

Received on 02 January 2015; received in revised form, 23 January 2015; accepted, 30 January 2015; published 01 February 2015

FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING MICROBEADS OF SUMATRIPTAN

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ABSTRACT: Sumatriptan is a potent and selective 5-hydroxytryptamine agonist. It is an effective agent in the treatment of acute migraine attack. Sumatriptan is rapidly but incompletely absorbed following oral administration and undergoes first-pass metabolism resulting in a low absolute bioavailability of 15%. The biological half-life of Sumatriptan is about 2.5 h. The aim was to develop gastro-retentive floating microbeads which improve the absolute bioavailability of Sumatriptan by avoiding the presystemic metabolism and thereby to reduce the dose frequency. Drug and polymer compatibility was studied by subjecting physical mixtures of drug and polymers to FTIR spectrophotometry, capability of floating in the gastric condition was evaluated. The beads were prepared by Ionotropic gelation method. By using Sodium alginate, hydroxyl propyl methylcellulose K4M and guar gum grade in 1:1, 1:2, 1:3 ratios. The beads were evaluated for percent drug entrapment efficiency, and *in-vitro* drug release. The *in-vitro* drug release study of the beads was carried out in simulated gastric media by USP dissolution method. Beads formulated employing Sodium alginate alone could not sustain the drug release, whereas beads formulated with mixture of sodium alginate and copolymers demonstrated sustained release of Sumatriptan for 12 h.

Keywords: Sumatriptan, Gastric residence time, Floating drug delivery systems

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INTRODUCTION: Oral delivery of drugs is the most preferable route of drug administration due to ease of patient compliance and flexibility in formulation¹. Several difficulties are found while designing controlled release systems, especially to obtain better absorption and enhanced bioavailability.

Floating drug delivery system (FDDS) or hydro dynamically balanced system (HBS) are among the several approaches of controlled drug delivery systems that have been developed to increase the gastric retention time of dosage^{2,3}.

Gastro retentive floating drug delivery system (GRFDDS) has a bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time⁴. Both single and multiple unit system have been developed. Both have several advantages over immediate release dosage form, including the minimization of fluctuations in drug concentration in plasma and at

	<p>QUICK RESPONSE CODE</p>
	<p>DOI: 10.13040/IJPSR.0975-8232.IJLSR.1(2).41-47</p> <p>The article can be accessed online on www.ijlsr.com</p>
<p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJLSR.1(2).41-47</p>	

the site of action over prolonged periods⁵. But among them, the multiple unit dosage forms may be better suited because they are claimed to reduce the inter-subject variability in absorption and lower the probability of dose dumping⁶. Such a dosage form can be distributed widely throughout the gastrointestinal tract, affording the possibility of a longer lasting and more reliable release of the drug from the dosage form. Sumatriptan is a potent and selective 5-hydroxytryptamine agonist chemically it is 3-[2-(dimethylamino) ethyl]-N-methyl-1H-indol-5-methanesulfonamide butane-1,4-dioate it is an effective agent in the treatment of acute migraine attack. It provides rapid symptoms relief up to 85-90% of migraine patient within two hours of treatment. It is white amorphous powder, freely soluble in water and is rapidly but incompletely absorbed following oral administration and undergoes first-pass metabolism resulting in a low absolute bioavailability of 15%. The biological half-life of Sumatriptan is about 2.5 h^{9,10}.

In the present study, an attempt has been made to develop and characterize floating microbeads of Sumatriptan by inotropic gelation method. On oral administration, it prolongs the gastric residence time, increases the drug bioavailability and sustained the action for a longer period.

MATERIALS AND METHODS:

Materials: Sumatriptan was obtained from Dr. Reddy's Lab, Hyderabad, India. Sodium alginate was purchased from Krishna Pectins Pvt. Ltd., India, guar gum was obtained from S.D. Fine Chem. Ltd, India, HPMCK4M was obtained from Colorcon Industries, India Calcium Chloride was

taken from B. F. Goodrich Chemicals Co., USA, water was from Universal Medicare Pvt. Ltd., Mumbai.

