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Formulation and Evaluation of Floating Microspheres of Enalapril Maleate Using Sodium Alginate and Gum Acacia

Mr. Asmit*, Dr. Gurpreet Singh, Dr. Rajesh Sharma, Dr. Jeyabalan G., Dr. Praveen Goyal

*Corresponding Author: Mr. Asmit, M.Pharm. Research Scholar, Alwar Pharmacy College, M.I.A. Alwar, Rajasthan, India

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ABSTRACT:

This research aimed to prepare gastroretentive floating microsphere of antihypertensive drug. Nine batches of g*um* acacia alginate-based microspheres of Enalapril maleate were formulated by ionic gelation technique, each having 5mg drug strength. (F1 - F9) Compatibility studies confirmed no interaction between drug & excipients. Prepared microspheres were evaluated for physicochemical characteristics, entrapment efficiency, mucoadhesion potential and *in vitro* drug release potential. The drug loading (%) and entrapment efficiency (%) was calculated and it was observed that entrapment efficiency ranges from 69% to 95.59%. Batch F6 having maximum entrapment efficiency of 95.59% and in this batch Sodium Alginate & Gum Acacia are present in the ratio of 1:1. Results of in vitro drug release of batch F6 was compared with release of pure drug and it was found that pure drug showed 98.91% release in 3hours and batch F6 showed 98.39% release in 24 hours. Batch F6 showed very good stability profile as well. It was observed that the formulated microspheres of Enalapril maleate (F6) were superior, economic and effective in achieving patient compliance.

Keywords: gastroretentive, microsphere, antihypertensive, Enalapril maleate, mucoadhesion.

1. INTRODUCTION:

Oral controlled release (CR) dosage forms (DF) have been extensively used to improve therapy of many important medications. Gastroretentive dosage forms (GRDFs) are a drug delivery formulation that are designed to be retained in the stomach for a prolonged time and release there their active materials and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract [1,2]. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome [3-5].

Hypertension is the most common modifiable risk factor for cardiovascular diseases (CVD), stroke and renal failure [6]. It is the second leading cause of chronic kidney disease (CKD). It is estimated that more than one billion adults are hypertensive worldwide and this figure is projected to increase to 1.56 billion by the year 2025, which is an increase of 60 % from 2000. Cardiovascular diseases and Hypertension are accounting for loss of 4 % gross domestic product for low and middle income countries annually which is amounting 500 billion USD [7]. Clinical evidence suggests that lowering blood pressure (BP) with antihypertensive drugs reduces the risk of myocardial infarction, stroke, heart failure, revascularization procedures and end-stage renal diseases in hypertensive patients [8].

Enalapril maleate is an ACE inhibitor used to treat high blood pressure (hypertension), heart failure, and asymptomatic left ventricular dysfunction. It relaxes blood vessels, making it easier for the heart to pump blood. Common side effects include cough, dizziness, fatigue, and low blood pressure. The aim of the current research work is to formulate floating microspheres of Enalapril maleate to increase the residence time of drug and provide sustained release action [9].

To increase therapeutic efficacy, reduce frequency of administration and for better patient compliance, twice daily-sustained release Enalapril maleate gastroretentive dosage forms will be prepared. Enalapril maleate belongs to the class III of BCS (Biopharmaceutical classification of system), exhibiting high solubility and low permeability. Hence, enhanced gastric retention time of Enalapril maleate controlled release dosage form will increase its absorption. Therefore, Enalapril maleate is selected as a suitable drug for designing gastroretentive drug delivery system (GDDS) with a view to improve its oral bioavailability.

2. Materials & Methods:

2.1. Materials:

Enalapril maleate (API), was obtained as a gift sample from Intas Pharmaceutical Ltd., Dehradun and other excipients Gum acacia, Sodium alginate, Hydrochloric acid, Ethanol AR, Hexane LR, Calcium chloride, Magnesium chloride, Sodium chloride, Potassium chloride, Disodium hydrogen phosphate, Sodium bicarbonate, Sodium acetate, Sodium citrate were procured from R.S. Enterprises, Jaipur, India manufactured by Central Drug House (P) Ltd – CDH, New Delhi, India. All chemicals used were of analytical grade.

2.2 Methods:

2.2.1 Preformulation Studies:

The drug Enalapril maleate, selected for present study was identified using different methods reported in the literature viz. melting point determination, partition coefficient determination, determination of absorption maxima (λ_{max}), and drug excipient interaction studies.

