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Chitosan and Sodium Alginate–Based Bioadhesive Vaginal Tablets

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ABSTRACT Metronidazole was formulated in mucoadhesive vaginal tablets by directly compressing the natural cationic polymer chitosan, loosely cross-linked with glutaraldehyde, together with sodium alginate with or without microcrystalline cellulose (MCC). Sodium carboxymethylcellulose (CMC) was added to some of the formulations. The drug content in tablets was 20%. Drug dissolution rate studies from tablets were carried out in buffer pH 4.8 and distilled water. Swelling indices and adhesion forces were also measured for all formulations. The formula (FIII) containing 6% chitosan, 24% sodium alginate, 30% sodium CMC, and 20% MCC showed adequate release properties in both media and gave lower values of swelling index compared with the other examined formulations. FIII also proved to have good adhesion properties with minimum applied weights. Moreover, its release properties (% dissolution efficiency, DE) in buffer pH 4.8, as well as release mechanism (n values), were negligibly affected by aging. Thus, this formula may be considered a good candidate for vaginal mucoadhesive dosage forms.

KEYWORDS: metronidazole, chitosan, sodium alginate, mucoadhesion, swelling, release study

INTRODUCTION

The use of natural polymers is valuable based on proven biocompatability and safety. In this respect, the polysaccharides chitosan and sodium alginate, a cationic and an anionic agent, respectively, have received particular attention.[1]

Chitosan possesses favorable properties and hence has applications in the pharmaceutical and biomedical fields.[2] It is a promising bioadhesive material at physiological pHs. This polymer possesses OH and NH_2 groups that can give rise to hydrogen bonding. Its linear molecules express sufficient chain flexibility, and their conformation is highly dependent on ionic strength. These properties are considered essential for mucoadhesion.[3,4] Moreover, chitosan is suited for repeated adhesion, since it did not become inactivated after the first contact and no drop in mucoadhesion resulted.[5] A general observation is that chitosan achieves a sustained release behavior at a concentration ≥ 50% of tablet weight.[6,7]

Formation of interpolymer complexes of chitosan with alginate[1] and sodium carboxymethylcellulose (CMC) was investigated.[8,9] It has been reported that drug release from in situ polyion complexes affords more sustained effect than the preformed complexes.[10] Polymer blends can combine attributes of different polymers to give a superior quality for the dosage form.[11] Moreover, polyionic interaction of chitosan with anionic polymers will permit a considerable reduction of chitosan concentration in tablet.[11]

Although chitosan has been used in tablets intended for oral sustained-release preparations, its administration into the vagina has not been reported. This study accounts for the possible use of chitosan in mixture of different ratios with anionic polymers for the preparation of mucoadhesive tablets to be used as a vaginal delivery system for metronidazole.

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MATERIALS AND METHODS

Chemicals

Metronidazole powder came from Sigma Chemical Co (St. Louis, MO). Avicel PH 102 (microcrystalline cellulose [MCC]) was courtesy of Pharco Pharmaceuticals (Alexandria, Egypt). Chitosan (CS) of low-viscosity grade (molecular weight = 625 000) came from Protan Laboratories (Redmond, WA). Sodium alginate (Sod alg.) with glucoronic acid content of 69% with a medium polymerization degree of 400 to 600 came from Coloplast (Cambridge, UK). Sodium carboxymethylcellulose (Sod CMC) came from BDH Chemicals Ltd (Poole, England; degree of substitution not less than 0.4). A 1% w/v solution in water has a viscosity at 20°C of 8 cP. All other chemicals were of analytical grade.

Preparation of metronidazole vaginal tablets

Chitosan (0.4 g) was soaked in 5.5 mL of 10% acetic acid for 48 hours; the lumps were homogenized using a spatula and left for 1 hour at room temperature. The mass was then taken by a plastic syringe and extruded onto a teflon plate, left for 1 hour at room temperature, then dried in an oven at 50°C for 8 hours.[12]

Table 1. Composition of Metronidazole Tablet Formulations*

Formula	Drug, %	CS, %	MCC, %	Sod alg, %	Sod CMC, %
I	20	6	50	24	—
II	20	6	—	24	50
III	20	6	20	24	30
IV	20	8.9	—	35.6	35.6

*CS indicates chitosan; MCC, microcrystalline cellulose; sod alg, sodium alginate; sod CMC, sodium carboxymethylcellulose.

