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RESEARCH ARTICLE

Design and *In Vitro* Evaluation of Sustained Release Matrix Tablets of Levofloxacin by Using Natural and Synthetic Polymers

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ABSTRACT

Sustain release tablets of Levofloxacin were made up from *Aloe verabarbadensis*, Karaya gum, Locust bean gum, HPMC K100 and Ethyl cellulose. The results of pre-compression studies revealed that they were within prescribed limits that indicate good flowing property. Physical characteristics like hardness, weight variation, friability and drug content were evaluated. All the formulations were found to be within the official limits. A better-sustained drug release (97.45%) was obtained with the matrix tablet (F-2) of the HPMC K 100 gum for the period of 12 hours. Results showed that the drug release from matrix tablets prepared by using natural polymers could be sustained for more than 10 hrs and the drug release vary with concentration of polymer in matrix tablet. Thermograph of levofloxacin didn't show any interaction between drug and matrix materials. Then value lies between 0.729 to 0.948 (Korsmeyer-Peppa's model) demonstrating that the mechanism of drug release was Anomalous (non-Fickian) diffusion for the formulations (F-1 to F-15).

KEYWORDS

No key words are provided by author

INTRODUCTION

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years[1]. Regular research is going on for the use of naturally occurring biocompatible polymeric material in designing of a dosage form for oral controlled release administration. Natural gums are biodegradable and nontoxic, which hydrateand swell on contact with aqueous media, so these have been used for the preparation of dosage form.[2]Levofloxacin is the optical S- (-) isomer of ofloxacin. Ofloxacin is a racemic mixture, but the S-isomer has antibacterial activity 32- to 128-fold more potent than the R-isomer – hence most of the antibacterial activity of ofloxacin is due to the S-isomer.

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Levofloxacin has been developed to take advantage of this antibacterial potency while requiring only about half the usual dose of ofloxacin to achieve similar efficacy, but potentially with an improved toxicity profile. The absolute bioavailability of a 500 mg oral dose of levofloxacin is approximately 99%.The mean terminal plasma elimination half-life of levofloxacin ranges from approximately six to eight hours following single or multiple doses of levofloxacin given orally or intravenously. The mechanism of action of levofloxacin and other quinolone antibacterial involves inhibition of DNA gyrase, an enzyme required for DNA replication, transcription, repair, and recombination[3].The objective of the present work is to design andevaluate sustained release matrix tablets of Levofloxacin by using natural, synthetic polymers, filler.

MATERIALS AND METHOD

Levofloxacin was obtained from swarnaroop chemicals, Ahmedabad. Karaya gum is obtained from Yarrow chem. Mumbai, HPMC K-100; microcrystalline cellulose was purchased from Research- Lab Fine Chem Industries, Mumbai. SCMC, Magnesium Stearate, Talc, PVP K 30 were purchased from SD Fine Chemicals Ltd, Mumbai.

EXTRACTION OF ALOE VERA MUCILAGE

PROCEDURE

The fresh *Aloe barbadensis* Miller leaves were collected and washed with water. Incisions were made on the leaves and left overnight. The leaves were crushed and soaked in water for 5–6 hrs, boiled for 30 minutes and left to stand for one hr to allow complete release of the mucilage into the water. The mucilage was extracted using a multi-layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40°C, collected, grounded, passed through a # 80 sieve and stored in desiccators at 30°C & 45% relative humidity until use.

Table No 1: Chemical tests for aloe mucilage

S. N	Phytochemical tests	Observations
1	Test for Alkaloids (Wagner's test)	+ve
2	Test for Carbohydrates (Molish's test)	+ve
3	Test for Proteins	+ve
4	Test for Tannins (Ferric chloride test)	-ve

1. Wagner's test:

The sample was treated with a solution of iodine in potassium iodide (Wagner's reagent). The formation of brown precipitate indicates the presence of alkaloids.

2. Biuret reagent (Protein test):

The Biuret reagent is made of sodium hydroxide (NaOH) and hydrated copper sulfate, together with potassium sodium tartrate. Potassium sodium tartrate is added to complex to stabilize the cupric ions. Proteins in the alkaline environment reduce Cu^{2+} to Cu^{+}, which forms a coordination complex with proteins, leading to a blue to pink color change.

