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Ranitidine HCl gastroretentive floating tablets based on hydrophilic polymers

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ABSTRACT

This investigation describes the preparation and *in vitro* evaluation of gastroretentive floating tablet of ranitidine hydrochloride by direct compression technique using varying concentrations of different grades of polymers (HPMC K4 M and HPMC K15 M) with sodium bicarbonate and citric acid were evaluated for their gel forming and release controlling properties. Sodium bicarbonate and citric acid were incorporated as gas generating agents. Ranitidine H_2 receptor antagonist having short biological half life (2-3.5 h), absorption in the initial part of the small intestine and 50% absolute bioavailability of drug favor development of sustained release floating formulation. The effects of soluble components (sodium bicarbonate and citric acid), gel forming agents and amount variation of ranitidine hydrochloride on drug release profile and floating properties were investigated. Tablets were prepared by direct compression technique. The tablets were characterized by lag time, floating time, weight variation, drug content and dissolution profile. The results indicated that a high amount of floating agent and combination of HPMC K4 M and HPMC K15 M (1:1) polymer favoured the sustained release of ranitidine hydrochloride from gastroretentive tablet formulations. Drug release study was evaluated for 12 hours using USP XXII paddle-type dissolution apparatus using 0.1N HCl as dissolution medium drug release of 97% of F6 formulation. The release mechanisms were explored and explained with zero order, first order, Higuchi and Korsmeyer equations. It was found that polymer content and amount of floating agent significantly affected the mean dissolution time, percentage drug release after12 hours, release rate constant and diffusion exponent.

Keywords: ranitidine hydrochloride, HPMC K 4 M, *in vitro* buoyancy, *invitro* release, zero order, first order, Higuchi and Korsmeyer equations..

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INTRODUCTION

Ranitidine hydrochloride is a histamine H_2-receptor antagonist that inhibits stomach production. Its chemical name is N'-[2-[[5-(Dimethylaminomethyl)-2-furyl]methylsulfanyl]ethyl]-N-methyl-2-nitro-ethene-1,1-diamine [1]. It is commonly used in treatment of peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD). Ranitidine is also used alongside fexofenadine and other antihistamines for the treatment of skin conditions such as hives. Ranitidine HCl, the model drug for this study, is a histamine H_2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of ranitidine 4 times a day [2]. 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 sustained-release dosage form of Ranitidine HCl is desirable [3]. The short biological half-life of the drug (~2.5-3 hours) also favors development of a sustained-release formulation. A traditional oral sustained-release formulation releases most of the drug at the colon; thus, the drug should have an absorption window either in the colon or throughout the gastrointestinal tract. Ranitidine is absorbed in only the initial part of the small intestine and has 50% absolute bioavailability [4,5]. Moreover, colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon [6]. These properties of Ranitidine HCl do not favor the traditional approach to sustained-release delivery. Hence, clinically acceptable sustained-release dosage forms of Ranitidine HCl prepared with conventional technology may not be successful. The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. It is also reported that oral treatment of gastric disorders with an H_2-receptor antagonist like ranitidine or famotidine used in combination with antacids promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the drugs' ability to reduce acid secretion [7]. This principle may be applied for improving systemic as well as local delivery of Ranitidine HCl, which would efficiently reduce gastric acid secretion.

An oral controlled release system has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. Gastro retentive dosage forms significantly extend the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance. Such retention systems are important for those drug that are degraded in the intestine like antacids or certain antibiotics, enzymes that act locally in the stomach [8,9].

In the present investigation floating tablets of ranitidine hydrochloride by direct compression technique using varying concentrations of different grades of polymers (HPMC K4

M and HPMC K15 M) with sodium bicarbonate and citric acid were evaluated for their gel forming and release controlling properties. The aim of the work was to evaluate the effect of gel forming polymer methocil on floating properties and release characteristics of ranitidine hydrochloride tablets.

