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DEVELOPMENT AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF LEVOFLOXACIN

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Abstract

The present study concerns the development of floating tablets of Levofloxacin which were designed to prolong the gastric residence time after oral administration. Levofloxacin is a fluoroquinolone antibacterial agent which is highly effective against gram positive and gram negative bacteria. By applying direct compression technique floating tablets of Levofloxacin were prepared. The proportion of sodium bicarbonate was varied to get the least possible lag time, also the polymer part varied to get the desired release.The formulation developed using Hydroxy Propyl Methyl Cellulose (HPMC K100M) and Xanthan gum were used as swelling agents and sodium bicarbonate as effervescent agents. Six formulations (H1-H3 and X1-X3) were prepared and evaluated for various physical parameters, Hardness, friability, drug loading, floating ability and drug release profiles were assessed. Selected formulations were able to float immediately and showed buoyancy for at least 12 hrs. Meanwhile, sustained profiles of drug release were also obtained. All the formulation showed compliance with pharmacopieal standards. Based on the evaluation results, H3 formulation were selected as the best formulation and were checked for stability as per ICH guidelines. These results indicated that the selected formulation were stable. The drug release profile of the best formulation was well controlled and uniform throughout the dissolution studies.

Keywords: Levofloxacin, Xanthan gum, Floating time, Stability study.

Introduction

The concept of floating drug delivery system offers experiencing engaging or choking by some person while swallowing medicinal pills. The researcher suggested that difficulty could overcome by providing pills having a density of less than 1.0g/ml. So that pill will float on water surface since then several approaches have been proposed for ideal floating delivery system. This buoyant delivery system includes hollow microspheres powder granules, tablet, capsules and laminated films.[1,2] Effervescent floating drug delivery systems generate gas (CO2), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and released the drug slowly at a desired rate. Depending on the mechanism of buoyancy two distinctly different menthods viz. effervescent and non effervescent system have been used in the development of floating drug delivery systems (FDDS).[3,4] Levofloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class and is used to treat severe or life-threatening bacterial infections or bacterial infections that have failed to respond to other

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antibiotic classes.[5,6] It is sold under various brand names, such as Levaquin and Tavanic, the most common. In form of ophthalmic solutions it is known as Oftaquix, Quixin and Iquix.

Materials and methods

Materials

Levofloxacin was supplied from Hindustan Antibiotic, Pune, India. Sodium bicarbonate was a kind gift from Fine Chemical Industries, Mumbai, India. HPMC K100M was a kind gift from Colorcon Asia Pvt.Ltd., Goa and Xanthan gum was a kind gift from Loba chemicals, Mumbai, India. All other Excipients used in our work were of analytical grade.

Preparation of Floating Tablets of levofloxacin

Effervescent Floating tablets containing levofloxacin were prepared by direct compression technique using varying concentrations of different grades of polymers with Sodium bicarbonate. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except Magnesium stearate all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, Magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The tablets were compressed using tablet punching machine. The weights of the tablets were kept constant for all formulation. The formulation are showed in table no.1

Evaluation of effervescent floating tablet formulations[7-20]

Evaluation of Powder blend

The flow properties of granules (before compression) were characterized in terms of angle of Repose[7], tapped density, bulk density, Carr's index and Hausner ratio. Physical evaluation of famotidine floating tablets two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for uniformity of weight using 20 tablets 10, hardness (Monsanto tester), friability using 10 tablets (Roche type friabilator).

Determination of Swelling Index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 24 h. The swelling index (SI), expressed as a percentage, and was calculated from the following equation,

$$SI = \frac{\text{Weight of Swollen tablet-Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

In vitro buoyancy studies

The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

In vitro dissolution studies

The release rates of metronidazole from floating tablets were determined using United State Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl at 37° ± 0.5°C and 50 rpm. A sample (10ml) of the solution was withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium. The samples were filtered through 0.45 µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions were measured at 293.5 nm using a UV/Visible spectrophotometer. The Cumulative percentage drug release was plotted against time to determine the release profile.

Stability studies

The promising formulation was tested for a period of 3 months at 40^0C with 75% RH, for their drug content and other parameters.

