THE PHARMA RESEARCH

A Journal of Pharmacy Research

Original Article ISSN- 0975-8216

Impact- 0.529 Refer website

DESIGN, DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE MUCOADHESIVE MICROCAPSULES OF GABAPENTIN

LOHIA SARITA*, MUZAFFAR FAIZI, CHAUHAN LALIT

Affiliation:

Department of Pharmaceutics, Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University, Meerut-250002, Uttar Pradesh, India

ABSTRACT

An effort has been made to prepare sustained release alginate microcapsules of Gabapentin by orifice-ionic gelation method using Hydroxypropyle methylcellulose (viz, K4M & K100M) as mucoadhesive polymer. Microcapsules were discrete, spherical and free flowing. Encapsulation efficiency varied from 82.95% to 97.75%. Microcapsules were evaluated for drug excipient interactions (DSC & IR spectroscopy), % yield, drug content estimation, particle size distribution, surface morphology (scanning electron microscopy), swelling index, *in vitro* drug release profile and mucoadhesion study by *in vitro* wash off test. The formulation prepared by using alginate-HPMC K4M & HPMC K100M in the ratio of 8:1:1 along with 6% magnesium stearate emerged as the overall best formulation based upon their drug release characteristics (in 0.1N HCl). This formulation showed slow release for more than 16 hours. In vitro drug release followed first order kinetics. All the microcapsules exhibited good mucoadhesive property in the wash off test. These mucoadhesive microcapsules are thus suitable for oral sustained release of Gabapentin.

Key Words: Gabapentin, mucoadhesive microcapsules, orifice ionic gelation method, Hydroxypropyl methylcellulose (K4M & K100M), Magnesium stearate.

INTRODUCTION

Microencapsulation is a process whereby small discrete solid particles or small liquid droplets are surrounded and enclosed, by an intact shell. Essentially, the term "micropartical" refers to a particle with a diameter of 1-1000µm, irrespective of the precise interior structure. Within the broad category of microparticles, "microspheres" or microbeads specifically refer to spherical microparticals and the subcategory of "microcapsules" applies to microparticles which have a core surrounded by a material which is distinctly different from that of the core. The core may be solid, liquid or even gas. *1.2.3.*

Drugs that are really absorbed from the gastrointestinal tract and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. The development of oral sustained-controlled release formulation is an attempt to release the drug slowly into the gastrointestinal tract and maintain an effective drug concentration in the systemic circulation for a long time. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time of the drug delivery. Prolong gastric retention improves bioavailability, increase the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high P*H* environment.*4-7*

Gastrotentive drug delivery is an approach to prolong the gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time of drugs.*8,9*

Gabapentin is a new antiepileptic agent, which is not significantly metabolized in the body and hence does not show any interaction with other drugs due to which it can be used alone for the treatment of partial seizures or in combination with other AEDs for the treatment of generalized seizures.

But the difficulty is that the bioavailability of Gabapentin is not dose proportional; i.e. as dose is increased, bioavailability decreases. Bioavailability of Gabapentin is approximately 60%, 47%, 34%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in three divided doses, respectively.

MATERIALS AND METHOD:

Gabapentin was supplied by Glenmark, Hydroxy propyl methyl cellulose (K4M & K100M) was purchased from Sigma aldrich, Sodium alginate, Barium chloride and Magnesium stearate were purchased from Central Drug House. The concentration of Gabapentin was measured by UV-visible spectrophotometer, Thermo Scientific. All the reagents used were of analytical grade. The experimentation has been conducted at the laboratory of pharmaceutics, Kharvel Subharti College of pharmacy, Swami Vivekanand Subharti University, Meerut, UP.

PREPARATION OF MICROCASULES:

Orifice ionic gelation method: (syringe method) *10-13*

Gabapentin mucoadhesive microcapsules were prepared by the orifice Ionic deletion method. Microcapsules were prepared by employing sodium alginate in combination with different mucoadhesive polymers like hydroxy propyl methyl cellulose (K4M) and hydroxy propyl methyl cellulose (K100M) in different polymer ratios keeping the drug polymer ratio constant.

