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RESEARCH ARTICLE

Formulation and Evaluation of Microspheres for Nasal Delivery of Antihypertensive Drug

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ABSTRACT

Purpose: Lisinopril is an angiotensin converting enzyme inhibitor used in the treatment of hypertension and heart failure in prophylactic treatment after myocardial infarction and in diabetic nephropathy. However, it is very poorly absorbed from gastro-intestinal tract. Intranasal administration is an ideal alternative to the parenteral route for systemic drug delivery. Formulating multiparticulate system with mucoadhesive polymers may provide a significant increase in the nasal residence time. The aim of the present approach was to overcome the drawbacks of the conventional dosage forms of lisinopril by formulating intranasal microspheres with Carbopol 974P NF and HPMC K4 M along with film forming polymer ethyl cellulose.Methods: The microspheres were prepared by emulsion solvent evaporation method. The prepared microspheres were characterized for encapsulation efficiency, drug loading, particle size, and surface morphology, degree of swelling, ex-vivo mucoadhesion, drug release, ex-vivo diffusion studies. Formulations C4 and H6 displayed the best results for Carbopol and HPMC based microspheres respectively. Entrapment efficiency was 84.95±0.50% and 17.92±0.0.777%; mucoadhesion was 62.66% and 96.33%; and drug release up to 40 minute was 53.66 % and 98.68% for C4 and H6 respectively. Combination of microspheres i.e. HC4 shows drug release upto 98.55%. Ex-vivo studies revealed that the formulations C4, HC4 and H4 showed good bioavailability compared to oral drug administration. Both in-vitro and Ex-vivo studies conclude that combination of Carbopol and HPMC based microspheres are better than single carbopol based microspheres for the delivery of lisinopril.

Keywords: Microspheres, Lisinopril, Solvent evapuoration method.

INTRODUCTION

Oral drug delivery is the most desirable route for drug administration whenever systemic effects are intended. Therefore, it is not surprising that the prediction of human oral bioavailability of new drug candidates is currently targeted from the earliest stages of drug discovery and development programmes [1, 2]. However, although the oral route remains the most popular for systemic drug administration but low oral bioavailability of some compounds has prompted the search of more effective routes for their systemic delivery [3].

Nasal drug delivery system has shown great attraction in the past years to optimized therapeutic effect of drug, due to high permeability of nasal epithelial membrane so that rapid absorption of drug is possible, as compared to other non-invasive routes[1,2] Nasal drug delivery system provides easy application of drug, with the possibility of self administration by removing the chance of unwanted painful condition associated with injection form of drug delivery. Furthermore, lipophilic and low molecular weight drugs can easily penetrate through nasal

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mucosa with less degradation. Fast absorption can be achieved due to large absorption surface area and high vascularisation. Nasal route can be used as an alternative to parenteral in case of emergency therapy.[3,4] Nasal drug delivery system is a potential route for direct delivery of drug to the central nervous system through olfactory region bypassing hepatic first pass metabolism.[5,6] Side by side nasal drug delivery system has some limitations like large dose cannot be administered by this route conveniently due to administrative problems. Administration of solid formulation is quite difficult by nasal route.[5] Fast clearance of the administered formulation occurs from the nasal cavity as the result of mucociliary clearance causes poor absorption of drug.[7] These difficulties of nasal route can be minimized by utilization of various kinds of mucoadhesive polymers in the formulation. These polymers can effectively increase the retention time with improved permeation enhancing effect. In some research these polymers also possess the controlled release of drug. A variety of polymers have been discovered which includes, synthetic as HPMC, HEC, Chitosan, Carbopol and natural as gelatin, albumin, starch. Utility of synthetic polymers are associated with large numbers of risk such as high cost, toxicity, environmental pollution during synthesis, non renewable sources, side effects and poor patient compliance.[8] These limitations of synthetic polymers may be avoided by utilization of natural polymers as they are biodegradable, chemically inert, less expensive, nontoxic, and widely available.[1,8] Natural products are now accepted worldwide due to their biodegradability, which leads low chance of risk during uses.

Lisinopril is an angiotensin-converting –enzyme inhibitor that inhibits ACE activity, thereby reducing plasma angiotensin II and aldosteron and increasing plasma rennin activity. Lisinopril produces smooth, gradual blood pressure reduction in hypertensive patients without affecting heart rate or cardiovascular reflexes. The antihypertensive effect begins within 2 h, peaks around 6 h, and lasts for at least 24 h. so to get quick effect lisinopril is administered by nasal route as drug enters directly into systemic circulation and gives quick onset of action. To avoid this initial lag period of 2 h it is needed to administer it by nasal route as onset of action starts within 10 to 15 min. lisinopril does not produce hypokalemia, hyperglycemia, hyperuricemia, or hypercholesterolemia. Renal blood flow remains stable or increases. Lisinopril increases cardiac output, and decreases pulmonary capillary wedge pressure and mean arterial pressure in patients with congestive heart failure. Lisinopril is well tolerated and have good safety index. Lisinopril is available in tablet form only in market which gives oral bioavailability of 25% only so to increase the bioavailability and quick onset o action it is given by nasal route.

Following are the reasons why lisinopril is given by nasal route and how it is suitable for nasal administration:

Maximum antihypertensive drugs degrade in GIT but it is avoided by using nasal route. Hepatic first pass metabolism is avoided as antihypertensive drugs undergo hepatic first pass metabolism. Rapid drug absorption and quick onset of action can be achieved.

The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach. Smaller drug molecules having poor bioavailability can be given by nasal route as drugs upto molecular weight 500 daltons can be absorbed through nasal mucosa. The nasal bioavailability for smaller drug molecules is good. When drugs are given by nasal route it directly enters into systemic circulation so drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery. Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs. Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.

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Drugs possessing poor stability in G.I.T. fluids are given by nasal route. Antihypertensive drugs are mostly polar in nature so these polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.

MATERIALS AND METHODS

All chemicals used were of analytical grade. Lisinopril was purchased from Rajesh chemicals Mumbai. ethyl cellulose, KBr ,methanol , ethanol , dichloromethane, span 80, HCL all are from Loba chemicals. Carbopol 934 from Research lab Mumbai.

