Chitosan Tablets for Controlled Release of Theophylline: Effect of Polymer–Drug Wet or Dry Blending and Anionic–Cationic Interpolymer Complex

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ABSTRACT: Chitosan tablets containing theophylline were prepared by directly compressing the wet or dry blended polymer–drug powders. The effects of the viscosity and swelling ability on the release rates of drugs were examined. The theophylline releasing rates of tablets prepared by polymer–drug wet blending increase with a decrease in the viscosity of the blending chitosan solution. On the other hand, the swelling ability of the polymer greatly influences the release kinetics of the tablets prepared by polymer–drug dry blending. Tablets prepared by both polymer–drug wet and dry blending were acid-nonresisted. Tablets in simulated gastric fluid disintegrated quickly, and the drugs were released within four hours. To retard the disintegrated rate of chitosan tablets in acid medium, interpolymer complex of chitosan with anionic polyelectrolyte (alginate) is needed. By this treatment, the swelling and erosion rate of the chitosan tablets could be reduced, then controlling the release rate of the theophylline can be achieved. Drug release mechanism of the various tablets were investigated by the model of Peppas; in addition, a nuclear magnetic resonance imagine microscopy is also introduced to examine the swelling or diffusion mechanism of various tablets.
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Key words: chitosan; controlled release; drug wet blending; drug dry blending; drug tablets; ionic interpolymer complex

INTRODUCTION

In the recent years, controlled release technology has undergone a rapid development in various fields, and its products now span a variety of applications including medical, agricultural, and biochemical agents.[1–7] One approach that has received a great attention as a means of controlled release of active agents has been the incorporation of solutes in solid polymers. The application of hydrogels in drug delivery has been well studied. The swellable polymers recently used in formulating controlled release dosage forms contain PHEMA, PVA, HPMC, and CMC.[8–18]

Chitosan [poly(1,4-β-D-glucopyranosamine)] is an amino polysaccharide polymer that processes valuable properties as a biomaterial. It is a cationic polyelectrolyte and gels in acid media differing from commercially available hydrogels, which are nonionic or polyanionic.[19] Biomedical applications of chitosan include wound and burn healing, soft and hard contact lenses, and artificial kidney membranes.[20] Moreover, the biocompatibility and biodegradability of this novel polysaccharide has been examined.[21–23] Recently, chitosan also has been investigated as a disintegration agent because of its ability to absorb water well. It was reported that chitosan contained in tablets at levels below 60%

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act as disintegration agents.[24] Besides, Nigalaye et al. investigated the sustained release characteristics of chitosan in the presence of citric acid or carbomer–934P in tablets, containing theophylline as the model drug.[25] The rate of drug release was slower in the tablets containing citric acid or carbomer–934P used as anionic complex agents than containing chitosan alone.

In this study, several types of chitosan matrix systems are prepared in order to achieve sustained release. These include a hydrophobic system, from which the drug is liberated by diffusion; hydrophilic matrices, which swell or dissolve in water; and release controlled by diffusion or erosion. As a hydrophilic system, tablets are prepared by chitosan–drug wet or dry blending. Erosion or swelling type of drug release is observed in a wet or dry blending tablet. As a hydrophobic system, tablets are prepared by chitosan–anionic polymers–drug dry blending. The anionic polymers used for complex with chitosan are alginates. By this treatment, the tablet is only slightly swelling and nonerodiable, then decrease the release rate of drug.

EXPERIMENTAL

Preparation of Chitosan Tablet

Tablets Prepared by Polymer–Drug Wet Blending

Theophylline powder (Sigma Chemical Company, St. Louis, MO), 60 mg, was wet granulation using 10–1260 cps of chitosan solution. Chitosan (Fluka, Switzerland) solution was prepared in 0.5% acetic acid in water. The drug was ground to 100 mesh before use. Chitosan used as binder solution was added to the theophylline in the mortar and mixed with drug for 15 min. The wet mass was passed through a #12 US standard sieve, and the resultant granules were passed through a #20 mesh. Finally, the granules were compressed into 6 mm flat-faced tablets at a compression force of 1.2–1.5 kN, using a press mechanize (Carver, U.S.A.). Tablet prepared by this method was marked as CW tablet.

Tablet Prepared by Polymer–Drug Dry Blending

The dry blending tablets were prepared by powder mixing method. Chitosan was ground by ball mills or spray-dried to obtain spherical polymer powder using a spray drying mechanism (Buchi, B-191, Switzerland). 6 mm flat-faced tablets (55–60 mg) were prepared from polymer dry blending with drug, at a compression force of 1.2–1.5 kN, using a press mechanize (Carver, U.S.A.). Tablet prepared by ground chitosan powder–drug or spray-dried chitosan powder–drug dry blending was marked as a CDG or CDS tablet, respectively.

Tablet Prepared by Interpolymer Complex

Drug, chitosan, and the anionic polymer, alginate (Sigma Chemical Company, St. Louis, MO), were dry-blended to prepare the tablet as described in the tablet prepared by the polymer–drug dry blending previously. The tablet prepared by ground chitosan–alginate–drug dry-blending was marked as the CDGA tablet.

Nuclear Magnetic Resonance Imagine Study

A single tablet was affixed by a Teflon holder to the base of glass nuclear magnetic resonance (NMR) tube and the holder was allowed to dry. The tablet was hydrated in excess double-distilled water at 37°C. The water was removed by inverting the tube, and the sample was placed in the core of the NMR (Bruker, MSL-300, Germany) microscope for imaging. The NMR microscope was based around a 7.05 T, 150 mm bore superconductive magnet, providing a proton resonance frequency of 300 MHz. Imagines 650 μm thick sections were obtained, with an in-place resolution of 100 μm, using an echo time of 6.5 ms. Imagines with an adequate signal-to-noise ratio could be generated in a time of 10 min.

Scanning Electron Microscopy Study

The tablets prepared by different method were placed in pH 1.2 and 7.2 mediums for one hour, then placed in an oven for drying. The final dried tablets were gold-coated to about 500×10^{-8} cm thickness using an Hitachi coating unit IB-2 coater under a high vacuum, 0.1 Torr, high voltage, 1.2 kV, and 50 mA. Coated samples were examined using a Hitachi S-2300 SEM microscope.

