International Journal of Pharmaceutics 370 (2009) 144–150

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Scintigraphic evaluation of colon targeting pectin–HPMC tablets in healthy volunteers

L.A. Hodges[a,*], S.M. Connolly[a], J. Band[a], B. O'Mahony[a], T. Ugurlu[b], M. Turkoglu[b], C.G. Wilson[a,c], H.N.E. Stevens[a,c]

[a] Bio-Images Research Ltd., Within Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, Scotland, UK
[b] Department of Pharmaceutical Technology, Marmara University, Haydarpasa, 34668 Istanbul, Turkey
[c] Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0NR, Scotland, UK

ARTICLE INFO

Article history:
Received 25 September 2008
Received in revised form
28 November 2008
Accepted 3 December 2008
Available online 7 December 2008

Keywords:
Compression-coated tablets
Colon-specific drug delivery
Gamma scintigraphy
HPMC
Pectin

ABSTRACT

The *in vivo* evaluation of colon-targeting tablets was conducted in six healthy male volunteers. A pectin–hydroxypropyl methylcellulose coating was compressed onto core tablets labelled with 4 MBq ^{99m}Tc-DTPA. The tablets released in the colon in all subjects; three in the ascending colon (AC) and three in the transverse colon (TC). Tablets that released in the TC had reached the AC before or just after food (Group A). The other three tablets released immediately upon AC entry at least 1.5 h post-meal (Group B). Release onset for Group B was earlier than Group A (343 min vs 448 min). Group B tablets exhibited a clear residence period at the ileocaecal junction (ICJ) which was not observed in Group A. Prolonged residence at the ICJ is assumed to have increased hydration of the hydrogel layer surrounding the core tablet. Forces applied as the tablets progressed through the ICJ may have disrupted the hydrogel layer sufficiently to initiate radiolabel release. Conversely, Group A tablets moved rapidly through the AC to the TC, possibly minimising contact times with water pockets. Inadequate prior hydration of the hydrogel layer preventing access of pectinolytic enzymes and reduced fluid availability in the TC may have retarded tablet disintegration and radiolabel diffusion.

1. Introduction

Pectin is a ubiquitous polysaccharide found in the fruit of many edible plants, with high concentrations found in apples, quinces and oranges. Isolation from plant cell walls by stepwise processing methods produces pectins of various degrees of methoxylation (DM) (Ashford et al., 1994). The source of pectin also contributes to the type of pectin generated. Conventionally, the 50% DM value boundary divides pectin into high methoxy (HM) and low methoxy (LM) pectins (Jain et al., 2007). While the overall water solubility of pectins is relatively high, HM pectins are less water-soluble than their LM counterparts.

At acidic pH values, pectin exists as macromolecule aggregates but these aggregates dissociate and swell at neutral pH. Pectin is also resistant to proteolytic enzymes which are active in the upper gastrointestinal (GI) tract, whereas it is digested by the microflora of the colon (L. Liu et al., 2003). These properties make this polymer a suitable candidate to achieve colon-specific drug delivery. Delivery to the colon has been investigated for more than 20 years to achieve (a) sustained delivery that allows reduction in dosing frequency; (b) prevention of drug release until arrival in the colon for treatment of local diseases; (c) time-delayed delivery to coincide with periods of increased susceptibility to disease symptoms (chronotherapy); and historically, (d) delivery to a region of the gut which is more conducive to absorption of molecules which are prone to acid and enzymatic degradation (Wilson, 2000).

In order to capitalise on its characteristic selective degradation in the colon but not in the upper GI tract, the high solubility of pectin has been modified by the physical addition of other polymers such as ethylcellulose (Wakerly et al., 1996) as well as hydroxypropyl methylcellulose (HPMC) and chitosan (Macleod et al., 1999; Ofori-Kwakye et al., 2004). Addition of these polymers can also improve the compressibility of the tabletting mixture as pectin alone produces poor compacts (Kim and Fassihi, 1997a). Alternatively, chemical modification of pectin by amidation (Ahrabi et al., 2000) and calcium cross-linking (Adkin et al., 1997) also allows for manipulation of the solubility profile.

