

Preparation and evaluation of mucoadhesive cefdinir microcapsules

Prabhakar Reddy Veerareddy,
Swathi Tedla,
Srinivas Reddy Banda,
Suresh Bandari, Raju Jukanti

Department of Pharmaceutics,
St. Peter's Institute of Pharmaceutical
Sciences, Vidyannagar, Hanamkonda,
Warangal, Andhra Pradesh, India

J. Adv. Pharm. Tech. Res.

ABSTRACT

The mucoadhesive microcapsules were prepared by using various concentrations of three different mucoadhesive polymers, namely, chitosan, Carbopol 934P, and methyl cellulose as wall materials and cefdinir as the core material employing orifice-ionic gelation method. The prepared microcapsules were characterized by scanning electron microscope (SEM) and Fourier transform infrared spectrometry (FT-IR). The prepared microcapsules were found to be spherical with particle size ranging from 765 ± 20 to $985 \pm 10 \mu\text{m}$ and encapsulation efficiencies in the range of 55%–92%. The formulation containing Carbopol 934P as mucoadhesive polymer was found to be best with particle size $946 \pm 10 \mu\text{m}$. The *ex vivo* wash-off test showed that the mucoadhesion after 1 h was 80% and the *in vitro* drug release was extended for more than 12 h. FT-IR spectra indicate that there was no interaction between drug and the polymers used in the formulation. Cefdinir is better absorbed from the upper part of the gastrointestinal tract, it suffers from low oral bioavailability (20–30%), shorter biological half-life (1–2 h), and less transit time. Thus, it can be concluded that microcapsules prepared using Carbopol 934P have promising properties for use as mucoadhesive carrier to increase the residence time of cefdinir.

Key words: Carbopol 934P, chitosan, encapsulation efficiency, methyl cellulose, orifice-ionic gelation, scanning electron microscopy

INTRODUCTION

The technique of mucoadhesion utilizes the property of bioadhesion of certain polymers that become adhesive on hydration and hence mucoadhesive drug delivery systems can be used to target the drug to a particular region of the body for controlled release of drug for extended periods of time.^[1,2] Most of the hydrophilic polymers attract water from the mucous gel layer adherent to the epithelial surface thus adhering the mucosal surface. This is the simple mechanism

of adhesion and is called as “adhesion by hydration.” Various types of forces, such as hydrogen bonding exist between the adherent polymer and the substrate, that is mucus, at the molecular level.^[3–8] Bioadhesion is an interfacial phenomenon, which involves two materials, one of which must be biological, and these are held together by interfacial forces.^[9] Carbopol polymers are known to create a strong bond with the mucous membrane, which results in strong bioadhesion.^[10–13]

Chitin is the second highly abundant natural biopolymer, which is derived from the exoskeletons of crustaceans and also from cell walls of fungi and insects.^[14] Chitosan is a product derived from *N*-deacetylation of chitin in the presence of hot alkali. It is widely used due to its versatile biological activity, excellent biocompatibility, and complete biodegradability with low toxicity.^[15] The mucoadhesive property of chitosan is due to ionic interactions between the positively charged primary amino groups on the polymer and negatively charged sialic acid and sulfonic acid substructures of the mucus.^[16]

Cefdinir is an expanded-spectrum, oral, third-generation cephem antimicrobial agent active against Gram-positive and Gram-negative bacteria.^[17,18] It is used in the treatment

Address for correspondence

Dr. V. Prabhakar Reddy,
Department of Pharmaceutics, St. Peter's Institute of
Pharmaceutical Sciences, Warangal - 506 001, Andhra Pradesh,
India. E-mail: vpreddyindia@yahoo.com

Access this article online

Quick Response Code:



Website:

www.japtr.org

DOI:

10.4103/2231-4040.82955

of acute chronic bronchitis, rhinosinusitis, and pharyngitis and uncomplicated skin and skin-structure infections in adults and adolescents; it is indicated for acute otitis media, acute sinusitis, and community-acquired pneumonia.^[19,20] Cefdinir requires controlled release because of its short biological half-life of ~1.5 h.^[21] In this study, cefdinir mucoadhesive microcapsules were prepared using various concentrations of three different mucoadhesive polymers employing orifice-ionic gelation method.

