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RESEARCH ARTICLE

PREPARATION AND EVALUATION OF LEVOFLOXACIN HEMIHYDRATES FLOATING TABLETS

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ABSTRACT

In the present investigation, an attempt was made to formulate floating tablets of Levofloxacin hemihydrates using with gum kondagogu, xanthum gum and HPMC K100M as release modifier. Eight batches of floating tablets of Levofloxacin hemihydrates were prepared by using different drug : polymer (Levofloxacin hemihydrates, HPMC K100M + karaya gum) ratios viz. F_1,F_2,F_3,F_4 and drug : polymer (Levofloxacin hemihydrates, HPMC K100M + xantham gum) ratios viz.F_5,F_6,F_7,F_8. The compressed tablets were evaluated for hardness, uniformity of weight, friability, drug content. All the readings are within the prescribed limits. There was no interaction between the drug, polymer and excipients it was found out by IR studies. Swelling index studies were also carried out. The *in vitro* release data were fitted to different order of reactions such as zero order and Korsmeyer-Peppas reaction. It was found that, the drug release follows Korsmeyer-Peppas reaction.

KEYWORDS: Levofloxacin hemihydrates, Karaya gum, Xantham gum, HPMC K100M, Wet granulation method

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, GI transit time, drug release from the dosage form and site of absorption. Gastric emptying of dosage forms is an extremely variable process, due to unpredictable gastric emptying rate and short gastric residence time. Gastric retention provides, longer residence time in the stomach that improves bioavailability for drugs that are readily absorbed upon release in the GI tract [1]. These drugs can be delivered ideally by slow release from the stomach. Floating drug delivery, this system basically floats in the gastric fluid because of its lower density, than the gastric medium. Levofloxacin is a synthetic flouroquinoline antibacterial agent that inhibits bacterial DNA replication. It is L-isomer of Ofloxacin. It has a half life of 6 hrs and the absorption of Levofloxacin is dose dependent, which increases with increase in dose. It is used in treating various infections caused by microorganisms like bacillus anthracis, Chlamydia infection, cystitis, epidydimitys, gonorrhea etc. The dose ranges from 250mg to 750mg.It is first choice drug used for treatment of *H.pylori* infections. Floating drug

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delivery system of Levofloxacin hemihydrates can localize the drug action within the stomach to treat gastric ulcers caused by *Helicobacter pylori.* In the present study, natural polymers such as gum kondagogu and xanthum gum are selected for the preparation of floating tablets of Levofloxacin hemihydrates. Sodium bicarbonate was used as gas generating agent. Tablets were prepared by wet granulation method using these polymers.

MATERIALS AND METHODS

Materials

Levofloxacin hemihydrate.was obtained as gift sample from Hetero Labs, Hyderabad, Gum kondagogu, Gum kondagogu, Xanthum gum, HPMC K100M, PVP K 30, Isopropyl alcohol, Hydrochloric acid. sodium bicarbonate, magnesium stearate, were obtained from commercial sources.

Preparation of Levofloxacin hemihydrate floating tablets

Floating tablets of Levofloxacin hemihydrate were prepared by using different drug: polymer (Levofloxacin hemihydrates + HPMC K100M + Natural polymer) ratios. The tablets were formulated by employing wet granulation method using PVP K 30 as binder and isopropyl alcohol as granulating fluid. All the formulations contain 250 mg of Levofloxacin hemihydrate, sodium bicarbonate as gas generating agent, magnesium stearate as lubricant and talc added as glidant. The details of composition of each formulation are given in Tables 1-2.

EVALUATION PARAMETERS

Flow properties of granules.[2]

a) **Bulk Density (D_b):** It is the ratio of total mass of granules to the bulk volume of granules. It was measured by pouring the granules (passed through standard sieve # 20) into a measuring cylinder and initial weight will be noted. This initial volume is called bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by

Bulk Density (g/ml) = Mass of the powder/Bulk Volume

b) **Tapped Density (D_t):** It is the ratio of total mass of the granules to the tapped volume of the granules. Volume was measured by tapping the granules for 750 times and the tapped volume will be noted, if the difference between these two volumes is less than 2%. If it is more than 2%, tapping was continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

Tapped density (g/ml) = Mass of the powder/Tapped volume

c) **Angle of Repose (θ):** The friction forces in greanules can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was calculated by measuring the height and radius of the heap of granules formed.

$\theta = \tan^{-1} (h / r)$

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Where, □ is the angle of repose.

h is the height in cms

r is the radius in cms

d) **Carr's index (or) % compressibility:** It indicates granule flow properties. It is expressed in percentage and is given by Carr's Index (%) = [(Tapped density – Bulk Density) / Tapped Density] × 100

e) **Hausner ratio:** Hausner ratio is an indirect index of ease of granules flow. It is calculated by the following formula. Hausner's Ratio = Tapped density / Bulk Density

Evaluation of tablets

a) **Hardness[3]:** The hardness of the tablet was measured by Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The hardness was measured in terms of kg/cm^2.

b) **Drug content [4]:** 20 tablets were weighed and powdered the powder weight equivalent to 100mg of Levofloxacin trihydrate was dissolved in 100ml of 0.1N HCl and filtered. 5ml of this was diluted to 50ml with water and drug content was estimated using UV-VISIBLE spectrophotometer at 293nm.