A weighed quantity of sodium alginate (coating material) was dissolved in 32 ml of distilled water to form a homogenous solution. To this solution a weighed quantity of mucoadhesive polymer hydroxy propyle methyl cellulose (K4M or K100M or both as required) was dissolved and a homogenous polymer solution was formed.

Magnesium stearate was added to the core material Gabapentin in 4 to 6 % w/w concentration by thoroughly mixing with the drug by spatulation. This mixture of drug and magnesium stearate was added to the prepared polymer solution. It was properly stirred in homogenous solution at a 500 rpm.

The resulting dispersion was added drop wise to a Barium chloride (10% w/v) [40 ml] solution through a syringe fitted with a needle of 26 gauge. The added droplets were retained in the barium chloride solution for 6 hours to complete the curing reaction and to produce spherical, rigid microcapsules. The microcapsules were collected by filtration. After air drying the microcapsules were dried in hot air oven for 12 hours at 40*o*C.

Table 1: Composition of formulations of mucoadhesive microcapsules

Formulation Code	Drug (gm)	Sodium Alginate (mg)	Magnesium Stearate (%)	HPMC K4M (mg)	HPMC K100M (mg)
F1	1	800	4	200	-
F2	1	800	6	200	-
F3	1	900	4	-	100
F4	1	900	6	-	100
F5	1	800	4	100	100
F6	1	800	6	100	100

EVALUATION OF THE PREPARED MUCOADHESIVE MICROCAPSULES:

i) Determination of % yield of microcapsules *14-16*

The percentage yield was calculated using prescribed formula.

ii) Particle size analysis *17-19*

Particle size distribution was done by sieving distribution. Size distribution plays an important role in determining the release characteristics of the microcapsules.

iii) Angle of repose

Angle of repose was determining by using fixed funnel method, the accurately weighed microcapsules were taken in funnel. The blends were allowed to flow through funnel freely onto surface. The diameter of microcapsules cone was measured, angle of repose was calculated by using the following equation.

$$\text{Tan } \theta = h/r$$

θ = angle of repose h – Height of pile r – Radius of base pile

iv) Compressibility index:

It was determine by using the formula-

$$Ci = \{(Vo-Vt)/Vo\} \times 100$$

Where Vo and Vt are the volume before and after tapping respectively.

v) Hausnner's ratio:

It was determined by using the formula-

$$\text{Hausnner's ratio} = V/Vt$$

Where V and Vt are the volume before and after tapping respectively.

vi) Determination of drug content:

Accurately weighed 100 mg microcapsules were crushed in mortar and pestle and powdered microcapsules were suspended in 100 ml of 0.1 N Hydrochloric acid. After 24 hours the solution was filtered and the filtrate was analyzed for the drug content using UV-Visible spectrophotometer.

vii) Encapsulation efficiency

Encapsulation efficiency was calculated using the following formula-

$$\text{Encapsulation efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100$$

viii) Swelling studies *20*

A known weight (50 mg) of microcapsules was placed in a glass vial containing 10 ml of distilled water at 37 ± 0.5*o*C in incubator with occasional shaking. The microcapsules were periodically removed, blotted with filter paper and their changes in weights were measured during the swelling until equilibrium was attained. Finally, weight of the swollen microcapsules was recorded after a period of 3 hours, and the swelling ratio (SR) was then calculated from the formula. The studies were carried out in triplicate.

$$\text{Swelling Ratio (SR)} = \frac{We - Wo}{Wo}$$

Where,

Wo – initial weight of the dry microcapsules,

We – weight of the swollen microcapsules at equilibrium swelling in the media.

ix) *In vitro* wash-off test *21*

The mucoadhesive property of microcapsules was evaluated by an *In vitro* adhesion testing method known as wash-off method. Freshly excised piece of gastric mucosa (2 x 2 cm) from goat were mounted onto glass slides (3 x 1 inch) with cyanoacrylate glue and the glass slide was connected with a suitable support, about 100 microcapsules were spread onto each wet rinsed tissue specimen and immediately thereafter the support was hung on to the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given slow, regular up-and-down moment in the test fluid (900 ml of 0.1N HCl) at 37 ± 0.5*o*C. At the end of one hour and at the hourly intervals up to 10 hours, the machine was stopped and the

number of microcapsules still adhering to tissue was calculated.