Results and discussion

Floating tablets levofloxacin were developed to increase the gastric residence time of the drug, so that they can be retained in stomach for longer time and help in controlled release of drug to minimum 12 h. The tablets were made using different gel forming polymers such as HPMC K100M and Xanthan gum along with effervescing agent sodium bicarbonate to optimize the drug content, in vitro

buoyancy, swelling index and in vitro drug dissolution studies.

Magnesium stearate was employed for their glidant and lubricating properties. The prepared tablets of all the formulations were evaluated for precompression parameters like angle of repose, bulk and tapped density and compressibility index and physical characters like tablet hardness, friability, weight variation, buoyancy lag time, total floating time, in-vitro drug release. The main aim was to optimize the formulation for 12 hours in-vitro release and total floating time 12 hours.

Precompression parameters of Levofloxacin granules

The formulations showed good flow property and compressibility index (Table no.2). Angle of repose ranged from 26.8±0.64 to30.5±0.20, Hausner ratio ranged from 1.25± 0.01 to 1.32±0.02 and the compressibility index ranged from 17.13±0.62 to 27.75±0.14(%). The bulk density and tapped density of the prepared granules ranged from 0.570±0.007 to 0.585±0.003 and0.728±0.005 to 0.742±0.003 respectively. The results of angle of repose indicates good flow property of the granules and the value of compressibility index further showed support for the flow property.

Post compression parameters of levofloxacin tablets

The shape of the tablets of all formulations remained off white, smooth, flat faced circular with no visible cracks. The thickness of tablets was measured by vernier calipers and was ranged between 4.2±0.2mm to 4.5±0.05 mm. In the formulations from H1-H3 hardness was observed in the range of 5.0±0.2to 5.5±0.2and formulations from X1-X3 hardness was observed in the range of5.3±0.1 to 6.0±0.3 respectively. The friability was measured by Friabilator and was found to be 0.29±0.08 to 0.47±0.13%, which is an indication of satisfactory mechanical resistance of the tablets. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits. The results was shown in table no.3

Buoyancy lag time (BLT) and total floating time (TFT)

Effervescent floating tablet of different formulations were noted, where H1 BLT of 64 sec and TFT of 10 hours, H2 BLT of 41 sec and TFT of >12 hrs, H3 BLT OF 23 sec and TFT of >12 hrs, X1 BLT of 83 sec and TFT of 12 hrs, X2 BLT of 35 sec and TFT of >12 hrs, X3 formulation was burst after 9 hrs. With reference to buoyancy studies results it can be concluded that the batches containing HPMC K100M polymers showed good buoyancy lag time (BLT) and total floating time (TFT) than Xanthan gum. The results was shown in table no.4

In vitro dissolution studies

The in vitro studies showed that batch X3 containing higher concentration of polymer and sodium bicarbonate showed drug release at the end of 10 hrs due to more channels formation in polymeric matrix which leads to tablet swelled rapidly and increase the possibility of bursting effect. When sodium bicarbonate was used in 10% and 15% was found there is no significant effect on drug release profile. Similar result was found with HPMC K100M. Therefore, drug release profile was better retarded by HPMC K100M as compared to Xanthan gum.

Hence, it was concluded that H3 was the best among the all formulations with a sustained release at the end of 12 hrs. Thus a formulation F7 was selected as the promising formulation, containing sodium bicarbonate (80 mg) as it achieved optimum in vitro buoyancy, floatability at 12 hrs as well as controlled and sustained in vitro drug release.

Stability study of optimized formulation (H3)

The optimized floating tablets (H3) were selected for stability study on the basis of in vitro drug dissolution studies. The tablets were investigated at 40°C/75% RH for 3 months. From the data, the formulation is found to be stable under the conditions mentioned above since there was minimum significant change in the percentage amount of drug release (Table 6). Thus, it was found that the floating tablets of Levofloxacin (H3) were stable under these storage conditions for at least 3 months.