Drug Release Test

The releases of drug from various chitosan tablets were measured by using the dissolution (Hanson research, Dissoette II) and autosampling (Hanson research, SR6) systems. The dissolution medium was 500 mL of pH 1.2 and 7.2 solution to simulate gastric and intestinal juice, respectively. The medium was placed in a 1 L round flask fitted with a pump for autosampler to remove the me-

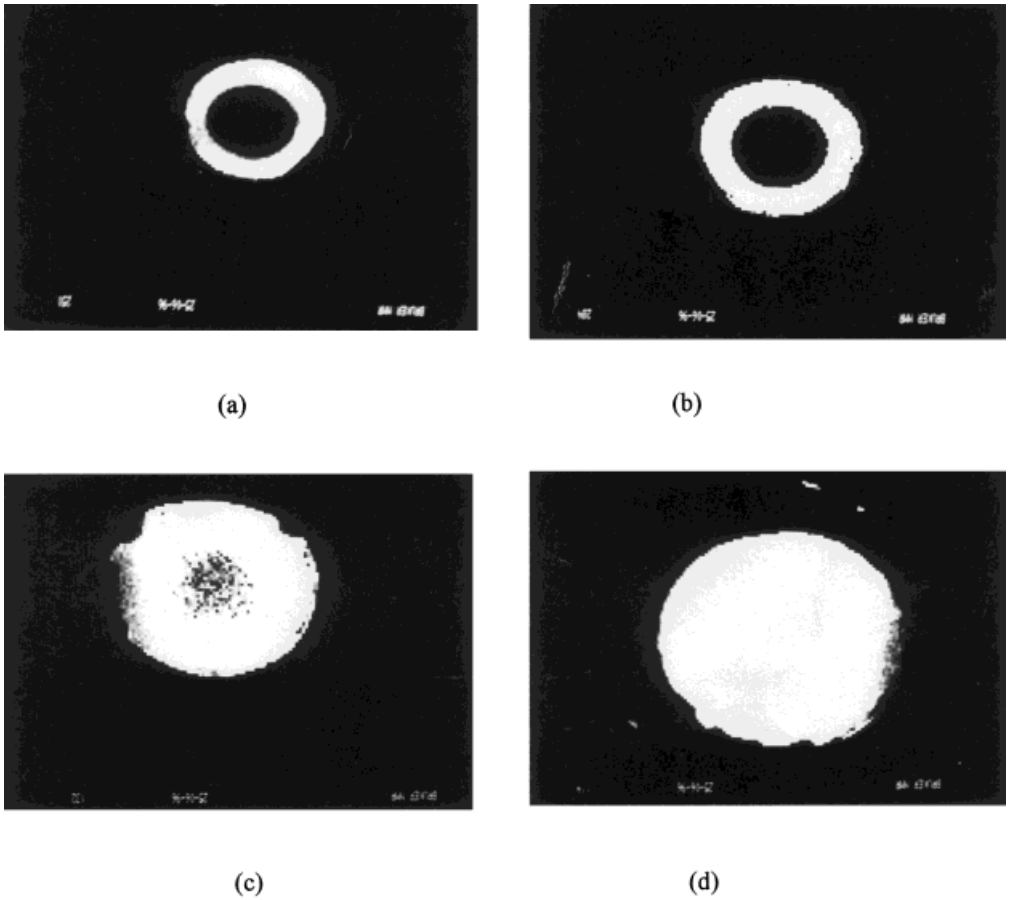


Figure 1 Images of a CW chitosan tablet undergoing hydration after (a) 15, (b) 50, (c) 150, and (d) 300 min in the radial plane.

dium, then it was stirred with a mechanical stirrer at a rate of 50 rpm. The dissolution medium temperature was maintained at 37.5 ± 0.5°C. An equivalent quantity of the 60 mg tablet was placed in the dissolution medium. After a predetermined interval, 5 mL of the medium was removed and replaced with fresh medium to maintain the original volume. The amounts of theophylline were analyzed spectrophotomertically at 273 nm by an ultraviolet (UV) spectrophotometer.

RESULTS AND DISCUSSION

NMR Imagine Study

The mechanism of water penetration into tablet was studied by NMR microscopy. In this study, the NMR signal is used to produce a two-dimensional map of the density of nuclei within a thin slice of object. Usually, the nucleus of interest is ^{1}H, located in water molecules; and images, thus, show the spatial variation of the local water concentration within the sample. For swelling type of tablets, the formation and growth of the surface-hydrated layer could be seen in the NMR imagine initially and move inward gradually. Whereas, for the diffusion type of tablets, spots like hydrated voids were seen and gradually became brighter. Figure 1 shows the NMR images of the CW tablet. In the pH 7.2 medium, water penetrated into the tablet slowly. After being dissolved in the medium for two hours, the tablet matrices also show little hydration. This result indicates that dissolution of the tablet is induced by gradually hydrating the CW tablet matrix and finally eroding the drug powder. Figure 2 shows the nuclear resonance imaging (NRI) study of the CDS tablet. When an initially glass chitosan tablet is placed into the pH 7.2 medium, molecules of the penetrant begin to diffuse into the glassy region in a more or less well-defined front. The presence of penetrant molecules in the glassy system cause stress, which is then accommodated by an increase in the radius of gyration and root mean square end-to end distance of the polymer molecules. The increase in the radius of gyration of the polymer molecules is

