www.sphinxsai.com

PharmTech

International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.3, No.3, pp 1488-1494, July-Sept 2011

Study of Secnidazole-Serratiopeptidase Alginate/HPMC Gels For Periodontal Delivery

Maurya Priyanka*, Bajpai Meenakshi

College of Pharmaceutical Sciences, Raj Kumar Goel Institute of Technology,5th km. Stone (Opp. Jain Tube Co. Ltd.), Delhi-Meerut Road,Ghaziabad (U.P.)-201003, India.

Corres.author: priyanka23maurya@gmail.com
Phone no: 09044330103

Abstract: The main goal of this study was to develop a controlled release periodontal formulation of Secnidazole Serratiopeptidase that can be used in the treatment of periodontitis by direct intrapocket administration, thus ensuring a high effective concentration of antimicrobial agent at the site of infection. This minimizes the occurrence of systemic side effects and bacterial resistance. Serratiopeptidase, a proteolytic enzyme with anti-inflammatory activity, is widely used in dental treatment. The topical use of enzymes is also associated with a significant increase in the concentration of antibiotic at the wound and decrease in the rate of infection. Therefore, localized delivery of the enzyme along with antibiotic may provide better relief than antibiotic alone. The pH sensitive and mucoadhesive formulations consist of non-toxic polymer, Sodium alginate (1%), HPMC E50Lv (1-8%w/w). To modulate the gel strength and the bioadhesive force of gel HPMC E50Lv was used as viscosity enhancer. Viscosity studies indicated pseudo plastic (shear thinning) behavior of gel. Increase in polymer concentration showed increase in the viscosity thereby affecting the drug release. Dissolution studies demonstrate diffusion release of drug and enzyme from the gel thus alginate/HPMC gels can be used as an in-situ gelling vehicle to enhance periodontal drug delivery.
Keywords: Periodontal Drug Delivery, Secnidazole, Serratiopeptidase, Alginate, HPMC.

INTRODUCTION

Recent report on burden of diseases in India and a multicentric oral health survey [1] have revealed the prevalence of dental caries to be around 40-45% , and periodontal diseases in more than 90% of the Indian population, malocclusion in 30% of children, endemic fluorosis in 17 out of 32 states affecting 66 million and oral cancer in 12.6/100,000 population.

Periodontal diseases is a general term which encompasses several pathological conditions affecting the tooth supporting structures. Periodontal diseases include conditions such as chronic periodontitis, aggressive periodontitis, systemic disease associated periodontitis and necrotizing periodontitis[2]

These conditions are characterized by a destruction of the periodontal ligament, a resorbtion of the alveolar bone and the migration of the junctional epithelium along the tooth surface. The clinical signs of periodontitis are changes in the morphology of gingival tissues, bleeding upon probing as well as periodontal pocket formation. This pocket provides an ideal environment for the growth and proliferation of anaerobic pathogenic bacteria [3]

The microorganisms colonizing the subgingival area represent the principal etiological factor in the development of the inflammation and

tissue destruction. Healthy periodontium is associated with a simple bacterial population which predominantly consists of non-mobile coccoid cells and rods. The microflora found in periodontitis is complex and composed mainly of Gram negative anaerobic bacteria [4]

The periodontal pocket, however, remains and if it continues to harbour the bacteria associated with the disease, a potential for a further destructive phase exists. The disease may then require extensive treatment, failing which the teeth may be lost.

Therefore, clearance of the subgingival infection and elimination of the periodontal pocket are considered a priority in the treatment of periodontitis[5]

The periodontal pocket provides a natural reservoir, which is easily accessible for the insertion of a delivery device, the GCF provides a leaching medium for the release of a drug from the dosage form and for its distribution throughout the pocket. These features, together with the fact that the periodontal diseases are localized to the immediate environment of the pocket, make the periodontal pocket a natural site for treatment with local delivery systems.

