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**Research article****Formulation and Evaluation of Sustained Release Alginate microbeads enclosed Gabapentin****Gayathri S\*, Muthukumaran M, Krishnamoorthy B**Montessori Siva Sivani Institution of Science & Technology-College of Pharmacy,  
Andhra Pradesh-521230(Received: 15<sup>th</sup> November 2013;Accepted: 16<sup>th</sup> December 2013)**Abstract**

The objective of the present study was to develop sustained release beads of gabapentin by ionotropic gelation technique by using different proportions of sodium alginate, HPMC- E15, K4M, Sodium carboxyl methyl cellulose and pectin. The drug-polymer compatibility was studied by FTIR and DSC. The obtained microbeads were characterized for particle size determination, swelling ratio, drug entrapment, scanning electron microscopy (SEM), drug content, *in-vitro* release, kinetic models and stability studies. The prepared beads were found to be optimal in terms of particle size and entrapment efficacy. There was no compatibility issues was found to be in prepared microbeads, which were confirmed by FTIR and DSC studies. *In-vitro* drug release profile of microbeads coated with sodium alginate and pectin was examined 98.3% of drug release with in 12h. The release data from all the formulation was found to fit Higuchi's model. The release kinetics data indicated that the drug release from microbeads was diffusion-controlled and the microbeads were stable in nature. From this study, it was concluded that the microbeads of gabapentin could be successfully prepared by ionotropic gelation technique with high entrapment efficiency and sustained release characteristics.

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**Key Words**Gabapentin, Sodium alginate,  
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## INTRODUCTION

Conventional oral drug administration does not usually provide rate-controlled release or target specificity. In many cases, conventional drug delivery provides sharp increase in drug concentration often achieving toxic level and following a relatively short period at the therapeutic level of the drug concentration eventually drops off until re-administration. In order to obtain maximum therapeutic efficacy, it becomes necessary to deliver an agent to the target tissue in the optimal amount for the required period of time, thereby causing less toxicity and minimal side effects<sup>1</sup>. Natural polymers such as polysaccharides and its derivatives are widely used in pharmaceutical and food industry as biodegradable and biocompatibility. Alginate and pectin are the most extensively studied polysaccharides and has shown great potential as a drug carrier and large number of applications such as binding, thickening, emulsifying, gelling agent etc<sup>2</sup>. Microparticulate drug delivery systems are considered and accepted as a reliable one to deliver the drug to the target site with specificity, to maintain the desired concentration at the site of interest without untoward effects<sup>3</sup>. Microencapsulation is a useful method which prolongs the duration of drug effect significantly and improves patient compliance. Eventually the total dose and few adverse reactions may be reduced since a steady plasma concentration is maintained<sup>4</sup>. Gabapentin is used as an anticonvulsant to treat epilepsy, and currently is also used to relieve neuropathic pain<sup>5</sup>. The Gabapentin has a biological half-life<sup>6</sup>

in the terminal phase ( $t_{1/2}$ ) of 5-7 h and the usual oral dosage regimen is 300mg<sup>7</sup> taken two to three times a day, which necessitates dosing of immediate release formulations every 6 h. The aim of present study was to develop sustained release pharmaceutical formulation to reduce the dosing frequency and minimize the peak-to-trough fluctuations.

## MATERIALS AND METHOD

### Materials

Gabapentin was a gift sample from Delta Pharm, Egypt; HPMC-K4M from S.D. Fine Chem. Ltd., Mumbai L.R, Sodium alginate and Calcium chloride gift samples were from Sigma Aldrich and VWR Scientific USA respectively. The other chemicals used were all of analytical and HPLC grade.

### Preparation of alginate- microbeads

The beads were prepared by the ionotropic gelation technique<sup>8</sup>. Aqueous solution of sodium alginate prepared in 100ml of deionised water. In 50ml of sodium alginate solution, weighed quantity of gabapentin was dispersed uniformly and homogenized for 15min. The dispersion was sonicated for 30min to remove any air bubbles that may have been formed during stirring process. Microbeads containing gabapentin prepared by employing sodium alginate in combination with different concentration (1:1), (1:1:1), of Pectin

and HPMC-K4M incubated for predetermined times were prepared. Bubble free dispersion was dropped through a hypodermic syringe with needle (20G) into the 5% w/v calcium chloride solution stirred for 30 min at 50rpm. After stirring for 30min, the gelled beads were separated by filtration, washed with distilled water and finely dried in hot air oven for 3 h at 60°C until attained constant weight.

