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A novel plug-controlled colon-specific pulsatile capsule with tablet of curcumin-loaded SMEDDS

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ABSTRACT

This study developed and evaluated a colon-specific pulsatile capsule with tablet of self-microemulsifying drug delivery system (SMEDDS). This system is based on an impermeable capsule containing a rapid-disintegrating curcumin-loaded SMEDDS tablet inside it, and a highly methoxylated pectin (H-pectin)/lactose tablet plugged in the capsule mouth. The SMEDDS tablet enhanced the solubility of curcumin, a water-insoluble drug. An *in vitro* release study of the pulsatile capsule showed a typical pulsatile release profile with a specific lag time. The lag time, which determines the efficiency of colon-specific delivery, could be regulated by varying the H-pectin/lactose ratio. Pectinase and rat cecal contents added to the release medium significantly shortened the erosion time, which proved that the H-pectin plug is sensitive to enzyme degradation. These results show that the pulsatile capsule with SMEDDS tablet has potential for the colon-specific delivery of water-insoluble drugs.

1. Introduction

Oral colon-specific drug delivery systems have recently attracted much interest for their application in the local treatment of a variety of colonic diseases, and their potential for protein and therapeutic peptide delivery (Sinha et al., 2007). However, designing oral colon-specific drug delivery systems has some challenges. First, such drug delivery systems need to protect the incorporated drugs from enzymatic and chemical degradation while traveling through the upper gastrointestinal (GI) tract. Second, the system should release the drugs immediately upon reaching the colon. Then, the released drugs need to be absorbed efficiently to be therapeutically effective (Patel & Amin, 2011).

A time-dependent pulsatile capsule drug delivery system has recently been developed (Krogel & Bodmeier, 1998, 1999). The system consists of an insoluble drug-filled capsule body with an erodible plug tablet at the capsule opening. The lag time of drug release is determined mainly by the erosion properties of the plug tablet. These pulsatile capsules were used to efficiently deliver a water-soluble drug to the colon (Liu et al., 2012). However, water-insoluble drugs are incompletely release in the colon because the colon contains less fluid than the small intestines and stomach (Yehia, Elshafeey, & Elsayed, 2011).

Many of the current drugs have poor solubility and are poorly absorbed. Therefore, their solubility and bioavailability should be improved. Recently, much attention has focused on self-microemulsifying drug delivery system (SMEDDS). SMEDDS is already one of the most common strategies for increasing hydrophobic drug solubility and adsorption (Patel & Sawant, 2009). The SMEDDS is a homogeneous, clarifying, stable liquid preparation that contains a mixture of oils, surfactants, cosurfactants, and a drug. SMEDDS form microemulsions under the gentle agitation provided by the digestive motility in the stomach and intestines. SMEDDS is a promising approach to improving the solubility and enhancing the oral bioavailability of poorly water-soluble drugs. Liquid SMEDDS formulations suffer from a few drawbacks, such as inconvenient usage, limited dosage preparations, finite shelf life, and incompatibility with soft gelatin capsules (Sander & Holm, 2009). Normally, solid dosage forms are more stable and convenient than liquid forms. Liquid SMEDDS have been transformed for use with solid particles (powders, granules, or pellets), which could be placed inside capsules or compressed into tablets through techniques such as spray drying (Yi, Wan, Xu, & Yang, 2008), adsorption on solid carriers (Kim, Kang, Oh, Yong, & Choi, 2012), and solid dispersion (Heo et al., 2005). Solid SMEDDS combine the advantages of liquid SMEDDS

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with those of solid drug delivery systems, while avoiding the disadvantages of liquid formulations. Thus, the new solid SMEDDS demonstrate more commercial potential and higher patient compliance.

Curcumin (CUR) is a natural polyphenol extracted from *Curcuma longa* that acts against cancer, heart disease, and Alzheimer's disease. The efficacy of CUR against colon cancer has also received increasing attention (Chauhan, 2002; Elias, Anil, Ahmad, & Daud, 2010; Prajakta et al., 2009). British investigators have recently shown that CUR interferes with the proliferation of various types of colon cancer (Patel & Majumdar, 2009). Unlike other anticancer drugs that weaken the immune system, CUR actually enhances it by acting as an "immunorestorer" (Shehzad, Wahid, & Lee, 2010). However, CUR is poorly water soluble, which results in low oral bioavailability.

