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FORMULATION & EVALUATION OF LEVOFLOXACIN & RANITIDINE GASTRORETENTIVE FLOATING MATRIX TABLET

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ABSTRACT

The purpose of this research was to develop gastro-retentive delivery system of levofloxacin and ranitidine, which was prolonged drug delivery and GI tract, is to control the gastric residence time with desire in vitro release profile. The formulation of levofloxacine & ranitidine floating matrix tablet at the different parameters for the prevention of GERD and Emesis simultaneously. The tablets were prepared by direct compression method using variables concentration of HPMC and CMC with citric acid, Sodium Bi Carbonate, Talc and Magnesium Stearate. The tablets were evaluated for *in vitro* release for 12 hours. The tablets were prepared by the combination of HPMC E15 and CMC Shows better floating ability as well as better release profiling.

KEYWORDS: Levofloxacin, Ranitidine, Gastro-retentive floating matrix tablet, GERD and Emesis.

INTRODUCTION

The oral dosage form is the most popular dosage form in use now a days due to patient compliance, and flexibility in formulation etc. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity.[1] One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time, i.e. gastro retentive dosage form.[2] The gastric retention of an oral dosage form in the stomach, various approaches have been developed; e.g. floating systems, swelling and expanding systems, bioadhesive systems, altered density systems and other delayed gastric emptying devices.[3]

The different gastroretentive system, the gastric floating drug delivery systems are maximum advantages over the gastric retentive systems. These systems have a density lower than the gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach.[4, 5, 6]

Ranitidine is a histamine H_2 receptor antagonist. It is widely prescribed in active duodenal ulcer, gastric ulcer, Zollinger-Ellision syndrome, gastro esophageal reflux disease and erosive esophagitis and levofloxacin is one of the most widely used fluroquinolones. It has been used to treat variety of infections. Following oral administration, the bioavailability of levofloxacin in the tablet formulation is approximately 99%.[7-9] Maximum serum concentrations are achieved one to two hours after an oral dose. It was also found to show linear and predicable pharmacokinetics after single and multiple doses. Approximately 32% of the drug in plasma is protein bound. So the objective of the study is the formulation & evaluation of Levofloxacine & Ranitidine floating matrix tablet at the different parameters for the prevention of GERD and Emesis simultaneously. Patient satisfied Physico-chemical parameters, floating time, swelling index and In-vitro drug release profile requirements for a floating drug delivery system.

MATERIAL AND METHOD

Ranitidine Hydrochloride and levofloxacin was obtained as a gift by Symbiosis Pharmaceuticals Pvt. Ltd. Himachal Pradesh. HPMC E15, CMC, Citric Acid, Sodium Bicarbonate, Magnesium Stearate and Talc were purchase from hymedia chemical.

Pre- Compression Evaluation of Tablet

Angle of Repose

The angle of repose of powder blend was determined by the funnel method. The accurately weighted powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$: Where, h and r are the height and radius of the powder cone.

Bulk Density and Tapped Density

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2gm of powder blend from each formula, previously shaken to break any agglomerates

formed, was introduced into 10ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

LBD = (Weight of the powder blend)/ (Untapped volume of the packing)

TBD = (Weight of the powder blend)/ (Tapped volume of the packing)

Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below.

Carr's Index (%) = ([TBD-LBD] x 100)/TBD

Hausner's Ratio

It is the ratio of bulk volume to tapped volume or tapped density to bulk density. Hausner's ratio is an important character to determine the flow property of powder and granules. This can be calculated by the following formula.

Hausner's Ratio= (Tapped density)/ (Bulk density)

Formulation of Floating Tablet

Floating tablet containing levofloxacin and Ranitidine where prepared by direct compression method using variables concentration of HPMC and CMC with citric acid, Sodium Bi Carbonate, Talc and Magnesium Stearate. The pre-sieved ingredients were accurately weighted and then mixed other in increasing order of their weight expected Mg. Stearate and Talc. The powder blend was thoroughly lubricated with magnesium separate (1%w/w) and Talc (1%w/w) and compressed on single punch tablet machine.