### Particle size analysis

The microbeads were analyzed for particle size by optical microscope<sup>9</sup>. Size distribution plays a very important role in determining the release characteristics of the microbeads. The instrument was calibrated and found that 1 unit of eyepiece micrometer was equal to 12.5µm. Nearly about 100 Microbeads sizes were calculated under 45 x magnifications.

### Percentage Yield

Thoroughly dried microbeads were collected and weighed accurately. The percentage yield was then calculated using formula given below<sup>10</sup>.

% yield = (Mass of microbeads obtained/Total weight of drug and polymer) X100

### Swelling ratio studies

The extent of swelling measured in terms of the percentage weight gain by the beads. Swelling behaviours of all the dried formulation microbeads were studied. 50 mg of beads from

each formulation was kept in petridish containing phosphate buffer solution of pH 7.4. At the end of 1 h, the beads were withdrawn, soaked with tissue paper and weighed. Then for every 1 hour, weights of beads were noted and the process continued till the end of 8h. The percentage of weight gain by the beads was calculated by the following formula.

$$\text{Swelling ratio} = \frac{W_t - W_0}{W_0} \times 100$$

Where  $W_0$  &  $W_t$  are initial weight and Final weight of microbeads respectively

### Determination of Drug loading and Entrapment efficiency<sup>11</sup>

Accurately weighed samples (50mg) drug loaded microbeads from each batch were dissolved in 100ml of phosphate buffer solution of pH 7.4 by shaking on a mechanical shaker for 24h. The solution was filtered through Whatmann filter paper. An aliquot following suitable dilution was assayed spectrophotometrically (UV-1700 Shimadzu Corporation, Japan) for gabapentin at 210nm. Drug loading was determined by using the formula

$$\text{Drug Loading Efficiency} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

### Fourier Transform Infrared Spectroscopy (FTIR)

The drug-polymer interactions were studied by infrared spectroscopy to confirm the presence of any

interaction between the polymer and drug. The polymer and drug were finely ground with KBr to prepare the pellets under a hydraulic pressure 600psi and spectra scanned between 500 and 3500cm<sup>-1</sup>.

### Differential Scanning Calorimetry (DSC)

DSC thermograms were performed by using an automatic thermal analyzer system (NETZSCH, DSC 200 PC). The DSC studies on the samples were performed by heating samples at a heating rate of 10°C/min over a temperature range of 50°C – 350°C in a closed aluminium pans.

### Microbeads morphology by scanning electron microscopy (SEM)

The morphology of the Microbeads surfaces was investigated using scanning electron microscopy. Microbeads were spread on a carbon double-adhesive layer on a metal holder and gold-coated using Ion-Sputtering device (100 and 50 A<sup>0</sup> thickness respectively).The coated samples were then observed under a scanning electron microscope at 10KV.

### In vitro drug release studies<sup>12</sup>

Dissolution studies of the different batches of microbeads were carried

out using USP XXIII (type II) dissolution test apparatus for 12 h with continuous stirring of 50 rpm at 37 ± 0.2°C in 900 ml of phosphate buffer pH 7.4 . An aliquot 5 ml of the sample was periodically with drawn at suitable time interval and the same volumes were replaced with fresh dissolution medium in order to maintain the sink condition. The sample was analyzed spectrophotometrically at 210 nm<sup>13</sup>.

### Kinetics of the in vitro drug release

The kinetic parameters for the *in vitro* release of gabapentin were determined and then analyzed in order to find the drug release. Zero, first order kinetics, Higuchi diffusion and Mayer peppas were investigated.

### Stability studies

Selected formulation (F4) was subjected to stability studies for three months as per ICH guidelines and at the end of the every month, dissolution studies were carried out.

Tab1. Accelerated condition for stability studies

Accelerated stability conditions (Temperature/%RH)	Period (Month)
25°C/60%	3
30 °C /75%	3
40 °C /75%	3

## RESULTS AND DISCUSSION

Microbeads containing gabapentin prepared ionotropic gelation method by employing sodium alginate in

Tab.2. Formulation design for the preparation of gabapentin loaded alginate microbeads