Intra-pocket drug delivery systems are highly desirable due to; the potentially lower incidence of undesirable side effects, improved efficacy and enhanced patient compliance, the attractiveness of treating periodontal diseases by the intra-pocket drug delivery systems is based on the prospects of maintaining effective high levels of drug in the GCF for a prolonged period of time to produce the desirable clinical benefits.

For these systems, the delivery vehicles can be of natural origin or semi synthetic or synthetic nature. Recent developments in polymer sciences have disclosed biocompatible and biodegradable synthetic polymers, which can be modified to meet pharmacological and biological requirements.

To be useful for periodontal therapy, it is desirable to have a bioerodible drug delivery system that can maintain an effective drug release rate in the periodontal pocket while simultaneously eroding throughout the duration of treatment up to several days[4]

Bio-adhesion is defined as[6] a state in which two bodies, one or both of which are of biological nature, are hold together for extended period of time by interfacial force, or bio-adhesion is defined as the ability of the material (synthetic or biological) to adhere to a biological tissue for an extended period of time.

For drug delivery purposes, the polymer /drug carrier is usually a non biological macromolecular or hydrocolloid material that adheres primarily to mucus layer or alternatively may attach to the underlying epithelium.

The delivery system which utilizes property of bioadhesion of certain water soluble polymers, which become adhesive on hydration, and hence can be used for targeting a drug to a particular region of the body for extended period of time.

For bioadhesion to occur, a succession of phenomena, whose role depends on the nature of the bioadhesive, is required[7,8,9,10,11,12] The first stage involves an intimate contact between a bioadhesive and a membrane, either from a good wetting of the bioadhesive surface, or from the swelling of the bioadhesive. In the second stage, after contact is established, penetration of the bioadhesive into the crevices of the tissue surface or interpenetration of the chains of the bioadhesive with those of the mucus takes place. Low chemical bonds can then settle.For polymer gels that are already in equilibrium swelling, swelling and wetting step is unlikely to be involved. To explain the fundamental mechanisms of adhesion. In a particular system one or more theories contribute to the formation of bioadhesive bonds. Proposed theories of bioadhesion include wetting, diffusion, electronic, adsorption and fracture .

Adhesion of a polymer to a tissue involves contribution from three main regions;The surface of the bioadhesive material, The first layer of the natural tissue, The interfacial region between the two layers.Adhesion between a polymer and tissue is primarily due to three types of interactions; Physical or mechanical bonds, Chemical bonds or ionic, Primary or covalent chemical bonds.

Bioadhesive systems[6] have three distinct advantages when compared to conventional dosage forms;The bioadhesive systems are readily localized in the region applied to improve and enhance the bioavailability of drugs, These dosage forms facilitate intimate contact of the formulation with underlying absorption surface, The bioadhesive dosage forms also prolong residence time of the dosage form at the site of application and absorption to permit once or twice a day dosing.

pH sensitive in-situ gel was formulated for local delivery to the periodontal pockets as it bypasses the complications associated with oral administration, maintains drug levels in therapeutic range, increases patient compliance, reduces dose.

The objective of the present study is to obtain an effective concentration of Secnidazole-Serratiopeptidase in the periodontal pockets, to study the release characteristics of drug-enzyme from the prepared formulations, to compare the dissolution profiles of the prepared formulations. Secnidazole and serratiopeptidase were chosen for the study,

Secnidazole, an antibiotic used for anaerobes found in the periodontal pockets and Serratiopeptidase, an anti-inflammatory agent which also increases the concentration of antibiotic at the site of action.

EXPERIMENTAL

Materials

Secnidazole was kindly gifted by Unichem laboratories, Ghaziabad,(U.P.) India, Serratiopeptidase was kindly gifted by Unichem laboratories, Baddi,(H.P.) India. All chemicals used were of analytical grade and were used as such.