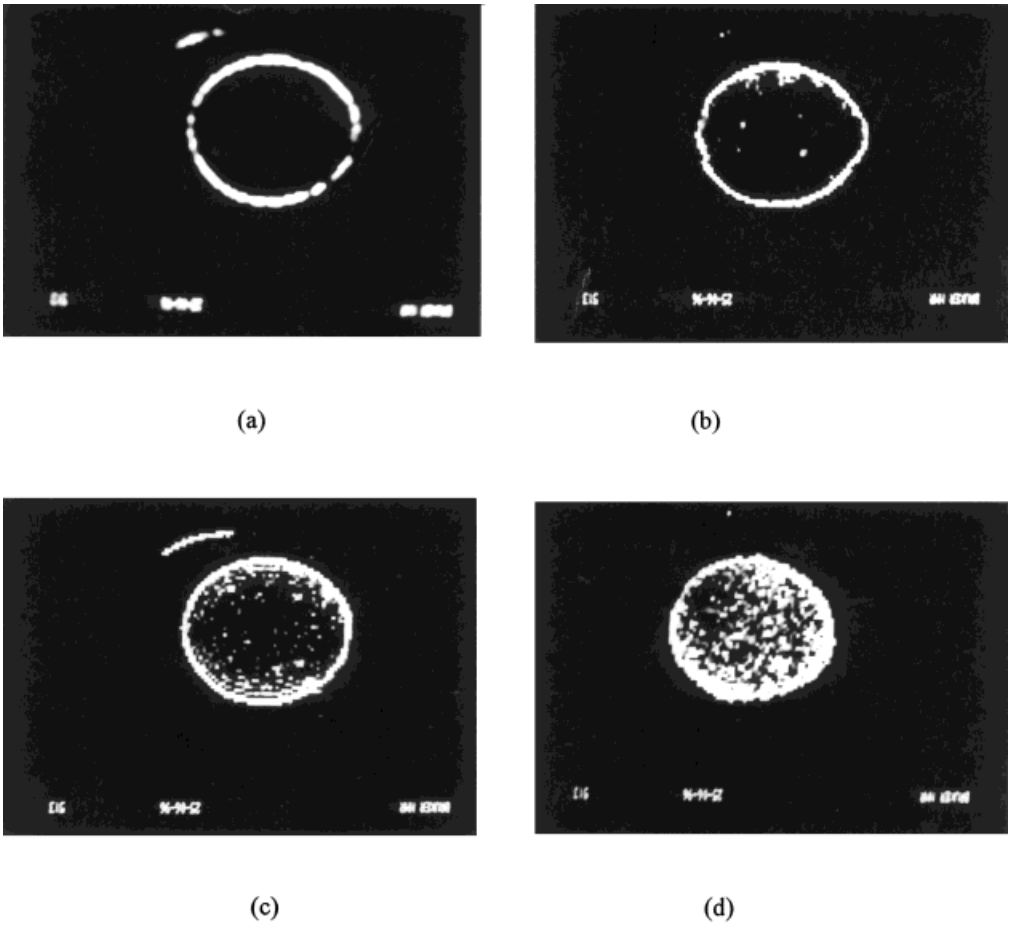


Figure 2 Images of a CDS chitosan tablet undergoing hydration after (a) 15, (b) 50, (c) 150, and (d) 300 min in the radial plane.

seen macroscopically as swelling. In figures of NRI study, one can observe that the polymer–penetrant interface moves outward into the penetrant medium; at the same time, the glassy–rubbery interface moves into the glassy region. In a pH 1.2 medium, one can only observe that the glassy–rubbery interface to move into the glassy region for both polymer–drug wet (CW) or dry blending (CDG or CDS) tablets. The polymer–penetrant interface could not move outward into the penetrant medium because of gradual erosion of the swollen chitosan. In the pH 1.2 medium, the CDGA tablets show initially limited glassy–rubbery interface transition and continuous penetrating of dissolution medium because of the reduced swelling ability of the tablet by using the interpolymer complex method.

SEM Study

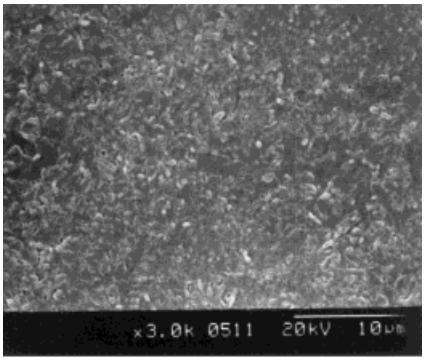
Tablets prepared by wet or dry drug–polymer blending all have smooth and dense surfaces initially, whereas the morphology of the tablets after dissolving in a pH 1.2 or a 7.2 medium for one hour were obviously different. Figure 3 shows that the crystals of theophylline on the surface of the CW tablet are different after dissolving in the pH 1.2 and 7.2 mediums for one hour, respectively. The crystals of theophylline on the surface of tablet dissolving in the pH 7.2 medium seem to be intact, whereas erosion of the drug crystal was observed on the surface of tablet dissolving in the pH 1.2 medium. The result would be attributed to the fact that chitosan in the CW tablet acts not only as a binder of the tablet but also as a surface protector of drug powder. In the lower pH medium, chitosan dissolved quickly, and the drug powders on the surface of tablet were eroded seriously within one hour. Figure 4 shows the morphology of the CDG tablets after dissolving in the pH 1.2 and pH 7.2 medium for one hour, respectively. Chitosan powder was intact on surface of the CDG tablet after dissolving in pH 7.2 medium but was dissolved to form a gel-like layer on the

surface of the CDG tablet in pH 1.2 medium. This is due to chitosan being an cationic polymer that is able to swell and finally dissolve in an acidic environment of pH 1.2 medium. Figure 5 shows the morphology of the CDS tablets after dissolving in pH 1.2 and 7.2 mediums. Spray-dried chitosan powders were swelling and staying sphere-like on the surface of the CDG tablet after dissolving in pH 7.2 medium but were dissolved quickly in the pH 1.2 medium, so the gel-like layer was not observed on the surface of the CDG tablet after dissolving in pH 1.2 medium for one hour. Figure 6 shows the morphology of the CDGA tablets after dissolving in pH 1.2 and 7.2 mediums. After dissolving the CDGA tablet in the pH 1.2 medium, the alginate could slightly and slowly swell and finally form an interpolymer network with dissolved chitosan in the CDGA tablet. In the pH 7.2 medium, chitosan powder was intact, but the alginate quickly swelled and dissolved to form gel-like layer on the surface of CDGA tablet.