Formulation of Microspheres:

The microspheres were formulated by emulsion solvent evaporation method. The polymer was composed of EC, carbopol and HPMC K4m. Briefly, the fixed amount of drug and the polymer (1:1, 1:2, and 1:3) were dissolved in a mixture of dichloromethane and ethanol (1:1). Polyethylene glycol (PEG) is also added in polymeric solution along with sodium taurocholate as absorption enhancer. Then, the dispersion solution was injected into 100 ml of light liquid paraffin containing 2.5% span 80.. The resultant emulsion was stirred at 8000 rpm using a propeller-type agitator for 10 min and then continued at 1000 rpm for 2 hrs. The microspheres were separated by vacuum filtration, washed with n-hexane and vacuum-dried at room temperature for 24 hr. The optimized parameters for emulsion solvent evapuoration is as shown table no.1.It is desirable to develop an expectable pharmaceutical formulation in the shortest period of time using minimum number of man-power and raw materials. The drug polymer concentration is used mainly as variable because three different drug -Polymer ratio (w/w) affects the % Drug release and bioadhesion time. Therefore these parameters were chosen for optimization of mucoadhesive microsphere characteristics. The Microspheres were prepared using different polymer-drug ratio (w/w) such as 1:1, 1:2, 1:3 1:4 as shown in table no 2 good results were found with these ratios, so this ratio was further considered for combination of microsphere preparation. The bioadhesion of microspheres is depend on the Carbopol and HPMC concentration therefore this is important factor for the preparation of bioadhesive microspheres. For study of effects of bioadhesion time it was one of the variable parameter considered for preparation of microspheres.

RESULTS AND DISCUSSION:

Characterization Of Microspheres:[6]

Percent yield:

The percentage of production yield (wt/wt) was calculated from the weight of dried microspheres (W_1) recovered from batches and the sum of the initial dry weight of starting materials (W_2) as the following equation:

$$\% \text{ Production Yield} = \frac{W_1}{W_2} \times 100$$

The yields of production were calculated as the weight percentage of the final product after drying, with respect to the initial total amount of lisinopril and EC: Carbopol: HPMC mixture used for the preparations.

Entrapment Efficiency

The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The Lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation

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% Entrapment = Actual content/Theoretical content x 100.

Particle size, Shape and Morphology

All the microspheres were evaluated with respect to their size and shape using optical microscope fitted with an ocular micrometer and a stage micrometer. The particle diameters of more than 100 microspheres were measured randomly by optical microscope [106,107]. Scanning Electron photomicrographs of drug-loaded microspheres were taken. A small amount of microspheres was spread on gold stub. Afterwards, the stub containing the sample was placed in the Scanning electron microscopy (SEM). A Scanning electron photomicrograph was taken at an acceleration voltage of 20KV.

Swelling Index

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 given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using microbalance. The hydrogel microspheres then dried in an oven at 60° for 5 h until there was no change in the dried mass of sample. The swelling index of the microsphere was calculated by using the formula [84].

Swelling index= (mass of swollen microspheres - mass of dry microspheres/mass of dried microspheres) .100.

***In Vitro* wash-off test**

A 1 cm x 1 cm piece of rat stomach mucosa was tied onto a glass slide (3 inch x 1 inch) using a thread. Microsphere was spread onto the wet, rinsed, tissue specimen and the prepared slide was hung onto one of the groves of the USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that that the tissue specimen regular up and down movements in a beaker containing the simulated gastric fluid. At the end of every time interval, the number of microsphere still adhering on to the tissue was counted and there adhesive strength was determined using the formula.

FTIR study

IR spectroscopy can be performed by Fourier transformed infrared spectrophotometer. The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000- 600 cm-1. FTIR study was carried on pure drug, physical mixture, formulations and empty microspheres.

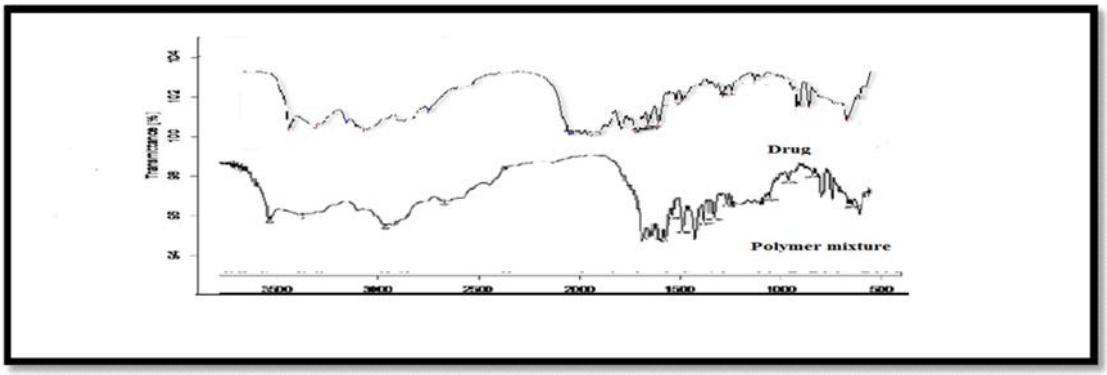

Fig. 01:FTIR graph of drug and physical mixture

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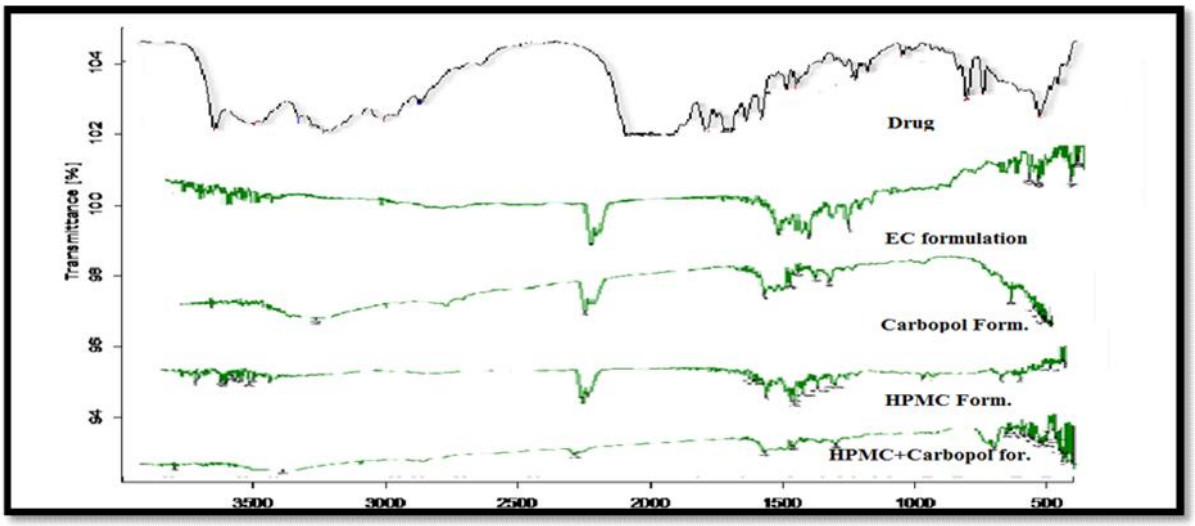