EXPERIMENTAL

Materials

Ranitidine hydrochloride sample gift sample from m/s Micro labs pvt. ltd., Hosur Tamilnadu., HPMC K4 M and HPMC K15 M. as a gift sample from Dr. Reddy Laboratories Hyderabad., Sodium Bicarbonate and Citric acid, was purchased from S.D. Fine Chemicals Mumbai. Talc and Magnesium Stearate was purchased from Merk India Ltd, Mumbai. Other chemicals used where analytical grade.

Bulk density: Apparent bulk density was determined by placing pre-sieved drug excipient blend in to a graduated cylinder and measuring the volume and weight as it is [10].

Tapped density: Tapped density was determined by USP method II tablet blend was filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula

$$Dt = M/Vb$$

Where, M = Weight of powder taken; Vb = tapped volume [11].

Angle of Repose: Angle of repose was determined by using funnel method. Tablet blend were poured from funnel, that can be raised vertically until a maximum cone height h was obtained diameter heap D, was measured. The repose angle q was calculated by

$$\text{Formula } Tanq = 2h/D.$$

Compressibility index and Hausner ratio:

This was measured for the property of a powder to be compressed; as such they are measured for relative importance of interparticulate interactions.

Compressibility index was calculated by following equation

$$\text{Compressibility index} = (Dt - Db) \times 100$$

Where, Dt = tapped density; Db = bulk density;

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Hausner ratio

Hausner ratio was calculated by following equation

$$\text{Hausner ratio} = Dt/ Do$$

Where, Dt = tapped density; Do = bulk density [12]

Evaluation of tablet

Weight variation: Twenty tablets were randomly selected from each batch individually weigh, the average weight and standard deviation of 20 tablet calculated [13].

Thickness: The thickness of the tablet was measured by using digital venire caliper, twenty tablets from each batch were randomly selected and thickness was measured [14].

Hardness: Hardness was measured using Pfizer hardness tester, for each batch three tablets were tested [17].

Friability: Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted weight [15].

Drug content uniformity: The drug content was determined by taking an accurately weight amount of powdered ranitidine hydrochloride 100 mg with water and solution was filtered through 45µ membrane. The absorbance was measured at 314nm m, using double beam uv visible spectrophotometer [16].

Preparation of floating tablets

Effervescent Floating tablets containing ranitidine hydrochloride were prepared by direct compression technique using varying concentrations of different grades of polymers (HPMC K4 M and HPMC K15 M) with sodium bicarbonate and citric acid. All the ingredients were accurately weighed as show in Table -1 and passed through different mesh sieves accordingly. Then, except Magnesium stearate and talc all other ingredients were blended uniformly in glass mortar After sufficient mixing of drug as well as other components, Magnesium stearate and talc was added, as post lubricant, and further mixed for additional 2-3 minutes. The blend was characterized for the different physical parameters such as bulk density, Tapped density, Angle of repose, Hausners ratio and Carr's index. The tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation. Tablets were compressed at 400 mg weight on an 8-station mini rotary tableting machine (General Machinery Co, Mumbai, India) with 12-mm punches.

***In- vitro buoyancy* studies**

In-vitro buoyancy studies were performed for all the ten formulations as per the method described by Rosa *et al* [17]. The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT) tablet is given in Table 3

Drug Content Estimation

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 314nm using 0.1 N hydrochloric acid as blank.

Estimation of ranitidine hydrochloride [18].

Ranitidine hydrochloride content in the tablets was estimated by using UV spectrophotometric method based on the measurement of absorbance at λ max 314nm in phosphate buffer solution (PBS, $_{P}$H 3.0). Ranitidine hydrochloride content of the tablet is given in Table 4.

