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Formulation, design, optimization and evaluation of cimetidine floating tablets by using 3^2 factorial design

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ABSTRACT

The present study was aimed to formulate and evaluate floating tablets of Cimetidine which is a histamine H_2 receptor antagonist in increasing usage in the medical management of peptic ulcer. In this study, excipients like HPMC K4M, HPMC K100M were used as polymers and sodium bi- carbonate were incorporated in 9 different concentrations (F1-F9) along with other excipients.to formulate floating tablets. Then all the nine formulations were evaluated for uniformity of weight, hardness, thickness, friability test, floating lag time, drug content, dissolution studies and stability studies. The 3^2 Factorial design experiments helps the investigator in resource management and economy. The dissolution profile of F2 was observed to be better than other formulations. Trial-F2 formulation showed a good dissolution profile for a controlled period of time which was noticed to be as 98 % at the end of 12th hour. Thus, it can be concluded that the floating drug delivery system of cimetidne using the appropriate polymers in right amount may enhance the activity of the drug by prolonging the gastric residence time or reducing the floating lag time.

Keywords: HPMC K4M, HPMC K100M, Cimetidine, 32 Factorial design

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INTRODUCTION

Oral drug delivery is by far the most preferable route of drug delivery due to the Ease of administration, patient compliance and flexibility in formulation, etc. It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT).[1-5] Dosage forms with a prolonged GRT, i.e. gastro retentive dosage forms (GRDFs), will provide us with new and important therapeutic options. GRDFs extend significantly the period of time over which the drug may be released. Thus, they not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms. This application is especially effective in delivery of sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes significant factor affecting drug absorption. To address this, oral administration of sparingly soluble drugs are carried out frequently, often several times per day.

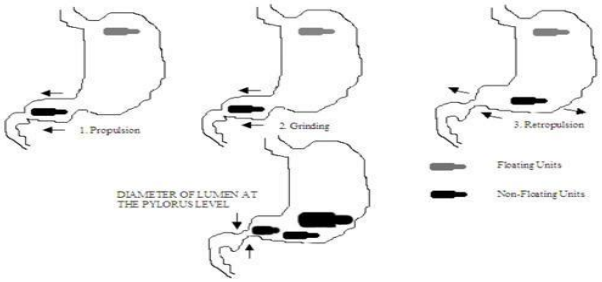

Figure 1: Intragastric residence positions of floating and non floating units

In order to formulate a successful gastroretentive drug delivery system, several techniques are currently used such as floating drug delivery system, low density systems, raft systems incorporating alginate gel, bio adhesive or mucoadhesive systems, high density systems, super porous hydrogel and magnetic system. Among these, the floating delivery system is most commonly used.

The main efficacy of Floating drug delivery systems have a bulk density less than the gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. It is evident that a drug having such an "Absorption window", the effective oral CRDDS should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for a long period of time. For such type of drugs, increased or more predictable availability would result in controlled release system and thus the drug could be retained in the stomach for extended period of time. This results in an increased gastric retention time and control of the fluctuation in plasma drug concentration.[7]

Mechanistic aspects of floating drug delivery system:

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric- emptying delaying devices and co administration of gastric-emptying delaying drugs.

Among these, the floating dosage forms have been used most commonly. However, most of these approaches are influenced by a number of factors that affect their efficacy as a gastro retentive system.

Incorporation of the drug in a controlled release gastro retentive dosage form(CR-GRDF) Can yield significant therapeutic advantages due to a variety of pharmacokinetic and pharmacodynamic factors.[8-12]

Pharmacokinetic aspects:- Absorption window-validation that the drug is within the category of narrow window

- Enhanced bioavailability
- Enhanced first pass biotransformation
- Improved bioavailability due to reduced P-glycoprotein(P-gp)activity in the duodenum.

Pharmacodynamic Aspects:

Reduced fluctuation of drug concentration.

Improved selectivity in receptor activation.

Reduced counter-activity of the body.

Extended time over critical (effective) concentration.

