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FABRICATION AND CHARACTERIZATION OF OIL ENTRAPPED FLOATING ALGINATE BEADS OF FEXOFENADINE HYDROCHLORIDE

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ABSTRACT

Fexofenadine hydrochloride (FH) is a second-generation non- sedating histamine H_1 receptor antagonist extensively used in seasonal allergic rhinitis. The objective of the present investigation was to formulate and evaluate floating alginate beads of FH for prolonged buoyancy with sustained delivery of the drug in to the gastric content. Developed oil entrapped floating alginate beads of FH using sodium alginate by emulsion gelation technique and studied on formulation factors for improved drug entrapment efficiency, bioavailability and *In-vitro* drug release. Different concentration of sodium alginate as a polymer (2%,4%), oils(mineral oil, olive oil in 10%, 15%, 20%) act as a barrier and prolongs the effect of drug in the upper GI tract for prolong period of time and 5% cross linking agent of calcium chloride was used. The prepared beads were evaluated for physical characterization like diameter measurement, surface morphology, *In-vitro* buoyancy, entrapment efficiency, swelling index study, *In-vitro* drug release studies and kinetics study. The prepared beads were found to be spherical, free flowing and remain buoyant for 12 hours with short floating lag time. Percentage of drug release in the optimized formulation of F5 for mineral oil and F10 for olive oil was found to be in the range of 98.03% to 96.7% and formulation F10 exhibited 85.8% of drug entrapment efficiency. Swelling properties of all formulation increased as the concentration of polymer increased. *In-vitro* release profile of optimized formulation followed Higuchi with non-fickian diffusion law.

INTRODUCTION

Oral dosage form capable of having prolonged retention in the stomach to extend drug delivery to a longer period of time has been receiving much attention currently. Gastric residence time one of the most important factors affecting the bioavailability of the drug in pharmaceutical dosage forms [1]. Drug bioavailability can be reasonably increased by prolonging GRT through gastro retentive floating dosage form, which has to be retained in the absorption zone (upper GIT and stomach) for a prolonged period of time, during which they release the drug on controlled principle [2,3]. Beads are distinct spherical microcapsules that work as the solid substrate on which the drug is coated or encapsulated in the core of beads. Beads can provide controlled release properties, followed by bioavailability of drug can be

enhanced. Floating alginate beads achieve the aim of development of gastro retentive drug delivery system is not only to sustain the drug release but also to prolong gastric residence of the dosage forms until all the drug is completely released at desired period [4]. These multiparticulate drug delivery systems are the most accepted and extensively used dosage form as there are numerous advantages over single unit dosage forms which provide better availability of products with therapeutic possibilities and substantial benefits for patients [5, 6].Fexodenadine HCl is a selective, non- sedative first-generation histamine (H_1) receptor antagonist, for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in children. It does not readily cross the blood- brain barrier and is therefore less likely to cause drowsiness in comparison with other antihistamines [7,8] . Despite of these promising biological effect of FH, a major drawback is slightly soluble nature in water, which leads to low bioavailability and also limits its absorption in the upper part of small intestine[9]. To overcome the above problems the present investigation is to developing a floating alginate beads to be remained buoyant in the stomach, thereby increasing the gastric residence time, stability and enhancing the bioavailability of drug through sustained release.

MATERIALS AND METHODS: Fexofenadine Hydrochloride was obtained from Aurobindo Pharmaceutical, Hyderabad. Sodium alginate, Liquid paraffine were procured from Nice chemicals Pvt.Ltd., India. Olive oil was obtained from Qualigens Fine Chemicals, India. Calcium chloride was obtained from Central Drug House (P)Ltd., New delhi, India. All other chemicals were used of analytical grade.

Development of Fexofenadine Hydrochloride Floating Alginate Beads: Emulsion Gelation Method was selected for the preparation oil entrapped floating alginate beads .The formulation composition of different batch was shown in Table 1. In this method, different ratio of (2%, 4%) sodium alginate solution was prepared with water. Oils (Mineral oil, Olive oil in different concentration 10%, 15% and 20% v/v), were then added to the polymer solution to make homogenized mixtures at 10,000 rpm using a homogenizer for 10 min. FH was then dispersed in the formed emulsion. The bubble-free emulsion was extruded; using a 23G syringe needle into 250 ml gently agitated 5% of solution of calcium chloride at room temperature. The emulsion gel beads were allowed to stand in the solution for 20 min before being separated and washed with distilled water. The beads were air dried at room temperature and stored in a air tight container[10].

