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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF FLOATING TABLET OF RANITIDINE HYDROCHLORIDE FOR THE TREATMENT OF DUODENAL ULCER

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Abstract

Ranitidine hydrochloride (RHCl) is a histamine H_2-receptor antagonist. It is widely prescribed in Duodenal ulcers, gastric ulcers, Zollinger- Ellison syndrome, gastro esophageal reflux disease, and erosive esophagitis**.** The H_2-antagonists are comparative inhibitors of histamine at the parietal cell H_2 receptor. They suppress the normal secretion of acid by parietal cells. The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily.

The present study involved the preparation of floating tablet of ranitidine. The tablets were prepared with both direct compression and wet granulation methods. 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.(R01) was prepared by direct compression but it was failed because it was not compressed so this batch failed. Then we prepared batches (R02-R10) by wet granulation and studied their release kinetic. The formulations were studied for their floating behaviour using simulated gastric fluid; the floating lag time and duration of floating were noted for each formulation. The tablets were also studied for drug release for 12 h using 0.1N HCl as dissolution media. Lubricated blends were characterized for physical properties like loose bulk density, tapped density, angle of repose, Carr's index, Hausner´s ratio; all blends showed satisfactory properties. All lubricated blends were compressed into tablets using round shaped punches. Tablets were evaluated for uniformity of weight, thickness, hardness, percentage (%) friability and in vitro release studies. The release kinetics of the final batch (R06) and batch (R07) was carried out and it was found batch followed zero order kinetic model and less floating lag time. The optimized formulation has drug release profile up to 12 hours.

Keywords: Zollinger- Ellison syndrome, Carr's index, Hausner´s ratio, angle of repose.

INTRODUCTION

Ranitidine is a H_2 antihistamine drug used to block the action of histamine on gastric parietal cells in the stomach decreasing acid production by these cells. They accomplish this by two mechanisms: first, Histamine release by ECL cells in the stomach is blocked from binding of parietal cells H_2 receptors which stimulate acid secretion. Second, other substances that promote acid secretion (gastrin and acetylcholine) have a reduced effect on parietal cells when h2 receptors are blocked. It has a furan ring. It has melting point 69-70 °C. The wavelength of ranitidine at 229 nm and 315 nm (water used as medium). The chemical formula of Ranitidine is $C_{13}H_{22}N_4O_3S$ having molecular weight 314. The IUPAC name of Ranitidine is dimethyl (5-(((2-((e)-1-(methylamine)-2-nitroethenyl) amino) ethyl) sulfanyl) methyl) furan-2-yl) methyl) amino. It is mentioned under the class III in biopharmaceutical classification system. Dry it in vacuum at 60 ˚C for 3 hrs it loses not more than 0.75% of its weight. The residue of ignition is not more than 0.1%.

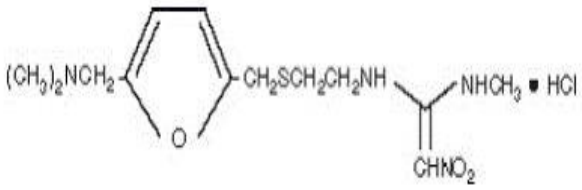


Figure 1: Structure of Ranitidine Hydrochloride

The bioavailability of Ranitidine Hydrochloride is 50% when administered orally. The elimination half life is approximately 2-3 hrs. The volume of distribution of the drug is about 1.4L/Kg having serum protein binding is 15%. It has hepatic metabolism. It is metabolized to the N –oxide (4%), S-oxide (1%) and N-dimethyl metabolites (1%) of the dose. The principal route of excretion is the urine (active tubular excretion, renal clearance 410 ml/min) with approximately 30 % or the orally administrated dose collected in the urine as unchanged drug in 24 hrs urinary excretion of unchanged drug I.V is 70-80%. It has 29 ml/min in clinically significant renal function impairment and 3ml/min/kg in neonatel patients.

Materials and Methods

Ranitidine Hydrochloride was gifted from Belco Pharmaceutical, Bahadurgarh, and Haryana. Guar Gum and Pectin were purchased from Thomas baker (chemicals) PVT. LTD Mumbai. Isopropyl alcohol and Lactose were purchased from S.d fine chem. LTD. Mumbai. Magnesium stearate was purchased from Merck LTD. Mumbai. Talc was purchased from Lobachemie PVT. LTD. Mumbai. Sodium bicarbonate and citric acid were purchased from Merck supplement PVT. LTD. Mumbai.

