Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2016, 8 (1):197-205
(http://scholarsresearchlibrary.com/archive.html)

Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Preparation and evaluation of mefenamic acid loaded microspheres using synthetic and natural polymers

K. Anusha[1] and Krishna Sailaja A.[2]

[1]RBVRR Women's College of Pharmacy, Hyderabad
[2]RBVRR Women's College of Pharmacy, Affiliated to Osmania University, Hyderabad

---

ABSTRACT

The main objective of the work is to prepare mefenamic acid loaded microspheres for sustained release using different polymers ethyl cellulose as synthetic polymer and sodium alginate as natural polymer and compare and selecting best suitable polymer among them. For preparing mefenamic acid microspheres ethyl cellulose used as synthetic polymer in solvent evaporation method and sodium alginate as natural polymer used in inotropic gelation technique. All formulations were prepared by varying the drug and polymer concentrations. The obtained microspheres were characterized for surface morphology, stability and evaluated for yield, drug content, entrapment efficiency and Invitro drug release. Comparative study was performed between the best formulations of Ethyl cellulose and sodium alginate polymers. zeta potential value, Drug content, Entrapment efficiency of the best formulation of Mefenamic acid microspheres using ethyl cellulose was found to be -78.2mv, 93.4%, 92.5%whereas for using sodium alginate it was found to be -65.1mv, 91.7%, 90.1%respectively. The drug release was found to be 90.4% till 12hrs following first order rate constant with fickian diffusion for the best formulation using ethyl cellulose whereas for using sodium alginate, the drug release was 92% till 11hrs. Ethyl cellulose was found to be the best polymer for preparing the mefenamic acid microspheres with good stability, drug content, entrapment efficiency and sustained drug release for 12hours.

Key words: mefenamic acid, ethyl cellulose, sodium alginate, microspheres, solvent evaporation method, inotropic gelation technique.

INTRODUCTION

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug .To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs[1, 2].

Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. It has a particle size of (1-1000nm)[3,4].

Mefenamic acid is a widely prescribed NSAID and used as first line therapy for the treatment of ailments such as Arthritis and Dysmonorrhoea and its half-life $t_{1/2}$ 1.5-2hrs. It is considered to be a BCS Class II drug (low soluble and high permeable).Mefenamic acid binds the prostaglandin synthetase receptors COX-1 and COX-2, inhibiting the action of prostaglandin synthetase. As these receptors have a role as a major mediator of inflammation, the symptoms of pain are temporarily reduced.Ethyl celluloseis non-biodegradable, bio-compatible, non-toxic synthetic polymer and widely used in oral and topical formulation. Sodium alginate is a biodegradable natural polymer [5,6]. It is used in the preparation of sustained release oral formulations since it can delay the dissolution of a drug. The main objective of this work as mefenamic acid has less biological life $t_{1/2}$ 1.5-2hrs. Hence frequent administration of drug 200-400mg twice daily is required to maintain the desired steady state level so, formulating such drug into controlled drug delivery system i.e., microspheres using different polymers is expected to increase the sustain release action and to improve patient compliance by reducing the dosing frequency[7,8].

MATERIALS AND METHODS

Materials

Mefenamic acid was supplied as a gift sample from Sigma Aldrich Chemicals Pvt. Ltd., Bangalore. Ethyl cellulose was supplied from S.D Fine chemicals Ltd, Mumbai. Sodium alginate was supplied from SD fine-chem Limited, Mumbai.

Methodology

Preparation of mefanamic acid microspheres by solvent evaporation method:

Various parameters were optimized for the preparation of microspheres such as organic solvent (ethyl acetate), stirring speed (700rpm), and organic to aqueous ratio (1:10).Ethyl cellulose was taken in a crucible is dissolved in ethyl acetate to form a homogenous solution. Mefanamic acid was added to the homogenous solution and mixed thoroughly. Dispersion was then added as a thin stream to 100ml of aqueous mucilage of 0.5% sodium cmc contained in a 250 ml beaker while being stirred at 700 rpm to emulsify the added dispersion as a fine droplets. The solvent removal was achieved by continuous stirring at room temperature for three hours to produce spherical microspheres. The microspheres formed were collected by filtration and washed repeatedly with distilled water. The product was then air dried[9].

