Volume 3 (5), 2015, Page-862s-873s
CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Original Article

Design Formulation and Evaluation of Ranitidine HCl Gastro Retentive Floating Tablets

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ARTICLE INFO

Received: 22 Oct 2015
Accepted: 08 Nov 2015

ABSTRACT

The main objective of present investigation is to formulate the floating tablets of Ranitidine.HCl using **3^2** factorial design. Ranitidine.HCl, H2-receptor antagonist belongs to BCS Class-III. The Floating tablets of Ranitidine.HCl were prepared employing different concentrations of HPMCK4M and Guar Gum in different combinations as a release rate modifiers by Direct Compression technique using 3^2 factorial design. The concentration of Polymers , HPMCK4M and Guar Gum required to achieve desired drug release was selected as independent variables, X_1 and X_2 respectively whereas, time required for 10% of drug dissolution ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) were selected as dependent variables. Totally nine formulations were designed and are evaluated for hardness, friability, thickness, % drug content, Floating Lag time, *In-vitro* drug release. From the Results concluded that all the formulation were found to be within the Pharmacopoeial limits and the *In-vitro* dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Polynomial equations were developed for **$t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$**. Validity of developed polynomial equations were verified by designing 2 check point formulations(C_1, C_2). According to SUPAC guidelines the formulation (F_5) containing combination of 22.5% HPMCK4M and 22.5% Guar Gum, is the most similar formulation (similarity factor f_2=85.01, dissimilarity factor f_1= 15.358 & No significant difference, t= 0.169) to marketed product (**ZANTAC**). The selected formulation (F_5) follows Higuchi's kinetics, and the mechanism of drug release was found to be Non-Fickian Diffusion (n= 0.922).

Keywords : Ranitidine.Hcl, **3^2**Factorial Design, Gastro retentive Floating Tablet, HPMCK4M ,Guar Gum, Floating Lag Time, SUPAC, Non-Fickian Diffusion Mechanism

1. INTRODUCTION

Oral administration is the most convenient, widely used route for both conventional and novel drug delivery systems, and preferred route of drug delivery for systemic action. Tablets are the most popular oral

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solid formulations available in the market and are preferred by patients and physicians alike. There are many reasons for this, not the least of which would include acceptance by the patient and ease of administration . patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed.

In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages[1]. However, when administered orally, many therapeutic agents are subjected to extensive presystemic elimination by gastrointestinal degradation and/or first pass hepatic metabolism as a result of which low systemic bioavailability and shorter duration of therapeutic activity and formation of inactive or toxic metabolites[2]. Rapid gastrointestinal transit can result in incomplete drug release from a device above the absorption zone, leading to diminished efficacy of the administered dose. Therefore, different approaches have een proposed to retain the dosage form in the stomach. These include bioadhesive systems, swelling and expanding systems and floating systems. Large single-unit dosage forms undergo significant swelling after oral administration, and the swollen matrix inhibits gastric emptying even when the pyloric sphincter is in an uncontracted state[3]. Gastric floating drug delivery system (GFDDS) can overcome at least some of these problems and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. The GFDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug.

Gastroretentive dosage forms significantly extend the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance.4,5 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. This 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, thus ensuring optimal bioavailability.

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, the goal in the designing sustained / controlled drug delivery system is to reduce the dosing frequency or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery[3].

Since the early 1950s, the application of polymeric materials for medical purposes is growing very fast. Polymers have been used in the medical field for a large extent [4]. Natural polymers remain attractive primarily because they are inexpensive, readily available, be capable of chemical modifications, non-carcinogenicity, mucoadhesivity, biodegradable, biocompatible, high drug holding capacity and high thermal stability and easy of compression [5]. This led to its application as excipient in hydrophilic drug delivery system. The various natural gums and mucilages have been examined as polymers for sustained drug release in the last few decades for example; guar gum, tragacanth gum, xanthan gum, pectin, alginates etc. In the development of a Gastro retentive Floating tablet dosage form. Availability of wide variety of polymer and frequent dosing interval helps the scientist to develop sustained release product. cellulose derivatives such as carboxymethyl cellulose (CMC), sodium carboxymethyl cellulose, hydroxyproyl cellulose (HPC), and hydroxypropyl methyl cellulose (HPMC) have been extensively studied as polymer in the

Floating tablet formulations along with gas generating agent like $NaHCO_3$[6]. These polymers are most preferred because of its cost effectiveness, broad regulatory acceptance, non-toxic and easy of compression. These dosage forms are available in extended release, targeted release, delayed release, prolonged action dosage form. Some factors like molecular size, diffusivity, pKa-ionization constant, release rate, dose and stability, duration of action, absorption window, therapeutic index, protein binding, and metabolism affect the design of sustained release formulation. The future of sustained release products is promising in some area like chronopharmacokinetic system, targeted drug delivery system, mucoadhesive system, particulate system that provide high promise and acceptability.

