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FORMULATION AND CHARACERTISATION OF CINNARIZINE FLOATING MICROSPHERES USING IONOTROPIC GELATION METHOD

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ABSTRACT

The objective of present work was to prepare a floating drug delivery system of Cinnarizine in order to increase the gastric residence time for enhance solubility in gastric fluid, because of cinnarizine have lower solubility in intestine. Floating microspheres were prepared by ionotropic gelation method using HPMC K100M and HPMC-K4M as polymer, sodium bicarbonate and calcium carbonate as gas generating agent. The floating microspheres were evaluated for flow properties, particle size, incorporation efficiency, as well as in-vitro floatability and drug release. The shape and surface morphology of the microspheres were characterized by optical and scanning electron microscopy. The *in vitro* drug release was carried out in 0.1N HCL for 12 hrs. The drug release kinetic was fitted in different mathematical models like- zero order, first order, higuchi and peppas model. Amongst all the formulations, F4 and F10 were found to be better formulations F4 contains 1:4 ratio of drug & Polymer (HPMC K-100) and 40 mg of sodium bicarbonate. F10 contains 1:5 ratio of drug 7 Polymer (HPMC K4M) and 50 mg of calcium carbonate. Among these two formulations F4 having good percentage of drug loading. The *in vitro* drug release showed 100.02% at 12 hrs. Thus, it may be concluded that the cinnarizine floating tablet can be successfully formulated for improve absorption of cinnarizine with increase in the gastric residence time.

INTRODUCTION

The development of oral controlled release drug delivery system (OCRDDS) by overcoming physiological adversities like short gastric residence time and unpredictable gastric emptying time is a challenge for today's scientist. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT). Gastro retentive drug delivery systems (GRDDS) are the systems which are retains in the stomach for a prolonged period of time and thereby improve the bioavailability. GRDDS extend significantly the period of time over which the Drugs will be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms[1]. The gastric retention of the dosage forms can be achieved by several methods such as floatation, mucoadhesion, swellable system, hydro dynamically balanced system, sedimentation, expansion modified shape systems, and so on. Out of the techniques, floatation is the convenient and effective method for the gastric retention. Floating drug delivery systems (FDDS) can be buoyant in the gastric medium for prolonged period of time due to its lower

bulk density compared to the gastric medium. While the system is floating on the gastric contents, the drug will be released constantly at a desired rate from the dosage form and the GRT will be enhance. Due to increase in the GRT of the dosage form, more amount of the drug can be released in the gastric region, so that improves the bioavailability of the drug and also a better control of fluctuations in the plasma drug concentrations is achieved[2]. Floating microspheres (Hollow Microspheres) are gastro- retention drug delivery system based on non-effervescent approach. The microspheres are characteristically free flowing powders consisting of protein or synthetic polymers, which are biodegradable in nature. Microspheres are small in size and therefore have large surface to volume ratios[3]. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Cinnarizine is a potent, highly selective antiemetic and anti vertigo drug widely prescribed in control or prevents motion sickness, vertigo, nausea and vomiting. Cinnarizine is a BCS class-II drug having short biological half-life of 2 to 4 hrs. It is weakly basic drug and rapidly absorbed in stomach and upper part of gastrointestinal tract. Hence, the gasto-retentive drug delivery system used to increase the residence time in the stomach and there by gives prolong action for 12hrs[4].

The present work aimed to prepare and evaluate Cinnarizine floating microspheres by ionotroic gelation method and study the influence of two novel polymers in combination with gas generating agents to control the release of cinnarizine in the form of floating microspheres.

MATERIAL AND METHODS

Materials: Cinnarizine purchased from Yarrow Chem Products, Mumbai, Sodium alginate, Calcium carbonate, Sodium bicarbonate, Citric acid, HPMC K100M and $CaCl_2$ were obtained from S.D. Fine Chem. Ltd, Mumbai and all the other chemicals were used as Analytical grade.

Determination of absorption maxima: An accurately weighed 10 mg of Cinnarizine pure drug was transferred in a 100ml volumetric flask. To flask 15ml of Methanol was added in small proportion so as to dissolve Cinnarizine. The volume was made up to 100 ml with 0.1 N HCL. 20 µg/ml solution of Cinnarizine was prepared in dilution. The resulting solution was scanned in UV-Vis sepectrophotometer from 400-200 nm to determine the λmax.