MATERIALS AND METHODS

Materials

Cefdinir was a gift sample from (Aurobindo Pharmaceuticals Limited, Hyderabad, India). Carbopol 934P was a gift sample from (Noveon, Inc., USA). Chitosan of molecular weight 150–650 kDa and deacetylation degree of 80% was a gift sample from (Degussa, Germany). Sodium alginate of viscosity 4000 cps (Qualikems Fine Chemicals Pvt. Ltd, New Delhi, India), methyl cellulose of viscosity 450 cps (Qualikems Fine Chemicals Pvt. Ltd, New Delhi, India), and calcium chloride (Universal Laboratories Pvt. Ltd, Mumbai, India) were obtained from commercial sources. All other reagents used were of analytical grade.

Methods

Preparation of microcapsules

Cefdinir mucoadhesive microcapsules were prepared employing sodium alginate in combination with three mucoadhesive polymers—chitosan, Carbopol 934P, and methyl cellulose—as coat materials. The polymer concentrations used were in the range of 50–350 mg. An orifice-ionic gelation process, which has been extensively used to prepare large alginate beads, was employed to prepare the microcapsules.^[22,23]

Sodium alginate (200 mg) and the mucoadhesive polymer were dissolved in 10 mL of purified water and mixed thoroughly to form homogeneous polymer solution. The active substance, cefdinir (100 mg), was added to polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added dropwise manually into calcium chloride (2% wt/vol) solution using a syringe with a needle of size no. 18. The added droplets were retained in the calcium chloride solution for 15 min to complete the curing reaction and to produce spherical rigid microcapsules. The microcapsules were collected by decantation, and the product thus separated was washed repeatedly with water and dried at 45°C for 12 h. The microcapsules prepared along with their coat composition are listed in Table 1.

Estimation of cefdinir

Cefdinir content in the microcapsules was estimated by a UV spectrophotometric method (Systronics, 2202, Ahmedabad, India) based on the measurement of absorbance at 277 nm

in phosphate buffer of pH 6.8. The method was validated for linearity, accuracy, and precision.

Microencapsulation efficiency

Microencapsulation efficiency was calculated using the following formula.^[24]

$$\text{Microencapsulation efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100$$

Scanning electron microscopy

The microcapsules were observed under a SEM (FEI-Philips XL-30). They were mounted directly onto the SEM sample stub using double-sided sticking tape and coated with gold film of thickness 200 nm under reduced pressure of 0.001 mmHg.

In vitro drug release study

Release of cefdinir from the microcapsules was studied in 900 mL of 0.1 N HCl for first 2 h and in 900 mL of phosphate buffer pH 6.8 for the next 10 h using a United States Pharmacopeia (USP) apparatus I Basket type (Electrolab, TDT-08L, India) at 100 rpm and 37°C ± 0.5°C. A sample of microcapsules equivalent to 50 mg of cefdinir was used in each test. Samples of dissolution fluid were withdrawn through a filter of 0.45 µm at different time intervals and were assayed at 277 nm for cefdinir content using a UV spectrophotometer. The drug release experiments were conducted in triplicate.

Mucoadhesion testing by ex vivo wash-off test

The mucoadhesive property of the microcapsules was evaluated by an *ex vivo* adhesion testing method known as the wash-off method.^[5] Freshly excised pieces of intestinal mucosa of 2 cm² from pig were mounted onto glass slides of 3 × 1 inch with cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread onto each wet rinsed tissue specimen, and immediately thereafter the support was hung onto the arm of a USP tablet disintegrating test apparatus (Electrolab, Mumbai, India). When the disintegrating test machine was

Table 1: Formulations of microcapsules with different coat compositions

Formulation code	Coat composition
F1	Alginate: Chitosan (1:1)
F2	Alginate: Chitosan (1:1.5)
F3	Alginate: Chitosan (1:2)
F4	Alginate: Chitosan (1:2.5)
F5	Alginate: Carbopol 934P (1:1)
F6	Alginate: Carbopol 934P (1:1.5)
F7	Alginate: Carbopol 934P (1:2)
F8	Alginate: Carbopol 934P (1:2.5)
F9	Alginate: Methyl cellulose (1:1)
F10	Alginate: Methyl cellulose (1:1.5)
F11	Alginate: Methyl cellulose (1:2)
F12	Alginate: Methyl cellulose (1:2.5)

operated, the tissue specimen was given a slow, regular up-and-down movement in the test fluid at 37°C contained in a 1 L vessel of the machine. At the end of 30 min, at the end of 1 h, and at hourly intervals up to 12 h, the machine was stopped and the number of microcapsules still adhering to the tissue was counted. The test was performed at both gastric pH 0.1 N HCl, pH 1.2 and intestinal pH phosphate buffer, pH 6.8.