Rods obtained were cut into small pieces and soaked in 5% glutaraldehyde for 1 minute (≈ 1.5 mL/0.4 g chitosan). They were then filtered, left to dry in a desiccator overnight, and powdered in a mortar. Under the conditions of the time of cross-linking and the amount of glutaraldehyde used, a loose cross-linking is achieved.[13]

Tablets containing 20% metronidazole and weighing 200 or 500 mg were prepared by direct compression of drug powder mixture using flat face, 9- or 12-mm punch (**Table 1**). A particle size of less than 160 µm for all components was selected to avoid any fraction segregation.

Evaluation of the prepared tablet formulations

Average drug content

Tablets of each formulation were ground in a mortar to a powder form. An accurately weighed amount of the powder, equivalent to 100 mg of metronidazole, was transferred to a 100-mL volumetric flask. The powder was dissolved in 10% acetic acid using a magnetic stirrer overnight. After filtration, the solution was assayed spectrophotometrically (Ultrospec III, Pharmacia LKB Biochrom, Cambridge, England) for metronidazole at 286 nm against 10% acetic acid as blank. The content was calculated using a preconstructed calibration curve for the drug (1-2.5 mg%) in 10% acetic acid. No interference from any of the tablet components was observed under the conditions of the assay procedure.

Dissolution rate study

The drug release rate was determined using USP dissolution apparatus II. A tablet (500 mg) was glued in the center of a 9-cm-diameter glass disc. Dissolution media were 650 mL of either distilled water pH 5.5 or citrate buffer pH 4.8 maintained at 37°C ± 0.1°C and stirred at 25 rpm. Two different media were used to examine the difference between the release of drug in water and in buffer. Samples (5 mL) withdrawn at suitable time intervals were compensated with fresh dissolution medium and assayed spectrophotometrically at 319 nm. No interference occurred due to tablet excipients or to α-cyanoacrylate glue at this wavelength. Samples were assayed in triplicate.

Swelling study

The weight of medicated tablets was determined (W_1). Each tablet was placed separately in a 25-mL beaker containing 5 mL citrate buffer pH 4.8. The beakers were stored at 25°C and 37°C ± 0.1°C. Tablets were removed at different time intervals (0.25, 0.5, 1, 2, and 4 hours), wiped with filter paper, and reweighed (W_2). The swelling index was calculated as follows[14]:

Swelling index = $(W_2–W_1)/ W_1$

Swelling index of FI could not be measured because the tablets completely disintegrated as soon as 5 mL of buffer pH 4.8 was added, at both temperatures. Each experiment was performed in triplicate using 500-mg tablets.

Determination of bioadhesive properties

A modified balance method[14] was adopted to measure bioadhesion properties. A rabbit intestine was dissected and placed in normal saline after being washed of all food debris. The intestine, cut into 5-cm lengths, was adhered to a moving platform with α-cyanoacrylate glue. Tablets (200 mg) were glued to different weights (1, 2, 5, and 10 g) with α-cyanoacrylate glue. This was followed by taring the balance. A volume (0.1 mL) of buffer pH 4.8 was slowly added using a plastic syringe over the mucosal sample. The platform was slowly raised until the tablet touched the mucosa. The tablet and mucosa were left in contact for 15 minutes, after which the balance was retared, and corresponding weights were added to the pan. The addition was stopped upon detachment of the tablet from the mucosa. The equivalent adhesion force[15] was then calculated in g/cm^2. Each adhesion experiment was repeated 6 times.

Effect of aging on the selected formulation

Tablets of (500 mg) FIII were stored in closed glass containers in a desiccator protected from light. The effect of aging on the dissolution rate of the selected formulation was determined after 18 months of storage.

RESULTS AND DISCUSSION

Average drug content was 101.02 % ± 2.1, and the results of the content uniformity test proved that there was homogenous drug distribution.

