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Formulation and Evaluation of Effervescent Floating Tablet of Levofloxacin by Using Limonia acidissima and Xanthan as Natural Gum

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ABSTRACT: ***The main objective of the study is the formulation and evaluation of effervescent floating tablet of levofloxacin by using limonia acidissima and xanthan as natural gum. The preformulation study of levofloxacin was conducted and λmax was found at 288 nm. The Effervescent Floating tablets containing levofloxacin were prepared by direct compression technique using Limonia acidissima and xanthan gum combination and varying concentrations of different ratio of polymers with Sodium bicarbonate and citric acid. All the ingredients were accurately weighed and passed through different mesh sieve no. 40. Drug, Polymer and other excipients (except talc and magnesium streate) were mixed thoroughly, passed thoroughly, passed through sieved number 40. Then, except Magnesium stearate all other ingredients were blended uniformly in glass mortar. Various formulations of effervescent floating tablet of levofloxacin F1,F2,F3,F4,F5,F6,F7 and F8 was prepared. The prepared granules was evaluated for different parameters like Bulk density, Tapped density, Angle of repose, Carr's index, Hausner's ratio, which shows the excellent flow properties of formulation. The physical characteristic of levofloxacin effervescent floating tablets (F1 to F8) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and results of the formulations (F1 to F8) found to be within the limits specified in official books. The drug content of all the formulation were found to be in the range of 95.2 to 99.2. Effervescent floating tablet of different formulations were noted. With reference to buoyancy studies results it can be concluded that the batch containing limonia acidissima showed good buoyancy lag time (BLT) and total floating time (TFT). Formulation F1 and F8 containing xanthan gum showed good BLT of 28 and 78 sec and TFT of more than 12 hrs. The drug released from formulation F1 to F4 was found to be 93.2, 93.3, 94.2 and 90.1% for levofloxacin respectively. The drug released from formulation F5 to F8 was found to be 89.3, 88.1, 90.1 and 95.1 % for levofloxacin respectively. These results are indicating that has higher drug retarding ability for long duration.***
Keywords: ***Effervescent floating tablet, levofloxacin, limonia acidissima, Xanthan Gum, buoyancy lag time, Total floating time, In- Vitro drug released.***

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1. INTRODUCTION

Levofloxacin is a broad-spectrum, third-generation fluoroquinolone antibiotic and optically active L-isomer of ofloxacin with antibacterial activity. Levofloxacin diffuses through the bacterial cell wall and acts by inhibiting DNA gyrase (bacterial topoisomerase II), an enzyme required for DNA replication, RNA transcription, and repair of bacterial DNA. Inhibition of DNA gyrase activity leads to blockage of bacterial cell growth.

One of the purpose of these formulations was to maintain in vitro buoyancy as well as in vivo duration of floating stable for at least 24/12 hours. Floating drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for treatment for many acute and chronic diseases.

Hence, in the present work, an attempt is made to develop effervescent floating tablets of levofloxcin, with the use of Limonia acidissima and xanthan as natural gum for their floating effect. Direct compression technique is used for tablet formulation along with the addition of suitable additives by using of sodium bicarbonate, citric acid, magnesium stearate, lactose and talc.

2. MATERIALS AND METHOD

1. MATERIALS

Levofloxacin was received as a gift sample from Gift sample from Cypco Company ,Rau, Indore (M.P). Limonia acidissima was purchased from local market. Sodium bicarbonate , Citric acid, Microcrystalline cellulose(MCC), Magnesium stearate and talc from SD- Fine Chemicals. All other solvent and reagent are used was of analytical grade.

2. EXPERIEMENTALS

2.1 Identification of Drug

2.1.1 By UV Spectroscopy

Identification of the drug, levofloxacin was done by UV Spectrophotometric method using Shimadzu Spectrophotometer UV-1800 (Shimadzu Corp. Japan). 100 mg of levofloxacin was accurately weighed and transferred to a 100 ml volumetric flask. It was dissolved in sufficient amount of 0.1 N NaOH and volume was made upto 100 ml with 0.1 N NaOH. Exactly 10ml of the stock solution was pipetted out and was diluted to 100 ml with 0.1 N NaOH (10 µg/ml). The spectrum was recorded in the range of 200-400 nm. Spectrum was recorded. The λ max of levofloxacin was obtained at 288 nm. The UV spectrum of levofloxacin drug is shown in the fig. 1.