Drug release study

The releases of ranitidine hydrochloride from different formulations were determined using *United States Pharmacopeia* (USP) paddle apparatus 2 under sink conditions. The dissolution medium was 900 ml of a 0.1 N HCl solution (pH=1.2), at 37±0.2°C and the stirring speed was 75 rpm of the A samples (10ml) were with drawn with every one hour up to a period of 24 hrs. The sample were diluted suitably and filtered. The required dilutions were made with and the solution was analyzed for the drug content by using Schimadzu UV- 1700 UV/VIS double beam spectrophotometer at λ max 314nm. From this percentage drug release was calculated and this was plotted against function of time to study the pattern of drug release. The in-vitro drug release profiles of tablet from each batch (F1 to F7) were shown in Table 5. The plot of cumulative percentage drug release versus time (hr) was plotted and depicted as shown in Figure 5. The release data obtained were treated according to zero-order [19] (cumulative amount of drug release versus time), first-order [20] (log cumulative percentage of drug remaining versus time), Higuchi [21] (cumulative percentage of release versus square root of time) and Korsmeyer-Peppas [22] (log cumulative percentage of drug released versus log time) equation models

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RESULTS AND DISCUSSION

The physical characteristics of tablets (F1 to F7) such as tablet size, hardness, friability and weight variation were determined and the results are shown in Table-4. Preformulation studies of the powder and physical parameters of the compressed tablets (Table.2) were found to be satisfactory. The hardness of the formulations satisfied the acceptance criteria. The friability and weight variation was found to be within the limits specified in Pharmacopoeia. The drug content was found spectrophotometricaly for all the formulations (F1 to F7). The values are shown in Table-5 the drug content was found to be within a narrow range as specified in Pharmacopoeia (90-100%) in all formulations. Buoyancy lag time and duration of floating were determined using 100 mL beaker containing 0.1N HCl medium are shown in Table-3 and the results it can be concluded that the batch containing only HPMC K4M and HPMC K15M showed good Buoyancy lag time is 20 t0 130 sec and Total floating time is 12h. The floating formulations F1 to F7 were subjected for the dissolution studies using USP dissolution apparatus 2 (paddle) in 900 mL of 0.1N HCl medium. The effervescent floating tablets of ranitidine hydrochloride were formulated in seven different batches F1 to F7 by using hydrophilic polymers HPMC K 4 M and HPMC K 15M along with effervescing agent sodium bicarbonate and citric acid as showing in table 1. The first trial F1 was carried out using the polymer HPMC K4M (low viscosity polymer) with 50mg of sodium bicarbonate and 25 mg of citric acid other excipients to control the release of drug. The floating lag time and the total buoyancy time were found to be 142 sec. The drug release obtained was 32 in first two hours, 96 % of the drug was found to be released in subsequent 12 hours respectively (table 4).The first trial F2 was carried out using the polymer HPMC K4M (low viscosity polymer) with 75mg of sodium bicarbonate and 50mg citric acid other excipients to control the release of drug. The floating lag time and the total buoyancy time were found to be 125 sec. The drug release obtained was 30 in first two hours, 94 % of the drug were found to be released in subsequent 12 hours respectively (table 4). The first trial F3 was carried out using the polymer HPMC K15M (high viscosity polymer) with 50mg of sodium bicarbonate and 25 mg of citric acid other excipients to control the release of drug. The floating lag time and the total buoyancy time were found to be 105 sec. The drug release obtained was 29 in first two hours, 96 % of the drug was found to be released in subsequent 12 hours respectively (table 4). The first trial F4 was carried out using the polymer HPMC K15M (high viscosity polymer) with 75mg of sodium bicarbonate and 50mg citric acid other excipients to control the release of drug. The floating lag time and the total buoyancy time were found to be 84 sec the drug release obtained was 27 in first two hours, 95 % of the drug was found to be released in subsequent 12 hours respectively (table 4). To get desired drug release a combination of two grades were planned in further trials. The next trial F5 was planned using a combination of HPMC K4M and HPMC K15M in the ratio of 1:1. With 50mg of sodium bicarbonate and 25 mg of citric acid the floating lag time and total buoyancy time was found to be 30 sec. The drug release obtained was 34 in first two hours, 97 % of the drug were found to be released in subsequent 12 hours respectively (table 4). The next trial F6 was planned using a combination of HPMC K4M and HPMC K15M in the ratio of 1:1. With 75mg of sodium bicarbonate and 50mg citric acid the floating lag time and total buoyancy time was found to be 25 sec. The drug release obtained was 35 in first two hours, 97 % of the drug were found to be