Experimental methods

Formulation development of floating tablet of ranitidine hydrochloride:

The composition of different formulations of floating tablet of Ranitidine Hydrochloride was shown in table 1 and 2. The ingredients were weighted accurately and mix thoroughly. Tablets of Ranitidine were prepared by direct and wet compression method and their release profiles were compared to select the manufacturing process for further study.

Selection of manufacturing processes:

Table 1: Formulation of ranitidine by direct compression:

Ingredients	R01(mg/tab)
Drug	150
Guar Gum	80
Pectin	-
Citric acid	30
Sodium bicarbonate	70
Magnesium stearate	3
Talc	3
Lactose	64

Table 2: Composition of different formulations of ranitidine floating tablets using wet granulation

Ingredients (mg per tablet)	Formulation									
	R02	R03	R04	R05	R06	R07	R08	R09	R10	R11
Ranitidine HCl	150	150	150	150	150	150	150	150	150	150
Lactose	144	144	104	104	64	64	104	104	144	144
Sodium bicarbonate	70	70	70	70	70	70	70	70	70	70
Citric acid	30	30	30	30	30	30	30	30	30	30
Guar gum	40	40	40	40	80	80	80	80	-	-
Pectin	-	-	40	40	40	40	-	-	40	40
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3

*All the quantities are in mg

Each tablet contains uniform weight of 400 mg and containing Isopropyl alcohol.

In Vitro Evaluation

Evaluation of pre-compressed granules

The methods for characterization powder flow attempts to correlate the various measures of powder flow to manufacturing properties. The following methods are used as flow ability indicators.

Angle of Repose:

The angle of repose can be measured by the friction force in a loose powder. It is defined as the maximum angle possible between the surface of the pile if the powder and the horizontal plane. The angle of repose was determined by the funnel method. The weighed amount was taken in a funnel. The height of funnel was adjusted in such a way that the tip of the funnel just touches the apex of heap of blend. The blend was now allowed to flow through the funnel freely on the surface. The diameter of the powder cone was determined and angle of repose is determined by the following formula:

$$\mathbf{Tan\ \theta = h/r}$$

Where ɵ =angle of repose
h =height of the cone
r = radius of the cone base

The angle of repose on flow properties is mentioned in table 3

Table 3: Flow properties and corresponding Angles of repose

Flow properties	Angle of repose (degree)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor	46-55
Very poor	56-65
Very, very poor	>66

Bulk Density (D_b)

Bulk density (D_b) is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ cm^3 .The bulk density is then obtained by dividing the weight of sample in cm^3.

$$D_b = M/V_b$$

Where M =mass of powder in gm
V_b = bulk density of the powder

Tapped density (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder. It was determined by placing a graduated cylinder containing a known mass of drug - excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 seconds intervals. The tapping was continued until the difference between successive volumes is less than 2%. It is expressed in gm/ml.

$$\mathbf{D_t = M / V}$$

Where M= mass of powder
V_t =volume of tapped packing

Hausner's Ratio

Hausner ratio is an indirect index of ease of powder flow and is given by-

$$\mathbf{Hausner\ ratio = D_t / D_b}$$

Where D_t = tapped density
D_b = bulk density
<1.25 –Good flow properties
1.25 –Poor flow properties

The value of both the indices were found by putting the values of bulk density and tapped density in the respective formulas, and the corresponding flow character was interpreted using Table 4

Table 4: Interpretation of flow properties of powder as mentioned in USP XXXII

Carr's index (%)	Hausner's Ratio	Flow character
<10	1.00-1.11	Excellent flow
11-15	1.12-1.18	Good
16-20	1.19-1.25	Fair
21-25	1.26-1.34	Passable
26-31	1.35-1.45	Poor
32-37	1.46-1.59	Very poor
>38	>1.60	Very very poor

Carr's index or % compressibility

It is expressed in percentage and indicates powder flow properties and is given by-

$$\mathbf{I = \frac{D_t - D_b}{D_t} \times 100}$$

Where D_t –tapped density of the powder
D_b – bulk density of the powder

Table 5: Micromeritic properties of formulations (Powder blend)