Fig. 02:FTIR graph of drug and formulation

X- ray diffraction analysis(XRD):-

X-Ray diffraction patterns of the pure drug, polymers, physical mixture and different formulation batches were examined by using X-Ray Differactometery (Bruker-AXS-DHR-1) using Cr filtered (α) radiations, a voltage of 40 kv, current of 25 mA and receiving slit of 0.2 In. The instruments were operated over 2θ scale. The angular range was 5 to 50^{o} (2θ) and counts were accumulated for 0.8 second at each step.

Mucoadhesion Measurement Study:[146]

The in vitro Mucoadhesion study of microspheres was assessed using falling liquid film technique. Goat nasal mucosa was obtained from the animal slaughter house from Peth vadgaon. The nasal mucosa of goat was removed and rinsed with phosphate buffer pH 6.4. a strip of nasal mucosa was mounted on a glass slide and 50 mg of microsphere were scattered uniformly on the surface of the nasal mucosa. Then, the nasal mucosa with microspheres was placed in a desiccators maintained at 90% relative humidity at room temperature to allow the polymer to interact with the membrane and finally placed on stand at an angle of 45^{0} . The nasal mucosa was rinsed with phosphate buffer (pH 6.4,) for 60min at a rate of 5ml/min. The time required for detachment of microspheres from stomach mucosa was noted by visual inspection. Also the detached particles are collected and weighed.

$$\% \text{ Mucoadhesion} = \frac{\text{weight of sample} - \text{weight of detached particles}}{\text{Weight of sample}} \times 100$$

***In Vitro* diffusion studies**

In Vitro diffusion studies were performed using in vitro nasal diffusion cell [109]. The receptor chamber was filled with buffer maintained at 37±2°C. Accurately weighed microspheres equivalent to 10 mg were spread on sheep nasal mucosa. At selected time intervals 1 ml of diffusion samples were withdrawn through a hypodermic syringe and replaced with the same volume of prewarmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples were analyzed spectrophotometrically.

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The diffusion study of ethyl cellulose microspheres is carried out using Franz diffusion cell. The goat nasal mucosa is removed from its hard boney tissue and kept in water containing few drops of gentamicin injection to remove traces of blood. 50 mg of microspheres weighed and spread on nasal mucosa and phosphate buffered saline solution is added to wait the microspheres. After that 1 ml of solution is withdrawn and diluted to 10 ml and absorbance is noted. The sample is withdrawn at 10 minute interval and continued for one and half hour. The maximum drug release was found at 70 minute. The microsphere ratio of 1:4 shows maximum release upto 98.65% while the pure drug shows the release upto 96.2 %. (Table no. 4) The microspheres of ratio 1:1, 1:2, 81.82% and 96.46 % respectively. The microsphere ratio 1:3 shows maximum drug release at 90 minute i.e. 94.53%. The microspheres obtained for all the formulations were discrete and uniform. The production yield, entrapment efficiency, drug loading, particle size, degree of swelling and percent mucoadhesion of all the batches of microspheres is shown in table no.3. The production yields of microspheres were found to be between 73 to 90%. The values for drug loading were in the range of 27 to 37% for ethyl cellulose based microspheres. Also, particle size was reduced at higher stirring rate. The degree of swelling and percent mucoadhesion was upto 21%. The mucoadhesive strength of ethyl cellulose microspheres was very low so due to that the microspheres are prepared in combination with carbopol to increase the mucoadhesive property and also to study the effect of drug release**.** The microspheres obtained for all the formulations were discrete and uniform. The production yield, entrapment efficiency, drug loading, particle size, degree of swelling and percent Mucoadhesion of all the batches of microspheres is shown in table no5. The production yields of microspheres were found to be between 84 to 90%. The values for drug loading were in the range of 17 to 84 % for carbopol microspheres. Also, particle size was reduced at higher stirring rate. The degree of swelling and percent Mucoadhesion was upto 22% and 78% respectively. The maximum drug release was found at 40 minute. The microsphere ratio of 1:1 shows maximum release upto 66% while the pure drug shows the release upto 96.2 %. The microspheres of ratio 1:2 , 1:3 , 1:4, 2:1, 3:1 shows 65, 61, 53, 62, 37 respectively. The microsphere ratio 4:1 shows maximum of drug release at 60 minute i.e. 45 %.(Table no. 6).

The Mucoadhesion strength of Carbopol microspheres is increased sufficiently but drug release is low compared to ethyl cellulose microspheres. Therefore to increase the mucoadhesion strength and diffusion HPMC microspheres were prepared and evaluated. The microspheres obtained for all the formulations were discrete and uniform. The production yield, entrapment efficiency, drug loading, particle size, degree of swelling and percent mucoadhesion of all the batches of microspheres is shown in table no. 7. The production yields of microspheres were found to be between 76 to 89%. The values for drug loading were in the range of 17 to 33 % for HPMC microspheres. Also, particle size was reduced at higher stirring rate. The degree of swelling and percent Mucoadhesion was upto 11% and 96% respectively. The diffusion study of HPMC microspheres the maximum drug release was found at 40 minute. The microsphere ratio of 1:3:1 shows maximum release upto 98% while the the microspheres of ratio 1:1 ,1:2 , 1:3 , 1:4, 2:1, 4:1 shows 59, 60, 64, 88, 89 and 68% respectively. (Table no. 8)To study the effect of drug release and Mucoadhesion strength the microspheres are prepared in combination with HPMC and carbopol. The microspheres obtained for all the formulations were discrete and uniform. The production yield, entrapment efficiency, drug loading, particle size, degree of swelling and percent mucoadhesion of all the batches of microspheres is shown in table no.9. The production yields of microspheres were found to be between 81 to 94%. The values for drug loading were in the range of 19 to 54 % for combination type of microspheres. Also, particle size

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was reduced at higher stirring rate. The degree of swelling and percent mucoadhesion was upto 27% and 94% respectively.(table no. 10 &11).

