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Time and pH dependent colon specific, pulsatile delivery of theophylline for nocturnal asthma

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Abstract

In this study, investigation of an oral colon specific, pulsatile device to achieve time and/or site specific release of theophylline, based on chronopharmaceutical consideration. The basic design consists of an insoluble hard gelatin capsule body, filled with eudragit microcapsules of theophylline and sealed with a hydrogel plug. The entire device was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved. The theophylline microcapsules were prepared in four batches, with Eudragit L-100 and S-100 (1:2) by varying drug to polymer ratio and evaluated for the particle size, drug content and *in vitro* release profile and from the obtained results; one better formulation was selected for further fabrication of pulsatile capsule. Different hydrogel polymers were used as plugs, to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. *In vitro* release studies of pulsatile device revealed that, increasing the hydrophilic polymer content resulted in delayed release of theophylline from microcapsules. The gamma scintigraphic study pointed out the capability of the system to release drug in lower parts of GIT after a programmed lag time for nocturnal asthma. Programmable pulsatile, colon-specific release has been achieved from a capsule device over a 2–24 h period, consistent with the demands of chronotherapeutic drug delivery.

Keywords: Pulsatile; Colon-specific device; Chronotherapeutics; Nocturnal asthma; Eudragit microcapsules; Gamma scinitigraphy

1. Introduction

Among modified-release oral dosage forms, increasing interest has currently turned to systems designed to achieve time-specific (delayed, pulsatile) and site-specific delivery of drugs. These systems constitute a relatively new class of devices the importance of which is especially connected with the recent advances in chronopharmacology (Sangalli et al., 2001). In the last decade numerous studies in animals as well as clinical studies have provided convincing evidence, that the pharmacokinetics and/or the drug's effects-side effects can be modified by the circadian time and/or the timing of drug application within 24 h of a day (Lemmer, 1991; Hrushesky, 1994; Bjorn, 1996).

On the other hand, colon-specific drug delivery systems (CDDS) have been developing as one of the site-specific drug delivery systems. Along with many applications in local and systemic delivery of drugs the CDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis. (Bi-Botti, 2004; Sarasija and Stutie, 2005). So by developing the pulsatile device for specific colonic delivery, plasma peak is obtained at an optimal time, number of doses per day can be reduced; saturable first pass metabolism and tolerance development can also be avoided. (Morta et al., 1998; Richard and Susan, 1998; Gwen, 2002).

The necessity and advantage of CDDS have been well recognized and reviewed recently (Watts and Illum, 1997; Kinget et al., 1998; Libo et al., 2002). There were currently few strategies to achieve colonic specificity such as bacterially triggered, pressure controlled, pH dependent and time dependent CDDS (Libo et al., 2002; Abdul and John, 2003; Chourasia and Jain, 2003).

Recent studies with sensitive and reliable equipment contradict the traditional view and provide evidence of a decrease

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in pH at the gastrointestinal region between the ileum and the colon. Apparently the colon has a lower pH value (6.5) than that of the small intestine (7.0–7.8) (Bajpai et al., 2003). Based on the concept that a formulation on leaving the stomach arrives at the ileocaecal junction in about 6 h after administration and difference in pH throughout GIT, a time and pH dependent pulsatile device proposed for colonic targeting was designed, for achieving the selective delivery of drugs to colon, which is a chronopharmaceutical approach for the better treatment of nocturnal asthma.

The designed capsule device consists of a non-disintegrating capsule body and a soluble cap. The microencapsulated drug formulation prepared by using pH sensitive methacrylic acid copolymers (Eudragit L-100 and S-100) as coat and Theophylline (TPH) as core material, is filled within the capsule body and separated from the water-soluble cap by a hydrogel plug. The entire capsule was enteric coated to prevent variable gastric emptying. The enteric coating prevents disintegration of the soluble cap in the gastric fluid. On reaching the small intestine, the capsule will lose its enteric coating and the water-soluble hydrogel polymer plug inside the capsule swells to create a lag phase that equals the small intestinal transit time. This plug ejects on swelling and releases the microencapsulated drug from the capsule in the colon. Further, the controlled release of theophylline was achieved for up to 24 h as it was microencapsulated in the pH sensitive polymers. In addition, the colon-specific characteristic of modified pulsatile capsule in rabbits was established by gamma scinitgraphic technology. Scitigraphic imaging was performed using radiolabelled units intended for colon-specific release in order to assess their actual time and anatomical site of break-up. The proposed device can be manufactured using currently applicable pharmaceutical technologies and materials recognized as safe. With this system our goal was to avoid drug delivery in the upper GIT and target drugs to the terminal ileum and colonic region. The objective of including the microencapsulated theophylline was to offer a controlled release of drug in this intestinal zone, and to achieve the chronotherapy of nocturnal asthma.