Minimum adverse activity at the colon.

Pre compression Parameters

Angle of Repose: Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. Performed to determine the flow rate of powder done by the funnel method. The powder mass was allowed to flow through the funnel orifice kept vertically to a plane paper kept on the horizontal surface, giving a heap angle of powder on paper. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation:

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

Posology: Posology or study of Flow rate of powder has been defined as the rate at which particular mass emerges through the orifice of the funnel of a suitable diameter. The flow rate of powder of each formulation was determined by pouring accurately weighed quantity of powder in funnel with an orifice of 8mm diameter. The time required for complete powder mass to emerge out of the orifice was recorded using a stopwatch. The flow rate was calculated from following equation

Bulk Density: Bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. The sample of bout 50 cm^3 of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2- second intervals on to hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$$Df = M / Vp$$

Where, Df = bulk density, M = weight of sample in grams, Vp = final volume of powder in cm^3.

Tapped density: The tapped density was obtained by dividing the mass of powder by tapped volume in cm^3.The sample of about 50 cm^3 of powder, previously been passed through a standard sieve no.20, is carefully introduced in to a 100 ml graduated cylinder. The cylinder was dropped at 2- second intervals on to hard wood surface three times from a height of 1 inch. The tapped density of each formulation was then obtained by dividing the weight of sample in grams by the final tapped volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$$Do = M / Vp$$

Where, Do = bulk density, M = weight of sample in grams, Vp = final tapped volume of powder in cm^3