Table no 1: List of formulations

Formulations	Ratios
F1	1:1
F2	1:1.5
F3	1:2
F4	1:2.5
F5	1.5:1
F6	2:1
F7	2.5:1

Preparation of mefenamic acid microspheres by ionotropic gelation technique

Parameter optimized for the preparation of microspheres such as calcium chloride concentration. Mefenamic acid loaded microspheres were prepared by dissolving sodium alginate in distilled water by gently heating it on using magnetic stirrer to get a bubble free solution comprising different concentrations (1%to2.5 %).Mefenamic acid was accurately weighed and dissolved in methanol and added to the polymeric solution to form a clear solution. The dispersions were sonicated for 30 min to remove any air bubbles that may have been formed during the stirring process. The homogenous dispersion were added dropwise via a 20-gauge hypodermic needle fitted with a syringe into 50 mL of 4 % solution of gelling agent $cacl_2$ being stirred at 200 rpm for 10 min. The droplets from the dispersions instantaneously gelled into discrete mefenamic acid-alginate matrices upon contact with the solution of gelling agents. The formed alginate microspheres were further stirred in the solution of gelling agents for an additional 1 h. On expiration, solution of gelling agent was decanted and the microspheres were washed with distilled water. The microspheres were filtered and air dried.

Table no.2: List of formulations

Formulation	Ratios
FF1	1:1
FF2	1:1.5
FF3	1:2
FF4	1:2.5
FF5	1.5:1
FF6	2:1

CHARACTERIZATION AND EVALUATION OF MICROSPHERES

The microspheres prepared by the above techniques were characterized for

1)Particle size
2)Zeta potential
3)Drug-polymer interaction

Scanning Electron Microscopy (SEM)

Suspension was made to obtain Photomicrographs of the mefenamic acid loaded microspheres using the SEM Scanning Electron Microscopy is used to determine the shape, size and surface morphology of the microspheres[10].

Zeta potential

The prepared microspheres were dispersed in deionized water and sonicated for 30 minutes.
The resultant dispersion was diluted and observed for zeta values.

FourierTransfom-Infrared Spectroscopy FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATR- FTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

The microspheres prepared by the above techniques were evaluated for

1) Percentage yield
2) Drug content
3) Entrapment efficiency
4) Invitro drug release

Percentage yield: The yield of the prepared formulations was calculated as the percentage of the weight of the dried product at room temperature compared to the theoretical amount. Product yield is calculated by using the following Equation

$$\text{Product yield} = \frac{\text{Weight of the product}}{\text{Weight of raw materials}} \times 100$$

Drug content:

The various batches of the microspheres were subjected for drug content analysis. Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres were dissolved in adequate quantity of ethyl acetate in two necked round bottomed Flask. With the help of mechanical stirrer allow it to stir for 3 hours then filter. The UV absorbance of the filtrate was measured using a UV spectrometer at 285nm.

$$\text{Drug content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Entrapment efficiency:

The prepared formulations were examined for entrapment efficiency. 40mg of the prepared formulation was taken in equivalent quantity of 7.4 phosphate buffer. The suspension is ultra-centrifuged at 17240rpm for 40 minutes.

EE= Total amount of drug- Amount of drug in supernatant
---------- × 100
Total amount of drug

Invitro drug release study of microsphere formulations in phosphate buffer p^H 7.4:
The dissolution rate testing apparatus was employed to study the release of mefanamic acid using phosphate buffer p^H 7.4 as a dissolution medium. 50mg equivalent of mefanamic acid microspheres was taken and dissolution test was being carried out at 50rpm maintained at $37^0c \pm 0.5^0c$. 5ml of sample were withdrawn at specific time interval for 12 hours. The sample volume was replaced by an equal volume of fresh medium. The concentration was determined spectrophotometric ally at 285nm.The same procedure was repeated for other formulations also.

