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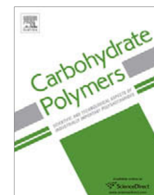

In vitro characterization of coevaporates containing chitosan for colonic drug delivery

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ABSTRACT

A relative simple drug delivery system in the form of coevaporates were prepared and analyzed. They were based on chitosan (CS), a polysaccharide that undergoes specific degradation by colonic enzymes. Enteric polymers, namely cellulose acetate phtalate (CAP) and hydroxypropylmethylcellulose phtalate (HPMCP), were incorporated, due to their insolubility in environments presenting low pH values. The systems were physically characterized, demonstrating that CS affects the swelling properties of the samples. The ability of these systems to reach the colonic region was assessed *in vitro* in simulated gastric, enteric and colonic fluids. Korsmeyer–Peppas and Weibull models were applied to analyze the drug release kinetics and the results suggested that the drug release from the coevaporates follows a complex release mechanism, in which several processes, including diffusion, swelling, and erosion, are involved and may occur simultaneously. The results demonstrated that it is possible to prepare relative simple drug carrier systems able to reach the colonic environment, since their swelling capacity can be controlled by varying the composition.

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1. Introduction

The colon is a potential site for targeted drug delivery, especially for local treatment of some diseases, such as ulcerative colitis, Crohn's disease, colon cancer, and amebiasis. Delivering a drug molecule directly to its site of action may allow a lowering of the administered dose, consequently reducing potential systemic side effects, which constitute a major issue in therapy (Basit, 2005). In order to achieve specific colonic drug delivery, different approaches have been reported over the last years (Sinha & Kumria, 2003). Most techniques used to deliver drugs to the colon are based on the variation of the pH value throughout the gastrointestinal tract (GIT), enzymatic degradation by colonic bacteria and even the relatively constant transit time in the small intestine (Sinha & Kumria, 2003; Yang, 2008). Enteric formulations have long been clinically used for the treatment of such pathologies, but with limited success, since drug release in this case depends on pH variation.

Recently, a study (McConnell, Short, & Basit, 2008) also showed that microbially triggered drug delivery to the colon was more site-specific than pH-responsive drug delivery. A novel formulation able to provide efficient treatment of colon diseases should combine biopolymer colloidal drug carriers that allow prolonged residence time and controlled release of the drug at the action's site.

Chitosan (CS) is a natural polysaccharide extensively used for the development of solid dosage forms for drug delivery to the colon. The rationale for the development of a polysaccharide based delivery system for colonic action is the ability of the colonic microflora to degrade various types of polysaccharides that escape small bowel digestion (Vandamme, Lenourry, Charrueau, & Chaumeil, 2002).

Previous findings from our research group have demonstrated the reliability of such systems. For example, microparticles with CS and alginate (AL) or pectin (PC), cross-linked or not with glutaraldehyde were obtained by complex coacervation. Although the particles could reach the colon, as verified by *in vivo* assays in rats (Lucinda-Silva & Evangelista, 2003), a great amount of the incorporated drug, isoniazid, was rashly *in vitro* released in gastric and enteric simulated juices. This inadequate premature release resulted from the swelling process the particles underwent. Others partial results showed that the addition of gastric resistant polymers, among them cellulose acetate phtalate (CAP) and hydroxypropylmethylcellulose phtalate (HPMCP), is able to decrease considerably the swelling degree and, consequently, the rashly release of the drug in the gastric milieu (Oliveira, Ferrari, & Evangelista, unpublished results).

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The aim of the present work was to prepare relative simple systems constituted by coevaporates containing metronidazole (MT), CS and gastric resistant polymers and to assess their ability to release the drug in the colonic region. Additionally, the mechanism responsible for drug release was analyzed in order to improve the design of colonic drug delivery systems.

2. Materials and methods

2.1. Materials

Metronidazole, hydroxypropylmethylcellulose phtalate and cellulose acetate phtalate were purchased from Sigma (São Paulo, Brazil) and chitosan was obtained from Galena (Campinas, Brazil). All other reagents and solvents were of analytical grade.

2.2. Methods

2.2.1. Preparation of coevaporates

Coevaporates were prepared by a solvent evaporation method. At first, each compound was dissolved in an appropriated solvent (acetic acid or sodium hydroxide) under continuous stirring. The dispersions were prepared in the following concentrations: 0.5% QS in 0.1 N acetic acid pH 4.8; 0.5% CAP in 0.05 N sodium hydroxide pH 5.2; 0.5% and 1.0% HPMCP in 0.05 N sodium hydroxide pH 5.1; and 0.5% and 1.0% MT in 0.1 N acetic acid pH 5.2 (Lucinda-Silva & Evangelista, 2003). All samples contained CS and MT, to some of them CAP or HPMCP was added and other samples were compounded with both polymers. The weight composition of the samples is described in Table 1. After mixing all components, the solvents were evaporated in rotating evaporator for 2.5 h at 60 °C under partial vacuum. The samples were then freeze-dried for 24 h. The lyophilized material was manually pulverized with mortar and pestle for 10 min.