Release Test

Tablet Prepared by Polymer–Drug Wet Blending

The drug release behavior of the wet-blended chitosan tablet is significantly influenced by polymer viscosity. Chitosan used in the wet-blended tablet acts as a binder. An increase in the viscosity of the binder caused a decrease in the dissolution rate of the CW tablet. The viscosity of chitosan varied with the concentration or molecular weight of polymer (Table I). In this study, chitosan was degraded to lower molecular weight by using enzyme digestion. Lysozyme digests the *N*-acetylglucosacetamide units in the polymer chain of chitosan. The viscosity of 1.5% (w/v), 70,000 M_w chitosan decreases from 1260 to 275 cps within 24 h by using 2000 U/C.C. lysozyme. In the pH 7.2 medium, 90% of the drug dissolved within 1 h when 10 cps chitosan was employed as binder; only 30% of the drug dissolved when 1260 cps chitosan was used in CW tablet preparation (Fig. 7). It is postulated that at higher binder viscosity, increasing the adhesion force between the polymer and drug finally reduced the porosity and capillary pore size. Thus, wicking of water into the tablet is markedly reduced; consequently, the disintegration or dissolution rate is slowed. The tablet dissolving in the pH 1.2 medium was much quicker than that in the pH 7.2 medium because of easy erosion of the binder in lower pH medium (Fig. 8). In the pH 1.2 medium, the releasing of theophylline from the CW tablet is a nearly zero-order release mechanism. In the pH 7.2 medium, the release mechanism deviated from the zero-order release mechanism; and the deviation increased with the increase of the viscosity of the binder solution since the rates of penetration of the dissolution medium into the core of tablet and



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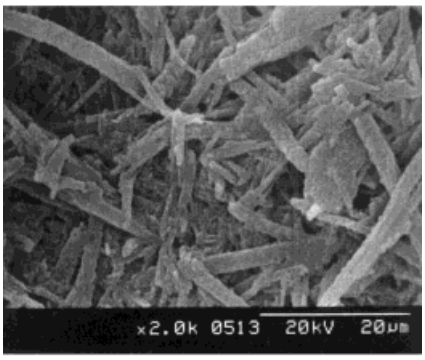
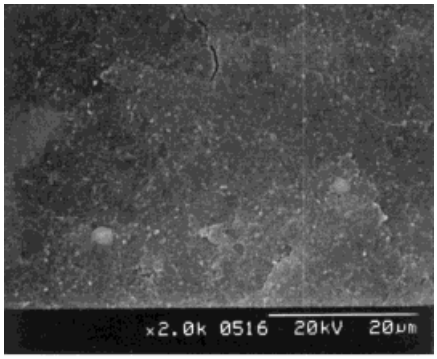


(b)

(c)

Figure 3 Scanning electron micrographs of CW tablet (a) before dissolution, (b) dissolved in pH 1.2 for 30 min, and (c) dissolved in pH 7.2 for 30 min.



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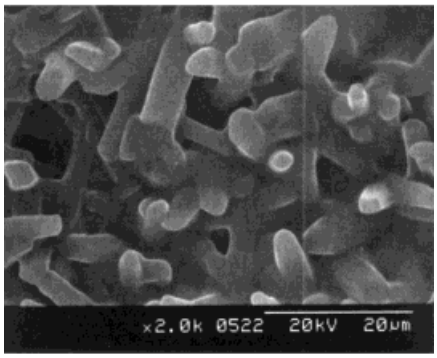

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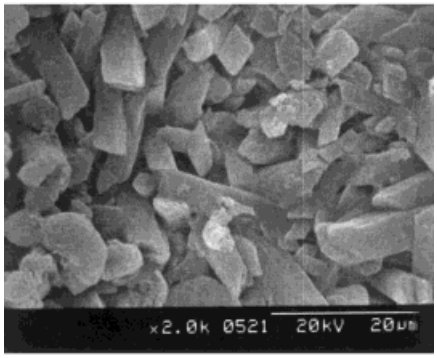


(c)

Figure 4 Scanning electron micrographs of CDG tablet (a) before dissolution, (b) dissolved in pH 1.2 for 30 min, and (c) dissolved in pH 7.2 for 30 min.

erosions of the polymer–drug matrix are not in equilibrium.

Tablet Prepared by Polymer–Drug Dry Blending

Ground chitosan powder acts as a disintegration agent in the CDG tablet. The release behaviors of chitosan tablet show a quicker dissolving rate in the pH 7.2 medium than that in the pH 1.2 medium. This result is attributed to the good gel formation ability at a lower pH, but poor gel formation ability at a neutral and a high pH. The gel formed on the outer layer of the tablet as soon as it made contact with the acid medium. The gel formation on the surface not only reduced the contact of water of the nondissolved drug but also acts as the binder of the drug–polymer matrix to prevent the powders disintegrating quickly. As shown in Fig. 9, the dissolution rate of the tablet decreases with an increase in the polymer-to-drug ratio in the pH 1.2 medium, whereas it increases with an increase in the polymer-to-drug ratio in the pH 7.2 medium (Fig. 10). The result demonstrated that ground chitosan powder in the tablet acts as a disintegration agent in the pH 7.2 medium.

To retard the dissolution rate of the tablet in the pH 7.2 medium, spray-dried chitosan microspheres were used for preparing tablet using polymer–drug dry blending. Tablet prepared by directly blending the drug with spray-dried chitosan powder may achieve swelling controlled drug release behavior in the pH 7.2 medium. The spray-dried chitosan microspheres are hydrophilic and water-swellable because of slight protonation and reduction of the crystal of chitosan. Release of theophylline from the CDS tablet in the pH 7.2 medium is shown in Figure 11. Increasing the polymer-to-drug ratio or the molecular weight of spray-dried chitosan powder could reduce the dissolution rate of the tablet. At lower polymer containing, swollen chitosan microspheres could not close each one to form a continuous polymer block to fill the intraparticulate voids in the polymer–drug matrix; so the dissolved drug diffuses out of the tablet through the tortuous network of channels, finally increasing the dissolution rate of the tablet. The slower the dissolution rate of the CDS tablet prepared by high-molecular-weight chitosan should also be attributed to the same effect arising with the good swelling ability of the chitosan with the higher molecular weight. The result can be conveniently analyzed using the following equation[12]:

$$\frac{M_t}{M_o} = kt^n$$

where M_t is the drug released at time t and M_o is the total drug. The power n describes the mechanism of drug release. A value of n equal to 0.5

