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Chitosan-based controlled porosity osmotic pump for colon-specific delivery system: Screening of formulation variables and in vitro investigation

Hui Liu [a,c], Xing-Gang Yang [a], Shu-Fang Nie [a], Lan-Lan Wei [a], Li-Li Zhou [b], Hong Liu [c], Ren Tang [c], Wei-San Pan [a,*]

[a] School of Pharmacy, Shenyang Pharmaceutical University, 103 Wenhua Road, P.O. Box 122, Shenyang 110016, PR China
[b] School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, 103 Wenhua Road, P.O. Box 122, Shenyang 110016, PR China
[c] Department of Pharmacy, Wuhan General Hospital, 627 Wuluo Road, Wuhan 430070, PR China

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Abstract

A microbially triggered colon-targeted osmotic pump (MTCT-OP) has been studied. The gelable property at acid condition and colon-specific biodegradation of chitosan were used to: (1) produce the osmotic pressure, (2) form the drug suspension and (3) form the in situ delivery pores for colon-specific drug release, respectively. The scanning electron microscopy (SEM) study and the calculation of membrane permeability were applied to elucidate the mechanism of MTCT-OP. The effects of different formulation variables, including the level of pH-regulating excipient (citric acid) and the amount of chitosan in the core, the weight gain of semipermeable membrane and enteric-coating membrane, and the level of pore former (chitosan) in the semipermeable membrane, have been studied. Results of SEM showed that the in situ delivery pores could be formed in predeterminated time after coming into contact with dissolution medium, and the number of pore was dependent on the initial level of pore former in the membrane. The amount of budesonide release was directly proportional to the initial level of pore former, but inversely related to the weight of semipermeable membrane. The effects of variations in the level of citric acid and chitosan in the core formulation on drug release were studied. The different levels of enteric-coating membrane could prevent cellulose acetate membrane (containing chitosan as pore former) from forming pore or rupture before contact with simulated colonic fluid, but had no effect on the drug release. Budesonide release from the developed formulation was inversely proportional to the osmotic pressure of the release medium, confirming that osmotic pumping was the major mechanism of drug release. These results showed that MTCT-OP based on osmotic technology and microbially triggered mechanism had a high potential for colon-specific drug delivery.

Keywords: Microbially triggered; Colon targeting; Osmotic pump; Chitosan; Budesonide

1. Introduction

There has been considerable exploration in developing colon-specific drug delivery systems during the last few years. Targeting drugs to the colon not only ensure direct treatment of colon diseases, but also are utilized as a means of achieving chronotherapy for diseases that are sensitive to circadian rhythm. Furthermore, delivery of drugs to the systemic circulation through colonic absorption provides a novel peroral route of introducing degraded/poorly absorbed peptides and proteins because of the relatively low proteolytic enzyme activities and longer retention time in the colon.

The various approaches developed for the purpose of achieving colonic targeting include time-controlled delivery systems (Steed et al., 1997; Hebden et al., 1999), pH-dependent delivery systems (Markus et al., 2001; Cole et al., 2002), pressure-controlled delivery systems (Muraoka et al., 1998; Shibata et al., 2001), prodrugs (Ahrabi et al., 2000; Maris et al., 2001) and microflora-triggered delivery systems (Brondsted et al., 1998; Katsuma et al., 2002; Yano et al., 2002). Among these approaches, there appears more interest in microflora-activated systems since the abrupt increase of the bacteria population

* Corresponding author. Tel.: +86 24 2395 3241; fax: +86 24 2395 3241.
E-mail address: pharmacymanLH@163.com (W.-S. Pan).

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and associated enzyme activity in the colon represent a non-continuous event that is independent of GI transit time.

Chitosan is a high molecular weight cationic polysaccharide (Singla and Chawla, 2001). It has favorable biological properties such as non-toxicity and biocompatibility. Chitosan has been evaluated for its potential as colon-specific drug delivery in several forms such as capsules (Tozaki et al., 1997, 1999, 2002), matrices (Zambito and Colo, 2003), hydrogels (Shu et al., 2001; Zhang et al., 2002), and microspheres (Lorenzo-Lamosa et al., 1998).

Osmotic systems utilize the principle of osmotic pumping for the delivery of drugs. Various types of osmotic pumps and formulation aspects have been reviewed (Verma et al., 2002). Osmotic pump which was patented as OROS-CT has already been established to target the drug locally to the colon for local or systemic therapy (Theeuwes et al., 1990). OROS-CT was designed with a 3–4 h post-gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. This system was essentially a time-controlled release system. Even through the transit time in small intestine is rather consistent, high variation of gastric retention time makes this system complicated in predicting the accurate location of drug release.