Table 1. Composition of floating matrix tablets of Levofloxacin and Ranitidine

Formulation Code	D1 (mg)	D2 (mg)	D3 (mg)	D4 (mg)	D5 (mg)	D6 (mg)
Levofloxacin	200	200	200	200	200	200
Ranitidine	150	150	150	150	150	150
HPMC E15	50	60	70	80	90	100
CMC	100	90	80	70	60	50
Citric Acid	20	20	20	20	20	20
Sodium Bi Carbonate	40	40	40	40	40	40
Talc	10	10	10	10	10	10
Mg. Stearate	10	10	10	10	10	10
Total	600	600	600	600	600	600

Evaluation of Physical Parameters of Floating Tablets of Levofloxacin and Ranitidine

Thickness[10]

The thicknesses of the tablets were determined by using vernier callipers. Thickness of ten tablets was determined randomly. It was expressed in mm.

Hardness[10, 11, 12]

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation is determined by using Pfizer Hardness tester.

Friability[12, 13]

It is measure of mechanical strength of tablets. Roche friabilator is used to determine the friability by following procedure. Pre weighed tablets are placed in the friabilator. 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 are rotated in the friabilator for at least 4 minutes.

At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as Formula:

% Friability= (Weight (initial)-Weight (final))/ (Weight (initial)) x100

Weight variation test[12, 13]

The punched tablets were weighed individually using digital balance. The weight data from the tablets were analyzed for sample mean and percent deviation.

Uniformity of Drug Content[14]

Two tablets were powdered in a glass mortar and the powder equivalent to 1mg of drug was placed in a 500ml conical flask. The drug was extracted with 500ml of pH 1.2 solution with vigorous shaking on a mechanical gyratory shaker (100rpm) for 1hr. Absorbance was measured by spectrophotometer against blank.

Floating Lag Time

The lag time was carried out in beaker containing 100ml of 0.1N HCl as a testing medium maintained at 37°C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

At Initial time **After 10 sec.** **After 12 hrs.**

Fig.1: Floating lag time of Levofloxacin and Renitidine floating matrix tablet

Buoyancy Time

Floating time was determined by using IP tablet dissolution apparatus at 50rpm using 900ml of 0.1N HCL at 37±0.5°C temperatures. The floating duration was the time during which the tablet remains buoyant and floating lag time was the time between tablet introduction and its buoyancy. Duration of floating and floating lag time was measured by visual observation.

In vitro release studies for floating tablets[14,15]

The release rate of drug from floating tablets was determined using United States Pharmacopeia (USP) dissolution testing apparatus II (Paddle method). This dissolution test was performed using 900ml of 0.1N HCL, at 37±0.5°C and 75 rpm. A sample (10ml) of the solution was withdrawn from the solution apparatus hourly for 12hrs and the sample were replaced with fresh medium. The sample diluted to suitable concentration with 0.1N HCL. Absorbances of these solutions were measured at respective wavelength using UV- Visible double beam spectrophotometer. The cumulative % drug release was calculated using the equation obtained from a standard curve.

Drug release kinetics of Floating Tablets

The dissolution profile of all factorial batches was fitted to various models such as zero order, first order, Higuchi[16], and Korsemeyer and Peppas[17] to ascertain the kinetics of drug release. The method described by Korsemeyer and Pappas was used to describe the mechanism of drug release.

RESULTS AND DISCUSSION

Pre-compression parameter

The prepared powder for the matrix tablet were characterized with respect to the angle of repose, Bulk density untapped, Bulk density tapped, Hausner ratio and Carr's index, which is

shown in Table 2 for the above formulation. The angle of repose for the formulated blend was carried out and the results were plotted in Table 6.7. It concludes that all the formulation blends was found to be in the range 28.36±0.57 to 28.30±0.21, indicating fair to good flow properties. Carr's Index was carried out and was found between 16.08±0.02 and 16.09±0.30 indicating the powder blend has required flow property for compression. The Hausner's ratio of powder blend of drug was found to be in the range of 1.191±0.09 to 1.191±0.11. The result implies good flow property for the compression.