Procedure

To the test solution, a few drops of 0.7 % copper sulfate solution were added. Formation of a purplish violet color indicates the presence of amino acids

2. To Ferric chloride test: To the test solutions, a few drops of 5% ferric chloride solution were added. Formation of a bluish-black or greenish-black color indicates the presence of phenolic compounds and tannins[4].

All chemical results were shown in Table no: 1

Preparation of levofloxacin tablets

Thematrix tablets were prepared by wet granulation method. A non aqueous granulation process was adopted to prepare Levofloxacin matrix tablets. The drug and all other ingredients were sifted through sieve # 60 shown in Table 2 and 3. The sifted ingredients were mixed thoroughly in a mortar with the pestle for 15 min. IPA with PVP was added into a well-mixed powder till the desired wet mass are formed this wet mass was sifted through sieve #16. The prepared granules were dried at 60^0 C for 1 hour in a hot air oven, and then it was sifted through sieve # 16 and transferred the granules into a polybag. Magnesium stearate and talc were sifted through sieve # 40 and mixed with the prepared granules in a polybag for 5 min. Finally, tablets were compressed at 500 mg weight on a ten station mini rotary tablet punching machine (10 Station shakti pharma tech Pvt Ltd, Ahmedabad).

Table no 2: Tablet composition of Levofloxacin sustained release matrix tablets prepared with different release retardant polymers (F-1 to F-9):

FORMULATION CODE	F1	F2	F3	F4	F5	F6	F7	F8	F9
DRUG	250	250	250	250	250	250	250	250	250
HPMC K100	100	150	200	-	-	-	-	-	-
ETHYL CELLULOSE	-	-	-	100	150	200	-	-	-
KARAYA GUM	-	-	-	-	-	-	100	150	200
ALOE	-	-	-	-	-	-	-	-	-
MCC	110	60	10	110	60	10	110	60	10
MAGNESIUM	10	10	10	10	10	10	10	10	10
TALC	5	5	5	5	5	5	5	5	5

Table No 3: Tablet composition of Levofloxacin sustained release matrix tablets prepared with different release retardant polymers (F-10 to F-15).

FORMULATION CODE	F10	F11	F12	F13	F14	F15
DRUG	250	250	250	250	250	250
*ALOE BARBADENSIS*MILLER MUCILAGE	100	150	200			
LOCUST BEAN GUM	-	-	-	100	150	200
MCC	110	60	10	110	60	10
MAGNESIUMSTERATE	10	10	10	10	10	10
TALC	5	5	5	5	5	5

RESULT

Evaluation of Fabricated Matrix Tablets[5, 6]

Pre Compression Parameters:

1. Bulk density(Db):

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by, $D_b = M / Vo$

Where, D_b = Bulk density (gm/cc) M is the mass of powder (g)

Vo is the bulk volume of powder (cc)

1. Tapped density (D_t):

10 gms of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 Ts from a constant height and tapped volume were read. It is expressed in gm/cc and is given by,

$D_t = M / Vt$

Where, D_t = Tapped density (gm/cc) M is the mass of powder (g)

Vt is the tapped volume of powder (cc)

2. Compressibility Index

The compressibility of the powder was determined by the Carr's compressibility index.

Carr's index (%) = [(TBD – LBD) x 100]/TBD

Where, TPD is Tapped bulk density

LBD is loose bulk density

3. Angle of repose (θ):

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel until the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using the formula,

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

Where, θ = angle of repose,

h = height of pile, &

r = radius of the base of the pile.

Post Compression Parameters:

1. Thickness and diameter:

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet were measured using Vernier calipers. It is measured in mm.

2. Hardness:

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. A scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. Hardness was expressed in Kg/cm2.

3. Friability(F):

Tablet strength was tested by Roche friabilator. Pre-weighed tablets were allowed for 100 revolutions (4min), taken out and were de-dusted. The percentage weight loss was calculated rewriting the tablets.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Where, F = Percentage friability

W initial = Initial weight before friability test.

W final = Final weight after friability test.

4. Weight variation:

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

Where, PD = Percentage deviation,

W avg = Average weight of tablet,

W initial = individual weight of tablet.