Natural polysaccharides have been used to deliver drugs specifically to the colon because of the abundance of various bacteria and hydrolytic enzymes that can degrade disaccharides, trisaccharides, and polysaccharides (Kosaraju, 2005). Pectin, a non-toxic polysaccharide obtained from plant cell walls, is selectively degraded in the colon (Sriamornsak, 2011; Wong, Colombo, & Sonvico, 2011). Thus, many pectin-based, colon-specific drug delivery systems have been developed in recent years (Liu, Fishman, Kost, & Hicks, 2003; Oehme, Valotis, Krammer, Zimmermann, & Schreier, 2011).

We designed a pulsatile capsule with a SMEDDS tablet that not only enhances the solubility, dissolution rate, and oral bioavailability of CUR based on the SMEDDS tablet, but also can deliver CUR to the colon using an impermeable capsule with a highly methoxylated pectin (H-pectin)/lactose plug in its opening and an enteric cap that covers the capsule mouth. The formulation of the CUR-loaded SMEDDS tablet was optimized and the reconstitution properties of the CUR-SMEDDS tablet were evaluated. The effects of the plug tablet formulation and the different *in vitro* release media were investigated to study the drug release mechanism.

2. Experimental

2.1. Materials

The following materials were obtained from commercial suppliers and used as received: curcumin (CUR, 98.5%, Zhejiang Dongsheng Reagent Co., Ltd, China), high methoxy pectin (H-pectin, the degree of esterification is should be 85%, Quzhou Pectin Co., Ltd, China), pectinase (Tianjin Lihua Enzyme Preparation Co., Ltd, China), lactose (Meggle Granulac200, Meggle, Germany), ethyl cellulose (Ethocel, Colorcon Co., Ltd, China), ethyl oleate (EO, Tianjin Guangfu Chemical Co., Ltd, China), Cremophor RH40 (BASF, Germany), Transcutol P (Gattefosse, France), microcrystalline cellulose (MCC, FMC, USA), talcum powder, Sodium carboxymethyl starch and magnesium stearate (Anhui Shanhe Pharmaceutical Co., Ltd, China), gelatin capsules, enteric capsules and enteric cap (Guangzhou Chaozhou Co., Ltd, China). All other reagents were of analytical grade.

Single punch tablet press (Shanghai Yuandong Pharmaceutical Machinery Factory, China) was used to prepare tablet. A spectrophotometer (UV-3150, Shimadzu, Japan) was used to determine the drug concentration in plasma. Male Sprague-Dawley rats (250 ± 20 g) were supplied by the Laboratory Animal Center of Chongqing Medical University. The experimental procedures were approved by the institutional animal ethical committee and were in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Preparation of impermeable capsules

Ethyl acetate, dichloromethane, and ethanol were mixed in an Erlenmeyer flask at a ratio of 4:0.8:0.2. Ethyl cellulose (EC) was then added into the mixture to produce 120 g/l of EC solution, which was placed inside uncapped gelatin capsules (size 0) fixed onto a self-made foam board. The capsules were refrigerated at 4 °C for 24 h to evaporate the solvent, and then placed in water to dissolve the gelatin models. The weights of the resultant impermeable capsule bodies were 77.66 mg ± 0.58 mg ($n = 5$).

2.3. Preparation of erodible plug tablet

H-pectin and lactose were sieved through a 180 μm sieve and blended in a mortar for 10 min. Then, 1% talcum powder, which acts as an external lubricant to prevent the tablets from sticking to the punches, was added and mixed in for 5 min. The 6 mm diameter plugs were prepared *via* direct compression using a single punch tablet press. The tablets weighed 100 mg, with a hardness of 50 N.

2.4. Preparation of liquid CUR-SMEDDS

Based on preliminary studies, the optimized blank self-emulsifying formulation contained 30% ethyl oleate (w/w) as the oil phase, 17.5% Transcutol P (w/w) as the cosurfactant, and 52.5% Cremophor RH40 (w/w) as the surfactant. The CUR-SMEDDS was prepared by mixing 120 mg of CUR and 1 g of blank SMEDDS with gentle stirring at room temperature. After complete dissolution, a clear and transparent CUR-SMEDDS solution was obtained.

