



FORMULATION AND EVALUATION OF MUCOADHESIVE MICROSPHERES OF NIFEDIPINE

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ABSTRACT:

In the present study, an attempt has been made to evaluate mucoadhesive microspheres of nifedipine by orifice ionic gelation method employing sodium alginate and different mucoadhesive polymers (HPMC, carbopol) alone and in combination of different proportions. The compatibility study was done between drug and polymer by FTIR which shows no interaction between the drug and polymer. The prepared microspheres were evaluated for particle size, angle of repose, carrs index, swelling index, microencapsulation efficiency, percent drug content, drug release, kinetics and mechanism of drug release. The microspheres were found discrete, spherical, free flowing and the particle size was found in the range of 765 to 792 μ . The encapsulation efficiency was found in the range of 55 to 69 %. Percent drug content was found to be in the range of 96 to 99 %. All the microspheres showed good muco adhesive property in the in vitro wash off test. Drug release from the microspheres was found slow, followed first order kinetics with non fickian release mechanism and release dependent on nature and concentration of polymers.

KEY WORDS: Mucoadhesive microspheres, Ionicgelation, nifedipine by orifice ionic gelation.

INTRODUCTION

Microspheres are frequently used drug delivery system and may also possess mucoadhesive properties. Microspheres form an important part of such novel drug delivery systems¹⁻³. They have varied applications and are prepared using assorted polymers⁴. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes⁵⁻⁸. This can be achieved by coupling mucoadhesion characteristics to microspheres and developing mucoadhesive microspheres. Mucoadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to the absorption site⁹⁻¹². Carbopol (acrylic acid homopolymer) is an anionic polymer that has been used in mucoadhesive systems by several researchers¹³⁻¹⁷. Carbopol has been selected as a polymer in the preparation of mucoadhesive microspheres because of its good mucoadhesive properties and is not absorbed by body tissues and being totally safe for human oral consumption. The objective of this study is to develop, characterize, and evaluate mucoadhesive microspheres of nifedipine employing mucoadhesive polymers for prolonged gastrointestinal absorption. Nifedipine, an effective antihypertensive that requires controlled release owing to its short biological half-life¹⁰ of 2.5 hours, was used in orifice ionic gelation method. The mucoadhesive microspheres were evaluated by in vitro and in vivo methods for controlled release.

Nifedipine has a short biological half-life of 2.5 h and is eliminated rapidly and its antihypertensive effect lasts only for few hours. As such controlled release products are needed for nifedipine to prolong its duration of action and to improve patient compliance. Controlled release products also avoid the vasodilator related adverse effects such as increase in heart rate, flushing and palpitation associated with conventional nifedipine tablets and capsules

MATERIALS & METHODS

Nifedipine was procured from Yarrow chemicals, sodium alginate from Lobachemie, calcium chloride from Thermo fischer scientific India Pvt.ltd, HPMC E15 LV from Lobachemie and carbopol 940 from Qualingens.

Preparation of standard graph of nifedipine: A spectrophotometric method based on the measurement of absorbance at 238 nm in a phosphate buffer of pH 6.8 containing 1% SLS was used in the present study for the estimation of nifedipine in the formulations and in vitro studies.

Preparation of microspheres

Batches of microspheres were prepared by orifice ionic gelation method which involves reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water of 25 ml to form a homogenous polymer mixture. The API (nifedipine) was added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added into a syringe of 18 gauge needle and allowed to fall as droplets into calcium chloride (10 %w/v) solution. These droplets were retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then dried. Microspheres were prepared as per the formula given in Table no. 1

Table: 1 List of microspheres prepared:

Formulation	Core:coat ratio	Coat composition
F1	1:2	Na alginate:HPMC(1:1)
F2	1:3	Na alginate : HPMC(1:2)
F3	1:2	Na alginate : Carbopol(1:1)
F4	1:3	Na alginate : Carbopol(1:2)
F5	1:3	Na alginate : HPMC :Carbopol(1:1:1)

IR compatibility studies

In the present study this was done to analyse the compatibility between drug and polymers used in the formulation i.e carbopol, HPMC, sodium alginate. The studies were carried out using combination of drug and polymers and drug alone.