Post Compression Evaluations of Floating Tablets

All prepared formulations were subjected for weight variation study and results given in table 2. The measured hardness of tablets from batch ranged between 5±0.2 to 6.16±0.28 kg/cm^2. This ensures good handling characteristics of all tablets. The values of friability test were tabulated in Table 2. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. The % weight variations for all formulations were tabulated in Table 2. All the formulated (D1 to D6) tablets passed weight variation test as the % weight variation was within the pharmacopeial limits between average 468.16±0.33 to 526±0.769 of the total weight. The weights of all the tablets were found to be uniform with low standard deviation values. The % of drug content for D1to D6 was found to be 98.21±1.07 to 102.33±0.21% of drug, it complies with official specifications. The result was shown in Table 2. On immersion in 0.1 N HCl solutions of pH 1.2 at 37°C, tablets floated and remained buoyant without disintegration. From the result it can be concluded that increase in concentration of HPMC polymer also increase in floating lag time (FLT). All formulations of prepared floating tablets were subjected to In-vitro release study these studies were carried out using dissolution apparatus in 0.1N HCl. The result obtaining In-vitro release study was plotted in graph. The release data obtained for formulation D1 to D6 were tabulated in Table 6.10 and Fig. 6.10 Shows plotted of cumulative drug release as function of time for different formulations. The In-vitro of all batches of floating tablets showed the release with an initial effect. The % drug release for batches D1 to D6 were found to be increased with increase in concentration of polymer i.e., HPMC and CMC.

Table 2: Pre-compressional and Postcompressional evaluation of floating tablets

Formulation	Bulk density gm/cm3	Tapped gm/cm3	Hausner's Ratio	Carr's Index (%)	Angle of repose (θ)	Thickness (mm) ±SD	Drug Content (%)	Friability (%)	Hardness (Kg/cm2) ±SD	Weight variation (gm) ±SD	Total Floating Duration (h)
D1	0.553±0.659	0.659±0.088	1.191±0.09	16.08±0.02	28.36±0.47	4.2±0.025	102.33±0.21	0.488	6.16±0.28	499±0.49	6.23±0.03
D2	0.558±0.036	0.660±0.057	1.182±0.12	15.45±0.45	28.31±0.59	4.16±0.025	99.52±0.74	0.644	5.04±0.04	526±0.769	8.75±0.05
D3	0.556±0.027	0.630±0.048	1.133±0.04	11.74±0.09	26.35±0.38	4.19±0.025	98.96±0.59	0.488	5.05±0.11	524.33±0.28	9.05±0.06
D4	0.562±0.027	0.672±0.055	1.195±0.03	16.36±0.12	27.82±0.61	4.25±0.025	101.14±1.59	0.689	5±0.2	517.10±0.45	8.35±0.01
D5	0.559±0.037	0.659±0.053	1.178±0.10	15.17±0.52	27.69±0.12	4.17±0.91	98.21±1.07	0.472	5.14±0.35	489.13±0.83	9.40±0.06
D6	0.558±0.046	0.665±0.049	1.191±0.11	16.09±0.30	28.30±0.21	4.03±0.026	101.50±1.81	0.644	5.83±0.28	468.16±0.33	10.30±0.02

All the values are expressed as mean ± SD. (n=3)

Swelling study was performed an all the batches (D1 to D6) for 12hrs. The result of swelling index was shown in Table 3. Swelling index plotted against time (hrs.) in Fig. 2. From the result it was concluded that swelling increase as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost polymer hydrates and swells and gel barrier are formed at the outer surface. As the layer progressively dissolved and/or is dispersed the hydration swelling release process continues towards new exposed surface thus maintaining the integrity of dosage form.

Table 3: Swelling Index Data of Levofloxacin and Ranitidine Floating Tablets

Time (h)	D1	D2	D3	D4	D5	D6
0	0	0	0	0	0	0
2	18.1	17.51	19.21	21	22	23
4	28	25	30	31	35	29
6	40	32	38	35	40	35
8	43	38	42	38	44	38
10	45	45	46	45	47	42
12	46	47	48	48	49	47

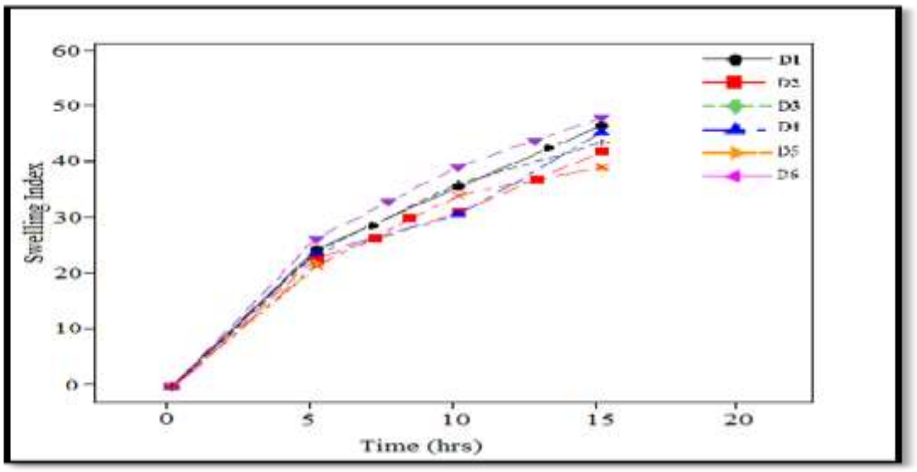

Fig 2: Swelling Index Profile of Levofloxacin and Ranitidine Floating Tablets]