Preparation of formulation

The alginate/HPMC [13] solutions were prepared by dispersing the required amount of HPMC in the desired concentration of alginate with continuous stirring until completely dissolved.Seccnidazole and Serratiopeptidase was dissolved in water and propylene glycol then added to the above solution. The drug solution was added to the alginate or alginate/HPMC solution under constant stirring until uniform, clear solution was obtained(Table 1). Distilled, deionized water was then added to make the volume up to 100 mL.

Evaluations of formulation in vitro

Bioadhesivity

A section of tissue was cut from the ileum of an overnight fasted rat and secured with mucosal side out on to each glass vial using a double sided adhesive. The vials with the tissues were stored at pH 6.8°C for 10 min. Next, one vial was connected to the balance and the other vial was placed on a height-adjustable pan .Alginate gels were added onto the tissue on the other vial. Then, the heights of the other vial was adjusted so that the gel could be placed between the mucosal tissues of both vials. The weights of the apparatus were kept raised until two vials became separated. Bioadhesive force, the detachment stress (dynes), was determined from the minimal weights that detached two vials[14,15] The tissue pieces were changed for each tensile measurement.

Rheological studies

The flow curves of thermosensitive and mucoadhesive gels were determined using a Bohlin Viscometer (Bohlin,Sweden). The measurements were performed in a cone- and plate geometry with a diameter of 30 mm (cone angle 5°). The shear rates ranged from 50 up to 150 s−1 with 30 secs equilibrium time at every rpm. Samples were applied to the lower plate using a spatula to ensure that formulation shearing did not occur. To test the effect of temperatures, the measurements were made at 37.2 °C. Each data point is the mean of at least three analyses.

In vitro release studies

The dissolution studies were performed using the dialysis method. Typically, 1 g of alginate gel was placed in a dialysis tube (MW 12 000 cutoff). The dialysis tube was then placed in a vessel containing 100 mL of phosphate buffer pH 6.8, maintained at 37.50C, and stirred at 100 rpm. Samples were collected periodically and replaced with fresh dissolution medium. After filtration through Whatman filter paper 41, the concentration of secnidazole was determined spectrophotometrically at 319 nm. The kinetic analysis of the release data was done using the Higuchi model.

The in-vitro diffusion study of the final batch(A6) was done using Franz diffusion cell. The release of the enzyme was measured at λmax 228.5 nm in phosphate buffer pH 6.8: Ethanol(1:1) as blank.

Table1: Formulation composition of different batches.*, $

Batch no.	Alginate(%w/w)	HPMC E50Lv(%w/w)	Propylene Glycol (%w/w)
A1	1	1	25
A2	1	2	25
A3	1	3	25
A4	1	4	25
A5	1	5	25
A6	1	6	25
A7	1	7	25
A8	1	8	25

*Secnidazole concentration kept constant at 5%w/w

$ Serratiopeptidase concentration kept constant at 0.5%w/w

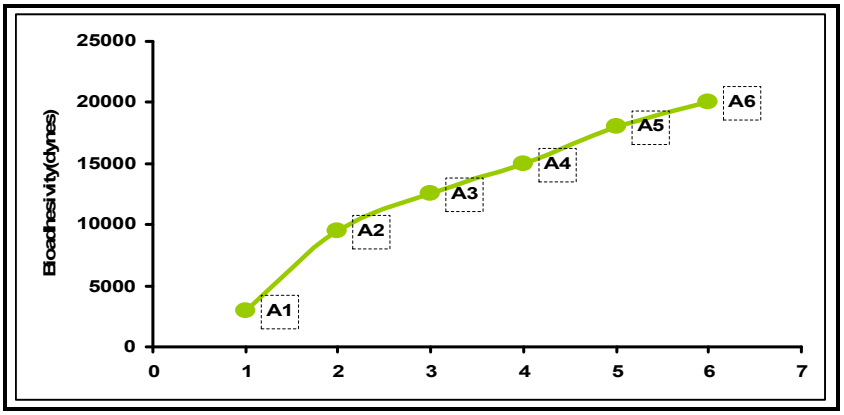

Figure 1: Bioadhesive force-measurement.

