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RESEARCH ARTICLE

Formulation and Evaluation of Microspheres of Rabeprazole Sodium for the Treatment of GERD

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ABSTRACT:

The objective of the work was to design multiple unit dosage form as microspheres of a drug meant for management of GERD disorder. Microspheres of Rabeprazole was obtained utilizing orifice ionic gelation technique using HPMC and sodium aliginate as a polymer with various ratios. The results of the density of bulkiness and density of tapping were mentioned in table. Bulkiness values were lies in 0.297 to 0.542 g/cm3 and density of tapping values lies in 0.508 to 0.654 g/cm3 i.e. less than 1.2, indicates good packing. The values of Average particle size and angle of repose were lies in between 291.46 ±8.3 to 432.62 ±7.3, and 250-12' to 300-20', respectively indicates acceptable particle size, flow property and also good packing ability. Best % yield was obtained for batch F6 - 96.47 %. Overall % recovery of microspheres obtained > 82%. The drug content of overall formulation we gave >84 % drug content. This batch gave 92.30 %, other formulations gave little bit drug loading than this batch. The *invitro* release studies formulations (F1, F2, F3) showed Rabeprazole sodium discharge speed in series of 91-94% when compared (F4, F5 and F6) demonstrated a Rabeprazole sodium discharge speed from 86. -93% up to duration of 12 hours. From above formulation F1 indicates the better results than other prepared batchs. As formulation F6 shown 97.78% cumulative drug release pattern, this was according to the Acceptance Table of Test 2 given in USP-NF 2007 time duration of 12 hrs.

Keywords: Microsphere, Rabeprazole sodium, GERD, *Invito* release, HPMC and sodium alginate.

INTRODUCTION:

Rabeprazole is an antiulcer drug in the class of proton pump inhibitors. It was developed by Eisai Co. and is marketed by Janssen-Cilag as the sodium salt. It is the choice of drug in management of GERD. Gastroesophageal reflux disease, or GERD, is a digestive disorder that affects the lower esophageal sphincter (LES), the ring of muscle between the esophagus and stomach.[1,2] Many people, including pregnant women, suffer from heartburn or acid indigestion caused by GERD. Doctors believe that some people suffer from GERD due to a condition called hiatal hernia. In most cases, heartburn can be relieved through diet and lifestyle changes; however, some people may require medication or surgery.[3]

In normal digestion, the lower esophageal sphincter (LES) opens to allow food to pass into the stomach and closes to prevent food and acidic stomach juices from flowing back into the esophagus. Gastroesophageal reflux occurs when the LES is weak or relaxes inappropriately, allowing the stomach's contents to flow up into the esophagus. The severity of GERD depends on LES dysfunction as well as the type and amount of fluid brought up from the stomach and the neutralizing effect of saliva.[4,5]

The objective of the work to prepare microsphere of rabiprazole was to design multiple unit dosage form as microspheres of a drug meant for management of GERD disorder. Microspheres offers numerous advantages for releasing one of the drugs or part of the same drug immediately while remaining drug or parts of the same can be sustained release. These are useful where drug-excipients and drug-drug interactions are predictable with single type dosage form.

Material and Method:

Material:

Rabeprazole sodium was obtained as gift sample from Ranbaxy labs, Gurgaon, India. Sodium alginate and Calcium chloride purchased from Himedia laboratory, Mumbai. Other chemical purchased from local market.

Method:

Preparation of Rabeprazole sodium loaded Microspheres

A solution of sodium alginate was prepared in 100ml of de-ionized water. In 50ml of sodium alginate and HPMC solution with different ratio. 200 mg of Rabeprazole sodium was dispersed uniformly. Bubble free dispersion was dropped through a syringe with a needle

into 100ml aqueous calcium chloride solution and stirred 500rpm. After stirring for 30minutes, the microspheres were separated by filtration, washed with distilled water and finely dried at 70^0C for 6h in an oven.[6]

Composition used formulations

Formulation code	**Sodium Alginate % (w/v)**	**Calcium Chloride % (w/v)**	**HPMC % (w/v)**
F1	2	1.25	0.5
F2	2	2.5	1
F3	2	5	1.5
F4	2	1.25	0.5
F5	2	2.5	1
F6	2	5	1.5