c) **Weight variation[3]:** Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.

$$\% \text{ Weight Variation} = \frac{\text{Average Weight - Individual Weight}}{\text{Average Weight}}$$

d) **Friability[3]:** The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.

$$\text{Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X 100$$

e) **Swelling Index [5]:** Formulated tablets were weighed individually (W_0) and placed separately in Petri dish containing 50 ml of 0.1 N HCl. The Petri dishes were placed in an incubator maintained at 37±0.5°C. The tablets were removed from the petri dish, at predefined intervals of time and reweighed (Wt), and the % swelling index was calculated using the following formula:

$$\% W_U = (Wt\text{-}Wo/Wo) \times 100$$

Where:

W_U – Water uptake

Wt – Weight of tablet at time t

Wo – Weight of tablet before immersion

f) **In vitro buoyancy study [6]:** This test is characterized by floating lag time and total floating time. The test was performed using USP-Type II paddle apparatus using 900 ml of 0.1N HCl at paddle rotation of 100 rpm at 37 ± 0.5^0 C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time.

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g) **In vitro dissolution test [7]:** The release of Levofloxacin hemihydrate from the tablet was studied using USP-Type II paddle apparatus. Drug release profile was carried out in 900 ml of 0.1N HCl maintained at 37 ± 0.5°C temperatures at 100 rpm. 5 ml of samples were withdrawn at regular time intervals. The samples was replaced by its equivalent volume of dissolution medium and was filtered through 0.45 µm Whatman filter paper and analyzed at 293 nm by UV spectrophotometer.

h) **Infra Red Spectral analysis[8]:** IR Spectral analysis was used to study the interactions between the drug, polymer and the excipients. The drug and excipients must be compatible with one another to produce a product stable, efficacious and safe.

RESULTS AND DISCUSSION

Floating tablets (F_1-F_4) of Levofloxacin hemihydrate were prepared by varying the concentration of HPMC K 100 M and gum kondagogu. The composition of formulations (F_1-F_4) is shown in table .1.The formulated granules were subjected to various micromeritic properties and the values were shown in table.3.The formulated tablets were subjected to various quality control tests like hardness, friability, weight variation and drug content various physical properties are shown in table 4.The formulations(F_1-F_4) containing xanthum gum in combination with HPMC K100M increase in drug release with increase in concentration of gum kondagogu when compared formulation containing only HPMC K100M. The drug release from formulation F_5 containing only gum kondagogu showed a maximum drug release at end of 10 hours. Drug release from the formulation containing HPMC K100M was lesser owing to its high viscosity and also due to less permeability of water, as the drug release rate is dependent on the viscosity grade and the concentration of the polymers used. To ascertain the mechanism of drug release, the dissolution data was analyzed by zero order, first order, and Higuchi and Peppas equations. The correlation coefficient values (r) revealed that the dissolution profiles follows Zero order kinetics and the mechanism of drug release was governed by Peppas model. The n values are found to be more than 0.5 (n>0.5) indicted that the drug release was predominantly controlled by non fickian diffusion. The in-vitro drug release kinetic data was shown in table 5 and figures 1,2 and 3.The swelling index studies showed a gradual increase with increase in concentration of gum kondagogu which indicates the natural tendency of it to swell 5-10 times of its original value. The swelling index values are shown in table.6 and figure.4.

The influence of xanthum gum concentration on drug release, formulations (F_5-F_8) were prepared using different concentrations of xanthum gum with HPMC K100M by wet granulation method. The composition of formulations (F_5-F_8)is shown in table.2 .The formulated granules were subjected to various micromeritic properties and the values were shown in table.7. The formulated tablets were subjected to various quality control tests like hardness, friability, weight variation and drug content various physical properties are shown in table.8.The formulations(F_5-F_8) containing xanthum gum in combination with HPMC K100M showed decrease in drug release with increase in concentration of

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xanthum gum when compared formulation containing only HPMC K100M(F_1). The drug release from the formulations (F_6-F_8) showed very slow release as compared to other formulations. The in vitro release data for formulations (F_6-F_8) was presented in table.9 and figure.5,6. The release rate followed zero-order release kinetics and the data was fitted in the Peppas plots.The exponential coefficient from the Peppas plots was found to be in between 0.75 to 0.88, indicating non fickian mechanism of drug release.The release rate of Levofloxacin hemihydrate was found to be retarded by xanthum gum with an increase in its concentration. The swelling index of tablets formulated with xanthum gum (F_6-F_8) was found to be higher than that of other formulations which can be attributed to high viscosity and high water retention property of both HPMC K100M and xanthum gum. The values of swelling index are tabulated in table.10 and shown in figure.8.

From the above table 11 it is clearly evident that the invitro release of drug from the floating tablet was influenced by nature of natural polymer. Based on the release rate constant and % of drug release at the end of 12 hours the release retarding capacities of the natural polymers were arranged in the following order. Xanthum gum> gum kondagogu.