Evaluation Parameters of Fexofenadine Hydrochloride floating alginate beads : The prepared beads were evaluated by measurement of bead size, drug entrapment efficiency, morphological study, *in-vitro* buoyancy (floating lag time, total floating time) *in-vitro* drug release studies and drug release kinetic data analysis.

Measurement of bead size: The diameter of the beads were determined by screw gauge, 20 dried beads were randomly selected from each batch and the mean diameter was calculated [11].

Determination of Percentage Drug Entrapment Efficiency (% DEE): The amount of drug entrapped was estimated by crushing the 50 mg of floating beads in mortar pestle and extracting it with methanol then the volume was made up to required quantity using 0.1N HCl (pH1.2). This solution was shaken with the help of rotary flask shaking machine for 5 hrs.and then kept for 24hrs. Then the solution was filtered with a help of whatman filter paper followed by dilutions were made and the absorbance was measured spectrophotometricaly at 220nm. The amount of drug entrapped in the floating beads was calculated by using the formula [12,13].

$$\% \text{ DEE} = \frac{\text{Actual drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Morphological Analysis: The surface characteristics and internal texture of the Fexofenadine HCL loaded floating alginate

beads were studied by Scanning Electron Microscope (SEM, JEOL, JSM-6100, Japan). The beads were fixed on a screw shaped stubs sample holder with double sided carbon adhesive tape. The samples were coated with gold palladium alloy under an argon atmosphere under vacuum condition by using ion sputter chamber (JFC-1100) and the floating beads were viewed at an accelerating voltage of 15 Kv at different magnifications [14].

***In-vitro* buoyancy:** The *in-vitro* buoyancy was characterized by floating lag time and total floating time. The test was performed using a USP dissolution apparatus type II (paddle type). The drug loaded beads (fifty numbers of beads) were placed in the dissolution vessel containing 900ml of acid buffer (pH1.2) maintained at 37 ± 0.5ºC for 12 h at 50 rpm. The floating ability of the beads was measured by visual observation. The time between the introduction of the beads into the medium and its rise to upper one third of the dissolution vessel or medium as a floating lag time and the duration for which the formulation constantly floated on the dissolution medium was noted as total floating time [16].

***In -vitro* drug release studies:** The drug release was studied using a USP dissolution apparatus type II at 50 rpm in 0.1N hydrochloric acid as dissolution medium (900 ml) maintained at 37±0.5°C. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at specified intervals and the samples were replaced with fresh dissolution medium to maintained sink condition.The samples were filtered through a 0.45 µm whatman membrane filter paper. Absorbance of these solutions was measured at 220 nm using UV-Visible spectrophotometer (Shimadzu 1700, Japan). All experiments were performed in triplicate for 12h. Cumulative percentage drug release was calculated [17].

FTIR spectral analysis: Spectra of pure drug, physical mixture and optimized formulation of beads were recorded using Fourier Transmission Infrared Spectroscopy (FTIR,Shimadzu RXI,Japan). The samples were thin film in KBr and compressed into disc/ pellet by application of pressure[18]. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 cm^{-1} and the resolution was 4 cm^{-1}.

Kinetic modeling of drug release: To analyze the mechanism for the release and release rate

kinetics of the dosage form, the data obtained were fitted to various kinetic equations such as zero order, first order, Higuchi matrix and Korsmeyer- Peppas equation. The regression co-efficient values were calculated and best fit model was selected [19, 20].

RESULTS AND DISCUSSION

Floating alginate beads: The mean particle diameter of the floating alginate beads was between 1.204 ± 0.03 – 2.1± 0.031 mm was presented in Table 2. As the oil and polymer concentration increases, the particle size also increases.

Compatibility studies (Fourier Transform Infrared Spectroscopic (FT-IR): Drug-polymer interaction was checked by comparing the IR spectra of the physical mixture (Fig.2**)** of drug with the excipients used with IR spectrum of pure drug (Fig.1)and optimized formulation (Fig**.** 3and 4). The results found that there was no possible interaction between drug and polymer.

Percentage drug entrapment efficiency: The entrapment of drug was increased as the concentration of the polymer was increased because of the increase in the viscosity of the solution. The encapsulation efficiency of the beads influence as polymer concentration increased due to the availability of excess polymer which ensured that the drug was optimally entrapped. The Entrapment efficiency of all formulations was found in the range of 41.16 ± 0.044% to 85.76 ± 0.021%. Among those highest loading efficacies was found in formulation**F10**(85.76 ± 0.021%) and its values are presented in Table 2.

