RESEARCH ARTICLE

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FORMULATION AND EVALUATION OF ELETRIPTAN HYDRO-BROMIDE MICROSPHERES BY USING NATURAL POLYMERS

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Abstract:

Purpose: The aim of present work to develop competent and efficient sustained release microspheres of *Eletriptan hydrobromide*, prepared by Ionotropic gelation technique in order to reduce the frequency of administration and achieve patient compliance.

Method: Microspheres of *Eletriptan hydrobromide* were prepared by Ionic gelation method using natural polymers like sodium alginate, chitosan, karaya gum and guar gum. The morphology, particle size distribution and production yield were investigated. Release of *Eletriptan hydrobromide* was evaluated by *In-vitro* dissolution method using USP type I apparatus.

Result: Results showed that microspheres were spherical, discrete in shape. The percentage yield of the prepared microspheres was found to be 80.46% to 87.12%. Particle size distribution of the prepared microspheres was in the range of 487.0 – 802.5µm. *In-vitro* release studies revealed a controlled release of microspheres suitable for preoral administration. Formulation FEC1 showed 90.82% ± 0.26 of drug release for 12 hours in predetermined rate.
Conclusion: Based on the results the formulation FEC1 was found to be best when compared to other formulations.

Keywords: *Eletriptan*, Chitosan, SEM analysis and *in-vitro* studies.

Introduction

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and having a short half-life are eliminated quickly from the blood circulation, so they require frequent dosing. To avoid this drawback, the oral sustained-controlled release formulations have been developed in an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the serum for longer period of time. Novel drug delivery systems that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare systems. However problem frequently encountered with controlled release dosage forms is the inability to increase residence time of the dosage at the site of absorption. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation.

Microencapsulation is used to modify and retard drug release. In pharmaceutical sustained release preparations, the uniqueness of microcapsules lies in the wide distribution throughout the gastrointestinal tract. Microspheres provide constant and prolonged therapeutic effect, reduced the GI toxic effects and dosing frequency and thereby improve the patient compliance. The drugs which are poorly soluble and unstable in intestinal fluids these systems are useful.
Eletriptan hydrobromide microspheres for sustained release in order to improve efficiency. *Eletriptan hydrobromide* was an anti-migrine drug which has been used to treat migraines, head-ache, pain and other related migraine symptoms. *Eletriptan* belongs to a class of drug known as triptans. It acts by effecting natural substance serotonin which causes narrowing of blood vessels.

Microsphere drug administration offers a number of advantages in therapeutics, where the controlled releases of drug delivery as well as the predictable and reproducible drug release kinetics are important feature of them.

The present work is to develop competent and efficient sustained release microspheres of *Eletriptan hydrobromide*, prepared by ionotropic gelation technique inorder to reduce the frequency of administration and achieve patient compliance. The prepared microspheres were evaluated by particle size determination, drug entrapment efficiency, *in-vitro* drug release studies.

Materials and Methods:

Materials:

Eletriptan hydrobromide drug is the gift sample from Hetero drugs ltd, Hyderabad. Sodium alginate and Calcium chloride from Thomas baker chemicals, Mumbai. Guargum, Chitosan from Yarrow chem. Products, Mumbai. Karayagum from cochin fisheries, Cochin. Liquid paraffin from fine chem chemicals, Chennai. N-hexane from hi pure fine chemicals Chennai.

Methods:

Determination of λ_{max} (UV-Spectroscopy):

Standard solution of *Eletriptan* was prepared by taking 10mg of *Eletriptan* and add small amount of ethanol and make up the volume with phosphate buffer pH 6.8 upto 10ml. The final concentration of standard solution of drug is 1µg/ml. A solution of 1µg/ml of *Eletriptan* was scanned by using UV spectrometer in the range of 200-400nm to get the λ_{max} of *Eletriptan*.