Preparation calibration curve: 100 mg of Cinnarizine pure drug transferred into 100 ml volumetric flask and makeup the final volume with 0.1N HCL. 1 ml of this stock solution was taken and make up to 100ml using 0.1 N HCl to get a concentration 10 µg/ml. From this stick solution different concentration 2 – 10 µg/ml was made up with 0.1N HCL. From each concentration sample was taken & the absorption was measured at 253 nm by using UV spectrophotometer by using 0.1N HCL as a blank. The graph was plotted by taking concentration on X-axis and absorption on Y-axis. The experiment was performed in triplicate and based on average absorbance; the equation for the best line was generated.

Drug – Excipient compatibility studies: Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of interaction between drug and other excipients. In the current study 1:1 ratio drug and excipient physical mixture was used for analysis of compatibility studies. FTIR studies were carried out with a Bruker, ATR FTIR facility using direct sample technique[5].

Preparation of Floating Microspheres: The microsphere was prepared by ionotropic gelation method. The 50 mg of Cinnarizine was dispersed uniformly in aqueous mucilage of Sodium alginate. To this dispersion desired polymer was mixed in suitable proportion. Then, gas-forming agent such as Calcium carbonate and sodium bicarbonate was separately added to the solution. The resulting solution was dropped through a 26G syringe needle into 5 % $CaCl_2$ solution which is prepared in water containing 10 % acetic acid. This process was done with constant stirring (600 rpm) at 60 - 70^{o}C. The solvent is slowly evaporated. The solution containing suspend microsphere was kept for 1.5 hr. To improve the mechanical strength of the microsphere and allowed to complete the reaction to produce gas. The fully formed microspheres were

collected, washed with distilled water and subsequently air dried[6].

Characterization of Prepared Microspheres

Micromeritic Properties: Microspheres were characterized for their micromeritic properties viz., bulk density, tapped density, Carr index and angle of repose.

Bulk and Tapped Density: Accurately weighed quantities of prepared microspheres were carefully poured intothe10 ml graduated cylinder. The initial volume was measured without disturbing the cylinder. The tapping method was adapted to find out the tapped density. The graduated cylinder was tapped for 100 times with an interval of 2 seconds onto a hard wood surface from a height of 1 inch. After that the volume was measured. Bulk and tapped density were calculated by the following equation[7].

Bulk Density = W/Vo

Tapped Density = W/VF

Where, W= Weight of microspheres, Vo= Bulk Volume, VF = Final Volume

Compressibility Index: The Carr index is an indication of the compressibility of solids. The Carr index is frequently used in pharmaceutics as an indication of the flowability of a powder. Compressibility parameter evaluates the flow property of powder by comparing the bulk density and tapped density. Carr's index was calculated by using following formula. A Carr's index greater than 25 is considered to be an indication of poor flowability[7].

Carr's index = ((Tapped density - bulk density) / Tapped density) X 100

Angle of Repose: Angle of repose is defined as the maximum possible angle between the surface of a powder pile or granules and the horizontal plane. Angle of repose of microspheres was determined by fixed funnel method. The granules were allowed to flow through a funnel fixed to a stand at a definite height. The angle of repose (Θ) was then calculated by measuring the height (h) and radius (r) of the formed granules heap and incorporating these values into the under mentioned formula[7].

$$\Theta = \tan^{-1}(h/r)$$

Determination of mean particle size: The particle size was measured using an optical microscope, and the mean particle size was calculated by measuring 200 particles with the help of a calibrated ocularmicrometer6. A small amount of dry microspheres was suspended in purified water (10 ml). A small drop of suspension thus obtained was placed on a clean glass slide. The slide containing microspheres was mounted on the stage of the microscope and diameter of at least 100 particles was measured using a calibrated optical micrometer[8].

Determination of incorporation efficiency: To determine the incorporation efficiency, 10 mg microsphere were thoroughly triturated and dissolved in minimum amount of methanol. The resulting solution was made up to 100 ml with 0.1 N HCL and filtered. Drug content was analyzed spectophotometrically at 253 nm. The percentage incorporation efficiency was calculated by using the following formula[9].