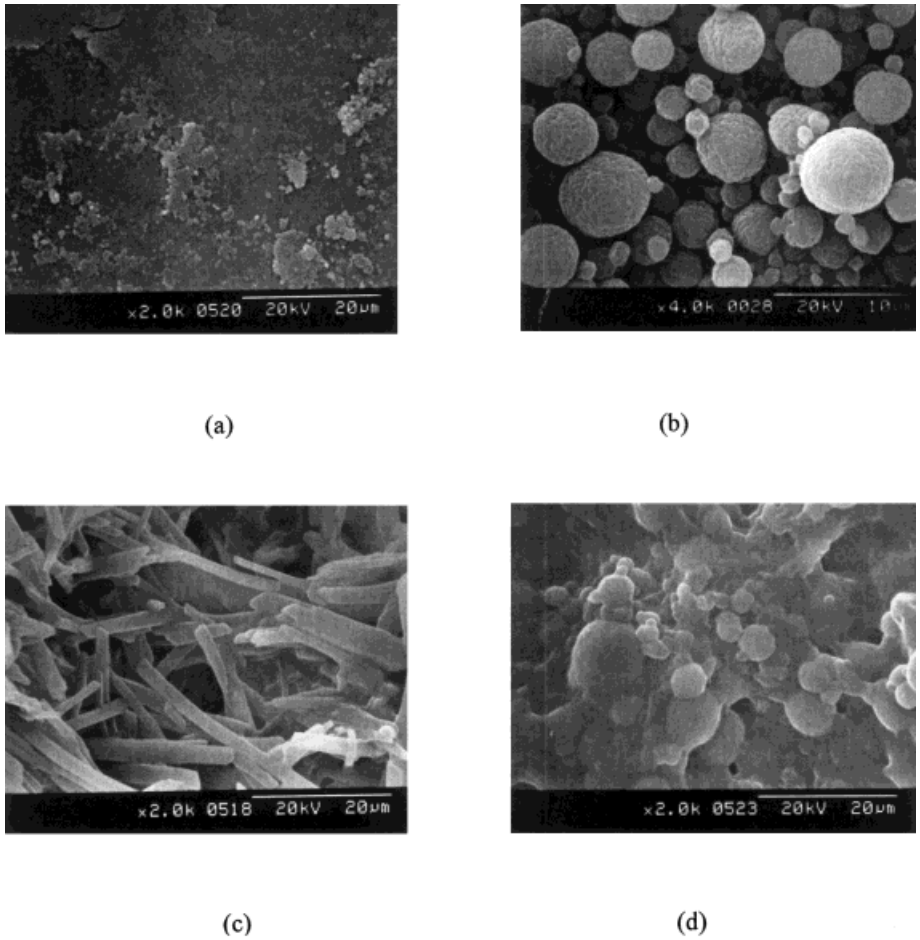
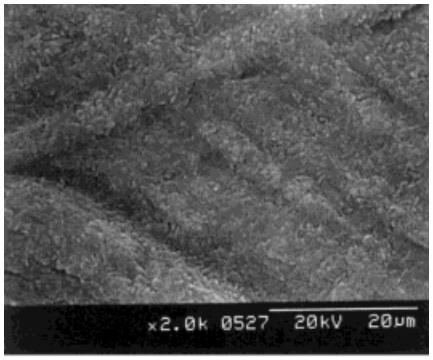


Figure 5 Scanning electron micrographs of CDS tablet (a) before dissolution, (b) spray-dried chitosan powder, (c) dissolved in pH 1.2 for 30 min, and (d) dissolved in pH 7.2 for 30 min.

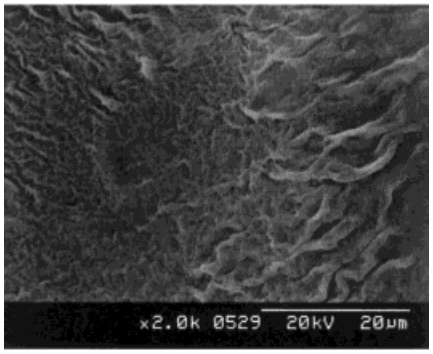
indicates the drug release mechanism approach to Fickian diffusion-controlled release, whereas a value of n equal to 1.0 indicates the drug release mechanism approach to zero-order release. The n value between 0.5 to 1 is a drug release mechanism of chain–relaxation control. Either the CDG or CDS tablet dissolved in the pH 1.2 medium demonstrates the erosion type of the zero-order release mechanism. In the pH 7.2 medium, CDG or CDS show greatly different drug release types. As shown in Table II, in the pH 7.2 medium, the n value of the CDS tablets prepared by a higher polymer-to-drug ratio and the molecular weight of chitosan seems to approach 1. The constant release rate observed in such formulations was explained earlier.[8,26] By optimizing the ratio between the drug and the polymers, the rates of advancement of the swelling front into the glassy core and the attrition of the rubbery state polymer were made equal so that the diffusional path length for the drug remained constant. The CDG tablet disintegrated in the pH 7.2 medium quickly, and none of the drug release model could be used to fit the release data of the CDG tablet.

