Original Article

Formulation and characterization of calcium chloride guar gum microsphere of theophylline

Abstract

Aim: The aim of the present work was to formulate and characterize an effective colonic drug delivery system for nocturnal asthma based on the time- and pH-dependent system. **Materials and Methods:** The microsphere of calcium chloride guar gum was prepared by using theophylline. It was prepared by the method of emulsification and coating was done by the method of solvent evaporation with the pH-sensitive eudragit polymers. The prepared microsphere was characterized by particle size, surface morphology, entrapment efficiency, and degree of swelling. **Results:** The drug release was confirmed by the *in vitro* drug release in various pH progression medium and dissolution medium. The controlled release of theophylline after a lag time was achieved with developed formulation for colon drug delivery. **Conclusion:** The pH-dependent solubility behavior of eudragit and gelling properties of guar gum are found to be responsible for delaying the release.

Key words:
Colon, delay release, microsphere, targeted drug delivery

Introduction

Colon is one of the promising ways for systemic delivery of drug moiety.[1] It is not only concerned with the local treatment of disease but also potential delivery of protein and peptide drug molecules.[2] Delivery of drug into the colon helps in reducing the side effects in colon via gastrointestinal (GI) tract by maximizing therapeutic index through protection of a drug from degradation in the stomach and small intestine and then ensures abrupt or controlled release in the proximal colon. Delivery of drug in colon can be achieved using polymers such as guar gum, pectin, chitosan, insulin, alginate, cellulose, and their derivatives.[3,4] There are various primary approaches for achieving colon targeting, including delivering of drug as a prod rug, by delaying the drug release, or by microbial way.[5,6] However, these approaches have many disadvantages or have some limitations that enforce over new colon developed system which are better than former ones. Colonic drug delivery is useful to improve treatment of disease depending on the diurnal rhythm such as asthma and arthritis. The pH-dependent system exploits the generally accepted view that pH of human GI tract increases progressively from the stomach, small intestine, and then to colon. Most commonly used polymer for the coating is eudragit which is methacrylic acid copolymer.[7]

Guar gum is a naturally occurring polysaccharides obtained from the seeds of *Cyamopsis tetragonolode* having gelling property that retards release of the drug from the dosage form as well as it is susceptible to degradation in the colonic environment.[8]

The purpose of this research work was to achieve the chronotherapy for the bronchial asthma. In order to get the drug release into the colon, the prepared microsphere was coated by pH-dependent polymer.

Materials and Methods

Theophylline was obtained as a gift sample from M/s. Cipla Ltd., Mumbai, India. Guar gum was procured from HiMedia

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laboratories Pvt. Ltd., Mumbai, India. Light liquid paraffin, calcium chloride, Span 80, Span 85, and Tween 80 were procured from Central drug house Pvt. Ltd., Mumbai, India. Eudragit S-100 and L-100 were obtained as a gift sample from M/s. Roehm chemische, Fabrik, GmBH, Germany. All other chemicals used were of analytical reagent grade and were used as received.

Preparation of guar gum microspheres

Guar gum microspheres were prepared by using the method reported by Chaurasia *et al*. with slight modification.[9] Guar gum dispersion was prepared by mixing of guar gum with Tween 80 (0.2% w/w) followed by the addition of distilled water in which THEO was previously dissolved and allowed to swell for 2 h. This aqueous phase was dispersed in light liquid paraffin (100 ml) containing span 80 (0.5% w/w) and maintained at 60°C. This dispersion was stirred using a mechanical agitation with propeller stirrer (Remi, Mumbai, India) at 2000 rpm. After 10 min, concentrated sulphuric acid (0.2 ml) was added to the dispersion followed by the addition of calcium chloride (0.5 ml) and stirring was continued for 2 h at constant speed. The microspheres were centrifuged (CFC-FREE, C-24, Cooling centrifuge, REMI, India), washed with n-hexane, methanol, and acetone to remove the oil, and dried under vacuum oven (Dolphin, India). Guar gum microspheres were prepared using different drug: polymer ratios, i.e., 1:1, 1:2, and 1:4.

