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GASTRO RETENTIVE RANITIDINE HYDROCHLORIDE MICROCAPSULES WITH NATURAL POLYMERS

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Keywords:

Ranitidine Hydrochloride, Microcapsules, Poly dextran, Poly starch, Titanium dioxide

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ABSTRACT

Aim: The main aim of the present work was to prepare and evaluate gastro retentive microcapsules for the controlled release of Ranitidine Hydrochloride using natural polymers.

Methods: The microcapsules were prepared by the coacervation phase separation technique. The drug was checked for its compatibility with polymers used by Differential Scanning Calorimetric (DSC) and Fourier Transform Infrared spectroscopic (FTIR) analysis. The surface morphology of prepared microcapsules was studied by scanning electron microscopic (SEM) studies. The prepared microcapsules were evaluated for physiochemical and drug release characteristics. The optimized formulation (F-6) was tested for its stability. The DSC and FTIR studies revealed that the drug is compatible with excipients used. All the prepared microcapsules were found to have good physiochemical and the release of drug from the microcapsules extended up to 12 hours. The release kinetics data and characterization studies indicate that drug release from microcapsules was diffusion controlled and that the microcapsules were stable. The accelerated stability studies revealed that the optimized formulation was stable.

Conclusion: The study revealed that Poly dextran, Poly starch in combinations yields microcapsules with promising characteristics.

INTRODUCTION

Microcapsules drug delivery systems made using natural, biodegradable polymers have been attracted by several researchers for last decade in sustaining the drug delivery [1]. The success of microcapsules is limited due to their short residence time at the site of absorption/action [2]. High density micro capsules provide an increase gastric residence time by making them to sink at the bottom of stomach. This can be achieved by coupling high density materials which has higher density then gastric fluid [3]. High density systems have advantages like increased gastric residence time and specific targeting of drugs in the absorption site, efficient absorption and enhanced bioavailability [4, 5]. Titanium dioxide was used as high density material in formulating microcapsules [6, 7].
Ranitidine Hydrochloride is a histamine H_2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastro esophageal reflux disease and erosive esophagitis. The recommended adult oral dosage of Ranitidine Hydrochloride is 150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of Ranitidine Hydrochloride 4 times a day. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 hours but not up to 10 hours. An alternative dose of 300 mg leads to plasma fluctuations; thus a controlled release dosage form of Ranitidine Hydrochloride is desirable. The short biological half-life of drug (~2.5-3 hours) also favors development of a controlled release formulation. In contest of the above principle, a strong need was recognized for the development of a dosage form to deliver sustained release gastro retentive delivery system of Ranitidine Hydrochloride [8].

MATERIALS AND METHODS

Materials

Ranitidine Hydrochloride was obtained as a gift sample from Waksman Selman Pharmaceuticals, Anantapur, India (Batch # R 00254), Poly dextran, Poly starch, Formaldehyde and Titanium oxide were procured from SD Fine Chemicals, Mumbai, India. Sunflower oil was procured from MORE super market, Anantapur, India. All the regents were of analytical reagent grade and double distilled water was used throughout the experiment.

Preformulation Studies

Solubility analysis

Preformulation solubility analysis was done to select a suitable solvent system to dissolve the drug and also to test its solubility in the dissolution medium which was to be used.

Melting Point determination

Melting point determination of the obtained sample was done because it is a good first indication of purity of the sample since the presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range.

Compatibility Studies

Differential Scanning Calorimetric (DSC) analysis

Differential Scanning Calorimetry (DSC) thermo grams were obtained by a differential scanning calorimeter (Schimadzu DSC-50, Tokyo, Japan) at a heating rate of 10°C/min from 30-300°C in nitrogen atmosphere (20 ml/min) with a sample weight of 3mg.

Fourier Transform Infrared Spectroscopy

Fourier Transformed Infrared (FTIR) spectrums of Ranitidine Hydrochloride with natural polymers used were obtained individually and in combinations on a Fourier Transform Infrared (FTIR) spectrophotometer (Perkin Elmer, spectrum-100, Japan) using the KBr disk method (5.0115 mg sample in 300.0008 mg KBr). The scanning range was 500 to 4000 cm^{-1} and the resolution was 1 cm^{-1}. This spectral analysis was employed to check the compatibility of drugs with the polymers used.