Tablet Prepared by the Interpolymer Complex

Chitosan is a cationic polymer that is able to be ionized in an acid environment. The ionized chitosan carries positive charges like amine groups (NH^{3+}). In the past work, chitosan gel beads were prepared by a polymer–counterion complex of chitosan and sodium tripolyphosphate.[27] The anionic counterion, tripolyphosphate (TPP), acting as a crosslinking agent, can form either intermolecular or intramolecular linkage with the positively charged amino groups. The crosslinked chain scission by hydrolysis of the phosphorous–amino complex results from reprotonating the amine group of chitosan. This induces the quick disinte-



(a)



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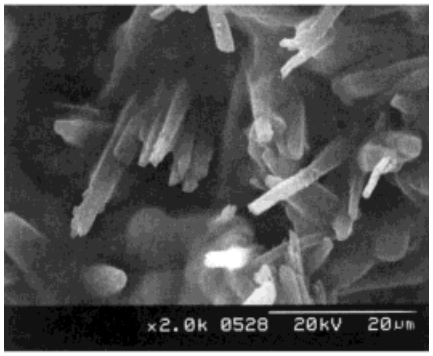

(c)

Figure 6 Scanning electron micrographs of CDGA tablet (a) before dissolution, (b) dissolved in pH 1.2 for 30 min, and (c) dissolved in pH 7.2 for 30 min.

gration of the complex tablet in the pH 1.2 medium (see Fig. 12). In the previous investigation,[28–29] the polyelectrolyte complex gel prepared from Xanthan (or *k*-carrageenan) and chitosan by mixing these two polymer solutions was stable in water. In this study, alginate powder was used as an anionic polymer to be mixed with chitosan powder by dry blending. Tablets prepared from the dry-blended chitosan–alginate powder could form a stable polyelectrolyte complex matrix in the pH 1.2 medium. An interpolymer crosslinking network was achieved by the complex reaction between chitosan and alginate, which could reduce the hydrolysis rate of the complex chain. Figure 13 shows the dissolution rate of CDGA tablets in the pH 1.2 medium. By this treatment, the dissolution period of CDGA tablets in the medium has been extended, as compared to a tablet prepared by the complex of chitosan with low-molecular-weight TPP.

Table I Viscosity of Chitosan Solutions

M_w	Concentration (% w/v)	Viscosity (cps)
70,000	0.1	6
70,000	0.5	28
70,000	1.0	289
70,000	1.5	1245
70,000	2.0	4470
70,000	2.5	7820
2,000,000	1.5	2450

The result of the drug release rate in a different dissolution medium indicated that the binding ration of the complex was affected by pH. Since the pKa value of chitosan was reported to be 6.3, the

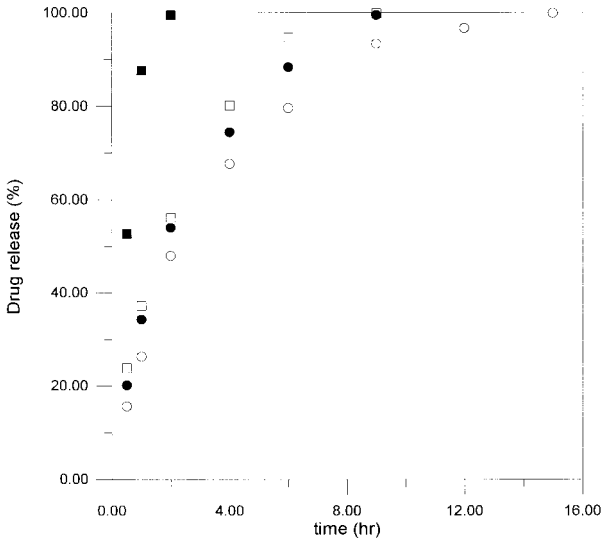

Figure 7 Effect of the viscosity of chitosan solution on the rate of theophylline releasing from the CW tablet in the pH 7.2 medium. Key: (■) 10 cps; (□) 70 cps; (●) 220 cps; (○) 1260 cps.

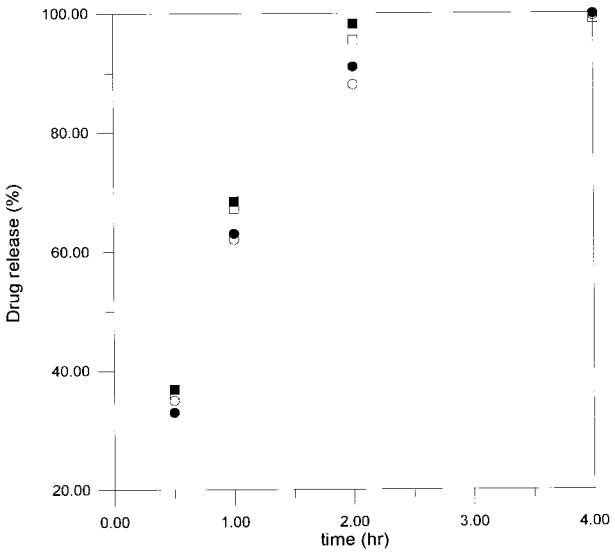

Figure 8 Effect of the viscosity of chitosan solution on the rate of theophylline releasing from the CW tablet in the pH 1.2 medium. Key: (■) 10 cps; (□) 70 cps; (●) 220 cps; (○) 1260 cps.

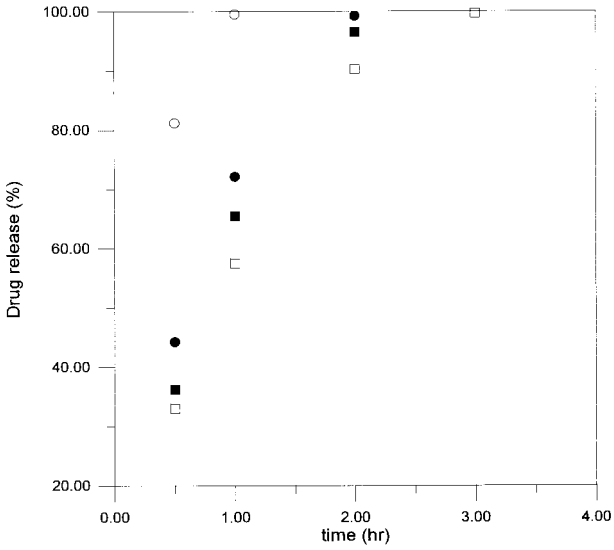

Figure 10 Effect of the polymer-to-drug ratio on the rate of theophylline releasing from the CDG tablet in the pH 7.2 medium. Key: 70,000 M_w, (■) pure drug; (□) polymer-to-drug ratio is 3 : 40; (●) polymer-to-drug ratio is 3 : 20; (○) polymer-to-drug ratio is 3 : 10.