% Incorporation efficiency = Actual drug content/Theoretical content × 100

Production yield: Production yield of microspheres containing a drug was determined by the weight ratio of the dried microspheres to the loading amount of the drug and Polymer. Production yield was calculated using equation[10].

Yield (%) = wt of microspheres in gm/ wt of total amount of materials in gm × 100

Percentage Buoyancy: The floating test was carried out to investigate the floatability of the prepared microspheres. To assess the floating properties, the microspheres were placed in 0.1N HCL containing 0.02% tween 20 (pH 2.0, 100 ml) to simulate gastric conditions. The mixture was stirred at 100 rpm in a magnetic stirrer. After 12 h, the layer of buoyant micro particles and sinking particulate layer were separated by filtration. Particles of both types were dried in an oven at 65^0C until constant weight. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles. Results of Percentage buoyancy calculated by using the following formula[11].

%Buoyancy = weight of Floating microsphere/Initial weight of microspheres × 100

Floating time: It is defined as the time taken by floating microspheres to remain buoyant in the medium. The floating microspheres were placed in the beaker containing 200 ml of 0.1N HCL and examined for the duration of time till they float[12].

***In vitro* drug release study:** The release rate of Cinnarizine from microspheres was determined using USP dissolution testing apparatus I (Basket type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 100 rpm. Microspheres equivalent to 50 mg of Cinnarizine were used for the test. Aliquots (5 ml) were withdrawn at hourly intervals for 12 hours. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through whatman filter paper and solutions were analyzed at 253 nm using UV spectrophotometer[13].

Drug Release Kinetics: In order to understand the kinetics and mechanism of drug release from optimized formulation F4, the result of *in vitro* drug release study of microspheres were fitted with various kinetic equations like zero order (cumulative % release vs. time), first order (log % drug remaining vs. time), Higuchi's model (cumulative % drug release vs. square root of time). R^2 and k values were calculated for the linear curve obtained by regression analysis of the above plots[14].

RESULT AND DISCUSSION

Determination of absorption maxima: The 20 µg/ml Cinnarizine solution was scanned in UV - Vis spectrophotometer from 400- 200 nm to determine the λmax. The λmax was found to be at 253 nm, so the calibration curve of Atorvastatin calcium was developed at this wavelength.

Standard graph of Cinnarizine in 0.1N HCL: The standard graph of Cinnarizine in 0.1N HCL was constructed by making the concentration range 2 - 10 µg/ml solutions. The absorbance of solutions was examined under UV- spectrophotometer at an absorption maximum of 253 nm. The curve obeyed Beer-Lambert's law and the correlation coefficient value (R^2) of buffer was 0.998

Drug - Excipient Compatibility Studies: The FTIR spectra of the Cinnarizine and formulation excipients were shown in Figures. The spectra of drug and excipients employed were showed a broad peak at the same place of the peak observed at the spectrum of pure Cinnarizine has been observed, which indicated that there was no chemical interaction with the formulation excipients.

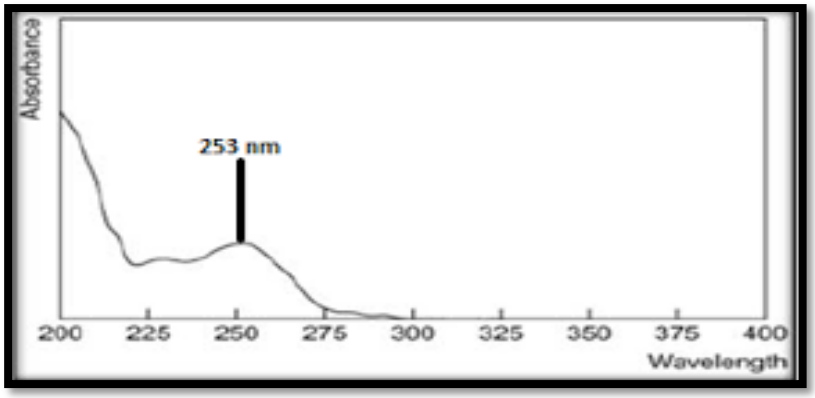
Preparation of Floating Microspheres: Cinnarizine floating microspheres were prepared by ionotropic gelation method using HPMC K100M and HPMC-K4M as polymer, sodium bicarbonate and calcium carbonate as gas generating agents. Total of 10 different formulations (F1 to F10) were prepared successfully according to the procedure given in the methods. First five formulations F1 – F5 were prepared with combination of HPMC K-100 and sodium bicarbonate at five different drug polymer ratio. Formulation F6 – F10 were prepared with combination of HPMC E15 and calcium carbonate at five different drug polymer ratio. For the prepared formulations various evaluation tests were performed and the results are given as below.