Evaluation:

Micromeritics Studies

Determination of Bulk Density

It is ratio of weight by volume. It was resolute by utilizing mark off cylinder, the precisely measured quantity of product microspheres inserted to cylinder and three times tapped. Noted the level, and calculated bulk density using formula.[7]

Formula:

$$\rho b = M/V$$

Where,

m = mass of sample,

v = volume of sample,

ρb =Density

Tapped Density

The sample of about 10 cm^3 of powder was carefully introduced in 25 ml glass cylinder. The cylinder tapped at 1 inch height, with intervals of 2-3 second on a rough wood surface three-four times. Density of Bulkiness calculated by using equation

Below

$$\mathbf{Do = M / Vp}$$

Here,

Do = Tap density

M = samples wt (gm)

Vp = final material volumes (cm^3)

Angle of repose

It was carried out, using funnel, at sufficient height funnel was fixed and, microcapsules were added through it until the pile touched at bottom of funnel. Pile height as well as radius measured and using formula angle of repose calculated.[8]

$$\mathbf{\tan \Theta = h/r}$$

Here,

r = height

and r = is radius of pile

Particle size determination

The diameter of microspheres was found using an optical microscope as well as polarized light near about 50-100 microspheres were examined and average diameter was calculated using ocular micrometer.[9]

Percentage yield

It was determined by weighing after drying. The précised mass of produced microspheres were divided with mass of total non–volatile components utilized for the microspheres preparation, which gave the total percentage yield of microspheres.[10]

$$\% \text{ Yield} = \frac{\text{Actual weight of product} \times 100}{\text{Total weight of excipients and drug}}$$

Drug Entrapment Efficiency (DEE)

From accurately weighted samples of prepared microspheres was extracted into buffer pH 7.4. Then extracts diluted using buffer solution (pH – 7.4). Resultant extract analysed for Rabeprazole sodium sphectrophotometricaly at 292 nm.[11]

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Morphological Study using SEM

Formulation mounted directly on scotch double adhesive tape analyzed under scanning electron microscope SEM model XL-30, operated at 15K SEM thickness of 100% using FEI-Philips Analytical Electron microscope (Diya labs,Mumbai).[12]

***In-vitro* drug release profile of formulated microspheres**

The dissolution studies executed utilizing (type II) XXIV USP dissolution rate test apparatus in 0.1 N HCl for 2 hrs followed by pH 7.4 900ml dissolution media, at 50 rpm and 37 ± 1^0C temperature upto 12 hrs. using Simadzu U.V. Spectrophotometer double beam, 5ml of samples taken at different time gaps and 5ml of same dissolution medium added to uphold sink condition. Withdrawn aliquots diluted and analyzed spectrophotometrically at 292 nm. The percent release of Rabeprazole sodium calculated and graph plotted against time. [13, 14]

Accelerated Stability Studies of the optimized batch

The microspheres from the selected and optimized batch were studied for stability and kept under the accelerated conditions of temperature and moisture (humidity) for the period of six

months. This microspheres stability was studied at Temperature 40°C and Humidity 75% RH conditions. Every sample separately weighed and enclosed by aluminum foils and sealed in black PVC bottle and kept in specified conditions at humidity chamber for six months. The formulation was checked for physical changes also analyzed for dissolution study.[15]

Result and Discussion:

Rabiprazole microspheres were prepared by the emulsion solvent diffusion evaporation method.

Micromeritics Studies of microspheres

The results of the density of bulkiness and density of tapping were mentioned in table.2 Bulkiness values were lies in **0.297** to **0.542 g/cm3** and density of tapping values lies in **0.508** to **0.654 g/cm3** i.e. less than 1.2, indicates good packing.

The values of Average particle size and angle of repose were lies in between 291.46 ±8.3 to 432.62 ±7.3, **and 250-12'** to **300-20',** respectively indicates acceptable particle size, flow property and also good packing ability.