2.5. Preparation of CUR-SMEDDS tablet (T-SMEDDS)

The wet granulated tablet formula contained 18.1% liquid CUR-SMEDDS (containing active ingredient, w/w), 16.2% mannitol (adsorbent, w/w), 16.2% citric acid (adsorbent, w/w), 32.3% microcrystalline cellulose (adsorbent, w/w), 16.2% sodium carboxymethyl starch (disintegrant, w/w) and 1% magnesium stearate (lubricants, w/w). The powders (mannitol, citric acid, and microcrystalline cellulose) were sieved through 180 μm mesh and blended in a mortar for 15 min. The liquid CUR-SMEDDS was then added slowly into the resultant powder mixture and blended for 10 min. Water, which acts as a wetting agent, was added slowly to the blend to prepare the wet granules. The resultant granules were spread evenly on a tray and dried at 50 °C for 1 h. After adding 1% magnesium stearate (lubricants, 1%, w/w), the final granules were mixed for 5 min. The resultant blend was passed through a 1.25 mm sieve and pressed into 200 mg tablets using 6.0 mm shallow concave punches with a single punch tablet press.

2.6. Assembly of the pulsatile capsule

The T-SMEDDS were inserted into the impermeable capsule bodies, and erodible H-pectin/lactose plugs were then placed over the mouth of the capsules and positioned flush with the end of the impermeable body (Fig. 1). The capsules were enclosed in an enteric cap (the thickness of the cap is 0.11 mm), and the joint of the capsule was sealed with a small amount of 8% EC solution. It is very important to maintain the distance between the plug tablet and the rapid-disintegrating tablet. Otherwise, the reproducibility of the lag time would be significantly affected.

2.7. Reconstitution properties of the CUR-SMEDDS tablets

2.7.1. Droplet size and zeta potential determination

A CUR-SMEDDS tablet (200 mg) was placed in 200 ml of distilled water and stirred for 30 min in darkness on a magnetic stirrer.

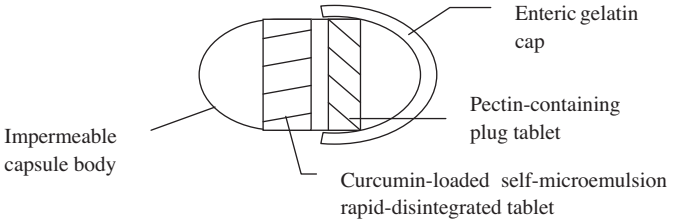

Fig. 1. Configuration of colon-specific plug-controlled pulsatile capsule delivery system with curcumin-loaded self-microemulsion tablet.

The resulting sample (15 ml) was filtered through a 0.45 μm filter membrane. The average droplet size and zeta potential of the microemulsion droplets from the CUR-SMEDDS tablet were determined *via* laser light scattering at 25 °C using a Malvern Zetasizer (Nano-ZS, Malvern Instruments, UK). The droplet size and zeta potential of the initial liquid CUR-SMEDDS were also assessed as described above.

2.7.2. Differential scanning calorimetry (DSC)

Thermograms of the blank SMEDDS, liquid CUR-loaded SMEDDS, blank adsorbents, T-SMEDDS powders, and the pure drug were obtained using a DSC instrument equipped with an intracooler. Each sample was heated from 100 °C to 300 °C at a rate of 10 °C/min in a nitrogen atmosphere.

2.7.3. Disintegration time

The disintegration time of tablet was performed by a disintegration tester (ZBS-6C, Tianjin, China) at 37 °C. Six tablets were tested to report the average disintegration time.

2.8. Determination of the percentage of remaining plugs

The percentage of remaining plugs was determined using a water bath oscillator at 75 times/min and 37 °C ± 0.5 °C. The plug tablet (100 mg) was placed in a flask filled with 100 ml of release medium. The release medium included HCl solution (0.1 M, pH 1.2), phosphate buffer solution (pH 5.0), phosphate buffer solution (pH 6.8, PBS 6.8), pectinase solution (0.5% pectinase in citrate buffer solution, pH 5.0), and rat cecal content medium (pH 7.4). The rat cecal content medium was prepared according to procedures described by Liu et al. (2012). The plugs were taken out at the predetermined time points and dried to a constant weight at 105 °C in weighing bottles. The percentage of remaining plugs with respect to time was calculated according to the following formula:

$$\text{Percentage of remaining plugs}\,(\%) = \frac{W_d}{W_i} \times 100\%,$$

where W_i is the initial mass of the plug, and W_d is the constant weight of the plug taken out at different time points.