Developing Floating formulations BCS Class-III drugs has become a challenge to the pharmaceutical technologists. Fast release drug generally causes toxicity if not formulated as extended release dosage form. Among various formulation approaches, in controlling the release of water-soluble drugs, the development of sustained release coated granules has a unique advantage of lessening the chance of dose dumping which is a major problem when highly water-soluble drug is formulated as matrix tablets.

Oral sustained release dosage form by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms[7].

The selection of the drug candidates for Floating drug delivery system needs consideration of several biopharmaceutical, pharmacokinetic and pharmacodynamic properties of drug molecule[8].

In the present study, a Gastro retentive floating dosage form of Ranitidine.HCl has been developed that makes less frequent administering of drug also to improve Bioavailability.

Ranitidine hydrochloride (RHCl) is a histamine H2-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[8]. 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 RHCl is desirable[9]. The short biological half-life of drug (~2.5-3 hours) also favors development of a sustained release formulation.

Atraditional oral sustained release formulation releases most of the drug at the colon, thus the drug should have absorption window either in the colon or throughout the gastrointestinal

tract. Ranitidine is absorbed only in the initial part of the small intestine and has 50% absolute bioavailability[10,11]. Moreover, colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon[12,13]. These properties of Ranitidine.HCl do not favor the raditional 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.

Thus, there is a need to maintain Ranitidine.HCl at its steady state plasma concentration. Hence, the study was carried out to formulate and evaluate Floating dosage form of Ranitidine.HCl as a model drug and had a aim that final batch formulation parameters should shows prolong drug release.

Development of dosage form depends on chemical nature of the drug/polymers, matrix structure, swelling, diffusion, erosion, release mechanism and the in vivo environment.

It is an important issue is to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. For this purpose, response surface methodology (RSM) utilizing a polynomial equation has been widely used. Different types of RSM designs include 3-level factorial design, central composite design (CCD), Box-Behnken design and D-optimal design. Response surface methodology (RSM) is used when only a few significant factors are involved in experimental optimization. The technique requires less experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating sustained release dosage forms[14,15,16,17].

Hence an attempt is made in this research work to formulate Floating Tablets of Ranitidine.HCl using HPMCK4M and Guar gum . Instead of normal and trial method, a standard statistical tool design of experiments is employed to study the effect of formulation variables on the release properties.

Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The Floating tablets formulation by direct compression method is most acceptable in large scale production.

A 3^2 full factorial design was employed to systematically study the drug release profile . A 3^2 full factorial design was employed to investigate the effect of two independent variables (factors), i.e the amounts of HPMCK4M and Guar Gum on the dependent variables, i.e. $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (Time taken to release 10%,50%75%,90% respectively)

2. MATERIALS AND METHODS

Materials used in this study were obtained from the different sources. Ranitidine.HCl was a gift sample from Aurobindo pharma Ltd, Hyderabad, India. HPMCK4M, Guar gum, Di Calcium Phosphate, sodium bicarbonate were procured from Loba Chemie Pvt.Ltd, Mumbai. Other excipients such as Stearic acid, citric acid, Aerosil and talc were procured from S.D. Fine Chem. Ltd., Mumbai.

2.1 Formulation Development of Ranitidine.HCl Sustained Release Tablets

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses[18] .

A selected three level, two factor experimental design (3^2 factorial design) describe the proportion in which the independent variables HPMCK4M and Guar Gum were used in formulation of Ranitidine.HCl Floating Tablets. The time required for 10% ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) drug dissolution were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($p<0.05$) for Final Equations. Polynomial equations were developed for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (step-wise backward Linear Regression Analysis).

The three levels of factor X_1 (HPMCK4M) at a concentration of 15%, 22.5%, 30%. three levels of factor X_2 (Guar Gum) at a concentration of 15%, 22.5%, 30% (% with respect to quantity of active

ingredient i.e, 336mg) was taken as the rationale for the design of the Ranitidine.HCl floating tablet formulation. Totally nine Ranitidine.HCl floating tablet formulations were prepared employing selected combinations of the two factors i.e X_1, X_2 as per 3^2 Factorial and evaluated to find out the significance of combined effects of X_1, X_2 to select the best combination and the concentration required to achieve the desired prolonged release of drug (by providing gastro retentivity) from the dosage form.