2.2.2 Drug Polymer Interaction Studies

The drug was white in color and when blended with polymer, the appearance of the physical mixture remains the same. In case of storage at accelerated condition (40±2˚C and 75±5% RH), there was no significant change in the physical characteristics of the drug in the presence of the polymer in closed container.

2.2.3 Design of *gum acacia*-alginate microspheres:

Enalapril maleate loaded microspheres were formulated using ionic gelation technique. Briefly appropriate quantities of gum acacia and sodium alginate were dissolved in distilled water with continuous stirring to polymeric solution. The weighed quantity of metformin hydrochloride was dissolved in polymeric solution with continuous stirring. The ratio of polymer to drug was maintained as per shown in table. The resulting medicated polymeric solution was injected in 100 ml of 7% w/v calcium chloride solution using 24-G needle with continuous stirring at 2600 rpm using magnetic stirrer. The resulting polymeric dispersion was stirred for 30 minutes for crosslinking of alginate in presence of calcium ions. After stirring continuous stirring for specified time, the dispersion was kept in standing for 1 hour for complete crosslinking of polymer. After 1 hour the microspheres were collected by filtration, washed with double distilled water and finally dried in hot air oven at 40ºC for 10 hours [10].

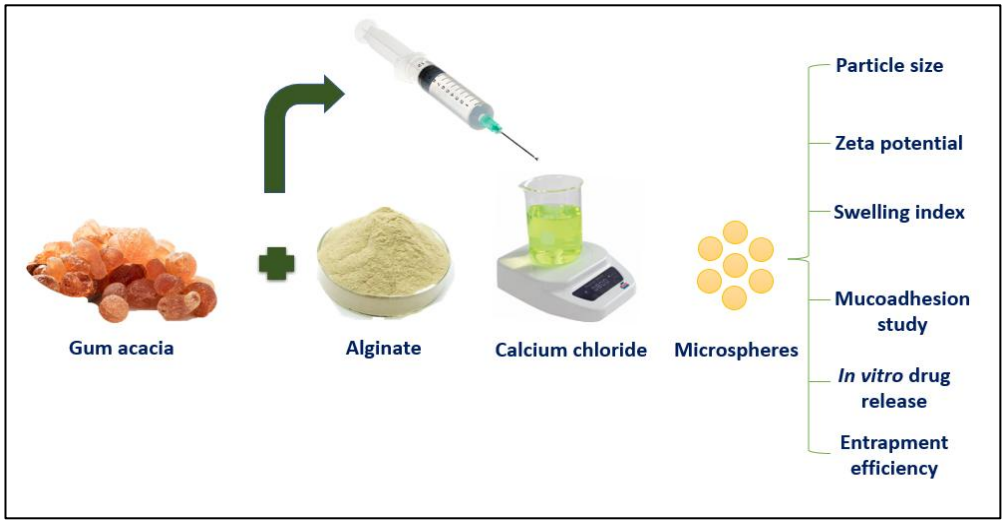

Figure 1: Overview of preparation and evaluation of gum-alginate microspheres

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Table 1: Composition of different formulation of Enalapril maleate microspheres

Batch No.	Sodium Alginate (%w/v)	Gum Acacia (g)	Enalapril (mg)	% w/v $CaCl_2$ Solution	rpm
F1	0.5	0.5	5	2%	2600
F2	1	0.5	5	2%	2600
F3	1.5	0.5	5	2%	2600
F4	2	0.5	5	2%	2600
F5	0.5	1	5	2%	2600
F6	1	1	5	2%	2600
F7	1.5	1	5	2%	2600
F8	2	1	5	2%	2600
F9	1	0	5	2%	2600

3. Evaluation of *Gum acacia*-alginate microspheres

3.1 Percentage entrapment efficiency (EE %) and Drug Loading (%)

10 mg of floating beads were weighed and was dissolved in 10 ml of methanol with agitating at room temperature for 12 hours. Then it was filtered through wattmann's filter paper. The filtrate was assayed by spectrophotometrically at maximum wavelength (204nm). The drug loading (%) and entrapment efficiency (%) was calculated according to following relationship.

% Drug Loading = Weight of drug loaded in beads in gms / Weight of quantity of beads in gms

$$EE\ (\%) = WA/Wr \qquad \text{.....(1)}$$

Where:

WA = Actual drug content

Wr = theoretical drug content

The drug loading (%) and entrapment efficiency (%) was calculated and the results are shown in table 2. It was found that batch F5 showed 96.88% entrapment efficiency.