RESULTS AND DISCUSSION

The prepared microspheres using ethylcellulose as a synthetic polymer Seven formulations F1,F2,F3,F4, F5,F6 and F7 were evaluated for product yield,drug content, entrapment efficiency,and invitro drug release. The drug content results for F1,F2,F3,F4,F5,F6 and F7 was found to be 80.1%,82.7%,88.4 %,93.4%,81.9%,84.3%,85.5 .Entrapment efficiency of F1,F2,F3,F4,F5,F6,F7 was found to be 86%,87.1%,89.2%,92.5%,86.4,85.4,82% .Invitro drug release of F1,F2,F3,F4,F5,F6,F7 was found to be 96.8% in 6hrs,98.2% in 8hrs,94.2% in 9hrs,90.4%in 12hrs,97.8% in 7hrs,95.4% in 5hrs,97.2% in 4hrs .Among all the formulations of microspheres F4 formulation was found to be best with drug content of 93.4%,entrapment efficiency of 92.5%, drug release 90.4% for 12hours followed first order release with fickian diffusion mechanism. FTIR studies revealed no drug polymer interactions.

The prepared microspheres using sodium alginate as a natural polymer six formulations FF1, FF2, FF3, FF4, FF5 and FF6 were evaluated for product yield,drug content, entrapment efficiency,and invitro drug release. The drug content results for was found to be

81.6%, 83.1%, 91.7%, 89.7%, 87%, 90.7%. Entrapment efficiency of FF1, FF2, FF3, FF4, FF5, and FF6 was found to be 86.8%, 88.1%,90.1%, 84.5%, 85.3%, and 87.6%. Inviro drug release of FF1,FF2,FF3,FF4,FF5,FF6 was found to be 95.8% in 8hrs, 98.4% in 9hrs,92% in 11hrs, 98.6% in 10hrs, 97.2% in 6hrs, 97% in 5hr.Among all the formulations of microspheres FF3 formulation was found to be best with drug content of 91.7%, entrapment efficiency of 90.1%, drug release of 92% for 11 hours followed first order release with fickian diffusion mechanism.FTIR studies revealed no drug polymer interactions.

The best formulations of microspheres using ethyl cellulose and sodium alginate polymers, were found to be F4 and FF3 respectively. A comparative study was done among the best formulations.

Comparative study between the best formulations of microspheres using ethyl cellulose and sodium alginate polymers.
A Comparative study was performed for the best formulations of mefenamic acid loaded microspheres for size and surface morphology, product yield, drug content, entrapment efficiency, stability, invitro drug release studies.

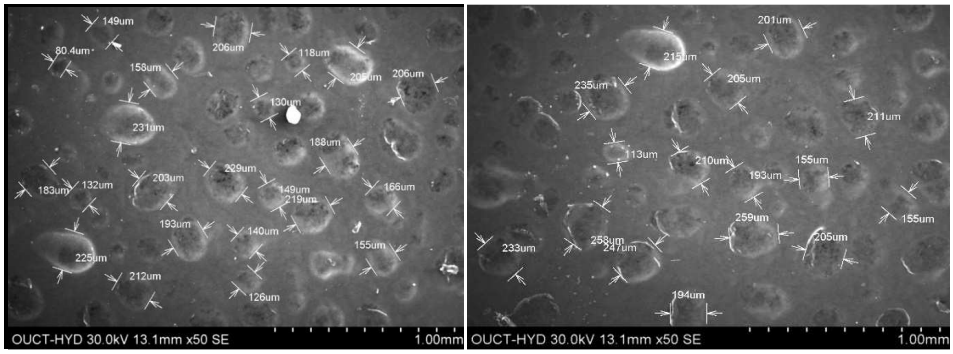

Fig 1: SEM images of best formulations of microspheres using ethyl cellulose and sodium alginate polymer

Size and surface morphology: The best formulations of microspheres using ethyl cellulose and sodium alginate polymers were compared for the size and surface morphology.