The maximum drug release was found at 40 minute. The microsphere ratio of 4:1shows maximum release upto 98.55% while the pure drug shows the release upto 96.2 %. The microspheres of ratio 1:1, 2:1, 3:1, 1:2, 1:3, 1:4shows drug release upto 84, 59, 38, 53, 64, 55 respectively. The microsphere ratio 1:1:2, 1:1:3, 1:1:4 shows maximum drug release at 50 minute i.e. 88, 73, 83% respectively.

Lisinopril is hydrophilic drug i.e. freely soluble in water having molcular weight of 441 dalton . The drugs having molecular weight of upto 1000 dalton can esily cross nasal epithelial cells but to increase the permiability of epithelial cells the use of absorption enhancer is tried. The absorption enhancer sodium taurocholate is used. 50 mg of sodium taurocholate is added in combination type of microspheres. thus a separate batch is prepared and evaluated. It is observed that drug release is increased so much using absorption enhancer as shown in table no.12.

Batch code	E1	E2	E3	E4	Pure drug
Time in minute	**% DR**	**%DR**	**%DR**	**%DR**	**%DR**
0	0	0	0	0	0
10	10.5±0.28	22.86±0.304	23.46±0.233	15.8±0.636	9.4±0.353
20	19.12±0.30	29.86±0.282	33.53±0.049	17.86±0.056	20.8±0.636
30	24.16±0.205	41.73±0.742	38.8±0.282	21±0.473	63.6±0.296
40	49.45±0.629	48.33±0.063	27.93±0.671	23.66±0.530	79.53±0.482
50	56.66±0.947	49.6±0.452	32.33±0.226	25±0.007	85.46±0.558
60	78.96±0.127	58±0.021	38.93±0.381	41±0.332	96.2±0.890
70	81.82±0.692	96.46±0.360	45.33±0.247	98.65±0.714	97.54±0.947
80	87.77±0.98		57.8±0.565		98.64±0.551
90	88.33±0.495		94.53±.601		

Table 01. Diffusion study of ethyl cellulose microspheres

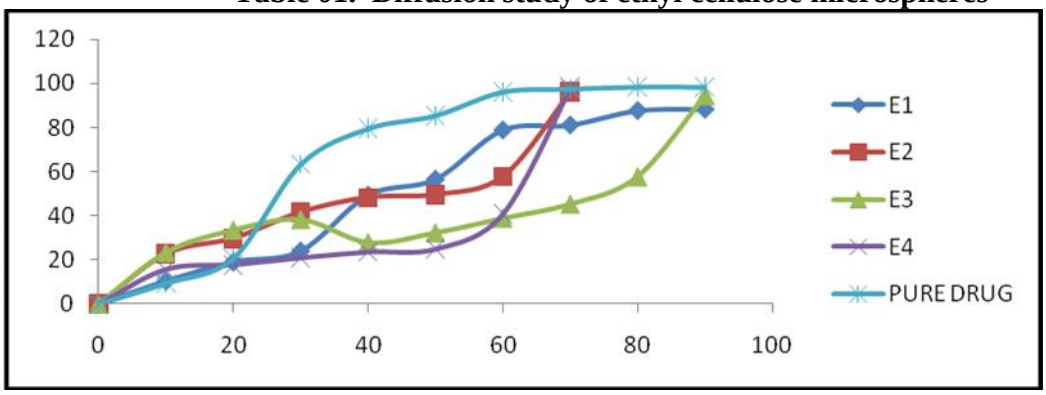

Fig. 03: Diffusion study of ethyl cellulose microspheres

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Batch code	H1	H2	H3	H4	H5	H6	H7

Batch code	C1	C2	C3	C4	C5	C6	C7
Time in minute	**%DR**	**%DR**	**%DR**	**%DR**	**%DR**	**%DR**	**%DR**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	**15±0.728**	**18.53±0.257**	**20.26±0.106**	**32.41±0.869**	**9.66±0.650**	**3.06±1.30**	**8.2±0.494**
20	**15.33±1.41**	**19.06±0.813**	**30.53±0.728**	**39.06±0.685**	**14.4±0.636**	**5.26±0.091**	**14.33±0.664**
30	**17.8±0.777**	**23.73±0.395**	**42±0.014**	**43.33±0.134**	**33.8±0.424**	**22.73±0.707**	**23.6±0.212**
40	**66.26±0.756**	**65.26±0.091**	**61.66±1.05**	**53.66±0.537**	**62.66±0.459**	**37.2±0.155**	**29.13±0.162**
50						**39.86±0.530**	**40.06±0.084**
60						**40.46±0.685**	**45±0.530**

Table no.02: Diffusion study of carbopol microspheres

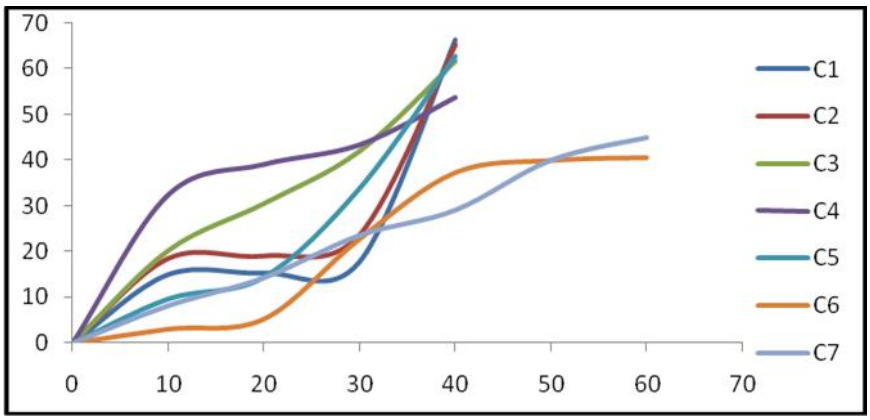

Fig.04: Graph of diffusion of Carbopol microspheres.

