DESIGN AND EVALUATION OF LEVOFLOXACIN HEMIHYDRATE FLOATING TABLETS

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ABSTRACT: In the present study, the tablets were prepared by melt granulation method, using the polymer, hydroxy propyl methyl cellulose (HPMC K100M) with different amounts and other excipients and sodium bicarbonate as gas generating agent. The present study is to develop a floatable drug delivery system of Levofloxacin hemihydrate for sustained drug delivery and gastric retentive property with special emphasis on optimization of formulations for floating matrix tablets. Thus the study aims to improve the oral bioavailability of the drug and to achieve extended retention in the stomach which may result in prolonged absorption. Tablets were evaluated by different parameters such as weight uniformity, content uniformity, thickness, hardness, IR spectral analysis, *in vitro* release studies, Buoyancy determination and kinetic analysis of dissolution data, stability studies Levofloxacin floating tablet drug delivery system showed improved in-vitro bioavailability and extended drug release which may favour the reduced dose frequency and patient compliance**.**

Keywords: Levofloxacin Hemihydrate**,** Floating tablets, *in vitro* release study, Buoyancy determination.

INTRODUCTION

Levofloxacin hemihydrate is used as antimicrobial agent for the treatment of a variety of infectious diseases.[1-4] Levofloxacin is a safe and effective in first, second, and third line Helicobacter Pyroli eradication. Eradication rates were over 90% for the Levofloxacin based therapy. Levofloxacin is currently available in the forms of Tablets, Single –use vials and Infusions. Gastro retentive floating tablets have been emerged as an efficient means of enhancing the bioavailability of many drugs. The increasing sophistication of delivery technology will ensure the development of increasing number of Gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit an absorption window, low bioavailability and extensive first pass metabolism. The control of gastro-intestinal transit could be focus of the next decade and may result in new therapeutic possibilities with substantial benefits for patients. Rapid gastro-intestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of administered dose. Floating tablets of Levofloxacin hemihydrate were developed to prolong gastric residence time and to increase its bioavailability. The tablets were prepared by melt granulation method, using the polymer, Hydroxy propyl methyl cellulose (HPMC K100M) with different amounts and other excipients and sodium bicarbonate as gas generating agent. The present study is to develop a floatable drug delivery system of Levofloxacin hemihydrate for sustained drug delivery and gastric retentive property with special emphasis on optimization of formulations for floating matrix tablets. Thus the study aims to improve the oral bioavailability of the drug and to achieve extended retention in the stomach which may result in prolonged absorption.

MATERIALS AND METHODS

Materials

Levofloxacin hemihydrate was received as a gift sample from Promed Research Centre, New Delhi India. HydroxyPropyl Methylcellulose K4M [5-7] was received as gift samples from Micro labs Limited; Hosur, India Sodium bicarbonate[8-10]was purchased from Paxmy speciality chemicals, Chennai. India. Ethyl cellulose [11-13] was procured from S.d. fine chemical, Pvt., Ltd, Mumbai, India., Bees Wax, Magnesium stearate[14-15], and Talc [16-18] were purchased from S.D. fine – chem. Pvt., Ltd, Mumbai .India. All other ingredients were of laboratory grade.

Methods

Preparation of Levofloxacin hemihydrate Floating Tablets [19]

Seven formulations of Levofloxacin hemihydrate floating tablets were prepared. (Table-6).Beeswax was melted in a china dish, and the required quantity of Levofloxacin hemihydrate was added to the molten mass. Previously prepared geometric mixture of HPMC K4M and /or Ethyl cellulose and sodium bicarbonate were added to the molten Levofloxacin hemihydrate-Beeswax mixture and stirred well to mix. The mass was removed from the hot plate and subjected to scraping until it attained room temperature. The coherent mass was passed through a 36- mesh sieve, and the resulting granules were resifted on a 100-mesh sieve to remove the fines. Then the granules were mixed with 10mg of talc and 5mg of magnesium stearate per tablet. The lubricated blend was compressed in to tablets.

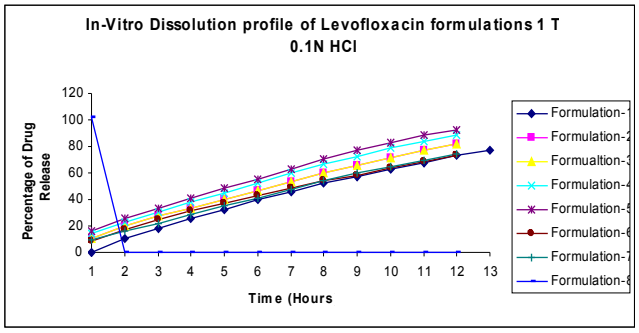
TABLE: 1.COMPOSITOION OF LEVOFLOXACIN HEMIHYDRATE FLOATING TABLETS.