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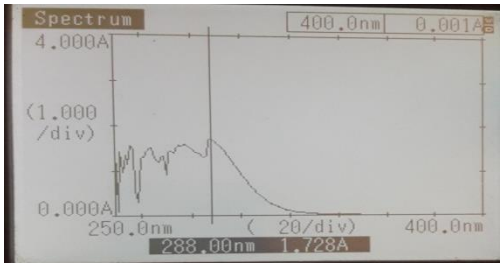

Figure 1: Spectrum of levofloxacin by UV Spectroscopy

2.1.2 By melting point determination

The melting point of drug sample was determined by using melting point apparatus. The melting point was found to be in the range of 226- 228^{0}C, which is found to be similar as given in the reference. The melting point of levofloxacin is shown in the table 2.

Table 2: Melting Point of Levofloxacin

Drug	Observed	Refrence
Levofloxacin	226-228^{0}C	225^0-227^{0}C

2.1.3 Preparation of standard Calibration curve of levofloxacin in 0.1 N NaOH (λmax 288 nm)

Calibration curve of levofloxacin was prepared in 0.1 NaOH at 288 nm. The absorbance values (mean of three determinations) with their standard deviation at different concentration in the range of 2-12 µg/ml for 0.1 N NaOH are tabulated. The drug obeys Beer's Lambert law in the concentration range. Linear regression analysis for all calibration curves of levofloxacin is given in Table. So, this equation was used for the calculation of the solubility of the drug in different solvent, drug content and drug release. The calibration curve of levofloxacin is shown in fig 4.

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Table 3: Data of standard calibration curve of levofloxacin in 0.1 N NaOH

S.No.	Concentration (µg/ml)	Absorbance (nm)
1.	0	0
2.	2	0.102
3.	4	0.187
4.	6	0.276
5.	8	0.361
6.	10	0.441
7.	12	0.515

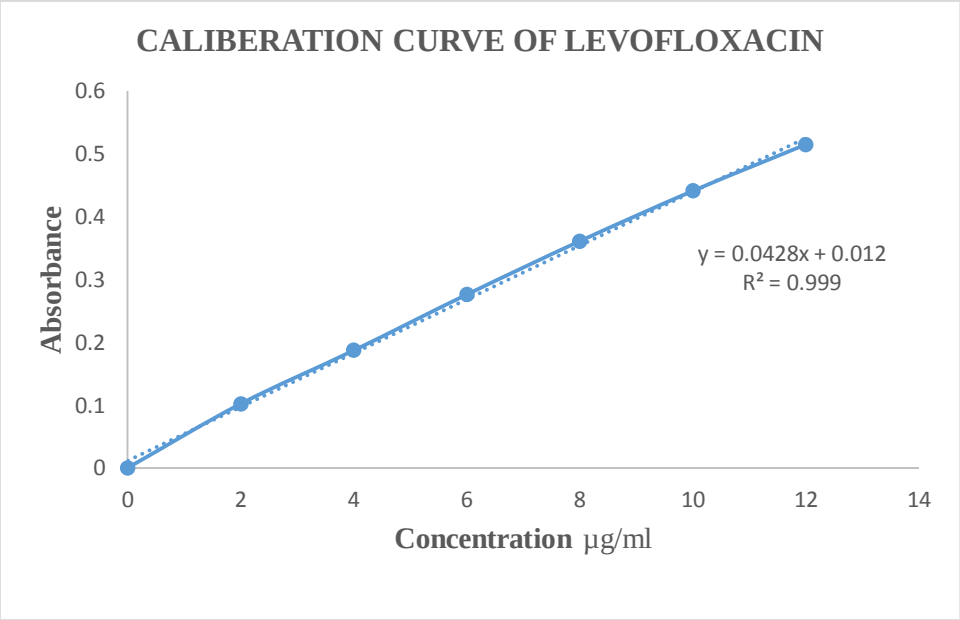

Fig 4: Calibration curve of levofloxacin in 0.1 N NaOH.

2.4 Solubility studies of drug

Quantitative solubility analysis of levofloxacin was determined in different solvents. The drug levofloxacin was found to be more soluble in ethanol, methanol, Hcl and NaOH. This shows that drug

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is more soluble only in organic solvents, which shows the lipophilic nature of the drug. The results are found to be similar as given in the reference. The results are disclosed in table 5.