Methods:

A) FTIR Spectroscopy: The drug - excipients interaction was studied using Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA). An IR spectrum for the drug was recorded in an FTIR for pure drug and physical mixture of pure drug and polymers with potassium bromide (KBr) pellets. The spectra were scanned over the 3600 to 400 cm⁻¹ range.

B) Formulation Design:

Preparation of Microbeads: Iontropic Gelation Technique: Microbeads of Sumatriptan was prepared by ionotropic gelation technique. In the present work, three sets microbeads were prepared by using (1:1, 1:2, 1:3) sodium alginate alone in different concentrations and with different concentrations of polymers like HPMCK4m, guar gum and Calcium chloride as the counter-ion. The detailed composition of the various formulations prepared is, as mentioned in **Table 1**.

Preparation of Sodium Alginate Microbeads:

The beads were prepared in three batches. In the first set, three formulations of microbeads were prepared (F1, F2, F3). Solutions of sodium alginate in different ratios were used. In the second set, another three formulations were developed with HPMC K4M and Sodium alginate in different ratios (F4, F5, F6). In the third set, Guar gum was used along with the sodium alginate in different ratios (F7, F8, F9).

TABLE 1: FORMULATION DESIGN OF MICROBEADS

S. no	Ingredients	Formulations								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Sumatriptan	1	1	1	1	1	1	1	1	1
2	Sodium alginate	1	2	3	0.5	1	1.5	0.5	1	1.5
3	HPMC K4 M	-	-	-	0.5	1	1.5	-	-	-
4	Guar Gum	-	-	-	-	-	-	0.5	1	1.5

A polymer solution was prepared in 100 ml of deionized water. In 50 ml of the polymer solution, weighed quantity (250 mg) of Sumatriptan was dispersed uniformly in all three solutions separately. Bubble free dispersion was dropped through a syringe into a 100 ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 min, the gelled beads were separated

by filtration, washed with distilled water, air-dried and finally dried at 600 for 6 h in the oven.

C) Evaluation of Physicochemical Parameters of Floating Beads:

Determination of Bead Diameter: The diameter of a sample of gel beads (25 beads) of each formulation was determined using a dial thickness

meter. Measurement for each sample was repeated ten times. Mean diameter and standard deviations were recorded.

Surface Morphology (SEM):¹¹ Scanning Electron Microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of the fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to the simplicity of sample preparation and ease of operation. SEM studies were carried out by using a JEOL JSM T-330A scanning microscope (Japan). The samples were gold coated before the scanning. For examination of the internal structure of the beads, they were cut in half with a steel blade.

Percentage Yield:¹¹ Percentage practical yield of Sumatriptan beads was calculated to know about percentage yield or efficiency of any method. Thus it helps in the selection of the appropriate method of production. The practical yield was calculated as the weight of Sumatriptan beads recovered from each batch about the sum of starting material. The percentage yield of Sumatriptan beads prepared was determined by using the formula.

$$\text{Percentage Yield} = \text{Practical yield} / \text{Theoretical yield} \times 100$$

Drug Entrapment Efficiency:¹¹ 200 mg beads were crushed using a porcelain mortar and a pestle and dispersed in a suitable solvent (0.1 N HCl). The dispersion was sonicated for 15 min and left overnight for 24 h; then the dispersion was filtered. A 1 ml sample was taken and diluted with a suitable solvent (0.1 N HCl) and analyzed using a UV-visible spectrophotometer at λ_{max} of 230 nm. The percentage of drug entrapment efficiency (%EE) of each bead formulation was calculated using the following equation:

$$\text{EE \%} = \text{Actual drug content} / \text{Theoretical drug content} \times 100$$

Buoyancy Behavior:^{12, 13} The time between the introduction of the FDDS into the medium and its buoyancy to the upper one-third of the dissolution vessel (floating lag time) and the floating ability was determined using USP dissolution tester apparatus II (Paddle method). Fifty beads were put in the vessel, and the paddles were rotated at 50 rpm in 900 ml 0.1 N HCl pH 1.2, maintained at

37 ± 0.5 °C for 12 h. The floating ability of the beads was measured by visual observation. The preparation was considered to have buoyancy, only when all beads floated on the test solution immediately.

