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Factors Affecting Preparations of Chitosan Microcapsules for Colonic Drug Delivery

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Abstract

This work aimed at studying factors affecting preparations of chitosan microcapsules for colonic drug delivery. Chitosan microcores (CS, 45kDa, 87% degree of deacetylation) containing diclofenac sodium (DS) coated with Eudragit®S100 (ED) were prepared by a desolvation technique. Sodium sulfate was used as a desolvating agent and the drying process was freeze-drying. Factors affecting morphology, particle size and zeta potential of microcapsules were evaluated, i.e. weight ratio of DS:CS:ED, surfactant (polysorbate 80), anti-adherent (silicon dioxide), and the use of sonication or homogenization in preparation processes. The weight ratio of DS:CS:ED at 1:2:6 provided the smallest microcapsules of about 82.37±1.61 micrometer in diameter and they were in aggregated forms. Zeta potential of the microcapsules was around -25.74 +4.78 mV which indicated that the core particles of CS and DS with zeta potential of 42.14±1.74 mV were encapsulated by ED. Increasing the amount of CS and ED, the size of microcapsules was increased but the zeta potential was not affected. Adding of polysorbate 80 could not reduce the size of microcapsules, but silicon dioxide could reduce the size and aggregation of microcapsules. Finally, the use of sonication and homogenization were effective in reducing of the size of microcapsules to 53.45 +0.63 and 58.72+1.28 micrometers, respectively.

Key words : chitosan microcapsules, Eudragit, colonic drug delivery

Introduction

Colon-selective drug delivery systems, not only for local but also for systemic therapy, have been the focus of increasing interest for the last decade. At present, the specific drug delivery to the colon is considered as an important alternative for the treatment of serious local diseases such as Crohn's disease, ulcerative colitis, carcinomas and infection.[1, 2] In the treatment of inflammatory bowel disease (IBD), 5-aminosalicylicacid (5-ASA) and steroidal or non-steroidal anti-inflammatory drugs (NSAID) are frequently administered orally to the patients. Administration of these drugs at a large and frequent dose for a long period causes significant prolonged absorption of the drugs from the small intestine, often leading to toxic effects.[3, 4] Therefore, specific deliveries of drugs to diseased parts have been developed, however, they are not satisfactory, and improved systems are expected.[5, 6, 7]

Chitosan is a biocompatible and biodegradable polymer, and is considered to be useful as a material for oral drug delivery systems due to its safety. Chitosan itself exhibits mucobioadhesive properties to the mucosal membrane probably because of its cationic and viscous properties[6] and is considered suitable for the delivery to specific sites of the intestine.[8] Recently, chitosan microparticles have been used for colonic drug delivery.[9] However, as chitosan is easily dissolved in the acidic stomach, simple oral administration results in dissolution or collapse. In this study, chitosan (CS) microparticles loaded with an NSAID, diclofenac sodium (DS),

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were prepared and encapsulated with a pH dependent polymer, Eudragit® S100 (ED), to protect the microparticles from dissolution or collapse under gastric and proximal intestine conditions by a desolvation technique.[10, 11, 12] Furthermore, factors affecting particle size and zeta potential of the microcapsules were evaluated, i.e. weight ratio of DS:CS:ED, adding of surfactant (polysorbate 80) or antiadherent (silicon dioxide), and the use of sonication or homogenization in preparation processes.

Materials and Experimental Procedures

Materials: Chitosan [45 kDa, 87% degree of deacetylation] was purchased from Seafresh Co. Ltd. Diclofenac sodium was purchased from Amoli Organics Ltd. Eudragit® S100 was obtained from Degusa. Glacial acetic acid was purchased from Carlo Erba, Ammonium solution was purchased from Merck, Sodium sulphate was purchased from Fisher Scientific. All other chemicals were of reagent grade.

Preparation of microcapsules Figure 1. : Drug : CS were varied in 2 ratio, 1:2 and 1:4 and core : coating were also varied in 2 ratio 1:2 and 1:4, therefore ;four ratios (1:2:6, 1:2:12, 1:4:10 and 1:4:20; DS:CS:ED) were evaluated in this study. In addition, microcore size reduction techniques were applied in 2 ratios (1:2:6 and 1:4:10; DS:CS:ED).

