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Controlled Release and Stabilization of Cefaclor from Alginate-based Matrices for Oral Delivery Design

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ABSTRACT–Alginate based polymeric matrices were designed for controlled release and stabilization of cefaclor in gastrointestinal fluid. Cefaclor is known to be acid stable and subjected to be degraded at neutral and alkaline pHs. In order to achieve an effective release profile of cefaclor in gastrointestinal tract, a particular strategy in dosage form design should be required from the view point of maintaining its activity. The amphiphilic nature of cefaclor allowed its controlled release using ionic polymers based on ionic interaction between the drug and polymers. The thrust of this study was to develop a technique that delivers cefaclor keeping effective release rate in the intestinal tract. Considering the fast degradation of cefaclor in the intestinal fluid, the matrices were designed to release surplus amount of cefaclor. The alginate based matrices demonstrated increase in release rate in the simulated intestinal fluid, which was favorable to compensate the degraded portion of cefaclor. In addition, stabilization of cefaclor in the intestinal fluid was obtained by employing citric acid that provides an local acidic environment. The matrices might be valuably used for the development of an oral cefaclor dosage form.

Key words–Controlled release, Cefaclor, Stabilization, Alginate, Polymer matrices

Introduction

Cefaclor is a semisynthetic cephalosporin and used in the treatment of1 otitis media, lower and upper respiratory infections, urinary tract infections. Cefaclor is water-soluble antibiotic, which is well absorbed in the intestine. Since the serum half-life in the normal subjects is 0.6 to 0.9 hour, approximately 60 to 85 percent of drugs are excreted unchanged in the urine within eight hours.[1] Cefaclor is known to be acid stable and subjected to be degraded at neutral and alkaline pHs.[2] To avoid intensive degradation in intestinal tract, releasing techniques that provide prolonged release in the stomach would be favored,[3-8] i.e., swelling or floating systems,[3] mucosa-adhesive systems.[8] However, only prolonged gastric residence of cefaclor may be limited to obtain its optimal bioavailability. The thrust of this study was to develop a technique that delivers cefaclor with an effective release rate in the intestinal tract while maintaining its activity.

Hydrophilic polymer matrices, i.e., ionic polysaccharides, have been utilized for oral controlled release dosage form design.[9-15] Various properties of polymers [16-18] and the stability of drugs in gastrointestinal fluid were main issues for the design of oral controlled delivery.[19] Cefaclor is a zwitterionic drug with pKa_1=1.5 and pKa_2=7.17 for the dissociation of carboxylic acid and the -amino group, respectively.[20] Ionic interaction between polymer and cefaclor is thus expected to affects drug release aspects at various pH conditions. Meanwhile, cefaclor is acid stable (most stable at pH3.5) and loses its activity at neutral and alkaline pHs. This property seriously requires a stabilization technique of cefaclor especially for controlled release design in the intestinal tract. The gastric residence time may not be sufficient to obtain effective sustained release profile and overall therapeutic efficacy of cefaclor. In this study, an acidifying agent, citric acid, which can provide local acidic environment was incorporated into polymer matrices. The objectives of this study were to achieve an optimal controlled release pattern of cefaclor in gastrointestinal fluid and to improve the stability of cefaclor in intestinal fluid by introducing acidifying agent.

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Experimental

Materials

Cefaclor, sodium alginate and chitosan were purchased from Showa (Japan). Hydroxypropylmethylcellulose, citric acid and lactose were purchased from Fisher (USA). All other chemicals and solvents were of analytical grade.

Matrix fabrication

Matrices were prepared by direct compression using different ratios of each hydrophilic polymer as listed in Table I. Magnesium stearate (1%) was used as a lubricant prior to com-

Table I–*Composition of cefaclor contained polymer matrices (mg)*

	Cefaclor	Alginate	Chitosan	HPMC	Lactose	Citric acid
1	250	54.5			195.5	
2	250	109			141	
3	250	218			32	
4	250	250				
5	250		250			
6	250					
7	250			250		
8	250	125		125		
9	250		125	125		
10	250	125		50		75
11	250	50	200			

*All tablets contained 1% Magnesium stearate as lubricant.