Preparation of microspheres of *Eletriptan hydrobromide:*

Alginate microspheres containing *Eletriptan hydrobromide* were prepared by emulsification ionic gelation technique. Sodium alginate and copolymers were dispersed in deionised water (30 ml) separately with continuous stirring to form homogenous polymer dispersion and both the dispersions were added in different ratio as mentioned in formulation chart. *Eletriptan hydrobromide* was added to polymer dispersion and mixed thoroughly to form a viscous suspension. The dispersions were sonicated for 30 minutes to remove any air bubbles that may have been formed during stirring. The stream of smooth viscous suspension was added to light liquid paraffin in the form of a thin stream. Stirring of the above mixture was done in a beaker placed on mechanical stirrer. Then 100 ml of calcium Chloride solution (5% w/v) was added slowly while stirring for ionic gelation reaction. The stirring was continued for 15 minutes. The mixture was allowed to settle and product was separated. Obtained microspheres were washed several times with n-hexane to remove the adhering paraffin and dried in room temperature (Table 1).

Evaluation and characterization of prepared microspheres

Production yield (%):

The production yield of microspheres of various bathes were calculated using the weight of the final product after drying with respect to the initial weight of the drug and polymer used for the preparation of microspheres and percentage production yield was calculated as per the following formula:

$$\text{Percentageyield}(\%) = \frac{\text{Practicalmass (Microspheres)}}{\text{Theoriticalmass (Drug + Polymer)}} \times 100$$

Particle size analysis:

Particle size of prepared microspheres was determined by optical microscopy. The optical microscope is fitted with an ocular micrometer and stage micrometer. The eyepiece micrometer
was calibrated. The particle diameters of more than 200 microspheres were measured randomly.

Shape and surface morphology:

The shape and surface characteristics of the prepared microspheres were evaluated by means of scanning electron microscopy. The scanning electron microscopy samples were prepared by lightly sprinkling the microspheres powder on a double adhesive tape, which is stucked to an aluminium stub. The stubs were then coated with gold using a sputter coater under high vacuum and high voltage to achieve.

***In-vitro* drug release studies:**

The *in-vitro* drug release of *Eletriptan hydrobromide* from formulated tablets was carried out in acid buffer pH 1.2 for 2 hours and then continued in phosphate buffer pH 6.8 for 10 hours. The studies were performed in USP dissolution apparatus I, (Dissolution Test Apparatus, Model DS 8000, Lab India Pvt Ltd) at 37 ± 0.5° C and 100 rpm speed. Samples were taken at hourly interval and analyzed for *Eletriptan* content at 255.0 nm by using UV–visible spectrophotometer.

Results and discussion:

Determination of λ_{max} of Eletriptan:

A solution of 1µg/ml of *Eletriptan* was scanned in the range of 200 to 400 nm. The drug exhibited the λ_{max} at 233nm in phosphate buffer pH 6.8 and has good reproducibility shown in graph 1.

Production yield:

The production yields of microspheres prepared by ionic gelation method were found to be between 80.46 to 87.12%. It was observed that as the polymer ratio in the formulation increases, the product yield slightly decreases. The probable reason behind this may be the high viscosity of the solution which decreased its syringe ability resulting in blocking of needle and wastage of the drug- polymer solution which ultimately decreased the production yields of microspheres. The percentage yield of the prepared microspheres was recorded in table 2.

Particle Size Analysis:
The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres of *Eletripan hydrobromide* using Sodium alginate alone had a size range of 613.25 µm to 665.0 µm, microspheres using Guar gum as copolymer exhibited a size range between 762.25µm to 802.5µm and microspheres using Karaya gum as copolymer 568.75µm and 600.75µm. Microspheres with Chitosan as copolymer exhibited a size range between 487.0µm to 527.0µm.The particle size data of an optimized formulation was presented in table 3.

Determination of Shape and Surface Morphology by SEM analysis:
Morphology of the microspheres was investigated by Scanning electron microscopy. The results of SEM revealed that the microspheres of *Eletriptan* using sodium alginate, Guar gum, Karaya gum and Chitosan were spherical and their surface was smooth and devoid of cracks giving them a good appearance. The figures were showed from 1 to 4.

***In-vitro* drug release studies:**
Dissolution studies of all the formulations were carried out using dissolution apparatus USP type-I using 0.1 N HCl at P^H 1.2 and phosphate buffer at P^H 6.8 as dissolution medium. The results of the *in-vitro* dissolution studies data of all the formulations were shown in tables 4 and 5. The plots of Cumulative percentage drug release Vs Time were plotted. Graph 2 and 3 shows the comparison of cumulative percentage drug release for all the formulations. The formulation FEC1 contain chitosan in the ratio of 1:1 was showed better drug release (90.82%).