Evaluation of microspheres

A. Size analysis¹⁸

Microscopic analysis was performed to determine average size of microspheres. The microspheres prepared were dispersed in liquid paraffin. A drop of above dispersion was put on a glass slide and observed under a microscope. The diameter of 100 microspheres was determined using calibrated eye piece micrometer and stage micrometer. The average diameter was calculated using the following formula.

$$\text{Average diameter} = \sum \frac{n \cdot d}{n} \times C.F$$

Where n = number of microspheres, d =diameter of microcapsules, C.F = calibration factor

B.Carrs index¹⁹

Carrs index was calculated using the formula

$$\text{Carrs index (c)} = \frac{\text{Bulk density} - \text{Tapped density}}{\text{Tapped density}} \times 100$$

C.Angle of repose¹⁹

A funnel was fixed in a stand in such a way that the top of the funnel was at a height of 2 cm from the surface. The microspheres were passed from the funnel so that they form a pile. The height and the radius of the heap were measured and the angle of repose was calculated using the equation.

$$\theta = \tan^{-1} (h/r)$$

D. Swelling index of microspheres²⁰

Swelling of formulation excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the dosage form.

METHOD:

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer to ensure the complete equilibrium, exactly weighed amount of microspheres were allowed to swell in the given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using balance. The microspheres then dried in an oven at 60°C for 5 hrs until there was no change in the dried mass of sample. The swelling index of the microspheres was calculated by using the formula

Swelling index = (mass of swollen microspheres - mass of dry microspheres) × 100

E. Percent drug content: ¹⁹

Nifedipine microspheres were estimated by UV spectroscopic method based on the measurement of absorbance at 238 nm in phosphate buffer of pH 6.8. From each batch 20 mg of microspheres were crushed to fine powder in a mortar, extracted with 10 ml of methanol for half an hour, the methanolic solution was subsequently diluted with phosphate buffer of pH 6.8 and assayed for nifedipine by measuring absorbance at 238 nm. Nifedipine content of microspheres was calculated using the calibration curve shown in figure 1.

F. Microencapsulation efficiency²¹:

Microencapsulation efficiency was calculated using the following formula.

$$\text{Microencapsulation efficiency} = \frac{\text{estimated \#drug content}}{\text{theoretical\% drug content}} \times 100$$

G. Invitro wash-off test for microspheres²²

The mucoadhesive properties of the microspheres were evaluated by in vitro wash-off test. A 1-cm by 1-cm piece of rat stomach mucosa was tied onto a glass slide (3-inch by 1-inch) using thread.

Microspheres were spread (50) onto the wet, rinsed, tissue specimen, and the prepared slide was hung onto one of the grooves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movement in a beaker containing saline. At the end of 5 hrs the percentage mucoadhesion was calculated by the following equation.

$$\% \text{ Mucoadhesion} = \frac{\text{number of microspheres adhered}}{\text{number of microspheres applied}} \times 100$$

Invitro drug release: ¹⁹

The drug release study was performed using USP XXIV paddle stirrer at 37°C ± 0.5°C and at 50 rpm using 900 mL of phosphate buffer (pH 6.8) containing 1% SLS as a dissolution medium. Microspheres equivalent to 20 mg of nifedipine were used for the test. Five milliliters of sample solution was withdrawn at predetermined time intervals, filtered, diluted suitably, and analyzed spectrophotometrically. An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug released at different time intervals was tabulated and graph was plotted against % drug release vs time.

Kinetics of drug release

To know the mechanism of drug release from the microspheres. The results obtained from the invitro drug release studies were analysed by various kinetic models.

1. Zero order drug release: cumulative % drug release Vs time.
2. First order drug release: log cumulative % drug retained Vs time
3. Higuchi's classification diffusion equation: cumulative % drug release Vs square root of time
4. Peppaskorsemyer exponential: log cumulative % drug release Vs log time.