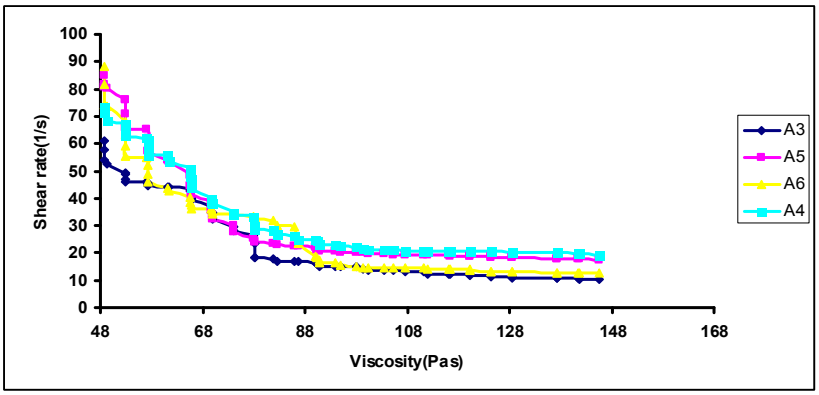

Figure 2: Shear thinning behaviour of gels.

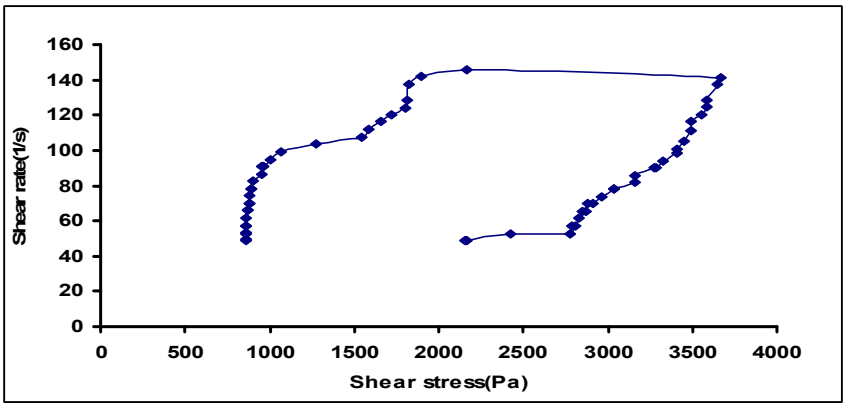

Figure 3: Rheological profile of A3

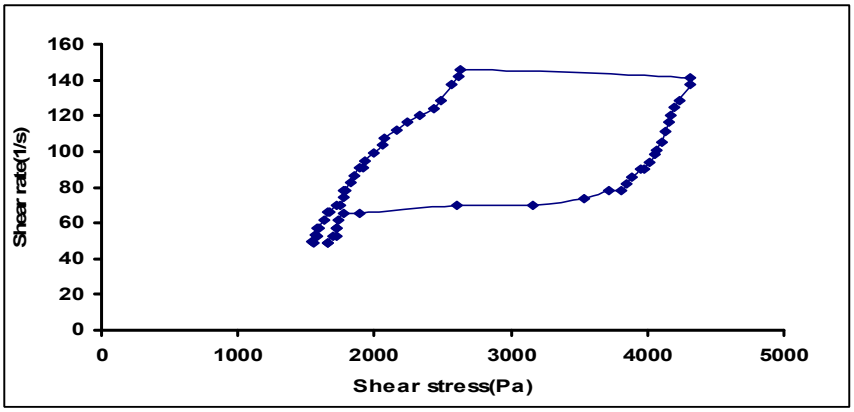

Figure 4: Rheological profile of A4

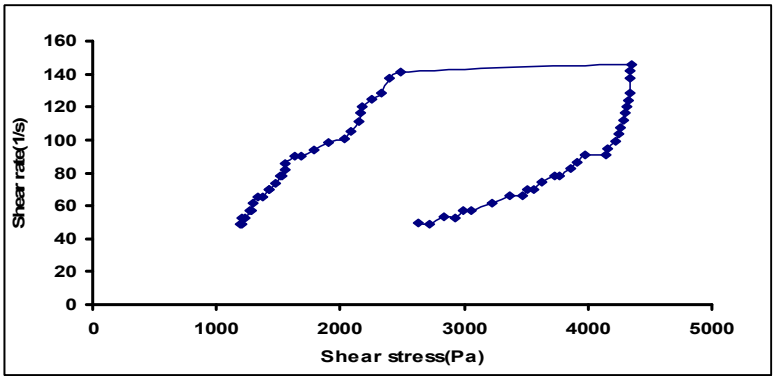