5. Uniformity of drug content:

Weigh and powder 20 tablets. Weigh accurately a Quantity of the powder equivalent to 100 mg of Levofloxacin, transfer to a 250 ml volumetric flask. Add about 150 ml of 0.1N HCL, shake well and sonicate it for 25-30 min. Make up the volume up to 250 ml with 0.1N HCL. Filter the solution, take 10 ml of filtrate in 100 ml volumetric flask and make up the volume with 0.1N HCL. Measure the absorbance, of the resulting solution at the maxima at about 293 nm spectrophotometrically. Measure the concentration of drug in tablet powder using following equation:

Cu = Concentration of unknown sample,

Cs = Concentration of Standard sample

Au = Absorbance of unknown sample&

As = Absorbance of standard sample.

***In-vitro* dissolution study:**

Dissolution tests were performed in a USP Dissolution Test Apparatus II (Paddle method) at 37± 0.5°C. The Paddles were rotated at a speed of 50 rpm. The prepared tablets of

(Levofloxacin) tablets were placed in the dissolution vessel containing 0.1 N HCl solutions (pH 1.2) for 2hrs.These were then transferred to phosphate buffer (pH 7.4) and continue dissolution. Aliquots of 5 ml were withdrawn at different time intervals, filtered through 0.45 µm filter paper and the content of Levofloxacin was determined spectrophotometrically at a wavelength of 293nm.At each (hour) time of Withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask. The release studies were conducted, and results were noted in respective tables.

Kinetic analysis of in-vitro release rates of controlled release tablets of Levofloxacin.

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi‟s model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa‟s model – Log cumulative percent drug released versus log time.

Zero order kinetics:

Zero order release would be predicted by the following equation:-

At = A0 – K0t

Where, At = Drug release at time‘t’.

A0 = Initial drug concentration.

K0 = Zero – order rate constant (hr-1).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order release kinetics, with a slope equal to K0

1. First Order Kinetics:

First – order release would be predicted by the following equation:-

Log C = log C0 –Kt / 2.303

Where,

C = Amount of drug remained attime‘t’.

C0 = Initial amount of drug.

K = First – order rate constant (hr-1).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant „K‟ can be obtained by multiplying 2.303 with the slope values.

Higuchi’s model:

Drug release from the matrix devices by diffusion has been described by following Higuchi‟s classical diffusion equation.

Q = [D / (2 A - Cs) CSt] 1/2

Where, Q = Amount of drug released at time t‟.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix. Cs = he solubility of the drug in the matrix.

ε= Porosity of the matrix.

ι= Tortuosity.

ι = Time (hrs) at which ‘q’ amount of drug is released.

Above equation may be simplified if one assumes that ‘D’, ‘Cs’, and ‘A’, are constant. Then

Equation becomes:

Q = Kt1/2

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to ‘K’ (Higuchi’s 1963).

1. Korsmeyer equation / Peppa’s model:

To study the mechanism of drug release from the sustained – release matrix tablets of Levofloxacin the release data were also fitted to the well – known exponential equation (Korsmeyer equation / Peppa's law equation), which is often used to describe the drug release behavior of polymeric systems.

Mt / Ma = Ktn

Where, Mt / Ma = the fraction of drug released at time't'.

K = constant incorporating the structural and geometrical characteristics of the drug / polymer

N = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides, and we get

Log Mt / Ma = Log K + n Log t

When the data is plotted as a log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept.

For Fickian release 'n' = 0.5 while for anomalous (non – Fickian) transport 'n' ranges between 0.5 and 1.0. The result of *in vitro* drug release study of all the formulation as shown below.

COMPATABILITY STUDIES OF DRUG WITH EXCIPIENTS:

FTIR study of Levofloxacin: FTIR spectra of the selected (Optimized) formulations were taken and compared with the spectrum of the pure drug. The characteristic peaks of the drug were checked in the formulation spectra.

Effect of filler:

The effect of filler was investigated on the matrix structure. The filler selected were Microcrystalline cellulose.

Stability studies:

Stability studies of pharmaceutical products were done as per ICH guidelines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions.

Method:

Selected formulation was stored at different storage conditions at elevated temperatures such as 25oC± 20C / 60% ± 5% RH, 300C ± 20C / 65% ±5% RH and 400C ± 20C / 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of fifteen days and checked for physical changes.