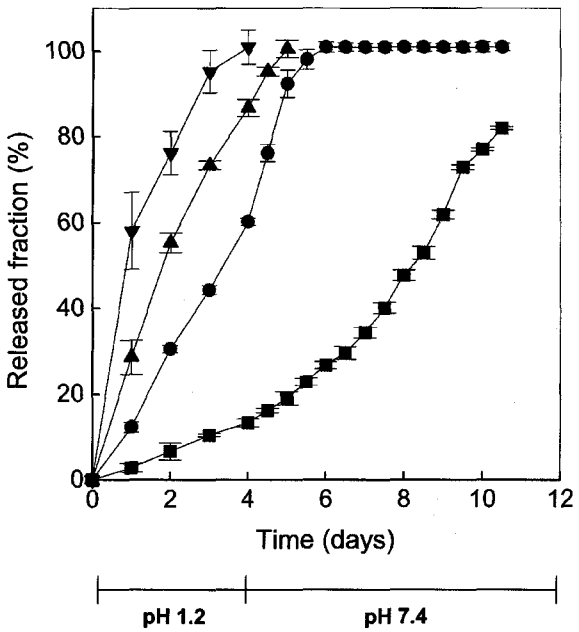

Figure 1–Release profiles of cefaclor from various polymer matrices. (■) Cefaclor:alginate=250:250(mg), (●) cefaclor:chitosan=250:250, (▲) cefaclor:HPMC=250:250, (▼) cefaclor:lactose =250:250.

pression. Blends of polymer, cefaclor (250 mg), and/or lactose (500 mg total weight) were directly compressed using a hydraulic press (Fred S. Carver, WIS, USA) equipped with a manometer at 9000 lbs for 60s; a flat punch of 13mm diameter was used.

Release experiment

In vitro release tests of cefaclor were performed using modified USP XXII apparatus 2, at 200 rpm paddle speed, 37°C in 400 ml of pH 1.2 buffer solutions (simulated gastric fluid) for the first 4 hrs and pH 7.4 buffer solution (simulated intestinal fluid) for the following 7 hrs. Releasing medium was replenished with fresh medium every 30 minutes. In the case of whole medium exchange, total releasing medium was withdrawn and replenished with flesh medium at predetermined time interval. Drug concentration was assayed using a high-pressure liquid chromatography (Waters 510, MA, USA). The condition of HPLC analysis were as follows : column : μ-Bondapak C18, mobile phase : MeOH : water = 40 : 60, detection : UV detector at 263 nm, flow rate : 1.0 ml/min, attenuation : 32, sensitivity : 0.01 aufs, temperature : room temperature, injection volume = 10 μl, retention time = 4.30 – 4.60 min.

Results and discussion

Figure 1 demonstrates the release of cefaclor from matrices composed of alginate, chitosan, HPMC and lactose as a control. Since HPMC is a nonionic polymer, no ionic interaction between polymer and cefaclor was expected. Release of cefaclor from HPMC matrix followed typical first-order release kinetics. HPMC matrix showed sustained release profile of cefaclor compared with lactose matrix but completed release within 4 hrs in gastric fluid. It could be postulated that ionic polymer matrices might provide prolonged release owing to ionic interaction between cefaclor and polymers. Positively charged chitosan matrix demonstrated no significant sustained release profile compared with that of HPMC matrices. Since the pKa_1 of cefaclor is 1.5, amino group is protonized and about half of carboxylic group is dissociated at pH 1.2. The electrostatic repulsion between cefaclor and the protonized amino group of chitosan might induce fast release for 4 hrs within gastric residence time. In contrast, sodium alginate, an anionic polymer, showed a significantly sustained release profile for about 10 hrs. This duration of release may cover overall gastrointestinal residence time. The retarded release rate from alginate matrix at pH 1.2 was not affected by the ionic-interaction since alginate was in undissociated form. Meanwhile, alginate is negatively ionized and cefaclor retains overall negative charge at pH 7.4. The release of cefalcor from polymer matrices was probably accelerated by the ionic repulsion between cefaclor and alginate though change in water uptake of alginate at pH 7.4 might not be ignored. Fast degradation of cefaclor in the intestinal fluid should also be taken into account. The matrices thus need to be designed to release surplus amount of cefaclor in intestinal fluid. From this aspect, advantage of using alginate for controlled release of cefaclor could be recognized and used for the following release studies.

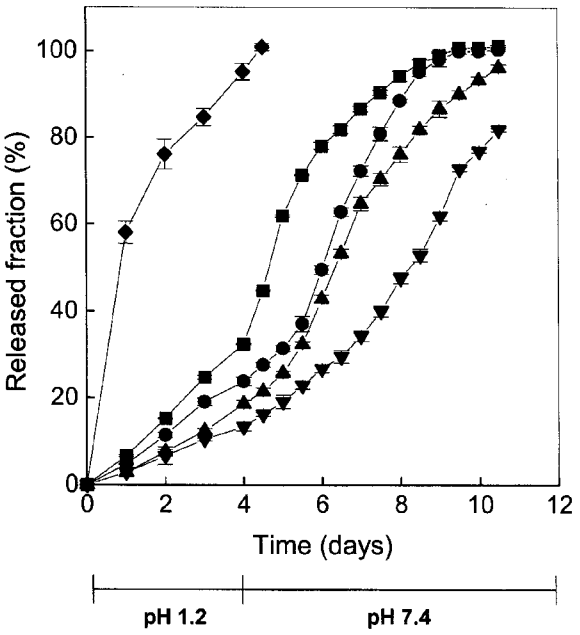

Figure 2–Release profiles of cefaclor from alginate based matrices. (■) Cefaclor:alginate:lactose=250:54:196(mg), (●) cefaclor:alginate: lactose=250:109:141, (▲) cefaclor:alginate:lactose=250:218:32, (▼) cefaclor:alginate=250:250, (◆) cefaclor:lactose=250:250.

