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Research Article

FORMULATION AND EVALUATION OF FLOATING MATRIX TABLET OF RANITIDINE HYDROCHLORIDE

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Abstract

Gastric ulcer, one of the most widespread, is believed to be due to an imbalance between aggressive and protective factors. The gastric mucosa is continuously exposed to potentially injurious agents such as acid, pepsin, bile acids, food ingredients, bacterial products (*Helicobacter pylori*) and drugs. These agents have been implicated in the pathogenesis of gastric ulcer, including enhanced gastric acid and pepsin secretion, inhibition of prostaglandin synthesis and cell proliferation growth, diminished gastric blood flow and gastric motility. Drug treatment of peptic ulcers is targeted at either counteracting aggressive factors (acid, pepsin, active oxidants, platelet aggravating factor "PAF", leukotrienes, endothelins, bile or exogenous factors including NSAIDs) or stimulating the mucosal defences (mucus, bicarbonate, normal blood flow, prostaglandins(PG), nitric oxide). The goals of treating peptic ulcer disease are to relieve pain, heal the ulcer and prevent ulcer recurrence.

Keywords: Ranitidine, histamine receptor, FTIR etc.

Introduction

Ranitidine is a H_2 antihistamine drug. It is a drug used to block the action of histamine on parietal cells in the stomach decreasing acid production by these cells. It has a furan ring. It has melting point 69-70 °C. The wavelength of ranitidine is at 229 nm and 315 nm (water used as medium). The chemical name of Ranitidine HCl is N [2-[[[5-[(dimethylamino) methyl]-2furanyl] methyl] thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, HCl.

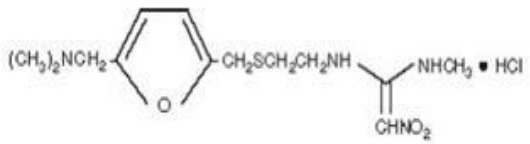


Figure 1: Structure of Ranitidine Hydrochloride

It was a white or pale yellow crystalline powder drug having melting point 136-142 °C. It is freely soluble in water, methanol and ethanol (95%), sparingly soluble in ethanol, very slightly soluble in chloroform and in dichloro methane. The molecular formula of Ranitidine HCl is $C_{13}H_{22}N_4O_3S$•HCl and the molecular weight is 350.87. It is preserve in well closed container, Protected from light. Ranitidine HCl is H_2 receptor antagonist inhibits acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of parietal cells. It competitively inhibits histamine action at all H_2 receptors but their main clinical use is as inhibition of gastric acid secretion. It inhibited histamine stimulation and gastrin stimulated acid secretion. It decreases both basal and food stimulated acid secretion by 90% or more, but promote healing of duodenal ulcer.

Table 1: Pharmacokinetics of Ranitidine

Bioavailability	45-50%
Plasma Half Life	2 hrs.
Plasma Protein Binding	15- 20%
Peak Plasma Concentration (C_{max})	1- 3 hours
Excretion	Renal Excretion (65-70%) Metabolic Excretion (30-35%)
Renal Clearance	600 ml/min
Drug Interaction	It does not inhibit hepatic microsomal enzyme CYTP450 system and hence does not interact with drugs which are substrate for CYTP450 systems like Warfarin, Pheytoin, Quinidine, Caffiene etc. It does not block androgen receptors and do not cause Gynaecomastia and impotence like cimetidine.

Materials and Methods

Ranitidine was received as a gift sample from Gifted from Belco Pharma, Bahadurgarh. Ethyl cellulose, microcrystalline cellulose, xanthan gum, dibasic calcium phosphate and hypromellose were purchased from Central Drug House, Mumbai. Povidone was purchased from Merck Specialities Pvt Ltd, Mumbai. Magnesium stearate and talc were purchased from Qualikems Fine Chemicals Pvt Ltd, Delhi. Lactose was purchased from Central Drug House (P) Ltd. New Delhi, India. Isopropyl alcohol was purchased from Nice Chemicals Pvt Ltd, Cochin. HCl was purchased from Merck Specialities Pvt Ltd, Mumbai.**Experimental work**

Formulation of floating matrix tablet

Selection of manufacturing process

Batches were prepared with HPMC K15M using wet granulation method and direct compression method and their release profiles were compared. Formula is given in Table 2.