Table 5 : Quantitative solubility analysis:

S.no	Solvents	Solubility mg/ml
1.	Water	52.3
2.	Ethanol	112
3.	NaOH	102.2
4.	Hcl	101.8
5.	Methanol	123

3. FORMULATION AND EVALUATION OF EFFERVESCENT FLOATING TABLET OF LEVOFLOXACIN

3.1. Formulation of effervescent floating tablet of levofloxacin by direct compression method

Formulation of effervescent floating tablet includes the selection of natural gum, polymer, gas generating agent, buffering agent, diluent, lubricant and glidant. The effervescent floating tablet was prepared using Limonia acidissima and xanthan as natural gum, Poly vinyl pyrrolidone K30 as polymer, Sodium bicarbonate as gas generating agent, Citric acid as buffering agent, Micro Crystalline Cellulose as Diluent, Magnesium stearate as Lubricant and Talc as Glidant**.** Several formulations was prepared by taking different drug concentration in natural gum and polymers with varying ratio of binder to lubricants. The formula is shown in the table 6.

The Effervescent Floating tablets containing levofloxacin were prepared by direct compression technique using Limonia acidissima and xanthan gum combination and varying concentrations of different ratio of polymers with Sodium bicarbonate and citric acid. All the ingredients were accurately weighed and passed through different mesh sieve no. 40. Drug, Polymer and other excipients (except talc and magnesium streate) were mixed thoroughly, passed thoroughly, passed through sieved number 40. 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. After Pre

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compression characterization the tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation.

Table 6: composition of levofloxacin floating tablet

Ingredients (Mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
levofloxacin	250	250	250	250	250	250	250	250
Limonia acidissima	10	20	30	40	50	60	70	80
Xanthan gum	80	70	60	50	40	30	20	10
Microcrystalline cellulose	15	15	15	15	15	15	15	15
Polyvinyl pyrolidine K30	15	15	15	15	15	15	15	15
Sodium bicarbonate	50	50	50	50	50	50	50	50
Citric acid	20	20	20	20	20	20	20	20
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total	450	450	450	450	450	450	450	450

3.2 Evaluation of Effervescent Floating Tablet of Levofloxacin:

3.2.1 Bulk Characterization of levofloxacin granules:

The bulk density of various formulations were found to be between 30 to 35.3, tapped density between 0.261 to 0.619, Hausner's ratio between 0.292 to 0.543, Carr's index between 8.438 to 10.38, which shows the good compressibility index of formulations. The angle of repose was found to be between 4.77 to 5.72, which shows the excellent flow properties of formulation. Results of measurements such as Tapped density, Angle of repose, Carr's index, Hausner's ratio are presented in the table 7.

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Table 7 : Determination of flow properties of granules:

Batch code	Bulk density(g/cm$^{3)}$	Tapped density(g/cm^3)	Hausner's ratio	Carr's ratio%	Angle of repose
F1	32.36	0.261	0.292	9.723	5.42
F2	35.4	0.521	0.352	8.438	4.77
F3	32.2	0.504	0.323	8.902	5.02
F4	28.9	0.545	0.442	10.38	5.72
F5	30.2	0.619	0.543	10.02	5.43
F6	29.7	0.546	0.378	9.423	5.22
F7	27.5	0.480	0.530	9.832	5.34
F8	30.3	0.520	0.480	8.463	5.43

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3.2.2 Physico-Chemical Characterization of levofloxacin effervescent floating Tablets

Table no. 8 Physico-Chemical Characterization of levofloxacin effervescent floating Tablets

Formulation Code	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Weight variation (mg)
F1	4.42	6.31	0.680	378.15
F2	4.32	6.56	0.509	387.25
F3	4.41	6.79	0.427	397.65
F4	4.32	6.48	0.567	396.05
F5	4.54	6.52	0.515	394.05
F6	4.25	6.78	0.669	395.75
F7	4.51	6.81	0.670	392.3
F8	4.38	6.85	0.682	391.5

3.2.3 Drug Content:

The drug content of all the formulation were found to be in the range of 95.2 to 99.2, Which is within the specified limit as per Indian Pharmacopoeia 1996 (i.e. 90-110% w/w). The results are shown in the table no.9.

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Table no.9 Drug content of various formulations.