Percentage yield
Percentage yield of both the best formulations were compared

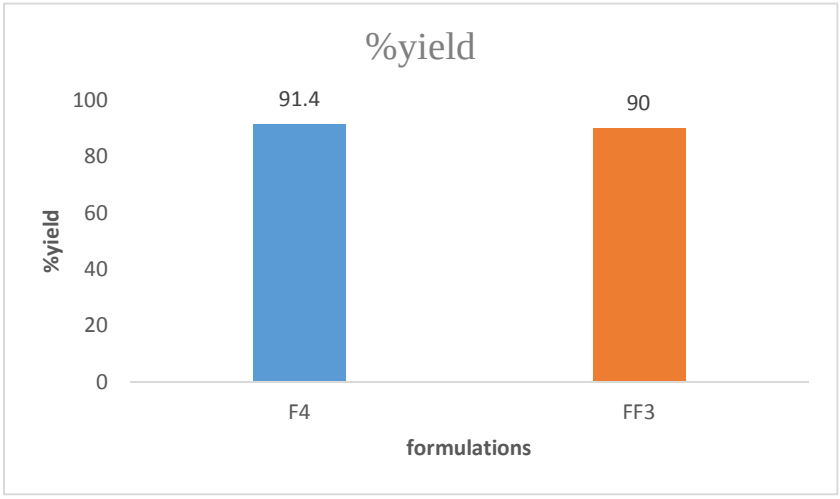

Fig2: Comparison of %yield of best formulation of mefenamic acid loaded ethyl cellulose and sodium-alginate microspheres

Percentage yield of F4&FF3 formulation was found to be 91.4%, 90%respectively.out of two best formulations F4 formulation yielded highest results.

Drug content
Drug content of both the best formulations were compared

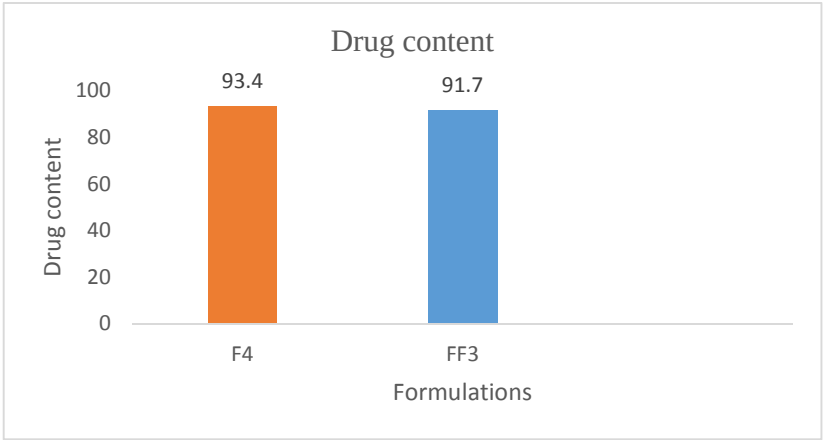

Fig3: Comparison of drug content of best formulation of mefenamic acid loaded ethyl cellulose and sodium-alginate microspheres

Drug content of F4&FF3 was found to be 93.4%, 91.7% respectively and the highest was found for F4 formulation.