Table.1* : *Composition of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum kondagogu

Ingredients	**F_1 (mg)**	**F_2 (mg)**	**F_3 (mg)**	**F_4 (mg)**
Levofloxacin hemihydrate	250	250	250	250
HPMC K 100 M	90	60	30	0
Gum Kondagogu	30	60	90	120
Sodium bicarbonate	100	110	110	110
PVP K 30	5	5	5	5
Magnesium stearate	12	7.5	7.5	7.5
Talc	13	7.5	7.5	7.5
Total	500	500	500	500

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Table.2 : Composition of Levofloxacin hemihydrate floating tablets formulated with different concentrations of xanthan gum.

Ingredients	**F_5(mg)**	**F_6(mg)**	**F_7(mg)**	**F_8(mg)**
Levofloxacin hemihydrates	250	250	250	250
HPMC K 100 M	90	60	30	0
Gum Xanthum	30	60	90	120
Sodium bicarbonate	110	110	115	115
PVP K 30	5	5	5	5
Magnesium stearate	7.5	7.5	5	5
Talc (2%)	7.5	7.5	5	5
Total weight	500	500	500	500

Table.3 : Micromeritic properties of Levofloxacin hemihydrate granules formulated with different concentrations of gum kondagogu

Formulation code	**Angle of repose**	**Bulk density**	**Tapped density**	**Compressibility index**	**Haussners ratio**
F_1	29.89±0.241	0.268±0.011	0.307±0.025	12.70±0.019	1.145±0.019
F_2	28.41±0.250	0.271±0.021	0.313±0.017	13.41±0.011	1.154±0.014
F_3	29.33±0.214	0.280±0.017	0.320±0.031	12.50±0.024	1.142±0.025
F_4	30.81±0.233	0.281±0.015	0.319±0.019	12.70±0.016	1.146±0.017

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Table.4 : Physical properties of Levofloxacin hemihydrates floating tablets formulated with different concentrations of gum kondagogu.

Formulation	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating lag time (min)	Total floating time (hrs)
F_1	4.8±0.044	500.47±0.44	0.62±0.024	99.45±0.15	1.40	>14
F_2	4.7±0.027	501.39±0.94	0.37±0.012	101.89±0.16	2	13
F_3	4.2±0.082	499.54±0.55	0.37±0.101	99.58±0.17	2.15	13
F_4	4.5±0.023	500.34±0.60	0.39±0.124	101.45±0.13	3.15	11

Table.5 : In vitro drug release kinetic data of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum kondagogu.

Formulation	Correlation Coefficient Value				Release Rate Constant (mg/hr)k_0	Exponential Coefficient (n)	T_{50}	T_{90}
	Zero Order	First Order	Matrix	Peppas				
F_1	0.9892	0.9490	0.9038	0.9742	17.7442	0.8250	7	12.7
F_2	0.9761	0.9756	0.9552	0.9671	19.4295	0.6271	6.4	11.6
F_3	0.9733	0.9725	0.9602	0.9708	21.1625	0.6449	5.9	10.6
F_4	0.9788	0.9416	0.9451	0.9543	22.7780	0.6307	5.5	9.9

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Figure.1 : Comparative in vitro drug release profile of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum kondagogu.

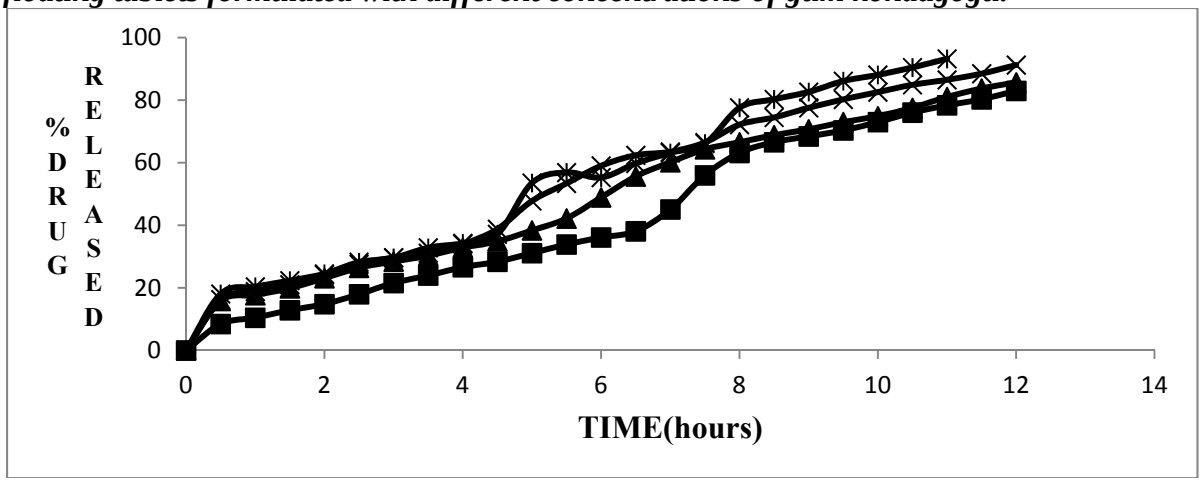

Figure.2 : Comparative Zero order plots of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum kondagogu