Characterization of Prepared Microspheres

Micromeritic Properties: All of the formulated microspheres were tested for bulk density and tapped density to ensure the flow properties of microspheres. The bulk and tapped density of microspheres ranged between 0.27 - 0.38 gm/ml and 0.33 - 0.45 gm/ml. Formulated microspheres exhibited good flow properties within the range of 11.72 – 22.41 for Carr's index and hausner's ratio between 1.12 - 1.28 and found to be within the I.P limits. Results of angle of repose for formulated microspheres were ranged between 23.16 - 25.03 that indicating the good flow properties of microspheres.

Determination of mean particle size: The particle size of all formulations was determined by using optical microscope and was found to be in the range between 221.98 ± 5.21 - 475.36 ± 3.74 µm. The variation in the particle size might be due to the difference in the drug: polymer ratio during the preparation of microspheres. From the results it was found that with increasing the polymer concentration the particle size also increases.

Determination of incorporation efficiency: The drug entrapment efficiency of all formulations was found to be in the range between 70.48 to 92.1%.



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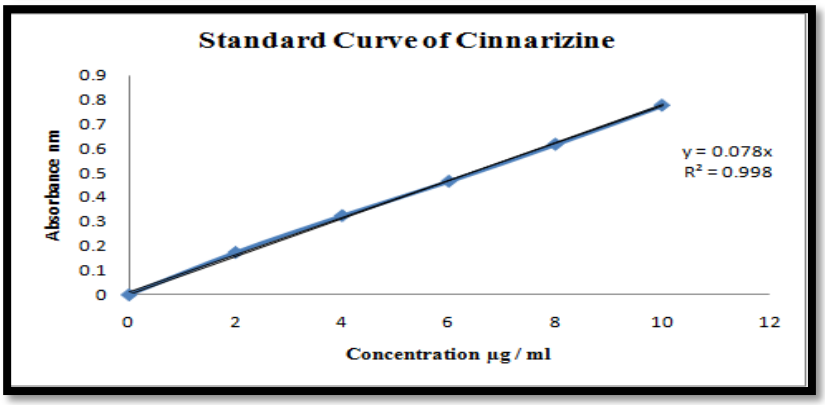

2. **Fig-1: λmax of Cinnarizine** **Fig - 2: Standard curve of Cinnarizine**

3. **Table - 1: Formulation of Cinnarizine Floating Microspheres**

Formulation Code	Drug (mg)	Na. Alginate (mg)	Drug Polymer Ratio		$NaHCO_3$ (mg)	$CaCO_3$ (mg)	Citric acid (mg)	$CaCL_2$ (%)
			HPMC-K 100	HPMC-K4M				
F1	50	5	1:1	--	10	--	5	5
F2	50	5	1:2	--	20	--	5	5
F3	50	5	1:3	--	30	--	5	5
F3	50	5	1:3	--	30	--	5	5
F4	50	5	1:4	--	40	--	5	5
F5	50	5	1:5	--	50	--	5	5
F6	50	5	--	1:1	--	10	5	5
F7	50	5	--	1:2	--	20	5	5
F8	50	5	--	1:3	--	30	5	5
F9	50	5	--	1:4	--	40	5	5
F10	50	5	--	1:5	--	50	5	5