DISCUSSION

Aloe barbadensis miller mucilage, Karaya gum, Locust bean gum, HPMC K100 and Ethyl cellulose is used as a retardant. Microcrystalline cellulose is used as filler Magnesium stearate is used as a lubricating agent and Talc is used as a glidant. Melting point was found to be 225ºC, and it is within the range specified in the official limits. Compatibility study is important to understand the interaction between the drug and polymers. It saves costs, and it makes easier to choose a few excipients from the long list of excipients for a better formula. Drug–excipients compatibility studies were carried out at an accelerating condition of 300C ± 20C / 60% ± 5%RH.A small quantity of each mixture was evaluated by FTIR with the control i.e. the pure Levofloxacin and the excipients were studied. It was found that all peaks corresponding to different functional groups of a pure drug were present in the drug-excipient mixture. This shows the absence of interaction between the drug and excipients listed in figure 4 to 7. The angle of repose values for the formulations wee ranges from 24.9± 1.71 to 29.02± 1.34. The readings indicate excellent flow properties. It was found that the compressibility values of the powders were below 15% and hence the exhibit good flow characteristics. The Carr's Index (Compressibility) of the powders was in the range of 8.52 ± 0.85 to11.56 ±1.34. The hardness of the tablets was found to be in the range of 5.9±0.18 to6.7±0.11Kg/cm2. It was within the range of monograph specification. Thicknesses of the tablets were found to be in the range of 1.90±0.02 to1.94±0.10mm. The friability of the tablets was found to be less than 1%, and it was within the range of standard specification.

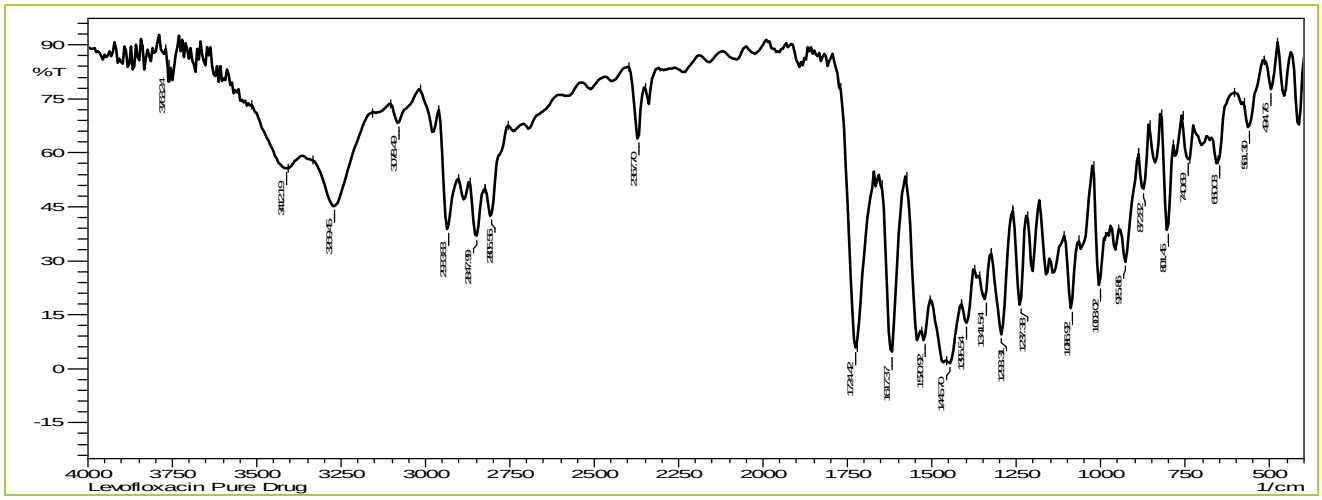

Figure No 4: FT-IR of pure Drug (Levofloxacin)