Dissolution rate study

The release of metronidazole in either distilled water or buffer pH 4.8 from different matrix formulations is shown in **Figures 1a and 1b**, respectively. No lag time was observed in any of the formulations studied in both dissolution media. **Table 2** shows values of dissolution efficiency (DE) calculated at 8 hours for the different formulations in both media. DE is a parameter that represents the percentage between the area under the curve at time t and the area of the rectangle defined by 100% dissolution at the same time t.[16]

In the case of FI, in buffer pH 4.8, there is an initial burst effect seen visually in the early stage of the dissolution run. This phase may be due to the disintegrative effect of MCC (50%), which takes water rapidly by capillarity through available pores in the matrix.[17] After this initial phase, hydration and gel formation of chitosan (pka = 6.5) in acid buffer medium (pH 4.8) causes clogging of pores, thus hindering the entrance of water, which then occurs by slow diffusion through the gel layer.[18]

In water, the initial burst effect almost disappeared. This effect may be due to easy hydration and gelation of sodium alginate, leading to early clogging of available pores in the matrix and, therefore, to much slower tablet disintegration and drug dissolution. Although the number of available positive chitosan molecules decreases in water, there is an increase in available negative alginate molecules. This may change the packing arrangement of the tablet components.[19] The overall effect will result in a different pattern of dissolution compared with that in buffer.

On the other hand, release in water in the case of FII, FIII, and FIV showed an obvious increase compared with release in buffer. This difference may be due to the presence of sodium CMC (pka ≈ 4.17),[20] which was reported to interact with chitosan by ionic bond as the primary bonding force.[8] It was suggested that the optimum interaction pH is within the range of 2.5 to 5.0,[9] a range

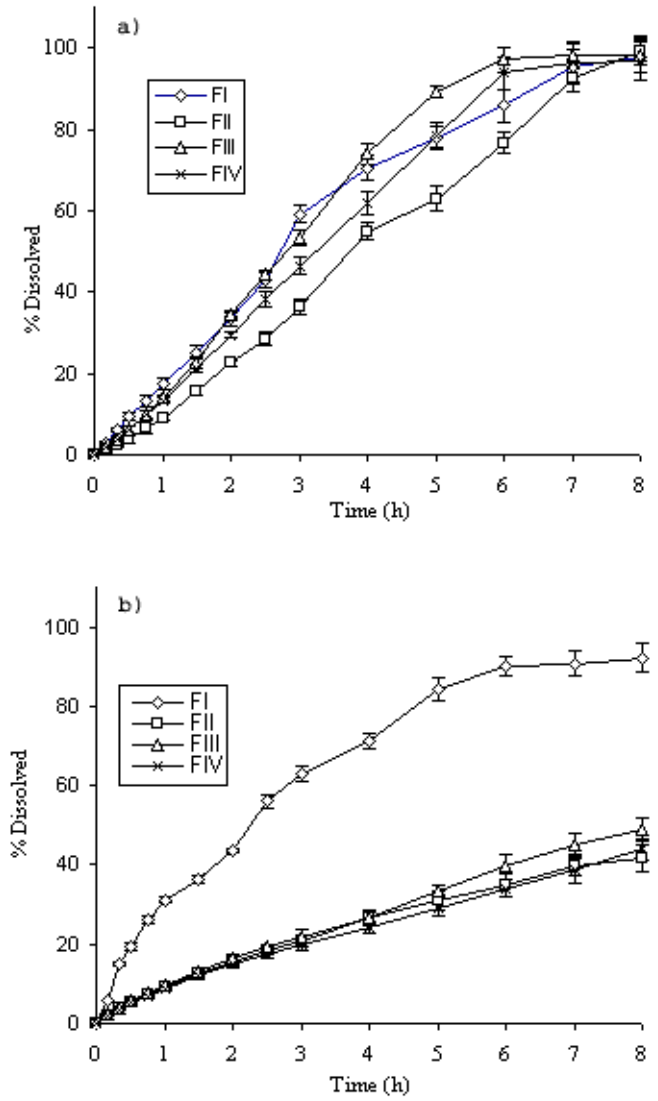

Figure 1. Metronidazole release profile from different tablet formulations in (a) distilled water and (b) buffer pH 4.8 (burst effect is clear during the first hour in FI). Error bars represent SD (n = 3).

that includes the pH of the buffer (pH 4.8). Moreover, in the latter medium, no disintegration of the tablets was observed during the test period, a fact that may be due to the persistent gel layer surrounding the tablets.[6]

It was reported that upon hydration, a mixture of MCC and sodium CMC as present in FIII generates a rheological system showing thixotropic properties over a pH range of 3.5 to 11.0.[21] This latter behavior results from the formation of a three-dimensional gel structure leading to immobilization of water molecules inside it and slowing drug release in buffer.[22] The network produced would involve hydrogen bonding between the negative oxygen of the carboxyl group of sodium CMC and hydrogen of the hydroxyl group of MCC. The increased