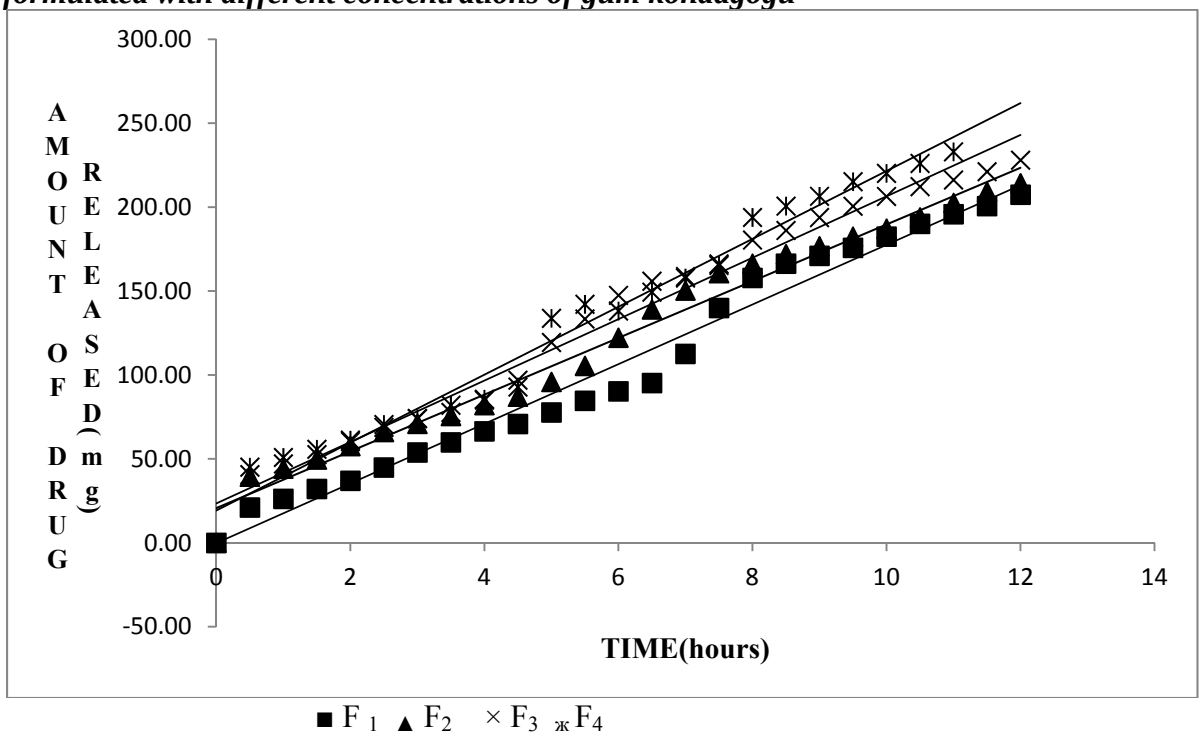

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Figure.3 : Comparative Peppas plots of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum kondagogu

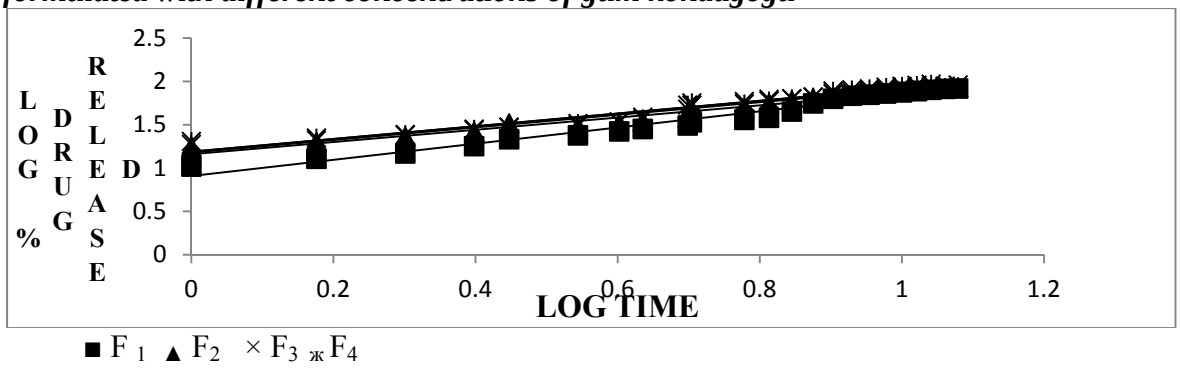

Table.6 : Swelling index values of Levofloxacin hemihydrate tablets formulated with different concentrations of gum kondagogu

Formulation code	Swelling index		
	Time in hours		
	after 1 hour	after 2 hours	after 8hours
F_1	66.99	83.89	148.50
F_2	68.34	86.49	157.05
F_3	57.06	80.91	155.46
F_4	56.31	79.35	137.42

Figure.4 : Comparative swelling index plot of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum kondagogu