Analysis of release data

The rate and mechanism of release of nifedipine from the prepared microcapsules were analysed by fitting the release data into zero-order equation, $Q = Q_0 - K_0 t$ (1), where Q is the amount of drug release at time t and K_0 is the release rate; first order equation $\ln Q = \ln Q_0 - K_1 t$ (2), where K_1 is the release rate constant and Higuchi's equation, $Q = K_2 t^{1/2}$ (3), where Q is the amount of drug released at time t and K_2 is the diffusion rate constant. The release data were also analysed as per Peppas's equation³. $M_t/M_\infty = K t^n$ (4), where M_t/M_∞ is the fractional release of the drug, t is the release time, K is a constant incorporating structural and geometric characteristics of the release device, 'n' is the release exponent indicative of mechanism of release. For non-Fickian (anomalous/zero order) release, 'n' value is between 0.5 to 1.0; for Fickian diffusion, $n \leq 0.5$; for zero order release, $n = 1$; for super case transport II, $n > 1$; 'n' is estimated from linear regression of $\log (M_t/M_\infty)$ Vs $\log t$.

RESULTS AND DISCUSSION

Table:2 Calibration Curve for the Estimation of Nifedipine in Phosphate Buffer of pH 6.8

Nifedipine Concentration ($\mu\text{g / ml}$)	Absorbance
5	0.118 \pm 0.5
10	0.245 \pm 0.5
20	0.486 \pm 0.5
25	0.598 \pm 0.5
30	0.719 \pm 0.5

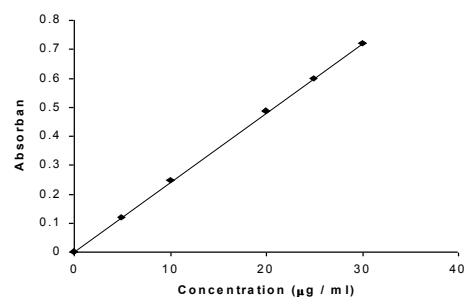


Fig1: standard calibration curve

Compatibility studies

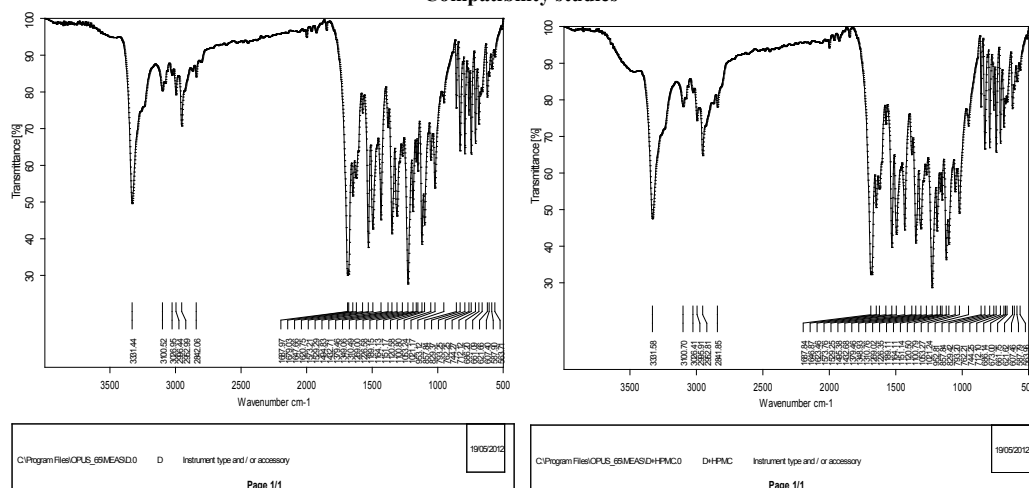


Fig 2 : FTIR spectra of pure drug nifedipine Fig 3 : FTIR combination of drug and HPMC