Figure 5: Rheological profile of A5

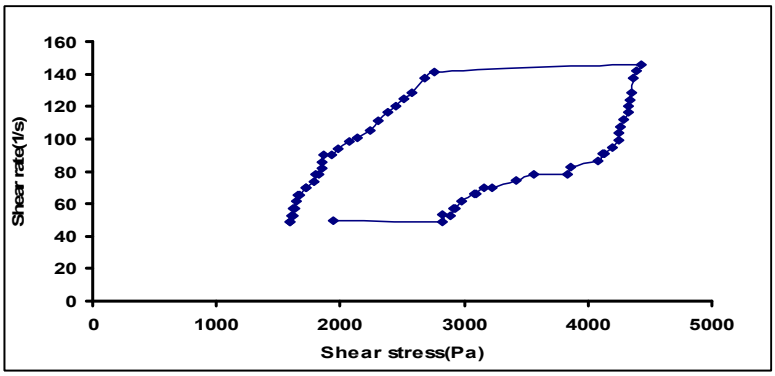

Figure 6: Rheological profile ofA6

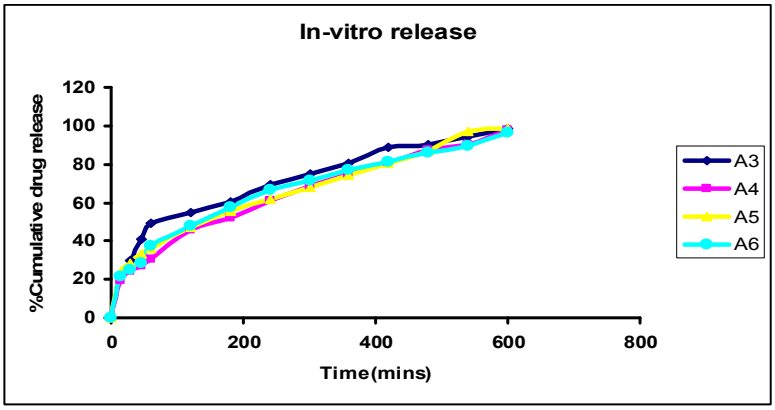

Figure 7: In-vitro drug release profiles.

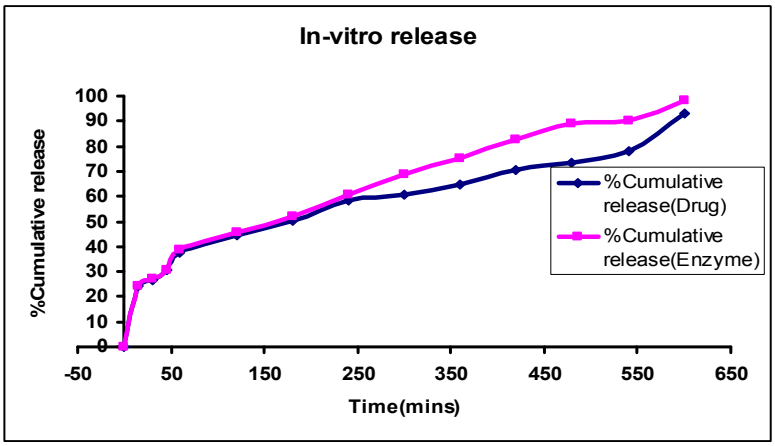

Figure 8: In-vitro drug-enzyme release profiles.