2.2 Preparation of Ranitidine.HCl Floating Tablets

Ranitidine.HCl was dispersed in chloroformic solution of required quantity of stearic acid. The dispersion of stirred and evaporated to form Ranitidine Hcl-Stearic acid mixture.

This mixture was then blended with other ingredients such as HPMCK4M, Guar gum, , Sodium bicarbonate, Citric acid. The powder blend was lubricated with Aerosil, Talc blended for 5-6 minutes. Lubricated powder blend was compressed by using rotary tablet punching machine (RIMEK), Ahmedabad). Compressed tablets were examined as per official standards and unofficial tests. Tablets were packaged in well closed light resistance and moisture proof containers.

2.3 Experimental Design

Experimental design utilized in present investigation for the optimization of polymer concentration such as, concentration of HPMCK4M was taken as X_1 and concentration of Guar Gum was taken as X_2. Experimental design was given in the Table 1. Three levels for the Concentration of HPMCK4M were selected and coded as -1= 15%, 0=22.5%, +1=30%. Three levels for the Concentration of Guar Gum were selected and coded as -1= 15%, 0=22.5%, +1=30%. Formulae for all the experimental batches were given in Table 2 [19].

2.4 Evaluationof Ranitidine.Hclsustained Release Tablets

2.4.1 Hardness [20]

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 kg/cm^2 is considered adequate for mechanical stability.

2.4.2 Friability [20]

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

2.4.3 Content Uniformity[20]

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or more than 115% of the labelled drug content can be considered as the test was passed.

2.4.4 Assay [20]

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. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 315nm using 0.1 N Hydrochloric acid as blank.

2.4.5 Thickness [20]

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers.

2.4.6.In Vitro Buoyancy Studies[21]

The tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

2.4.7 In-vitro Dissolution Study [22]**:**

The *In-vitro* dissolution study for the Ranitidine.HClsustained release tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 315 nm using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).

***2.5 Kinetic modeling of drug release*:** [23,24,25,26].

The dissolution profile of all the formulations was fitted in to zero-order, first-order, Higuchi and Korsmeyer-peppas models to ascertain the kinetic modeling of drug release

3. RESULTS AND DISCUSSION:

Gastro Retentive Floating tablets of Ranitidine.HCl were prepared and optimized by 3^2 factorial design in order to select the best combination of different release rate modifiers, HPMCK4M, Guar Gum and also to achieve the desired prolonged release of drug from the dosage form(by retaining drug at gastric environment). The two factorial parameters involved in the development of formulations are, quantity of HPMCK4M & Guar Gum polymers as independent variables (X_1, X_2), and *In vitro* dissolution parameters such as $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ & $t_{90\%}$ as dependent variables. Totally nine formulations were prepared using 3 levels of 2 factors and all the formulations containing 336 mg of Ranitidine.HCl (equivalent to 300 mg of Ranitidine) were prepared as a sustained release tablet dosage form by Direct Compression technique as per the formulae given in Table 2.

Table 1: Experimental Design Layout

Formulation Code	X_1	X_2
F_1	1	1
F_2	1	0
F_3	1	-1
F_4	0	1
F_5	0	0
F_6	0	-1
F_7	-1	1
F_8	-1	0
F_9	-1	-1

Table 2: Formulae For The Preparation Of Ranitidine.Hcl Floating Tablets As Per Experimental Design

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Ranitidine.HCl	336	336	336	336	336	336	336	336	336
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
HPMCK4M	100	100	100	75	75	75	50	50	50
Guar Gum	100	75	50	100	75	50	100	75	50
Stearic acid	40	40	40	40	40	40	40	40	40
Citric acid	10	10	10	10	10	10	10	10	10
Di Calcium Phosphate	12	37	62	37	62	87	62	87	112
Aerosil	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6
Total Weight	660	660	660	660	660	660	660	660	660

All the prepared tablets were evaluated for different post compression parameters, drug content, mean hardness, friability, mean thickness, mean diameter as per official methods and results are given in Table 3. The hardness of tablets was in the range of 4.42-4.69 Kg/cm^2. Weight loss in the friability test was less than 0.68%. Drug content of prepared tablets was within acceptance range only. Results for all Post-compression parameters were tabulated or shown in Table 3.