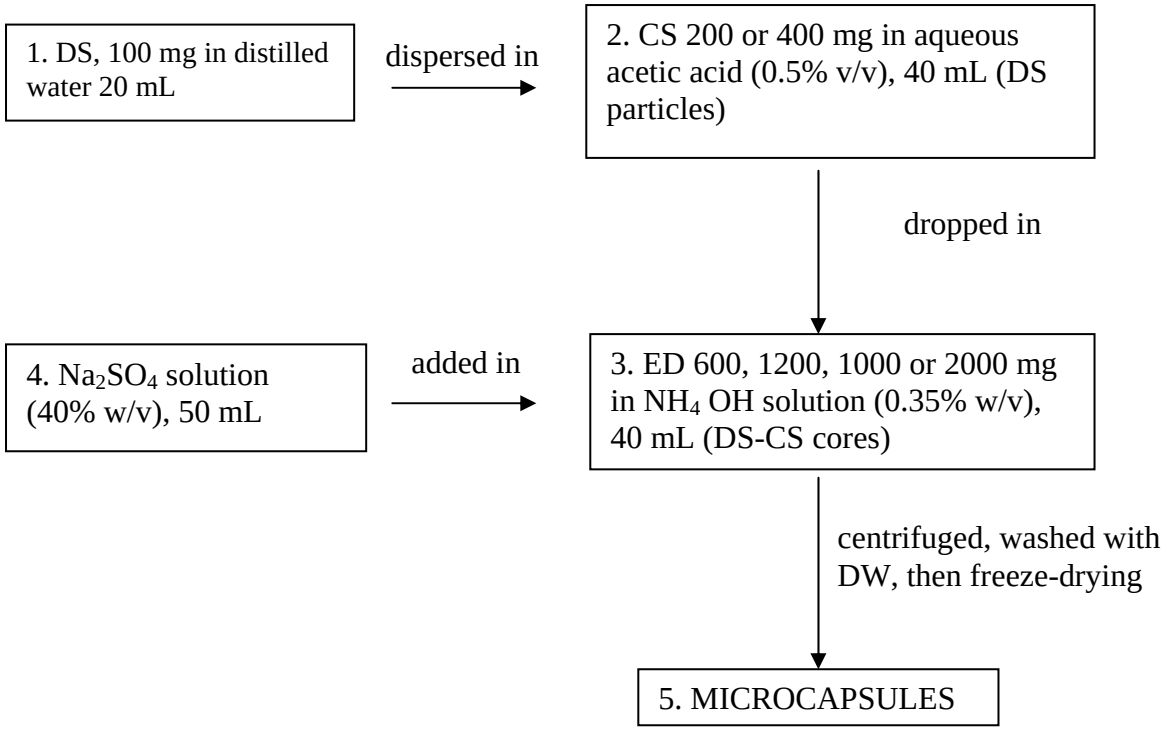
Evaluation of microcapsules: Morphology using scanning electron microscopy (SEM; MX2000, Camscan, UK), particle size and zeta potential of microcapsules by particle size distribution analyzer (LA-950, Horiba, Japan) and zeta potential analyzer (Zeta Plus, Brookhaven, USA) were evaluated.

Results and Discussions

Morphology

Median particle sizes of DS microcores in CS solution at both ratios (DS:CS at 1:2 and 1:4) were 28.23 to 14.24 μm (Table 1) and the size of DS-CS microcore before encapsulation process was bigger than DS microcores. From Figure 2. CS microcapsules were aggregated particles with mean particle size of around 65-117 μm in diameter and zeta potential -34 to -39 mV (Table1). Microcapsules will be larger when increasing the

Figure 1. Microcapsules preparation process



amount of ED because ED with negative charge tended to attach at the positive charge of DS-DS microcore. The weight ratio of DS:CS:ED at 1:2:6 provided the smallest microcapsules of about 65.82 micrometer in diameter.

potential of DS microcore in 1:2 and 1:4 DS:CS ratio were 32.12±2.20 and 35.18 mV, respectively. DS microcore show positive zeta potential because CS may cover the surface of DS microcore so NH_4^+ group of CS can express their positive charge

Table 1. Median particle size and zeta potential of DS particles, DS-CS cores and microcapsules.

DS:CS:ED ratio	Particle size of DS (μm)	Zeta potential of DS (mV)	Particle size of DS-CS core (μm)	Zeta potential of DS-CS core (mV)	Particle size of microcap-sules (μm)	Zeta potential of microcap-sules (mV)
1:2:6	9.45±0.08	32.12±2.20	13.34±0.14	-25.74±4.48	65.82±2.76	-36.75±1.32
1:2:12	8.22±0.05	35.18±1.16	10.35±0.05	-26.32±1.61	81.78±2.92	-34.11±4.39
1:4:8	9.45±0.08	32.12±2.20	47.43±9.73	-19.11±7.60	82.37±1.61	-42.11± 2.19
1:4:20	8.22±0.05	35.18±1.16	111.91±22.37	-22.02±2.26	117.85±42.95	-39.26±2.17