2.9. In vitro dissolution studies

Dissolution studies were performed using a water bath oscillator at 100 times/min and 37 ± 0.5 °C. The liquid SMEDDS, T-SMEDDS, and T-SMEDDS in the impermeable capsule bodies without plugs and caps, or the complete pulsatile capsule were placed in different release medium (200 ml). The release medium included HCl solution (0.1 M, pH 1.2), phosphate buffer solution (pH 6.8), pectinase solution (0.5% pectinase in citrate buffer solution, pH 5.0), and rat cecal content medium (pH 7.4). In addition, the external capsule bodies were weighted with copper wire to ensure that the capsules sank to the bottom of the flask. Samples were collected at predetermined time points and filtered through 0.45 μm filters. A UV–visible spectrophotometer (UV-3150, Shimadzu, Japan) was used to analyze the samples at 424 nm.

3. Results and discussion

3.1. Evaluation of adsorbents for the liquid SMEDDS

Six adsorbent powders were evaluated as carriers for the solid SMEDDS formulation to screen for suitable adsorbent for further research. The ability to adsorb liquid SMEDDS and the dissolution rate of the adsorbents with SMEDDS were evaluated to determine the best adsorbent formulation.

Liquid CUR-SMEDDS was added to six different adsorbents (mannitol, PEG6000, citric acid, Aerosil 200V, microcrystalline cellulose, and starch) to obtain flowing powders, which were evaluated for maximum adsorption capacity.

The dissolution rate, defined as the release percentage at 45 min, is an important characteristic for solid SMEDDS. Many adsorbents had low dissolution rates because of their strong adsorption of the SMEDDS ingredient, which decreases their oral bioavailability.

The drug release properties of the selected adsorbent powders containing the liquid SMEDDS were examined on a water bath oscillator at 100 times/min and 37 °C ± 0.5 °C. Mixed absorbent powders containing liquid CUR-loaded SMEDDS were placed into a 250 ml flask containing 150 ml of water. Samples were collected after 45 min and analyzed using an UV–visible spectrophotometer (UV-3150, Shimadzu, Japan).

As shown in Table 1, Aerosil 200V has the highest maximum adsorption, but the lowest dissolution rate. Among the different adsorbents, microcrystalline cellulose was selected because of its high adsorption capacity and excellent dissolution rate. Mannitol was added to increase the dissolution rate further. Citric acid was added to the mixture of adsorbent powders as a stabilizer because CUR is more stable in acidic environments (Sharma, Gescher, & Steward, 2005).

Microcrystalline cellulose, mannitol, and citric acid were mixed in a 2:1:1 ratio. The maximum adsorption capacity of the mixed adsorbents was 0.583 ± 0.025 (liquid/powder, g/g), and the dissolution rate was 71.8% ± 3.6%. Moreover, the solid SMEDDS was transformed into a tablet formulation. Sodium carboxymethyl starch was added as a disintegrant. The CUR-SMEDDS tablets were prepared using liquid CUR-SMEDDS (18.1%, w/w), mannitol (16.2%, w/w), citric acid (16.2%, w/w), microcrystalline cellulose (32.3%, w/w), sodium carboxymethyl starch (16.2%, w/w), and magnesium stearate (1%, w/w).

3.2. Reconstitution properties of T-SMEDDS

3.2.1. Globule size and zeta potential determination

Droplet size distribution after microemulsification is the most important characteristics of SMEDDS because it determines the rate and extent of drug release. The droplet sizes of

Table 1
The maximum adsorption capacity and the dissolution rate of different adsorbents.

Adsorbents	Mannitol	PEG6000	Citric acid	Aerosil 200V	Starch	MCC
The maximum adsorption capacity (liquid/powder)/g/g	0.104 ± 0.012	0.155 ± 0.007	0.101 ± 0.018	1.234 ± 0.014	0.421 ± 0.027	0.444 ± 0.022
Dissolution rate (%)	87.37 ± 3.4	79.24 ± 2.8	83.02 ± 3.5	38.97 ± 1.9	89.14 ± 2.0	85.11 ± 2.3

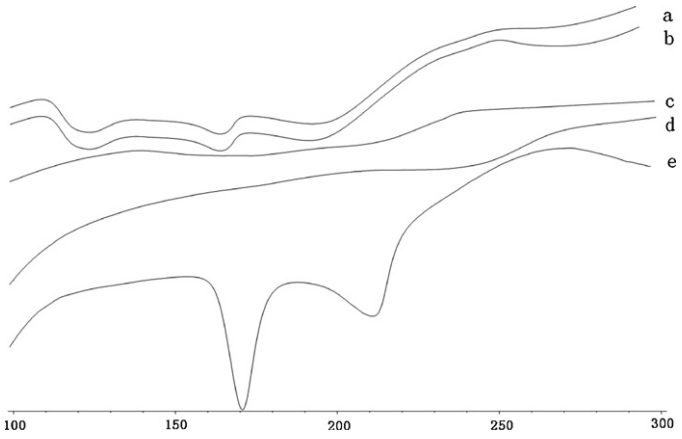

Fig. 2. The DSC thermogram of blank adsorbents (a), T-SMEDDS powders (b), blank SMEDDS (c), liquid CUR-loaded SMEDDS (d) and pure drug (e).