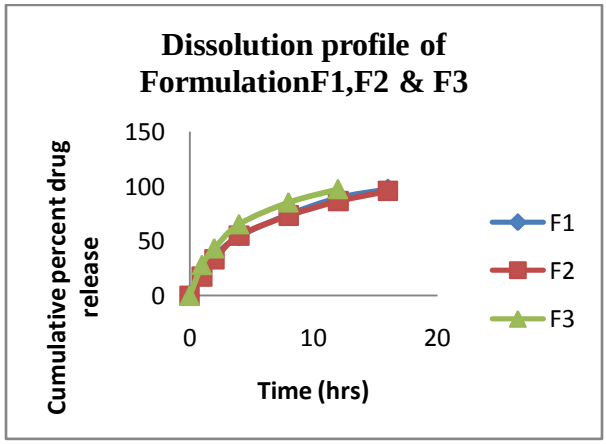
x) *In vitro* dissolution studies *22*

Dissolution studies were carried out for all the formulations employing dissolution apparatus (basket type) at 37 ± suitable time intervals and the volumes were replaced with a fresh dissolution medium in order to maintain the sink condition. The sample was analyzed Spectrophotometrically at 218 nm.

xi) Kinetics of drug release *23*

In order to understand the mechanism and kinetics of drug release, the drug release data of the *in-vitro* dissolution study were analyzed with various kinetic models like zero order, first order, Higuchi's, Korsmeyer-peppa's and correlation coefficient (r*2*) values were calculated for the linear curves by regression analysis of the above plots.

Figure 1: Dissolution profile of mucoadhesive microcapsules



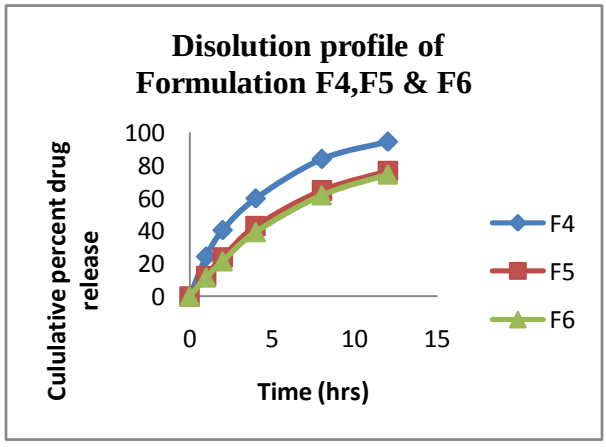


Table 2: *in vitro* release kinetic data for mucoadhesive microcapsules

Formulation code	Zero order R*2*	First order R*2*	Higuchi Square root R*2*	Korsmeyer-peppas	
				R*2*	n
F1	0.895	0.967	0.987	0.983	0.540
F2	0.892	0.980	0.978	0.966	0.599
F3	0.867	0.972	0.981	0.980	0.502
F4	0.887	0.998	0.984	0.981	0.537
F5	0.921	0.997	0.985	0.977	0.697
F6	0.935	0.999	0.990	0.984	0.720