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (mg)	500	500	500	500	500	500	500	500	500
Drug : Sodium alginate	1:1	---	---	---	---	---	---	---	---
Drug : Sodium alginate : HPMC-E15	---	1:1:1	---	---	---	---	---	---	---
Drug : Sodium Alginate : HPMC-K 4M	---	---	1:1:1	---	---	---	---	---	---
Drug : Sodium Alginate : Pectin	---	---	---	1:1:1	---	---	---	---	---
Drug : Sodium Alginate : Sodium CMC	---	---	---	---	1:1:1	---	---	---	---
Drug : Sodium Alginate : HPMC-E15 : Pectin	---	---	---	---	---	1:1:1:1	---	---	---
Drug : Sodium Alginate : HPMC-K 4M : Pectin	---	---	---	---	---	---	1:1:1:1	---	---
Drug : Sodium Alginate : Sodium CMC : Pectin	---	---	---	---	---	---	---	1:1:1:1	---
Drug : sodium alginate	---	---	---	---	---	---	---	---	1:2
Calcium chloride (%)	5	5	5	5	5	5	5	5	5
Curing time (min)	30	30	30	30	30	30	30	30	30

Tab.3. Mean particle size, Percentage yield, swelling ratio, Percentage entrapments efficiency, Percentage drug content of gabapentin loaded alginate Microbeads

Formulation Code	Particle size ( $\mu\text{m}$ )	% Yield	Swelling ratio	Entrapment efficiency (in %)	Drug Content (%)
F1	1239.5 $\pm$ 2.3	56 $\pm$ 1.52	218 $\pm$ 1.14	73.53 $\pm$ 1.54	97.56 $\pm$ 1.11
F2	1120 $\pm$ 2.21	73 $\pm$ 1.22	220 $\pm$ 1.13	83.23 $\pm$ 1.84	98.52 $\pm$ 1.15
F3	1143.4 $\pm$ 1.42	76 $\pm$ 1.56	234 $\pm$ 1.15	86.97 $\pm$ 1.2	96.71 $\pm$ 1.2
F4	1223.2 $\pm$ 0.9	83 $\pm$ 1.11	242 $\pm$ 1.2	90.76 $\pm$ 0.33	99.88 $\pm$ 2.1
F5	1172.5 $\pm$ 1.3	80 $\pm$ 1.12	244 $\pm$ 1.5	90.57 $\pm$ 0.58	98.31 $\pm$ 1.45
F6	1153 $\pm$ 2.8	70 $\pm$ 1.15	260 $\pm$ 1.51	95.49 $\pm$ 1.05	98.39 $\pm$ 1.35
F7	1228.6 $\pm$ 1.7	75 $\pm$ 1.2	265 $\pm$ 2.54	87.18 $\pm$ 0.1	98.37 $\pm$ 1.65
F8	1276 $\pm$ 2.35	79 $\pm$ 1.4	272 $\pm$ 1.25	82.73 $\pm$ 0.43	98.19 $\pm$ 1.05
F9	1353.8 $\pm$ 1.8	81 $\pm$ 1.1	293 $\pm$ 1.33	81.46 $\pm$ 0.31	99.58 $\pm$ 1.35

combination with different concentrations of Pectin and HPMC were nearly spherical except at the point of contact with the petridish used for drying the preparation, where it was slightly flattened. The percentage yields of microbeads of all formulation were found in the range of  $56 \pm 1.52$  to  $83 \pm 1.11\%$ . The microbeads were uniform in size with a mean size of the various formulations of microbeads were obtained in the range between  $1120 \pm 2.21$  to  $1353.8 \pm 1.8 \mu\text{m}$ . The drug content determination showed that even if the polymer composition was changed the process was highly efficient to give microbeads having maximum drug loading. The drug content of prepared formulations was found in the range of  $96.71 \pm 1.2$  to  $99.88 \pm 2.1$ . The drug entrapment efficiency of all the formulations was in the range of  $73.53 \pm 1.54$  to  $95.49 \pm 1.05 \%$ .

The FTIR spectral analysis showed that there was no appearance or disappearance of any characteristic peaks of pure gabapentin and the optimized formulation of drug and polymer, which confirms the absence of chemical interaction between drug and polymers shown in fig 1. The IR spectra of pure drug show characteristic functional peaks<sup>14</sup> at

701.03, 1292.12, 1389.97, and 1526.65  $\text{cm}^{-1}$ . Similarly the IR spectra of optimized formulation show characteristic functional peaks at 763.70, 1263.22, 1392.72, and 1579.38  $\text{cm}^{-1}$  indicated that the compatibility of drug with excipients.

DSC thermogram was carried out to study change in thermal properties of drug, the sharp peak was observed<sup>15</sup> at  $169^\circ\text{C}$  in the formulation as presented in fig 5, with no notable change in endotherm. This clearly indicates that, the excipients used to formulate microbeads had no effect on thermal properties of drugs.