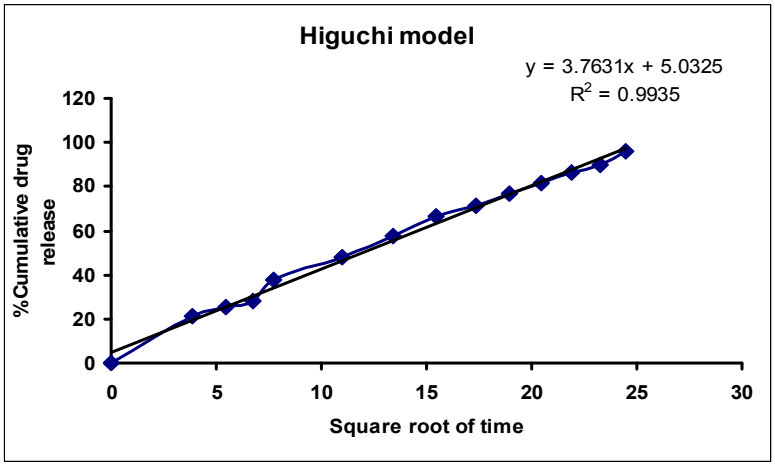

Figure 9: Higuchi model

RESULT AND DISCUSSION

Bioadhesivity

The detachment force increased significantly with the concentration of HPMC (Fig.1)The results of the study of detachment force support the hypothesis that the possible mechanism of the mucoadhesion exhibited by the gels is the dehydration of the mucosa (i.e., water uptake by the mucoadhesive material). The amount of water taken up by the gels governed the mucoadhesive force; the gel having greater water uptake capacity showed greater mucoadhesion.(A6 with 6%w/w HPMC).

Rheological studies

These results suggest that alginate changed to the gel phase upon exposure to gingival fluid. So HPMC E50Lv as the viscosity-enhancing agent can enhance the viscosity of the preparation and decrease the amount of alginate in the preparation(Fig.2). This might improve patient compliance.

Alginate gels show shear thinning and a decrease in the viscosity with increased angular velocity, the formulations showed non-Newtonian behavior, the up curve did not coincide with the down curve, indicating the presence of thixotropy, with a wide hysteresis loop(Fig 3-6). The area of the hysteresis loop increased with the concentration of HPMC and moved to a higher shear stress value, indicating compact structure of the gels. But the recovery of the consistency was slow when there were higher amounts of HPMC .

It was assumed that if the rate of shear were reduced once the desired maximum rate had been reached, the down curve would be identical to the superimposed up curve in the case of Newtonian systems, whereas the down curve for non-Newtonian systems could be displaced with regard to the up curve, this indicates a breakdown of structure (and hence shear thinning) that does not reform immediately when the stress is removed or reduced. The recovery process is not instantaneous; rather, there is progressive restoration of consistency.

In-vitro release studies

The in vitro release profile provides insight into the efficiency of the drug delivery system proposed for the controlled release of the drug(Fig 7-8).These results indicate that formulation A6 (1% alginate/6% HPMC E50Lv) has a better ability to retain drugs. These results also suggest that the alginate/HPMC aqueous system can be used as an in situ gel-forming system for periodontal drug delivery systems. Furthermore, by plotting cumulative amount versus the square root of the time curve(Fig 9) for formulation A6 (up to 75% of total drug released) a linear relationship with a correlation coefficient higher than 0.99 was obtained.

This observation is in accordance with the carbopol/hydroxypropyl methylcellulose systems reported by Kumar and Himmestein (1995). The linear relationships in conjunction with the slow dissolution rate suggest that the in vitro drug release from formulation A6 under physiological conditions occurs primarily by diffusion.

