs at low pH values in the case of a possible premature failure of the intermediate retarding layer. Moreover, provided that this inner enteric layer is made of material soluble at pH > 6.5–7, the system might be capable of targeting a specific region of the colon by exploiting the pH profile (i.e., the fall of pH in the caecum followed by a significant rise at the hepatic flexure) (Evans et al., 1988; Wilson, 1989).

We prepared and tested a multiple unit system that consists of compressed disintegrating cores, which contain ketoprofen as a model drug and are coated with three layers. Starting from the external surface, the layers are respectively made of an acrylic resin soluble at pH > 5, high-viscosity hydroxypropylmethylcellulose (HPMC), and an acrylic resin soluble in alkaline medium.

The high-viscosity HPMC layer was obtained using a recently developed spraying procedure as an alternative to the compression coating technique (Gazzaniga and Giordano, 1993; Maffione et al., 1993).

The present paper reports and discusses results concerning the preparation methods, in vitro dissolution/release profiles and some preliminary data relevant to in vivo experiments on rats.

3. Materials and methods

The following materials were obtained from the indicated sources: ketoprofen, Mol. Wt 254.29 (S.I.M.S.,Italy); toluidine blue O, Mol. Wt 305.83 (Aldrich Chimica S.r.l., Italy); lactose (USP grade), lactose powder D 80 (Meggle, Germany); maize starch (USP grade) (Roquette, France); magnesium stearate (USP grade) (F.A.C.I., Italy); hydroxypropylmethylcellulose (Methocel® K4M) (Dow Chemical, U.S.A.); poly(1-vinyl-2-pyrrolidone) (Kollidon® 90) (BASF, Germany); polyethylene glycol (PEG 400) (Hoechst, Germany); acrylic and methacrylic ester copolymers (Eudragit® L, Eudragit® S) (Rohm Pharma, Germany).

Ketoprofen (2.5 kg), lactose (6.2 kg) and starch (1 kg) mixtures were granulated with 2 l of a 10% Kollidon® 90 water solution; the mixtures were forced through a 1.25 mm screen and dried at 55 °C. The granules were lubricated with 0.5% of magnesium stearate and tableted in a rotary tablet press with a set of punches (2.5 mm in diameter and 2.5 mm radius of curvature). Tablets were checked for weight (8 mg), height (1.85 mm), hardness (40 N) and disintegration time (< 3

min). Cores containing toluidine blue as tracer substance were prepared analogously.

The enteric coating solutions were prepared by dissolving the acrylic resins (8% w/v) in an appropriate ethanol/water mixture and adding diethyl phthalate (2%) as plasticizer.

We prepared the coating dispersions of hydropropylmethylcellulose by adding the cellulose derivative and PEG 400 to suitable ethanol/water mixtures. The dispersions were allowed to stand at room temperature for at least 12 h.

The minitablets were coated in a conventional rotating pan (35 cm diameter, 15 l capacity). All coating dispersions were stirred for 30 min before being sprayed, and were continously stirred throughout the coating process.

Samples of coated cores were withdrawn at different times in order to obtain films of increasing thickness. The coated tablets were dried for 20 min, and checked for weight.

The release tests were performed in simulated intestinal fluid without enzymes (pH 7.5 ± 0.5) using the USP paddle apparatus (900 ml, 37°C, 50 rpm). The systems were also tested according to the modified half-change method. The finished systems were placed in simulated gastric fluid (pH 1.2). After a 60 min interval, half of the volume of simulated gastric fluid was withdrawn and substituted with an equal volume of simulated intestinal fluid. At 1-h intervals thereafter, half of the fluid was again withdrawn and substituted with fresh simulated intestinal fluid. Six tablets were tested simultaneously by means of a Sotax AT6 Dissolution Apparatus equipped with an automatic sampling device. The drug was assayed spectrophotometrically (Cecil 5500 UV Spectrophotometer) at 260.5 nm.

Finished systems were tested according to the USP XXII Disintegration test for enteric coated tablets.