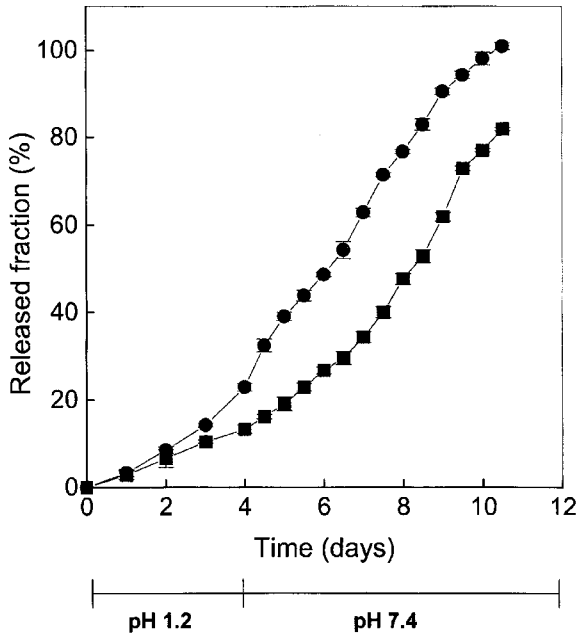

Figure 3–Release profiles of cefaclor from alginate based matrices using whole medium exchange method. (■) Cefaclor:alginate=250:250(mg), (●) cefaclor:alginate:HPMC=250:125:125.

The release profiles of cefaclor from alginate matrices with various contents are demonstrated in Figure 2. As the content of sodium alginate increased, the release rate of cefaclor was decreased while maintaining the similar aspect of release kinetics. The change in contents of alginate (the ratio of cefaclor: monomeric alginate is 2:1, 1:1, 2:1, respectively), caused gradual decrease in release rate of cefaclor. Meanwhile, enhancing effect on drug release at pH 7.4 was somewhat reduced. Further optimization of release pattern of cefaclor was attempted by employing HPMC to the alginate matrix and the result is shown in Figure 3. The effects of HPMC co-formulation on the release kinetics of cefaclor were: 1) Increasing the release rate to obtain complete release within 6 hours in pH 7.4 simulated intestinal fluid, 2) refining the release kinetics to be closer to zero order kinetics.

Figure 4 shows the release profiles of cefaclor from alginate/HPMC matrices when whole medium was not exchanged for sampling. Cefaclor in the release media was continuously exposed in pH 7.4 condition and thus subjected to degradation. The cumulative released amount of intact cefaclor appeared to be decreased at pH 7.4 medium, which indicated degradation of cefaclor. In contrast, the decrease in cefaclor was not significant in case of incorporating citric acid in matrix formulation. Citric acid maintained the local pH in the matrix around pH 5. Citric acid highly improved the stability of cefaclor in

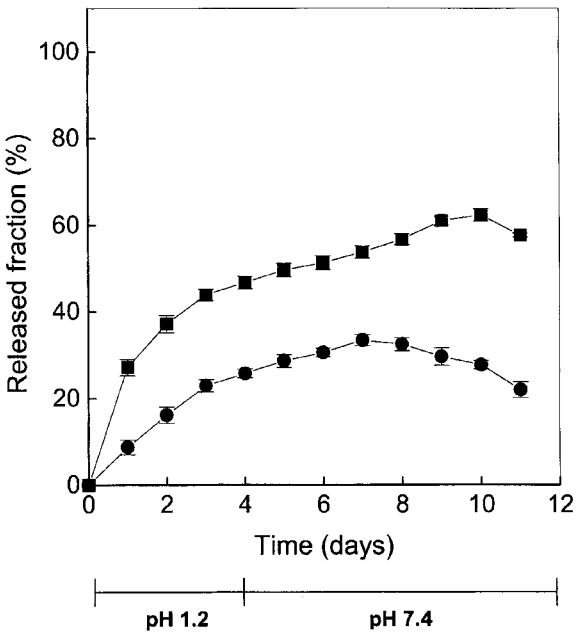

Figure 4–Release profiles of Cefaclor from alginate based matrices without using whole medium exchange. (■) Cefaclor:alginate:HPMC:citric acid=250:125:50:75(mg), (●) cefaclor:alginate:HPMC=250:125:125.

pH 7.4 condition. Since cefaclor is well absorbed in upper intestine, increasing the stability of cefaclor at pH 7.4 may be

advantageous. Local acidic condition for cefaclor may be required to increase the stability at pH 7.4 medium.