In-vitro Drug Release Studies:¹³ *In-vitro* release characteristics of Sumatriptan floating gel beads (n=3) were evaluated employing USP XIV dissolution testing apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl buffer as dissolution medium maintained at 37 ± 0.5 °C. The contents were stirred at 50 rpm. A 5 ml aliquot of the solution was withdrawn at predetermined time intervals for 12 h, and fresh 5 ml dissolution media was replaced to maintain sink condition. The sample aliquots were analyzed spectrophotometrically at a wavelength of 230 nm (UV spectrophotometer, 1601, Shimadzu, Japan).

Stability Studies: Stability studies were carried out according to ICH guidelines by storing the Formulation F4. Both intermediate and the accelerated stability studies were done simultaneously at $25^\circ\text{C} \pm 2^\circ\text{C} / 60\% \pm 5\% \text{ RH}$, $30^\circ\text{C} \pm 2^\circ\text{C} / 75\% \pm 5\% \text{ RH}$ $40^\circ\text{C} \pm 2^\circ\text{C} / 75\% \pm 5\%$ for six months in a programmable environmental test chamber (CHM-10S, Remi Instruments Ltd., Mumbai, India). The samples were withdrawn at 30 and 60 days and analyzed for the drug content, floating behavior, and in vitro drug release.

RESULTS AND DISCUSSION:

FTIR Spectroscopy: Compatibility studies were performed using FTIR spectrophotometer. The FTIR spectrum of pure drug and physical mixture of drug and polymers were studied. The characteristic absorption peaks were observed at 1076.57 cm^{-1} , 1293.98 cm^{-1} , 1556 cm^{-1} , 1703 cm^{-1} , 2934 cm^{-1} for the pure Sumatriptan and absorption peaks were observed at 1080 cm^{-1} , 1295 cm^{-1} , 1558 cm^{-1} , 1716 cm^{-1} , 2850 cm^{-1} for drug and polymer mixture show that how they were in official limits ($\pm 100 \text{ cm}^{-1}$) the drug is compatible with excipients **Fig. 1 & Fig. 2.**

Surface Morphology (SEM): SEM analysis of the f4 formulation showed that the external morphology was smooth as in the **Fig. 3** and **4** shows the internal structure was solid without pores.

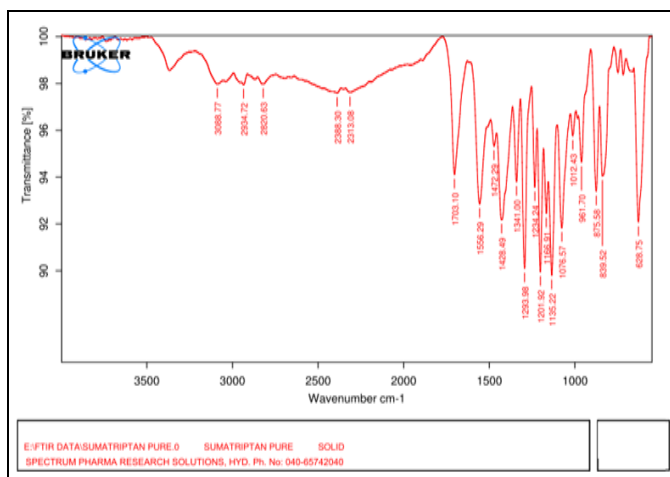


FIG. 1: FT-IR SPECTRA OF PURE DRUG (SUMATRIPTAN)