R2 – Coefficient of correlation

n – Diffusion exponent

Figure 2: First order drug release plot for mucoadhesive microcapsules

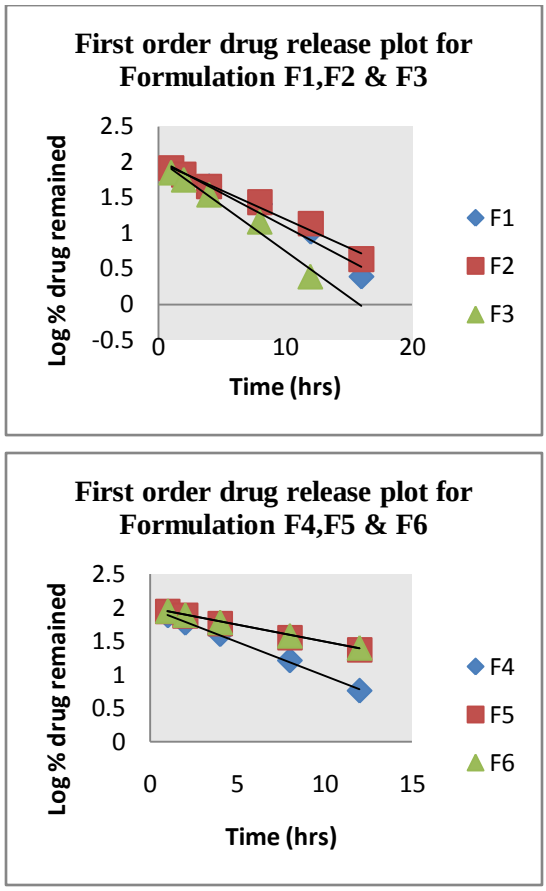


Figure 3: Higuchi plots for mucoadhesive microcapsules

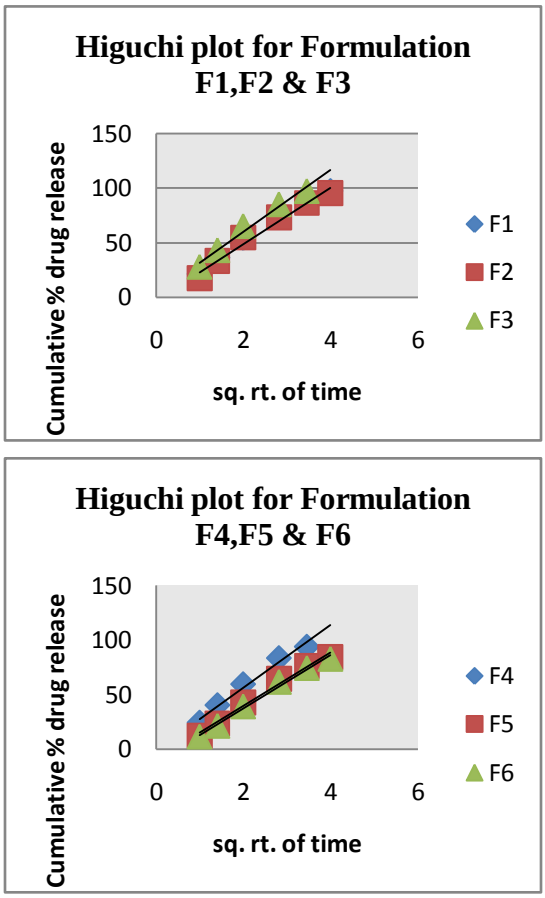
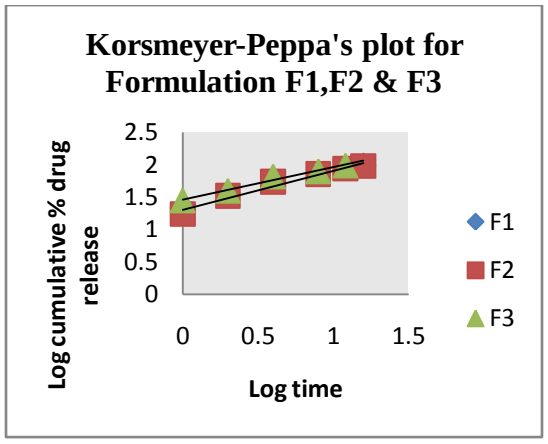
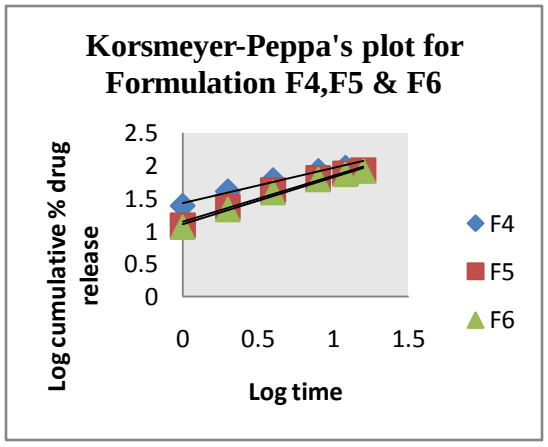


Figure 4: Korsmeyer-Peppa's plots for muchoadhesive microcapsules





xii) ATR spectroscopy

In this present work a study was carried out using ATR using BRUKER-ALPHA model. The samples of drug and other formulation excipients were examined and the spectra of drug and other excipients were compared with that of original spectra.