Table 2: Formulation of Ranitidine using HPMC K15M with direct compression and wet granulation methods

Batch No.	**P1 (Wet Granulation)**	**P2 (Direct Compression)**
Ingredients Name	**mg/tab**	**mg/tab**
Ranitidine	150	150
HPMC K15M	90	90
Sodium bicarbonate	70	70
Citric Acid	30	30
Lactose	39	-
Microcrystalline Cellulose	-	54
Povidone	15	-
Isopropyl Alcohol	q.s.	-
Magnesium Stearate	3	3
Talc	3	3
Total	400	400

Formulation of batches with different ratio of Sodium bicarbonate and Citric acid

Batches were prepared with HPMC K15M using wet granulation method to select the proportion of Sodium bicarbonate and Citric Acid and their release profiles were compared. Formula is given in Table 3

Preparation of trial batches with different polymers with different concentration

Formulation batches were prepared using different polymers (HPMC K15M, Xanthan gum, and Ethyl Cellulose). Formula is given in Table 4

Table 3: Formulation of batch with different ratio of Sodium bicarbonate and Citric acid

Batch No.	P1	P3	P4
Ingredients	**mg/tab**	**mg/tab**	**Mg/tab**
Ranitidine	150	150	150
HPMC K15M	90	90	90
Sodium bicarbonate	70	80	90
Citric Acid	30	20	10
Lactose	39	39	39
Povidone	15	15	15
Isopropyl Alcohol	q.s.	q.s.	q.s.
Talc	3	3	3
Magnesium Stearate	3	3	3
Total	400	400	400

Table 4: Formulation of different batches with different polymer concentration

Batch no.	P4	P5	P6	P7	P8	P9	P10
Ingredients	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**Mg/tab**	**mg/tab**	**mg/tab**
Ranitidine	150	150	150	150	150	150	150
HPMC K15M	90	110	120	90	80	70	60
Ethyl Cellulose	-	-	-	-	-	25	40
Xanthan Gum	-	-	-	25	40	-	-
Sodium bicarbonate	90	90	90	90	90	90	90
Citric Acid	10	10	10	10	10	10	10
DCP	-	-	-	14	9	34	-
Lactose	39	19	9	-	-	-	29
Povidone	15	15	15	15	15	15	15
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc	3	3	3	3	3	3	3
Magesium Stearate	3	3	3	3	3	3	3
Total	400	400	400	400	400	400	400

Effect of various diluents with their elastic or plastic properties:

Formulations were prepared using different diluents such as dibasic calcium phosphate and Lactose and compared to select the best diluent for further formulations. Formula is given in Table 5.

Evaluation of floating matrix tablet

Characterization of granules prepared by selected manufacturing process for all the formulation batches

Flow property of all formulation batches was accessed through the parameters like Tapped density, Bulk density, Angle of repose, Carr's index, Hausner's ratio.

Among all the batches it was found that batches P1, P8, P9 and P10 exhibited acceptable flow property with respect to angle of repose, Carr's index, Hausner's ratio.

Evaluation of tablets:

Hardness, Thickness, Friability, Average weight was performed for all the batches (P1 to P11) and the data are presented in Table 7

Parameters like Hardness, Thickness, Friability, Average weight were found to give satisfactory results for all trials.

In vitro buoyancy studies

On immersion in 0.1 N HCl solutions (pH 1.2) at 37° C, all the tablets first sank in the release medium and then they float to the surface. All the tablets remained buoyant up to 24 h. Results are shown in Table 8

Table 5: Formulation of Ranitidine by using different diluents with their elastic or plastic properties

Batch no.	P8	P11
Ingredients	**mg/tab**	**mg/tab**
Ranitidine	150	150
HPMC K15M	80	80
Xanthan Gum	40	40
Sodium bicarbonate	90	90
Citric Acid	10	10
Lactose	-	9
DCP	9	-
Povidone	15	15
Isopropyl Alcohol	q.s.	q.s.
Talc	3	3
Magnesium Stearate	3	3
Total	400	400

Table 6: Tapped density, Bulk density, Angle of repose, Carr's index, Hausner's ratio values of different batches blend of Ranitidine