Preparation of microcapsules

Poly dextran, Poly starch and Titanium dioxide mixture containing Ranitidine Hydrochloride microcapsules were prepared by coacervation phase separation technique utilizing temperature chance. Poly dextran, Poly starch and Titanium dioxide were dissolved in 10ml of water which was previously heated to 50^{o} C, to this Ranitidine Hydrochloride was added and stirred at 300 rpm with the help of magnetic stirrer for 15 minutes to get a stable dispersion. The dispersion was poured drop wise into the 10ml of sunflower oil which was also previously heated to 50^{o}C on a water bath. The mixture was stirred with a help of magnetic stirrer for 2 hours at 300rpm at room temperature. At the end of 2 hours crosslinking agent formaldehyde 0.5ml was added to the dispersion medium and stirring was continued for next 30 minutes. Finally it was kept in refrigerator for 24 hours to ensure the rigidness of microcapsules [9, 10]. This Procedure was followed to prepare 6 batches of Ranitidine Hydrochloride microspheres with different ratios of Poly dextran, Poly starch mixtures. The core: coat ratio, amount of drug and polymers used were given in Table No1.

Table No 1: Composition of Ranitidine Hydrochloride Micro spheres

Ingredient	F-1	F-2	F-3	F-4	F-5	F-6
Ranitidine Hydrochloride	150	150	150	150	150	150
Poly dextran (g)	1.0	2.0	-	-	1.0	2.0
Poly starch (g)	-	-	1.0	2.0	1.0	2.0
Titanium dioxide (g)	0.1	0.1	0.1	0.1	0.1	0.1

Flow Properties

Angle of repose

This was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height (h), was obtained. Diameter of heap,

(D), was measured. [11] The angle of repose (Θ) was calculated by the following equations.

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

Where, Θ = Angle of repose, h = height of the pile (cm) and r = radius of the pile.

Loose Bulk density

The sample under test was screened through sieve # 18, the sample equivalent to 25 g was accurately weighed and filled in a 100 ml graduated cylinder, the powder was leveled, and the unsettled volume, V_o was noted [11]. The bulk density was calculated in g/cm^3 by the following equation.

$$D_b = M / V_0$$

Where, M= Mass of powder, V_0= Bulk volume of the powder

Tapped Bulk Density

The sample under test was screened through sieve # 18 and the weight of sample equivalent to 25 g was filled in 100 ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a nominal rate of 300 drops per min for 500 times initially and the tapped volume V_0 was noted. Tapping was proceeding further for an additional tapping 750 times and tapped volume V_b was noted [11]. The difference between two tapping volume was less than 2%, so V_b was considered as a tapped volume V_f. The tapped density was calculated in g/ cm^3 by the following equation.

$$D_t = M / V_t$$

Where, M = Mass of powder, V_t = Tapped volume of the powder.

Compressibility Index

The bulk density and tapped density was measured and compressibility index was calculated by the following equation [11].

$$I_C = D_t - D_b / D_t$$

Where, D_t = Tapped density of the powder, D_b = Bulk density of the powder

Hausner ratio

The ratio of Tapped density and bulk density gives the Hausner ratio and it was calculated using the following equation [11].

$$H_R = D_t / D_b$$

Where, D_t = Tapped density of the powder, D_b = Bulk density of the powder

Particle Size Analysis

Particle size distribution was analyzed by placing 5 g of the formulated microspheres in a set of standard test sieves and shaken for a particular time interval using Indian Standard Sieves # 16, #20, #30, #40, #60 and #80. The particles collected in each sieve were weighed and the percentage particles retained was calculated.

Percentage yield The percent yield of each batch of formulation was calculated using the following equation.

% yield = (weight of microspheres)/weight of solid starting material ×100

Surface associated drug content

The Ranitidine Hydrochloride encapsulated microcapsules prepared were evaluated for surface associated drug content on the surface of microcapsules. From each batch, 100 mg of microcapsule was shaken in 20 ml of 0.1N HCl for 5 min and then filtered through what man filter paper 41. The amount of drug present in filtrate was determined spectrophotometric method and calculated as a percentage of total drug content. All the experiments were conducted in triplicate (n=3).