With all these considerations in mind, we designed a new microbially triggered colon-targeted osmotic pump (MTCT-OP) based on chitosan. Fig. 1 shows schematic diagram of MTCT-OP, which consists of an osmotic core (containing drug and chitosan with organic acid as excipient), an inner semipermeable membrane layer composed of the mixture of cellulose acetate and chitosan powder, and an outer enteric-coating layer. During its transit through the GI tract, MTCT-OP remains intact in the stomach due to the enteric-coating layer, but this layer will dissolve in the small intestine, where pH is above 6, and water is imbibed into the core. The acid aqueous environment produced by dissolution of organic acid in tablet core causes chitosan to swell and to constantly form a flowable gel through which water-insoluble drug dispersed. However, the drug is still not released because the pore former chitosan in the semiperme-

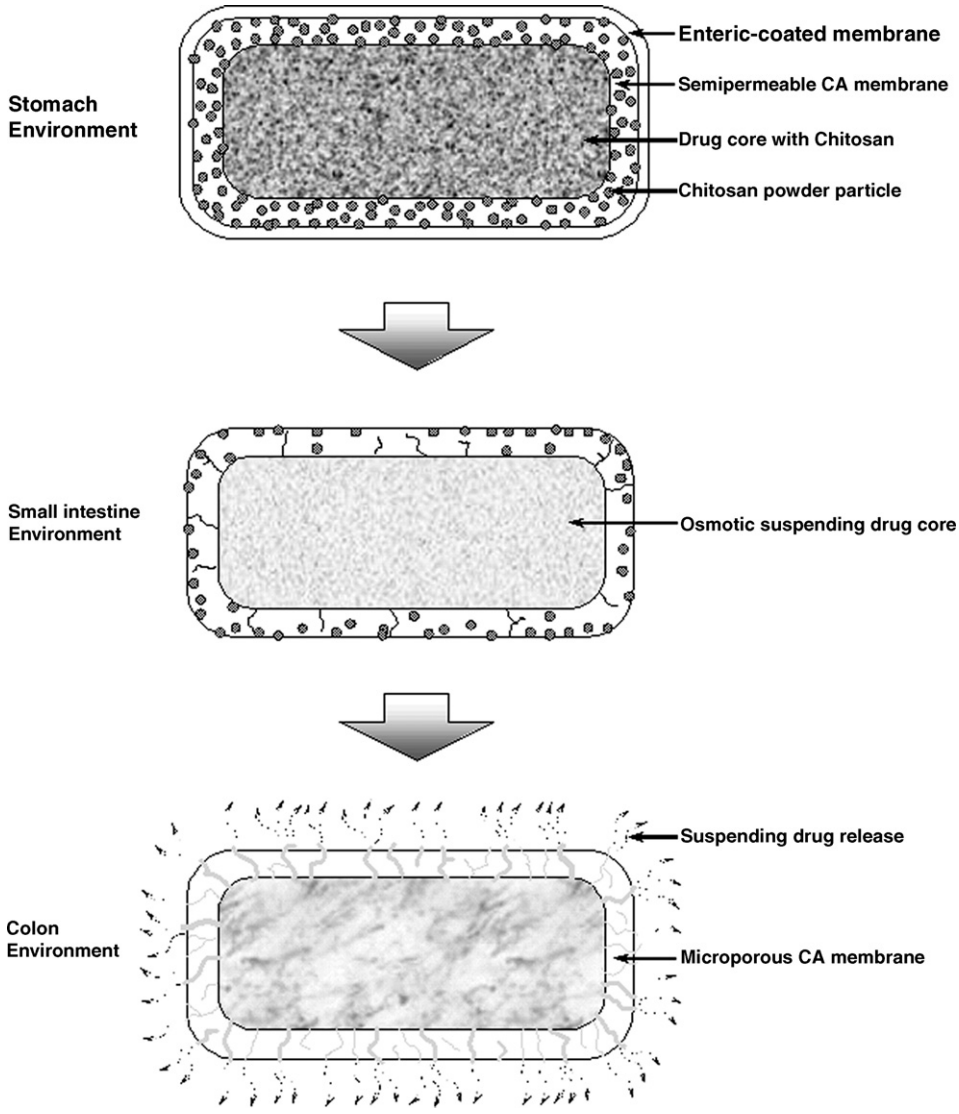

Fig. 1. Schematic diagram of MTCT-OP.