Compatibility study

Fourier transform infrared spectroscopy (FTIR) was carried out to confirm the cross-linking reaction between guar gum and drug theophylline [Figure 1a and b].

The KBr discs of uncoated guar gum microspheres (without drug) and pure guar gum were prepared and scanned in an FTIR spectrophotometer (Perkin Elmer - Spectrum RX-I, Lambda, USA). The scanning range and resolution were 400–4000 cm^{-1} and 4 cm^{-1}, respectively.

Encapsulation of guar gum microspheres

Guar gum microspheres (core) were coated with eudragit polymer by oil-in-oil solvent evaporation method.[10] Coating solution (5%) was prepared by dissolving 1:1 mixture of Eudragit S-100 and Eudragit L-100 in 10 ml of organic solvent (acetone: ethanol, 1:1). Guar gum microspheres (50 mg) were dispersed in this organic phase and poured in 70 ml light liquid paraffin containing 1% w/v Span 85. The system was stirred at 1000 rpm speed using a mechanical stirrer at room temperature for 3 h to allow the evaporation of solvent. Finally, the coated microspheres were collected by centrifugation, washed with n-hexane, freeze dried overnight (Heto Drywinner, Denmark), and kept in airtight container for further studies.

Surface morphology and particle size

The morphology and appearance of microparticles were examined by scanning electron microscopy (SEM). The prepared microspheres were freeze dried at -30 °C for 48 h and coated with gold palladium under an argon atmosphere for 150 s to achieve a 20 nm film (Sputter coater, SCD 004, BAL-TEC, Balzers, Furstentum, Lienchestein). The coated samples were then examined with a scanning electron microscope (Jeol JSM-1600, Tokyo, Japan). The particle size of prepared microspheres was determined by optical microscope using a calibrated ocular micrometer (Leica, Germany) [Figure 2a and b].

Entrapment efficiency

Entrapment efficiency was determined by using the method reported by Chaurasia *et al*. An accurately weighed quantity of guar gum microspheres (equivalent to 50 mg of theophylline) was incubated in 10 ml of phosphate-buffered saline (pH 7.4). The sample was ultrasonicated for three consecutive periods of 5 min each, with a resting period of 5 min each and kept for 48 h for complete extraction of theophylline. The solution was centrifuged and supernatant was assayed for theophylline spectrophotometrically (UV-1800 Spectrophotometer, Shimadzu, Japan) at 271.5 nm. Each determination was made in triplicate.

Swellability

A known weight (100 mg) of guar gum microspheres and Eudragit-coated guar gum microspheres were placed in enzyme-free simulated intestinal fluid and allowed to swell up to constant weight at 37 ± 0.5 °C in the dissolution apparatus (USP XXIII Model DT-06, Erweka, Germany). The microspheres were periodically removed, blotted with filter paper, and their change in weight was measured until attainment of equilibrium. The swelling ratio was then calculated using formula:

$$SR = Wt_g - Wt_0/Wt_g$$

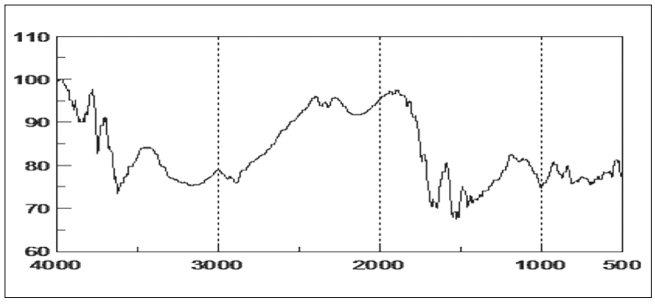

Figure 1(a): FTIR spectra of guar gum

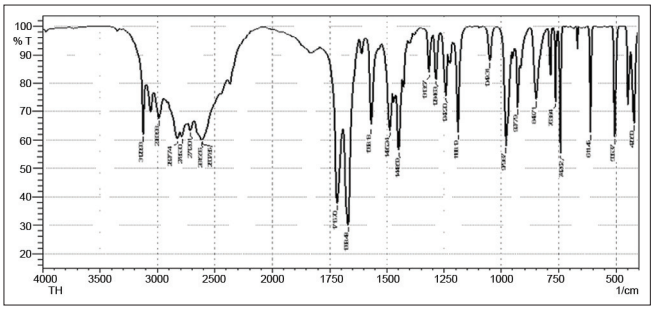

Figure 1(b): FTIR spectra of theophylline

where SR = swelling ratio, Wt_0 = initial weight of microspheres, and Wt_g = final weight of microspheres.