SUMMARY AND CONCLUSION
In this work an attempt was made to design a sustained release drug delivery system in the form of microspheres for *Eletriptan hydrobromide* using Sodium alginate and in combination with natural polymers such as Chitosan, guar gum and karaya gum as copolymers. The technique used for the preparation was ionic gelation method. Increase in the polymer concentration led to slight decrease in Percentage yield and increase in Particle size. Micromeritic studies revealed that the mean particle size of the prepared microspheres was in the size range of 487.0-802.5µm and are suitable for microspheres for oral administration.
SEM analysis of the microspheres revealed that all the prepared microspheres were discrete, spherical in shape and had satisfactory surface morphology. The *in-vitro* release study of all formulations showed a retarded release with increase in percentage of polymers. From the study it was concluded that formulation FEC1 were found to be best carriers for oral drug delivery of *Eletriptan hydrobromide* microspheres.

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Table 1: Composition of various formulations of Eletriptan hydrobromide microspheres

Ingredients		Formulation code	Drug: Sodium Alginate: Polymer ratio
Drug	**Polymers**		
Eletriptan hydrobromide	Sodium alginate	FES1	01:01:00
		FES2	01:02:00
		FES3	01:03:00
	Guar gum	FEG1	01:01:01
		FEG2	01:01:02
		FEG3	01:01:03
	Karaya gum	FEK1	01:01:01
		FEK2	01:01:02
		FEK3	01:01:03
	Chitosan	FEC1	01:01:01
		FEC2	01:01:02
		FEC3	01:01:03

Graph 1: λ_{max} of EletriptanHydrobromide

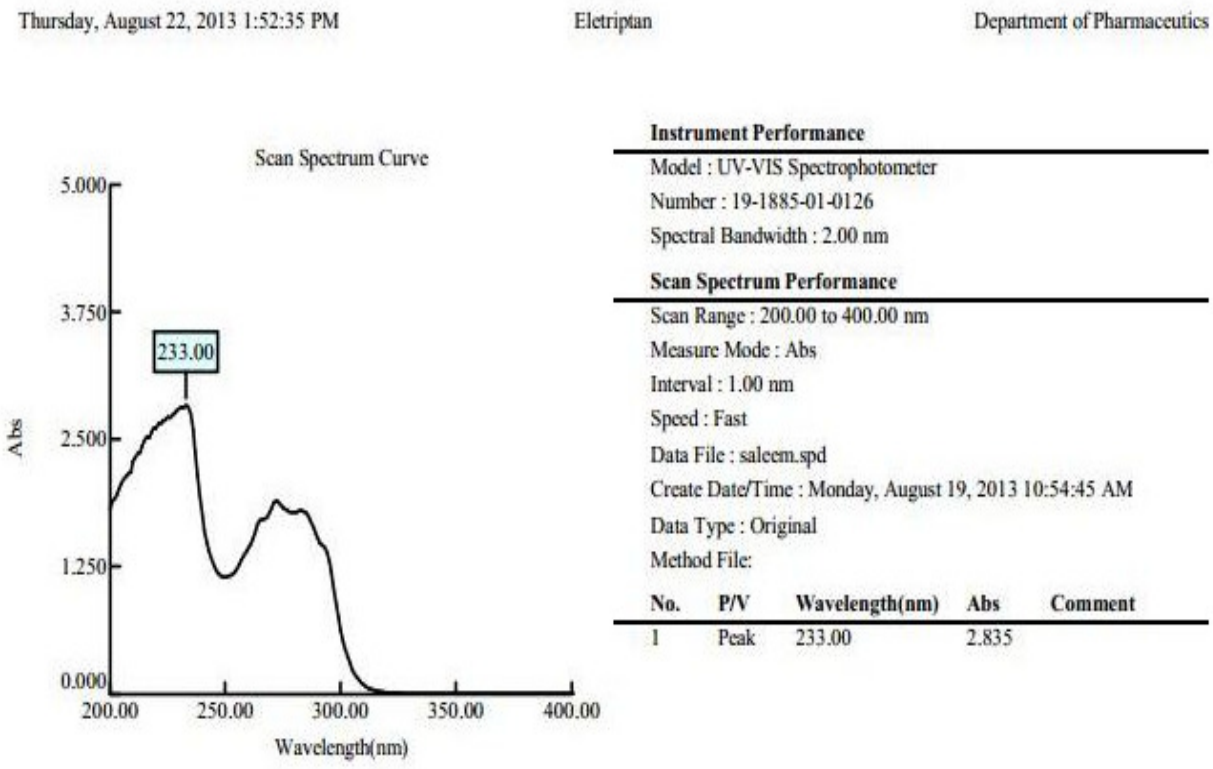


Table 2 : Percentage yield of Eletriptan microspheres using Sodium alginate with Karayagum, Chitosan, Guargum as copolymer.