3.2. Percentage (%) yield

The prepared floating beads were collected and weighed. The measured weight was divided by the total weight of all the excipients and drug. The % yield was calculated using following formula

$$\%\ yield = Total\ bead\ weight/Total\ weight\ of\ all\ excipients \text{ .....(2)}$$

The % yield was calculated and the results are shown in table. It was found that batch F5 showed maximum % yield. The drug loading (%) and entrapment efficiency (%) was calculated and the results are shown in table 2.

Table 2: Data representation of % yield and %EE of Aspirin containing Sodium Alginate beads

Formulation code	% Yield	%EE	Physical Appearance
F1	72.75	93.17	Oval
F2	74.45	86.72	Oval
F3	70.85	76.92	Round
F4	74.35	90.1	Round
F5	80.65	88.03	Oval
F6	**82.4**	**95.59**	**Round**
F7	74.25	81.82	Round
F8	72.35	75.57	Oval
F9	73.35	69	Round

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3.3 *In vitro* mucoadhesive and swelling behavior

Assessment of mucoadhesion potential and swelling ability of microspheres is essential evaluation parameter governing *in vivo* performance of microspheres based systems. The swelling behavior of microsphere in presence of phosphate buffer pH 6.8 has represented in figure 2. The microspheres showed increase swelling capability up to 6 hours with almost 65.12% swelling index. After the 6 hours swelling behavior of microspheres was progressively decline up to 12 hours. The reduction in swelling of microspheres after 8 hours could be due to slow erosion of polymer. The percent mucoadhesion of mucilage-alginate microspheres on porcine intestinal mucosa was found to be 65.12%. The formulated microspheres showed acceptable swelling and mucoadhesion capabilities [11].

Table 3: Swelling index of *Gum acacia*-alginate based microspheres microspheres

Time (Hrs.)	% Swelling
0	0
1	11.35
2	24.33
4	48.25
6	65.12
8	57.24
10	46.93
12	35.35

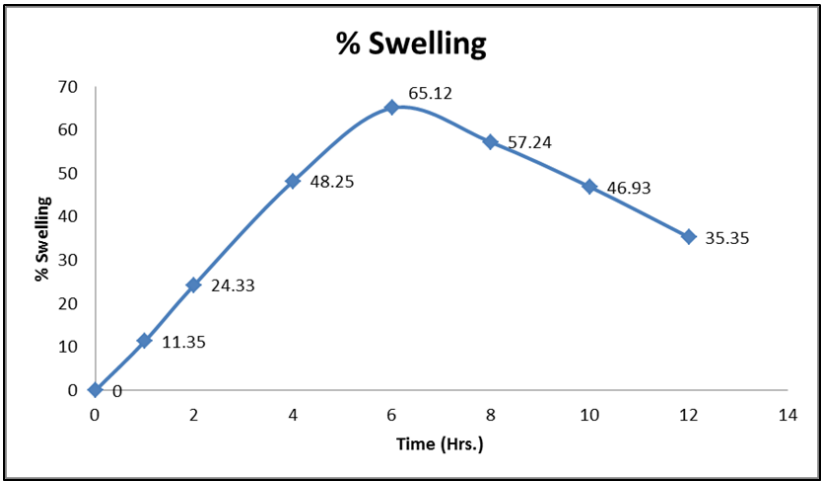

Figure 2: Swelling behavior of *Gum acacia*-alginate based microspheres

3.4 *In-Vitro* Drug Release Study [12,13]:

Dissolution studies were conducted to determine the release pattern of the product. Dissolution test for Drug was carried out as per USP method for dissolution test for tablets using LABINDIA DS-8000 apparatus-II. Dissolution medium used was 900ml of pH 1.2 HCl buffer rotating the paddle at 50 rpm with temperature37°C ± 0.5°C. An aliquot of 5ml of samples were withdrawn at different time periods (1, 2, 4, 6, 8, 12, 16, 20, 24 hrs.). The samples were filtered through nylon filters, suitably diluted and analysed at 209nm using double beam UV/Visible spectrophotometer (Shimadzu Corporation, UV-1601, Japan). The content of drug was calculated using equation generated from standard calibration curve. The dissolution study was continued for 24hours to get a stimulated picture if drug released *in vivo* condition.