Fourier transform infrared spectroscopy

Infrared spectra were recorded between 4000 and 450 cm^{-1} by Perkin-Elmer FT-IR spectrometer SPECTRUM 1000 (Norwalk, USA). Each sample is mixed with Potassium bromide (KBr) in the ratio of 1:100 and compressed at 70 kN in a Perkin-Elmer hydraulic press for the preparation of pellets. These pellets are then analyzed in the Perkin-Elmer FT-IR spectrometer (SPECTRUM 1000, Norwalk, USA).

RESULTS

Cefdinir microcapsules with a coat consisting of sodium alginate and a mucoadhesive polymer, such as chitosan, methylcellulose, or Carbopol 934P, in different ratios could be prepared by the orifice-ionic gelation process. Microcapsules could not be prepared with mucoadhesive polymer alone because of their hydrophilic nature. The microcapsules were evaluated for drug content, particle size, encapsulation efficiency, *in vitro* drug release, mucoadhesion testing by *ex vivo* wash-off test, and interaction between drug and excipients by FT-IR. Formulations were prepared with different coat compositions were given in Table 1. The particle size, drug content, and encapsulation efficiencies of all the formulations were given in Table 2.

Ex vivo Wash-off Test

The best formulation from each polymer was selected and their mucoadhesion was tested by *ex vivo* wash-off test. The ability of the microcapsules to adhere the intestinal mucosa of pig was compared with the microcapsules prepared with nonmucoadhesive material, that is, ethyl vinyl acetate. The test was performed for 12 h in both 0.1 N HCl and pH 6.8 phosphate buffer using USP tablet disintegrating test machine. The results are shown in Table 3.

Morphology of Carbopol 934P Microcapsules

The surface morphology of cefdinir microcapsules prepared by Carbopol 934P was seen by SEM. The surface morphology was done for formulation 8 with a magnification of $\times 60$ [Figure 1]. The microcapsules were spherical-shaped and the surface of microcapsules was smooth.

In vitro Drug Release Studies

Cefdinir release from the prepared microcapsules was studied in 0.1 N HCl for 2 h and in pH 6.8 phosphate buffer for 10 h. The drug release from the microcapsules was found to be slow and based on the composition of the coat, the drug release followed zero-order kinetics ($R^2 > 0.90$).

Microcapsules with coat containing alginate and chitosan gave relatively fast release when compared with others. The order of increasing release rate observed with various microcapsules was alginate-Carbopol 934P < alginate-methylcellulose < alginate-chitosan. The drug release from microcapsules F8 and F12 was slow and extended over a period of 12 h, and these microcapsules were found suitable for oral controlled-release formulations. The *in vitro* drug release studies of all formulations are shown in Figures 2-4.

Fourier Transform Infrared Spectroscopy

FT-IR spectra of drug, polymers used and the final formulation were taken to study the interaction between them. The results were shown in [Figure 5]. FT-IR spectrum peaks of Cefdinir are observed at 1080, 1180, 1685, 1769, and 3300 cm^{-1} . Alkene groups ($=\text{C}-\text{H}$ stretching) are seen at 3300 cm^{-1} . The ketone groups ($-\text{C}=\text{O}$) are observed at 1685–1769 cm^{-1} . Aromatic (Para) hydrogen bond stretching was observed at above 800 cm^{-1} that is at 807 cm^{-1} and 1080 cm^{-1} , and the peaks below 800 cm^{-1} and 700 cm^{-1} are aromatic (ortho) hydrogen bond stretching was seen.