released in subsequent 12 hours respectively (table 4). The next trial F7 (Table.1) was planned using a combination of HPMC K4M and HPMC K15M in the ratio of 1:1. With 50mg of sodium bicarbonate and 25mg citric acid the floating lag time and total buoyancy time was found to be 20 sec. The drug release obtained was 26 in first two hours, 95 % of the drug were found to be released in subsequent 12 hours respectively (table 4). Among these formulations, the release rate was increased in the following order: F2 > F4 > F7 > F1 > F5 > >F3 > F6. To know the mechanism of drug release from these formulations, the data were treated using zero order, first order, Higuchi plot, Korsmeyer Peppa's plot and Hixon-Crowell Model were shown in figure 1, 2, 3, 4 and 5 respectively. Optimized formulation F6 was subjected to curve fitting analysis, zero order, and first order, Higuhi Kinetics, Korsmeyer and Peppas model. The slope and r2 are shown in Table 6 and 7. Optimized formulation F6 fitted best for Korsemeyer – Peppas equation with R^2 value of 0.9613. The released the drug 97 % in 12 hours. It is thus concluded that effervescent floating tablet containing ranitidine hydrochloride (F6 formulation) gave slow and complete drug release spread over 12 hours.

CONCLUSIONS

This study discusses the preparation of floating tablets of ranitidine hydrochloride The effervescent-based floating drug delivery was a promising approach to achieve The addition of gel-forming polymer HPMC K4 M and HPMC K15 M and gas-generating agent sodium bicarbonate and Citric acid was essential to achieve *in vitro* buoyancy. The results indicated that a high amount of floating agent and combination of HPMC K4 M and HPMC K15 M (1:1) polymer favoured the sustained release of ranitidine hydrochloride from gastroretentive tablet formulations. At relatively higher polymer contents all formulations displayed better fitting with zero order release kinetics. Addition of citric acid, to achieve buoyancy under the elevated pH of the stomach, caused an enhancement in drug release. In all cases the increase of the floating agent content caused a lowering of the magnitude of release exponent indicating the shifting of release mechanism from non- Fickian. All these results indicated that a low amount of floating agent and high amount of hydrophilic polymer favored the sustained release of ranitidine hydrochloride from gastro retentive tablet formulations. A lesser FLT and a prolonged floating duration could be achieved by varying the amount of effervescent and using different polymer combinations. The *in vitro* drug release profiles obtained for tablets (F6) made with combinations of HPMC K4 M and HPMC K15 M showed lesser FLT (25s) and a prolonged floating duration (> 12hrs) which was a controlled release characteristic (97%) for 12 h.

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Table 1: Composition of different floating tablet formulations of ranitidine hydrochloride

S. No.	Item Name	F1	F2	F3	F4	F5	F6	F7
1	Ranitidine Hydrochloride	120	120	120	120	120	120	120
2	HPMC K 4 M	100	100	--	--	50	50	50
3	HPMC K 15 M	--	--	100	100	50	50	50
4	Sodium Bicarbonate	50	75	50	75	50	75	50
5	Citric Acid	25	50	25	50	25	50	25
6	PVP K-30	30	30	30	30	30	30	30
7	Directly Compressible Lactose	70	20	72	20	70	20	70
8	Magnesium Stearate	3	3	3	3	3	3	3
9	Talc	2	2	2	2	2	2	2
Total		400	400	400	400	400	400	400

Table 2: Table Show evaluations powder blend.