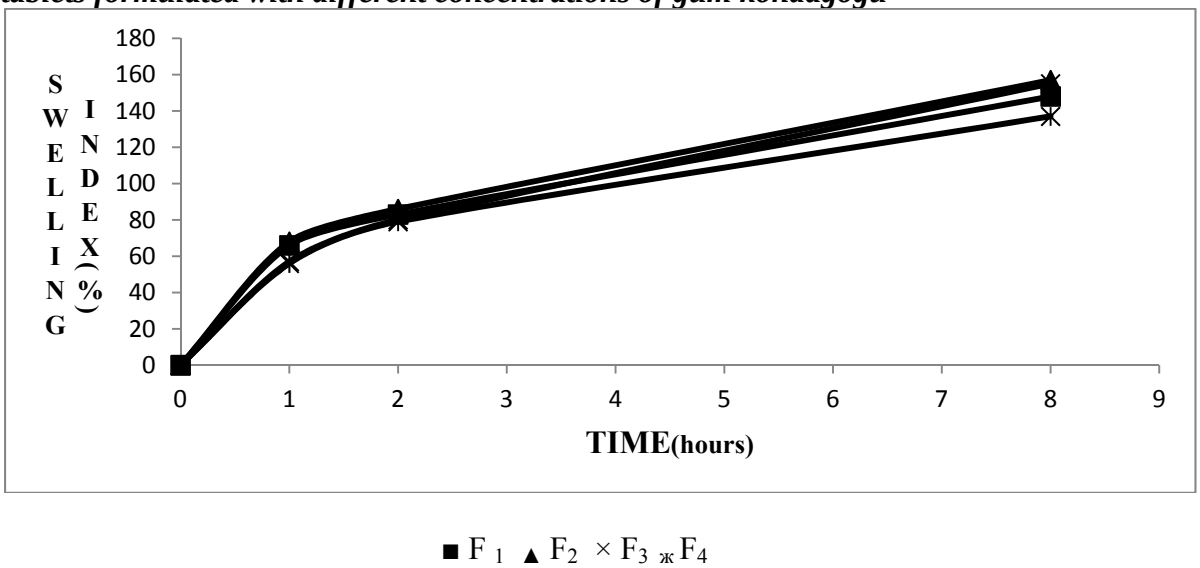

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Table.7 : Micromeritic properties of Levofloxacin hemihydrate granules formulated with different concentrations of xanthum gum.

Formulation code	Angle of repose	Bulk density	Tapped density	Compressibility index	Haussners ratio
F_5	25.76±0.05	0.255±0.025	0.291±0.005	12.37±0.024	1.142±0.014
F_6	26.40.0±0.07	0.271±0.021	0.316±0.011	14.240±0.019	1.166±0.019
F_7	27.32±0.09	0.314±0.018	0.366±0.019	14.207±0.027	1.165±0.011
F_8	26.54±0.13	0.353±0.027	0.400±0.014	11.750±0.017	1.133±0.027

Table.8 : Physical properties of Levofloxacin hemihydrate floating tablets formulated with different concentrations of xanthum gum.

Formulation	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating Lag time	Total floating time (hrs)
F_5	4.6±0.048	501.36±0.54	0.39±0.025	101.52±0.23	1.98 min	>15
F_6	4.4±0.032	501.66±0.49	0.35±0.019	99.87±0.41	3.25 min	>18
F_7	4.7±0.029	499.91±0.39	0.42±0.026	101.93±0.16	5.02 min	>22
F_8	5.2±0.054	500.08±0.51	0.40±0.032	100.23±0.46	6min	>22

Table.9 : Comparative in vitro drug release profile of Levofloxacin hemihydrate floating tablets formulated with different concentrations of xanthum gum

Formulation	Correlation Coefficient Value				Release Rate Constant (mg/hr)k_0	Exponential Coefficient (n)	T_{50}	T_{90}
	Zero Order	First Order	Matrix	Peppas				
F_5	0.9958	0.9620	0.9065	0.9907	16.5772	0.9411	7.5	13.6
F_6	0.9806	0.9476	0.8822	0.9689	16.0000	0.8777	7.8	14.1
F_7	0.9849	0.9499	0.8835	0.9790	15.1187	0.9330	8.3	14.9
F_8	0.9973	0.9716	0.9081	0.9943	14.1717	0.9607	8.8	15.9