Systems containing toluidine blue were used for in vivo experiments on rats (males 220–225 g body weight, fasted for 24 h). After surgical opening of the abdomen of lightly anaesthetized rats, three units (11.8 mg) were inserted in the duodenum through a small incision in the upper part. The wound was then sutured with metal clips. The rats were killed at 5, 10, 12, 18, 24 and 32 h from insertion. At the end of the experiments the gut was excised and the presence of the colour was ascertained.

4. Results and discussion

4.1. Formulation and processing aspects of high-viscosity HPMC coating dispersions

Whereas acrylic polymeric resins, which are widely employed in film coating, presented no particular obstacles to the preparation of the two pH-dependent layers, the use of high-viscosity HPMC as film coating agent does involve some technical difficulties. In particular, the use of an aqueous solution of high-viscosity HPMC requires a very low concentration in order to achieve acceptable sprayability, which in turn results in excessive processing times. It was possible partially to overcome these and other problems by dispersing the polymer in an appropriate ethanol/water mixture along with a commonly used plasticizer (Maffione et al., 1993). The relevant process conditions and coating dispersion composition are given in Tables 1 and 2, respectively.

The high-viscosity HPMC dispersion proved suitable for processing in a conventional coating

Table 1
Film coating dispersion composition (% w/w)

Methocel® K4M	3.7
PEG 400	0.5
Ethanol	81.4
Water	14.4

Table 2
Film coating process parameters

Batch size (kg)	0.25
Mode of spraying	intermittent
Inlet air temperature (°C)	46
Outlet air temperature (°C)	35
Tablet bed temperature (°C)	30
Temperature of dispersion (°C)	25
Nozzle distance (cm)	15
Nozzle port size (mm)	1.6
Atomizing air pressure (bar)	2.2
Pan rotating rate (rpm)	20

equipment and enabled us to achieve a continuous polymeric layer of desired thickness with satisfactory technological properties in terms of appearance, homogeneity and mechanical resistance.

4.2. In vitro testing

Units consisting of tablet cores covered only with the high-viscosity HPMC layer were prepared explicity in order to evaluate, without the influence of the enteric coatings, the ability of this hydrophilic swellable material to delay core disintegration and hence the onset of drug release. Moreover, these units enable us better to follow the continuous changes in morphology of the polymer, which are due to the interaction with an aqueous medium.

When the units are placed in water or in simulating biological fluids, the hydroxypropylmethylcellulose starts swelling and their thickness increases. The slow polymer-solvent interaction (glassy-rubbery transition), which leads to the formation of a gel layer, is capable of delaying contact between disintegrating core and dissolution medium. The interaction of Methocel® K4M based films with aqueous fluids, expressed in terms of release onset, has been proved to be practically independent of pH, at least in the physiological range. The same has been demonstrated for other layer formulations made of anal-

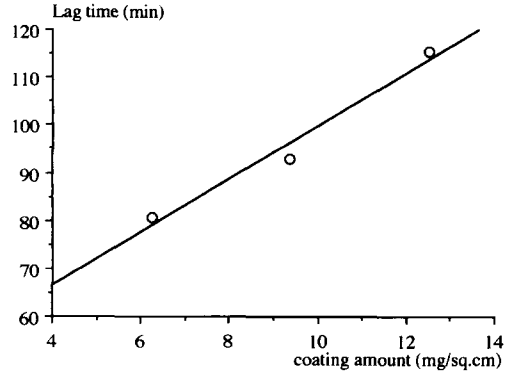

Fig. 2. Effect of amount of high-viscosity HPMC coating on time lag of coated cores.

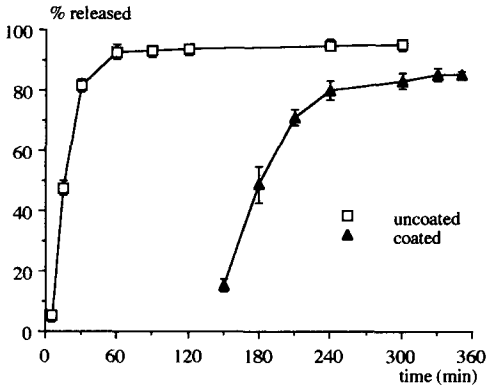

Fig. 3. Release curves of uncoated cores and cores coated with Eudragit® S (7.5 mg/cm^2) and Methocel® K4M films (12.5 mg/cm^2).