From the cumulative release data F6&F1 shows 21-25% of drug released within 1 h, all other formulations were showed the release of drug between 12-19%, however F4 shows only 9.61% of drug release within 1 h. when compared with other formulations, F4 which was prepared with 1:1:1 of drug, sodium alginate & pectin ratio shows less than 50% of drug release at the end 4<sup>th</sup> h and extended the drug release upto 12h. In the present study, the effect of drug: alginate: pectin at three other different polymeric concentrations, namely HPMC K 4M, E15 and Na CMC as showed in Fig 7b. The results

show markedly no difference in release rate of drug.

Figs 4c illustrate the effects of drug:sodium alginate ratio on gabapentin release from microbeads. A decrease in the rate and extent of drug release was observed with the increase in sodium alginate ratio.

The correlation coefficients for the different drug release kinetic models are shown in tab3. Models with the highest correlation coefficient were judged to be the most appropriate model for the *in vitro* release study. All the formulation was the best fitting linear parameter was Higuchi's models and their correlation coefficients were found between 0.910 and 0.986.

The formulations (drug, sodium alginate, pectin)(1:1:1) were subjected to stability studies; from the results, there was no appropriate change such as drug content, dissolution profile, hence it was found that the formulations were stable.

## CONCLUSION

Gabapentin microbeads were successfully prepared by ionotropic gelation method using a combination of polymers, sodium alginate and pectin. Gabapentin release from microbeads was influenced by sodium

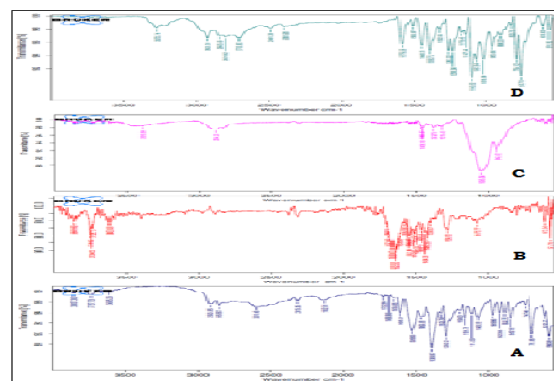


Fig 1. FT-IR Spectra for A) Gabapentin Pure B) Sodium Alginate C) Pectin D)Microbeads(F4)

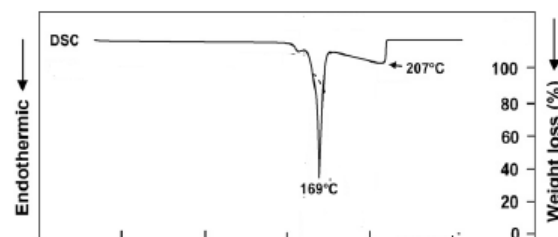


Fig 2. DSC Spectra for Microbeads (F4)

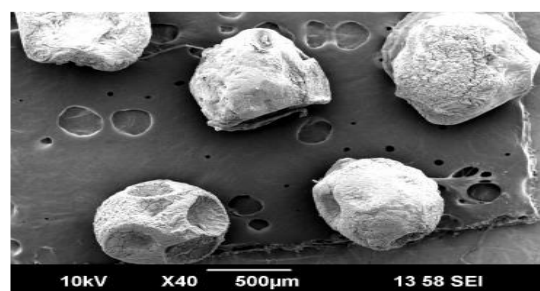


Fig 3. Scanning electron micrographs of Microbeads (F4)

alginate and pectin concentration. Among the different formulation of microbeads prepared, F-4 was found to be a best formulation because drug release in controlled manner and also high entrapment efficiency was observed. The result from accelerated stability study on the microbeads revealed that the formulations were stable. Therefore, one can assume that the Gabapentin microbeads are promising pharmaceutical dosage forms by providing sustained release drug delivery systems.

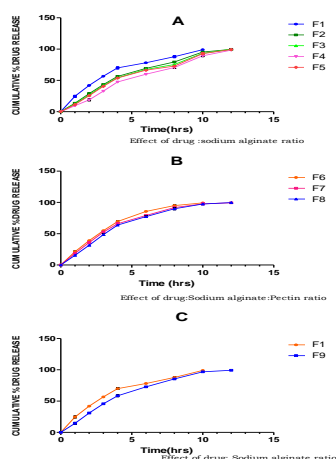


Fig 4. Dissolution comparison plot for gabapentin loaded alginate Microbeads

Tab 4. Kinetic release data for gabapentin loaded alginate Microbeads

Formulation code	Zero order $r^2$	First order $r^2$	Higuchi's $r^2$	Korsmeyer - Peppas
F1	0.926	0.864	0.986	0.659
F2	0.937	0.849	0.959	0.628
F3	0.952	0.792	0.951	0.57
F4	0.978	0.856	0.910	0.641
F5	0.954	0.837	0.944	0.619
F6	0.852	0.942	0.972	0.758
F7	0.884	0.886	0.969	0.71
F8	0.901	0.903	0.961	0.696
F9	0.928	0.925	0.964	0.723