Formulation Code	Percentage Yield
FES1	87.12
FES2	85.56
FES3	82.2
FEK1	86.02
FEK2	84.23
FEK3	80.62
FEC1	86.46
FEC2	83.54
FEC3	81.75
FEG1	84.56
FEG2	82.32
FEG3	80.46

Table 3 : Particle size data of optimized formulation FEC1

Particle size range in µm	Midpoint size range (d)	Frequency (n)	Nd	Average particle size
400-450	425	72	30600	487.0µm
450-500	475	57	27075	
500-550	525	44	23100	
550-600	575	13	7475	
600-650	625	8	5000	
650-700	675	4	2700	
700-750	725	2	1450	
		∑n =200	**∑nd=97400**	

Figure 1: SEM of formulation FES1

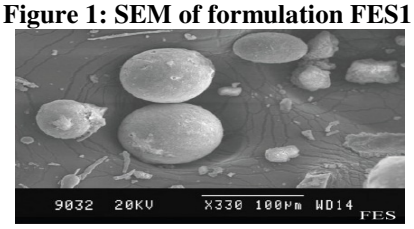


Figure 2: SEM of formulation FEK1

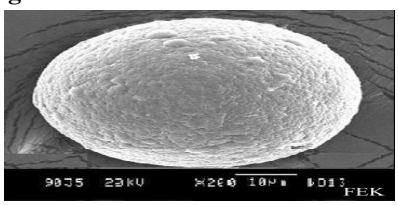


Figure 3: SEM of formulation FEC1

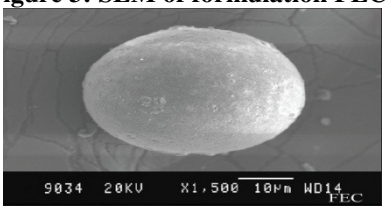


Figure 4: SEM of formulation FEG1

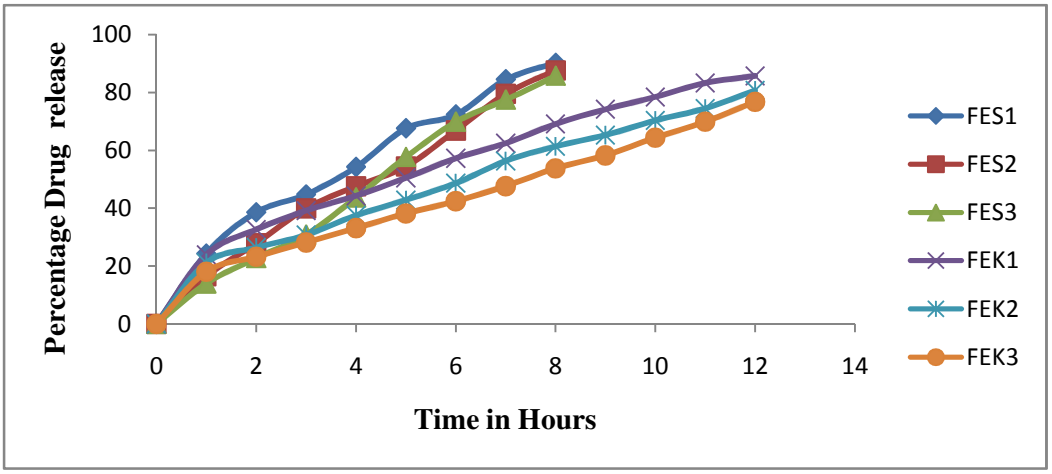
Table 4: *Invitro* drug release data of Eletriptan microspheres using Sodium alginate polymer.