Fomulation Code	Levofloxacin hemihydrate(mg)	HPMCK4M (mg)	Sodium Bicarbonate (mg)	Bees Wax (mg)	Ethyl Cellulose (mg)	Talc (mg)	Magnesium Stearate (mg)
F1	250	187.5	25	37.5	0	10	5
F2	250	162.5	25	37.5	25	10	5
F3	250	137.5	25	37.5	50	10	5
F4	250	125	25	37.5	62.5	10	5
F5	250	100	25	37.5	87.5	10	5
F6	250	112.5	25	62.5	50	10	5
F7	250	100	25	75	50	10	5

In vitro drug release studies [20]

In vitro drug release of the samples was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of 0.1N HCl, was placed into the dissolution flask maintaining the temperature of 37 ± 0.5°C and rpm of 50. One Levofloxacin hemihydrate tablet was placed in each paddle of dissolution apparatus. The apparatus was allowed to run for 12 hours. Samples measuring 2 ml were withdrawn every 1 hour intervals up to 12 hours using 2 ml pipette. The fresh dissolution medium (37°C) was replaced every time with the same quantity (2ml) of dissolution medium. Collected samples were suitably diluted with 0.1N HCl and analyzed at 293 nm using 0.1N HCl as blank. The percentage drug release was calculated. The percentage drug release was calculated and shown in Figure.1.

FIGURE: 1.PERCENTAGE DRUG RELEASE OF FLOATING TABLET FORMULATIONS OF LEVOFLOXACIN HEMIHYDRATE.



Buoyancy Determination[21]

i. **Buoyancy Lag Time (BLT): -** The time interval between introduction of Levofloxacin hemihydrate floating tablet into the dissolution medium and its flotation to the top of the dissolution medium was termed as BLT.

ii. **Duration of Buoyancy (DB)[22] -** The duration up to, which the dosage form floats, was termed as DB.

Stability studies:[23, 24]

Stability studies were aimed at determining the result of aging and storage under various conditions on the formulated floating release tablets. It was carried out to evaluate the stability of famotidine in formulated tablets after storing at different temperatures for 45 days. The prepared tablets were kept at three different temperatures 4° C ±2 ° C, 27° C ±2° C and 45° C ±2° C for 45 days at RH 75±5%. At 15 days intervals the tablets was evaluated for all physical parameter. The percentage of famotidine content and invitro drug release studies were determined by double beam UV visible spectrophotometer. The results are showed in table 4.

RESULTS:

EVALUATION OF LEVOFLOXACIN HEMIHYDRATE FLOATING GRANULES.[25-27]

The bulk density was found in the range of 0.32 – 0.35 gm/cm^3. It is within the acceptable limits. The tapped density was found in the range 0.37 – 0.4 gm/cm^3. The bulkiness of all formulations found in the range of 2.25 to 3.12.

The angle of repose of all the formulations was within 35^0. The result showed that the granules of all formulations showed good flow properties. The result of the Hausner ratio of all the formulations is between 1.14 – 1.18. If the Hausner ratio lies between 1.12 – 1.18, it shows good flow behavior of the granules or powder. The result indicates good flow property. The values are showed in table 2.

TABLE: 2.EVALUATION OF LEVOFLOXACIN HEMIHYDRATE FLOATING GRANULES

S.No	Parameter	Formulations						
		F1	F2	F3	F4	F5	F6	F7
1	Bulk density (gm/ml)	0.33± 0.005	0.35± 0.008	0.33± 0.012	0.33± 0.02	0.32± 0.012	0.32± 0.018	0.32± 0.008
2	Tapped density (gm/ml)	0.39±0. 008	0.4± 0.008	0.38 ±0.01	0.39± 0.008	0.38± 0.016	0.37± 0.012	0.37 ±0.02
3	Bulkiness (ml/gm)	3±0.04	2.85±0.0 6	3 ± 0.11	2.25 ±0.06	3.09 ±0.11	3.06 ±0.15	3.12± 0.07
4	Angle of repose (Θ)	34°03' ±0.28	31°27'± 0.66	31°58'± 0.72	33° 87' ±1.06	32° 56' ±0.33	34° 68'±0.249	30° 84±0.33
5	Compressibilit y index (%)	13.55± 0.18	12.93± 0.82	13.44 ±1.33	12.70± 1.6	13.74± 0.841	14.32± 0.287	14.53± 1.3
6	Hausner's ratio	1.18 ±0.005	1.14 ±0.01	1.15 ±0.01	1.14 ±0.02	1.15 ±0.014	1.16 ±0.0057	1.16± 0.02

EVALUATION OF LEVOFLOXACIN HEMIHYDRATE FLOATING TABLETS:

The tablets of all the formulation were subjected to many in-process parameters such as hardness, friability, thickness, content uniformity and weight variation. The hardness values were approximately 4-4.2 kg/cm^2. The weight loss was less than 1% in the friability test (0.17-0.5) was considered as acceptable value for conventional tablet. Good uniformity in drug content was found among different formulations of the tablet and the percentage drug content were more than 95%. All the formulations showed the thickness in the range of 4.2-4.6mm. All formulations showed buoyancy lag time in between 4 to 11.6 minutes and duration of buoyancy was greater than 17 hours. The results are showed in Table no .3.

