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Research paper

Gamma scintigraphic studies on guar gum-based compressed coated tablets for colonic delivery of theophylline in healthy volunteers

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ABSTRACT

The purpose of the present study was the development and in vitro/in vivo evaluation of the guar gum-based colon-specific compression-coated tablet formulation of theophylline, which can be used for the treatment of nocturnal asthma. The core tablets containing 100 mg of theophylline were compression coated with various amounts of guar gum. The physical properties of the tablets were tested and in vitro release studies were performed. Samarium oxide (152-Sm) was added to the core tablet as the tracer. Scintigraphy was used to monitor the tablet's movement and distribution through the GI system of six healthy volunteers. In vivo scintigraphic studies showed that the tablets reached the colon at 5,6 and 8 h in three of the six subjects. Theophylline delivery to the terminal ileum or colon can be achieved and the theophylline-guar gum compression coated tablets may be a promising system for the treatment nocturnal asthma. But, more formulation work may be necessary for the determination of the exact coating thickness and the development of optimum formulation.

1. Introduction

Site-specific drug delivery to the colon has attracted considerable interest in recent years, particularly for the treatment of diseases associated with the colon (inflammatory bowel disease, colorectal cancer, irritable bowel syndrome (IBS), infectious diseases, etc), because it may reduce the side effects of the drug and enable a reduced administered dose [1–4]. In addition, the time-related negative effects of diseases, such as nocturnal asthma, which is a circadian rhythm-dependent disease, can be eliminated with the systemic effects of colon-specific dosage forms [5,6].

Over the last few years, various different approaches have been reported as achieving colon-specific drug delivery. These approaches include the use of prodrugs, pH-sensitive polymers, microflora or enzyme activated systems, time-dependent delivery systems and pressure controlled based systems [1,7–12].

It has also been reported that pH-dependent systems have insufficient site specificity for drug release in the colon, and may either lead to a premature release of drug in the small intestine or no drug release in the colon [13,14]. For time-dependent systems, the location of initial drug release predominantly depends on the transit times in the gastrointestinal tract [15]. A more precise and accurate strategy for targeting drugs to the colon uses the ecosystem of the specific microflora present in the large intestine (i.e. microflora-activated systems) [2,12,16–18].

Natural polysaccharides, which are specifically hydrolyzed by the colonic microflora, are the most promising carriers for colon-specific dosage forms. Polysaccharide-based systems, either matrix [19–21] or compression coated tablets [22–24], have been prepared by many researchers.

Among the natural polysaccharides, guar gum displays good potential for use as a polymer for colon-specific dosage forms, due to its biodegradability with colonic enzymes. It is a natural, non-ionic polysaccharide and it consists of linear chains of (1–4)-b-D-mannapyranosyl units with a-D-galactopyranosyl units attached by 1–6 linkages. Guar gum in the form of either a matrix tablet or as a compression coat over a drug core may be degraded to a large

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extent by the action of the anaerobic microbial population of the large intestine [22,25,26].

Theophylline, which is commonly used for the treatment of chronic and nocturnal asthma, is an active agent [27]. A chronobiological approach underlies treatment with theophylline. Obtaining therapeutic blood levels during attacks, which are most common during sleep, or in the morning, is one of the most important aims. In this respect, preparation of colon-specific dosage forms gain importance, because the release and absorption of theophylline from a formulation taken at night may reduce asthma seizures in the morning.

Therefore, the aim of the present study was the development and in vitro/in vivo evaluation of a guar gum-based colon-specific compression-coated tablet formulation of theophylline, that can be used for the treatment of nocturnal asthma. Scintigraphy was used to evaluate the fate of the tablets in the human gastrointestinal tract. To our knowledge, no in vitro or in vivo study has been performed on guar gum based theophylline tablets.

2. Materials and methods

2.1. Materials

Theophylline was a gift sample from Adeka Phamaceutical Company, Turkey. Guar gum (DE 250) was kindly supplied by Dinesh Enterprises, India. The viscosity of the 1% w/v aqueous dispersion of the guar gum sample was 6993 cps at 25 °C. Other materials, namely Avicel PH 102 (FMC Biopolymer, Brussels, Belgium), magnesium stearate (Riedel Mannouen, Germany), Aerosil 200 (WerksbosChemigung, Germany) and Croscarmellose sodium (FMC Biopolymer, Brussels, Belgium) were of pharmacopeial grade (US/NF).