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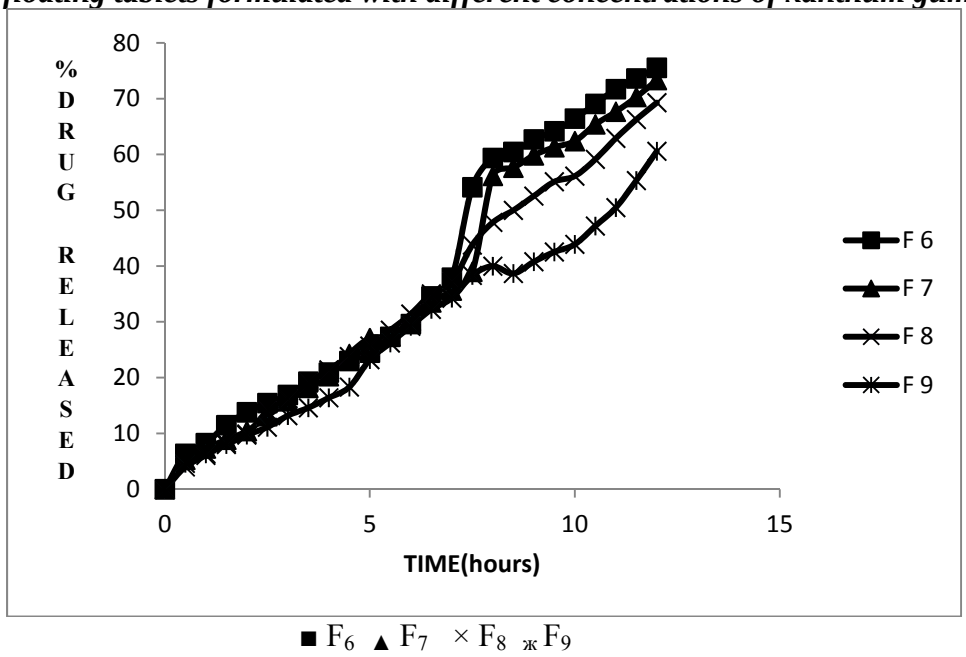
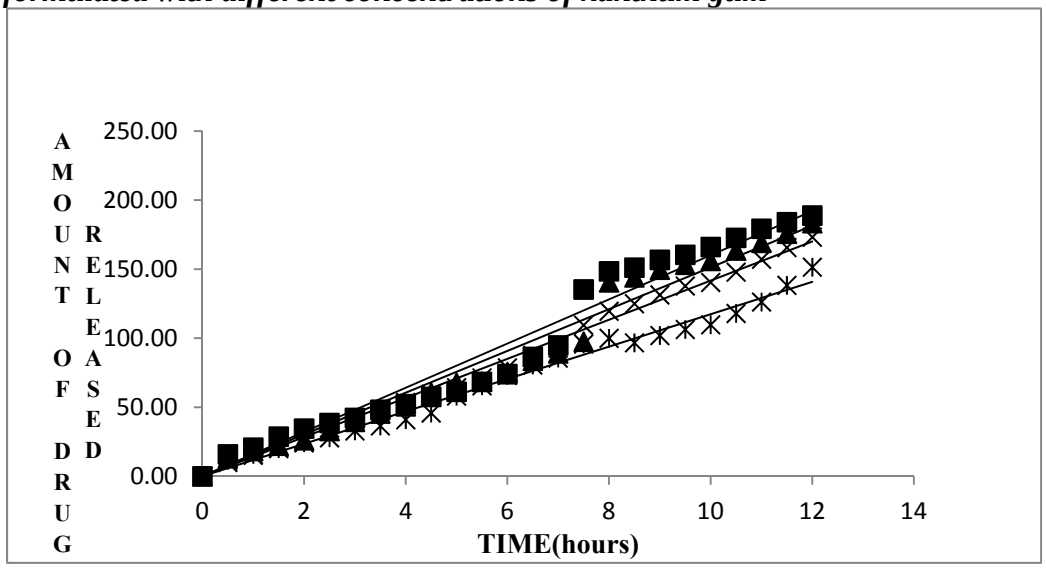
Figure.5 : Comparative in vitro drug release profile of Levofloxacin hemihydrate floating tablets formulated with different concentrations of xanthum gum



■ F_6 ▲ F_7 × F_8 ж F_9

Figure.6 : Comparative Zero order plots of Levofloxacin hemihydrate floating tablets formulated with different concentrations of xanthum gum



■ F_6 ▲ F_7 × F_8 ж F_9

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Figure.7 : Comparative Peppas plots of Levofloxacin hemihydrate floating tablets formulated with different concentrations of xanthum gum

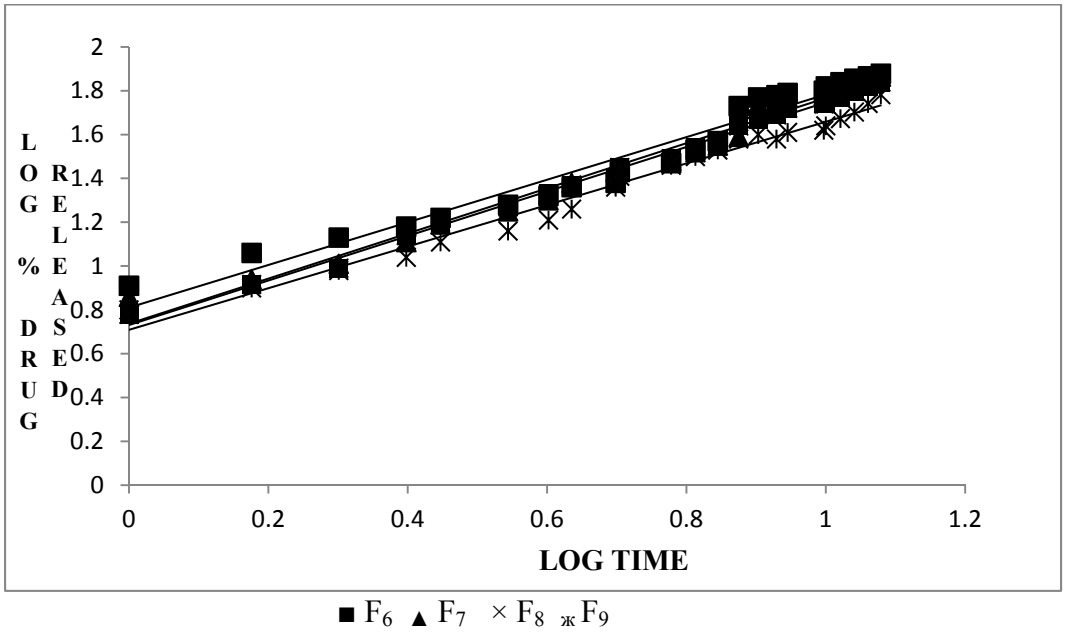

Table.10 : Swelling index values of Levofloxacin hemihydrates tablets formulated with different concentrations of xanthum gum