Table 2: Particle size, percentage drug content, and microencapsulation efficiency of formulations F1–F12

Formulation code	Mean particle size (μm)	Drug content (mg)	Micro-encapsulation efficiency (%)
F1	765.9 \pm 8.14	27.63 \pm 0.38	55.26 \pm 0.76
F2	821.3 \pm 8.44	30.56 \pm 0.29	61.13 \pm 0.59
F3	876.2 \pm 8.54	33.49 \pm 0.27	66.98 \pm 0.55
F4	949.2 \pm 6.81	35.72 \pm 0.41	71.45 \pm 0.82
F5	826.7 \pm 6.36	35.59 \pm 0.31	71.18 \pm 0.63
F6	893.6 \pm 7.94	38.73 \pm 0.28	77.47 \pm 0.57
F7	925.9 \pm 8.77	42.27 \pm 0.24	84.55 \pm 0.48
F8	946.1 \pm 8.34	46.06 \pm 0.48	92.12 \pm 0.97
F9	754.2 \pm 7.05	29.32 \pm 0.31	58.65 \pm 0.62
F1	798.6 \pm 6.34	31.52 \pm 0.48	63.04 \pm 0.96
F11	864.9 \pm 8.43	34.61 \pm 0.32	69.22 \pm 0.65
F12	985.8 \pm 8.05	36.74 \pm 0.34	73.48 \pm 0.69

Table 3: Results of ex vivo wash-off test to assess mucoadhesive properties of the microcapsules prepared

FC	Percentage of microcapsules adhering to tissue at different times (h)									
	In 0.1 N HCl, pH 1.2					In phosphate buffer, pH 6.8				
	1	2	4	6	8	1	2	4	6	8
F4	66	44	14	—	—	78	62	36	18	—
F8	80	72	44	24	—	74	56	28	12	—
F12	74	50	28	10	—	70	48	18	06	—
EVA	52	36	08	—	—	48	32	04	—	—

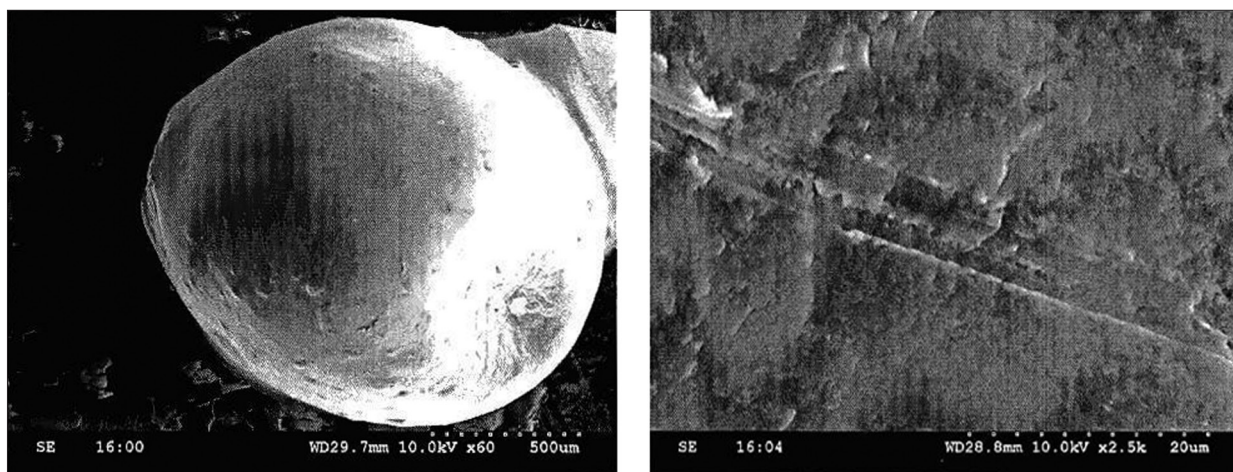


Figure 1: Scanning electron micrographs of Carbopol 934P microcapsules (F8)

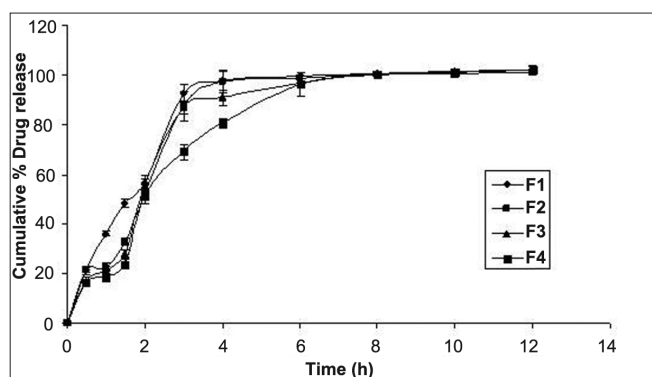


Figure 2: *In vitro* release of cefdinir from chitosan microcapsules. Each point represents mean \pm SD ($n = 3$)