Table 2. Dissolution Efficiency Values for Different Metronidazole Tablet Formulations in Buffer pH 4.8 and Water

Formula	% DE (± SD)	
	Buffer pH 4.8	Water
FI	65.5 ± 2.1	60.9 ± 2.5
FII	24.9 ± 1.1	50.5 ± 1.5
FIII	27.6 ± 0.9	63.5 ± 2.5
FIV	24.1 ± 1.2	58.5 ± 1.9

* DE indicates dissolution efficiency.

Table 3. Estimated Values of k and n by Regression of log M_t/M_∞ on log t*

Formula	r^2		n		k	
	Buffer pH 4.8	Water	Buffer pH 4.8	Water	Buffer pH 4.8	Water
I	0.993	0.985	0.804	0.798	1.077	0.697
II	0.986	0.928	0.667	0.813	0.639	0.383
III	0.988	0.955	0.681	0.827	0.641	0.512
IV	0.984	0.956	0.668	0.802	0.609	0.523

*$M_t/M_\infty = kt^n$. [23]

release in water compared with buffer is due to the fact that the combination of MCC and sodium CMC needs little hydration time in such a medium.[21]

Although the releases from FII and FIV were nearly similar in buffer, they exhibited an appreciable difference in water. FII, which contains a higher proportion of sodium CMC, showed a slower release. The excess free sodium CMC content in FII may form a gel layer surrounding the tablet and hindering dissolution.

The mode of drug release from the prepared tablets was evaluated using the equation $M_t/M_\alpha = kt^n$,[23] where M_t/M_α is the fraction solute released into dissolution medium, k is a constant that relates to the properties of the polymer and drug, and n is the diffusional exponent. **Table 3** summarizes the values of n for all the formulations tested in both dissolution media. The values found for n are between 0.667 and 0.827 in all cases, exhibiting a non-Fickian release behavior controlled by a combination of diffusion and chain relaxation mechanism.

Swelling study

Swelling is an important parameter to be studied before considering mucoadhesion. While some reports showed a direct relation between swelling and mucoadhesion, others did not.[24,25] The swelling results were expressed in terms of swelling index at 25°C and 37°C. The rank order for swelling index was FIV > FII > FIII at both temperatures studied. FI was excluded, because it readily disintegrated in contact with the medium. The results at 37°C were higher than those at 25°C. This may be due to the higher kinetic energy of water molecules moving inside the polymer matrix.

Taking the results at 37°C as a representative example for swelling index (**Figure 2**), the curves in general showed an initial rapid rise in the first 15 minutes due to the entry of water via metastable pores. This mechanism is known as hysteresis of the swelling.[26]

In the case of FIV, the curve gave a linear increase all over the time of the experiment with no plateau formation, indicating a loosening of the matrix with the creation of larger pores. In addition, the network structure formed because of polyionic interaction is capable of absorbing water yet still remaining insoluble.[27]

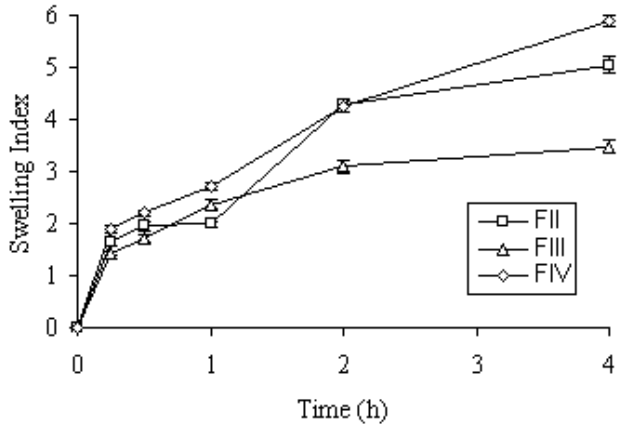

Figure 2. Swelling index profile of metronidazole tablet formulations at 37ºC in buffer pH 4.8. Error bars represent SD (n = 3).