Estimation of drug loading/incorporation efficiency

Drug loaded microcapsules equivalent to 150 mg were powdered and suspended in water and then sonicated (Power sonic 505, Hwashin technology co, Korea) for about 20 min. It was shaken for another (Orbitex, Scigenics biotech, India) 20 min for the complete extraction of drug from the microcapsules. The mixture was filtered through a 0.45 µm membrane filter (Millipore, Bangalore, India). Drug content was determined by UV-visible double beam spectrophotometer (Ellico SL210, India) at 313 nm. The percent entrapment was calculated using the following equation.

Total incorporation efficiency =surface associated drug + entrapped drug

Determination of wall thickness

Wall thickness of microcapsules was determined by the following equation.

$$h = [r (1-P) d_1/3\{Pd_2+ (1-P) d_1\}] \times 100$$

Where, h= wall thickness, r = arithmetic mean radius of microcapsules, d_1 and d_2 = densities of core and coat material respectively, P = proportion of medicament.

Estimation of Ranitidine Hydrochloride

The content of Ranitidine Hydrochloride in the microcapsules was estimated by a double beam UV spectrophotometer based on the measurement of absorbance at 313 nm in phosphate buffer (pH 7.4). The method obeyed Beer's law (at 1 to 10 mg/ml). The mean error and precision were found to be 0.9% and 1.0% respectively. These experiments were conducted for six times.

Drug Release Study

In vitro drug dissolution studies were performed using USP type I dissolution apparatus (DR-3, Campbell Electronics, Mumbai, India) at 75 rpm. The micro capsules were weighed and filled in the empty capsule shells and placed in the basket. The dissolution medium (900ml) consisted of 0.1M HCl for first 2 hours and then changed to phosphate buffer pH 7.4 from 3^{rd} to 12^{th} hour; Temperature was maintained at 37 ± 0.5^{o}C. A 5 ml sample was withdrawn at specific time intervals and replaced with an equivalent volume of dissolution fluid. Drug content was determined by UV– visible double beam spectrophotometer at 313 nm. The release studies were conducted in triplicate.

***In vitro* drug release kinetic studies**

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. The exact mechanism of Ranitidine

Hydrochloride release from the microsphere was further studied by kinetic models. The drug release data was analyzed by zero order, first order, Higuchi [12], Korsmeyer Peppa's [12] and Hixon Crowell models [13]. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test.

Scanning Electron Microscopy studies

The surface morphology of selected micro capsules (F6) was studied by scanning electron microscopy (SEM) (FE-SEM, Carl Zeiss, Germany). The samples were coated to 200A^{o} thickness with gold palladium using prior to microscopy. The SEM photographs were shown in Figure 10.

Accelerated Stability studies

The promising formulation (F-6) was tested for a period of 3 months at different temperature of 40^{o}C with 75% RH, for their drug content [12].

RESULTS AND DISCUSSION

The Ranitidine Hydrochloride sample was found to be freely soluble in water and in methanol, sparingly soluble in ethanol and very slightly soluble in methylene chloride. The melting point of the obtained drug sample was found to be 132^{o}C which is within the reported limit 133.5^{o}C. It complies with IP standards thus indicating the purity of the drug sample. The DSC thermo gram of Ranitidine Hydrochloride pure drug showed a short endothermic peak at 133.50^{o}C. The thermo gram of formulation (F-6) showed an endothermic peak at 130.02^{o}C indicating a slight change in terms of shifting towards the lower temperature (Fig. 1A and 1B). The FTIR spectrum of the pure drug was found to be similar to the standard spectrum of Ranitidine Hydrochloride. It was observed that all the characteristic peaks of Ranitidine Hydrochloride were present in the pure drug spectrum were present in combination spectra which indicates the compatibility of the drug with the polymers used. The FTIR spectrums were shown in Fig. 2 to 4.