Morphological Analysis: Morphological characteristics of prepared floating beads of optimized formulation **F5** was spherical shape with a uniform texture and smooth perforated surface. The less porous outer surface and a highly porous internal surface

supported controlled release of drug from the floating beads with good buoyancy. The porous nature and cavity formed would dictate the floating behavior of beads. The results was shown in Figure 5.

***In-vitro* buoyancy study:** The *in-vitro* buoyancy was characterized by floating lag time and total floating time. *In-vitro* buoyancy studies reveal that in spite of stirring the dissolution medium for 12 h, formulations were still continued to float without any apparent gelation, thus indicating that floating beads exhibit excellent buoyancies which can be attributed to the pores and cavities present in them which was confirmed by SEM. In general, with an increase in the amount of polymers, there is an increase in the buoyancy. The good buoyancy behavior of the floating beads may be attributed to the hollow nature of the floating beads. The floating time was significantly increased as the amount of oil was increased in each formulation. It was observed that floating ability increased with increasing average particle size of beads. The particle size was found to be larger for formulation **F6** in comparison with other formulations were tabulated in Table 2.

***In -vitro* drug release studies:** *In- vitro* drug release of floating beads of Fexofenadine HCL (for mineral oil and olive oil) was found to be from 66.40% to 98.03%. Among all formulation, F5 was found to be the best formulation for mineral oil as its release 98.03%, F10 was found to be the best formulation for olive oil as its release 96.71% in a sustained manner with constant fashion over extended period of time .The *in- vitro* drug release studies revealed that the formulation possessing 5% concentration of $CaCl_2$ and more concentration of sodium alginate made the swollen beads, which ensured floating and slow diffusion of drug from floating beads. Sodium alginate itself released the drug in a sustained manner. The comparative *in -vitro* release profile of the formulations were shown in Table 2and Figure 6-8.

Kinetic modeling of drug release: The results obtained from *in-vitro* drug release studies were applied to various kinetic models and equations to explain the release kinetics of drug from floating beads. In this study, *in vitro* drug release data were fitted to commonly employed release kinetic models, namely zero-order, first-order, Higuchi and Peppas models and Hixon - crowell model to analyze drug release mechanism from the polymeric system was shown in Table 3.The highest regression coefficient (r^2) value was obtained for Higuchi model (0.99) followed by first-order (0.987), Hixon-crowell model (0.983) zero-order (0.956), and Korsmeyer– Peppas (0.661) using Microsoft Excel software. The value of release exponent (n) was found to be greater than 0.5 that indicates non-Fickian diffusion (anomalous) based mechanism of drug release.

Table 1: Composition of Fexofenadine HCl Floating Alginate Beads

Formulation code	Amount of FH drug (mg)	Amount of Sodium alginate (%)	Amount of liquid paraffin (%)	Amount of olive oil (%)
F1	120	2	10	-
F2	120	2	15	-
F3	120	2	20	-
F4	120	4	10	-
F5	120	4	15	-
F6	120	4	20	-
F7	120	2	-	10
F8	120	2	-	15
F9	120	2	-	20
F10	120	4	-	10
F11	120	4	-	15
F12	120	4	-	20

Table 2: Evaluation of Fexofenadine HCl Floating Alginate Beads

Formulation code	Particle size (mm)	DEE (%)	Floating Lag Time	Floating Time (Hours)	Drug Release (%)
F1	1.2±0.04	44.57±0.03	41	12	92.0
F2	1.55±0.01	41.16±0.04	32	12	88.2
F3	1.69± 0.02	54.49 ± 0.02	10	12	78.6
F4	1.63±0.01	63.95± 0.05	12	12	82.4
F5	1.75±0.03	74.48 ± 0.01	6	12	98.03
F6	2.01±0.03	66.66 ± 0.02	4	12	77.3
F7	1.20± 0.03	57.03 ± 0.04	45	12	82.5
F8	1.56±0.02	59.39±0.06	15	12	87.3
F9	1.67±0.01	70.32 ± 0.03	10	12	79.6
F10	1.71±0.01	85.76 ± 0.02	3	12	96.7
F11	1.85± 0.34	48.6 ± 0.05	8	12	71.0
F12	2.1±0.03	65.83 ± 0.03	7	12	66.4