Batch No.	Bulk Density	Tapped Density	Angle of Repose	Hausner's ratio	Carr's index
P1	0.595	0.742	37.8(fair)	1.24 (fair)	19.81 (fair)
P2	0.547	0.767	49.6 (poor)	1.40 (poor)	28.68 (poor)
P3	0.582	0.754	42.2 (passable)	1.29 (passable)	22.81 (passable)
P4	0.570	0.768	43.4 (passable)	1.34 (passable)	25.78 (passable)
P5	0.584	0.787	44.3(passable)	1.34 (passable)	25.79 (passable)
P6	0.598	0.798	42.2 (passable)	1.33 (passable)	25.06 (passable)
P7	0.618	0.759	37.6 (fair)	1.22 (fair)	18.57 (fair)
P8	0.677	0.784	33.5 (good)	1.15 (good)	13.64 (good)
P9	0.604	0.764	41.8 (passable)	1.26 (passable)	20.94 (passable)
P10	0.625	0.778	36.2 (fair)	1.24 (fair)	19.66 (fair)
P11	0.652	0.776	37.7 (fair)	1.19 (fair)	15.97 (fair)

Table 7: Results of evaluation of parameters of tablets from different batches

Batch no.	Average weight (mg)	Thickness (mm)	Friability (%)	Hardness (kp)
P1	402	4.1	0.03	6
P2	397	3.9	0.05	4
P3	402	4.1	0.04	6
P4	400	4.0	0.06	6
P5	399	3.9	0.01	5
P6	402	4.1	0.08	6
P7	398	3.7	0.07	4
P8	399	3.8	0.03	6
P9	400	4.1	0.05	5
P10	401	3.9	0.04	5
P11	402	4.2	0.05	6

Table 8: Results of buoyancy study (Floating lag times and Floating duration)

Formulation code	Floating lag time (sec)	Floating Duration (h)
P1	140	24 h
P2	124	24 h
P3	116	24 h
P4	102	24 h
P5	125	24 h
P6	247	24 h
P7	97	24 h
P8	70	24 h
P9	81	24 h
P10	90	24 h
P11	121	24 h

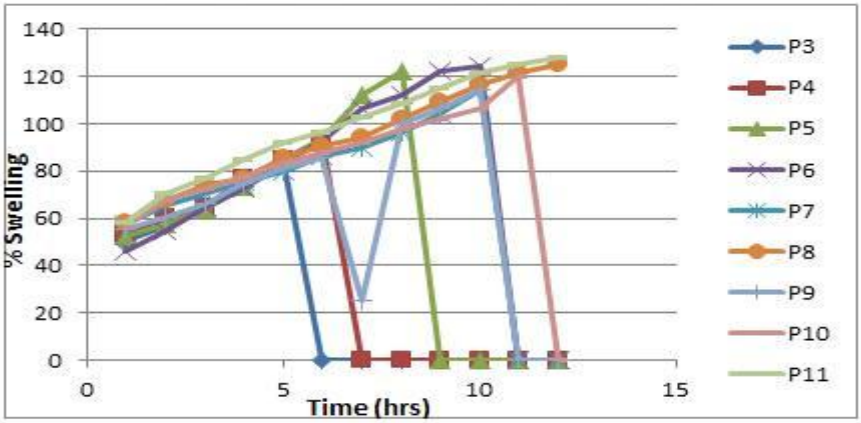
Swelling Index

The swelling of the polymers used (HPMC K15M, Ethyl cellulose, Xanthan Gum) were determined by water uptake of the tablet. The percent swelling of the tablet was determined for 12 h at different time intervals. Increase in percent swelling was found with increasing concentration of polymers. The percent swelling of P11 was found to be higher (128.16%) than that of other formulations. The percent swelling increased gradually up to 12 h. Results of swelling index shown in Table 9

Table 9: Results of swelling index

Time (hr)	P3	P4	P5	P6	P7	P8	P9	P10	P11
1	50.09	53.45	52.85	45.77	57.64	58.63	55.30	57.19	58.63
2	57.15	60.18	57.58	54.87	65.23	67.50	60.56	67.50	70.54
3	65.79	64.52	64.01	65.06	70.45	74.10	65.94	72.99	77.30
4	73.61	77.26	73.5	72.41	75.29	77.01	74.63	77.35	85.01
5	83.03	85.03	84.67	83.63	80.02	85.44	81.01	83.19	92.06
6	-	93.50	93.80	93.05	86.12	90.94	85.49	87.53	96.48
7	-	-	112.02	106.41	90.22	94.16	25.02	92.04	102.81
8	-	-	122.51	112.3	96.51	102.19	100.09	97.51	108.32
9	-	-	-	122.49	104.52	109.02	106.71	102.48	115.16
10	-	-	-	124.55	114.58	116.57	114.23	106.21	121.21
11	-	-	-	-	-	121.38	-	120.38	125.01
12	-	-	-	-	-	125.45	-	-	128.16