Table No. 01: Various formulation of Levofloxacin Effervescent sustained release tablets

Ingredients	H_1	H_2	H_3	X_1	X_2	X_3
Levofloxacin(drug)	200	200	200	200	200	200
HPMC K100M	40	60	80	-	-	-
Xanthan Gum	-	-	-	40	60	80
Sodium bicarbonate	40	60	80	40	60	80
Microcrystaline Cellulose	118	78	38	118	78	38
Magnesium Stearate	2	2	2	2	2	2
Total	400	400	400	400	400	400

Table No. 02: Result of study of physical parameters of Levofloxacin and formulation H1-H3 and X1-X3

Formulation	Angle of Repose (Ɵ) (n=3)	Bulk Density (g/cm^3) (n=3)	Tapped Density (g/cm^3) (n=3)	Carr's Index (%) (n=3)	Hausner ratio H_R (n=3)
H1	29.2±0.60	0.582±0.002	0.732±0.007	20.83±0.73	1.25± 0.05
H2	30.3±0.04	0.581±0.008	0.730±0.006	24.71±0.6	1.25± 0.01
H3	30.5±0.07	0.576±0.002	0.728±0.005	21.44±0.51	1.26±0.01
X1	29.6±0.40	0.570±0.007	0.729±0.003	23.52±0.43	1.27±0.02
X2	28.4±0.61	0.580±0.003	0.735±0.004	17.13±0.62	1.31±0.014
X3	27.3±0.46	0.585±0.003	0.732±0.006	18.33±0.76	1.31±0.057
P1	26.8±0.64	0.582±0.004	0.742±0.003	22.24±0.10	1.32±0.02
P2	29.7±0.04	0.582±0.006	0.740±0.008	27.75±0.14	1.27±0.05
P3	30.5±0.20	0.581±0.003	0.737±0.004	24.32±0.10	1.31±0.02

Table No. 03: Results of Post Compression Properties of Levofloxacin effervescent Tablets

Formulation	Weight Variation(mg) (n=3)	Hardness Kg/cm^2 (n=3)	Thickness (mm) (n=3)	Friability (%) (n=3)	Diameter (mm) (n=3)
H1	398±1.25	5.0±0.2	4.4±0.01	0.29±0.08	9.9±0.02
H2	398±1.35	5.3±0.8	4.5±0.01	0.34±0.12	10.1±0.04
H3	401±1.36	5.5±0.2	4.3±0.02	0.44±0.09	10.1±0.02
X1	402±1.58	5.7±0.2	4.5±0.05	0.47±0.13	10.1±0.01
X2	400±1.2	6.0±0.3	4.2±0.2	0.32±0.16	9.8±0.03
X3	400±1.2	5.3±0.1	4.5±0.02	0.37±0.12	9.9±0.05

Table No. 04 Results of In vitro buoyancy study of levofloxacin floating time

Formulation code	Buoyancy lag time (second)	Floating duration (h)
H1	64	10
H2	41	More than 12
H3	23	More than 12
X1	83	12
X2	35	More than 12
X3	26	Burst after 9 hrs

Table No. 05: In vitro drug release study of floating tablet

Time (hrs)	% Drug Release					
	H1	**H2**	**H3**	**X1**	**X2**	**X3**
1	18.18	16.06	14.52	20.18	17.16	15.47
2	30.92	27.84	19.43	26.06	21.05	24.23
3	35.83	34.03	28.64	31.27	26.73	37.20
4	42.71	47.02	34.57	36.04	34.49	43.92
5	50.87	52.41	41.34	45.41	42.26	53.38
6	59.34	57.28	47.28	49.03	48.91	64.07
7	64.98	62.80	54.91	55.10	53.94	72.22
8	69.60	67.18	61.84	58.83	57.52	76.46
9	73.06	71.27	74.35	64.30	64.55	89.47
10	80.33	78.39	88.12	68.48	69.03	**96.10**
11	85.18	83.46	93.81	71.39	74.47	-
12	**83.72**	**86.20**	**88.27**	**77.05**	**80.82**	**-**