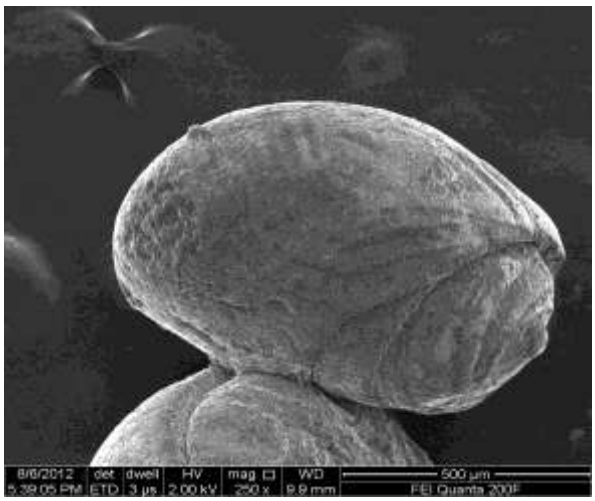
xiii)Differential Scanning Calorimetry (DSC)

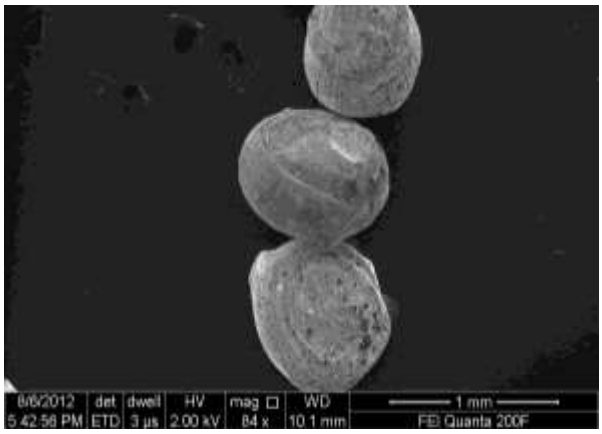
The DSC analysis was carried out to identify the compatibility between the drug and excipients. The DSC analysis of pure drug, 1:1 physical mixture of drug excipient was carried out using Shimadzu Corporation DSC-60, Japan.

xiv) Shape and surface characterization

The shape and surface characterization of microcapsules were observed under a Scanning Electron Microscope (SEM). The instrument used for this study was Environmental Scanning Electron Microscope model Quanta 200 FEG with Oxford-EDS system IE250 XMAX 80. The microcapsules were mounted directly on the SEM sample stub, using double-sided sticking tape.

Figure 5: Scanning Electron Micrograph (SEM) of the prepared mucoadhesive microcapsules Formulation F6





RESULT AND DISCUSSION:

All of the formulations were found to be spherical,discreete and free flowing with brownish-yellow color (Table 3). The SEM studies of microcapsules (F6) reveals that the microcapsules were nearly spherical and show a just about the smooth surface (Figure 5). Percent yield was in the range of 82.95% to 97.75%. The mean diameter of microcapsules was found to be in the range of 744.52µm to 783.87µm. Swelling ratio was found to be in the range of 0.588% to 0.767%. The mean percent drug content of the microcapsules ranged from 43.33% to 48.86%. Encapsulation efficiency ranged approximately from 86.66% to 97.72% (Table 4).

Table 3: Data for flow properties of mucoadhesive microcapsules of Gabapentin

Formulation code	Carr's index in %	Hausner ratio	Angle of repose
F1	12.50	1.14	22.3*o*
F2	10.84	1.11	21.9*o*
F3	13.15	1.15	23.7*o*
F4	11.76	1.13	22.8*o*
F5	10.71	1.12	21.5*o*
F6	07.14	1.07	20.7*o*

Table 4: Data for various evaluations of mucoadhesive microcapsules of Gabapentin

Formulation code	Yield (%)	Mean diameter in µm	Mean % drug content (X±S.D.) Ave. of 3 determinations	Encapsulation efficiency (%)	Swelling ratio (X±S.D.) Ave. of 3 determinations
F1	89.25	752.21	45.94±1.44	91.88	0.634±.0055
F2	92.83	744.52	46.31±1.43	92.62	0.664±.0066
F3	82.95	783.87	43.33±1.37	86.66	0.588±.004
F4	86.33	763.64	44.18±1.40	88.36	0.599±.0033
F5	95.50	756.46	47.59±1.45	95.18	0.697±.0252
F6	97.75	754.96	48.86±1.28	97.72	0.767±.0019

Alginate microcapsules with hydroxy propyle methyl cellulose as the muchoadhesive polymer exhibited good mucoadhesive properties in the *in vitro* wash off test. The result of the wash off test indicate that the microcapsules has very good mucoadhesive properties with approximately 73% retention for 10 hrs in 0.1 N Hydrochloric acid (Table 5).