In attempt to simplify the original Pulsincap^{TM} Technology, the complex synthetic hydrogel plug {Desmodur W [bis-(4-isocyanatocyclohexylmethane)] cross linked with hexane triol and polyethylene glycol of different molecular weight is not FDA approved}(Bajpai et al., 2003) has been replaced by pharmaceutically safe hydrophilic hydrogels. Although theophylline (TPH) preparations have generally fallen out of favor for the treatment of asthma, they may be useful in the treatment of nocturnal asthma when administered at specific times in relation to onset of symptoms (Gwen, 2002; Gothaskar et al., 2004). So with the proposed device a *new lease of life* to an existing drug molecule can be achieved.

2. Materials and methods

2.1. Materials

Theophylline was obtained from Cipla India Ltd., Mumbai. pH sensitive methacrylic acid co-polymers (Eudragit® L-100 and S-100) were supplied as gifts by Degussa India Pvt. Ltd., Mumbai. Hydroxypropylmethylcellulose-K_4M (HPMC) was obtained as gift from Colorcon, Goa. Guar gum and sodium alginate were from S.D. Fine Chem. Ltd., Mumbai. Cellulose acetate phthalate (CAP) for enteric coating was purchased from Spectrochem Pvt. Ltd., Mumbai. Elegant Pharmaceuticals, Hubli, India, supplied the hard gelatin capsules (100 and 500 mg capacity). Diethylene triamine penta acetic acid (DTPA) was gifted from Ramsco Chemical Industries, Mumbai, and ^{99m}Technitium solution was kindly supplied by KLES's Hospital and Medical research Center, Belgaum. The rest of the chemicals were obtained from the following commercial supplier and used as received without further purification: heavy liquid paraffin (Ranbaxy fine chemicals Ltd., New Delhi), Span 80 (Research Lab. Mumbai), Dibutylphthalate, acetone, petroleum ether (S.D. Fine Chem. Ltd., Mumbai) were of analytical grade.

2.2. Microencapsulation of TPH

From literature review, it was evident that the pH in the proximal colon ranges from 6.6 to 7.0. Therefore, the Eudragit L-100 and S-100 were combined in different ratios and solubility of these combinations was checked in different pH solutions. From the solubility parameters, it was found that Eudragit L-100 and S-100 in the ratios 1:2 was soluble in pH range of 6.6–7.0. Hence, this combination was selected for preparation of microcapsules.

2.2.1. Preparation method

Accurately weighed Eudragit L-100 and S-100 in 1:2 ratios were dissolved in 10 ml of acetone to form a homogenous polymer solution. Core material, i.e. TPH was dispersed in it and mixed thoroughly. This organic phase was slowly poured at 15 °C into liquid paraffin (100 ml) containing 1% (w/w) of Span-80 with stirring at 1000 rpm to form a uniform emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth-walled, rigid and discrete microcapsules were formed. The microcapsules were collected by decantation and the product was washed with petroleum ether (40–60 °C), four times and dried at room temperature for 3 h. The microcapsules were then stored in a dessicator over fused calcium chloride (Ahmed et al., 2002).

Four batches were prepared with different proportions of core to coat materials (drug: polymer = 1:0.5, 1:1, 1:1.5 and 1:2 (w/w) named TM-1–4, respectively).

2.2.2. Evaluation of microcapsules

Particle size and external morphology: Determination of average particle size of THP microcapsules was carried out by optical microscopy. SEM studies were carried out by using JEOL JSM T-330 A Scanning microscope (Japan). Dry microcapsules were placed on an electron microscope brass stub and coated with gold in an ion sputter. Picture of microcapsules were taken by random scanning of the stub.

Drug content: In a 100 ml volumetric flask, 25 mg of crushed microcapsules were taken, and volume was made up to mark with pH 6.8. The flask was shaken for 12 h using an orbital shaker incubator. Then the solution was filtered and from the filtrate