All formulations of prepared floating tablets were subjected to In-vitro release study these studies were carried out using dissolution apparatus in 0.1N HCl. The result obtaining In-vitro release study was plotted in graph. The release data obtained for formulation D1 to D6 were tabulated in Table 4 and Fig. 3 Shows plotted of cumulative drug release as function of time for different formulations. The In-vitro of all batches of floating tablets showed the release with an initial effect. The % drug release for batches D1 to D6 were found to be increased with increase in concentration of polymer i.e., HPMC and CMC. All the batches showed floating time more than 12 hours which is quite significant for a floating matrix tablet. It is also observed that formulations shows better controlled release behaviour while formulation D4 containing 90% released promising as controlled release floating matrix tablet.

Table 4: In-vitro Drug Release Study

Time (hrs.)	% Cumulative drug release					
	D1	D2	D3	D4	D5	D6
0	0	0	0	0	0	0
1	21.51	21.11	8.59	12.16	23.53	9.30
2	31.82	23.81	12.5	17.25	33.44	14.67
4	52.47	34.52	21.95	27.44	57.44	22.96
6	62.29	54.46	40.67	50.24	72.56	32.48
8	72.63	62.81	53.84	69.09	80.89	45.2
10	78.54	72.89	70.82	80.57	86.48	65.17
12	83.29	82.21	82.25	90.77	90.63	88.32

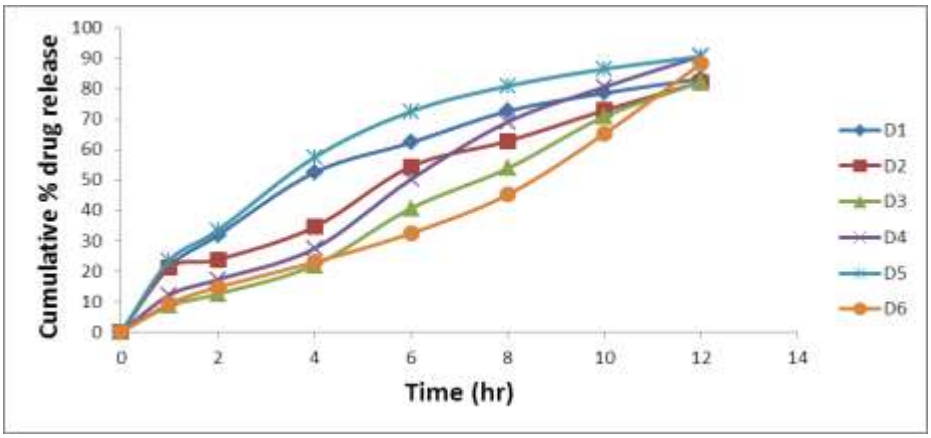

Fig 3: In-vitro Release profile of Levofloxacin and Ranitidine Floating Tablets of Batch D1 to D6

The values of the In-vitro release were attempted to fit into various mathematical models. The plots of Zero order, First order, Higuchi matrix and Korsmeyer – Peppas model depicted in Tables 6.11, 6.12, 6.13 and 6.14 respectively.

The drug release data were explored for the type of release mechanism followed. The best fit with the highest determination r^2 coefficient was shown by both Zero order and Higuchi models. Zero order release describes the release rate independent of drug concentration. Higuchi square root of time dependent process.

It describes release of drug by simple diffusion mechanism. The values of n with regression coefficient for all the formulations are shown in (Table 6.15). The value of n were in the range of 0.9640 to 0.5071 (n is not more than 0.5) showing Non-fickian release governed by the drug diffusion.