On the other hand, FII showed a decrease in swelling index from about 30 minutes to 1 hour compared with FIII and FIV. A protective gel layer caused by excess sodium CMC content may be formed before water enters the matrix and hydrates the inner layers.[28] However, an obvious increase of swelling index occurred from 1 to 2 hours. As the sodium CMC becomes hydrated and forms a swollen gel, dissolution and surface erosion of this water-logged gel occur simultaneously.[29] The plateau formation afterward may be due to the solvent fronts on each face of the matrix meeting in the center of the tablet and leaving no further unhydrated polymer to hydrate and expand.[28]

Regarding FIII, the values of swelling index were rather low at all times following the first 15 minutes with attainment of an equilibrium state. MCC is known to hydrate by capillary rise. The water intake by MCC was reported to be almost equal to the void space.[17] Moreover, involvement of MCC in thixotropic formation with sodium CMC upon hydration will decrease the rate and extent of swelling.[22]

Adhesion study

The results of the bioadhesion study are shown in **Figure 3**. The rank order for the different formulations was as follows: FIII > FIV > FII > FI.

It was suggested by several workers that the initial interaction between the polymer and the biological surface is through electrostatic interaction followed by mechanical interlocking of the polymer chains.[30] Therefore, the surface charge density of polymers is important for electrostatic behavior during the adhesion process.[30]

At acidic pH simulating that of the vagina (buffer pH 4.8), chitosan has been identified as a linear polycation that readily adheres to negatively charged surfaces.[5] In the case of FI, after a slight increase in weight from 1 to 2 g, the values of adhesion force remained constant. Despite the presence of a high content of positive charge in FI compared with the other formulations, FI exhibited a low bioadhesive strength. The low adhesion force values of FI may be due to its high content of MCC causing a discontinuity in the gel structure.[31] In the case of FII, the adhesion force slightly increased with an increase in applied weight from 2 to 10 g. FII has the highest content of negative charge among all the formulations, which decreases the net positive charge of chitosan available for adhesion. The force required for detachment increased slightly with the applied weight, probably due to better contact with the mucus layer.[32] The values of adhesion force obtained with FIII were more or less constant, showing a very slight decrease with the increase in applied weight. On the other hand, the values obtained with FIV showed an appreciable increase from 1 to 2 g applied weight, followed by a decrease at higher applied weights (5 to 10 g).

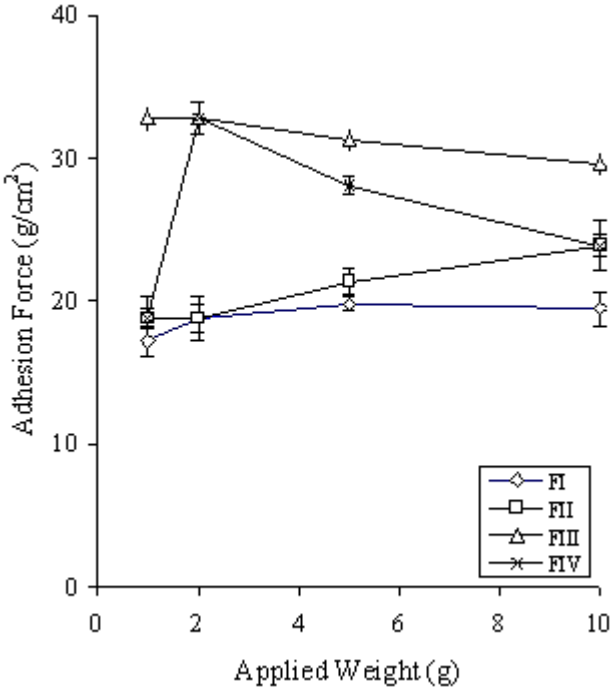

Figure 3. Adhesion force profile of metronidazole tablet formulations. Error bars represent SD (n = 6).

In these two formulations (FIII and FIV), no relationship could be found between swelling and bioadhesion,[25] although swelling ability of the bioadhesive formulation is said to be advantageous in obtaining a good polymer-mucosa interaction.[3] Adhesion occurs shortly after the beginning of swelling, but the bond formed may not be very strong. In the case of FIII, which was the least hy-

drated, as shown from the results of swelling index (**Figure 2**), FIII would be pressed into the cell surface instead of interacting with only the mucin layer; consequently, this could result in a higher force required for its detachment.[30] The formation of a rigid network due to cross-linking between sodium CMC and MCC,[22] associated with FIII's restricted hydration, may have enhanced mucoadhesion properties of FIII. Moreover, the involvement of carboxylic groups of sodium CMC in such cross-links would leave more free NH_2 groups in chitosan for binding with mucin.