Fig 2: Plot of swelling index versus time



Study of Release Kinetics of batch P8

Table 10: *In vitro* drug release parameters for P8

Time (hrs)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log time
1	22.58	1.3537	4.2620	1.8888	1	0
2	29.28	1.4665	4.1353	1.8495	1.4142	0.3010
3	45.62	1.6591	3.7886	1.7354	1.7320	0.4771
4	56.43	1.7515	3.5188	1.6391	2	0.6020
5	62.20	1.7937	3.3560	1.5774	2.2360	0.6989
6	66.85	1.8251	3.2123	1.5204	2.4494	0.7781
7	73.23	1.8646	2.9914	1.4276	2.6457	0.8450
8	79.56	1.9006	2.7341	1.3104	2.8284	0.9030
9	86.17	1.9353	2.4003	1.1408	3	0.9542
10	90.08	1.9546	2.1486	0.9965	3.1622	1
11	95.52	1.9800	1.6485	0.6512	3.3166	1.0413
12	100.31	2.0013	-0.6694	-0.5228	3.4641	1.0791

Fig 3: Ranitidine release kinetics of batch P8 according to Zero order kinetics.

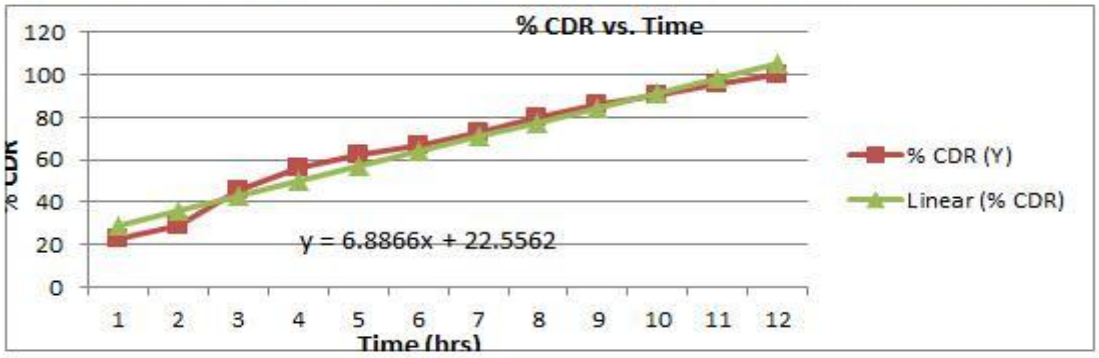


Fig 4: Ranitidine release kinetics of batch P8 according to First order kinetics.

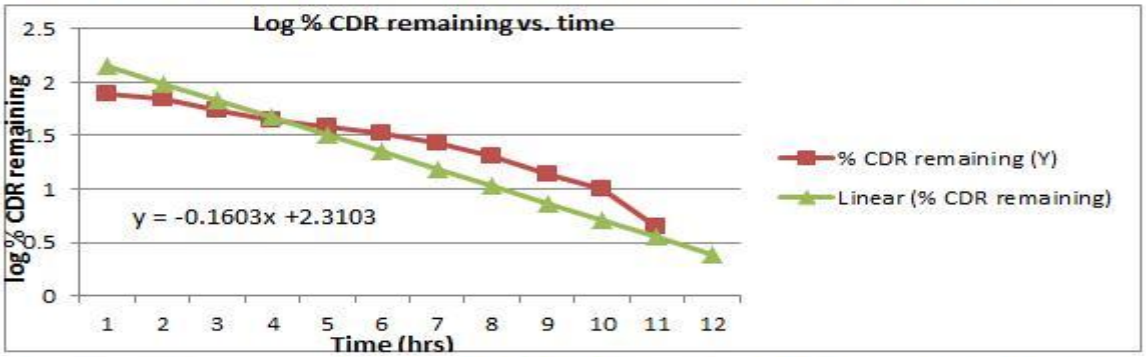


Fig 5: Ranitidine release kinetics of batch P8 according to Hixon-Crowell's kinetics.