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Time in minute	%DR	%DR	%DR	%DR	%DR	%DR	%DR
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	**8.5±0141**	**8.39±0.509**	**12.72±0.700**	**13.90±0.233**	**7.08±0.664**	**13.24±0.791**	**10.42±0.643**
20	**8.72±0.282**	**20.39±0.134**	**14.75±0.268**	**20.45±0.035**	**24.91±1.209**	**37.63±0.586**	**15.73±1.117**
30	**9.57±0.395**	**34.16±0.127**	**26.03±0.049**	**27.40±0.424**	**50.95±0.593**	**64.65±0.028**	**25.77±0.926**
40	**52.98±0.827**	**44.59±0.480**	**38.03±0.438**	**64.78±0.466**	**65.63±2.05**	**90.16±0.028**	**65.96±0.64**
50	**59.47±0.919**	**60.78±0.565**	**64.72±0.700**	**88.32±0.325**	**89.04±0.042**	**98.68±1.032**	**68.59±0.395**

Table no.03: Diffusion study of HPMC microspheres

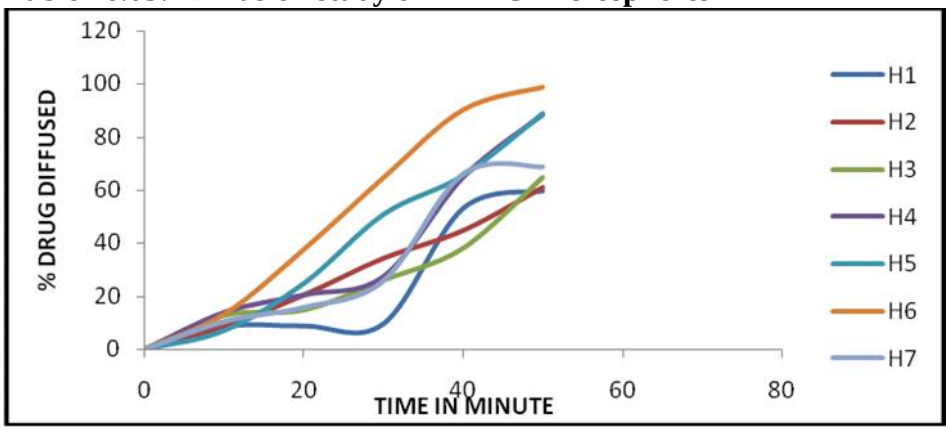

Fig. 05: Diffusion study of HPMC microsphere

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Batch code	HC6	HC7	HC8	HC9	HC10
Time in minute	**%DR**	**%DR**	**%DR**	**%DR**	**%DR**
0	**0**	**0**	**0**	**0**	**0**
10	**29.8±0.282**	**14.46±0.749**	**31.14±0.714**	**8.26±601**	**24.45±0.516**
20	**33.6±0.353**	**16.2±0.424**	**30.03±0.056**	**20.19±0.700**	**26.95±0.134**
30	**34±0.777**	**21.8±0.212**	**50.75±0.261**	**33.31±0.558**	**49.5±0.431**
40	**64.8±0.777**	**55.26±0.049**	**52.59±0.388**	**45.96±0.714**	**51.47±0.643**
50			**88.85±1.20**	**73.24±728**	**87.47±0.049**

Table 04: Diffusion study of combination microsphere

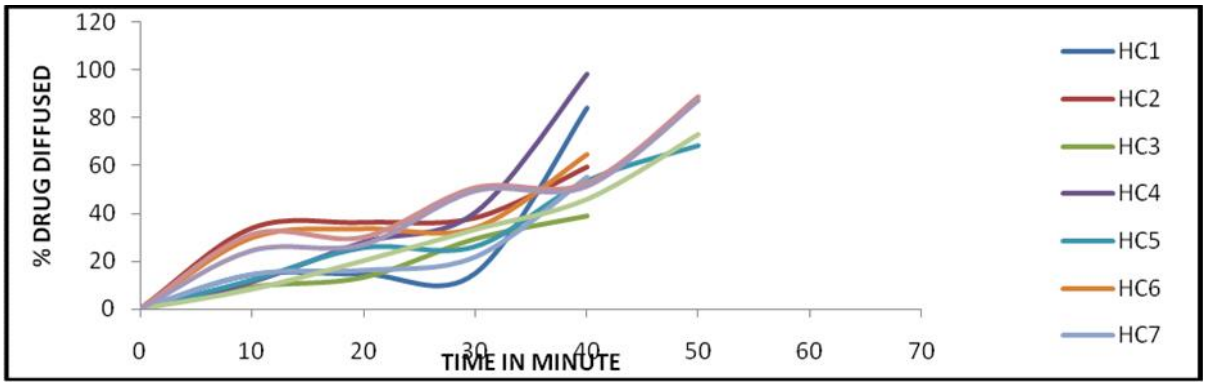

Fig. 06: Graph of % drug diffusion of combination type of microspheres:

SEM: Scanning electron microscopy was used to determine surface morphology of pure drug, and optimized microspheres. The formulations prepared by emulsion solvent evapuoration method were subjected to SEM studies. The distribution of drug in polymer matrix and interaction between drug and polymer was analysed.All the formulations shows the spherical particles with slightly rough surface. Microspheres formulated were found to be in the size range ranging from 5 µm to 100µm.