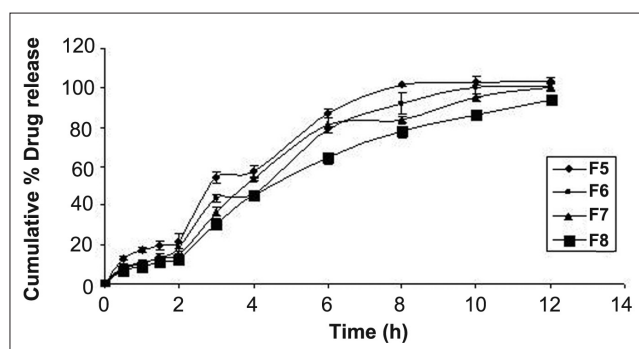


Figure 3: *In vitro* release of cefdinir from Carbopol 934P microcapsules. Each point represents mean \pm SD ($n = 3$)

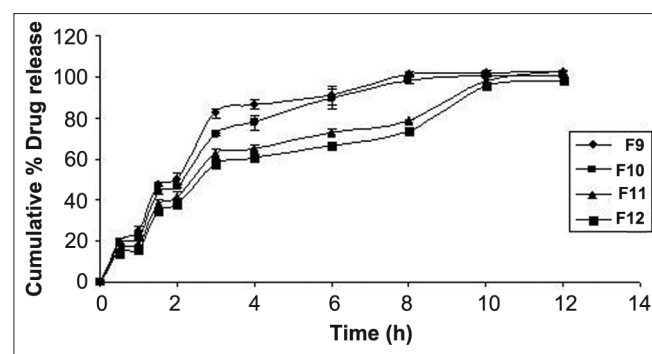


Figure 4: *In vitro* release of cefdinir from methyl cellulose microcapsules. Each point represents mean \pm SD ($n = 3$)

DISCUSSION

The prepared microcapsules were found to be discrete, spherical, and free-flowing. The microcapsules were uniform in size, with a size range of 760 ± 8.14 to $986 \pm 8.05 \mu\text{m}$. The SEM photograph indicates that the microcapsules were smooth and spherical [Figure 1]. From the results of FT-IR, it was clear that there was no interaction between drug and

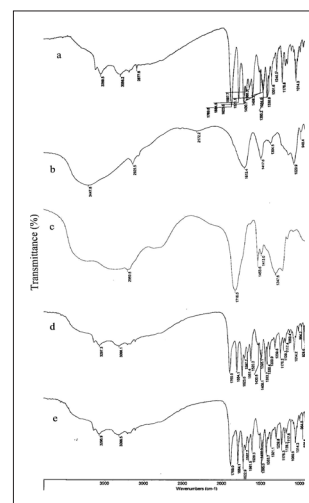


Figure 5: FT-IR spectra of (a) cefdinir, (b) sodium alginate, (c) Carbopol 934P, (d) physical mixture of Carbopol 934P microcapsules, and (e) Carbopol 934P microcapsules

polymers used in formulation [Figure 5].

The microencapsulation efficiency was in the range of 55–92%. Microcapsules with a coat consisting of alginate

and a mucoadhesive polymer exhibited good mucoadhesive properties in the *ex vivo* wash-off test. The wash-off was slow in the case of Carbopol 934P microcapsules with retention of 80% ± 1.35 after 1 h. The wash-off was faster at intestinal pH than at gastric pH in case of Carbopol 934P and methyl cellulose microcapsules. The rapid wash-off of Carbopol 934P microcapsules observed at intestinal pH is due to the ionization of carboxyl and other functional groups in the polymers at this pH,^[25] which increases their solubility and reduces adhesive strength; but for chitosan microcapsules the wash-off was faster at gastric pH due to the high solubility of chitosan at acidic pH. From the results of the wash-off test [Table 3], it is clear that the prepared microcapsules had good mucoadhesive properties.