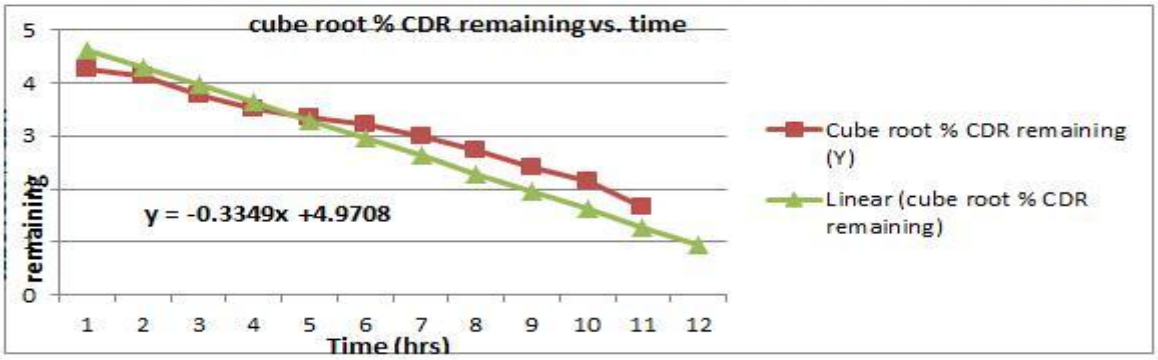


Fig 6: Ranitidine release kinetics of batch P8 according to Higuchi kinetics.

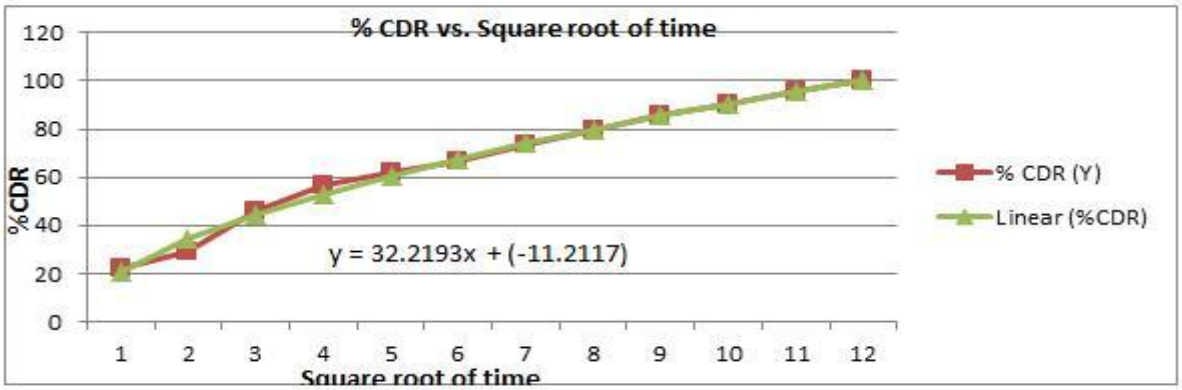
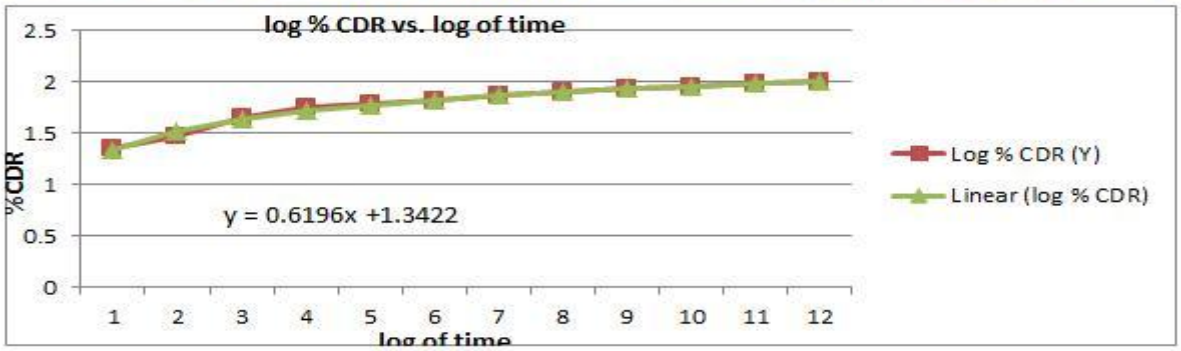


Fig 7: Ranitidine release kinetics of batch P8 according to Korsmeyer- Peppas kinetics.