Batches	Bulk density (g/ml)	Tapped density(g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose(^{0})
R01	0.696	0.791	12.01(good)	1.13(good)	35.801(fair)
R02	0.545	0.654	16.66(fair)	1.2(fair)	28.636(excellent)
R03	0.575	0.645	10.853(good)	1.12(good)	40.917(passable)
R04	0.531	0.635	16.378(fair)	1.19(fair)	35.809fair)
R05	0.545	0.645	16.667(fair)	1.2(fair)	26.031(excellent)
R06	0.587	0.703	16.501(fair)	1.19(fair)	27.271(excellent)
R07	0.552	0.663	16.742(fair)	1.20(fair)	28.636(excellent)
R08	0.502	0.620	19.032(fair)	1.23(fair)	35.801(fair)
R09	0.565	0.659	13.525(good)	1.16(good)	31.821(good)
R10	0.459	0.632	27.373(poor)	1.37(poor)	30.145(good)
R11	0.550	0.775	29.032(poor)	1.40(poor)	33.694(good)

From the result it was concluded that the powder blend had good flow properties and these can be used for tablet manufacture.

Evaluation tests for floating tablets in vitro evaluation methods:-

Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipments utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of weight

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance.

Table 6: I.P. Specification for uniformity of weight

S. No.	Average weight of Tablets (mg)	Maximum percentage Different allowed
1.	130 or less	10
2.	130-324	7.5
3.	More than 324	5

Tablet hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. Hardness of tablet of each formulation was determined using Monsanto Hardness tester and many other testers like the strong cob tester, the Pfizer tester, the Erweka tester, and the Schleuniger tester available for determining hardness of particular tablet.

Friability (F)

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A pre-weighed tablet was placed in the friabliator. Friabilator consist of a plastic- chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \textbf{ Friability} = (w_o - w)/w_o \times 100$$

Buoyancy lag-time studies

The *in-vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 1.2 pH solutions. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time.

In – Vitro Drug Release Study:

The *in – vitro* dissolution study was carried out in the USP dissolution test apparatus USP-II (paddles). 900 ml of the dissolution medium (0.1N HCl) was taken in vessel and the temperature was maintained at 37± 0.5^{o}C. The speed of the paddle was set at 50 rpm. 5 ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The sample withdrawn was filtered and diluted with 0.1 N HCl prior to analysis in the UV spectrophotometer (UV-1700 Shimadzu Corporation, Japan) at 249nm.

Dissolution parameters

Medium: 0.1N HCl
Volume: 900 ml
Apparatus: USP-II (paddle)
RPM: 50 rpm
Time Point: 1, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24 hrs.
Temperature: 37^{o}C ± 0.5^{o}C
Volume of sample withdrawal: 10 ml
λ_{max} for absorbance: 229 nm

The drug release profiles obtained were fitted into several mathematical models and drug release mechanism was determined from the matrix tablet.

Table 7: Evaluation of floating tablet of Ranitidine

Formulation	Thickness (mm)	Weight (mg)	Hardness (kg/cm^3)	Floating Lag Time (min)	Floating duration (hrs)	Friability
R01	2.32	302.5	-	-	12	-
R02	3.04	403.4	3.6	1:49	12	0.288
R03	3.03	401.2	3.4	1:48	12	0.289
R04	3.05	401.2	4.2	2:00	12	0.332
R05	3.06	402.2	4.3	2:00	12	0.329
R06	3.08	402.3	4.3	1:09	12	0.491
R07	3.03	401.5	4.4	1:08	12	0.405
R08	3.04	400.3	3.4	3:00	12	0.346
R09	3.05	401.3	3.5	2:50	12	0.344
R10	3.02	399.6	2.2	3:48	12	0.267
R11	3.03	400.1	2.1	3:55	12	0.265

The result showed that thickness, weight and hardness were within pharmacopoeial limits. So they pass the above tests. Parameters like hardness, thickness, friability, Average weight were found to give satisfactory results for all trials

Table 8: Release rate of combination of guar gum (20%) and pectin (10%) with their low concentration (R06)

Time ((hrs)	%CDR	Log %CDR	Cube root of % drug remaining	Log %drug remaining	Square root of time	Log time
1	7.42	0.87	4.523	1.966	1	0
2	15.32	1.185	4.391	1.927	1.414	0.3010
3	20.32	1.307	4.303	1.901	1.732	0.4771
4	26.42	1.142	4.19	1.866	2	0.6020
5	32.12	1.506	4.079	1.831	2.236	0.6989
6	38.12	1.5811	3.955	1.791	2.449	0.7781
7	45.4	1.657	3.793	1.737	2.645	0.8450
8	52.62	1.7211	3.618	1.675	2.828	0.9030
9	58.66	1.768	3.457	1.616	3	0.9542
10	65.44	1.815	3.257	1.538	3.162	1
11	73.38	1.865	2.985	1.425	3.316	1.0413
12	79.999	1.903	2.714	1.301	3.464	1.0791