liquid CUR-SMEDDS and T-SMEDDS were 31.1 nm ± 0.07 nm and 78.4 nm ± 2.67 nm, respectively. The composition of the resultant T-SMEDDS microemulsion changed unlike the liquid SMEDDS because small amounts of surfactant, cosurfactant, and oil were retained in the solid adsorbents, which could explain the difference in the droplet sizes between the liquid SMEDDS and the T-SMEDDS. The droplet sizes of both the T-SMEDDS and the liquid SMEDDS were smaller than 100 nm, which further confirmed their self-microemulsion capacity.

3.2.2. Differential scanning calorimetry (DSC)

The DSC thermograms of the blank SMEDDS, the liquid CUR-loaded SMEDDS, the blank adsorbents, the T-SMEDDS powders, and the pure drug are shown in Fig. 2. Pure CUR revealed a sharp, endothermic peak near 170 °C, which might represent the melting point of the drug. Both liquid CUR-SMEDDS and T-SMEDDS did not show any clear peak for CUR, probably because CUR was amorphous because of molecular dispersion in the matrix. The blank adsorbents and the blank SMEDDS also showed few obvious peaks near the CUR peak. No signification alteration in T-SMEDDS reconstitution characteristics were observed even after solidifying the liquid SMEDDS.

3.2.3. Disintegration time

The T-SMEDDS disintegration time was less than 1 min, which corresponded with the rapid drug release requirement.

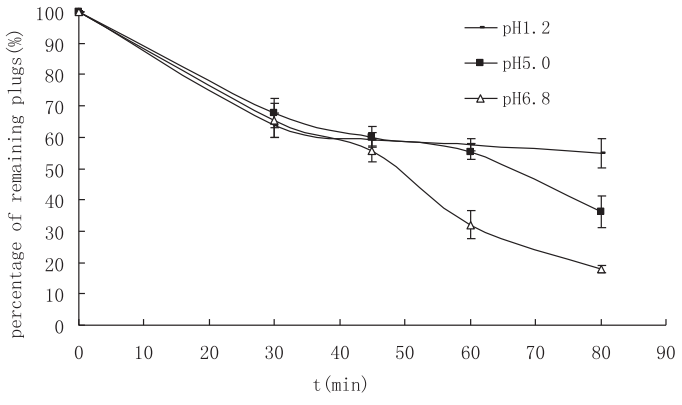

Fig. 3. The influence of pH on the percentage of remaining plugs (H-pectin/lactose = 5:5, w/w, $n = 3$).

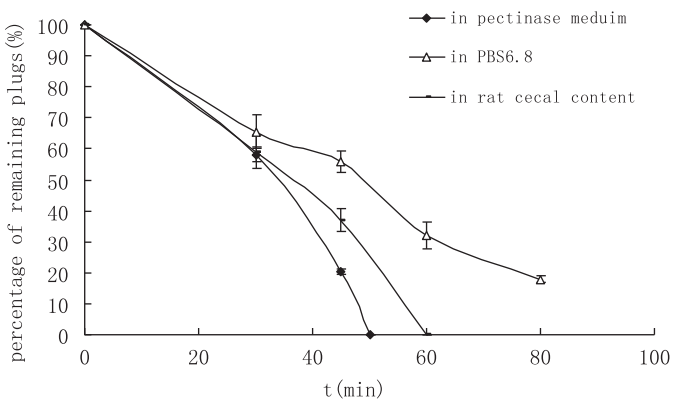

Fig. 4. The influence of the different mediums on the percentage of remaining plugs (H-pectin/lactose = 5:5, w/w, $n = 3$). These studies were carried out in PBS 6.8, pectinase medium and rat cecal content medium, respectively.