Table 3: Post-Compression Parameters For The Formulations

S.No	Formulation Code	Hardness (kg/cm^2)	Floating lag time	Diameter (mm)	Thickness (mm)	Friability (%)	Weight Variation	Drug Content (%)
1	F_1	4.66	2.50	9.95	4.65	0.64	658.07	97.46
2	F_2	4.67	1.70	9.96	4.66	0.62	658.32	97.07
3	F_3	4.69	2.40	9.96	4.68	0.57	658.05	94.60

4	F_4	4.51	1.70	9.95	4.52	0.69	658.60	99.79
5	F_5	4.59	2.25	9.98	4.55	0.65	657.44	99.92
6	F_6	4.62	1.05	10.05	4.61	0.53	654.90	100.14
7	F_7	4.42	2.30	10.00	4.45	0.68	658.23	99.30
8	F_8	4.49	0.60	10.02	4.50	0.61	657.66	97.19
9	F_9	4.54	0.44	10.01	4.54	0.55	659.30	97.34

Table 4: Regression Analysis Data of 3^2 Factorial Design Formulations of Ranitidine HCl

S.NO	Formulation Code	KINETIC PARAMETERS											
		ZERO ORDER			FIRST ORDER			HIGUCHI			KORSMEYER-PEPPAS		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F_1	8.193	5.528	0.987	2.001	0.044	0.983	6.121	21.102	0.976	0.951	0.861	0.983
2	F_2	2.246	6.437	0.994	2.04	0.051	0.99	13.509	24.168	0.966	0.734	1.114	0.985
3	F_3	8.508	5.39	0.959	2.012	0.046	0.923	4.699	20.243	0.932	1.018	0.769	0.947
4	F_4	11.433	6.265	0.985	2.004	0.058	0.993	5.824	24.379	0.992	0.983	0.916	0.956
5	F_5	7.227	6.506	0.986	2.034	0.06	0.973	9.047	24.584	0.964	0.946	0.922	0.984
6	F_6	19.957	6.185	0.948	1.954	0.065	0.996	0.511	25.138	0.997	1.081	0.876	0.916
7	F_7	1.347	6.995	0.996	2.08	0.06	0.966	17.155	25.679	0.946	0.708	1.136	0.996
8	F_8	2.604	6.717	0.982	2.1	0.06	0.9	16.827	24.233	0.917	0.712	1.088	0.999
9	F_9	0.679	7.927	0.993	2.132	0.085	0.949	18.921	29.248	0.948	0.763	1.143	0.992
10	MP	5.826	6.489	0.988	2.036	0.057	0.977	10.179	24.419	0.962	0.907	0.951	0.988

Table 5: Dissolution Parameters Of Ranitidine.Hcl Floating Tablets 3^2 Full Factorial Design Batches

S.NO	FORMULATION CODE	KINETIC PARAMETERS			
		$t_{10\%\ (h)}$	$t_{50\%\ (h)}$	$t_{75\%\ (h)}$	$t_{90\%\ (h)}$
1	F_1	1.043	6.862	13.725	22.804
2	F_2	0.889	5.846	11.691	19.425
3	F_3	0.998	6.564	13.128	21.812
4	F_4	0.789	5.189	10.378	17.243
5	F_5	0.764	5.027	10.054	16.705
6	F_6	0.705	4.635	9.271	15.403
7	F_7	0.761	5.005	10.011	16.633
8	F_8	0.759	4.995	9.99	16.598
9	F_9	0.54	3.553	7.105	11.805
10	MP	0.797	5.24	10.48	17.413

Table 6: Dissolution Parameters for Predicted and Observed Values For Check Point Formulations

Formulation code	Predicted value				Actual observed value			
	$t_{10\%\ (h)}$	$t_{50\%\ (h)}$	$t_{75\%\ (h)}$	$t_{90\%\ (h)}$	$t_{10\%\ (h)}$	$t_{50\%\ (h)}$	$t_{75\%\ (h)}$	$t_{90\%\ (h)}$
C_1	0.713	4.690	9.38	15.584	0.715	4.687	9.375	15.590
C_2	0.916	6.027	12.05	20.028	0.919	6.030	12.456	20.030