Formulation	Bulk Density	Tapped Density	Angle of Repose(θ)	Compressibility Index (%)	Hausner's Ratio
F1	0.498	0.582	25.32	14.43	1.16
F2	0.432	0.515	26.78	16.11	1.19
F3	0.502	0.591	28.14	15.05	1.17
F4	0.498	0.578	29.12	13.84	1.16
F5	0.487	0.559	30.01	12.88	1.14
F6	0.427	0.487	28.82	12.32	1.14
F7	0.496	0.576	29.81	13.88	1.16

Table No. 3: Batch Buoyancy Lag Total Floating

Batch	Time (seconds)	Time (hrs)
F1	142sec.	> 12
F2	125sec.	> 12
F3	105sec	> 12
F4	84sec.	> 12
F5	30sec.	> 12
F6	25sec	>12
F7	20sec	>12

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Table 4: Hardness, Friability, Weight variation, Drug content and Thickness of tablets of different formulation F1 to F7

Formulation	Hardness Test (Kg/cm^2)	Friability (%)	Weight variation	Drug content (%)	Thickness (mm)
F1	6.22	0.32	1.93	98.97	4.08
F2	5.72	0.76	1.22	99.12	4.10
F3	6.02	0.82	1.71	99.14	4..05
F4	5.24	0.49	2.13	99.58	4.15
F5	6.52	0.39	1.98	99.73	4.10
F6	6.29	0.59	2.39	99.45	4.08
F7	6.53	0.66	2.45	99.26	4.08

Table 5: Cumulative % drug released of F1 to F7 (0.1N HCl)

Formulation	2hr	4hr	6hr	8hr	12hr
F1	32	49	70	88	96
F2	30	44	68	84	94
F3	29	39	59	68	96
F4	27	37	56	65	95
F5	34	42	72	86	97
F6	35	76	88	99	103
F7	26	32	69	89	95

Table 6: Kinetic Values Obtained from *In-Vitro* Release Profile for floating Tablets of ranitidine hydrochloride (Zero order and First order)

Formulation	Zero Order Plot			First Order Plot		
	Slope (n)	Rate Constant Ko= -Slope	Regression Coefficient (r)	Slope (n)	Rate Constant K= -Slope X 2.303	Regression Coefficient (r)
F1	8.0286	-8.0286	0.9142	-0.1197	-0.27567	0.975
F2	7.9	-7.9	0.9268	-0.1044	-0.24043	0.9802
F3	7.6286	-7.6286	0.9752	-0.1084	-0.24965	0.8752
F4	7.55	-7.55	0.9821	-0.1008	-0.23214	0.8729
F5	8.0857	-8.0857	0.9178	-0.1273	-0.29317	0.9598
F6	7.95	-7.95	0.8989	-0.1378	-0.31735	0.9547
F7	8.4357	-8.4357	0.9115	-0.1169	-0.26922	0.9459

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Table 7: Kinetic Values Obtained from *In-Vitro* Release Profile for Floating Tablets of ranitidine hydrochloride (Higuchi, Korsmeyer Peppa's and Hixon-Crowell's models)

Formulation	Higuchi's		Korsmeyer Peppa's		Hixon-Crowell's	
	Slope (n)	Regression Coefficient (r)	Slope (n)	Regression Coefficient (r)	Slope (n)	Regression Coefficient (r)
F1	29.501	0.9748	0.512	0.9276	-0.2549	0.984
F2	28.744	0.9689	0.508	0.8938	-0.2345	0.9853
F3	26.976	0.9631	0.4732	0.8554	-0.2325	0.9416
F4	26.455	0.9523	0.4709	0.8181	-0.2224	0.9341
F5	29.452	0.9616	0.5042	0.897	-0.2632	0.9817
F6	29.643	0.987	0.5038	0.9613	-0.2709	0.9963
F7	29.915	0.9053	0.5466	0.7541	-0.2573	0.9405