Table No. 2 Micromeritics Studies of Microspheres

Batch	Avg microsphere size	Bulk Density	Tap Density	Angle of Repose
F1	291.46±8.3	0.298	0.522	250-15'
F2	323.44±6.9	0.542	0.654	260 -20'
F3	356.88±8.6	0.526	0.636	250-12'
F4	263.84±8.3	0.430	0.508	300-20'
F5	327.65±7.5	0.482	0.528	250-06'
F6	356.22±8.1	0.516	0.616	310-24'

Percentage recovery (i.e. Yield) of microspheres

Best % recovery was obtained for batch F6 - 96.47 %. Overall o% recovery of microspheres obtained > 82%.

Estimation of Rabeprazole sodium.

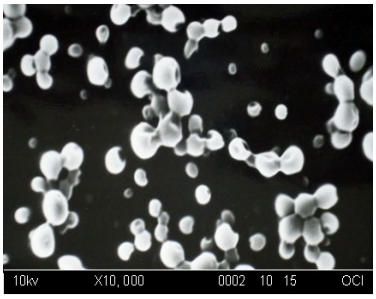
Formulation F6 gave well >84 % drug content. This batch gave 92.30 %, other formulations gave little bit drug loading than this batch. It can be happened due to viscosity caused by used material.

Table No. 3 Percentage yield and Percent drug entrapment of microspheres

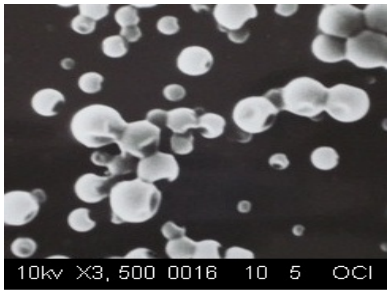
Batch	% yield	% Drug Entrapment
F1	84.14±0.9	82.92±1.4
F2	86.40±3.6	85.12±2.4
F3	90.25±1.9	86.30±1.1
F4	82.62±2.6	86.48±2.6
F5	82.71±1.4	85.94±1.5
F6	83.50±1.7	86.46±2.6

*All the values represent mean ± standard deviation (n=3)

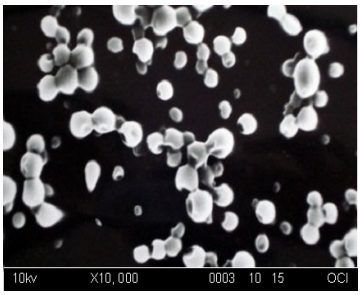
Morphological Study using SEM (F6)



(A)



(B)



(C)

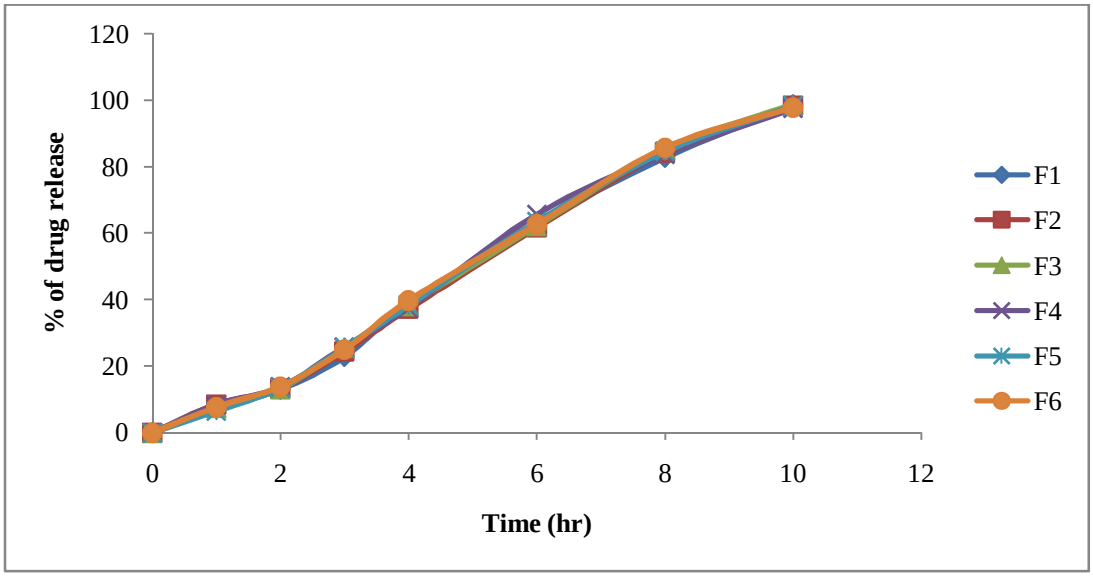
***In-vitro* Release Profile Study of Formulated microspheres:**