Figure 2 shows the release of cefdinir from the chitosan microcapsules. In all the formulations, the release media were changed after 2 h from simulated gastric fluid at pH 1.2 to a simulated intestinal fluid at pH 6.8 to mimic gastrointestinal transit. The drug release was faster at gastric pH than that of intestinal pH due to high solubility of chitosan at gastric pH. The drug release of all the formulations containing chitosan reached 100% in less than 6 h.

Figure 3 shows release of cefdinir from Carbopol 934P microcapsules. The drug release was less at acidic pH but release was increased at pH 6.8 in case of Carbopol microcapsules and the release was controlled up to 12 h. Figure 4 shows release of cefdinir from methyl cellulose microcapsules and it is clear from the graph that the release was higher at gastric pH and the release of drug was controlled up to 12 h.

FT-IR spectrum peaks of cefdinir were observed. By observing the FT-IR spectrum of Carbopol 934P microcapsules, the characteristic peaks with the same wave numbers as that of drug and polymers were observed, that is, there was no merging of peaks with the excipients was seen. As there was no merging of peaks, there was no interaction between the excipients and the drug.

CONCLUSION

The spherical microcapsules with a coat containing alginate and mucoadhesive polymer (chitosan, methylcellulose, or Carbopol 934P) could be prepared by an orifice-ionic gelation process. Among three polymers used in different formulations, Carbopol 934P microcapsules showed good mucoadhesive properties in the *ex vivo* wash-off test. Cefdinir release from the Carbopol 934P mucoadhesive microcapsules was slow and extended over longer periods of time and depended on the composition of the coat. Drug release was diffusion controlled and followed zero-order kinetics. From the results of FT-IR, it can be concluded that there is no interaction between the drug and the polymers used. The results of SEM show that the formulated microcapsules

were smooth and spherical in shape. The results of our study suggest that Carbopol 934P mucoadhesive microcapsules are suitable for oral controlled release of cefdinir.

ACKNOWLEDGMENTS

The authors acknowledge Aurobindo Pharmaceuticals Limited, Hyderabad, India, for providing the gift sample of cefdinir. The authors are also thankful to Mr. T. Jayapal Reddy, Director, St. Peter's Institute of Pharmaceutical Sciences, Warangal, India for providing necessary facilities.

REFERENCES

1. Kharenko EA, Larionova NI, Demina NB. Mucoadhesive drug delivery systems (Review). *Pharm Chem J* 2009;43:21-9.
2. Chowdary KP, Rao YS. Mucoadhesive microspheres for controlled drug delivery. *Biol Pharm Bull* 2004;27:1717-24.
3. Davies NM, Farr SJ, Hadgraft J, Kellaway IW. Evaluation of mucoadhesive polymers in ocular drug delivery II. polymer-coated vesicles. *Pharm Res* 1992;9:1137-44.
4. Lehr CM, Bowstra JA, Tukker JJ, Junginger HE. Intestinal transit of bioadhesive microspheres in an *in situ* loop in the rat. *J Control Release* 1990;13:51-62.
5. Lehr CM, Bouwstra JA, Tukker JJ, Verhoef AC, de Boer AG, Junginger HE, et al. Oral bioadhesive drug delivery systems—effects on G.I. transit and peptide absorption. *Pharm Res* 1990;7:PDD 7226.
6. Leung SH, Irons BK, Robinson JR. Polyanionic hydrogel as a gastric retentive system. *J Biomater Sci Polym Ed* 1993;4:483-92.
7. Smart JD. An *in vitro* assessment of some mucosa-adhesive dosage forms. *Int J Pharm* 1991;73:69-74.
8. Smart JD. Some formulation factors influencing the rate of drug release from bioadhesive matrices. *Drug Dev Ind Pharm* 1992;18:223-32.
9. Jimenez-Castellanos MR, Zia H, Rhodes CT. Mucoadhesive microspheres for controlled drug delivery. *Drug Dev Ind Pharm* 1993;19:143-94.
10. Anlar S, Capan Y, Hincal AA. Physico-chemical and bioadhesive properties of polyacrylic acid polymers. *Pharmazie* 1993;48:285-7.
11. De Leeuw BJ, Lueben HL, Perard D, Verhoef AC, de Boer AG, Junginger HE. The effect of mucoadhesive poly (acrylates) polycarboxyl and carbomer on zinc and calcium dependent proteases. *Proceed Intern Symp Control Rel Bioact Mater* 1995;22:2123.
12. Lueben HL, Bohner V, Perard, Langguth P, Verhoef JC, de Boer AG, et al. Bioadhesive Polymers for the peroral delivery of peptide drugs (polycarboxyl, Carbopol® 934P NF, chitosan). *Proceed Intern Symp Control Rel Bioact Mater* 1995;22:124.
13. Lueben HL, Lehr CM, Rentel CO, Noach AB, de Boer AG, Verhoef JC, et al. Effect of poly(acrylates) on the enzymatic degradation of peptide drugs by intestinal brush border membrane vesicles. *J Control Release* 1993;29:329-38.
14. Mourya VK, Nazma NI. Chitosan-modifications and applications: Opportunities galore. *Reac and Func Poly* 2008;68:1013-51.
15. Rinaudo M. Chitin and chitosan: Properties and applications. *Prog Polym Sci* 2006;31:603-32.
16. Hassan EE, Gallo JM. A simple rheological method for the *in vitro* assessment of mucin-polymer bioadhesive bond strength. *Pharm Res* 1990;7:491-5.
17. Inamoto Y, Chiba T, Kamimura T, Takaya T. FK482 a new orally active cephalosporin synthesis and biological properties. *J Antibiot (Tokyo)* 1988;41:828-30.
18. Kumar P, Kumar S, Kumar A, Chander M. Physicochemical