In vitro drug release study in simulated GI fluids

The dissolution apparatus (rotating paddle type) used at rotation speed of 100 rpm. The system was thermostated at 37 °C. Drug release was measured from accurately weighed amount of microspheres, equivalent to 100 mg of THEO, added to 500 ml of dissolution medium. For microspheres, simulation of GI transit conditions was achieved by pH progression medium.[11] The pH of the dissolution medium was kept 1.2 for 2 h with 0.1 N HCl. Then 1.7 g of KH_2PO_4 and 2.225 g of $Na_2HPO_4.2H_2O$ were added adjusting the pH 4.5 with 1.0 M NaOH and release rate study was continued for further 2 h. After 4 h, the pH of dissolution medium was adjusted to 7.0 and maintained up to the end of the study. The final volume in all cases was 500 ml. The samples were withdrawn from dissolution medium at various time intervals using a pipette fitted with a microfilter and analyzed spectrophotometrically at 271.5 nm. All dissolution studies were performed in triplicate [Figure 3a and b].

Results and Discussion

Guar gum microspheres of theophylline were successfully prepared by emulsification technique. Microspheres were prepared by using different drug: polymer ratios. The formulations of microspheres, i.e., GETM 1, GETM 2, and GETM 3 containing theophylline: guar gum in ratios of 1:1, 1:2, and 1:4, were prepared. These guar gum microspheres were coated with ES and EL (1:1) by oil-in-oil solvent evaporation method. Intermolecular interaction between guar gum and theophylline was confined by FTIR-spectroscopy. Uniform particle size and surface morphology showed a surface cross-linked and almost spherical microspheres. The coated microspheres were found to be of spherical shape as observed in SEM photomicrographs. The entrapment efficiency of guar gum microspheres varied from 60.42 ± 2.12% to 71.46 ± 2.46% with varying guar gum concentration from 1% w/v to 4% w/v. The highest entrapment efficiency was found with microspheres prepared using 4% guar gum. The effect of drug: polymer ratio on the particle size, percentage drug entrapment,