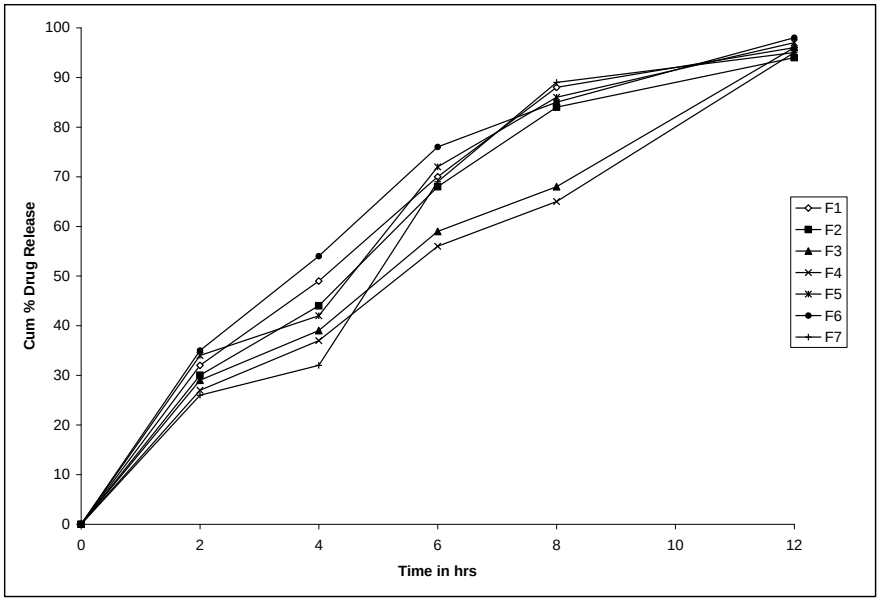

Fig: 1 Zero order release Plot of ranitidine hydrochloride floating matrix tablets

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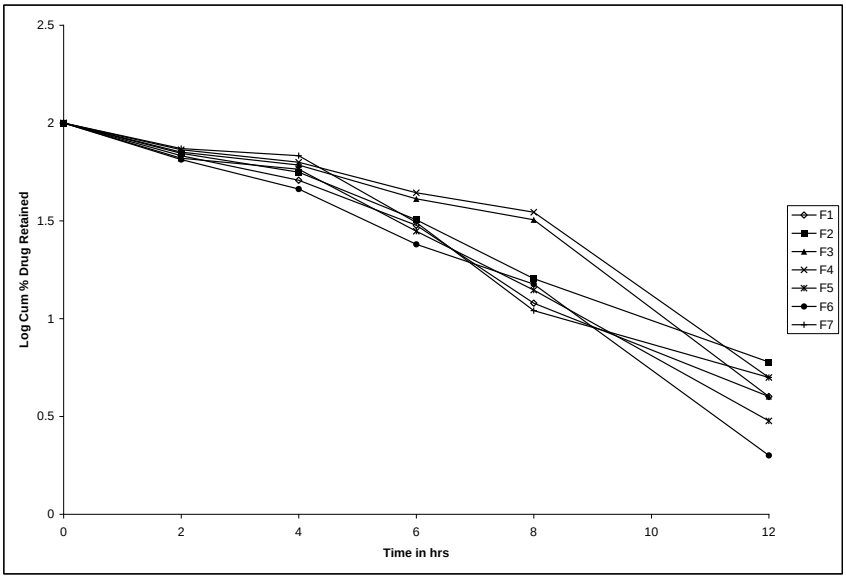