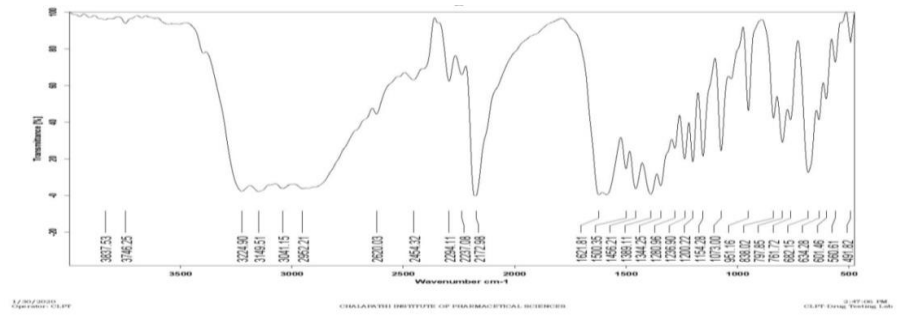

Figure 2: FT-IR spectra for Cimetidine

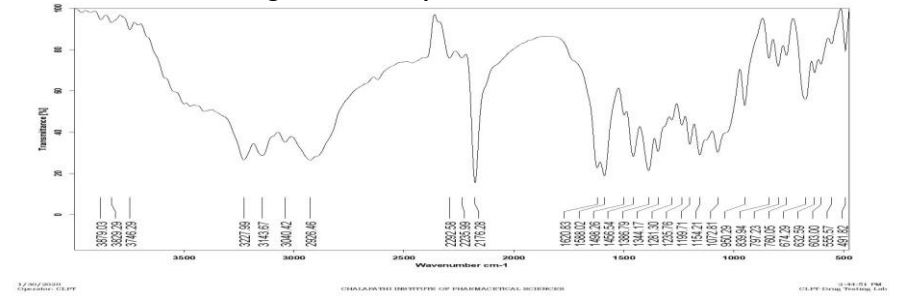

Figure 3: FT-IR spectra for Cimetidine + HPMC K4M

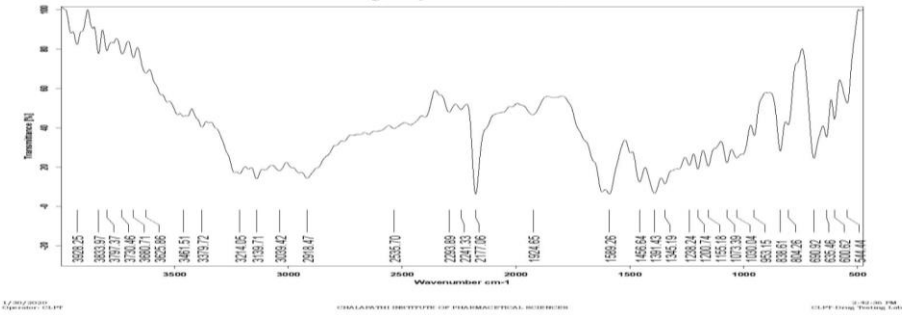

Figure 4: FT-IR spectra for Physical mixture

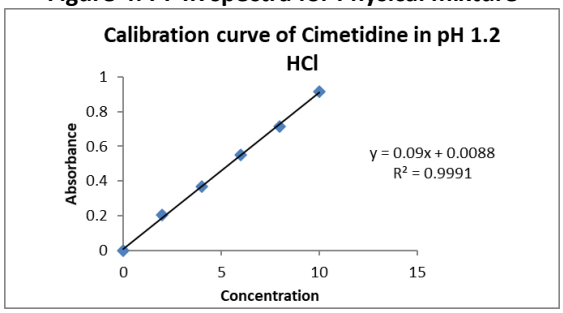

Figure 5: Calibration curve of Cimetidine

Carr's index: Carr's developed an indirect method of measuring powder flow from bulk densities. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability.

MATERIALS AND METHODS

Cimetidine and HPMC K4M and K100M were obtained as gift samples from Biophore India Pharmaceuticals Pvt.Ltd. Hyderabad. All the other excipients were obtained from CLPT Pharmaceutical Analysis Laboratories. [13-15]

METHODOLOGY

Preparation of Tablets by Direct compression method: The gastro retentive tablets were prepared by using direct compression method by using HPMC K4M controlled release grade useful as a rate retarding polymer and Sodium bicarbonate as a gas generating agent, microcrystalline cellulose as a disintegrating agent. Except the Drug, the other excipients were added into a mortar and comminuted to form a fine mass. To this fine mass Cimetidine was added and then triturated again for a final clear mass.

Drug – polymer-excipients compatibility studies: The compatibility studies were performed to ascertain interaction if any of drug with the excipients and polymers used in the preparation of tablets.

Table 1: Calibration of Cimetidine

Concentration (µg/ml)	Absorbance at 210 nm
0	0
2	0.203
4	0.369
6	0.549
8	0.715
10	0.917

Table 2: coded values for the independent variables

Coded Values	Actual Values(mg)	
	X1	X2
-1	50	-1
0	75	0
+1	100	+1

Table 3: Formulation of Cimetidine floating tablets

Ingredients (mg/Tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cimetidine	200	200	200	200	200	200	200	200	200
HPMC K4M	50	75	100	50	75	100	50	75	100
HPMC K100M	50	75	100	50	75	100	50	75	100
MCC	30	30	30	30	30	30	30	30	30
Sodium bicarbonate	75	75	75	75	75	75	75	75	75
Magnesium stearate	6.4	6.6	6.6	6.6	6.6	7.1	6.6	7.1	7.4
Talc	6.4	6.6	6.6	6.6	6.6	7.1	6.6	7.1	7.4

Table 4: Evaluation of Cimetidine Floating Tablets Design Formulations

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.54	0.62	11.33	1.10	23.20°
F2	0.58	0.67	10.88	1.12	22.12°
F3	0.50	0.61	12.25	1.14	27.15°
F4	0.47	0.51	11.22	1.05	24.22°
F5	0.48	0.54	13.25	1.12	21.36°
F6	0.44	0.52	12.44	1.13	21.32°
F7	0.46	0.51	11.22	1.05	24.22°
F8	0.45	0.56	14.65	1.26	26.75°
F9	0.42	0.54	13.25	1.12	21.36°