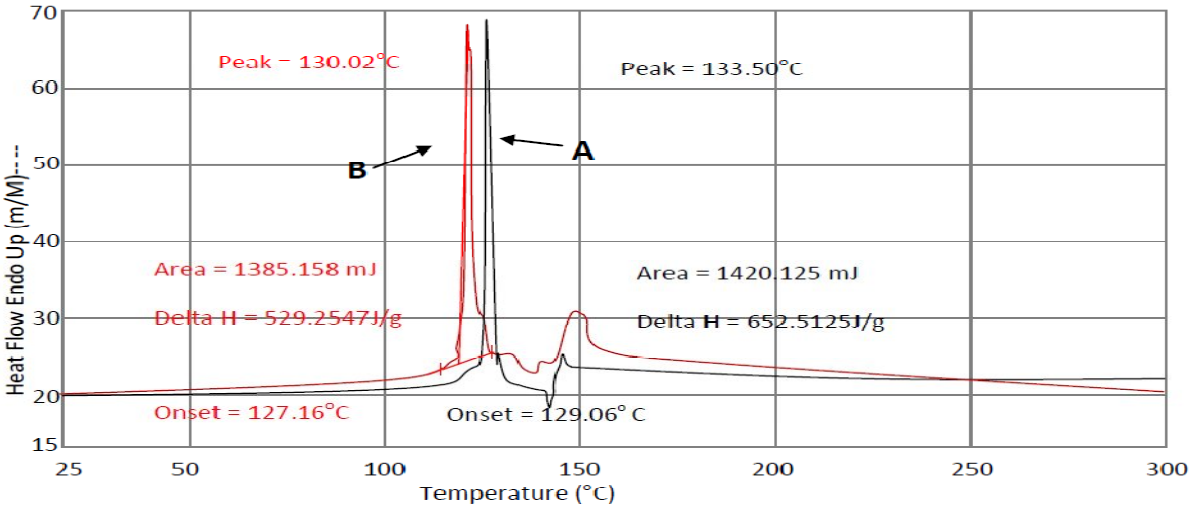

Fig. 1: The DSC thermo grams of A) Ranitidine HCl; B) Formulation F-6

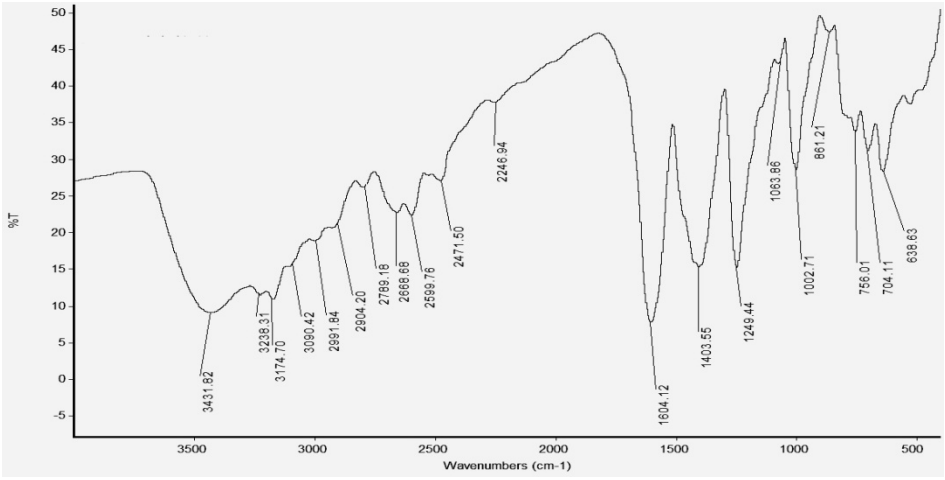

Fig. 2: FTIR spectrum of Ranitidine Hydrochloride

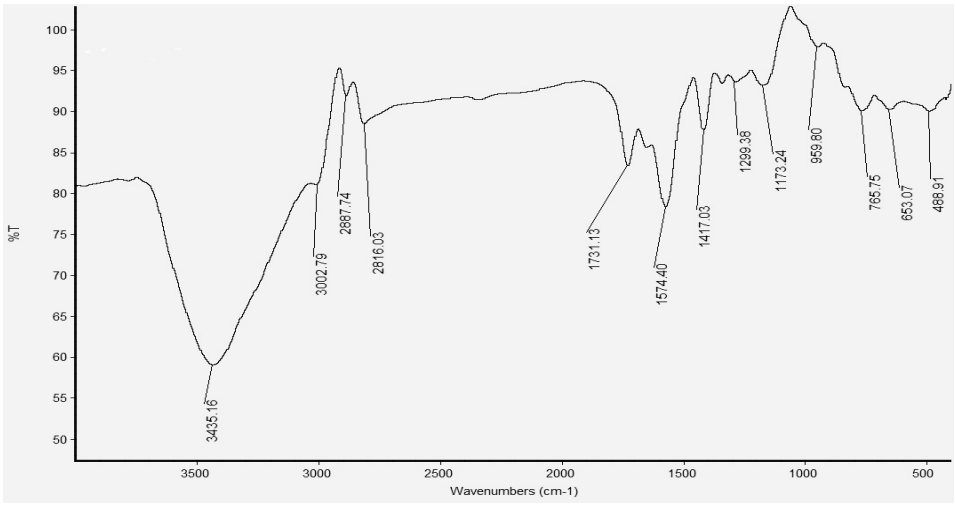

Fig. 3: FTIR spectrum of excipients used

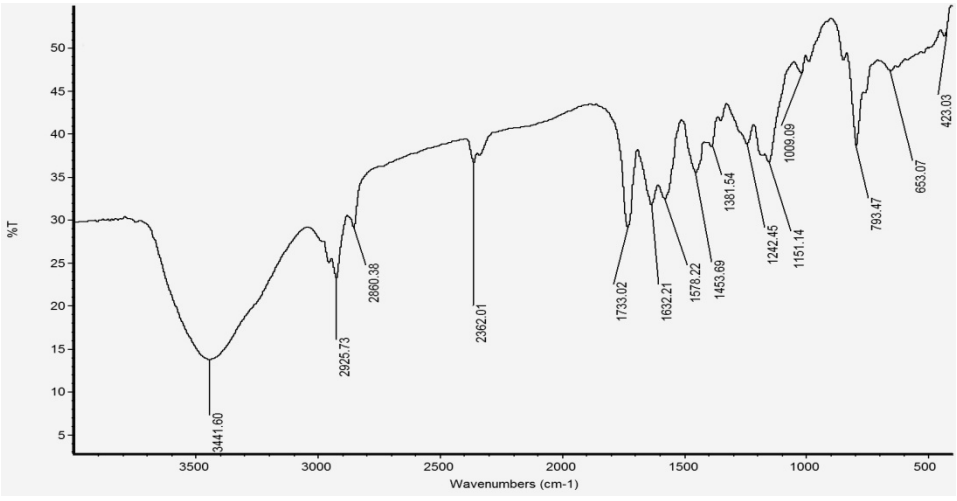

Fig. 4: FTIR spectrum of F-6 blend

The angle of repose of formulated microcapsules was ranged from 22.26±0.18 to 28.12±0.25^{o} which indicates the microcapsules have excellent flow properties. The Loose Bulk density of formulations was ranged from to 0.419±0.02 to 0.741±0.05 g/cm^3 and the tapped Bulk density of formulations were ranged from 0.584±0.08 to 0.875±0.05 g/cm^3. The Loose Bulk density and the tapped Bulk density values were utilized for determining the compressibility Index which was raged from 15.55±0.12 to 28.34±1.15 % and The Hausner ratio which was ranged from 0.010±0.001 to 1.176±0.001. These studies revealed the granules have good flow properties. All these values were represented in Table No 2.