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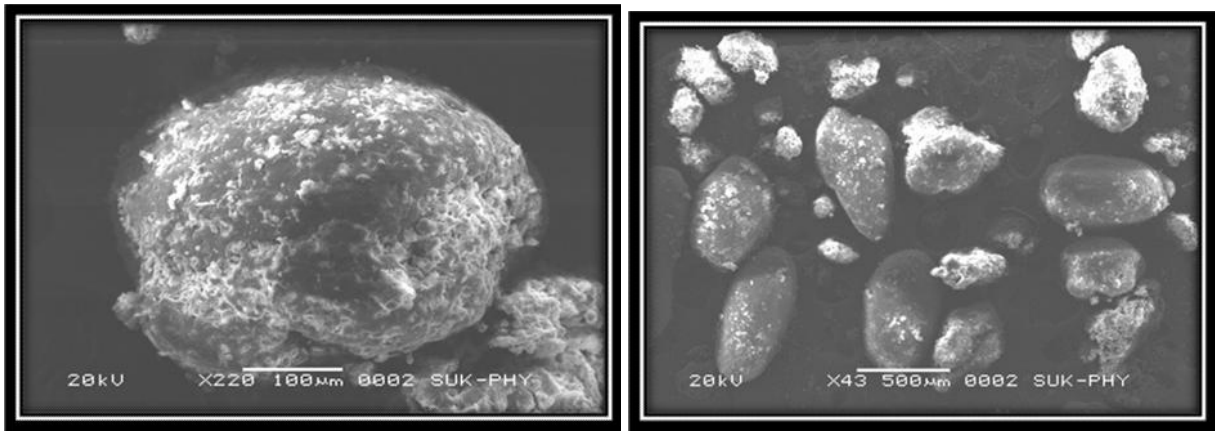

Fig 07: SEM of optimized batch of microsphere

XRD:X ray diffraction study was carried out on the optimized batch of microspheres which shows maximum solubility and diffusion. X ray diffraction study of pure lisinopril showed high intensity peak at 2θ of 19.78. prove its crystalline nature**.** HPMC showed prominent peak with the highest intensity at 2θ of 19.40‘. For the calculation of disorderness of microsphere batch the term relative degree of crystallinity (RDC) was used, this can be calculated as

$$RDC = \frac{\text{Highest peak intensity of formulation}}{\text{Highest peak intensity of drug}}$$

The XRD scan of pure lisinopril shows intense peak of Crystallinity where as the XRD scans of physical mixtures and microspheres shows reduction in both number and intensity of peaks as compared to pure drug. The RDC value was found to be 1.0005. Peak intensity of microsphere formulation was found to be less as compared to PM indicating amorphisation of drug.

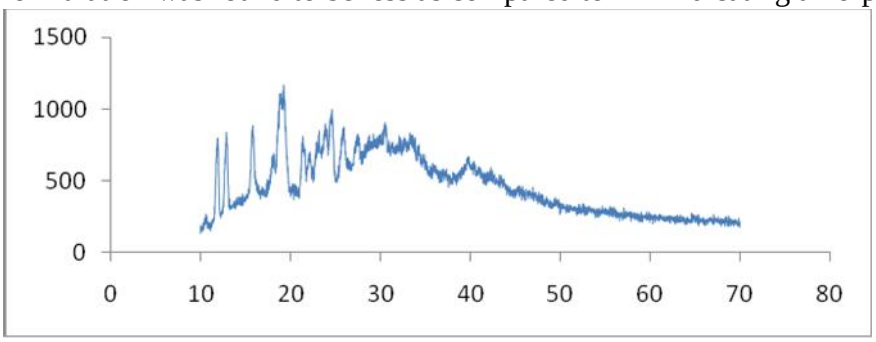

Fig.07: XRD of lisinopril

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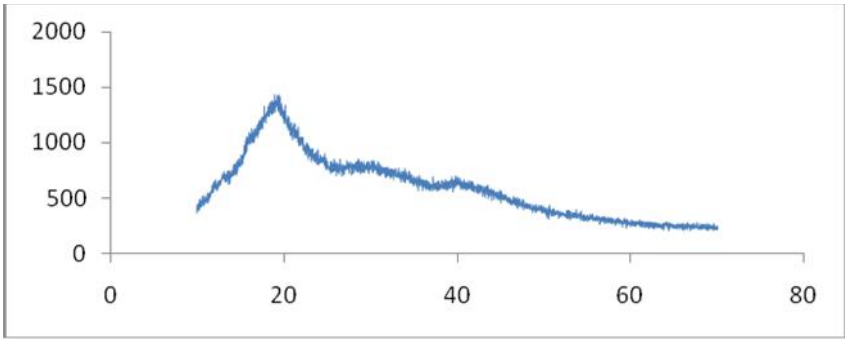


Fig.08: XRD of ethyl cellulose microspheres

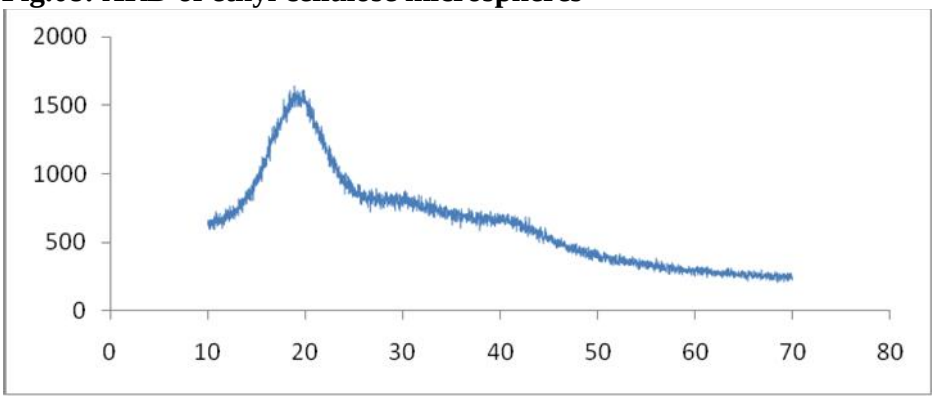
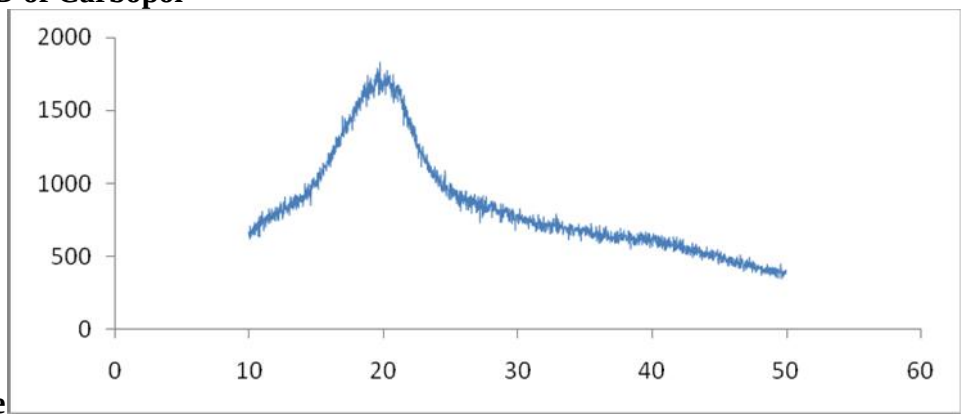