The statistical kinetics values for the batch P8 is represented in Table 11

Table 11: Statistical kinetics values of batch P8

Kinetic models	R^2	Slope
Zero-order	0.9902	6.8866
First-order	0.9958	-0.1603
Higuchi kinetics	0.9801	32.2193
Hixon-Crowell	0.9901	-0.3349
Korsmeyer-Peppas	0.9873	0.6196

Among the entire kinetic model studied for the batch (P8), it was found that the batch followed **first order kinetics** because of having maximum R^2 value of 0.9958 (closest to 1.0).

Study of Release Kinetics of batch P11

Table 12: *In vitro* drug release parameters for P11

Time (hrs)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log time
1	18.90	1.2764	4.3285	1.9090	1	0
2	31.16	1.4935	4.0983	1.8378	1.4142	0.3010
3	40.54	1.6078	3.9030	1.7742	1.7320	0.4771
4	53.69	1.7298	3.5910	1.6656	2	0.6020
5	58.50	1.7671	3.4621	1.6180	2.2360	0.6989
6	63.26	1.8011	3.3243	1.5651	2.4494	0.7781
7	71.28	1.8529	3.0623	1.4581	2.6457	0.8450
8	76.32	1.8826	2.8716	1.3743	2.8284	0.9030
9	81.17	1.9093	2.6604	1.2748	3	0.9542
10	85.34	1.9311	2.4474	1.1661	3.1622	1
11	89.52	1.9519	2.1883	1.0203	3.3166	1.0413
12	97.32	1.9882	1.3890	0.4281	3.4641	1.0791

Fig 8: Ranitidine release kinetics of batch P11 according to Zero order kinetics.

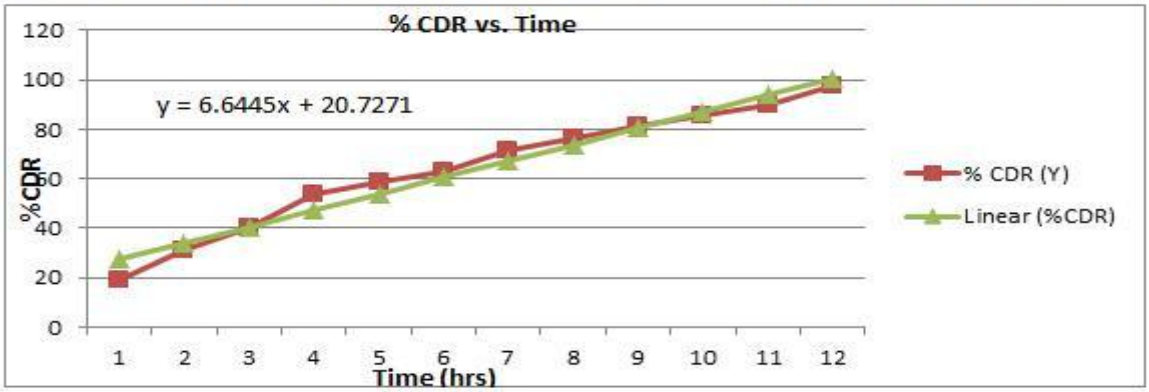


Fig 9: Ranitidine release kinetics of batch P11 according to First order kinetics.