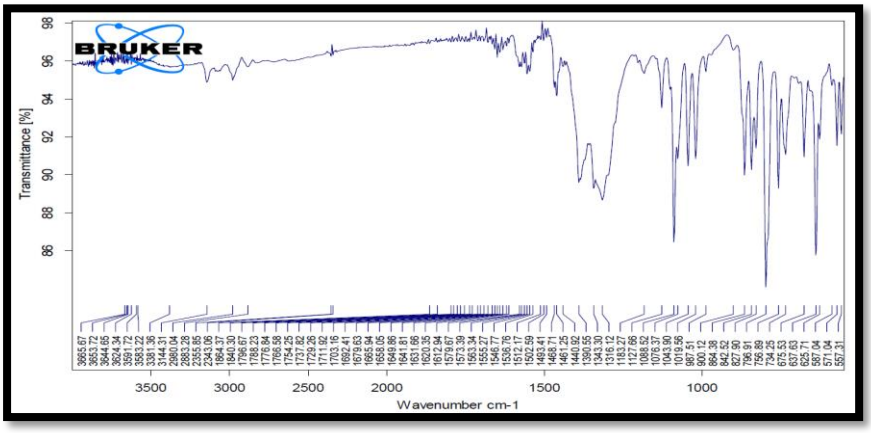

Fig - 3: FTIR graph of pure drug Cinnarizine

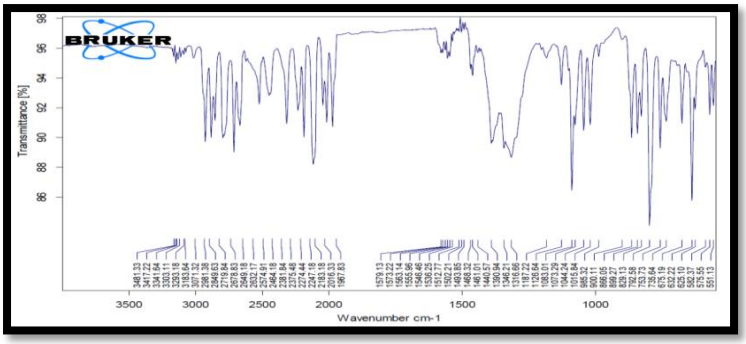

Fig - 4: FTIR graph of Cinnarizine + formulation excipients

Table - 2: Micromeritic properties of prepared microspheres

Batch No.	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index	Hausner's ratio	Angle of repose (θ)
F1	0.357 ± 0.23	0.416 ± 0.04	14.18 ± 0.13	1.16 ± 0.55	23.16 ± 0.31
F2	0.384 ± 0.12	0.454 ± 0.06	15.41 ± 0.21	1.18 ± 0.21	23.94 ± 0.36
F3	0.384 ± 0.13	0.454 ± 0.01	15.37 ± 0.03	1.18 ± 0.03	24.14 ± 0.05
F3	0.357 ± 0.25	0.416 ± 0.05	14.28 ± 0.05	1.16 ± 0.05	24.91 ± 0.07
F4	0.294 ± 0.08	0.333 ± 0.03	11.72 ± 0.07	1.13 ± 0.07	23.16 ± 0.08
F5	0.312 ± 0.07	0.384 ± 0.08	18.72 ± 0.23	1.21 ± 0.08	25.03 ± 006
F6	0.277 ± 0.05	0.357 ± 0.07	22.41 ± 0.12	1.28 ± 0.04	24.16 ± 0.08
F7	0.312 ± 0.03	0.357 ± 0.04	12.60 ± 0.13	1.14 ± 0.02	24.91 ± 0.07
F8	0.333 ± 0.21	0.416 ± 0.02	19.92 ± 0.25	1.12 ± 0.06	23.25 ± 0.24
F9	0.294 ± 0.13	0.333 ± 0.07	11.71 ± 0.08	1.13 ± 0.07	24.56 ± 0.42
F10	0.357 ± 0.23	0.416 ± 0.04	14.18 ± 0.13	1.16 ± 0.55	23.16 ± 0.31