Fig: 2 first order release Plot of ranitidine hydrochloride floating tablets

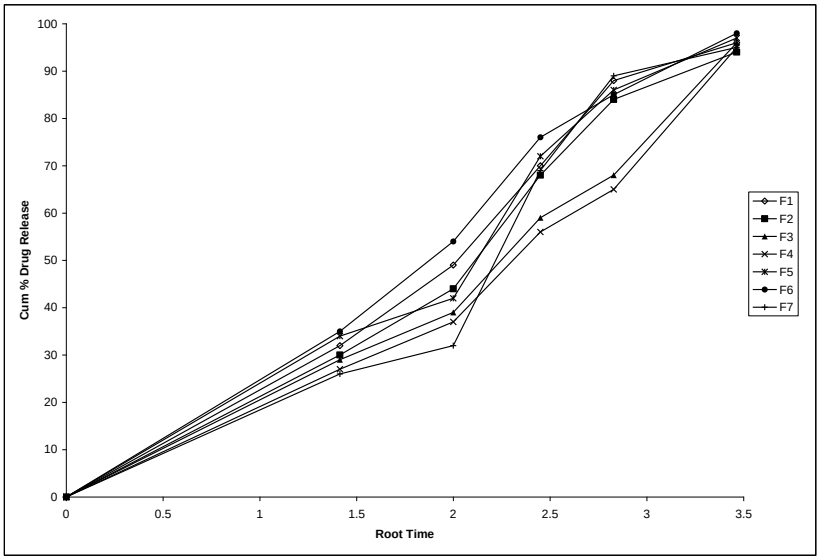

Fig: 3 Higuchi Plot of ranitidine hydrochloride floating tablets

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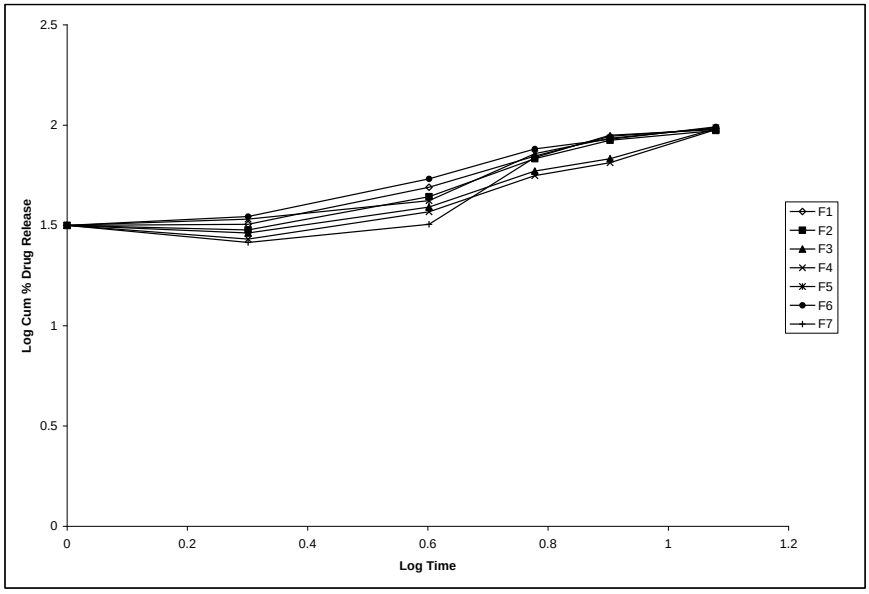