Fig 2: Ranitidine release of combination of guar gum (20%) and pectin(10%) according to zero order kinetic of (R06)

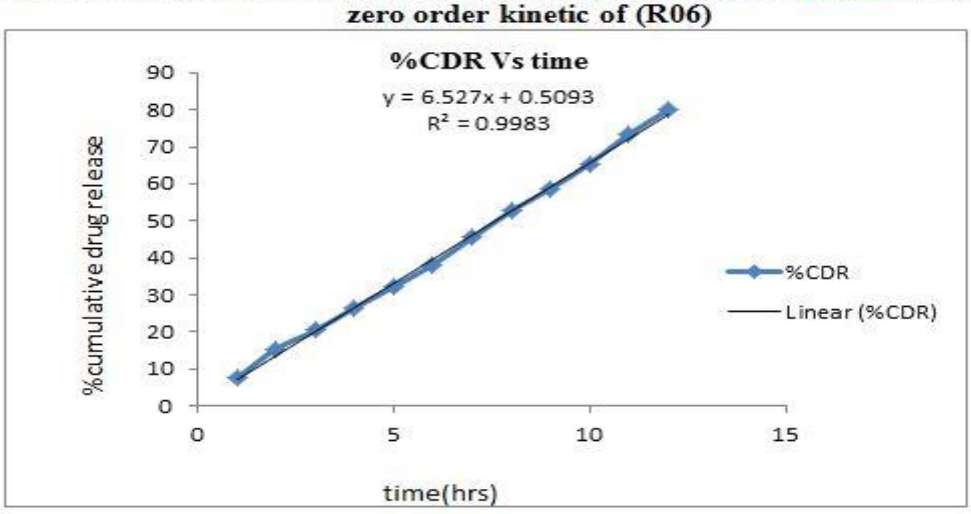


Fig 3: Ranitidine release of combination of guar gum (20%) and pectin(10%) according to first order kinetic of (R06)

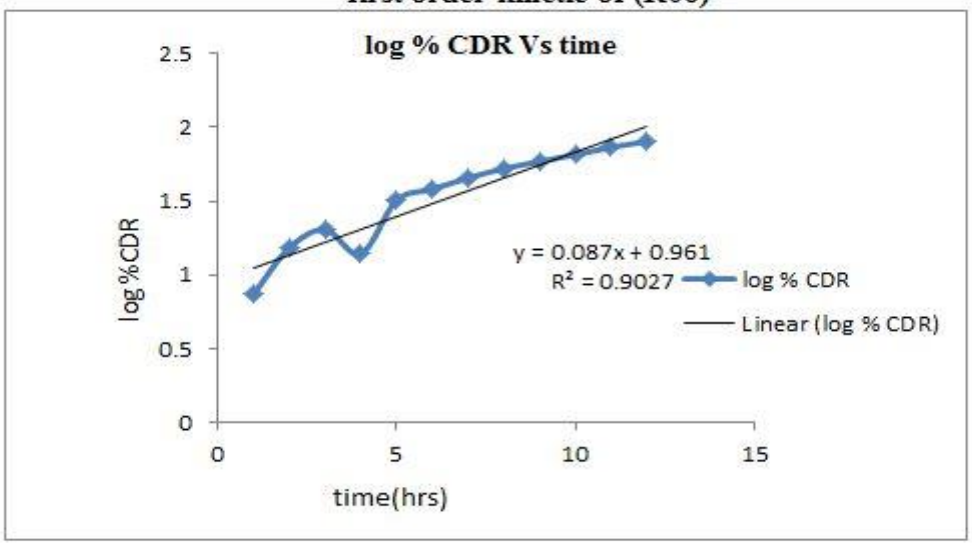


Fig 4: Ranitidine release of combination of guar gum (20%) and pectin(10%) according to Hixon-crowell kinetic of (R06)