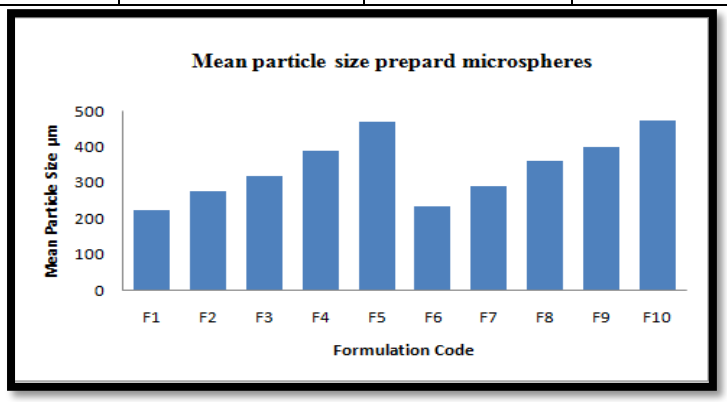

Fig - 5: Mean particle size of formulation F1 – F10

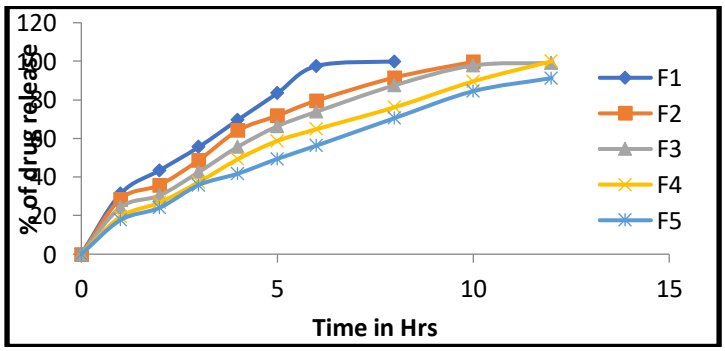

Fig - 6: *In vitro* Dissolution study of Cinnarizine Floating Microspheres (F1 to F5) with Sodium biarbonate and HPMC-K 100

Table 3: Result of Incorporation efficiency, % Yield, % Floating and Floating time

Batch No:	Incorporation efficiency%	Percentage yield	Percentage Floating	Floating Time *(hr)*
F1	70.4 ± 0.03	75.2 ± 0.65	69.20±0.07	12
F2	85.9 ± 0.57	80.2 ± 0.25	68.24±0.05	12
F3	88.6 ± 0.44	79.5 ± 0.24	67.33±0.05	13
F4	90.1 ± 0.81	85.4 ± 0.08	88.87±0.08	14
F5	92.1 ± 0.35	87.1 ± 0.82	73.78±0.45	15
F6	69.2 ± 0.33	79.5 ± 0.63	56.56±0.78	12
F7	75.4 ± 0.51	82.3 ± 0.04	58.24±0.65	13
F8	85.1 ± 0.63	85.2 ± 0.44	66.37±0.84	14
F9	88.3 ± 0.72	88.2 ± 0.32	72.96±0.75	13
F10	91.2 ± 0.45	89.4 ± 0.05	75.76±0.25	15

Table - 4: *vitro* Dissolution study of Cinnarizine Floating Microspheres F1 to F5

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	31.3	28.6	24.3	19.4	17.7
2	43.5	35.89	30.5	26.8	24.1
3	55.6	48.77	42.6	37.4	35.9
4	69.7	64.2	55.74	49.3	41.8
5	83.4	71.8	66.3	58.7	49.4
6	97.6	79.6	73.85	64.8	56.3
8	99.9	91.63	87.6	76.2	70.6
10		99.7	97.83	89.6	84.5
12			99.13	100.02	91.3

Table - 5: *In vitro* Dissolution study of Cinnarizine Floating Microspheres F6 to F10

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	38.31	32.33	27.67	23.31	20.15
2	49.91	45.54	36.88	30.55	27.25
3	61.3	55.61	45.72	41.63	38.47
4	74.3	68.74	62.16	56.74	50.68
5	89.6	79.40	72.88	67.37	59.86
6	100.0	94.65	82.65	74.85	65.72
8		99.98	93.67	88.68	77.32
10			99.75	97.83	90.70
12				99.13	99.90