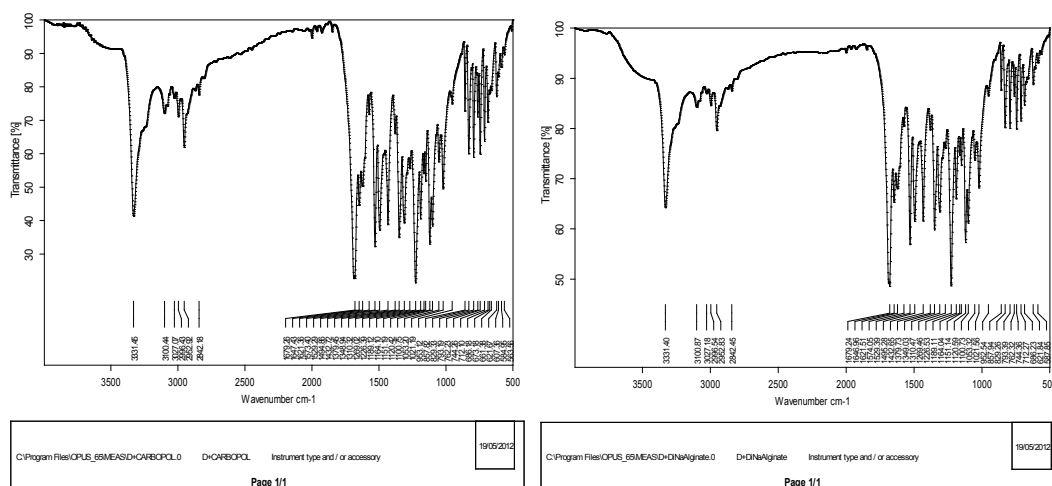


Fig 4 :FTIR spectra of drug and carbopol

Fig 5:FTIR spectra of drug and sodium alginate

Physicochemical evaluation of microspheres:

Table: 3 Angle of repose, carrs index, swelling index of mucoadhesive microspheres

S.no	Formulation	Angle of repose	Carrs index	Swelling index
1	F1	24.6 \pm 0.1	10.5	1.4
2	F2	24.3 \pm 0.3	12.25	1.45
3	F3	24.5 \pm 0.1	11.35	1.42
4	F4	24.7 \pm 0.2	11.45	1.5
5	F5	24.5 \pm 0.2	10.95	1.65

Table:4 Particle size, percent drug release, microencapsulation efficiency, % mucoadhesion of mucoadhesive microsphere

Formulation	Particle size(μ)	%Drug content	Microencapsulation efficiency	%Mucoadhesion
F1	765 \pm 0.5	95.25	55 \pm 0.7	59 \pm 0.5
F2	779 \pm 0.7	97.47	62 \pm 0.5	72 \pm 1.0
F3	770 \pm 0.6	96.68	56 \pm 0.3	62 \pm 1.5
F4	787 \pm 0.7	98.17	63 \pm 0.3	79 \pm 0.5
F5	792 \pm 0.5	99.5	69 \pm 0.6	85 \pm 0.5

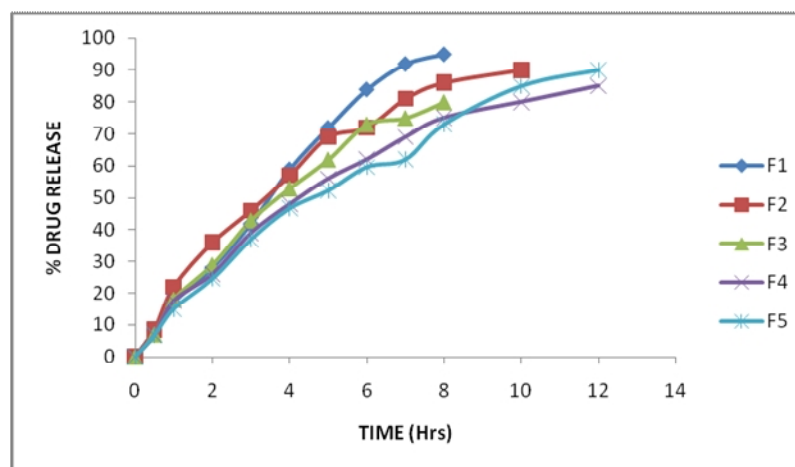


Figure 6 :Drug release profile for microspheres

Table:6 Correlation coefficient 'r' values in the analysis of release data of microspheres as per various kinetic models and 'n' value in peppas equation

Formulation	Zero order	First order	Higuchi	Peppas equation	n in Peppas equation
F1	0.9839	0.9452	0.9509	0.9499	0.9098
F2	0.9307	0.9931	0.9824	0.8759	0.7486
F3	0.9664	0.9941	0.9725	0.9052	0.8559
F4	0.9267	0.9969	0.9817	0.8674	0.7519
F5	0.9625	0.9738	0.9789	0.9005	0.8009