S.NO	Formulation Code	% Drug content
1.	F1	92%
2.	F2	90%
3.	F3	94%
4.	F4	94%
5.	F5	96%
6.	F6	92%

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

Effervescent floating tablet of different formulations were noted, where F1 BLT of 28 sec and TFT of >12 hours, F2 BLT of 30 sec and TFT of >10 hours, BLT of 32 sec and TFT of >11 hours, F4 BLT of 25 sec and TFT of >12 hours, F5 BLT of 45 sec and TFT of >13 hours, F6 BLT of 52 sec and TFT of >12 hours, F7 BLT of 65 sec and TFT of >11 hours, F8 BLT of 78 sec and TFT of >12 hours, With reference to buoyancy studies results it can be concluded that the batch containing limonia acidissima showed good buoyancy lag time (BLT) and total floating time (TFT). Formulation F1 and F8 containing xanthan gum showed good BLT of 28 and 78 sec and TFT of more than 12 hrs. The results are shown in table no 10

Table no. 10 Buoyancy lag time (BLT) and total floating time (TFT)

Formulation Code	Buoyancy lag times (sec)	Total Floating Time (hrs)
F1	28 sec	>12
F2	30 sec	>10
F3	32 ec	>11
F4	25 sec	>12
F5	45 sec	>13

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F6	52 sec	>12
F7	65 sec	>11
F8	78 sec	>12

3.2.5 In vitro dissolution studies:

Floating tablet showed sustained release of the drug in acidic condition (pH 1.2) and the drug release was found to be approximately linear. Approximately 8.71 % of the drug was released initially. Furthermore, drug release from the floating tablet was controlled by the polymer. As the polymer content was increased and the drug loading was decreased, the release of drug was decreased significantly. In order to increase the release rate of drug, the ratio of polymer was decreased and plasticizer was increased. The combination polymer of final formulation F6, F7 & F8showed best appropriate balance between buoyancy and drug release rate. Results of cumulative % release have been shown in tubular and graphical form. It was found cumulative percentage of drug release decreases with increase in limonia gum concentration.

The drug released from formulation F1 to F4 was found to be 93.2, 93.3, 94.2 and 90.1% for levofloxacin respectively. The drug released from formulation F5 to F8 was found to be 89.3, 88.1, 90.1 and 95.1 % for levofloxacin respectively.

The release rate of F8 was found to be higher when compared to other formulations this is due to increase in the concentration of limonia acidissima.

These results are indicating that has higher drug retarding ability for long duration. The results are shown in the table 11.

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Table 11 In- Vitro dissolution rate:

S.No	Time(h)	F1	F2	F3	F4	F5	F6	F7	F8
1	1	8.71	8.95	9.22	9.16	9.30	8.69	9.20	9.36
2	2	17.2	29.5	22.0	29.4	28.6	28.7	28.5	29.4
3	4	39.7	35.5	38.6	38.4	43.5	35.5	36.4	39.4
4	8	55.7	56.2	46.2	49.5	52.2	47.0	49.5	53.5
5	10	74.5	73.4	68.5	66.9	65.1	68.2	69.9	69.9
6	12	90	88	83.3	80.4	83.6	79.6	83.4	84.4
7	14	93.2	93.3	94.2	90.1	89.3	88.1	90.1	95.1

3.2.6 Stability Study:

After storage the formulation was analyzed for various physical parameters, results are showed in Table 12.

Table 12 : Stability study of best formulation F8

Characteristic	Initial	1st Month	2nd Moth	3rd Month
Hardness (kg/cm^2)*	6.85±0.03	6.82±0.26	6.80±0.28	6.77±0.29
Drug content (%)*	99.5±0.63	99.4±0.79	99.3±0.63	98.2±0.58
In vitro drug release at 14th hour*	95.1±0.65	95.0±0.56	94.8±0.59	94.9±0.57
Appearance	Yellow-White	No change	No change	No change

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4. CONCLUSION

The floating tablets were prepared by direct compression technique It may be concluded from the present study that slow and sustained release of levofloxacin over a period of 14 hr was obtained (F1 to F8) by the using Limonia gum was successful in the formulation of floating tablet and at the same time it is effective in retarding the drug release. The cumulative percentage of drug release was decreased by increase in Limonia gum concentration.

In present studies, formulation containing limonia acidissima and xanthan is probably showing release up to 95.1 % within 14 hrs.

According to stability study, it was found that there was no significant change in hardness, Drug content and dissolution rate of formulation F8 was 99% and 95.1 %.

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