Table 5: Percentage of Drug Release Vs Time

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	26.39	23.55	22.98	23.16	23.13	22.99	24.51	22.68	21.11
3	42.62	43.96	36.59	35.26	49.18	44.82	41.03	35.62	39.49
5	56.84	58.66	46.66	45.36	63.69	62.77	57.49	46.95	49.46
7	67.61	64.84	51.73	53.49	74.25	75.67	65.62	59.43	61.42
9	76.61	72.28	61.01	59.64	92.56	87.67	81.97	70.14	78.62
10	81.45	79.69	68.45	62.81	96.72	94.61	88.42	80.18	89.71
12	93.55	85.32	76.09	72.11	98.64	98.33	99.92	86.15	96.48

The C-N stretching ranges between 2294.11-2237.08 cm-' and the CH_2 in the range of 1456.21cm-'.The C-C bonds disubstituted in the range of 951 cm-' in a trans form. The N-H stretching at 2620 cm-'. The aliphatic ranges of the C-N ranges at 1236, 1200, 1154 and 1073 cm-'

FT-IR studies were performed to know the possible interactions between model drug cimetidine and other excipients. FT-IR of spectra of drug with carriers and other excipients showed similar peaks as that of Cimetidine pure drug. Based on FT-IR spectra obtained, it was evident that there was no significant interaction of Cimetidine with carriers and other excipients.

In order to optimize the process of this formulation 3^2 factorial design was used to design the experiment. The 2 independent factors such as HPMCK4M (X1) and HPMC K100M (X2) were taken as the inde-