Conclusion

Effective sustained release of cefaclor was obtained using alginate based matrices. Cefaclor could be stabilized by citric acid in pH 7.4 medium. The alginate based matrices could be used as a potential oral delivery tool for cefaclor by controlling release rate and improving the stability in the intestinal fluid.

Acknowledgment

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References

1) Remington : The science and Practice of Pharmacy 20th edition, Daniel Limmer (Ed.), Lippincott Williams & Wilkins, Philadelphia, U.S.A., pp. 1525 (2000).
2) A. Dimitrovska, K. Stojanoski, K. Dorevski, Kinetics of degradation of cefaclor: I. Effect of temperature, phosphate buffer, pH and copper (II) ion on the rate of degradation, *Int. J. Pharm.*, **115**, 175-182 (1995).
3) V.S. Gerogiannis, D.M. Rekkas, P.P. Dallas and N.H. Choulis, Floating and swelling used in controlled release technology, *Drug Development and Industrial Pharmacy*, **19**, 1061-1081 (1993).
4) Rajinder Singh P Matharu, A diffusion controlled drug delivery system for theophilline, *Drug Development and Industrial Pharmacy*, **20**, 1225-1238 (1994).
5) A.A. Deshpande, C.T. Rhodes, N.H. Shah, Controlled release drug delivery systems for prolonged gastric residence, *Drug Development and Industrial Pharmacy*, **22**, 531-139 (1996).
6) R. Bodmeier *et al.*, Preparation and evaluation of drug - contain chitosan beads. *Drug Development and Industrial Pharmacy*, **16**, 418-427 (1986).
7) C.G. Valelas, D.G. Dixon and C.A. Steiner, Zero-order biphasic polymer hydrogels, *J. Controlled Release*, **34**, 185-192 (1995).
8) J.D. Smart, An *in vitro* assessment of some mucosa-adhesive dosage forms, *Int. J. Pharm.*, **73**, 69-74 (1991).
9) Y. Sawayanagi, N. Nambu and T. Nadai, The use of chitosan for Sustained-release preparation of water soluble Drugs, *Chem. Pharm. Bull.*, **30**, 4213-4215 (1982).
10) N. Xi, Z. Tu, Y. Pei, D. Lui and L. Ma, Calcium alginate as matrix for sustained release tablets, Yao Hsueh Hsueb Pao, **16**, 277-282 (1981).
11) R. Bodmeier, H. Chen and O. Paeratakul, A Novel approach to the oral delivery of micro or nanoparticles, *Pharmaceutical Research*, **6**, 115-121 (1989).
12) P. Timmins, A.M. Delagy and C.M. Minchom, Influence of some process variables on product properties for a hydrophilic matrix controlled release tablet, *Eur. J. Pharm. Biopharm.*, **38**, 113-118 (1992).
13) Y. Kanazawa, A. Koreeda, A. Harada and T. Harada, Electron microscopy of gel - forming ability of polysaccharide food additives, *Agrc. Biol. Chem.*, **53**, 979-896 (1989).
14) T.C. Dahl et al., Influence of physico-chemical properties of hydroxypropyl methylcellulose on naproxen release from sustained release matrix tablets, *J. Controlled Release*, **14**, 1-10 (1990).
15) T. Tosa, T. Mori, K. Yamamoto, I. Takata, I. Nishday and I. Chibata, I. Immobilization of enzymes and microbial cells using carrageenan as matrix, *Biotechnol. and Biotech.*, **21**, 1697-1709 (1979).
16) D.S. Jamhekar and J. Cbby, pH and flow-rate-independent release of drug from uncoated slow-release tablets, *J. Pharm. Sci.*, **74**, 991-994 (1985).
17) K.V. Rango Rao and K.P. Devi, Swelling controlled released systems: recent developments and application, *Int. J. Pharm.*, **48**, 1-13 (1988).
18) Y. Horiuchi, K. Abe, F. Hirayama and K. Uekama, Release control of theophylline by β-cyclodextrin derivatives: hybridizing effect of hydrophilic, hydrophobic and ionizable - cyclodextrin complexes, *J. Controlled Release*, **15**, 177-183 (1991).
19) M.M. Talukdar and J.P. Vercammen, Evaluation of xanthan gum as a hydrophillic matrix for controlled release dosage form preparations, *Drug Development and Industrial Pharmacy*, **19**, 1037-1046 (1993).
20) E.C. Pasini and M.J. Indelicato, Pharmaceutical properties of loracarbef, *Pharm. Res.*, **9**, 250-254 (1992).