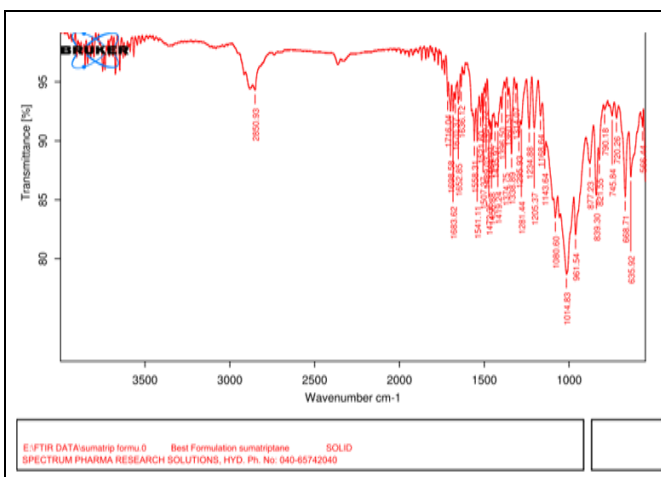


FIG. 2: FT-IR SPECTRA OF PHYSICAL MIXTURE OF POLYMERS AND DRUG

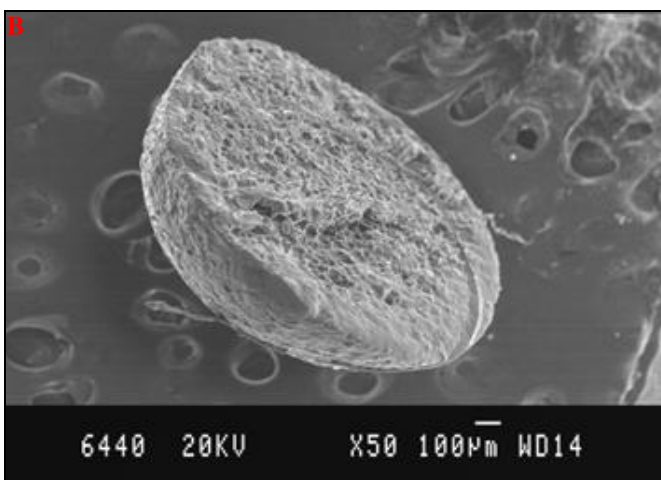
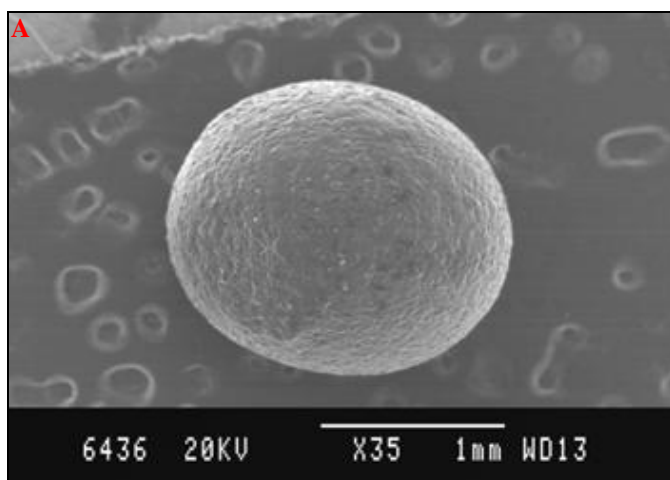


FIG. 3: SCANNING ELECTRON MICROSCOPY OF (A) EXTERNAL AND (B) INTERNAL STRUCTURE OF BLANK FLOATING BEADS (F4)