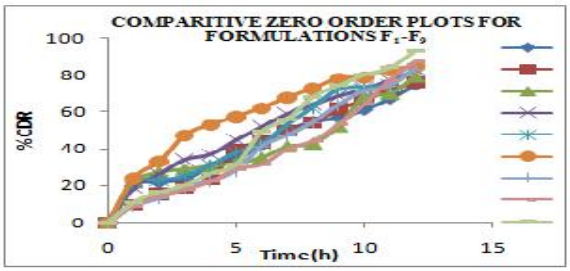

Fig 1: Comparative Zero Order Plots for F_1-F_9

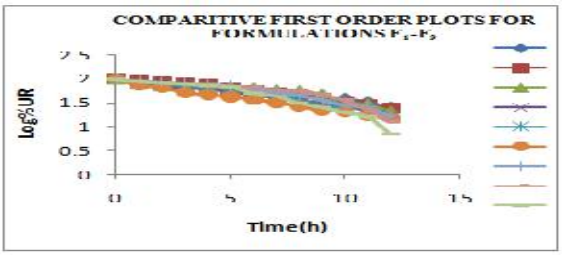

Fig 2: Comparative First Order Plots for F_1-F_9

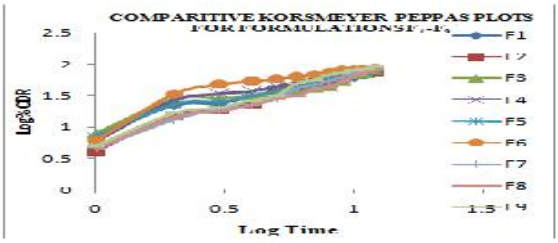

Fig 3: Comparative Korsmeyer-Peppas Plots for F_1-F_9

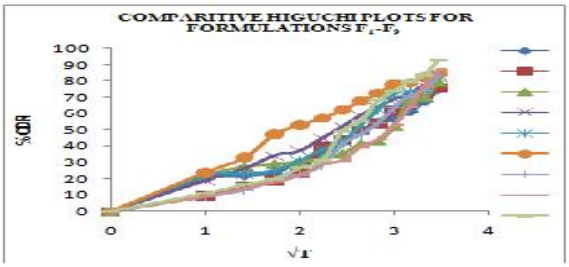

Fig 4: Comparative Higuchi Plots for F_1-F_9

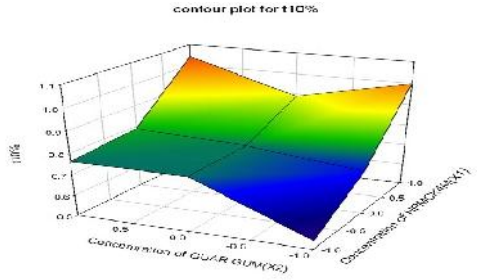

Fig 5: Response Surface plot for $t_{10\%}$

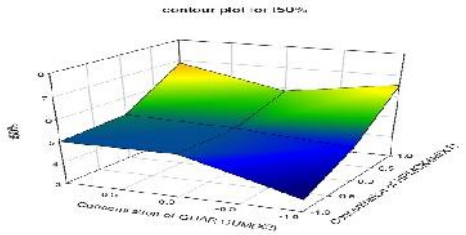

Fig 6: Response Surface plot for $t_{50\%}$

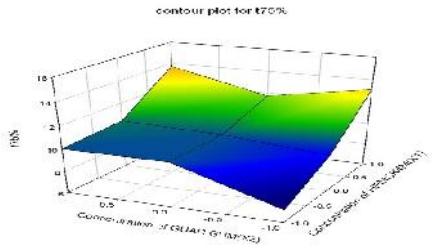

Fig 7: Response Surface plot for $t_{75\%}$

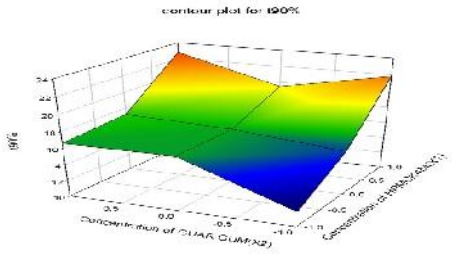

Fig 8: Response Surface plot for $t_{90\%}$

In-vitro Dissolution studies were performed for prepared tables using 0.1 N HCl as a dissolution media at 50 rpm and temperature 37±0.5°C. The *In-vitro* dissolution profiles of tablets are shown in Fig.1 and the dissolution parameters are given in Table 4. Cumulative % Drug release of Factorial Design Formulations F_1-F_9 at 12Hr were found to be in the range of 74.70-92.88 %. From the result it reveals that the release rate was higher for formulations containing Low level of HPMCK4M/Guar Gum compared with other Formulations containing Higher level, due to High concentration of polymer drug may have entrapped within a polymer matrix causing a decrease in rate of drug release. Therefore, required release of drug can be obtained by manipulating the composition of HPMCK4M and Guar Gum.