Pectin, as a physical admixture with HPMC alone, has been proposed as an excipient combination for a colon-specific delivery system (Turkoglu et al., 1999). This combination of pectin and HPMC has been used previously in a binary matrix tablet system that successfully produced zero-order release kinetics (Kim and Fassihi, 1997a,b). In the current study, this polymer mixture was

* Corresponding author. Tel.: +44 141 552 8791; fax: +44 141 552 7752.
E-mail address: leeann.hodges@bio-images.co.uk (L.A. Hodges).

0378-5173/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2008.12.002

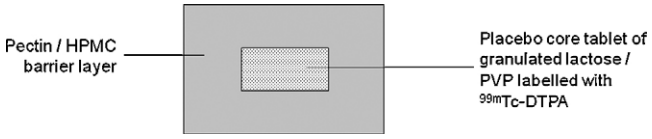

Fig. 1. Colon targeting drug delivery system.

compression coated onto a core tablet in order to delay release until colon arrival.

Fig. 1 shows a cross-section of the system under current investigation, constructed of a core tablet coated by a barrier layer of pectin and HPMC. This layer was formed by compression of a physical mixture of both polymers around the core tablet. Both are hydrophilic polymers which swell to form a hydrogel layer upon contact with aqueous media. The inclusion of high molecular weight HPMC increases the mechanical strength of the tablet, protecting the core tablet during transit in the GI tract and also partially modifies the high solubility of pectin.

In vitro tests were performed on the combination of pectin–HPMC in an 80:20% weight ratio compressed onto core tablets of 5-aminosalicylic acid (Turkoglu and Ugurlu, 2002) and nisin, a naturally occurring, ribosomally synthesised protein (Ugurlu et al., 2007). Tablets of this polymer composition ratio showed 25–35% erosion after 6 h in a pH change dissolution designed to reflect the pH environment of the GI tract. Addition of pectinase after 6 h increased the rate of tablet disintegration. Based on an average mouth–caecum transit time of 6–8 h (Washington et al., 2001), this *in vitro* observation indicated that delivery of drug to the colon was achievable with this system.

USP grade pectin was used in the tablet currently under investigation, which has a DM of approximately 70%. This grade of pectin, when tabletted as a mixture with HPMC is reported not to show any variability in gelation properties over pH 1–7.4 (Kim and Fassihi, 1997b). Lack of pH effect *in vitro* was also observed with the current tablet (Ugurlu et al., 2007). Significant increases of *in vitro* release rates were only observed when pectinase was added to the dissolution media, indicating that this system is more dependent on enzymatic activation rather than pH change for initiation of release.

Gamma scintigraphy, a non-invasive imaging technique, has been shown to be successful in determining the *in vivo* behaviour of various colon delivery systems. By incorporating small amounts of gamma-emitting radionuclides into the dosage forms, it is possible to establish the GI transit patterns of these systems within the body and determine site of disintegration and release. A common radioisotope used is technetium-99m (^{99m}Tc) which has a half-life of 6.03 h and a monoenergetic gamma emission of 140 keV. The behaviour of colon-targeting polysaccharide systems such as alginate gel beads (X. Liu et al., 2003), guar gum matrix tablets (Krishnaiah et al., 1998), enteric-coated tablets (Ibekwe et al., 2008) and xanthan/guar gum/starch matrix tablets (Sinha et al., 2005) has been successfully characterised *in vivo* using scintigraphic methods.