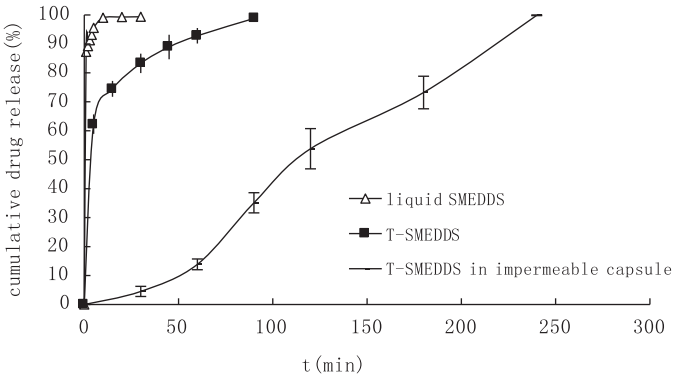

Fig. 5. The drug release comparison between liquid SMEDDS, T-SMEDDS and T-SMEDDS in unplugged, uncapped impermeable capsules ($n = 3$).

3.3. Determination of the percentage of remaining plugs

Pectin can be classified as high methoxylated pectin (H-pectin) or low methoxylated pectin (L-pectin) based on the degree of esterification, higher or lower than 50%, respectively. H-pectin has low aqueous solubility and it forms gels with sugar and acid. L-pectin reacts with calcium ions to form calcium pectinate gel, which is insoluble in the GI tract. Calcium pectinate gel formation leads to the poor reproducibility of the lag time of the pulsatile capsule (data not shown). Therefore, H-pectin is preferred for targeting the colon and for preventing the carrier from reacting with polyvalent ions in the GI tract.

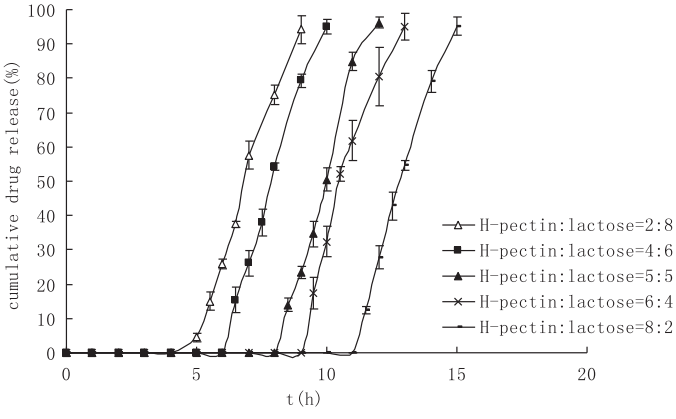

Fig. 6. The influence of the different ratios of H-pectin/lactose on the drug release from the capsules in PBS 6.8 ($n = 3$).

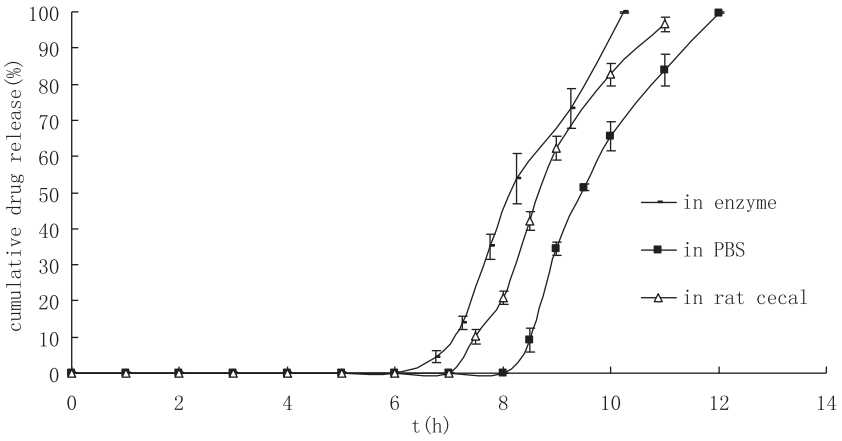

Fig. 7. The influence of different medium on the drug release from the capsules with the plugs (H-pectin/lactose = 5:5, $n = 3$). The dissolution study was performed first in pH 1.2 for 2 h, PBS 6.8 for 3 h, then into the 5% pectinase medium, rat cecal content medium, PBS 6.8, respectively.

The lag time of the pulsatile capsule was determined *via* plug erosion, and the drug was not released until the plug eroded completely. Before investigating the release behavior of the pulsatile capsule, the optimal formulation of the plug was identified by determining the percentage of remaining plugs.

3.3.1. Influence of pH on the percentage of remaining plugs

The percentage of remaining H-pectin/lactose (5:5, w/w) plugs was determined in 100 ml medium (pH 1.2 hydrochloric acid solution, pH 5.0 phosphate buffer, or pH 6.8 phosphate buffer), as indicated in Fig. 3. The H-pectin/lactose plug degradation might be pH-dependent and the degradation rate increased with increasing pH.