Table 5: Data for *in vitro* wash off test of mucoadhesive microcapsules of Gabapentin in 0.1N Hydrochloric acid

Formulation code	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr
F1	97	93	85	81	72	63
F2	98	94	87	83	74	66
F3	93	90	82	77	69	58
F4	95	91	84	79	71	61
F5	100	96	89	84	76	68
F6	100	97	92	86	79	73

A sustained release of the drug was observed from the alginate-HPMC microcapsules. The drug was being released by coupling of diffusion and erosion mechanism so called anomalous (non-fickian transport) diffusion. The formulation F6 (Gabapentin **1 gm**, sodium alginate **800mg**, HPMC K4M-**100mg**, HPMC K100M-**100mg** and **6%** magnesium stearate) was selected as optimized formulation with 82.9% of drug release at 16*th* hour (Table 6).

Table 6: Data for drug release of mucoadhesive microcapsules of Gabapentin

Formulation code	% drug release after1 hour	% drug release after 2 hours	% drug release after 4 hours	% drug release after 8 hour	% drug release after12 hours	% drug release after16 hours
F1	21.37	36.33	54.33	74.29	89.50	97.52
F2	17.43	33.40	54.90	73.23	86.40	95.70
F3	28.20	43.40	65.47	85.43	97.53	-
F4	24.27	40.37	59.67	83.71	94.23	-
F5	12.40	23.71	42.67	64.43	76.23	84.33
F6	11.60	21.43	39.23	61.67	74.33	82.70

MECHANISM OF DRUG RELEASE

In order to understand the complex mechanism of drug release from the mucoadhesive microcapsules, the in vitro Gabapentin release data were fitted to Higuchi's and Korsmeyer-peppas models and interpretation of release exponent values (n) enlightens the release mechanism from the dosage form. In our experiments, the in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plot shows high linearity (R*2* = 0.978 to 0.990). To confirm the diffusion mechanism, the data were fit into Korsmeyer-Peppas model.

All formulations F1 to F6 showed high linearity (R*2* = 0.966 to 0.984) with a release exponent (n) values ranging from 0.502 to 0.720 (Table 2) (Figure 1-4). This (n) values indicate that the coupling of diffusion and erosion mechanism so called anomalous (non-fickian transport) diffusion and may indicate that the drug release is controlled by more than a mechanism, which indicate that formulation F6 release the drug by diffusion coupled with erosion mechanism. These formulations also showed highest R*2* values for First order kinetics (0.967 to 0.999) indicating the Gabapentin release from the formulations follows first order kinetics.

CONCLUSION

All of the formulations exhibited anomalous (non-ficikan transport) diffusion mechanism and follow first order kinetics.

The formulation F6 (Gabapentin **1000 mg**, sodium alginate **800 mg**, HPMC K4M-**100 mg**, HPMC K100M-**100 mg** along with magnesium stearete **6%**) was selected as optimized formulation; with 82.70 % of drug release at 16*th* hour.

It may enhance the bioavailability of the drug along with reduced dosing frequency and improved patient compliance. Further in vivo studies are required for the clinical correlation.

Finally it is concluded that with a limited number of experiments an optimized formulation with targeted and sustained release and having good mucoadhesion can be developed.

REFERENCES:

1. Bansode S.S., Banarjee S.K., Gaikwad D.D., Jadhav S.L., THorat R.M., microencapsulation: a review, International journal of pharmaceutical sciences review and research, 2010; 1: 38-43.
2. Gupta M.R., Kapoor R., Sudheesh M.S., Patil U.K., an applauded novel drug delivery system for arthritis using NSAIDs

by microencapsulation technique- a review, Scholar's research library, 2010; 2: 335-345.