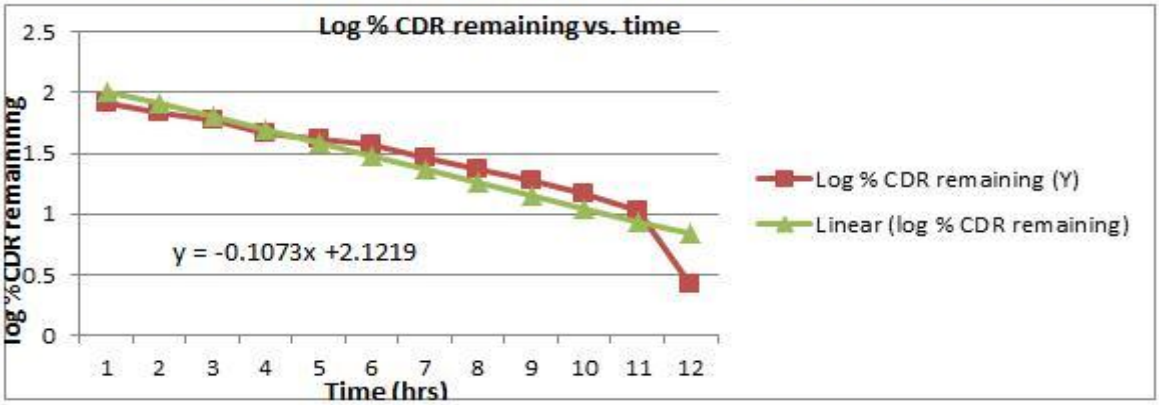


Fig 10: Ranitidine release kinetics of batch P11 according to Hixon-Crowell's kinetics.

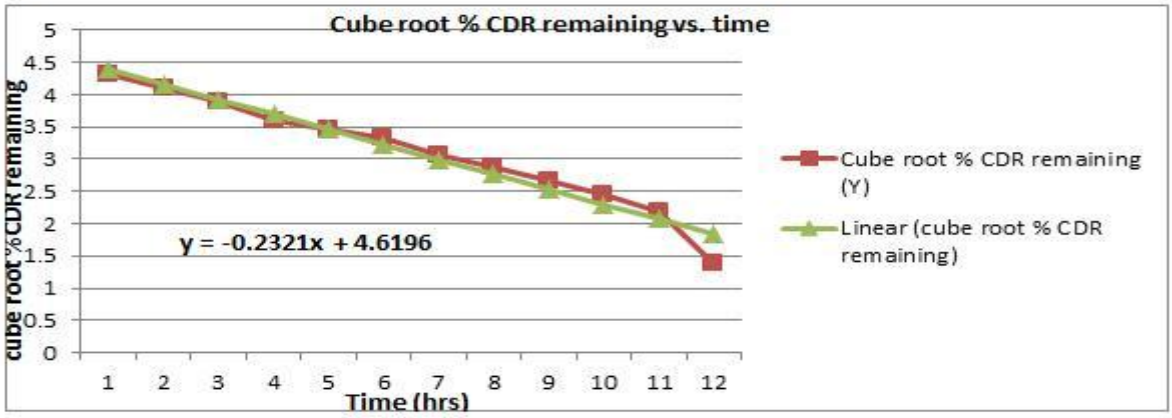


Fig 11: Ranitidine release kinetics of batch P11 according to Higuchi kinetics.

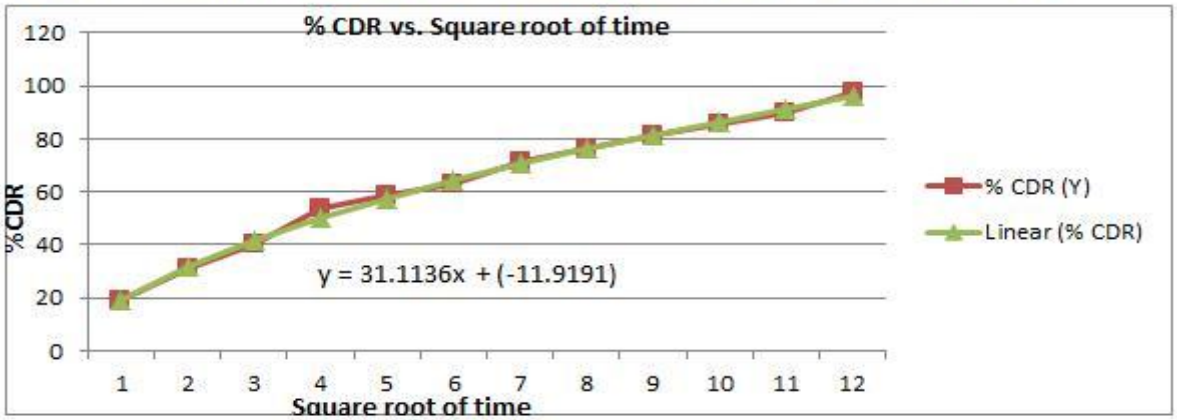
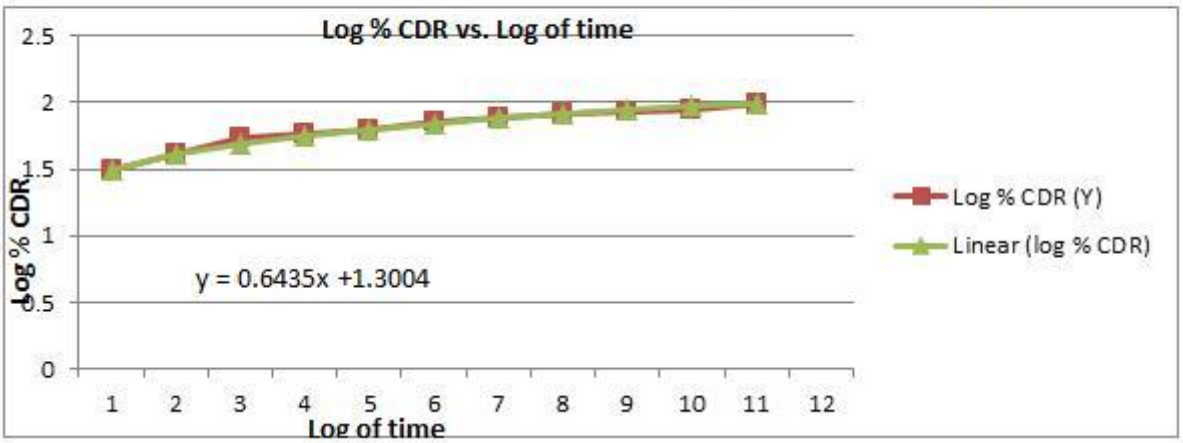