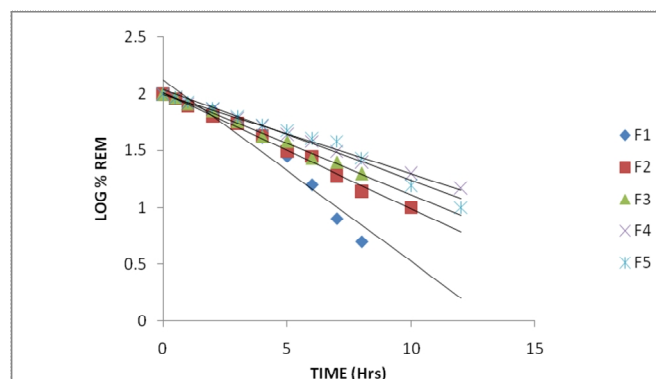


Figure 7 : First order plots for nifedipine microspheres

DISCUSSION:

FTIR spectral analysis:

The FTIR spectrum of pure nifedipine and nifedipine in combination with HPMC, carbopol, sodium alginate are presented in figures 2,3,4,5 respectively and it is observed that peaks were obtained as N-H stretch, C=O stretch and a C-H aromatic vibrations and a sharp peak of NO₂.

The FTIR spectra obtained from pure drug and in combination with polymers showed no shift from the original peaks and it indicates that there is no interaction between pure drug and the polymers.

Physical characteristics of microspheres:

Evaluation of microspheres shows that they are discrete, spherical, free flowing and the values are given in table 3. The size of the microspheres was determined by optical microscopy. The size analysis of different microspheres is shown in Table 4. Size analysis showed that they are almost uniform in size as they are made from same needle and the values range between 765 to 792 μ . Percent drug content of different microspheres is shown in Table 4 and the results shows that drug content was uniform and found to be within the limits. The microencapsulation efficiency was shown in Table 4. The values range between 55 to 69%. The order of

microencapsulation efficiency was found to be F5>F4>F2>F3>F1. To assess the mucoadhesivity of the microspheres in-vitro wash off test was performed for all the formulations for 5 hours. Formulation F5 showed the highest mucoadhesivity 85% due to the presence of combination of mucoadhesive polymers HPMC and carbopol and F1 showed the lowest mucoadhesivity 59% which is made up of only HPMC and the values are shown in Table 4.

Invitro drug release studies

Drug release from microspheres was studied in phosphate buffer pH 6.8 Containing 1 % w/v SLS as prescribed for nifedipine extended release tablets in U.S.P XXIV. The release data are given in Table 5 and Figure 6. Nifedipine release from all the microspheres was slow and spread over a period of minimum of 8 hours and maximum of 12 hrs and dependent on nature of polymer and concentration of polymer. The correlation coefficient (r) values in the analysis of release data as per different kinetic models are given in Table 6.

Analysis of release data as per zero and first order kinetic models indicated that nifedipine release from the microspheres followed first order kinetics. The correlation coefficient r values in the first order model were higher than

those in the zero order model. correlation coefficient r values in Higuchi equation near to one shows the release was controlled by diffusion mechanism and When the release data were analysed as per peppas equation the release exponent $n > 0.5$ with all the formulation indicating non fickian diffusion as the release mechanism.

CONCLUSION

Mucoadhesive microspheres showed good controlled release properties. The results of the present study demonstrated that nifedipine can be considered for mucoadhesive drug delivery containing HPMC & carbopol as mucoadhesive polymers for controlled release of the drug over a period of minimum 8 to maximum of 12 hrs which is dependent on the concentration and nature of polymers for the management of hypertension. After evaluating all the formulations, F5 which contains combination of polymers showed good entrapment efficiency, mucoadhesion, and drug release profile and therefore it can be considered as best formulation.