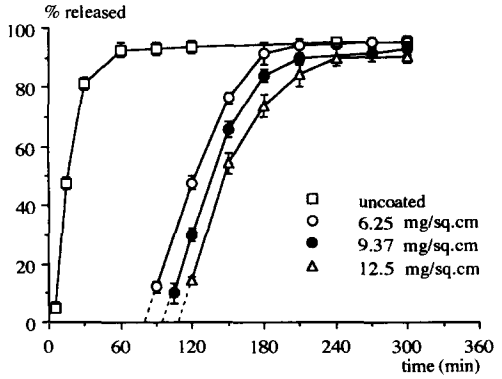

Fig. 1. Release curves of uncoated cores and cores coated only with the high-viscosity HPMC layer.

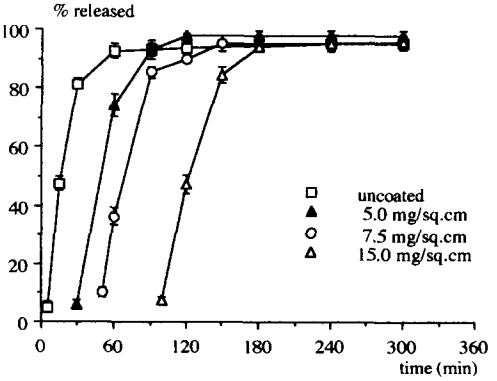

Fig. 4. Release curves of uncoated cores and cores coated with increasing amount of Eudragit® S.

ogous hydrophilic cellulose derivatives (Gazzaniga and Giordano, 1993).

The behaviour herein described directly influences the release profiles of the active principle from the units (Fig. 1). At the beginning of the test, drug release shows a lag time whose duration depends on the original thickness of the dry HPMC film. A correlation can be found by the