Entrapment efficiency
Entrapment efficiency of both the formulation were compared

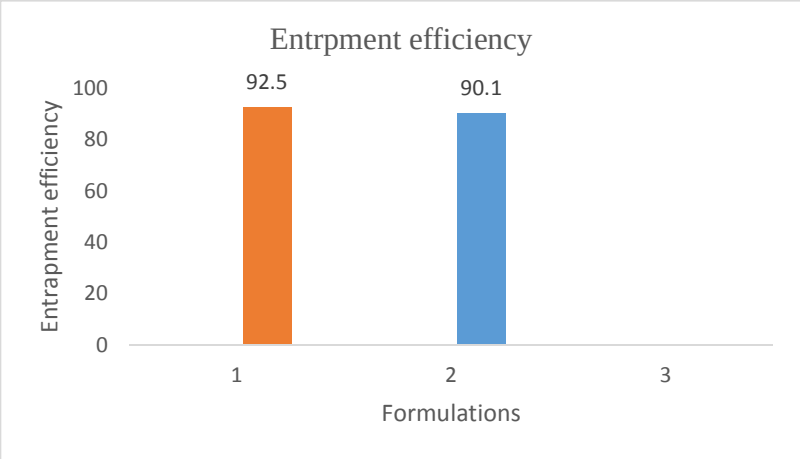

Fig4: comparison of entrapment efficiency of best formulations of mefenamic acid loaded ethyl cellulose and sodium-alginate microspheres

Entrapment efficiency of F4 & FF3 was found to be 92.5%, 90.1% respectively. On comparison F4 formulation was showing highest entrapment efficiency than the other formulation.

Zeta potential

Zeta potential of both the best formulations were compared

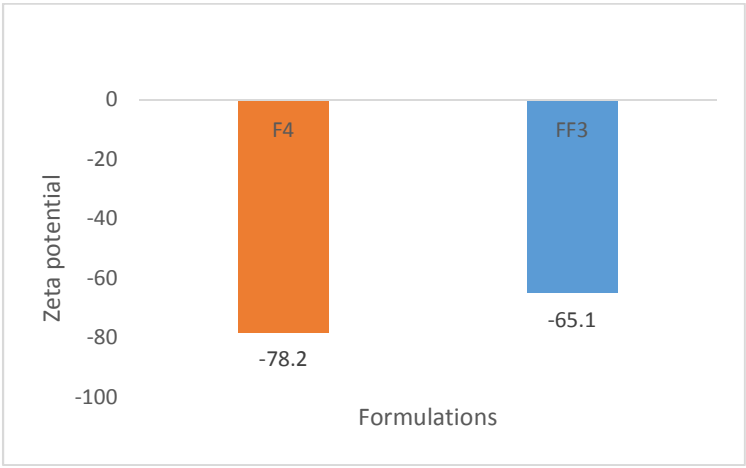

Fig5: comparison of zeta potential values of best formulation of mefenamic acid loaded ethyl cellulose and sodium alginate microspheres

The zeta potential value of F4 formulation was found to be -78.2mv whereas the zeta potential of FF3 formulation was found to be -65.1mv. On comparison the F4 formulation was showing higher zeta potential value than the other formulationindicating the greater stability.