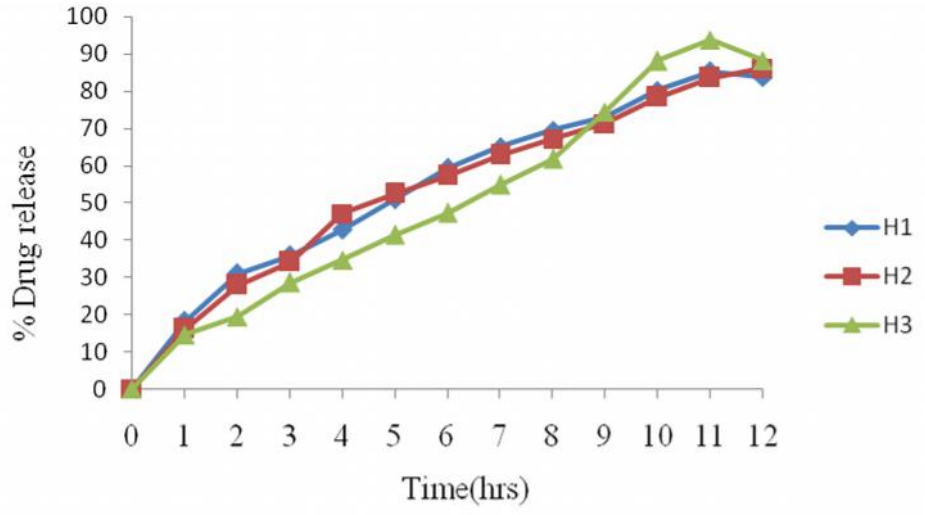

Fig. No. 01: In vitro Dissolution profile of batches H1-H3

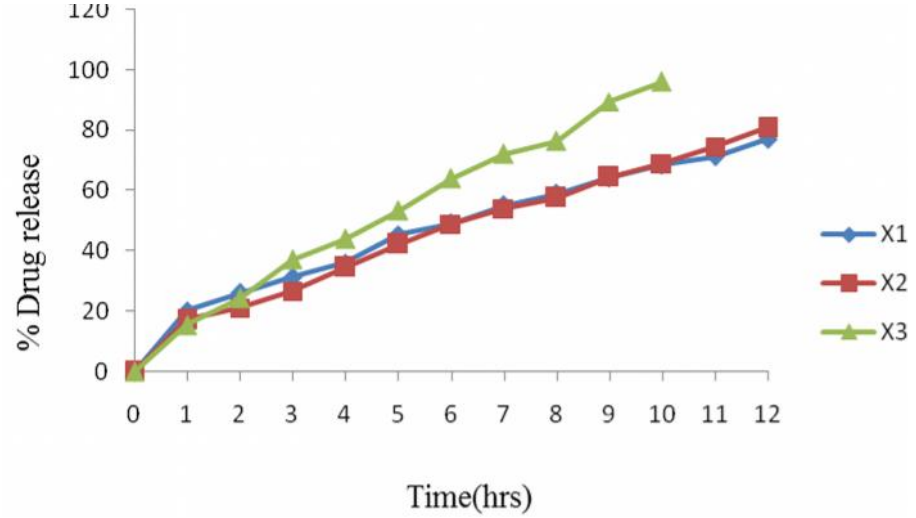

Fig. No. 02: In vitro Dissolution profile of batches X1-X3

Table No. 06: In-vitro Drug Release Profile of Optimized Formulation (H3) during Stability Study

Time (Hrs)	Cumulative % drug release		
	H3	1 month	3 Months
1	18.93	15.17	15.44
2	23.362	21.35	21.21
3	27.16	26.52	26.01
4	32.24	31.12	31.98
5	38.15	36.50	36.31
6	45.28	42.33	42.24
7	55.50	55.052	55.00
8	64.13	62.150	62.085
9	70.01	69.940	69.859
10	76.70	74.012	73.897
11	83.55	78.741	78.525
12	88.73	86.68	86.93

Conclusion

This study discusses the preparation of floating tablets of levofloxacin. The effervescent-based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of polymer HPMC K100M, Xanthan gum and gas-generating agent sodium bicarbonate was essential to achieve in vitro buoyancy.

The type of polymer affects the drug release rate and the mechanism. Polymer swelling is crucial in determining the drug release rate and is also important for flotation. A lesser FLT and a prolonged floating duration could be achieved by varying the amount of effervescent and using different polymer. The in vitro drug release profiles obtained for tablets (H3) showed a prolonged floating duration (at 12hrs) which was a controlled release characteristic (88.73%) for 12 h. Good stability was observed for 3 months during stability studies.

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