Fig 12: Ranitidine release kinetics of batch P11 according to Korsmeyer- Peppas kinetics.



The statistical kinetics values for the batch P11 is represented in Table 13

Table 13: Statistical kinetics values of batch P11

Kinetic models	R^2	Slope
Zero-order	0.9902	6.6445
First-order	0.9959	-0.1073
Higuchi kinetics	0.9807	31.1136
Hixon-Crowell	0.9905	-0.2321
Korsmeyer-Peppas	0.9873	0.6435

Among the entire kinetic model studied for the batch (P11), it was found that the batch followed **first order kinetics** because of having maximum R^2 value of 0.9959 (closest to 1.0).

Summary

In present work an attempt was made to prepare the Floating Tablet of Ranitidine using different polymers by wet granulation and direct compression method with Lactose, DCP and MCC as diluents, citric acid and Sodium bicarbonate as gas generating agent.

It was found that wet granulation method facilitated greater efficiency in controlling Ranitidine release behavior from the matrices. Hence, all further formulations were prepared with wet granulation technique. All the prepared formulations were evaluated for hardness, friability, uniformity of weight, thickness, in vitro buoyancy study, assay and in vitro release. Batches were prepared by HPMC and HPMC K15M+ EC, HPMC K15M+Xanthan gum. Ratio of polymers in formulation played major role in controlling the release rate of Ranitidine, which is evident from the prolongation in release of Ranitidine with HPMC: Xanthan gum. Concentration of sodium bicarbonate and citric acid affect the floating lag time and all the formulation float upto 24 hours. Effect of diluent on drug release was also studied by comparing lactose and dibasic calcium phosphate. Dibasic calcium phosphate had maximum retarding capacity followed by lactose. The release kinetics of all the batches were carried out and it was found final batch followed first order kinetics. The optimized formulation has drug release profile up to 12 hours.

Conclusion

The physical compatibility study at 40^{o}C/75% RH showed that Ranitidine and excipients used found to be physically compatible. Melting point of Ranitidine was found to be 139^{o}C.

Formulation was prepared with two processes i.e. direct compression and wet granulation; it was found that wet granulation method facilitated greater efficiency in controlling Ranitidine release behaviour from the matrices as compared to direct compression. Characterization of granules prepared by selected manufacturing processes like bulk density, tapped density, Carr's index, Hausner's ratio, Angle of repose was done and found to have good flow and compressibility. The tablets prepared were found to be within the limits with respect to hardness, average weight, %friability and thickness. From the different polymers used in polymer selection batches, combination of HPMC and Xanthan

gum were found to be satisfactory.Dibasic calcium phosphate was found to be the best diluent in controlling the release rate of drug and thus helps in extending the release profile. Under the study of kinetic models, five models have been studied namely Zero Order, First Order, Higuchi, Hixon-Crowell, Korsmeyer-Peppas model. It was found that the drug release model of final batch followed first order model (having maximum R^2 value of 0.9959).

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