Invitro drug release studies

Invitro drug release studies of both the formulations were compared

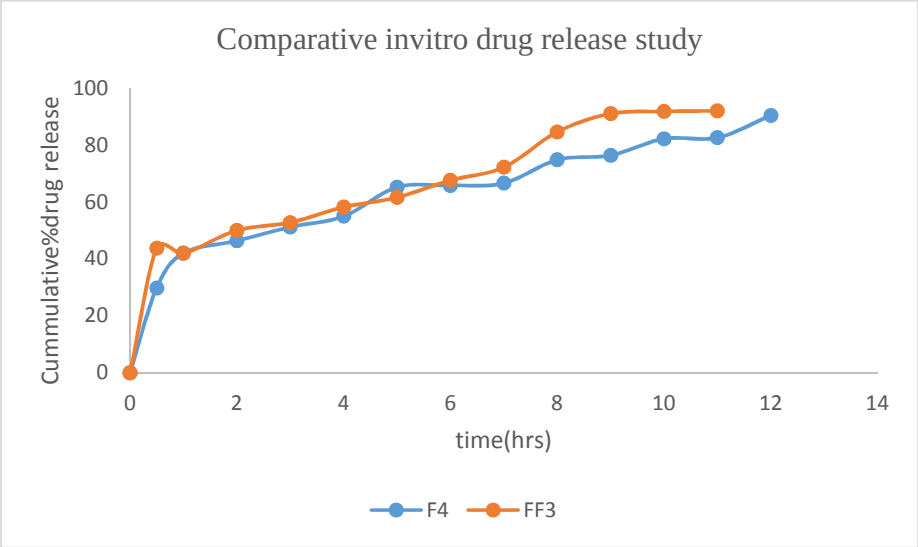

Fig6: Comparison of invitro drug release data of best formulation of mefenamic acid loaded ethyl cellulose and sodium-alginate microspheres

On comparison F4 formulation was showing sustained release for 12hours with drug release rate of 90.4% when compared to FF3 formulation which was sustained for 11hours with 92%drug release.

Finally the F4 formulation of microspheres using ethyl cellulose as a synthetic polymer, FF3 formulation of microspheres using sodium alginate as a natural polymer were compared. Among the two best formulations microspheres prepared using ethyl cellulose as a synthetic polymer were found to be the best for the formulation of mefenamic acid microspheres with the drug release of 90.4%for 12 hours.

Comparison of best formulation with various kinetic models:
Several plots (Zero order plot, first order plot, higuchi plot and peppas plots) were drawn in order to know the release kinetics and drug release mechanism.

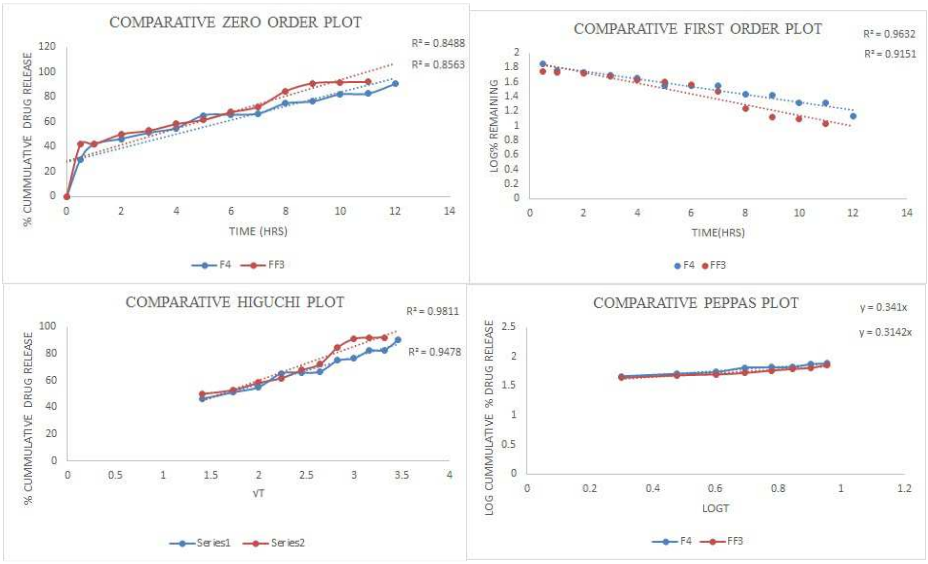

Fig7: Comparative plots of best formulations

Table no 3: Kinetic data of best formulations

Formulation	Zero order plot ($R^{2)}$	First order plot ($R^{2)}$	Higuchi plot ($R^{2)}$	Peppas plot (n)
F4	0.8488	**0.9632**	0.9811	**0.341**
FF3	0.8563	**0.9151**	0.9478	**0.3142**

F4 formulation of microspheres using ethyl cellulose as synthetic polymer followed first order kinetics with fickian diffusion mechanism. FF3 formulation of microspheres using sodium alginate as natural polymer followed first order kinetics with fickian diffusion mechanism.