amino group on the polymer chain of chitosan molecules were ionized in the medium used in this study (pH 1.2). In this pH region, alginate molecules are partly ionized as estimated from the pKa value of alginate; on the contrary, the degrees of ionization of alginate would decrease with the decrease in the pH value in the media. As a result, alginates only swell but scarcely dissolve in pH 1.2 medium. The dissolved chitosans then gradually diffuse into the swollen alginate and form an interpolymer crosslinking matrix. In the pH 1.2 medium, the CDGA tablet demon-

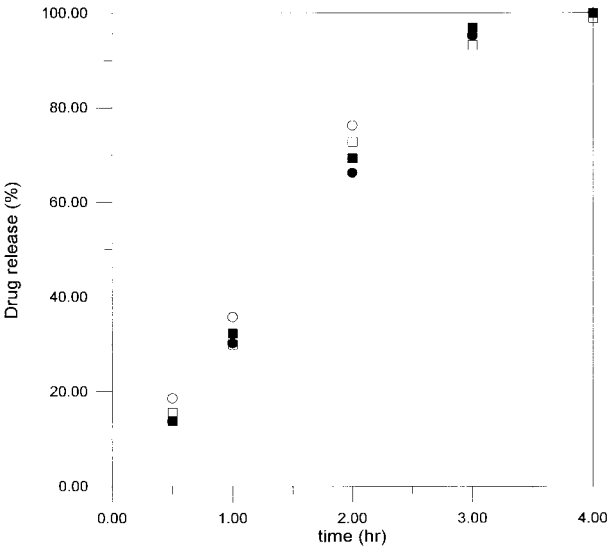

Figure 9 Effect of the polymer-to-drug ratio on the rate of theophylline releasing from the CDG tablet in the pH 1.2 medium. Key: 70,000 M_w, (■) polymer-to-drug ratio is 3 : 10; 2,000,000 M_w, (□) polymer-to-drug ratio is 1 : 1; (●) polymer-to-drug ratio is 3 : 10; (○) polymer-to-drug ratio is 1 : 1.

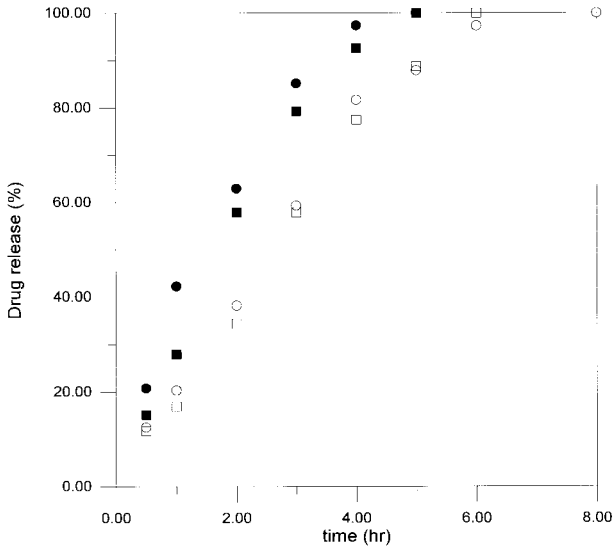

Figure 11 Effect of the polymer-to-drug ratio on the rate of theophylline releasing from the CDS tablet in the pH 7.2 medium. Key: 70,000 M_w, (■) polymer-to-drug ratio is 3 : 10; 2,000,000 M_w, (□) polymer-to-drug ratio is 1 : 1; (●) polymer-to-drug ratio is 3 : 10; (○) polymer-to-drug ratio is 1 : 1.

Table II Release Exponent *n* for Theophylline Release from Various Tablets

Tablet Type	Molecular Weight of Chitosan	Polymer to Drug Ratio	Exponent *n* Value
CDS	70,000	3 : 10	0.898
CDS	70,000	1 : 1	0.934
CDS	2,000,000	3 : 10	0.732
CDS	2,000,000	1 : 1	0.927
CDGA	70,000	1 : 1 : 10	0.603
CDGA	70,000	2 : 1 : 10	0.664
CDGA	70,000	3 : 1 : 10	0.712

strates a very slow dissolution rate as compared to CW or CD (CDG and CDS) tablet; whereas, the prolonging of the dissolution period in pH 7.2 medium is not found. Accordingly, if the active sites on the polymer molecules for the complex are not greatly affected by steric hindrance, the binding ratio should be altered with a change of the pH value in the media; so increase in the binding ratio should be responsible for the decrease of the dissolution rate of the complex tablet. As shown in Table I, in the pH 1.2 medium, the *n* values of CDGA tablets are about 0.6–0.7; and the drug release mechanism is a swelling-controlled release. The chitosan–alginate interpolymer

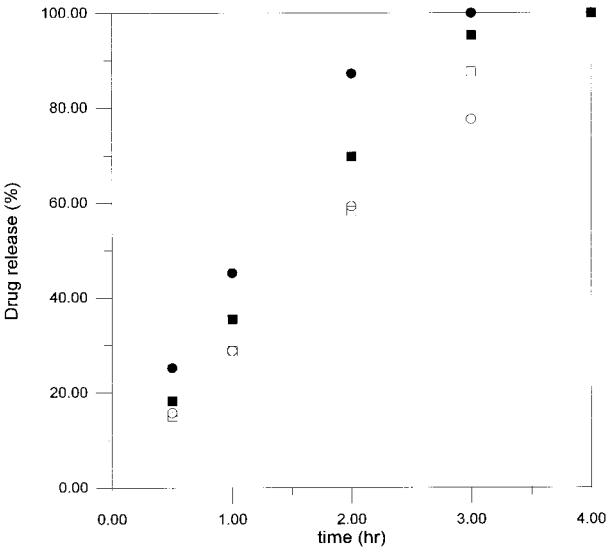

Figure 12 Effect of polymer-to-drug ratio on the rate of theophylline releasing from the CDS tablet in the pH 1.2 medium. Key: 70,000 M_w, (■) polymer-to-drug ratio is 3 : 10; (□) polymer-to-drug ratio is 1 : 1; 2,000,000 M_w, (●) polymer-to-drug ratio is 3 : 10; (○) polymer-to-drug ratio is 1 : 1.