Formulation code	Swelling index		
	Time in hours		
	after 1 hour	after 2 hours	after 8hours
F_6	52.69	76.64	145.00
F_7	53.53	89.89	154.00
F_8	58.53	96.10	168.50
F_9	65.33	105.41	171.34

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Figure.8 : Comparative swelling index plot of Levofloxacin hemihydrate floating tablets formulated with xanthum gum

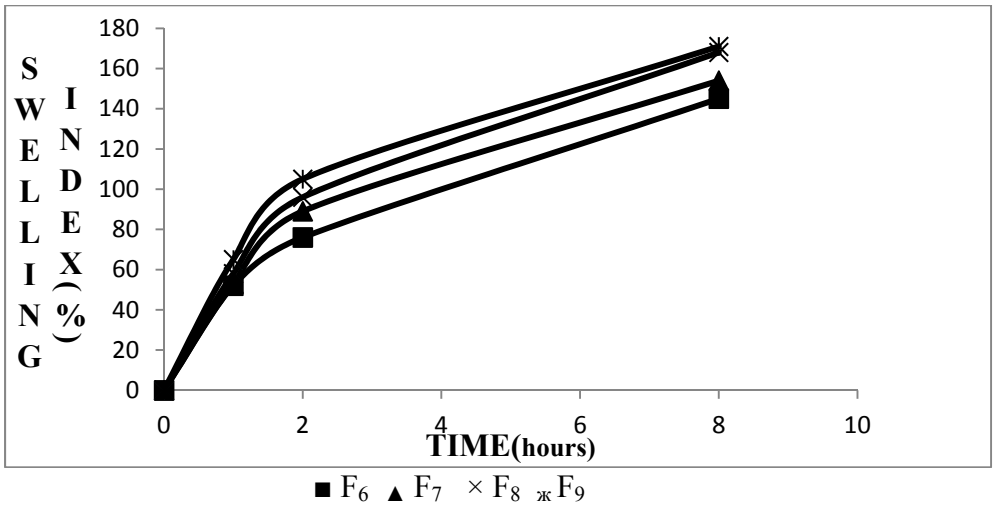

Figure.9 : IR spectrum of Levofloxacin hemihydratre.

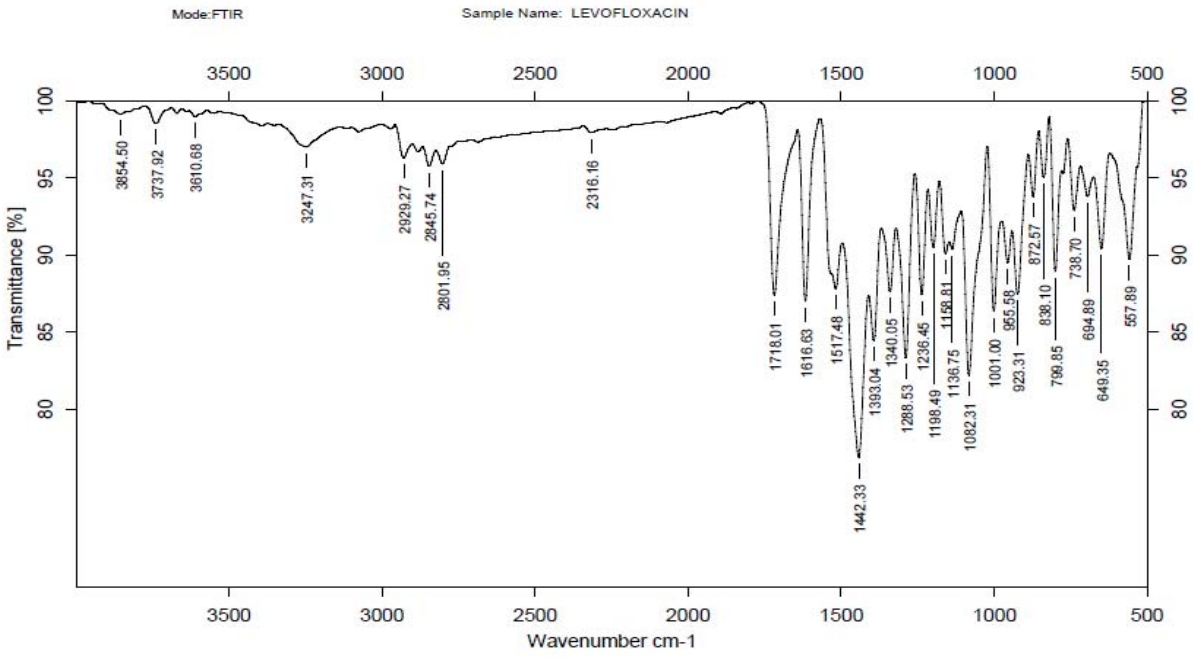

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Figure.10 : IR spectrum of Levofloxacin + gum kondagogu.