3.3.2. Influence of the different medium on the percentage of remaining plugs

The H-pectin/lactose plugs were evaluated for the enzyme sensitivity in pectinase solution and rat cecal content medium, as shown in Fig. 4. The comparison of the pectinase medium with phosphate buffer solution (pH 6.8, PBS 6.8) shows that pectinase accelerates plug degradation, which might indicate the enzyme sensitivity of the H-pectin/lactose plugs. Similarly, the rat cecal content medium acts as a pectinase, but to a lesser extent.

3.4. In vitro dissolution studies

3.4.1. T-SMEDDS dissolution studies

The dissolution curves obtained from liquid SMEDDS and T-SMEDDS in PBS 6.8 are shown in Fig. 5. Drug release from the liquid SMEDDS formulation was faster than that from the T-SMEDDS because the surfactant, cosurfactant, and the oil adsorbed on the T-SMEDDS excipient needed more time to release and form microemulsions in the medium. However, the drug release rate of the T-SMEDDS was still satisfactory, exceeding 90% drug release within 1 h.

We also examined drug release from T-SMEDDS in unplugged, uncapped impermeable capsules. Although T-SMEDDS disintegrated rapidly when exposed to the medium, the drug release rate from the tablet inside the impermeable capsule is much slower than that from T-SMEDDS in PBS 6.8, as shown in Fig. 5. The disintegration of the SMEDDS tablet is closely related to its contact area with the release medium. The larger the contact area, the faster was the tablet disintegration and the faster was the drug release.

3.4.2. Pulsatile capsule dissolution studies

The lag time of the pulsatile capsules with the H-pectin/lactose plug (at the ratio of 2:8, 4:6, 5:5, 6:4, 8:2) were determined to optimize the plug formulation. Fig. 6 shows that the pulsatile capsule with the plug of H-pectin/lactose (5:5, w/w) optimized the lag time for colonic drug delivery. In addition, the increased proportion of lactose in the plug significantly decreased the lag time. Both results prove that small lactose molecules accelerate the erosion of gel and shorten the lag time.

The pulsatile capsule dissolution studies were performed in three simulated colonic environments: (1) pH 1.2 hydrochloric acid solution for 2 h, PBS 6.8 for 3 h, and then into rat cecal content release medium; (2) pH 1.2 hydrochloric acid solution for 2 h, PBS 6.8 for 3 h, and then into pectinase medium; and (3) pH 1.2 hydrochloric acid buffer for 2 h, and then PBS 6.8.

Fig. 7 shows that the plugs (H-pectin/lactose = 5:5, w/w) responded most to the pectinase and the rat cecal contents. Compared with the release medium without any enzymes (PBS 6.8), both the pectinase and the rat cecal contents shortened the lag time, which was similar to the result of the remaining plugs experiment. After the lag time, the drug was completely released within 4 h.

4. Conclusion

The present study demonstrated that SMEDDS tablets in impermeable capsules with erodible plugs have potential for delivering poorly water-soluble drugs to the colon and the drug release could be controlled by optimizing the plug composition. T-SMEDDS was prepared using adsorbent powders as solid carriers and placed into impermeable capsules for specifically targeting the colon. The SMEDDS tablet formation maintains the rapid self-emulsification and drug release as liquid SMEDDS does.

After the capsule is ingested, the cap remains undissolved in the stomach until it reaches the small intestines. Then, the plug is exposed to intestinal fluids. In the small intestine, H-pectin in the plug underwent from swelling to dissolving; in the colon site, the polysaccharide digested by enzymes, and the loose structure favored enzyme attaching. The lag time of the optimized plug ensures the drug is protected as the capsule passes through the small intestines. As the capsule arrives at the colon, the rest of the plug tablet disintegrates enzymatically in the environment, and the poorly water-soluble drug in the SMEDDS tablet is rapidly released at the desired site.

The combination of SMEDDS and the pulsatile capsule provides a platform for delivering poorly water-soluble drugs for site-specific applications.

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References

Chauhan, D. P. (2002). Chemotherapeutic potential of curcumin for colorectal cancer. *Current Pharmaceutical Design*, *8*, 1695–1706.

Elias, E. J., Anil, S., Ahmad, S., & Daud, A. (2010). Colon targeted curcumin delivery using guar gum. *Natural Products Communication*, *5*, 915–918.