Table No 2: Flow Properties of Ranitidine Hydrochloride Microspheres

Batch	Angle of repose (^{0})	Loose Bulk Density (g/cm^3)	Tapped Bulk Density (g/cm^3)	Carr's Index (I_C)	Hausner's ratio (H_R)
Pure drug	32.12±0.45	0.299±0.06	0.358±0.01	17.46±0.44	1.211±0.021
F-1	22.26±0.18	0.541±0.04	0.639±0.01	18.43±1.29	0.010±0.001
F-2	24.20±0.26	0.561±0.05	0.629±0.02	21.74±0.98	0.139±0.0.02
F-3	28.12±0.25	0.419±0.02	0.621±0.04	28.34±1.15	0.060±0.001
F-4	25.27±0.15	0.457±0.06	0.584±0.08	26.06±0.11	0.081±0.001
F-5	24.21±0.06	0.438±0.01	0.626±0.04	28.04±2.22	0.119±0.011
F-6	25.31±0.14	0.741±0.05	0.875±0.05	15.55±0.12	1.176±0.001

All values were mentioned in mean ±S.D; Number of trials (n)=5

The average particle sizes of F-1 to F-6 formulations were Particle size (μm) 615.00, 494.00, 362.00, 562.00, 704.00 and 630.00 μm respectively. The sieve analysis details of Ranitidine Hydrochloride Microspheres were shown in Table No 3.