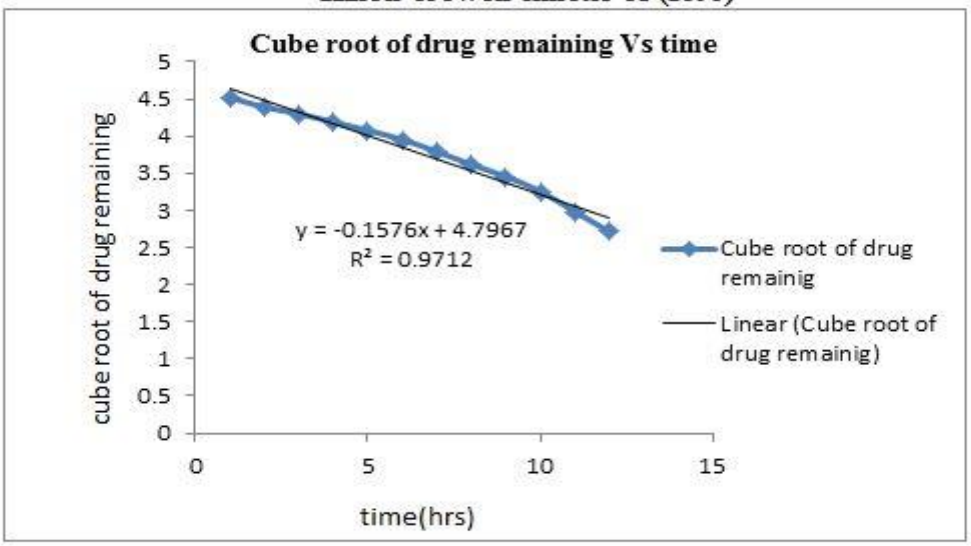


Fig 5: Ranitidine release of combination of guar gum (20%) and pectin(10%) according to krosmeyer- peppas kinetic of (R06)

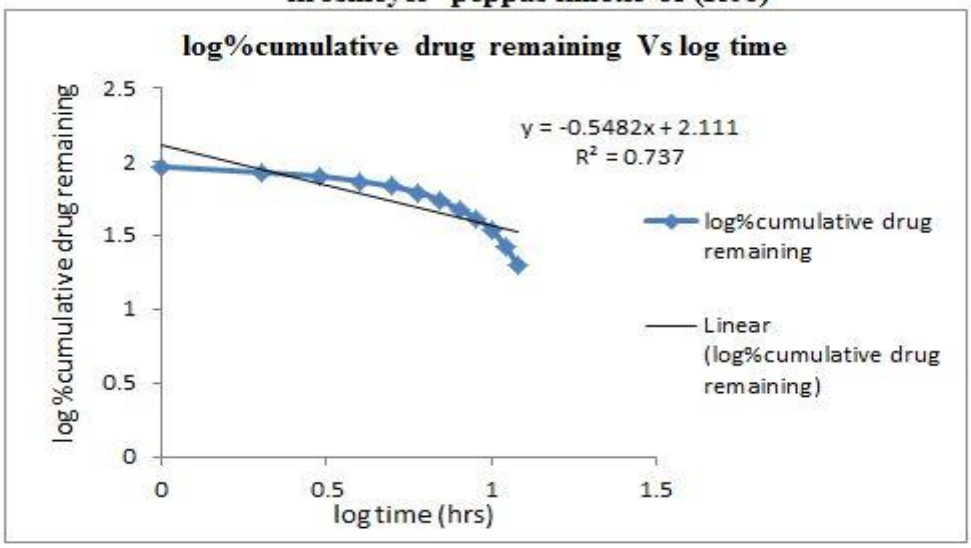
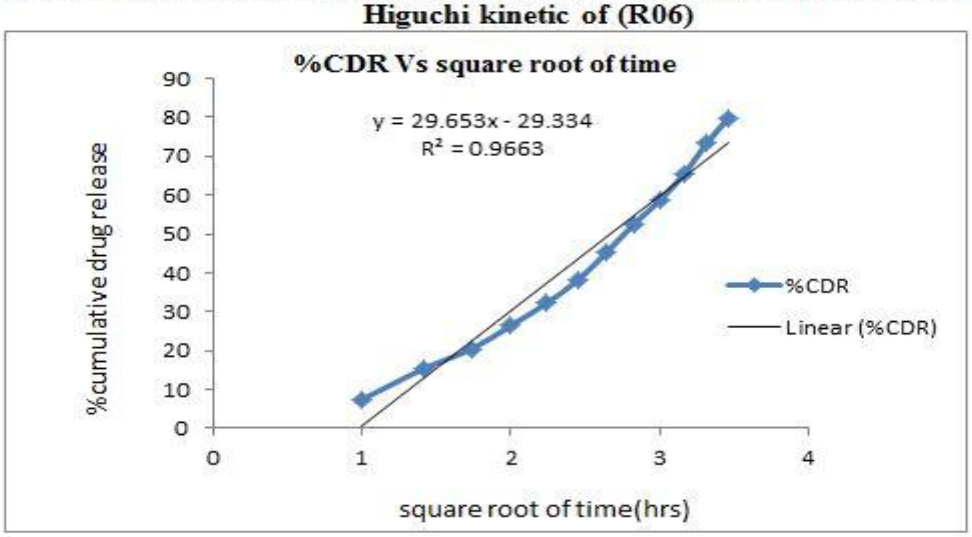