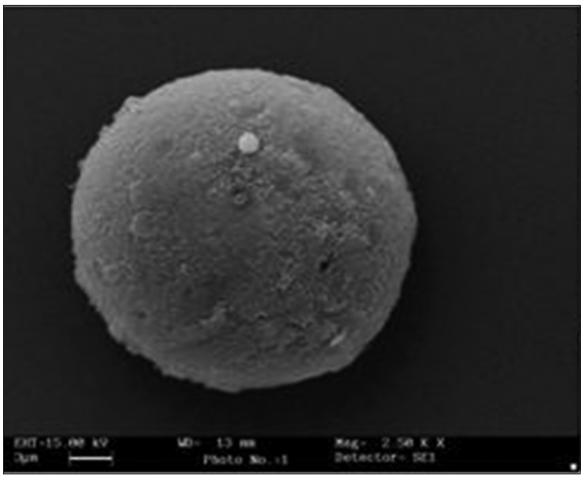

Figure 2(a): SEM of uncoated guar gum microsphere

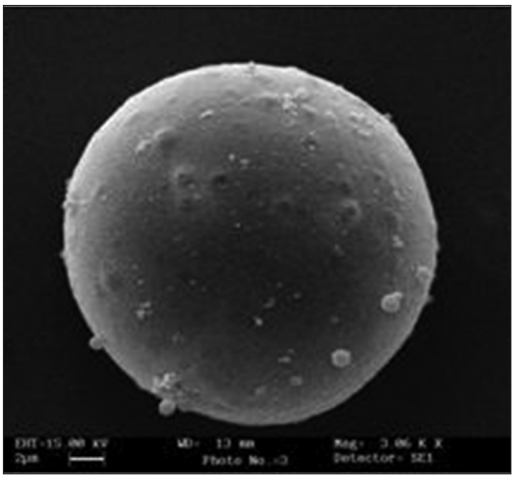

Figure 2(b): SEM-coated guar gum microsphere

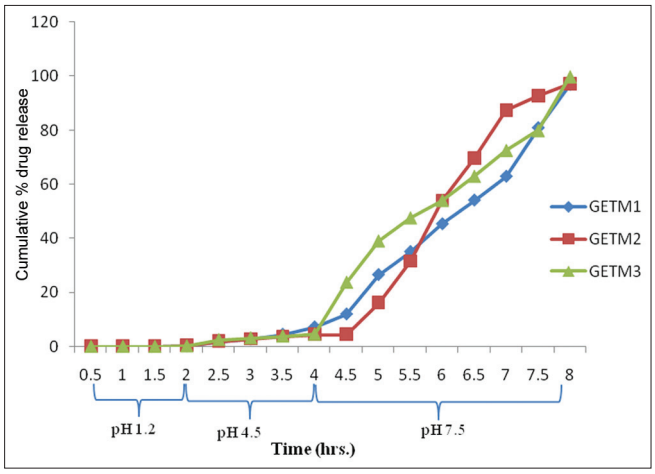

Figure 3(a): *In vitro* theophylline release of guar gum microsphere containing different drug: polymer ratio in progressive pH medium

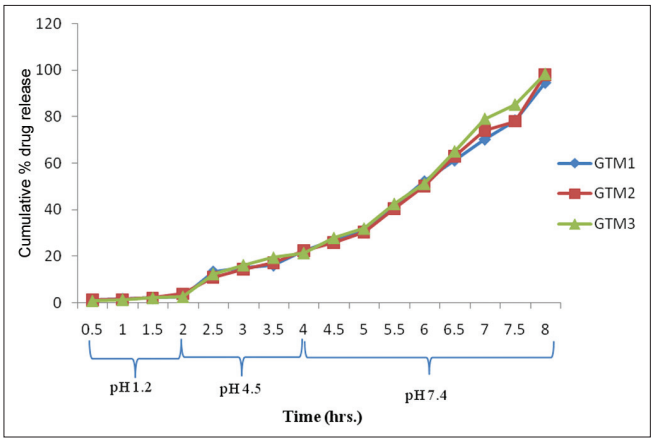

Figure 3(b): *In vitro* theophylline release of guar gum eudragit-coated microsphere containing different drug: polymer ratio in progressive pH medium

Table 1: Effect of drug: polymer ratio on the particle size, percentage drug entrapment, and degree of swelling of various guar gum microspheres

Drug: polymer ratio	Formulation code	Mean diameter (μm)	Drug entrapment	Degree of swelling
1:1	GTM 1	19.99±2.52	59.40±2.13	0.88±0.07
1:2	GTM 2	21.65±1.27	63.68±1.76	1.22±0.13
1:4	GTM 3	25.30±2.09	72.46±2.54	1.32±0.19

Table 2: Particle size of eudragit coated guar gum microspheres

Core: coating ratio	Formulation code	Mean diameter (μm)
1:5	GETM 1	42.0±3.98
1:5	GETM 2	44.20±2.89
1:5	GETM 3	51.17±5.50

and degree of swelling of various guar gum microspheres was shown in [Table 1]. And particle size of eudragit-coated guar gum microspheres was also shown in [Table 2]. This significant increment in entrapment efficiency could be attributed due to higher mass of guar gum for distribution. *In vitro* drug release study in pH progression medium *in vitro* theophylline release study of guar gum microspheres and eudragit-coated guar gum microspheres was performed in pH progression medium at 37.5 °C to mimic the physiological condition. The results showed that the rate of release of theophylline from guar gum microspheres was mainly influenced by polymer concentration. And it was observed from eudragit-coated guar gum microspheres that theophylline release was protected from acidic environment by eudragit coating.

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