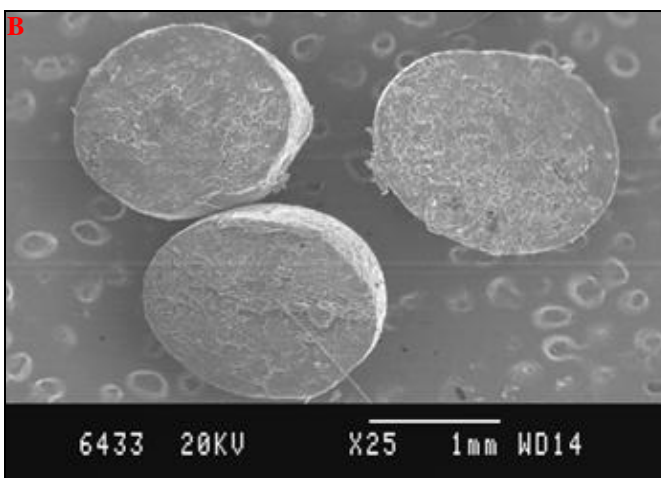
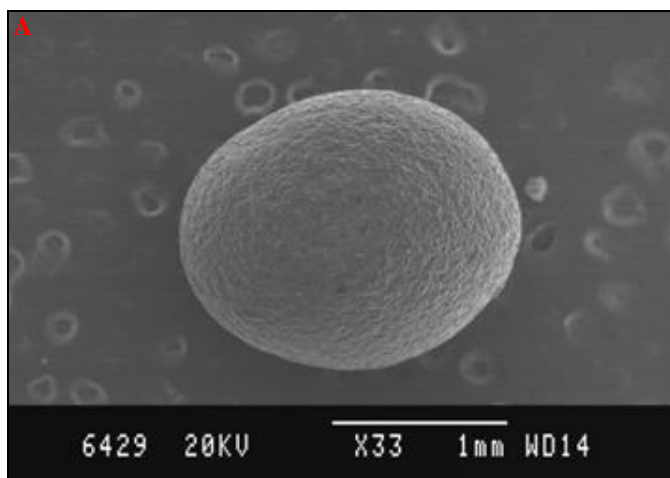


FIG. 4: SCANNING ELECTRON MICROSCOPY OF (A) EXTERNAL AND (B) INTERNAL STRUCTURE OF DRUG LOADED FLOATING BEADS (F4)

Determination of Beads Diameter: The prepared beads were almost spherical and translucent. The mean surface diameter of 09 formulations was between 1.700 ± 0.020 mm (SD) and 1.793 ± 0.015

(SD). It was found that incorporation of copolymers such as HPMC K4 and Guar gum to the alginate bead formulations result in further increase of the bead diameter as in case of

formulations F1 to F9 in each batch **Table 2**. As the process parameters were kept constant, the

added materials were responsible for the change in the size of the beads.

TABLE 2: CHARACTERIZATION OF SUMATRIPTAN FLOATING BEADS

S. No.	Formulation Code	Mean Diameter \pm SD (mm)	Percentage Yield	Entrapment Efficiency (%)	Floating time (h)
1	F1	1.700 \pm 0.020	84.76	71.51	>12
2	F2	1.740 \pm 0.026	89.74	72.38	>12
3	F3	1.793 \pm 0.015	95.45	75.95	>12
4	F4	1.720 \pm 0.030	86.24	86.97	>12
5	F5	1.723 \pm 0.021	89.87	88.38	>12
6	F6	1.727 \pm 0.015	96.63	90.83	>12
7	F7	1.707 \pm 0.015	85.56	75.78	>12
8	F8	1.733 \pm 0.021	93.34	76.90	>12
9	F9	1.780 \pm 0.020	89.56	79.78	>12

Percentage Yield: The percentage yield for Sumatriptan beads were found to be 84.76%, 89.74%, 95.45%, 86.24%, 89.87%, 96.63%, 85.56%, 93.4%, 89.56% for formulations F1, F2, F3, F4, F5, F6, F7, F8, F9 respectively as shown in the **Table 2**. In each batch as the concentration of polymers was the increased yield was increased.

Entrapment Efficiency: Entrapment efficiency increased with an increase in the polymer concentration in each batch of the formulation. The results obtained are given in **Table 2**. A maximum of 90.83% drug entrapment efficiency was obtained in Sumatriptan beads which were prepared using sodium alginate and HPMC K4 M (F6) and minimum entrapment was 71.51% in F1 prepared using sodium alginate, alone from which it is inferred that a combination of polymers would entrap more than a single polymer and also by increasing the polymer concentration, the encapsulation efficiency can be increased.