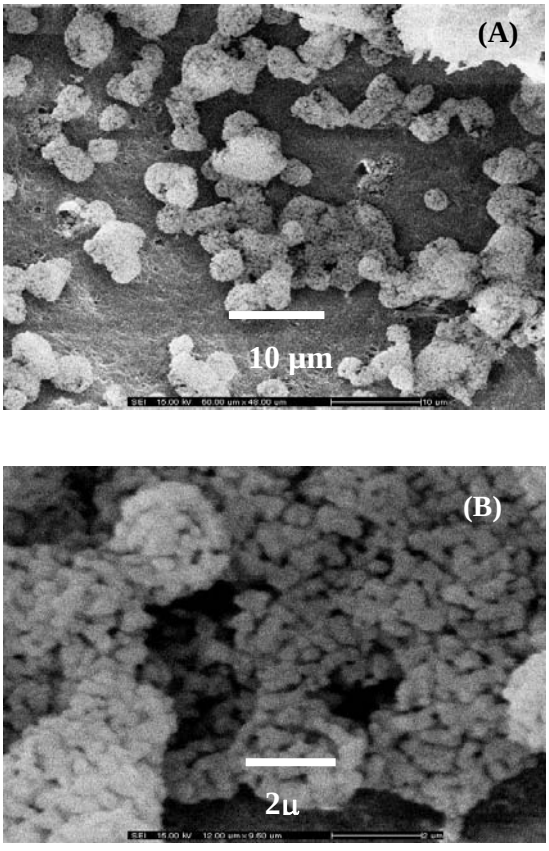


Figure 2. SEM micrographs of CS microcapsules (DS:CS:ED, 1:2:6) (A) 1000X and (B) 10000X magnification

The zeta potential of microcapsules in each drug polymer ratio was -34.11 to -42.11 mV. In the first step of microcapsules preparation the zeta potential result above leads to the conclusion that DS-CS microcores were coated with ED.

over DS surface. And after dropping DS-CS suspension in NH_4OH solution the zeta potential has turned to negative (-19.11 to – 26.32 mV) due to the fact that DS-CS microcore were surrounded by ED that exhibited of negative functional group (COO^-). Finally, after encapsulating by adding Na_2SO_4 and freeze-drying process the zeta potentials were still negative and tended to increase (-34.11 to-42.11mV) since after adding Na_2SO_4, ED was more deposited at microcore surface. The

Effect of Size Reduction Technique

Table 2 shows that both microcore reduction size techniques were effective to lower the size of DS microcores and microcapsules. The sizes of microcores at both ratios (DS:CS, 1:2 and 1:4) were reduced to around 7.16-8.44 μm and size distribution was also decreased after homogenization and sonication. Especially with microcore of DS:CS at ratio 1:4, the size was dramatically decreased from 14.24 to 2.61 μm after sonication. The reason for this outstanding sonication size reduction technique may be that CS chains were shortened during sonication. Moreover, smaller microcores from the size reduction technique can reduce the size of microcapsules, too. Furthermore, zeta potential of microcapsules at all ratios prepared from both size reduction techniques was not different from the original one.

Table 2. Median particle size and zeta potential of DS particles and microcapsules particle size after using size reduction techniques at 1:2:4 and 1:4:10 ratios.

Techniques	DS particle size after size reduction technique (μm)		Microcapsule size after size reduction technique (μm)	
	1:2	1:4	1:2:4	1:4:10
Homogenization	8.44±0.23	7.16±0.14	46.95±2.48	44.17±1.92
Sonication	7.25±0.41	2.61±0.33	28.65±1.44	23.20±0.37

Effect of Surfactant or Anti-adherance

Adding of polysorbate 80 could not reduce the size of microcapsules, but the particle size was increased to around 200 μm as polysorbate 80 covered the surface of the microcapsules. However, adding 1% of silicondioxide before the freeze-drying step can reduce microcapsule size from 65.82 to 21.91μm. Anti-aggregation mechanisms of silicondioxide in the freeze-drying process have been reported by Schaffazick, S.R. et al. They stated that the very small and round particles of silicondioxide may fill the spaces between microcapsules and thus prevent wall fusion during freeze-drying.

Conclusions

Microcapsules of CS-DS microcores coated with ED were successfully prepared by a simple coacervation or desolvation technique and the smallest microcapsules were obtained from a 1:2:6 ratio (DS:CS:ED). Increasing the amount of ED affected particle sizes. Additionally, homogenization and sonication of DS microcore were effective techniques to reduce microcapsule size and adding silicondioxide before the freeze-drying process can lower size of microcapsules as well. Furthermore, the SEM result showed that a single unit of structure was in nanometer size and each unit was aggregated in form of nanostructure.

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