Table No 3: Particle Size Distribution of Ranitidine Hydrochloride Microspheres

Sieve No.	Nominal mesh aperture	Sieve No. passed/ retained	Arithmetic mean aperture	Weight of powder retained (%)					
				F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
18	850	16/18	850	2.673	4.201	10.609	15.160	34.994	14.888
30	600	18/30	725	56.331	16.570	32.0254	25.258	45.966	49.121
44	355	30/44	477.5	37.413	36.469	43.984	39.891	10.985	21.164
60	250	44/60	302	2.280	42.809	13.020	19.780	5.190	15.861
Average diameter of particles (μm), D_{av}				**615.00**	**494.00**	**362.00**	**562.00**	**704.00**	**630.00**
D_{av} = ∑ wt. of powder retained % / 100									

The percentage yields of among formulated micro capsules, F-6 showed highest percentage yield of 86.75±0.24%. The surface associated drug content was least for F-6 (10.41±0.09). High drug entrapment efficiency was observed to the formulation F-6 and it was 92.58±2.39%. The wall thickness of formulated microcapsules was ranged from 15.54±0.02 to 24.16±0.54 µm. The wall thickness of formulated micro capsules was found to be increased from F-1 to F-6. All these values were shown in Table No 4.

Table No 4: Characterization of prepared Microspheres

Parameters	F-1	F-2	F-3	F-4	F-5	F-6
Yield (%)	83.65±0.15	81.18±0.25	81.95±0.16	85.19±0.23	84.27±0.25	86.75±0.24
Surface associated drug content (%)	15.56±0.15	14.22±0.15	14.15±0.11	12.25±0.18	11.36±0.19	10.41±0.09
Drug entrapment efficiency (%)	82.16±2.56	89.13±0.15	79.16±2.47	81.29±0.25	85.54±2.56	92.58±2.39
Wall thickness (µm)	15.54±0.02	19.25±0.35	21.54±0.27	22.17±0.14	22.42±0.23	24.16±0.54

All values were mentioned in mean ±S.D; Number of trials (n)=5

In vitro drug release kinetics data studies indicate that the formulations either followed zero order release or the Higuchi release model. Ranitidine Hydrochloride release from microcapsules was diffusion controlled. The *in vitro* kinetic data (Zero order, First order, Higuchi, Korsmeyer Peppas and Hixon Crowell) was tabulated in Table No 5, 6 and represented in Fig. 5, 6, 7, 8 and 9.

Table No 5: Kinetic Values Obtained From *In Vitro* Release Profile of Ranitidine Hydrochloride Microspheres

Batch	Zero Order Kinetic Data		First Order Kinetic Data	
	Regression coefficient (r)	k value	Regression coefficient (r)	k value
F-1	0.7079	9.5583	0.9790	-0.2101
F-2	0.7819	9.0740	0.9825	-0.1905
F-3	0.8369	9.6401	0.9909	-0.2281
F-4	0.9129	8.5804	0.9819	-0.1742
F-5	0.9314	7.7605	0.9853	-0.1390
F-6	0.9203	8.4579	0.9821	-0.1705

Table No 6: Kinetic Values Obtained From *In Vitro* Release Profile of Ranitidine Hydrochloride Microspheres

Batch	Higuchi data		Korsmeyer Peppas data		Hixon Crowell data	
	Regression coefficient (r)	k value	Regression coefficient (r)	k value	Regression coefficient (r)	k value
F-1	0.9792	28.4915	0.9854	37.7234	0.9539	-0.0525
F-2	0.9871	26.7877	0.9786	33.6650	0.9595	-0.0469
F-3	0.9946	24.8489	0.9872	24.9713	0.9868	-0.0441
F-4	0.9920	22.3757	0.9919	21.3011	0.9855	-0.0731
F-5	0.9934	24.7981	0.9865	23.5912	0.9859	-0.0459
F-6	0.9963	28.4629	0.9948	32.1230	0.9836	-0.0541