DEE : Drug entrapment efficiency

Table 3: Drug Release kinetics of Fexofenadine HCl Floating Alginate Beads

Formulation code	Zero order model	First order model	Higuchi model	Korsmeyer – Peppas model		Hixon- crowell model
	R^2	R^2	R^2	R^2	n	R^2
F1	0.915	0.973	0.981	0.641	1.196	0.981
F2	0.897	0.984	0.984	0.601	1.142	0.974
F3	0.924	0.919	0.97	0.581	1.046	0,938
F4	0.94	0.969	0.985	0.661	1.17	0.975
F5	0.911	0.831	0.989	0.603	1.158	0.938
F6	0.95	0.931	0.969	0.648	1.107	0.952
F7	0.956	0.972	0.985	0.623	1.113	0.983
F8	0.95	0.962	0.99	0.625	1.139	0.981
F9	0.913	0.933	0.981	0.601	1.085	0.943
F10	0.944	0.799	0.979	0.577	1.101	0.908
F11	0.955	0.987	0.977	0.629	1.084	0.983
F12	0.939	0.975	0.99	0.603	1.038	0.97

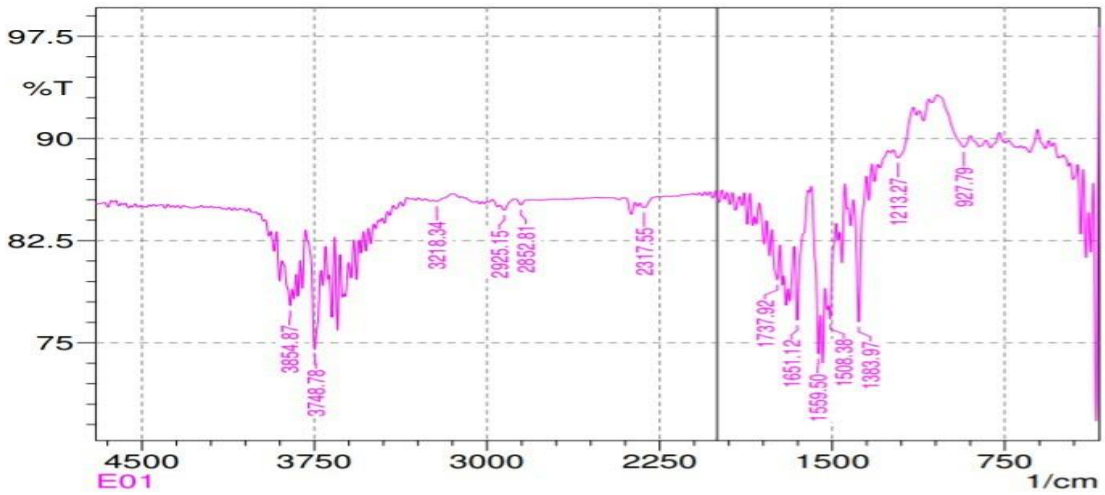

Figure 1: FT-IR Spectrum of pure drug Fexofenadine HCl

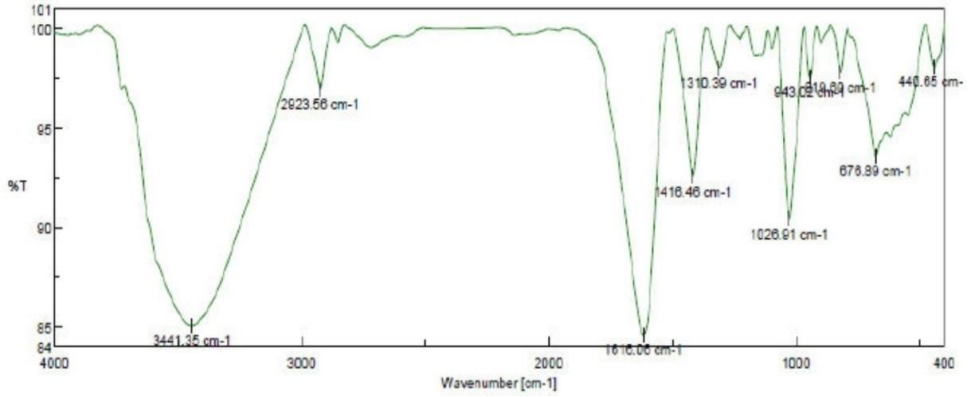

Figure 2: FT-IR Spectrum of physical mixture of Fexofenadine HCl and Sodium Alginate