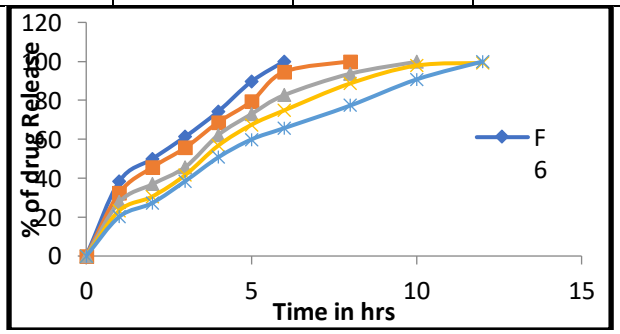

Fig -7: *In vitro* Dissolution study of Cinnarizine Floating Microspheres (F6 to F10) with Calcium Carbonate and HPMC-K 4M

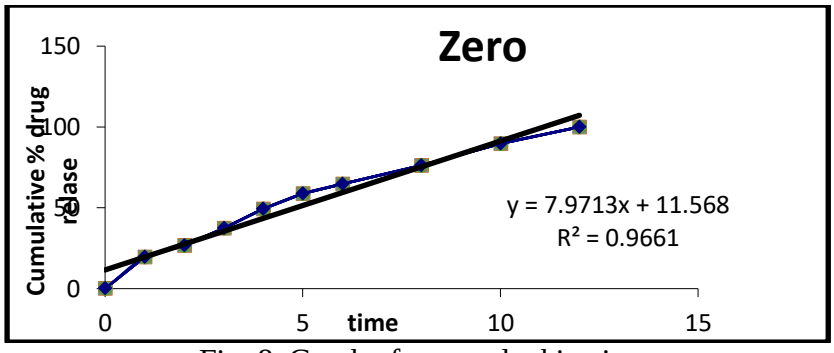

Fig -8: Graph of zero order kinetics

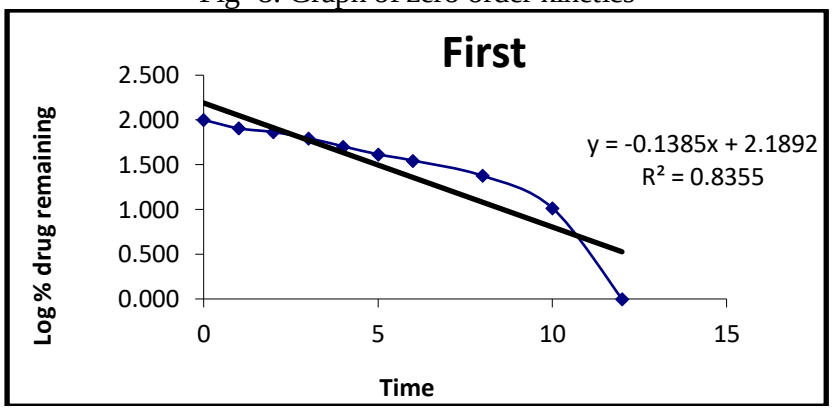

Fig -9: graph of first order release kinetics

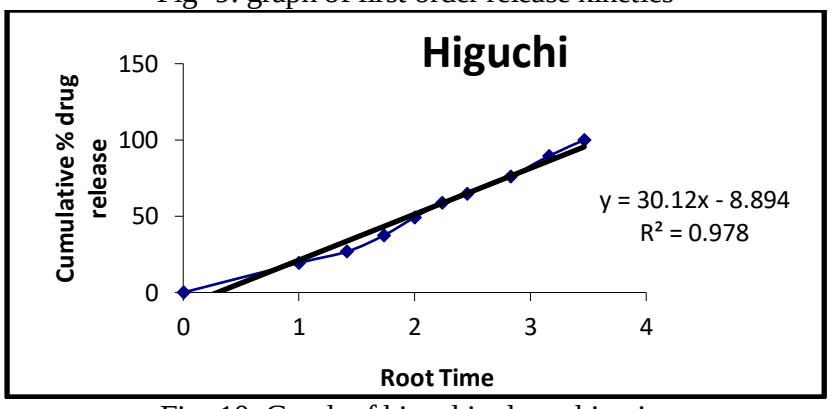

Fig -10: Graph of higuchi release kinetics

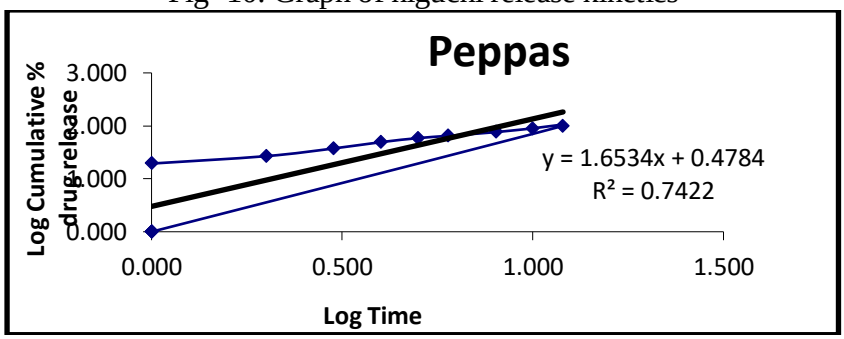

Fig -11: Graph of peppas release kinetics

With the increase in polymer concentration, increased entrapment efficiency was seen because with increasing polymer content, more particles of drug would be coated leading to higher encapsulation efficiency as can be observed.

Percentage yield: The Percentage yields of floating microspheres were found in the range of 75.2 – 89.4 %. It was observed that with the increase in the polymer concentration (i.e. decrease in drug to polymer ratio) in the formulation, the product yield increased. It was

found that average percentage yield was greater than 50 % for all the batches which shows the suitability of this method for preparation of microspheres.

Percentage floating: Excellent buoyancy was shown by prepared microspheres because of their hollow nature, which can be retained for a longer period of time in the upper part of gastrointestinal tract (GIT) in order to increase gastric residence time of the drug. Buoyancy of prepared microspheres was found to be in the range of 56 - 88%. Formulation F6 showed least percentage buoyancy of 56%, while F4 showed highest buoyancy of 88%.

Floating Time: The formulations prepared with the various drug and polymer ratios were evaluated for floating time. In the test of floating time, more than 80% microspheres remained floating for more than 12 hour. The good buoyancy behavior of the microspheres may be attributed to the hollow nature of the microspheres. As the concentration of polymers increases, buoyancy also increases.