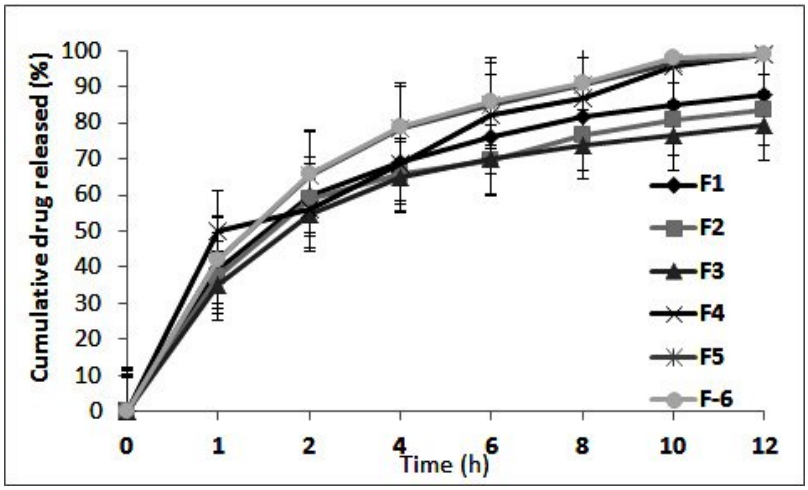

Fig. 5: Zero order plots

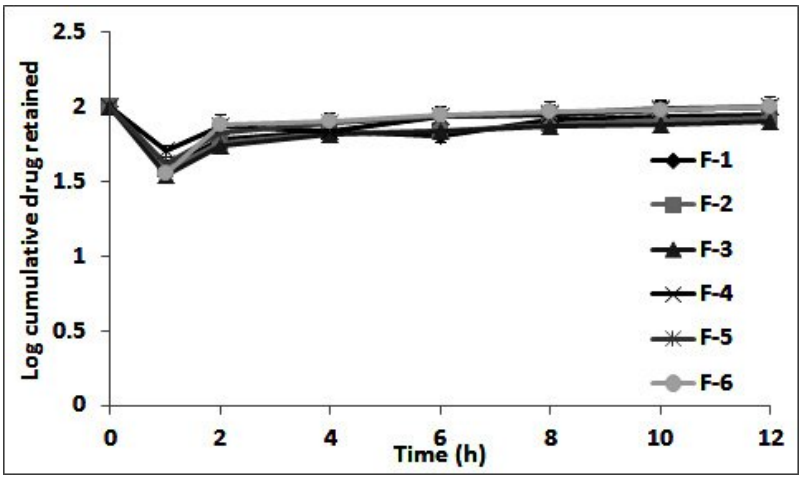

Fig. 6: First order plots

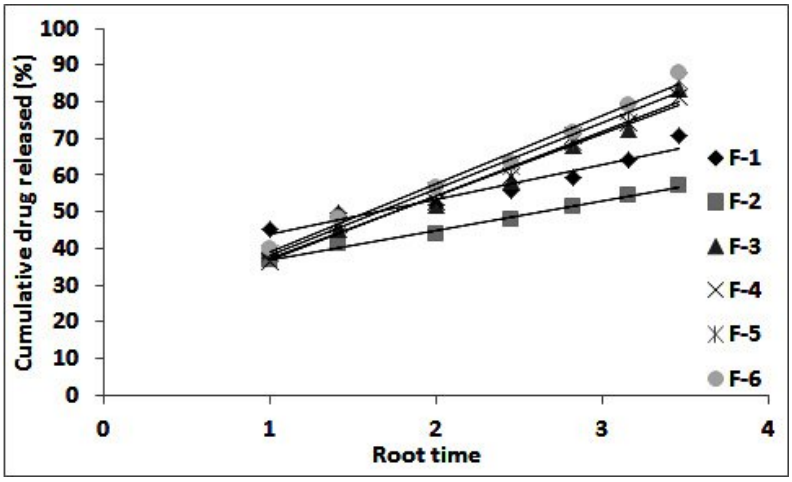

Fig. 7: Higuchi plots

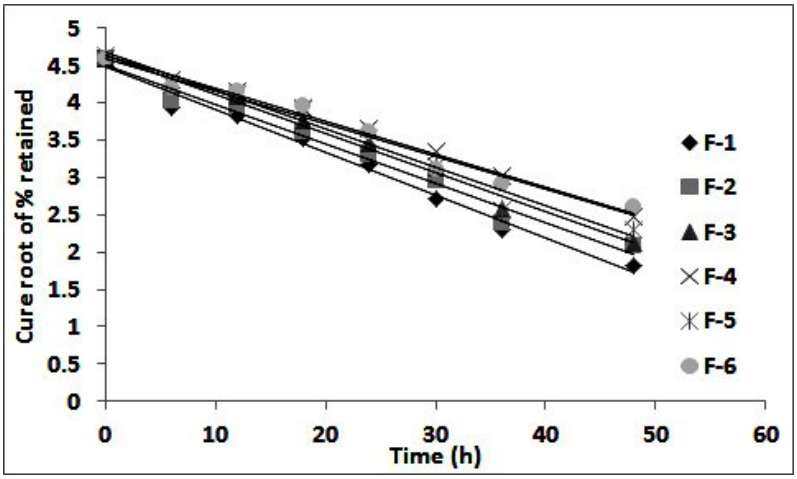

Fig. 8: Korsmeyer- Peppas plots

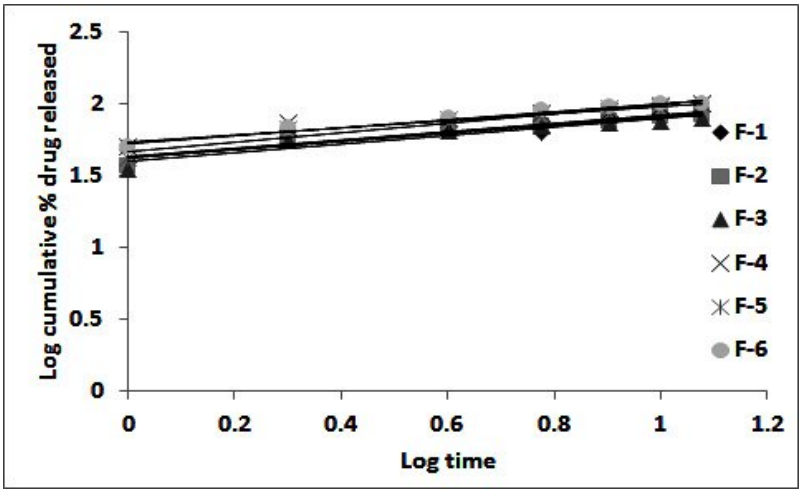

Fig. 9: Hixon Crowell plots

The accelerated stability revealed that the formulated Ranitidine Hydrochloride microcapsules were stable even at accelerated environmental conditions. The drug content in the formulation after stability studies were shown in Table No 7.

Table No 7: Percent Drug Content after Stability Studies

Batch	% Drug content after accelerated stability studies		
	After 15 Days	After 30 Days	After 60 Days
F-1	88.46	88.41	88.31
F-2	84.96	84.87	84.77
F-3	87.85	87.82	87.82
F-4	88.10	88.10	88.00
F-5	91.04	91.04	91.03
F-6	92.99	92.99	92.63

The SEM results shows that the microcapsules were spherical and with a smooth surface. The results indicate that F-6 formulation showed the slowest release rate while FTIR indicated that there was no drug polymer interaction. The results of accelerated stability study showed the stable nature of the drug. Good entrapment efficiency was observed with formulation F-6. SEM demonstrated the spherical nature of the microcapsules and the presence of drug particles on their surface.

CONCLUSION

The Ranitidine Hydrochloride microcapsules prolonged drug release for 12 hours or longer. The formulated Ranitidine Hydrochloride micro capsules reduce the frequency of administration and the dose-dependent side effects associated with the repeated administration of conventional Ranitidine Hydrochloride tablets. No drug polymer interaction was found and Ranitidine Hydrochloride was remained stable over a long period of time.

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