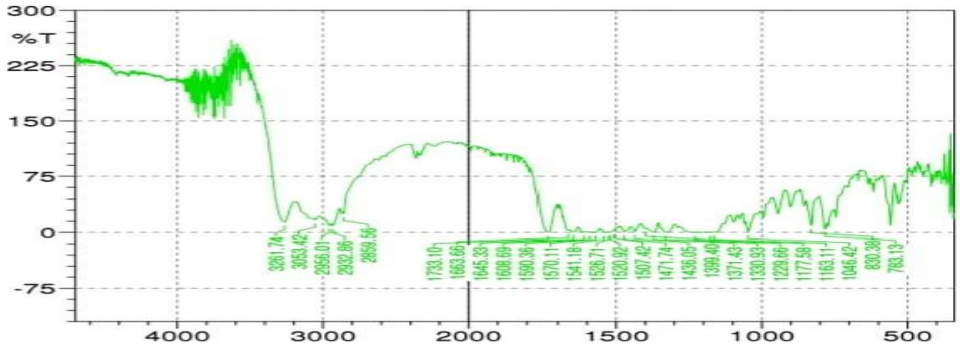

Figure 3: IR Spectrum of optimized formulation (F5)

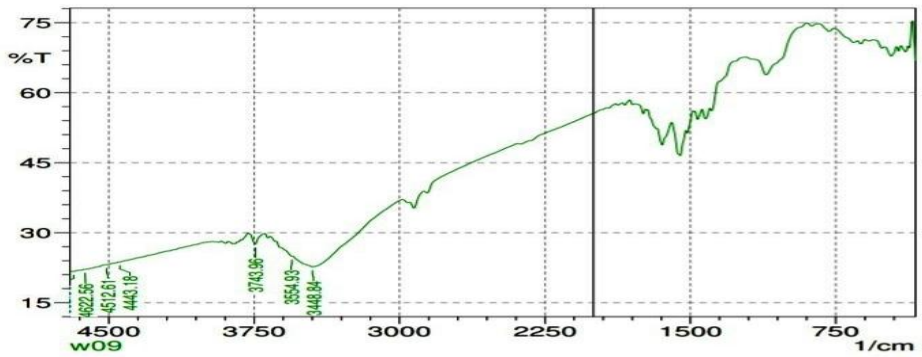

Figure 4:IR Spectrum of Optimised formulation (F10)

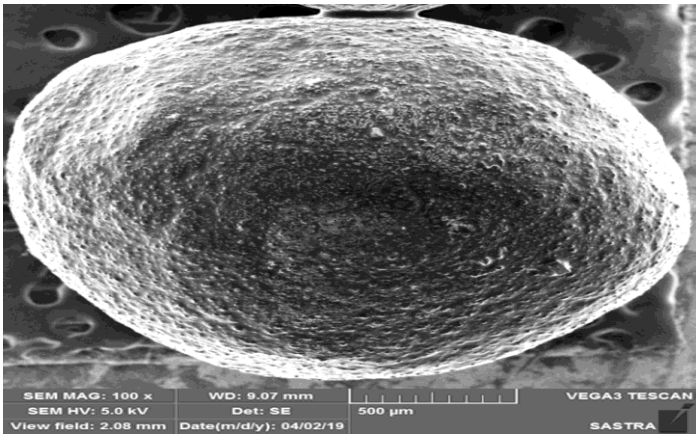

Figure 5: SEM Micrograph of optimised formulations(F5)