Fig. 09: XRD of Carbopol



microsphere

Fig.10: XRD of combination microspheres:

DSC: The DSC analysis of pure drug i.e. lisinopril , physical mixture and formulations are as shown in fig. DSC analysis of lisinopril shows single endothermic sharp peak at 165.10^0 C. It is concluded from DSC thermo gram of PM and microspheres that there is decrease in sharpness and intensity of characteristic endothermic peak of drug which could be attributed to conversion of most of the crystalline form of drug to amorphous form.

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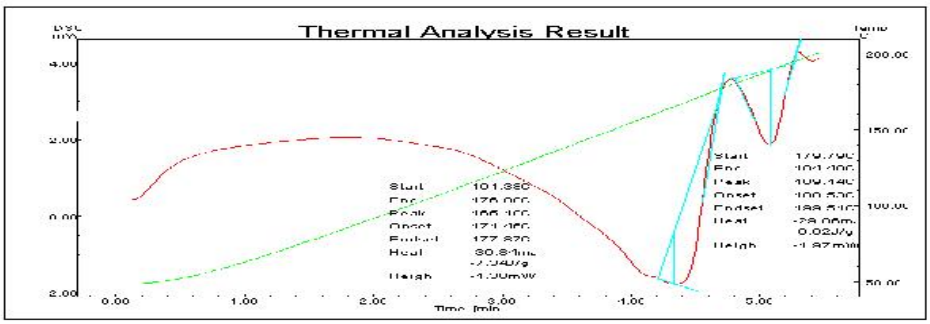

Fig.11: DSC analysis of lisinopril

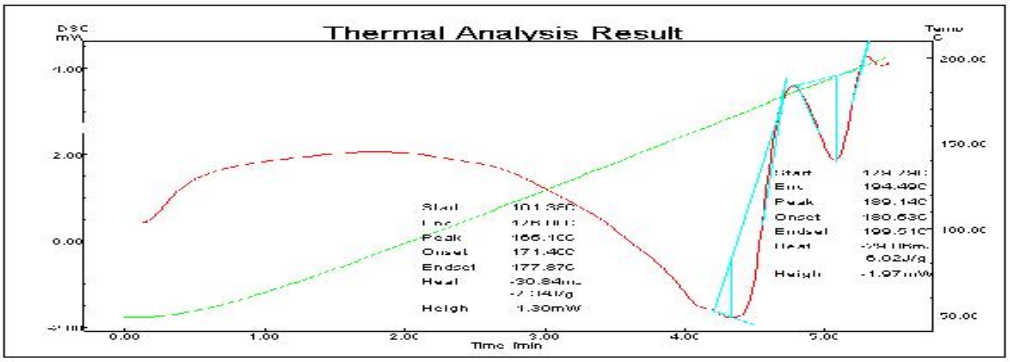

Fig. 12: DSC analysis of physical mixture

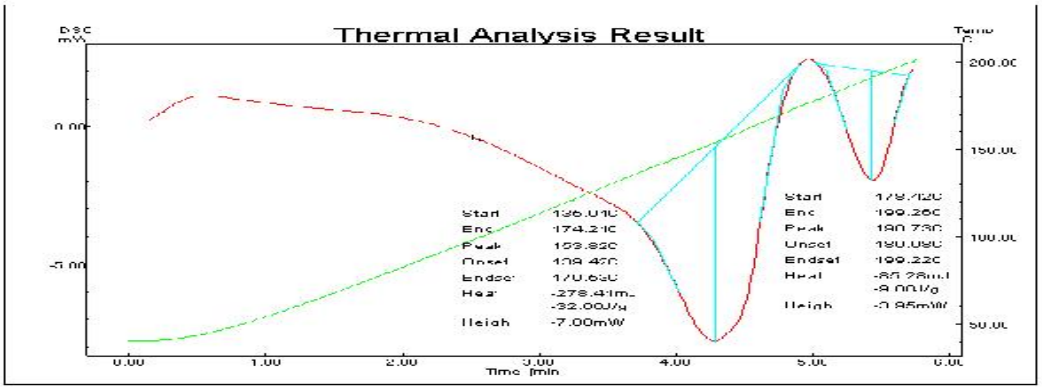

Fig.13: DSC analysis of microspheres

Particle size analysis:

In the present study the ethyl cellulose , carbopol and HPMC microspheres encapsulated with lisinoprl were prepared by emulsion solvent evapouration method. 200 microspheres of each batch were sized by optical microscope equiped with optical micrometer and average percentage frequency was plotted against size ranges. The mean size range of all batches of microspheres was estimated between 1-60um with nearly 51% lying between 45-50 um. 40% microspheres were found to be in the range of25-30um.36% microspheres were found in the range of 30-35%.

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CONCLUSION:

The scientific community has reached a new stage of nasal drug delivery. The nasal drug delivery is promising alternarive to injectable route of administration. It is very likely that in the near future more drugs will come in the market intended for systemic absorption in the form of nasal formulation. In this study it is observed that the absorption of lisinopril from nasal mucosa is successfully enhanced. The particle size was found to be in the range of 5-100um.the microspheres have roughly smooth surface which is observed in the SEM study. Initially the optimization of process and formulation variables was carried out which showed that emulsion solvent evapuoration method with w/o type of emulsion system is feasible for preparation of microspheres for water soluble compounds. Lisinopril is highly water soluble and soluble in organic solvents (ethanol, methanol) while ethyl cellulose is insoluble in water. So in the present investigation, organic solvent was used as polar phase to form w/o type of system.