Heo, M. Y., Piao, Z. Z., Kim, T. W., Cao, Q. R., Kim, A., & Lee, B. J. (2005). Effect of solubilizing and microemulsifying excipients in polyethylene glycol 6000 solid dispersion on enhanced dissolution and bioavailability of ketoconazole. *Archives of Pharmacal Research*, *28*, 604–611.

Kim, D. W., Kang, J. H., Oh, D. H., Yong, C. S., & Choi, H. G. (2012). Development of novel flurbiprofen-loaded solid self-microemulsifying drug delivery system using gelatin as solid carrier. *Journal of Microencapsulation*, *29*, 323–330.

Kosaraju, S. L. (2005). Colon targeted delivery systems: Review of polysaccharides for encapsulation and delivery. *Critical Reviews in Food Science and Nutrition*, *45*, 251–258.

Krogel, I., & Bodmeier, R. (1998). Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. *Pharmaceutical Research*, *15*, 474–481.

Krogel, I., & Bodmeier, R. (1999). Evaluation of an enzyme-containing capsular shaped pulsatile drug delivery system. *Pharmaceutical Research*, *16*, 1424–1429.

Liu, J., Zhang, L., Hu, W., Tian, R., Teng, Y., & Wang, C. (2012). Preparation of konjac glucomannan-based pulsatile capsule for colonic drug delivery system and its evaluation in vitro and in vivo. *Carbohydrate Polymers*, *87*, 377–382.

Liu, L., Fishman, M. L., Kost, J., & Hicks, K. B. (2003). Pectin-based systems for colon-specific drug delivery via oral route. *Biomaterials*, *24*, 3333–3343.

Oehme, A., Valotis, A., Krammer, G., Zimmermann, I., & Schreier, P. (2011). Preparation and characterization of shellac-coated anthocyanin pectin beads as dietary colonic delivery system. *Molecular Nutrition & Food Research*, *55*(Suppl. 1), S75–S85.

Patel, B. B., & Majumdar, A. P. (2009). Synergistic role of curcumin with current therapeutics in colorectal cancer: Minireview. *Nutrition and Cancer*, *61*, 842–846.

Patel, D., & Sawant, K. K. (2009). Self micro-emulsifying drug delivery system: Formulation development and biopharmaceutical evaluation of lipophilic drugs. *Current Drug Delivery*, *6*, 419–424.

Patel, M., & Amin, A. (2011). Recent trends in microbially and/or enzymatically driven colon-specific drug delivery systems. *Critical Reviews in Therapeutic Drug Carrier Systems*, *28*, 489–552.

Prajakta, D., Ratnesh, J., Chandan, K., Suresh, S., Grace, S., Meera, V., & Vandana, P. (2009). Curcumin loaded pH-sensitive nanoparticles for the treatment of colon cancer. *Journal of Biomedical Nanotechnology*, *5*, 445–455.

Sander, C., & Holm, P. (2009). Porous magnesium aluminometasilicate tablets as carrier of a cyclosporine self-emulsifying formulation. *AAPS PharmSciTech*, *10*, 1388–1395.

Sharma, R. A., Gescher, A. J., & Steward, W. P. (2005). Curcumin: The story so far. *European Journal of Cancer*, *41*, 1955–1968.

Shehzad, A., Wahid, F., & Lee, Y. S. (2010). Curcumin in cancer chemoprevention: Molecular targets, pharmacokinetics, bioavailability, and clinical trials. *Archiv der Pharmazie*, *343*, 489–499.

Sinha, V., Singh, A., Kumar, R. V., Singh, S., Kumria, R., & Bhinge, J. (2007). Oral colon-specific drug delivery of protein and peptide drugs. *Critical Reviews in Therapeutic Drug Carrier Systems*, *24*, 63–92.

Sriamornsak, P. (2011). Application of pectin in oral drug delivery. *Expert Opinion on Drug Delivery*, *8*, 1009–1023.

Wong, T. W., Colombo, G., & Sonvico, F. (2011). Pectin matrix as oral drug delivery vehicle for colon cancer treatment. *AAPS PharmSciTech*, *12*, 201–214.

Yehia, S. A., Elshafeey, A. H., & Elsayed, I. (2011). Pulsatile systems for colon targeting of budesonide: In vitro and in vivo evaluation. *Drug Delivery*, *18*, 620–630.

Yi, T., Wan, J., Xu, H., & Yang, X. (2008). A new solid self-microemulsifying formulation prepared by spray-drying to improve the oral bioavailability of poorly water soluble drugs. *European Journal of Pharmaceutics and Biopharmaceutics*, *70*, 439–444.