The radioisotope can be incorporated during the manufacturing process e.g. mixed in with the tablet granules prior to compression (Krishnaiah et al., 1998) or after complete manufacture of the film-coated tablet by 'drilling and filling' then re-sealing (Macleod et al., 1999; Ofori-Kwakye et al., 2004). However, if the manufacturing procedure prohibits the incorporation of the radiolabel at an early stage or the 'drill and fill' method is not suitable, there is the option of adding the isotopically enriched stable isotope of samarium-152 during manufacture which can then be converted to the gamma-emitting samarium-153 by neutron bombardment. This technique was used to investigate the *in vivo* behaviour of pectin-based tablets (Adkin et al., 1997) and enteric-coated HPMC capsules (Marvola et al., 2008) formulated for colon targeting purposes.

In this study, placebo systems consisting of a core tablet radiolabelled with technetium-99m-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) and compression coated with 80:20% (w/w) pectin–HPMC were evaluated in healthy volunteers using gamma scintigraphy. Tracking of the tablets through the body enabled release parameters (sites and times of onset and complete release) to be determined.

2. Materials and methods

2.1. Materials

The materials used in the clinical study were of pharmacopoeial grade: polyvinylpyrrolidone (PVP) K30 was a gift from BASF, Germany; lactose (Flow Lac 100) was a gift from Meggle, Germany; stearic acid was a gift from H. Foster & Co. Ltd., UK; pectin (GENU pectin (citrus) type USP/100) was a gift from CP Kelco, Denmark; HPMC (Metolose 90SH–100000 cps) was a gift from Shin-Etsu Chemical Co. Ltd. (Japan). ^{99m}Tc-DTPA was supplied by the West of Scotland Radionuclide Dispensary, Glasgow, UK.

Tablets used for validation of the radiolabelling procedure were made from the same batches of excipients used for the clinical study. The following materials used for *in vitro* dissolution studies were of reagent grade: hydrochloric acid, potassium dihydrate orthophosphate and sodium hydroxide (all supplied by VWR International, UK).

2.2. Methods

2.2.1. Assembly of radiolabelled tablets

The core tablet mixture was prepared by granulation of PVP K30 and lactose with water. The wet granulate was dried in an oven for 2 h, then pressed through a 1-mm sieve. Resultant granules were dried for another hour. Stearic acid (1% weight of dried granules) was added and mixed. The radioactive marker, prepared by drying ^{99m}Tc-DTPA onto lactose, was added to the resultant mixture. This was followed by compression at 2 tons pressure into 100 mg tablets using a 6-mm punch and die set. For *in vitro* validation purposes, the tablets contained between 1 MBq and 1.5 MBq ^{99m}Tc-DTPA at the start of the testing period. In the clinical study, the tablets contained approximately 4 MBq ^{99m}Tc-DTPA at time of dosing.

The coating mixture was prepared by mixing pectin and HPMC in an 80:20% weight ratio in a Turbula mixer. The core tablet was centralised on a 200-mg bed of the coating mixture contained in a punch and die set prior to addition of a further 200 mg of the coating mixture, followed by compression at 2 tons pressure. The complete tablet was approximately 500 mg in weight and was of the following dimensions: 10 mm (diameter) × 5 mm (thickness).

2.2.2. Validation of radiolabelling process

Prior to the clinical study, an *in vitro* validation study was conducted to ensure that release of radiolabel from the tablet could be visualised and was consistent with non-radiolabelled batches.

Three radiolabelled tablets underwent dissolution testing in USP Apparatus II (50 rpm, 37 °C) placed in front of a gamma camera fitted with a low energy, high resolution (LEHR) collimator. The initial dissolution medium was 500 mL 0.1N hydrochloric acid. After 2 h, the medium was replaced with 500 mL pH 6.8 phosphate buffer.

Static acquisitions of 25 s each were taken every 15 min until the release of the radiolabel was complete and no core tablet could be visualised. The scintigraphic images were analysed to determine the times of onset and completion of radiolabel release.

2.2.3. Clinical scintigraphic study

2.2.3.1. Study design. This was a single centre, open-label, single dose study. The study followed the tenets of the Declaration of