Fig 6: Ranitidine release of combination of guar gum (20%) and pectin (10%) according to Higuchi kinetic of (R06)



The Statistical kinetic values for batch (R06) is represented in table 9

Table 9: Statistical kinetic values for batch (R06) is represented in table

Kinetic models	R^2	Slope
Zero order	0.998	6.527
First order	0.902	0.087
Hixon-crowell	0.971	0.157
Korsmeyer-peppas	0.737	0.548
Higuchi	0.966	29.65

Formulation (R06) with intermediate concentration (20%) of guar gum and pectin (10%) showed slow release as compared to above formulation because when we increase the concentration of guar gum then the release of drug was decrease and followed controlled drug delivery system. This batch showed zero order kinetic having R^2 value of 0.998 (closest to 1) and having slope of 6.527.

Result and discussion:-

The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. 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 efficacy of drugs to reduce acid secretion. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydro dynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. In context of the above principles, a strong need was recognized for the development of a dosage form to deliver RHCl in the stomach and to increase the efficiency of the drug, providing sustained action. The present investigation applied a systematic approach to the development of gastroretentive RHCl dosage forms.

The present study involved the preparation of floating tablet of ranitidine. The tablets were prepared with both direct compression and wet granulation methods. It was found that wet granulation method facilitated greater efficiency in controlling ranitidine release behavior from the matrices. Hence, all further formulations

- FTIR spectra data showed that Ranitidine and

were prepared with wet granulation technique. We prepared 11 batches (R01-R10). (R01) was prepared by direct compression but it was failed because it was not compressed so this batch failed.Then we prepared batches (R02-R10) by wet granulation and studied their release kinetic. The formulations were studied for their floating behaviour using simulated gastric fluid, the floating lag time and duration of floating were noted for each formulation. The tablets were also studied for drug release for 12 h using 0.1N HCl as dissolution media. Batch (R02) followed Hixon-crowell kinetic having (R^2-0.989) and floating lag time was 1:49 min. Batch (R03) followed Higuchi kinetic having (R^2-0.982) and floating lag time 1:48 min. Batch (R04) followed Higuchi kinetic having (R^2-0.997) and floating lag time 2:00 min. Batch (R05) followed Higuchi kinetic having (R^2-996) and floating lag time 2:00 min. Batch (R06) followed zero order kinetic having (R^2-0.998) and floating lag time 1:09 min. Batch (B07) followed zero order kinetic having (R^2-995) and floating lag time 1:08 min. Batch (R08) followed Higuchi kinetic having (R^2-0.996) and floating lag time 3:00 min. Batch (R-09) followed Higuchi kinetic having (R^2-996) and floating lag time 2:50 min. Batch (R10) followed zero order kinetic having (R^2-0.991) and floating lag time 3:48 min. Batch (R011) followed zero order kinetic having(R^2-0.990) and floating lag time 3:55 min. Lubricated blends were characterized for physical properties like loose bulk density, tapped density, angle of repose, Carr's index, Hausner´s ratio; all blends showed satisfactory properties. All lubricated blends were compressed into tablets using round shaped punches. Tablets were evaluated for uniformity of weight, thickness, hardness, percentage (%) friability and in vitro release studies. The release kinetics of the final batch (R06) and batch (R07) was carried out and it was found batch followed zero order kinetic model and less floating lag time. The optimized formulation has drug release profile up to 12 hours.

Conclusions

The conclusions of the present research work are as follows:

- 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 69^oC.
- 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.
- 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, thickness, swelling index and in vitro dissolution study.
- *In vitro* dissolution studies of the best formulation (R06) and (R07) showed complete release of drug in 12 hrs.
- The fine particle grades are more compressible than the standard premium grades, resulting in harder tablets.
- Increasing tablet hardness provided a much great control over dissolution rate.
- Guar gum is the best polymer as compared to pectin because when we increase the concentration of guar gum the release was decrease and there was an increase in time of release of drug but when we increase the concentration of pectin the release was increase.
- The concentration of polymer is the determining factor in controlling the release of Ranitidine.
- 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 followed zero order kinetic (having maximum R^2 value of 0.998.

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