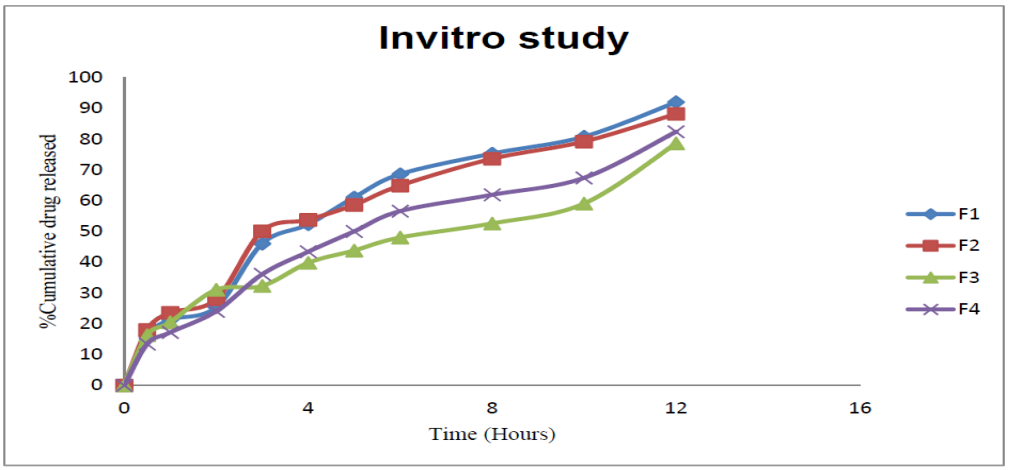

Figure 6: Cumulative % drug release of formulationF1-F4

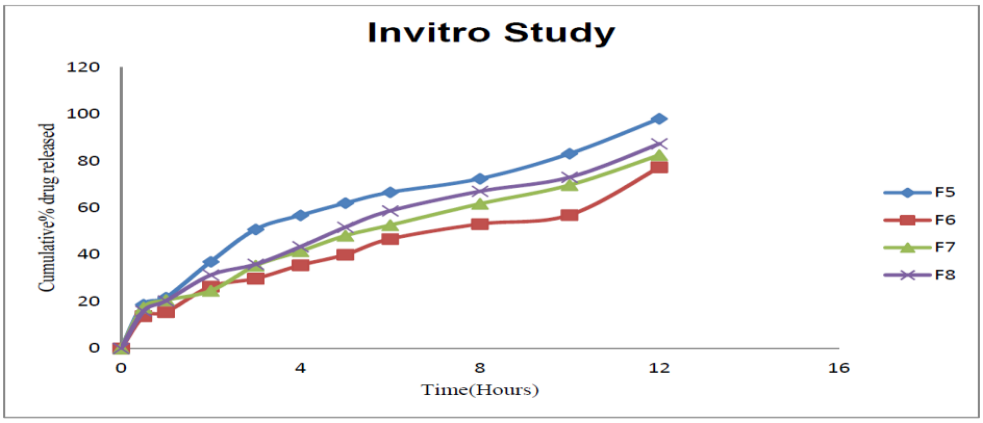

Figure 7: Cumulative % drug release of formulation F5-F8

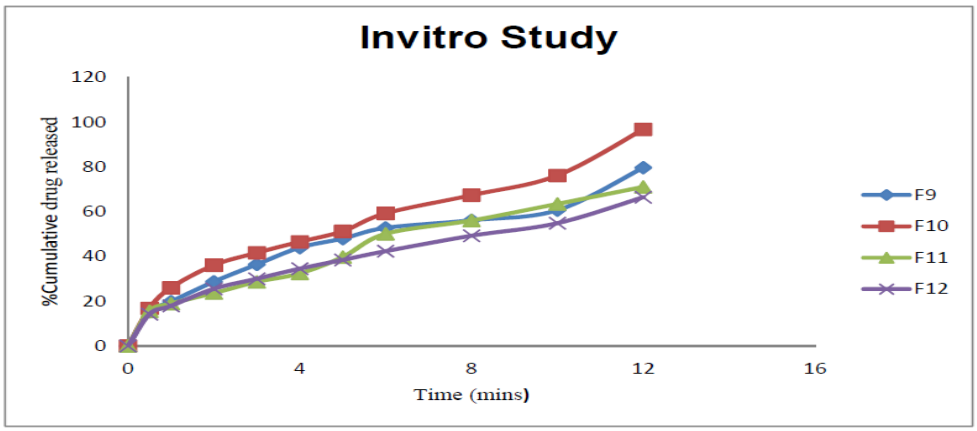

Figure 8: Cumulative % drug release of formulation F9-F12

CONCLUSION:

Fexofenadine HCl oil entrapped floating alginate beads were successfully prepared using sodium alginate as polymer and two different oil phases of mineral oil and olive oil by emulsion gelation method. FT-IR spectra of the physical mixture showed no significant shifting of the peaks, proved ingredients used in the study are suitable for the development of Fexofenadine HCl

floating beads formulations. The floating time of beads was found to be more than 12 hrs. The floating time and particle size were increased significantly as the amount of oil and polymer concentration increased in each formulation, where as a floating lag time was significantly decreased as the amount of oil was increased. Entrapment efficiency of all formulations were found in the range of 41.16 ± 0.044% to 85.76 ± 0.021%. The drug release of best formulations F5 and F10 (mineral oil and olive oil) were found to be 98.03% and 96.7 % in 12 hrs. Based on the result of dissolution study F5 and F10 were chosen as the optimized formulations that followed Higuchi kinetics, the release mechanism was non-Fickian diffusion. Hence finally it could be concluded that the prepared oil entrapped floating alginate beads of Fexofenadine HCl was safe and effective in sustained drug delivery system over an extended period of time which can reduce dosing frequency and improved bioavailability.

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