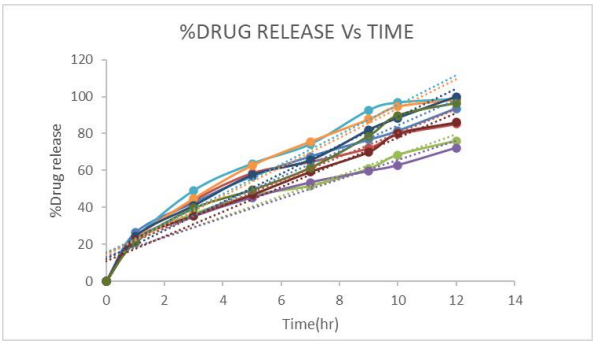

Figure 6: Drug release graph

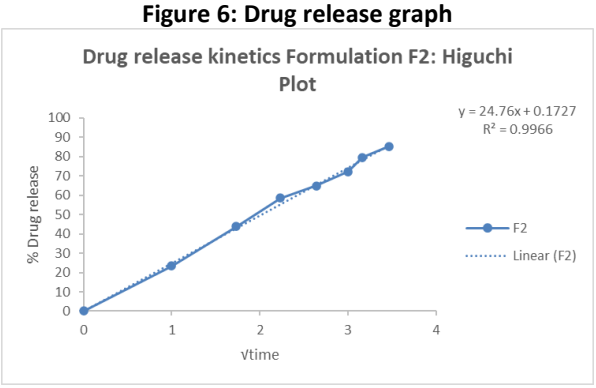

Figure 7: Higuchi plot of the F2 Formulation

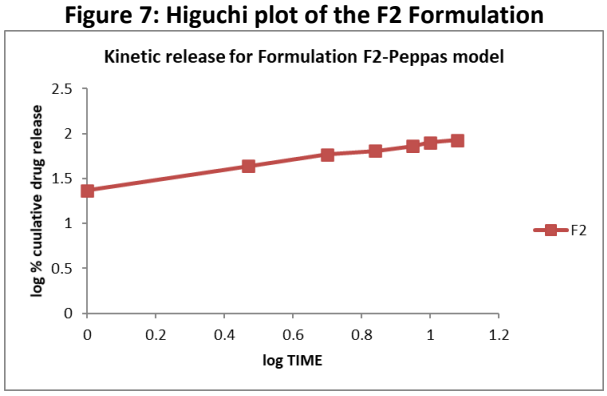

Figure 8: Peppas plot for the F2 Formulation

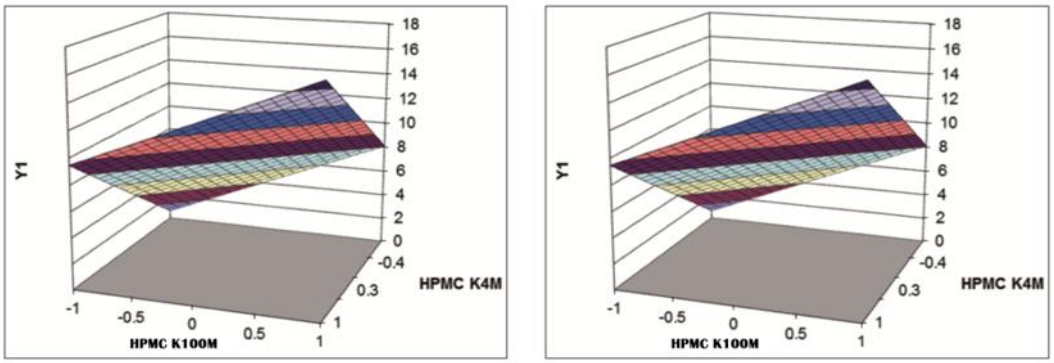

Figure 9: Contour plot graphs

pendent variables and the time required for 50% drug release t50% and the time required for 70% drug release t70% were taken as the responses. 3 different codes were taken for the 2 categorized factors for the design of the experiment.

Dissolution Parameters For 3^2 Factorial Design Batches

Formulation optimization has been done by using 32 square factorial design to determine the effect of amount of HPMC K4M (X1) and HPMC K100M (X2) on independent variables $t_{50\%}$ and $t_{70\%}$. The equations for $t_{50\%}$ and $t_{70\%}$ developed as follows, Y_1= 4.94 +2.392X1+2.915 X2... and Y2=8.774+3.817X1+ 4.493 X2.. respectively. The positive sign for coefficeient of X2 in Y1 and Y2 equations indicates that as the concentration of HPMCK4M increases, $t_{50\%}$ and $t_{70\%}$ value increases

Formulation of Cimetidine floating tablets

Preparation: In this work, direct compression method has been employed to prepare Cimetidine floating tablets with Hydroxyl propyl methyl cellulose (HPMC) K4M, sodium bicarbonate, Magnesium stearate and Talc

Procedure: All the ingredients were accurately weighed and passed through mesh #60. In order to mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 minutes then HPMC K4M, Lactose and sodium bicarbonate, talc and magnesium stearate were mixed one by one. After thoroughly mixing these ingredients, the powder blend was passed through # 44 mesh. Tablets were compressed on a single punch tablet machine (Cadmach, India) using 8 mm flat round punches.

Table 6: Responses of the Formulation

Formulation Code	Variable level in Coded form		$t_{50\%(h)}$	$t_{70\%(h)}$
F1	-1	-1	0.45	1.30
F2	-1	0	1.78	5.85
F3	-1	1	6.56	10.5
F4	0	-1	0.46	2.25
F5	0	0	3.55	7.25
F6	0	1	8.25	8.40
F7	1	-1	5.78	8.20
F8	1	0	8.40	8.60
F9	1	1	9.15	10.20

SUMMARY

Cimetidine floating tablets were prepared by using Direct compression method. FT-IR studies were performed to check whether the possible interaction between the Drug and the Hydrophilic polymers HPMC K4M and the effervescent agent NaHCO3. Estimation of the Cimetidine at a wave length of 225nm by using pH-1.2 HCl buffer, The dissolution results for the drug under the perfect fit lines as compared with the outlines. 3^2 design is used to get the desired responses and the optimized formulation. Out of all the formulations the F2 formulation shows a very good range of floating lag time and total floating time along with its Drug release at the specific intervals.

CONCLUSION

Cimetidine Floating tablets prepared by using the direct compression process have a very good range of dissolution efficiency and also a very good period of Total floating time.It can be concluded clearly as the concentration of both the polymers increase there is an equal increase in the time period for the dissolution time.

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