REFERENCES

- Gohel MC and Amin AF. Formulation optimization of controlled release diclofenac sodium microspheres using factorial design. *J. Control. Release.* 1998; 51: 115-22.
- Woo BH, Jiang G, Jo YW and DeLuca PP. Preparation and characterization of a composite PLGA and poly (acryloylhydroxymethyl starch) microsphere system for protein delivery. *Pharm. Re.* 2001; 18: 1600-06.
- Capan Y, Jiang G, Giovagnoli S and DeLuca PP. Preparation and characterization of poly (D,L-lactide-co-glycolide) microsphere for controlled release of human growth hormone. *AAPS PharmSciTech.* 2003; 4:147-156.
- Vasir JK, Tambwekar K and Garg S. Bioadhesive microspheres as a controlled drug delivery system, *Int. J. Pharm.* 2003; 255: 13-32.
- Nagai T, Nishimoto Y, Nambu N, Suzuki Y and Sekine K. Powder dosage form of insulin for nasal administration. *J. Control. Release.* 1984; 1: 15-22.
- Illum L, Furraj NF, Critcheley H and Davis SS., Nasal administration of gentamicin using a novel microsphere delivery system. *Int. J. Pharm.* 1988; 46: 261-65
- Ikeda K, Murata K, Kobayashi M and Noda K. Enhancement of bioavailability of dopamine via nasal route in beagle dogs. *Chem. Pharm. Bull.* 1992; 40: 2155-58.
- Schaefer MJ and Singh J. Effect of isopropyl myristic acid ester on the physical characteristics and *in-vitro* release of etoposide from PLGA microspheres. *AAPS PharmSciTech.* 2000; 1(4) : 49-54
- Lehr CM, Bouwstra JA, Schacht EH and Junginger HE. *In vitro* evaluation of mucoadhesive properties of chitosan and some other natural polymers. *Int. J. Phar.* 1992; 78: 43-48.
- Henriksen L, Green KL, Smart JD, Smistad G and Karlsen. J. Bioadhesion of hydrated chitosans: An *in vitro* and *in vivo* study. *Int. J. Pharm.* 1996; 145: 231-240.
- Rao SB and Sharma CP. Use of chitosan as biomaterial: studies on its safety and hemostatic potential. *J. Biomed. Mater. Re.* 1997; 34: 21-28.
- Chowdary KPR and 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(3) : 87-92.
- Liu Z, Lu W, Qian L, Zhang X, Zeng P and Pan J. *In vitro* and *in vivo* studies on mucoadhesive microspheres of amoxicillin. *J. Control. Release.* 2005; 102: 135-144.
- Chun MK, Cho CS and Choi HK. Mucoadhesive drug carrier based on interpolymer complex of poly(vinyl pyrrolidone) and poly(acrylic acid) prepared by template polymerization. *J. Control. Release.* 2002; 81: 327-334.
- Chun MK, Cho CS and Choi HK. Mucoadhesive microspheres prepared by interpolymer complexation and solvent diffusion method. *Int. J. Pharm.* 2005; 20: 288-295.
- Blanco-Mendez J. *In vitro* bioadhesion of carbopol hydrogel. *Int. J. Pharm.* 2004; 276: 51-58.
- Chickering D, Jacob J and Mathiowitz E. Bioadhesive microspheres II. Characterization and evaluation of bioadhesion involving hard, bioerodible polymers and soft tissue. *Reactive Polymers.* 1995; 25: 198-206
- Singh J and Robinson DH., Controlled release captopril microcapsules, effect of non-ionic surfactants on the release of ethyl cellulose microcapsules. *J of Microencapsul.* 1988; 5: 129-137.
- Mankala et al. Preparation and Characterization of Mucoadhesive Microcapsules of Glucalazide with Natural Gums. *S. J. Pharm. Sci.* 2011; 4(1): 38-48
- G. Fandueanu, M. Constantin, A. Dalpiaz, F. Bortolotti, R. Cortesi, P. Ascenzi., Preparation and characterization of starch/ cyclodextrin bioadhesive microspheres as platform for nasal administration of Gabexate Mesylate in allergic rhinitis treatment. *Biomaterial.* 2004 ; 25: 59-70.
- Chowdary KPR and Srinivasa RY., Preparation and evaluation of mucoadhesive microcapsules of Indomethacin, *Indian J. of Pharm Sci.*, 2003, 65(1), 49-52.
- Chowdary KP and Rao YS. Preparation and evaluation of mucoadhesive microcapsules of indomethacin. *Saudi pharmaceutical journal.* 2003 ; 11 (3): 97-103.

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