2.2. In vitro studies

2.2.1. Preparation of the core tablets

The core tablets of theophylline were prepared by the direct compression method. Each core tablet (160 mg) consisted of 100 mg theophylline, 48 mg Avicel PH102, 1.25 mg magnesium stearate, 0.75 mg Aerosil 200 and 10 mg Croscarmellose sodium. The powders were thoroughly mixed and passed through a 0.355 mesh sieve.

2.2.2. Preparation of the compression coated tablets

The core tablets were placed in the die cavity of a laboratory hydraulic press. Depending on the design, a coating mixture was used for the outer shell compression coating. The composition of the coating mixture is shown in Table 1. The weight of the coating around the tablets was 500 mg. The tablets were prepared using the same technical parameters at every turn.

Three mg of non-radioactive samarium oxide (152-Sm) was added to the core tablet of the compression coated tablets (Formulation T2) that were to be used in the in vivo studies (Table 2). The compression coated tablets containing non-radioactive samarium oxide (T2-S) were radiolabelled by irradiation in a neutron flux of 10^{12} n cm^{-2} s^{-1} to produce radioactive 153-Sm, 24 h prior to dosing in Çekmece Nuclear Research and Training Center (İstanbul, Turkey). 153-Sm activity was measured as 1 MBq for a single formulation (Capintec CRC120, Ramsey, NJ, USA).

Table 2
Composition of guar gum-based colon-targeted tablet containing samarium oxide (T2-S) used in vivo study.

Ingredients	Quantity (mg)	
	Core	Coat
	Formulation	Formulation
Theophylline	100	–
Avicel PH 102	45	260
Aerosil 200	0.75	7.5
Croscarmellose sodium	10	
Mg stearate	1.25	7.5
Guar gum	–	225
Samarium oxide	3.00	
Total weight (mg)	160	500

The physicopharmaceutical properties of T2-S formulation were tested. For this purpose twenty tablets were tested for weight (AB 104, Mettler Toledo, Switzerland), thickness (Vernier Caliper, portable dial hand micrometer, Russia), diametrical crushing strength (CGS, Hardness tester HDT 1V-3, Germany) and friability (Roche friability tester). The mean values were calculated with confidence intervals (CI).

Six tablets were randomly selected to perform the enteric coated (USP 26) disintegration procedure, using a disintegration tester (Aymes, Turkey). The disintegration times were reported in hours. For the determination of the drug content, ten tablets were individually weighed and then each of them were dissolved in 150 ml of pH 6.8 phosphate buffer solution. The drug content of the tablets was assayed spectrophotometrically at 270 nm after filtration and dilution. The analytical method validation was carried out according to USP 27.

2.2.3. In vitro release studies

A dissolution test was conducted in USP I apparatus at 100 rpm and at a temperature of 37 °C. The studies were carried out in simulated gastric juice at a pH of 1.2 followed by simulated intestinal juice at a pH of 6.8. The tablets were tested for drug release for 2 h in pH 1.2, based on the assumption that the average gastric emptying time is about 2 h [28,29]. Five mL of galactomannanase enzyme (from Aspergillusniger (5.9 U/mL) was added to the pH 6.8 medium at 4 h. The final concentration (32.8 U/L) was decided experimentally based on the previous studies [20,21,24,30]. Samples were taken at predefined time intervals from the same position each time and were analyzed spectrophotometrically at 270 nm. There were no extra peaks observed with the galactomannanase enzyme at 200–400 nm. The stability of theophylline was confirmed in the presence of the enzyme during the dissolution studies for 24 h.

Table 1
The content of the compression coated tablets.

Code	Core tablet (mg)	Samarium oxide (mg)	Guar gum (mg)	Avicel PH 102 (mg)	Aerosil 200 (mg)	Mg stearate (mg)
T1	160	–	200	285	7.5	7.5
T2	160	–	225	260	7.5	7.5
T2-S	160	3	225	260	7.5	7.5
T3	160	–	250	235	7.5	7.5
T4	160	–	350	135	7.5	7.5
T5	160	–	450	35	7.5	7.5