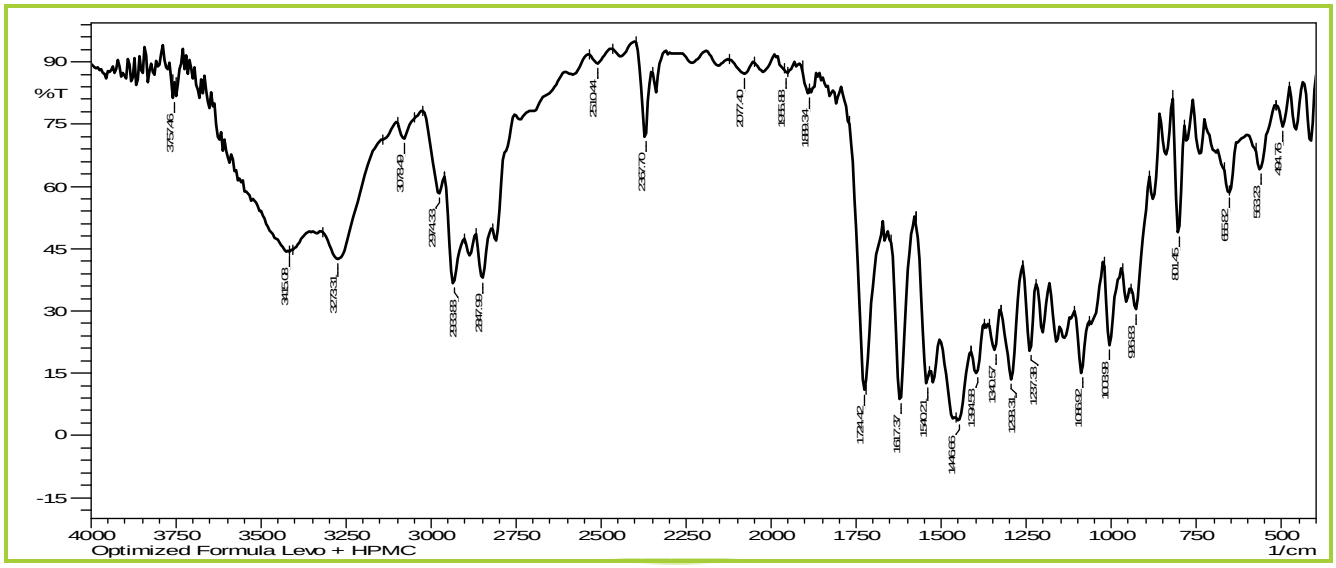

Figure No 5: FT-IR of Levofloxacin + HPMC K 100

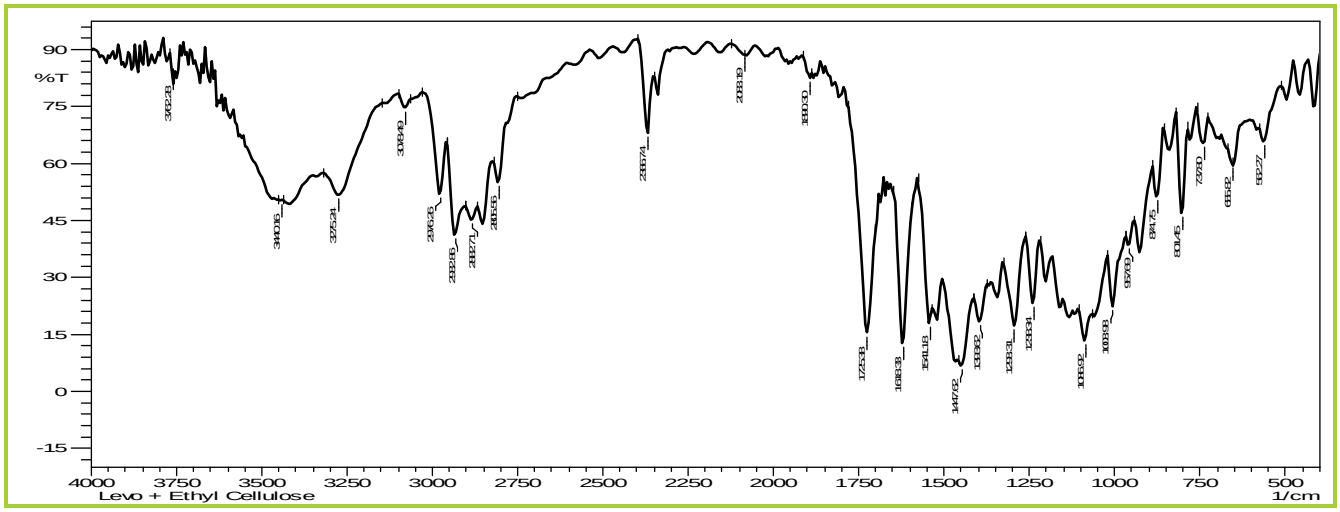

Figure No 6: FT-IR of Levofloxacin + Ethyl cellulose

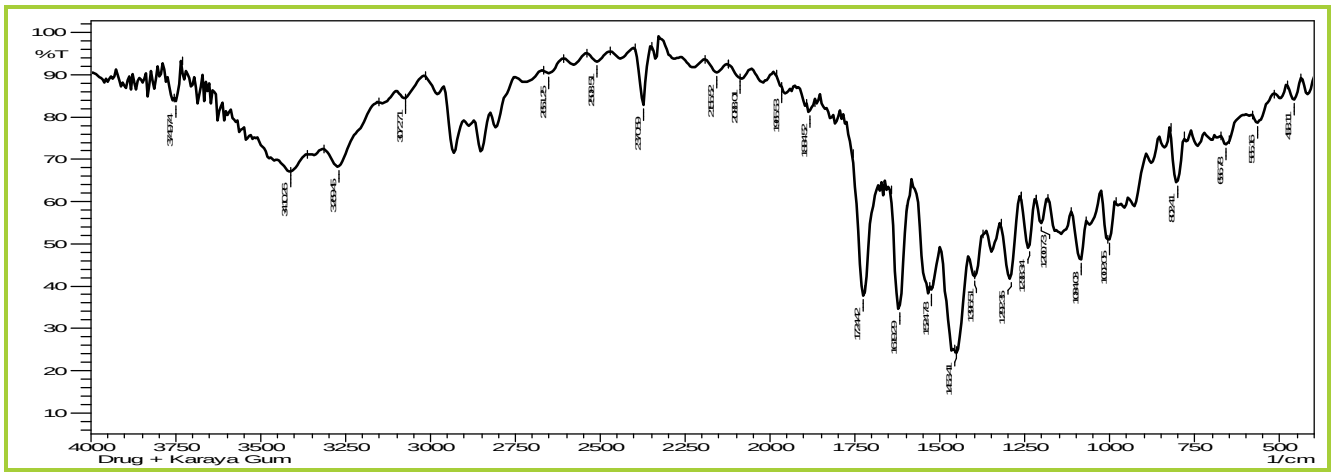

Figure No 7: FT-IR of Levofloxacin + Karaya gum

Weight variation test helps to check whether the tablet contains a proper quantity of the drug. From each of the formulations, twenty tablets were randomly selected and weighed. The average weights of the tablets were found to be within the prescribed official limits (IP). Drug content for each of the formulations was estimated. The drug content for all the batches was found to be in the range of 98.15 % to 99.44%.In vitro release studies were carried out for all the formulations as per USP XXII tablet dissolution tester employing rotating paddle at 50 rpm using 900ml of pH 1.2 HCl medium for 2 hours and phosphate buffer of pH 7.4 as dissolution medium remaining for 10 hours. (The results were evaluated for12hrs) the results were shown in figure 1 to 3.