In case of lisinopril which possesses low bioavailability with oral route this system provide a more steady plasma level of drug. Having high degree of mucoadhesion this system can be used for the delivery of lisinopril via nasal route which could eventually eliminate the fisrt pass effect and thus improving drugs bioavailability. The emulsion solvent evapuoration technique for obtaining ethyl cellulose. Carbopol and HPMC microspheres have proved to be useful tool in the preparation of microspheres for nasal delivery. By virtue of prolonged drug residence at the site of absorption, improved bioavailability can be achieved in contrast to oral dosage form. The FTIR studt of drugs and polymers carried out from that it is concluded that there is no any interaction between the drug and polymer. From the XRD study it is concluded that the RDC values for the drug , polymer, physical mixture and formulation remains constant. The optimized batch of HPMC microspheres shows the release of upto 98.68% and mucoadhesion 96.33%. the particle size mainly depends on the stirring rate . hence as the stirring rate increased , the particle size decreased irrespective of the concentration of mucoadhesive polymer. From the surface morphology results, microspheres obtained were discrete, uniform and spherical with smooth surface as speed of stirring is constant. The % mucoadesion of HPMC microspheres was higher than Carbopol and combination of Carbopol and HPMC microspheres. The swelling index was found to be in the range of combination of HPMC and Carbopol> Carbopol> HPMC> Ethyl cellulose.

REFERENCES

1. S. Upadhyay, A. Parikh, P.Joshi, U M Upadhyay and N P Chotai , Intranasal drug delivery system- A glimpse to become Maestro Journal of Applied Pharmaceutical Science 01 (03); 2011: 34-44.
2. S. Basu and A.K. Bandyopadhyay, Intranasal drug delivery :an overview Int J Pharm Sci Tech Vol-4, 2010 ISSN:0975-0525.
3. A. Pires, A.Fortuna, G. Alves and A. Falcon, Intranasal Drug Delivery: How, Why and What for?, J Pharm Pharmaceut S (www.cspsCanada.org) 12(3) 288 - 311, 2009 288.
4. U.R. Lokhande, V.D. Gorde, M.V. Gadhave., S.T. Tambe Nasal drug delivery system: a review International Standard Serial Number (ISSN): 2249-6793 International Journal of Universal Pharmacy and Life Sciences 2(2): 2012
5. D. Bhowmik, R. Kharel, J.Jaiswal, Chiranjib, Biswajit and K. P.Sampath Kumar. Innovative approaches for nasal drug delivery system and its challenges and opportunities, Annals of Biological Research, 2010, 1 (1): 21-26.
6. H. Parmar, S. Bakliwal, N. Gujarathi, B. Rane, S. Pawar. Different methods of formulation and evaluation of Mucoadhesive microsphere Volume: I: Issue-3: 2010.
7. K.Basavaraj, Nanjwade, A. Kemy. Parikh, Rucha V. Deshmukh, Veerendra K. Nanjwade, Kishori, R. Gaikwad, Sachin, A. Thakare and F. V. Manv , Development and Evaluation of Intranasal Mucoadhesiv Microspheres of Neostigmine Bromide, pharmaceutica analytica.

8. M. Shirui, J. Chen, Z. Wei, H. Liu, D. Bi (2004). Intranasal administration of melatonin starch microspheres. Int J Pharm. 272, 37-43.
9. Y.C. Huang, M.K. Yen, C.H. Chiang (2000). Formulation factors in preparing BTM-chitosan microspheres by spray drying method. Int J Pharm. 242, 239-42.
10. A. Raza, T. Mahmood Ansari and A.Rehman, "Spectrophotometric Determination of Lisinopril in Pure and Pharmaceutical Formulations". Journal of Chinese Chemical Society, 2005, 52, 1055-1059.
11. Indian pharmacopoeia, Government of India, Ministry of health and family welfare, controller of India: New Delhi; Volume I 2010; 187-193, 1337-1338.
12. R. C. Rowe, P.J. Sheskey, S. C.Owen; Handbook of Pharmaceutical Excipients, 5th edition; 2006, 201-203,701-703,132-135,430-433,687-689.
13. V.V Prasanth, A. Chakraborty, S T Mathew, R Mathappan, and V.Kamalakkannan , Formulation and evaluation of Salbutamol sulphate
Microspheres by solvent evaporation method, Journal of Applied
Pharmaceutical Science 01 (05); 2011: 133-137.
14. E. Gavini , G. Rassu , L. Ferraro , S. Beggiato , A. Alhalaweh , Sitaram Velaga , N. Marchetti , P. Bandiera , P. Giunchedi , A. Dalpiaz , Influence of polymeric microcarriers on the in vivo intranasal uptake of an anti-migraine drug for brain targeting. European Journal of Pharmaceutics and Biopharmaceutics (2012).
15. P. Sindhuri, M.Purushotama. Formulation and evaluation of Norfloxacin Microspheres using different polymers Int. J. Pharm & Ind. Res Vol – 01 Issue – 01 Jan - Mar 2011.
16. J Rita. Majithiya, K Pradip. Ghosh, "Thermoreversible mucoadhesive Gel for nasal delivery of sumatriptan" AAPS Article 67. (2006)
17. H ShivShankar, A. Jain., R. Patel., A. Kaushal., Formulation and Evaluation of mucoadhesive microspheres of ciprofloxacin 214-224 ISSN 2249-337. 2011.
18. F. Atyabi, A. Mohammadi, R. Dinarvand, Preparation of Nimodipine Loaded Microspheres: Evaluation of Parameters, Iranian Journal of Pharmaceutical Sciences Summer 2005: 1(3): 143-152.
19. P.Rout, A. Ghosh, U Nayak and B.Nayak , Effect of method of preparation on physical properties And *in vitro* drug release profile of losartan microspheres – a comparative study, International journal of pharmacy and pharmaceutical sciences, volume 1 issue 1 july sept 2009.
20. S.Abolghassem S. Tabassi, N. Razavi (2003). "Preparation and Characterization of albumin microspheres encapsulated with propranolol HCL" DARU volume 11 no. 4.
21. N. Manjunatha. S.Vasanti, N.Rajesh, N.Uma (2010)., " formulation and evaluation of biopolymer based microspheres for nasal drug delivery " 856-862 IJPRF vol.2 no.1.