- characterization of solid dispersions of cefdinir with PVP K-30 and PEG 4000. *Int J Pharm Sci Tech* 2010;3:948-56.
19. Marchese A, Saverino D, Debbia EA, Pesce A, Schito GC. Antistaphylococcal activity of cefdinir, a new oral third-generation cephalosporin, alone and in combination with other antibiotics, at supra- and sub-MIC levels. *J Antimicrob Chemother* 1995;35:53-66.
 20. Perry CM, Scott LJ. Cefdinir: A review of its use in the management of mild-to- moderate bacterial infections. *Drugs* 2004;64:1433-64.
 21. Laurence LB, Keith LP, Donald KB, Iain LOB. Goodman and Gilman's Manual of pharmacology and therapeutics. New York: McGraw-Hill; 2008. p. 744.
 22. Hari PR, Chandy T, Sharma CP. Chitosan/calcium alginate microcapsules for intestinal delivery of nitrofurantoin. *J Microencapsul* 1996;13:319-29.
 23. Kim CK, Lee EJ. The controlled release of blue dextran from alginate beads. *Int J Pharm* 1992;79:11-19.
 24. Chowdary KP, Rao YS. Design and *in vitro* and *in vivo* evaluation of mucoadhesive microcapsules of glipizide for oral controlled release: A technical Note. *AAPS PharmSciTech* 2003;4:E39.
 25. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. *Eur J Pharm Biopharm* 2000;50:27-46.

How to cite this article: Veerareddy PR, Tedla S, Banda SR, Bandari S, Jukanti R. Preparation and evaluation of mucoadhesive cefdinir microcapsules. *J Adv Pharm Tech Res* 2011;2:115-20.

Source of Support: Nil, **Conflict of Interest:** Nil.

Author Help: Reference checking facility

The manuscript system (www.journalonweb.com) allows the authors to check and verify the accuracy and style of references. The tool checks the references with PubMed as per a predefined style. Authors are encouraged to use this facility, before submitting articles to the journal.

- The style as well as bibliographic elements should be 100% accurate, to help get the references verified from the system. Even a single spelling error or addition of issue number/month of publication will lead to an error when verifying the reference.
- Example of a correct style
Sheahan P, O'leary G, Lee G, Fitzgibbon J. Cystic cervical metastases: Incidence and diagnosis using fine needle aspiration biopsy. *Otolaryngol Head Neck Surg* 2002;127:294-8.
- Only the references from journals indexed in PubMed will be checked.
- Enter each reference in new line, without a serial number.
- Add up to a maximum of 15 references at a time.
- If the reference is correct for its bibliographic elements and punctuations, it will be shown as CORRECT and a link to the correct article in PubMed will be given.
- If any of the bibliographic elements are missing, incorrect or extra (such as issue number), it will be shown as INCORRECT and link to possible articles in PubMed will be given.