CONCLUSION

Secnidazole- Serratiopeptidase were success - fully formulated as a pH-sensitive in situ gelling periodontal formulation using alginate with HPMC. The use of gels is of interest for bioadhesion purpose because these pharmaceutical dosage forms limits the drug delivery to the target site with little or no systemic uptake, and indicates high interactive potential with biological surfaces. The gel formed in-vitro produced sustained release over a period of 10 hr also important is its ease of administration and better

patient compliance. However, extensive pharmacokinetics and pharmacodynamics studies are required to establish Secnidazole-Serratiopeptidase delivery as an available alternative. Appropriate histopathological studies are also required to evaluate the biocompatibility of the polymer with the periodontium.

ACKNOWLEDGEMENTS

Authors are thankful to Unichem Ghaziabad and Unichem Baddi for providing gift samples of Secnidazole and Serratiopeptidase and CDRI Lucknow for Rheological studies.

REFERENCES

[1] Shah N. Oral and dental diseases: 2005.Causes, prevention and treatment strategies. In: Burden of Disease in India. National Commission on Macroeconomics and Health, Ministry of Health and Family Welfare Govt. of India.

[2] American Academy of Periodontology, 2000 Proceedings of the International Workshop for the classification of periodontal diseases, Ann. Periodontal.

[3] Marsh P.D., Host defences and microbial interactions, J. Dent. Res. (68) 1989. 1567-1575.

[4] Haffajee A.D., Sorensky S.S., Microbial etiological agents of destructive periodontal disease, Periodontology (1994) 78-111.

[5] Jain G. K., Khar R.K., et al.,. Recent approaches for the treatment of periodontitis Drug Discovery Today, Volume 13, Issues 21-22, November 2008 ,932-943.

[6] Vasir J.K. Bioadhesive microsphere as a controlled drug delivery system.Int J Pharm. 2003,255,13-32.

[7] Chowdhary K.P.R., Rao N.K., Malathi K., Ethyl cellulose microspheres of glipizide:characterization, in vitro and in vivo evaluation Indian J Pharm 2004,6(4) 412- 416.

[8] Gavini E, Rassu G, Sanna V., Cossu M., Mucoadhesive microspheres for nasal administration of antiemetic drug, Metoclopramide:in vivo-ex vivo studies. J P P, 2004,57,287-294.

[9] Govender S,Pilay V,Chetty DD,Essack SY,Danger CM , Optimisation and characterization of bioadhesive controlled release tetracycline microspheres. Int J Pharm 2005 306,24-40.

[10] Martinac A, Filipovic-Grcic J., Voinovich D.,Perisutti B.,Franceschinis E., Development and evaluation of bioadhesive properties of chitosan ethyl cellulose microsphere for nasal delivery. Int J Pharm2005, 291, 69-77.

[11] Patel J.K.,Bodar M.S.,Amin A.F.,Patel N.M.Formulation and optimization of mucoadhesive microspheres of metoclopramide.J Pharm Sci. 2004, 66(3) 300-305.

[12] Zhou HY,Guang Chen X,Liu CS,Meng XH,.Chitosan/cellulose acetate microspheres. Preparation and Ranitidine release In-Vitro. Pharmaceutical Development and Technology. 2005, 10(2) , 219-225.

[13] Pan W., Ding P., et al., Study of an alginate/HPMC-based in situ gelling ophthalmic delivery system for gatifloxacin, Int.J.Pharm. 2006, 315, 12-17.

[14] Ch'ng,H.S., Park,H., Kelly,P., Robinson, J.R., 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.

[15] Lehr,C.M., Bouwstra, J.A., Tukker, J.J., Junginger, H.E., Intestinal transit of bioadhesive polymers in an in-situ loop in the rat; a comparative study with copolymers and blends based on poly (acrylic acid) .J.Control Release 1990, 13,51-62.

*****