***In vitro* drug release study:** The comparison of the release rate of formulations prepared by using different ratio of polymers *in vitro* release study was done. *In-vitro* drug release studies were performed in 0.1 N HCL for 12 hr. The results of drug release were showed in graph was plotted between cumulative drug release and time. The cumulative release of drug significantly decreased with increase in polymer concentration. The increased density of polymer matrix at higher concentration resulted in an increased diffusion path length. This may decrease the overall drug release from the polymer matrix. And it was found that as the polymer concentration was increased the release rate decreases. The selected formulation percentage of drug released was found to be initially 19.4% at 1 hr and 100.2% up to 12 hr. Based on dissolution data of 10 formulations, the formulation F4 and F10 showed better release up to 12 hours. Among these formulations F4 having the low concentration of polymer compare to F10 and it showed the drug release within the specified limits. So F4 considered as optimised formulation.

Drug Release Kinetics: Dissolution data of the optimized formulation F4 was subjected to regression analysis and were fitted to kinetic models. The R^2 value of zero order and first order was found as 0.966 & 0.835 respectively. This result suggests that the drug released by zero order kinetics. Further to ascertain the exact mechanism of drug release the dissolution data of the optimized formulation was subjected to Peppas and Higuchi's diffusion equation. The R^2 value of Higuchi's and peppas diffusion equation was obtained as 0.978 and 0.742 respectively. This result suggests that the drug released followed diffusion mechanism.

CONCLUSION

Cinnarizine is a BCS class-II drug and it requires frequent dosing before meals due to short half life and thereby imposing side effects. The drug requires a novel gastroretentive drug delivery system which can provide an extended period of time in stomach and improve oral bioavailability. Floating microspheres of Cinnarizine were prepared by ionotropic gelation method, using biodegradable polymers such as HPMC K100M and HPMC-K4M and gas generating agent such as sodium bicarbonate and calcium carbonate in order to retain drug in body for longer period of time. This study was concluded that formulation of floating microspheres of Cinnarizine offers prolonged gastric residence time and continuous release of the medication over an extended period of time thus oral bioavailability of the drug and subsequent efficacy is improved.

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