Much variation was observed in the $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ due to formulation variables. Formulation F_5 containing 75 mg of HPMCK4M, 75 mg of Guar Gum showed promising dissolution parameter (**$t_{10\%}$= 0.764 h, $t_{50\%}$ = 5.027 h, $t_{75\%}$ = 10.054 h, $t_{90\%}$ = 16.705 h**). The difference in burst effect of the initial time is a result of the difference in the viscosity of the polymeric mixtures. Dortunc and Gunal have reported that increased viscosity resulted in a corresponding decrease in the drug release, which might be due to the result of thicker gel layer formulation[27].

The *In -vitro* dissolution data of Ranitidine.HCl Floating formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to assess the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4 and plots shown in fig.1,2,3,4. It was observed from the above that dissolution of all the tablets followed zero order kinetics with co-efficient of determination (R^2) values in the range of **0.948-0.996**. The values of r of factorial formulations for Higuchi's equation was found to be in the range of **0.917-0.976**, which shows that the data fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values ranges from **0.769- 1.143** that shows Non-Fickian diffusion mechanism. Polynomial equations were derived for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ values by backward stepwise linear regression analysis. The dissolution data (Kinetic parameters) of factorial formulations F_1 to F_9 are shown in Table 5.

Polynomial equation for 3^2 full factorial designs is given in Equation

$$\mathbf{Y= b_0+b_1 X_1+b_2 X_2+b_{12} X_1X_2+b_{11} X_1^2+b_{22} X_2^2\ldots}$$

Where, Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated co-efficient for factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. Validity of derived equations was verified by preparing Two Check point Formulations of Intermediate concentration(C_1, C_2).

The equations for $t_{10\%}$, $t_{50\%}$ $t_{75\%}$ and $t_{90\%}$ developed as follows,

$Y_1 = 0.805+0.145X_1+0.0583X_2-0.044X_1X_2+0.079X_1^2+0.002X_2^2$ **(for $t_{10\%}$)**

$Y_2 = 5.297+0.953X_1+0.384X_2-0.289 X_1X_2+0.521X_1^2+0.012 X_2^2$ **(for $t_{50\%}$)**

$Y_3 = 10.595+1.906X_1+0.768X_2-0.579 X_1X_2+1.041X_1^2+0.025 X_2^2$ **(for $t_{75\%}$)**

$Y_4 = 17.603+3.1675X_1+1.277X_2-0.959 X_1X_2+1.729X_1^2+0.041 X_2^2$ **(for $t_{90\%}$)**

The positive sign for co-efficient of X_1 in Y_1, Y_2, Y_3 and Y_4 equations indicates that, as the concentration of HPMCK4M increases, $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ value increases. In other words the data demonstrate that both X_1 (amount of HPMCK4M) and X_2 (amount of Guar Gum) affect the time required for drug release ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$). From the results it can be concluded that, and increase in the amount of the polymer leads to decrease in release rate of the drug and drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels. The Dissolution parameters for predicted from the polynomial equations derived and those actual observed from experimental results are summarised in Table 6. The closeness of Predicted and Observed values for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ indicates validity of derived equations for dependent variables. The Contour Plots were presented to show the effects of X_1 and X_2 on $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$. The final best (Optimised) formulation (F_5) is compared with marketed product (**ZANTAC**) shows similarity factor (f_2) 85.01, difference factor (f_1) 15.358 (There is no significant difference in drug release because t_{cal} is<0.05).

4. CONCLUSION

The present research work envisages the applicability of rate retarding agents such as HPMCK4M and Guar Gum in the design and development of Gastro Retentive Floating tablet formulations of Ranitidine.HCl utilizing the 3^2 factorial design. From the results it was clearly understand that as the retardant concentration increases the release rate of drug was retarded and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired sustained release of the drug for longer periods. The optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to be Non-Fickian Diffusion, Zero order release type, controlled by diffusion through the swollen matrix. On the basis of evaluation parameters, the optimized formulation **F_5** may be used once a day administration in the management of GORD, PEPTIC ULCERS.

5. ACKNOWLEDGEMENTS

The author would like to thank Management, Principal, Teaching, Non-teaching Staff of Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (D.t), A.P., India for providing support for successful completion of research work.

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Conflict of Interest: None

Source of Funding: Nil