Tab 5. Stability dissolution profile of F-4 for 1<sup>st</sup>, 2<sup>nd</sup> & 3<sup>rd</sup> months

Time (h)	1 <sup>st</sup> Month	2 <sup>nd</sup> Month	3 <sup>rd</sup> Month
0	0	0	0
1	9.60±0.51	9.58±0.22	9.56±0.51
2	18.82±0.22	18.81±0.51	18.80±0.18
3	32.86±0.51	32.85±0.22	32.84±0.22
4	47.47±0.18	47.44±0.51	47.43±0.63
6	59.83±0.63	59.82±0.31	59.81±0.18
8	70.57±0.51	70.56±0.63	70.54±0.51
10	89.27±0.63	89.25±0.22	89.23±0.22
12	98.36±0.22	98.35±0.51	98.35±0.51

## REFERENCES

- Jayakrishnan A, Latha MS. Biodegradable polymeric microbeads as drug carriers. In: Jain NK, Editor. Controlled and Novel drug delivery. New Delhi: CBS publishers. 1997; 236-255.
- Braccini I, Perez S. Molecular basis of  $Ca^{2+}$  induced gelation in alginates and pectins: the egg-box model revisited. *Biomacromolecules* 2001; 2:1089-1096.
- Vyas SP, Khar RK. Proteins and peptides delivery considerations. In: Vyas SP, Khar RK, Editor. Controlled drug delivery concepts and advances. 1<sup>st</sup> ed., New Delhi: CBS publisher and Distributor 2002; 549.
- Fu X, Ping Q, Gao Y. Effects of formulation factors on encapsulation efficiency and release behavior in vitro of huperzine A-PLGA microbeads. *J Microencap* 2005; 22(7): 705-714.
- Vedula SS. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *The New England Journal of Medicine* 361 (20):2009196371.doi: 1056/NEJMs0906126. PMID 19907043.
- Richens A. Clinical pharmacokinetics of gabapentin, In: Chadwick D (ed). *New trends in epilepsy management: the role of gabapentin*, London, Royal Society of Medicine, 1993; 41-6.
- Rose MA, Cam PCA. Gabapentin: pharmacology and its use in pain management. *Anaesthesia* 2002; 57:451-462.
- Thulasi V Menon. Formulation and Evaluation Of Sustained Release Sodium Alginate Microbeads Of Carvedilol. *Int J PharmTech*



Res2013:5(2).

9. Ansel HC, Allen LV, Popvich JNG. Pharmaceutical dosage forms and drug delivery systems. 7<sup>th</sup> ed. Philadelphia: Lippincott Williams and Wilkins 1999; 164-178.
10. Higuchi W, Rowe E, Hiestand E. Dissolution rates of finely divided drug powders. II. Micronized methylprednisolone. J Pharm Sci 1963; 52:162-164.
11. Pierre A, Hanna, Shadeed Gad, Hassan M, Ghonaim Mamdouh M, Ghorab. Optimization of Gabapentin Release and Targeting Absorption, Through Incorporation into Alginate Beads. British Journal of Pharmaceutical Research. 2013; 3(4): 597-616.
12. Rajinder Singh Gujral and Manirul Haque SK. A validation method without derivatization for the determination of gabapentin in bulk, pharmaceutical formulations and human urine samples. Int J Biomed Sci. 2009; 5(2): 169-174.
13. Rompicharla Bhargavi, Harika Duggimpudi, Suria Prabha K. Formulation Development and In-Vitro Evaluation of Gabapentin Matrix Tablets. Am. J. PharmTech Res 2012; 2(6):883-891.
14. Hsu CH, Ke WT, Lin SY. Progressive steps of polymorphic transformation of gabapentin polymorphs studied by hot-stage FTIR microspectroscopy. J. Pharm. Pharmaceut. Sci. 2010; 13: 67-77.
15. Sunaree C, Oratai Saisard, Kenneth J. Haller. Preparation and Characterization of Carboxylic Acid Adducts of Gabapentin. Engineering Journal 2012; 16(3):29-36.

Gayathri S, Muthukumaran M, Krishnamoorthy B. Formulation and Evaluation of Sustained Release Alginate microbeads enclosed Gabapentin. Int J Adv Pharm Gen Res 2013; 1(2): 66-74.