With FIV, an applied force of 2 g may provide enough surface area of contact between the hydrated tablet and the most upper layer of the mucus. However, the increase in applied weight with such a highly hydrated matrix may cause adhesive joint failure and therefore easy detachment.[30]

Dissolution rate after aging study

FIII gave suitable sustained-release properties in both media. Moreover, it exhibited good adhesion properties even at the lowest applied weight. The effect of aging on its release properties was therefore studied.

For comparison reasons, DE (%) was calculated and found to be (63.5, 27.6) before and (54.3, 30.9) after aging in water and in phosphate buffer pH 4.8, respectively. The release pattern showed a very slight increase in buffer pH 4.8 (% DE change = 3.3%), while a slight decrease in release was observed in water (% DE change = 9.2%). Also, the release mechanism was negligibly affected by aging, as indicated by the calculated n values before (0.827, 0.681) and after (0.812, 0.751) aging in water and in phosphate buffer pH 4.8, respectively. Statistical evaluation of the observed difference in % DE showed a statistically significant difference ($P \leq .05$) between the release of metronidazole before and after storage in water only.

During storage, some water from the environment is adsorbed on the tablet surface, causing the start of ionization of exposed carboxylate groups of sodium CMC and some interaction with hydroxyl groups of MCC, and production of a gel film around the matrix with subsequent clogging of the surface pores. Consequently, the retardation of drug release in water could be due to decrease of available pores for water penetration.

CONCLUSION

In conclusion, FIII containing 6% chitosan, 24% sodium alginate, 30% sodium CMC, and 20% MCC was found to be the best formulation regarding all the properties evaluated in order to achieve the aim of this study. Its matrix released about 100% of metronidazole content over a period of 8 hours in buffer pH 4.8. Moreover, maximum adhesion was obtained with a minimum pressure applied (1 g). This lack of pressure effect may be of value during insertion in the vagina, as it differentiates this formulation from other pressure-sensitive adhesive formulations.

The persistent gel layer surrounding the tablet formulations studied at acidic buffer pH 4.8, simulating that of the vagina, may prevent irritation to the vaginal mucosa.

Tablets were prepared by direct compression, which is an easy, rapid, and cheap method. No organic solvent was used during the preparation of the formulations. All excipients used are safe and available.

REFERENCES

1. Miyazaki S, Nakayama A, Oda M, Takada M, Attwood D. Chitosan and sodium alginate based bioadhesive tablets for intraoral drug delivery. Biol Pharm Bull. 1994;17:745-747.

2. Felt O, Buri P, Gurny R. Chitosan: a unique polysaccharide for drug delivery. Drug Dev Ind Pharm. 1998;24:979-993.

3. Peppas NA, Bury PA. Surface interfacial and molecular aspects of polymer bioadhesion on soft tissues. J Control Rel. 1985;2:257-275.

4. Robinson JR, Mlynek GM. Bioadhesive and phase-change polymers for ocular drug delivery. Adv Drug Del Rev. 1995;16:45-50.

5. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int J Pharm. 1992;78:43-48.

6. Sawayanagi Y, Nambu N, Nagai T. Use of chitosan for sustained release preparations of water soluble drugs. Chem Pharm Bull. 1982;30:4213-4215.

7. Nigalaye AG, Adusumilli P, Bolton S. Investigation of prolonged drug release from matrix formulations of chitosan. Drug Dev Ind Pharm. 1990;16:449-467.

8. Fukuda H, Kikuchi Y. Polyelectrolyte complexes of sodium carboxymethylcellulose with chitosan. Makromol Chem. 1979;180:1631-1633.

9. Lin SY, Lin PC. Effect of acid type, acetic acid and sodium carboxymethylcellulose concentrations on the formation, micromeretic, dissolution and floating properties of theophylline chitosan microcapsules. Chem Pharm Bull. 1992;40:2491-2497.

10. Meshali MM, Gabr KE. Effect of interpolymer complex formation of chitosan with pectin or acacia on the release behaviour of chlorpromazine HCl. Int J Pharm. 1993;89:177-181.