Time(hour)	%Cumulative drug release					
	FES1	**FES2**	**FES3**	**FEK1**	**FEK2**	**FEK3**
0	0	0	0	0	0	0
1	24.32	16.42	13.96	23.89	21.14	18.02
2	38.57	27.78	22.74	32.64	26.38	23.18
3	44.72	39.89	30.84	39.16	30.74	28.1
4	54.23	47.53	43.69	44.26	37.52	33.1
5	67.56	54.35	57.67	50.48	42.83	38.12
6	72.32	66.82	69.85	57.23	48.64	42.38
7	84.48	79.47	77.47	62.42	56.32	47.56
8	90.16	87.52	85.74	69.08	61.36	53.74
9	---	---	---	74.16	65.28	58.18
10	---	---	---	78.42	70.33	64.32
11	---	---	---	83.25	74.48	69.83
12	---	---	---	85.68	80.74	76.68

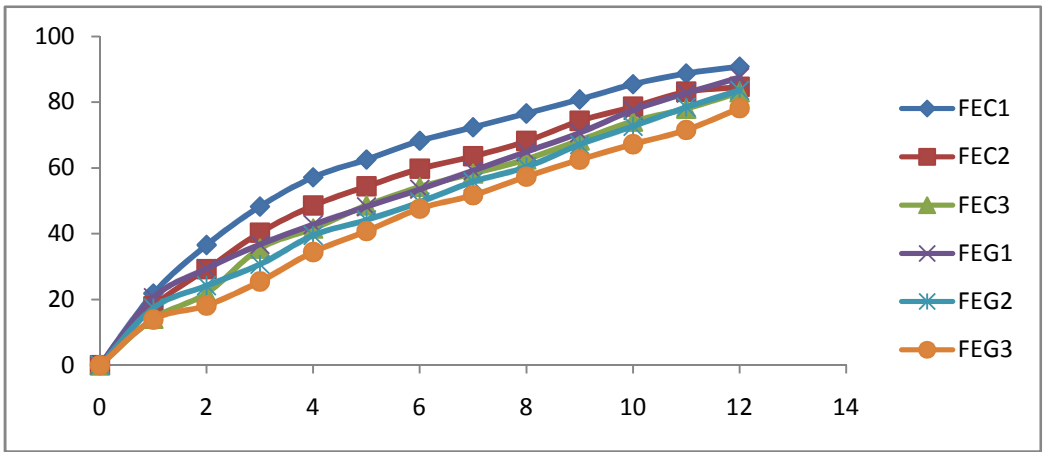
Table 5: *In-vitro* drug release data of Eletriptan microsphere using Chitosan and guar gum

Time in (Hours)	% Cumulative drug release					
	FEC1	FEC2	FEC3	FEG1	FEG2	FEG3
0	0	0	0	0	0	0
1	21.76±0.11	17.86±0.38	14.08±0.09	20.54±0.25	17.34±0.21	13.86±0.17
2	36.54±0.23	29.17±0.26	21.87±0.09	29.32±0.04	24.17±0.15	18.12±0.16
3	48.23±0.25	40.29±0.11	35.45±0.13	36.68±0.03	30.62±0.19	25.42±0.12
4	57.16±0.29	48.52±0.20	41.54±0.27	42.72±0.10	39.43±0.08	34.38±0.26
5	62.57±0.13	54.36±0.22	48.56±0.35	48.16±0.07	44.14±0.14	40.76±0.23
6	68.24±0.32	59.74±0.29	54.18±0.19	53.48±0.10	49.56±0.23	47.59±0.15
7	72.36±0.14	63.52±0.33	58.26±0.20	59.12±0.08	55.74±0.14	51.68±0.11
8	76.58±0.21	68.16±0.27	62.57±0.32	64.86±0.14	60.26±0.23	57.32±0.23
9	80.84±0.15	74.28±0.29	68.36±0.19	70.62±0.11	67.06±0.23	62.49±0.17
10	85.46±0.17	78.62±0.26	74.07±0.14	77.48±0.19	72.63±0.14	67.18±0.23
11	88.72±018	83.14±0.25	77.97±0.20	82.67±0.07	78.42±0.29	71.54±0.25
12	90.82±0.26	84.62±0.30	82.98±0.26	87.45±0.26	83.56±0.09	78.12±0.20

Graph 2: Comparison of *in-vitro* drug release profile of Eletriptan microspheres using Chitosan as polymer and Karaya gum as copolymer



Graph 3: Comparison of *in-vitro* drug release profile of Eletriptan microspheres using chitosan and guar gum as copolymer.



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