CONCLUSION

In the present study comparative study of mefenamic acid loaded microspheres using ethyl cellulose as synthetic and sodium alginate as natural polymers was done. Mefenamic acid is a hydrophobic drug can be better entrapped with ethyl cellulose and sodium alginate. Microspheres were prepared by using ethyl cellulose as polymer yielded sustained releasewith good safety profile.

Mefenamic acid microspheres were prepared using synthetic polymer ethyl cellulose and natural polymer sodium alginate. Microspheres have been prepared by solvent evaporation method using ethyl cellulose as the synthetic polymer. Process parameters have been optimized such as organic: aqueous ratio, different organic solvent, different speed. Seven formulations were prepared by varying drug: polymer ratios. Out of seven formulations F4 formulation i.e., (1:2.5) drug : polymer ratio was found to be the best formulation with the zeta potential value of -78.2mv, product yield of 91.4%,drug content of 93.4%,entrapment efficiency of 92.5% and invitro drug release of 90.4%for 12hours.

Microspheres have been prepared by inotropic gelaton technique using sodium alginate as the natural polymer. Process parameters have been optimized such as calcium chloride concentrations. Six formulations have been prepared by varying drug: polymer ratios. Out six formulations FF4 formulation i.e., (1:2)drug: polymer ratio was found to be the best formulation with the zeta potential value of -65.1mv product yield of 90%,drug content of 91.7%,entrapment efficiency of 90.1% and *invitro* drug release of 92% for 11hours.

Comparison were made between the best formulations F4&FF3 of microspheres prepared by using ethyl cellulose as synthetic and sodium alginate as natural polymers. Among these formulations microspheres prepared by using ethyl cellulose as polymer found to be the best formulation with highest zeta value of -78.2mv, highest drug content of 93.4%, entrapment efficiency of 92.5% and invitro drug release 90.4%for 12hours.and ethyl cellulose polymer was found to be the best formulation for the preparation of novel drug delivery system for mefenamic acid.

Acknowledgements
The authors would like to thank RBVRR Women's College of Pharmacy, Principal Dr.M.Sumakanth for providing funds for the work. The authors would like to acknowledge Mrs. K. Sumalatha and Mrs. D. Suvarna for providing us technical assistance.

REFERENCES

[1] N.K.Jain, Controlled and Novel drug delivery, 04 Edition, 236-237, 21.
[2] S.P.Vyas and R.K.Khar, Targeted and Controlled drug delivery, 07 Edition, 418.
[3] Karmakar U., Faysal M.M., *The Internet Journal of Third World Medicine*. **2009**; 8(1).
[4] http://www.drugbank.ca/drugs/DB00784
[5] Ainley wade & Paul J Weller, Handbook of pharmaceutical excipients, second edition, The Pharmaceutical Press, London, **1994**, 186-190.
[6] T.Sudhamani, K.Naveen kumar reddy,V.R.Ravi kumar,R.Revathi,V.Ganeshan, *International journal of pharma research and development*,vol-2,**2010**;119-125.
[7] MalayK.Das, PrakashC.Senapathi, *Acta Poloniae Pharmaceutica & Drug Research*, Vol-64, **2007**; 253-262.
[8] Saravanan.M., Dhanaraju.D, Sridhar.S.K,Ramachandran.S, Kishore Gran sam.S, Anand.P, Bhaskar.K & Srinivasarao.G , *Ind.J.Pharm.Sci*, 66(3), **2004**,287-292

[9] Rakesh Bagul, Vijay Mahajan, AvinashDhake, *International Journal of Current Pharmaceutical Research*, **2012**, Vol. 4(3), 29-38.
[10] A. Krishna Sailaja and Chandavath Vineela, *Der Pharmacia Lettre*, vol-6 ,**2014**; 210