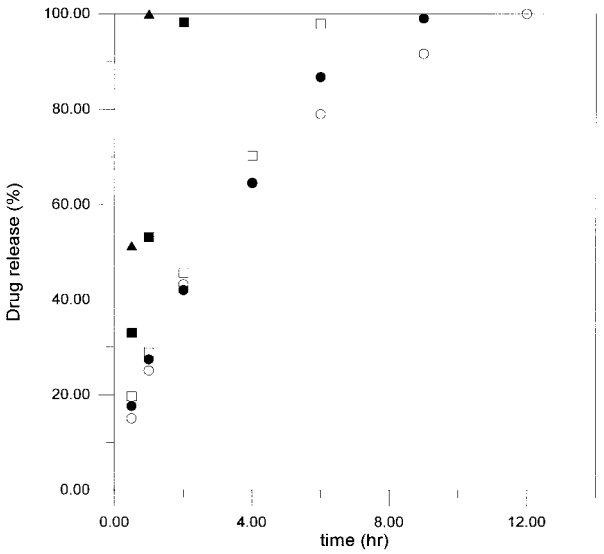

Figure 13 Effect of anionic polymer to cationic polymer ratio on the rate of theophylline releasing from the CDGA tablet in the pH 1.2 and 7.2 media. Key: (■) in pH 7.2 medium, alginate-to-chitosan drug ratio is 1 : 1 : 10; in pH 1.2 medium, (□) alginate-to-chitosan drug ratio is 1 : 1 : 10; (●) alginate-to-chitosan drug ratio is 2 : 1 : 10; (○) alginate-to-chitosan drug ratio is 3 : 1 : 10; (▲) tripolyphosphate-to-chitosan drug ratio is 1 : 1 : 10.

crosslinking density of the CDGA tablet depends on the chitosan-to-alginate binding ratio and is the most important factor to influence the drug release mechanism. Much larger amounts of alginate were required to interact with chitosan molecules in the pH 1.2 medium; so a higher alginate-to-chitosan blending ratio could improve the interpolymer binding ratio in the CDGA tablets. High crosslinking density of the CDGA tablet would change the drug release mechanism from the swelling-controlled approach to Fickian diffusion-controlled release.

REFERENCES

1. M. M. Ghorab, H. Zia, and L. A. Luzzi, *J. Microencapsul.,* **7,** 447 (1990).
2. Kjuni, J. Ogata, N. Matsui, M. Kubota, and M. Nakano, *Chem. Pharm. Bull.,* **33,** 1609 (1985).
3. M. C. Garcia, J. A. Diez, L. G. Vallejo, and M. C. Cartagena, *Ind. Eng. Chem. Res.,* **35,** 245 (1996).
4. Y. Nishioka, S. Kyotani, H. Masui, M. Okamura, M. Miyazaki, S. Ohnishi, Y. Yamamoto, and K. Ito, *Chem. Pharm. Bull.,* **37,** 3074 (1989).
5. Y. Ohya, T. Takei, H. Kobatashi, and T. Ouchi, *J. Microencapsul.,* **10,** 1-9 (1993).
6. D. C. Tsai, S. A. Howard, T. F. Hogan, C. J. Ma-

langa, S. J. Kandzari, and K. H. Ma, *J. Microencapsul.,* **3,** 181 (1986).
7. K. Watanabe, I. Saiki, Y. Matsumoto, I. Azuma, H. Sed, H. Okuyama, Y. Uraki, Y. Miura, and S. Tokura, *Carbohydr. Polym.,* **17,** 29 (1992).
8. S. K. Baveja and K. V. Ranga, *Int. J. Pharm.,* **31,** 169 (1986).
9. G. W. Davidson and N. A. Peppas, *J. Control. Release,* **3,** 243 (1986).
10. G. W. Davidson and N. A. Peppas, *J. Control. Release,* **3,** 259 (1986).
11. K. P. Devi, S. Baveja, M. Fathi, and M. Roth, *Pharm. Res.,* **6,** 313 (1989).
12. R. W. Korsmeyer and N. A. Peppas, *J. Control. Release,* **1,** 89 (1984).
13. P. I. Lee, *J. Control. Release,* **2,** 277 (1985).
14. N. A. Peppas and N. M. Franson, *J. Polym. Sci., Polym. Phys.,* **21,** 983 (1983).
15. L. B. Peppas and N. A. Peppas, *J. Control. Release,* **8,** 267 (1989).
16. D. Hariharan and N. A. Peppas, *Polymer,* **37,** 149 (1996).
17. J. L. Ford, M. H. Rubinstein, J. E. Hogan, and P. J. Edgar, *Int. J. Pharm.,* **40,** 223 (1987).
18. J. S. Lai, C. H. Chiang, and T. H. Wu, *Drug Dev. Ind. Pharm.,* **13,** 1399 (1987).
19. P. Adusumilli and S. Bolton, *Drug Dev. Ind. Pharm.,* **17,** 1931 (1991).
20. A. A. Muzzarelli, *Carbohydr. Polym.,* **3,** 52 (1990).
21. S. H. Pangburn, P. V. Trescony, and J. Heller, *Biomaterials,* **3,** 105 (1982).
22. H. Sashiwa, H. Saimoto, Y. Shigemasa, R. Ogawa, and S. Tokura, *Int. J. Biol. Macromol.,* **12,** 295 (1990).
23. R. A. Muzzarelli, *Carbohydr. Polym.,* **20,** 7 (1993).
24. G. C. Ritthidej, P. Chomto, S. Pummangura, and P. Menasveta, *Drug Dev. Ind. Pharm.,* **20,** 2019 (1994).
25. A. G. Nigalaye, P. Adusumilli, and S. Bolton, *Drug Dev. Ind. Pharm.,* **16,** 449 (1990).
26. S. K. Baveja and K. V. Ranga, *Int. J. Pharm.,* **39,** 39 (1987).
27. S. Shiraishi, T. Imai, and M. Otagiri, *Int. J. Pharm.,* **25,** 217 (1993).
28. C. H. Chu, T. Sakiyama, and T. Yano, *Biosci. Biotech. Biochem.,* **59,** 717 (1995).
29. T. Sakiyama, C. H. Chu, T. Fujii, and T. Yano, *J. Appl. Polym. Sci.,* **50,** 2021 (1993).