11. Lee JW, Park JH, Robinson JR. Bioadhesive-based dosage forms: the next generation. J Pharm Sci. 2000;89:850-866.

12. Hou W, Miyazaki S, Takada M, Komai T. Sustained release of indomethacin from chitosan granules. Chem Pharm Bull. 1985;33:3986-3992.

13. Wang YM, Sato H, Adachi I, Horikoshi I. Optimization of the formulation design of chitosan microspheres containing cisplatin. J Pharm Sci. 1996;85:1204-1210.

14. Parodi B, Russo E, Caviglioli G, Cafaggi S, Bignardi G. Development and characterization of a buccoadhesive dosage form of oxycodone hydrochloride. Drug Dev Ind Pharm. 1996;22:445-450.

15. Chitnis VS, Malshe VS, Lalla JK. Bioadhesive polymers "synthesis, evaluation and application in controlled release tablets. Drug Dev Ind Pharm. 1991;17:879-892.

16. Khan KA. The concept of dissolution efficiency. J Pharm Pharmacol. 1975;27:48-49.

17. Nogami H, Nagai T, Fukuoka E, Sonobe T. Disintegration of the aspirin tablets containing potato starch and microcrystalline cellulose in various concentrations. Chem Pharm Bull. 1969;17:1450-1455.

18. Miyazaki S, Yamaguchi H, Yokouchi C, Takada M, Hou WM. Sustained release of indomethacin from chitosan granules in beagle dogs. J Pharm Pharmacol. 1988;40:642-643.

19. Devi KP, Rao KVR, Baveja S, Fathi M, Roth M. Zero-order release formulation of oxprenolol hydrochloride with swelling and erosion control. Pharm Res. 1989;6:313-317.

20. Koh GL, Tucker LG. Characterization of sodium carboxymethylcellulose gelatin complex coacervation by viscosity, turbidity and coacervate wet weight and volume measurements. J Pharm Pharmacol. 1988;40:233-236.

21. Ofner CM III, Schnaare RL, Schwartz JB. Oral aqueous suspensions. In: Liebermann HA, Rieger MM, Banker GS, eds. Pharmaceutical Dosage Forms: Disperse Systems. Vol 2. 2nd ed. New York, NY: Marcel Dekker Inc; 1996:149-181.

22. Dolz M, Roldan C, Herraez JV, Belda R, Sobrino P. Viscoelastic behaviour of MCC hydrogels. Pharm Acta Helv. 1991;66:281-285.

23. Peppas NA. Analysis of Fickian and non Fickian drug release from polymers. Pharm Acta Helv. 1985;60:110-111.

24. Ch'ng HS, Park H, Kelly P, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery, II: synthesis and evaluation of some swelling water insoluble bioadhesive polymers. J Pharm Sci. 1985;74:399-405.

25. Bottenberg P, Cleymaet R, De Muynck C, et al. Development and testing of bioadhesive fluoride-containing slow-release tablets for oral use. J Pharm Pharmacol. 1991;43:457-464.

26. Carcia-Gonzalez N, Kellaway IW, Blanco-Fuente H. Design and evaluation of buccoadhesive metoclopramide hydrogels composed of poly (-acrylic acid) cross-linked with sucrose. Int J Pharm. 1993;100:65-70.

27. Noble L, Gray AI, Sadiq L, Uchegbu IF. A noncovalently cross-linked chitosan based hydrogel. Int J Pharm. 1999;192:173-182.

28. Mitchell K, Ford JL, Armstrong DJ, Elliott PNC, Hogan JE, Rostron C. The influence of drugs on the properties of gels and swelling characteristics of matrices containing methyl cellulose or hydroxypropylmethlyl cellulose. Int J Pharm. 1993;100:165-173.

29. Wan LSC, Heng PWS, Wong LF. Relationship between swelling and drug release in a hydrophilic matrix. Drug Dev Ind Pharm. 1993;19:1201-1210.

30. Tur KM, Ch'ng HS. Evaluation of possible mechanism(s) of bioadhesion. Int J Pharm. 1998;160:61-74.

31. Xu G, Sunada H. Influence of formulation change on drug release kinetics from hydroxypropylmethyl cellulose matrix tablets. Chem Pharm Bull. 1995;43:483-487.

32. Mortazavi SA, Carpenter BG, Smart JD. A comparative study on the role played by mucus glycoproteins in the rheological behaviour of the mucoadhesive/mucosal interface. Int J Pharm. 1993;94:195-201.