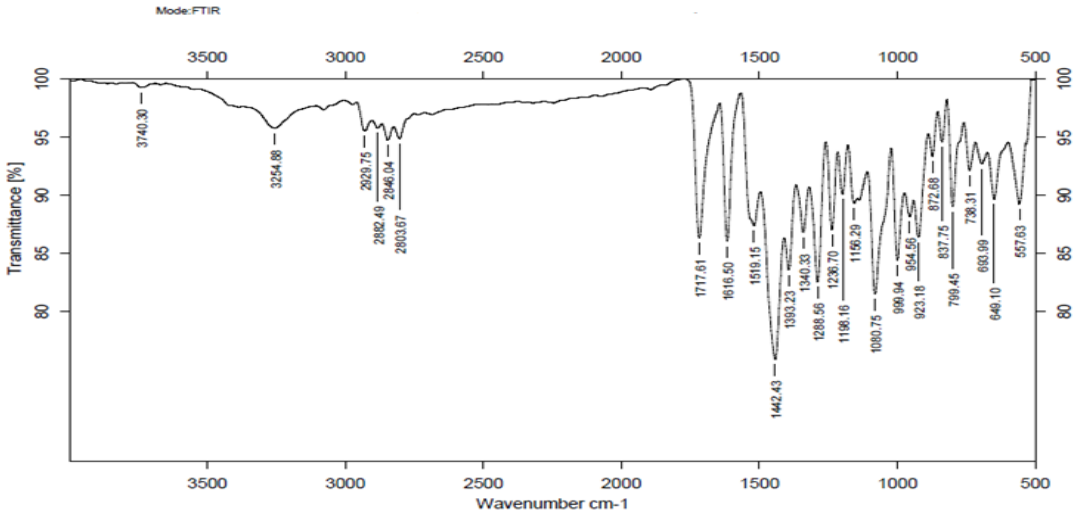

Figure.11 : IR spectrum of Levofloxacin + xanthum gum

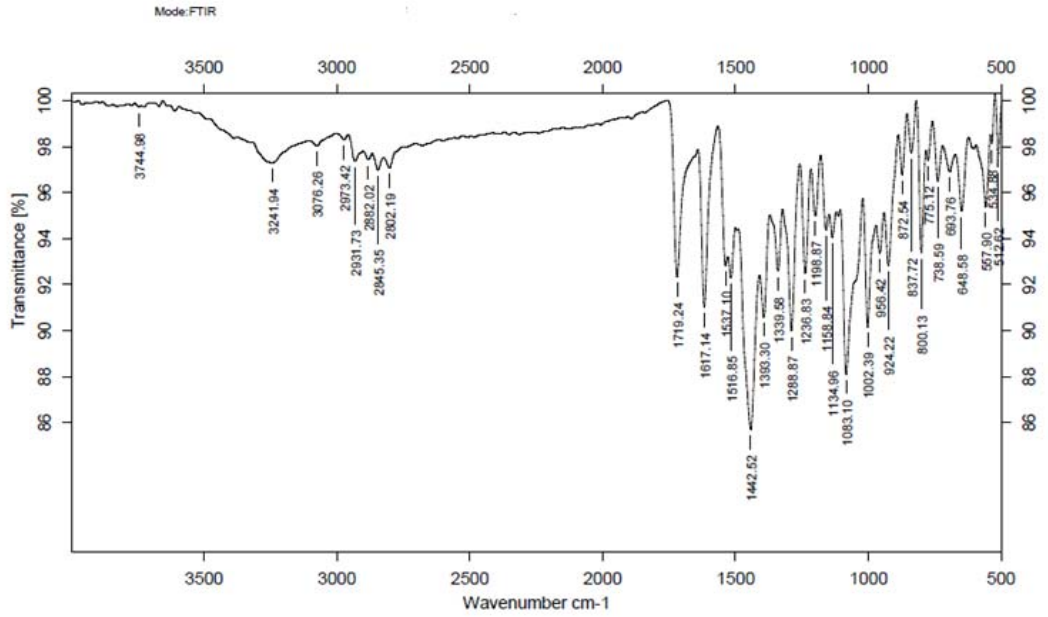

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Table.11: Comparative invitro release parameters of Levofloxacin hemihydrates floating tablets formulated with various natural polymers and HPMC K 100 M.(1:1 ratio)

Formulation	% Drug release at end of 12 hours.	Release Rate Constant k_0 (mg/hr)
F_3 (Levofloxacin+ gum kondagogu)	85.69	19.43
F_7 (Levofloxacin+xanthum gum)	73.33	15.11

CONCLUSION

The natural polymers used showed drug release retarding nature high viscosity value and good drug release retarding capacity and the release retarding nature of Xanthum gum was greater than gum kondagogu..From this study it could be concluded that natural polymers can be used in the preparation of floating tablets and in combination with synthetic polymers. Floating tablets of Levofloxacin hemihydrate prepared by employing natural polymers could be used for treatment of gastric ulcers caused by *H.pylorii* infection by prolonging the gastric residence time and its controlled release in the gastric environment thus completely eradicating the *H.pylo* from GIT.

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