3. Kumar A., Sharma P.K., Banik A., microencapsulation as a novel drug delivery system, International pharmaceutica sciencia, 2011; 1: 1-7.
4. Streubel A., Siepmann J., Bodmeier R., gastroretentive drug delivery system. Expert opin drug delivery 2006; 3: 217-33
5. Iannucelli V., Coppi G., Bernabei M.T., Camerorni R., air compartment multiple unit system for prolonged gastric residence. Part-1. Formulation study. Int. j. pharm 1998; 174: 47-54.
6. Dolas R.T., Dr. Hosmani A., Dr. Bhandari A., Kumar B., Somvanshi S., noval sustained release gastroretentive drug delivery system: A review, Int. J. of pharma research & development, 2011; 2: 26-34.
7. Lahoti S.R., Iftequar S., Sabina M., Dehghan M.H., Shoaib S., Mohiuddin S., an overview of gastroretentive drug delivery system research, Int. research J. of pharmacy 2011; 2: 50-57.
8. Santus G., Lazzarini G., Bottoni G., Sandefer E.P., Page RC, Doll W.J., Ryo U.Y., Digenis G.A., an in vitro-in vivo investigation of oral bioadhesive controlled release furosemide formulations**.** Eur J. pharm biopharm 1997; 44: 39-52.
9. Moes A., gastroretentive dosage forms. Crit rev ther drug carrier syst 1993; 10: 143-95.
10. Shankar N.B., Kumar N.U., Patro K.B., formulation design, preparation and in vitro evaluation of mucoadhesive microcapsule employiong controle release polymers to enhance gastroretention for oral delivery of Famotidine, Int J pharm sci tech, 2009; 2: 22-29.
11. Patil D.A., Patil G.B., Deshmukh P.K., Belgamwar V.S., Fursule R.A., chitosan coated mucoadhesive multiparticulate drug delivery system for Gliclazide. Asian journal of pharmaceutical and clinical research, 2009; 2: 62-68.
12. Sandhya R.S., Sundaramoorthy K., Vetrichelvan T., formulation, development and in vitro evaluation of Valsartan mucoadhesive microcapsules, International journal of pharmacy and technology, 2010; 2: 1315-1327.
13. Giri I.C., Bhanja S., Ellaiah P., Martha S.K., Sahu P.K., Tiwari S.P., Panigrahi B.B., Das D., design and evaluation of Acyclovir mucoadhesive microcapsules, International journal of pharmaceutical sciences review and research, 2010; 5: 18-24.
14. Gohel M.C., preparation and formulation optimization of sugar crosslinking gelatin microspheres of diclofenac sodium**,** Indian J. pharm.sci. 2005; 67: 575-581.

15. Arul B., Kothai R., Sangameswaran B., formulation and evaluation of microspheres containing Isoniazide, Indian journal of pharmaceutical science, 2003; 65: 640-642.

16. Alferd Martin, physical pharmacy, 4*th* edition, 427-429.

17. Aulton M.E., Pharmaceutics- The science of dosage form design, 2*nd* edition, 134.

18. Subramanyam C.V.S., Physical pharmaceutics, 2*nd* edition, 222-225.

19. Desai G.T., Gowthamarajan K., Suresh B., stability testing of pharmaceutical products: an overview, Indian J. pharm. Educ. Res. 2004; 38: 194-202.

20. Ahmed M.G., Satish K.B.P., Kiran K,G.B., formulation and evaluation of gastric-mucoadhesive drug delivery systems of Captopril, Journal of current pharmaceutical research, 2010; 2: 26-32.

21. Zhepeng L., Weiyue L., Lisheng Q., in vitro and in vivo studies on mucoadhesive microspheres of Amoxicillin, Journal of controlled release, 2005; 2: 135-144.

22. Banker G.S., Rhodes C.T., Modern pharmaceutics. Marcel Dekker. New York. 2001; 2*nd* edition, 635-648.

23. Dash S., Murthy P.N., Nath L., Chowdhury P., Kinetic modeling on drug release from controlled drug delivery systems, Acta poloniac pharmaceutica-drug research, 2010; 67: 217-223.