2.2.2. Infrared spectroscopy

The IR spectra of the substances alone and of the coevaporates were obtained and analyzed in order to detect if any chemical interaction resulted from the coevaporation process. For this assay, about 2 mg of each the drug, CS, enteric polymers and all coevaporates samples were throughout grounded with KBr and analyzed by infrared spectroscopy (Shimadzu 8300).

2.2.3. Liquid uptake studies

Liquid uptake measurements were carried out using an adapted Enslin apparatus (Cury, Castro, Klein, & Evangelista, 2008). For these studies, each sample was analyzed in simulated gastric fluid (pH 1.2) and simulated enteric fluid (pH 7.4). For the assay, 0.05 g of powdered samples was placed on the sintering filter and the volume of water absorbed after 30, 60, 90 and 120 min was measured with the graduated pipette. The assays were carried out in triplicate and the results expressed as % of liquid uptake in relation to the initial mass of the samples. Statistical analysis of the results was performed by Student's *t*-test with a significance level α of 0.05.

Table 1
Composition of the samples.

Samples	Composition (mg)			
	CS	CAP	HPMCP	MT
CS–0.5MT	100	–	–	50
CS–0.5HPMCP–0.5MT	100	–	50	50
CS–CAP–0.5MT	100	50	–	50
CS–CAP–0.5HPMCP–0.5MT	100	50	50	50
CS–CAP–1HPMCP–0.5MT	100	50	100	50
CS–CAP–0.5HPMCP–1MT	100	50	50	100
CS–CAP–1HPMCP–1MT	100	50	100	100

2.2.4. Particle size analysis

Particle size analysis was performed with a stereoscope Leica MZ APO plus Leica Qwin Image Systems Software. The Feret diameter at 0° of at least 250 particles was measured.

2.2.5. Dissolution tests

The dissolution studies were performed using a Hanson Dissolution Test Station SR8-Plus (Chastworth, USA) based on United States Pharmacopoeia Method I (rotating basket method). The samples containing coevaporates were poured in hard gelatin capsules (size 0) and placed in the rotating basket immersed in 400 ml of simulated gastric fluid (pH 1.2), simulated enteric fluid (pH 7.4) or simulated colonic fluid containing pectinase (pH 5.0). The acceptor fluid was maintained at 37 ± 0.5 °C and the baskets were submitted to rotation at 50 rpm. At appropriated time intervals, 5 ml of the samples were withdrawn and filtered through cellulose acetate membrane (0.45 μm). The filtrate was analyzed by UV spectrophotometry at 277 nm for simulated gastric fluid and 320 nm for simulated enteric and colonic fluids. The related concentrations were calculated using calibration profiles based on absorbance *versus* concentration curves using previously designed and standardized. The corresponding drug release profiles were represented by plots of the cumulative temporal percent amount of drug released (calculated from the total amount of MT contained in each sample).

2.2.6. Kinetics mechanisms

The *in vitro* drug release data were fitted (SigmaPlot 10.0 software) to two release kinetic models, namely Korsmeyer–Peppas (Korsmeyer, Gurney, Doelker, Buri, & Peppas, 1983) and Weibull (Papadopoulou, Kosmidis, Vlachou, & Macheras, 2006), which presented the highest adjusted coefficient of determination. This procedure facilitates de quantitative interpretation of the values obtained in the dissolution assay, since it analyzes the dissolution curve as a function of some parameters related with the pharmaceutical dosage form.

3. Results and discussion

3.1. Infrared spectroscopy

The infrared spectra of the coevaporates showed the typical bands of the pure substances, suggesting that no chemical interaction occurred (Fig. 1). This indicates that the coevaporates correspond to simple physical mixtures of the components; apparently, the drug is homogeneously distributed within all other components of the formulation. Table 2 depicts the main typical bands of the substances signalized in Fig. 1.

3.2. Liquid uptake studies

During the liquid uptake studies, it was observed that the samples swell. Therefore, these results were considered as a measure of swelling. Swellable pharmaceutical systems allow the incorporated drug to be released following a unique and complex fashion. All the samples, i.e., those constituted by mixtures and the pure substances, were analyzed in simulated gastric fluid and simulated enteric fluid. The CAP-containing samples showed higher swelling capacity than the samples containing HPMCP, and this fact is a possible explanation for the lack of influence of the increase of HPMCP concentration on the drug release rate in some fluids.

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