Buoyancy Test (Floating Test): The beads were for finding to be floating for 12 h, and they remained buoyant throughout the dissolution studies.

In-vitro Release Profile: *In-vitro* drug release study of Sumatriptan floating beads was carried in 0.1N HCl (pH 1.2), for a period of 12h. In the 0.1N HCl, the beads exhibited a biphasic release profile as an initial rapid drug release phase (burst effect) was followed by a sustained, gradually increasing drug release phase after 1h extending up to 12h. Formulation F4 contained sodium alginate and HPMCK4M, could sustain the Sumatriptan release up to 12h. It released the complete drug at the end of 12h. Whereas formulations contained sodium

alginate alone F1, F2 and F3 released 98.21%, 99.21% and 101.2% of drug respectively at the end of bellow 10 h.

The formulations contained sodium alginate and HPMC K4 M; F4, F5, and F6 released 99.84%, 92.63% and 91.33% of the drug at the end of 12h respectively. The formulations contained sodium alginate and Guar gum; F7, F8, and F9 released 80.85%, 72.93% and 64.5% of the drug at the end of 12h, respectively **Fig. 5**. F4 has shown good release pattern and followed zero order kinetics and Higuchi mechanism of release **Fig. 6 & Fig. 7**.

Stability Studies: Given the potential utility of the formulation, stability studies were carried out on formulation F4 for six months according to ICH guidelines **Table 4**. At the end of each interval, the formulations were subjected to drug assay, floating behavior and *in-vitro* release studies. Both the intermediate and accelerated stability studies were conducted simultaneously.