DISSOLUTIONS STUDIES

The dissolution rate studies were performed to evaluate the dissolution character of Levofloxacin from the floating tablets. The dissolution study of all formulations shows the percentage drug release were found to be F1-77.4%, F2- 82%, F3-84.6%, F4-88.13%, F5-92%, F6-73.5% and F7-74.1% in 12hour period. From all the formulations F5 showed faster drug release and F6 showed slow drug release when compared to other formulations. Hence F5 was considered to be the best formulation based on its release characteristics. The marketed sample showed drug release of 102% in less than one hour.

TABLE: 3. EVALUATION OF LEVOFLOXACIN HEMIHYDRATE FLOATING TABLETS

STABILITY STUDIES

At the time of stability studies, the tablet of the best formulations-5 was subjected to evaluate for the Physico-chemical parameters, for every 15 days intervals up to 45 days. The results showed that there was no change in the physico-chemical properties of the tablets for the best F5. No visible changes in the appearance of the controlled release tablets were observed at the end of the storage period and there was no change in the drug content. *In-vitro* drug release was observed after 15 days, 30days and 45 days (Table-4).

S.No.	Parameter	Formulations						
		F1	F2	F3	F4	F5	F6	F7
1	Hardness(Kg/cm2)	4.1±0.08	4±0.16	4.2±0.2	4±0.08	4±0.08	4.2±0.2	4.2±0.2
2	Friability (%)	0.36±0.01	0.17±0.04	0.61±0.08	0.38±0.09	0.2±0.04	0.4±0.04	0.5±0.08
3	Uniformity of Weight(mg)	514±1.78	515±3.2	515±3.6	515±1.1	515±3.2	516±4.4	515±0.98
4	Drug content (%)	96.6±0.34	98.1±0.73	97±0.47	99.2±0.49	99.3±0.24	96.1±0.33	95±0.08
5	Thickness (mm)	4.2±0.2	4.4±0.21	4.5±0.12	4.2±0.2	4.4±0.21	4.2±0.2	4.6±0.17
6	Buoyancy Lag Time(minutes)	11.6±1.24	7±0.81	6±0.81	5±0.12	4±0.81	10.3±1.5	11±0.81
7	Duration of Buoyancy(Hours)	>17	>17	>17	>17	>17	>17	>17

TABLE 4: STABILITY STUDIES OF LEVOFLOXACIN HEMIHYDRATE FORMULATIONS.

*All values are expressed as mean ± standard deviation, n =5

S.No	Parameters	observation		
		At 15 Days	At 30 Days	At 45 Days
1	Physical Appearance	No change	No change	No change
2	Weight Variation (mg)	515 ± 3.2%	514 ± 2.8 %	515 ± 3.0%
3	Thick ness (mm)	4.2±0.02	4.3±0.08	4.5±0.08
4	Hardness (Kg/cm2)	4.0 ± 0.08	4.1 ± 0.16	4.0 ± 0.2
5	Friability (%)	0.2 ± 0.04	0.25 ± 0.08	0.28 ± 0.04
6	Drug Content (mg/tab)	99.2 ± 0.49	99.3 ± 0.24	99.0 ± 0.1
7	Buoyancy lag time (Minutes)	5.0 ± 0.2	4.5 ± 0.1	4.5 ± 0.17
8	Duration of Buoyancy (Hours)	>17	>17	>17

DISCUSSIONS

The present study was aimed to make the formulation remain in the stomach for longer period of time and to release the drug (Levofloxacin) in controlled rate. Bees wax was selected as a hydrophobic meltable material to impart sufficient integrity to the tablets. Sodium bicarbonate generates carbon dioxide gas in the presence of hydrochloric acid present in gastric dissolution medium. The hardness values were approximately 4-4.2 kg/cm^2 all formulations showed buoyancy lag time in between 4 to 11.6 minutes and duration of buoyancy was greater than 17 hours. Formulations (F2-F5) showed more than 80% of drug release in 12hrs of dissolution study. Formulations F6 and F7 showed less than 80% of the drug release in 12hrs may be due to higher amount of bees wax was used. F1 also showed less than 80% of drug release in 12hrs may be due to higher amount of polymer. The IR spectrum showed that both drug and polymer were not interacted with each other and appeared as separate entities which were clearly shown in the spectra whose vibrational frequencies were tabulated. The data for stability studies were carried out for the optimized Formulation F5 at 4±2^{o}c, 27±2^{o}c and 45±2^{o}c for 45 days and it revealed that no considerable differences in drug content and dissolution rate and buoyancy were observed.

CONCLUSION

The effervescent based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel forming polymer (HPMC K4M) and gas generating agent sodium bicarbonate were essential to achieve the *in-vitro* buoyancy. The drug release form the tablets were sufficiently sustained due to the presence of polymer and Bees wax .Levofloxacin floating tablet drug delivery system showed improved *in-vitro* bioavailability and extended drug release which may favour the reduced dose frequency and patient compliance.

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