The results demonstrated that formulations (F1, F2, F3) showed Rabeprazole sodium discharge speed in series of 91-94% when compared (F4, F5 and F6) demonstrated a Rabeprazole sodium discharge speed from 86. -93% up to duration of 12 hours. This denotes that if quantity of rate retarding polymer raised, leads to retard discharge of drug. The synergistic effect was observed when the HPMC was combined with xanthan gum. Hence

batch F1 indicates the better results than other prepared batchs. As formulation F6 shown 97.78% cumulative drug release pattern, this was according to the Acceptance Table of Test 2 given in USP-NF 2007 time duration of 12 hrs. When the HPMC combined with the natural gums is used for retarding drug discharge. Process of Rabeprazole sodium liberate from matrix involve solvent diffusion in to the matrix, polymer gelation, solubilization Rabeprazole sodium and drug transfer along eddies of medium.

Table No. 4. In vitro Cumulative %drug release profile

S.no	Time	% drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	7.137	8.517	7.594	8.450	6.472	7.650
3	2	12.982	13.271	13.160	13.748	13.532	13.872
4	3	22.874	24.482	25.654	25.759	25.593	24.981
4	4	38.764	37.268	38.147	37.620	38.398	39.760
5	6	62.765	61.734	62.157	65.650	63.564	62.705
6	8	82.726	84.372	85.245	83.746	84.650	85.760
7	10	98.659	98.360	98.590	97.540	98.380	97.853



Accelerated Stability Studies

The microspheres from the selected and optimized batch (FH) were studied for stability and kept under the accelerated conditions like raised temperature and moisture up to period of six months. The results revealed no marked alterations in physical appearance and drug releasing properties.

Table No. 5. Accelerated stability testing effect of temperature and humidity on *in-vitro* drug release for formulation F6

Time (Hours)	Cumulative % Drug Released			
	At 0 Month	At 2ndMonth	At 4thMonth	At 6thMonth
0	0	0	0	0
1	20.96	19.69	19.19	18.89
2	27.47	25.87	24.17	23.97
3	33.63	31.83	30.93	30.13
4	42.72	41.12	40.92	40.32
5	54.19	52.87	52.17	51.97
6	61.15	60.13	59.83	59.23
7	73.81	71.89	71.21	70.11
8	82.72	81.26	80.86	80.21
9	88.63	86.93	86.13	85.33
10	90.94	88.24	87.94	87.14
11	94.49	93.94	93.14	92.64
12	97.78	95.81	95.12	94.82

Conclusion:

Microspheres of Rabeprazole sodium obtained utilizing orifice ionic gelation technique using HPMC and sodium aliginate as a polymer with various ratios. The prepared microsphere

were free flowing and non sticky. All the formulations were shown satisfactory results. In the above view it was concluded that HPMC when combined with the hydrophilic natural gums shows the synergistic effects and hence can be utilized to prolong the release of Rabeprazole sodium. The overall frequency of administration of a drug candidate like Rabeprazole sodium was successfully reduced to 2 times a day, which generally requires dosing in 3 to 4 times a day in conventional tablet dosage form. The improved patient convenience might thus be obtained by the administration of such a dosage form with minimal blood level fluctuations. Among the different combinations of natural polymers and drug many combinations were shown optimum results. The release retardant materials are cheap, readily available, safe, having wide regulatory acceptance and easy to handle for economic point of view. It may beneficial to adopt such simple technology for the commercial manufacture of persistent release microspheres.

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