Fig: 4 Korsmeyer Peppa's Plot of ranitidine hydrochloride floating tablets

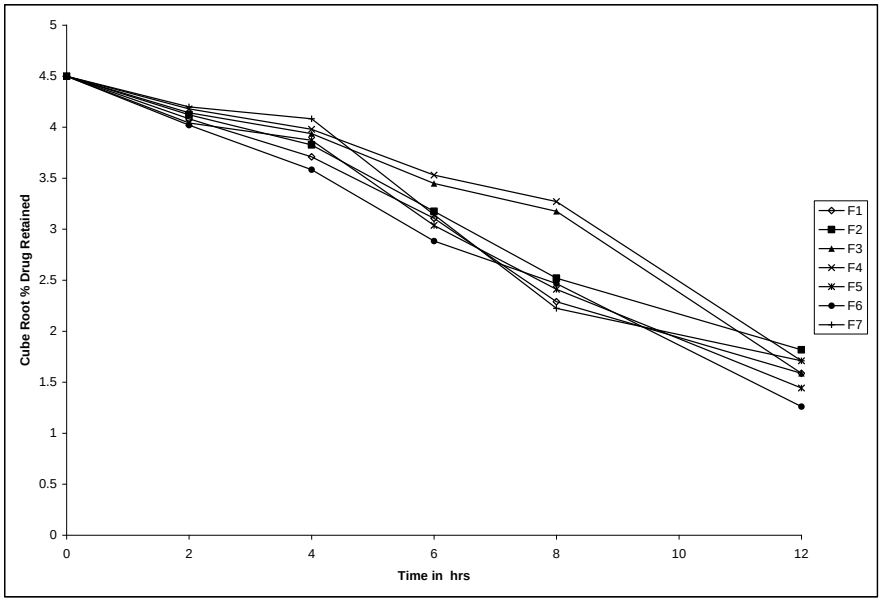

Fig: 5 Hixon-Crowell Plot of ranitidine hydrochloride floating tablets

REFERENCES

[1] Reynolds JEF. Martindale the Extra Pharmacopoeia, The Royal Pharmaceutical Society: London, 1996, pp.1218-20.

[2] Flynn M. Histamine H_2 antagonists. In: Hagemann RC, Threlkeld DS, eds. Drug Facts and Comparisons. 50th ed. St Louis, MO: Wolters Kluwer Co; 1996:1862-1876.
[3] Somade S, Singh K. Indian J Pharm Sci 2002;64:285.
[4] Lauritsen K. Clin Pharmacokinet 1990;19(2):94-125.
[5] Grant S. Drugs 1989;37:801-870.
[6] Basit A, Lacey L. Int J Pharm 2001;227:157-165.
[7] Coffin M, Parr A, inventors. Glaxo Inc, assignee. Ranitidine solid dosage form. US patent 5 407 687. April 18, 1995.
[8] Singh B, Kim K. J Control Release 2000; 63:235-59.
[9] Chawla G, Bansal A. Pharm Tech 2003;27:50-68.
[10] Basak SC, Shrinivasa R, Manavalan R and Rao P. Indian J Pharm Sci 2004; 66(6): 827-833
[11] Shabaraya AR and Narayanacharyulu R. J Pharm Pharmaceutical Sci 2000; 8(1): 231-236.
[12] Shirwaikar AA, Jacob S and Grover V. Indian J Pharm Sci 2005; 67 (1): 80-83
[13] Krishanaiah YS, Lath K, Nageshwara L, Karthikeyan RS, Bhaskar Pand Satyanarayana V. Indian J Pharm Sci 2003; 65 (4): 378-385
[14] The British Pharmacopoeia, department of health/by stationary office on behalf of the medicine and health care product regulatory agency, crown copy right, 2005; 5th Ed. 1303-1304, 2588-2589, A133.
[15] The United State of Pharmacopoeia 24/ Nf19 Asian Edition, The official compendia of standard United States Pharmacopoeial convection Inc. Rockville. 1995; 1015,1016, 1791
[16] Chaudhari PD. Indian Drug 2005; 42(10): 641-649
[17] Roldy RK, Midovert S and Redlen S. Pharm Sci Tech 2003; 4(4):55-59
[18] Rosa M, Zia H, Rhodes T. Int J Pharm 1994;105:65-70.
[19] Khan GM. The Sciences 2001; 1: 350-354.
[20] Morkhade DM. Indian J Pharm Sci 2006; 68: 53-58.
[21] Higuchi T. J Pharm Sci 1963; 52: 1145-1149.
[22] Peppas NA, Sahlin JJ. Int J Pharm 1989; 57:169–172.