Beads equivalent to weight 5 mg were taken and *in-vitro* dissolution study was carried out. Results of *In-vitro* drug release of pure drug & F6 formulation showed in table 4 and fig. 3.

Table 4: Percentage drug release of pure drug (Losartan) and F6 formulation

Time	Drug release of Pure Drug	% Drug release of F5 formulation
0	0	0
0.25	38.25	10.39
0.5	50.46	19.44
1	76.96	25.44
2	92.1	36.54
3	98.91	43.92
4	-	49.76
5	-	57.75
6	-	61.76
7	-	67.38
8	-	70.51
10	-	76.49
12	-	82.86
14	-	88.58
16	-	92.02
24	-	98.39

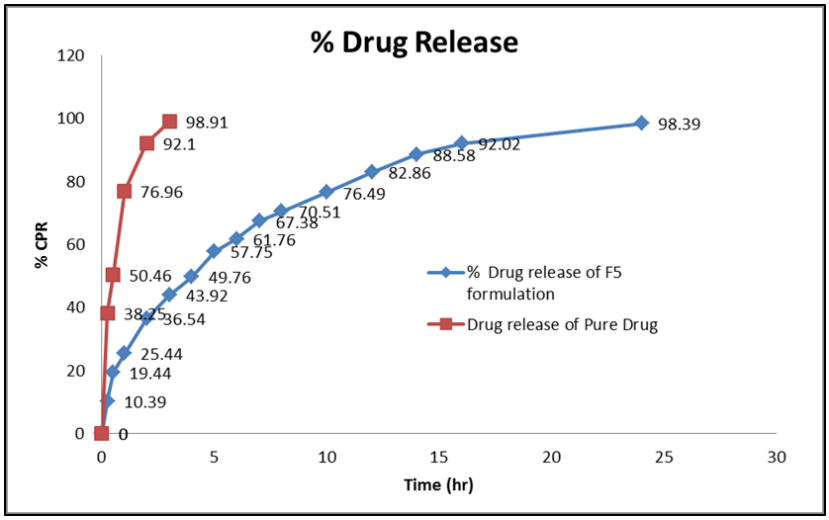

Fig 3: Percentage drug release of pure drug and Formulation

5. In vitro release Kinetics [14]

In-vitro drug release kinetic study data of formulation F6 was given below.

The data obtained for in vitro release shown in Table 4 were fitted into equation for the zero order, first order and higuchi and Korsmeyer peppas release models. The interpretation of data was based on the value of the resulting regression coefficients.

The zero order rates describes the system where the drug release independent of its concentration shows the cumulative amount of drug release Vs time for zero order kinetics. The first order rate describes the release from systems where the release of drugs from a matrix as a square root of a time- dependent process based on Fickian diffusion.

The calculated regression coefficients for zero order, first order and higuchi models and Korsmeyer were shown in Table 5 it was found that the in vitro drug release of F5 Formulation was best explained by higuchi model as the plot showed the highest linearity. The value of R^2 found to be 0.984 highest for the Korsmeyer peppas Model.

Table 5: Kinetic equation parameter of F6 Formulation

Formulation code	Zero order		First order		Higuchi		Peppas	
	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope
F6	0.836	3.7305	0.847	-0.0824	0.973	21.247	0.984	0.4859

6. STABILITY STUDIES [15]

In order to assess stability, the microspheres were packed in wide mouth air tight glass container and stored at (40 ± 2˚C and 75 ± 5% RH) for a period of 3 months. The tablets were withdrawn after a particular period of time, analyzed for physical appearance, entrapment efficiency, drug loading and % drug release.

7. Conclusion

Nine batches of g*um* acacia alginate-based microspheres of Enalapril maleate were formulated by ionic gelation technique, each having 50mg drug strength. (F1 - F9) Prepared microspheres were evaluated for physicochemical characteristics, entrapment efficiency, mucoadhesion potential and *in vitro* drug release potential. The drug loading (%) and entrapment efficiency (%) was calculated and it was observed that entrapment efficiency ranges from 69% to 95.59%. Batch F6 having maximum entrapment efficiency of 95.59% and in this batch Sodium Alginate & Gum Acacia are present in the ratio of 1:1. Results of *in vitro* drug release of batch F6 was compared with release of pure drug and it was found that pure drug showed 98.91% release in 3hours and batch F6 showed 98.39% release in 24 hours. From this observation it was concluded that the formulated microspheres of Enalapril maleate (F6) were superior, economic and effective in achieving patient compliance.

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