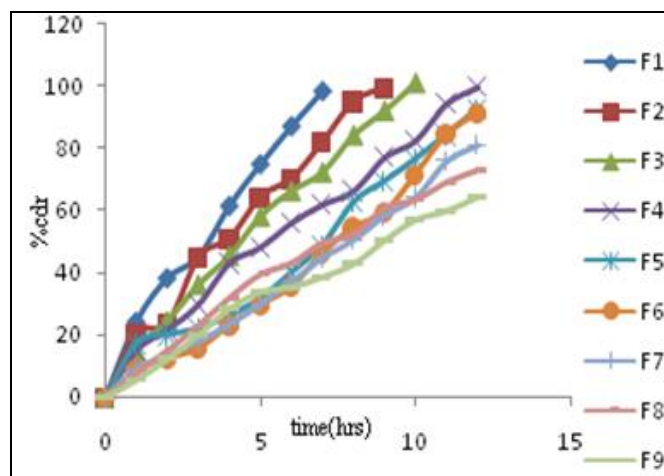


FIG. 5: IN-VITRO RELEASE OF FORMULATIONS F1-F9

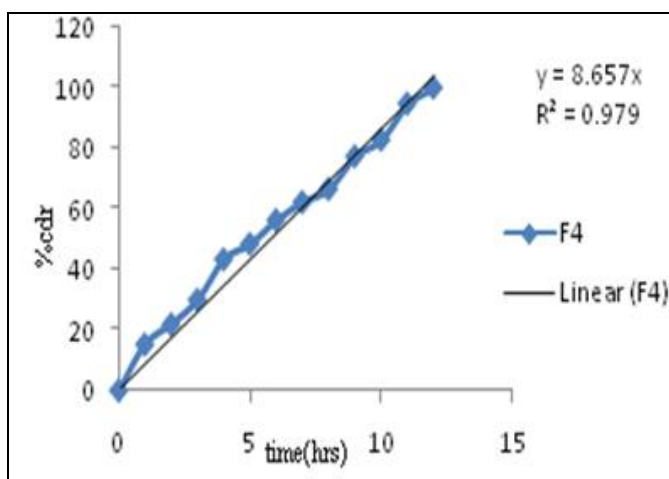


FIG. 6: ZERO ORDER KINETICS: F4

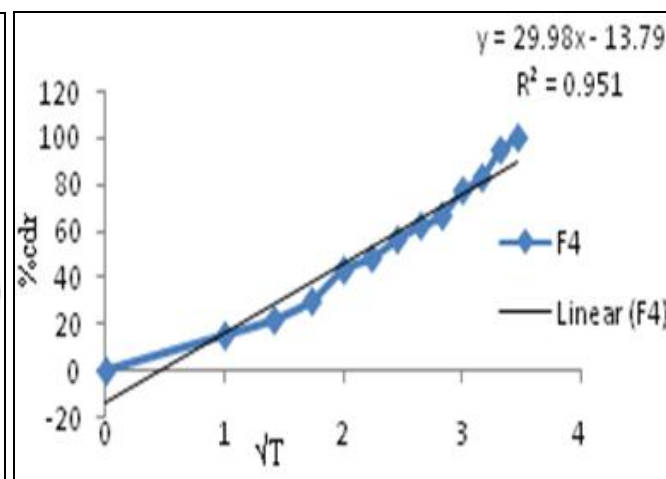


FIG. 7: HIGUCHI ORDER KINETICS: F4

TABLE 3: KINETICS OF RELEASE PATTERN OF F4

S. No.	Formulation code	r ² value for zero order equation	r ² value for first order equation	r ² for Higuchi equation	n value for Peppas equation
1	F4	0.979	0.876	0.951	0.7

TABLE 4: CONDITIONS FOR STABILITY STUDIES

S. no	Study	Storage conditions	Minimum time for recovery of data at submission
1	Intermediate	25 °C ±2°C /60% ± 5% RH 30 °C ±2°C /75% ± 5% RH	6 months
2	Accelerated	40 °C ±2 °C /75% ± 5% RH	6 months

TABLE 5: STABILITY STUDY OF FORMULATION F4

Time	Drug content ± SD (mg)	Floating behaviour		Drug release at the end of 12 h
		FLT (min)	Floating duration (h)	
Zero month	2.908 ± 0.057	0	24	99.55 ± 1.61
Third Month	2.923 ± 0.096	0	24	98.91 ± 1.78
Sixth Month	2.911 ± 0.079	0	24	97.49 ± 2.05

After subjecting the samples for different temperature and humidity conditions, there was not much difference in the drug content and the floating properties at the various time intervals. The *in-vitro* drug release profiles were super imposable, which confirms the stability of the product **Table 5**.

CONCLUSION: The inotropic gelation method was successfully utilised for developing microbeads of Sumatriptan. Drug and polymers were subjected to the compatibility study using FTIR Spectrophometry, which suggested that there is no interaction between the drug and polymer. All the beads showed satisfactory floating characteristics. The *in-vitro* drug release study shown that Sodium alginate alone could not sustain the drug release for sufficient period whereas incorporation of rate controlling polymers such as HPMC K4, and Guar gum as copolymers can effectively sustain the drug release from the beads. The results showed that

beads formulated with a mixture of Sodium alginate and HPMC K4 M (F4) shown the highest drug release compared to other formulations. So the formulation F4 was selected for stability studies and surface morphological studies by scanning electron microscopy. To analyze the mechanism of drug release from the beads, the *in-vitro* release data was fitted into various release models. It was observed that the release of the drug followed Zero Order kinetics and Higuchi model mechanism of drug release. The selected formulations did not show much change in drug content, floatability or *in-vitro* drug release profile after storage as per the ICH guidelines during stability study for six months.

ACKNOWLEDGEMENT: A sincere thanks to K Mahalakshmi and Dr .V. Uma Maheshwara Rao for their guidance and support in completion of this research work and also to CMR College of Pharmacy for providing the infrastructure.

CONFLICT OF INTEREST: Nil**REFERENCES:**

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How to cite this article:

Kumar BA, Mahalakshmi K and Rao VUM: Formulation and evaluation of gastro retentive floating microbeads of Sumatriptan. Int J Life Sci & Rev 2015; 1(2) 41-47. doi: 10.13040/IJPSR.0975-8232.IJLSR.1(2).41-47.

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