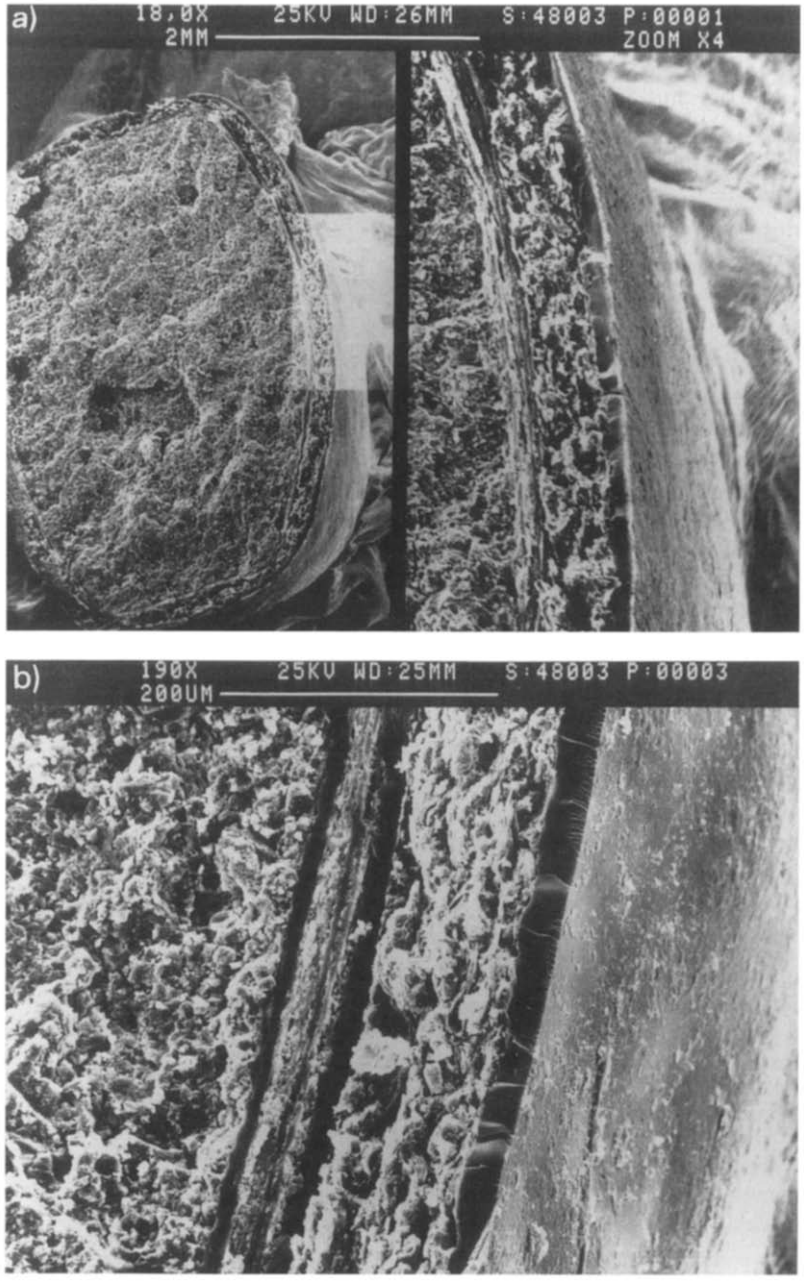

Fig. 5. SEM microphotographs of cross-section of a three-layer coated system at different magnifications: (a) 18 × (zoom 72 ×); (b) 190 × .

plotting of the release delays (min) vs the corresponding amounts (mg/cm^2) of polymeric film coating (Fig. 2). The time lag values were calculated from the time axis intercept of the straight lines that pass through the first two experimental release data for each kind of unit (see dotted lines in Fig. 1).

Fig. 3 reports the release curves of cores covered with the Eudragit® S and Methocel® K4M layers. Eudragit® S, which is known to be slowly soluble in simulated intestinal fluid, results in an additional increase in the lag phase according to the dissolution profiles presented in Fig. 4.

The further covering of the units with Eudragit® L (3.75 mg/cm^2) leads to the finished systems, whose cross-sectional SEM microphotographs are reported in Fig. 5a and b. Whereas the Eudragit® L film promptly dissolves (2–3 min) at pH > 6, the test performed in simulated gastric fluid indicated the film's ability to withstand acidic medium for a time that amply exceeds the USP requirements and thus imparts the desired characteristics to the finished systems. As a further in vitro release evaluation, we performed the test according to the modified half-change method. Fig. 6 displays the resulting release profile.

The data confirm the efficacy of the outer gastroresistant barrier as well the ability of the HPMC layer to delay the onset of drug release.

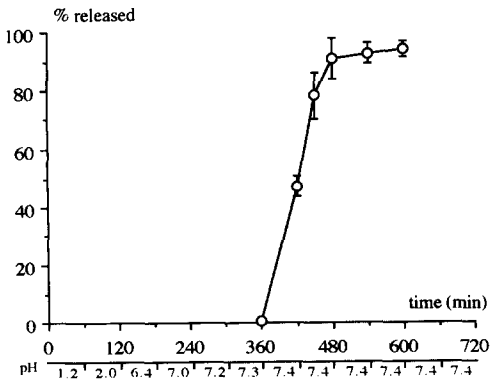

Fig. 6. Release curves of finished system at increasing pH.

4.3. *In vivo testing on rats*

The experiment evaluated the delay inherent to systems that contain toluidine blue as model substance. On the basis of the appearance of the colour, the results indicated that all the tested systems start releasing in the large bowel between the 5th and 10th hours, thus confirming the expected release behaviour.

This novel oral dosage form provides the expected delivery pattern. Drug release occurs after a predetermined time interval upon the dissolution of the external barrier, as is also indicated by the preliminary in vivo data on rats. This makes the systems very promising for colon-specific delivery.

From a technological point of view, the critical step associated with the use of high-viscosity HPMC as film coating agent was overcome and the overall feasibility of the system was ascertained. High-viscosity HPMC, through the slow interaction with aqueous fluids, proved to be a suitable material to achieve the desired delays, which depend on the amount of polymer applied to the cores.

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