However as indicated by the values of r^2 of the model (Higuchi and Korsmeyer-Peppas) were found to be efficient in describe the release of drug from the floating tablets. All the parameters runs 3 times (n=3). The difference in mean of Zero order, First order, Huguchi matrix and Korsmeyer-Peppas Equation between batch series D1 and batch D6 was indicated significant ($p<0.05$).

Table 6.15: *In vitro* release kinetics model for Levofloxacin and Ranitidine floating tablets

Formulation Code	Zero Order	First Order	Higuchi	Peppas	
	r^2	r^2	r^2	r^2	n
D1	0.9831	0.9001	0.9508	0.9611	0.9000
D2	0.9591	0.8038	0.8880	0.9615	0.8986
D3	0.9864	0.9811	0.9735	0.9781	0.9093
D4	0.9894	0.9844	0.9493	0.9729	0.9640
D5	0.8803	0.9866	0.9556	0.9636	0.5532
D6	0.9105	0.9844	0.9733	0.9804	0.5071

CONCLUSION

In this study, it is evident that a promising controlled release by bilayered floating tablets of Ranitidine HCl and Levofloxacin can be developed. Further detailed investigations are required to establish efficacy of these formulations. Further In-vivo investigations are required to correlate In-vitro release studies. Further preclinical and clinical study is necessary for use of Ranitidine HCl and Levofloxacin floating tablets as oral controlled drug delivery system. The work can be carried out to study the effect of other response parameter like bio-adhesiveness, etc. on floating and release rate of the drug. D4 formulation turned out to be the best because D4 showed a minimum lag time and maximum floating time with maximum release of drug percentage, so it is considered as a successful.

REFERENCE

1. Ozuah PO, et al. Oral rehydration, emergency physicians, and practice parameters: a national survey. Pediatrics CrossRef , Web of Science , Medline, 2002; 109: 259-261.
2. Charyulu RN, Patil AB, Deepika L, Prabhakar Prabhu CH, Shastry C. Development of gastro retentive floating matrix tablets of diltiazem hydrochloride, Nitte University Journal of Health Science., 2011; 1: 1-3.
3. Dahiya A, Rohilla A, Rohilla S, Khan MU. Gastroretentive Dosage Forms: An Approach to Oral Controlled Drug Delivery Systems. International Journal of Pharmaceutical & Biological Archives., 2011; 2(2): 615-620.
4. Sanjay Garg, Shringi Sharma. Gastro retentive drug systems. Pharmatech., 2003; 160-166.
5. Shirwaikar AA, Kumar SMR, Jacob S, Rashi W, Ravi K. Recent developments in floating drug delivery systems for gastric retention of drugs. An overview. Indian Drugs., Sep 2006; 43(9): 697-703.

6. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastro retentive dosage forms: Overview and special case of helico bacter pylori. J Control Release., 2006 Mar; 111: 1-2.
7. Histamine H2 antagonists. In: Drug facts and comparisons. St Louis, MO: Wolters Kluwer Co., 2002, 1192-1197.
8. McCarty-Dawson D, Sue SO, Morrill B et al. Ranitidine versus cimetidine in the healing of erosive esophagitis. Clin. Ther., 1996, 18: 1150-1160.
9. Ranitidine tablets, USP, package insert.
10. Martin A, Swarbrick J, Cammarata A. Physical Pharmacy, 4th edition, Philadelphia., 2000; 335-38: 431-32.
11. Indian pharmacopoeia, Ghaziabad, India: Indian Pharmacopoeia Commission., 2007; 1: 182-183.
12. Bomma R, Veerbrahma K. Development and evaluation of gastroretentive norfloxacin floating tablets. Acta Pharm., 2009; 59: 211-221.
13. Smith AA, Kottai Muthu A, Manavalan R. Formulation, Evelopment and Evaluation of ondansetron hydrochloride sustain release matrix tablet. J.pharm. sci. & res., 2009; 1(4): 48-54.
14. Ghosh N S, Ghosh S, Debnath S. Formulation of immediate dosage form of ranitidine hydrochloride tablets using HPMC and starch acetate film former. J Chem Pharm Res., 2010; 2(3): 147-157.
15. Gangadharappa HV, Balamuralidhara V, Kumar P. Formulation and *in vitro* evaluation of floating tablets of atenolol. J Phram Res., 2010; 3(6): 1450-1455.
16. Higuchi T. Mechanism of sustained action mediation, theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci., 1963; 52: 1145-9.
17. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophillic polymers. Int J Pharm., 1983; 15: 25-35.