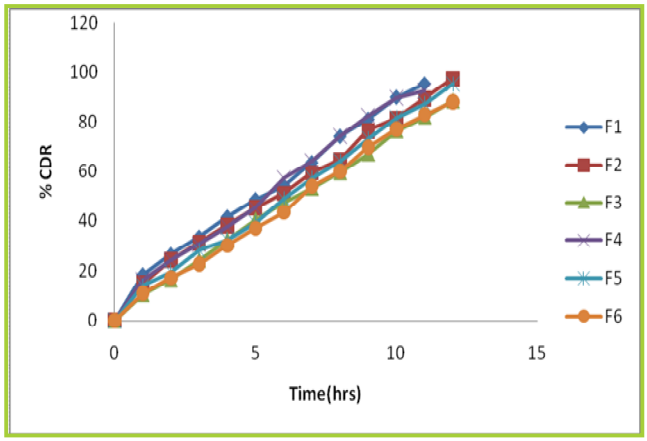

Figure No 1*: In Vitro* Dissolution Profile of F-1 to F-6 Formulations

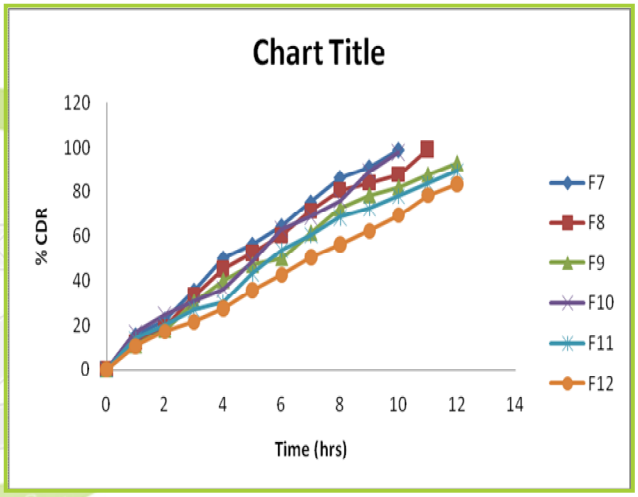

Figure No 2*: In Vitro* Dissolution Profile of F-7 to F- 12 Formulations

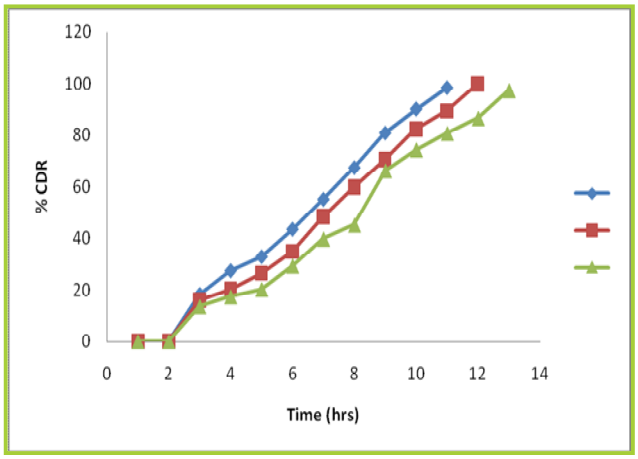

Figure No 3*: In Vitro* Dissolution Profile of F-13 to F- 15 Formulations

The Levofloxacin release from the matrix tablets prepared using natural polymers was slow to release up to 12 hrs, depending upon the concentration and type of natural polymer used. The order of increasing release retarding effect are observed with various natural polymers was HPMC K 100 < Ethyl cellulose < Karaya gum <Aloe Vera < Locust bean gum. The cumulative percent drug release was decreased by increasing natural polymer concentration. The comparative dissolution profile was analyzed. Based on the results of all formulations, F2 was selected as best formulation because it showed 97.45% cumulative drug release at the end of 12 hrs. The tablets of different formulations were evaluated for thickness, uniformity of weight, drug content, hardness, friability and in vitro dissolution. All the formulations showed uniform thickness. In a weight variation test, the pharmacopeial limit for the percent deviation for tablets of more than 500 mg is ± 5%.The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F-1 to F- 15 could be best expressed by zero order equation as the plots showed the highest linearity (R2: 10.998 to 0.993) than first order release kinetics (R2: 0.635 to 0.998). Then values obtained from Korsmeyer-Peppas plots range from (0.674 to 0.993) indicate that mechanism of release of formulations F-1 to F-15was Anomalous (non- Fickian) diffusion. The drug-polymer interaction was checked by comparing the IR spectra of the formulations with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectrums of the pure drug and also no additional peaks were seen in the selected formulations This confirms that no interaction between drug and excipients. Thermograph of Levofloxacin is shown in the figure. Which indicates of a pure drug is 225^0C, was observed in the figure, change in temperature is due to various concentrations of drug and other excipients in the physical mixture. This shows that there is no interaction between drug and optimized formula F-2 DSC studies released that there was no much shift in the melting of a drug in the physical mixture compared to the pure drug: this indicates there is no interaction between drug and matrix materials**.** Thermogram of optimized formulation (F-2) and pure drug are shown in figure8 and 9.

Differential scanning calorimetry:

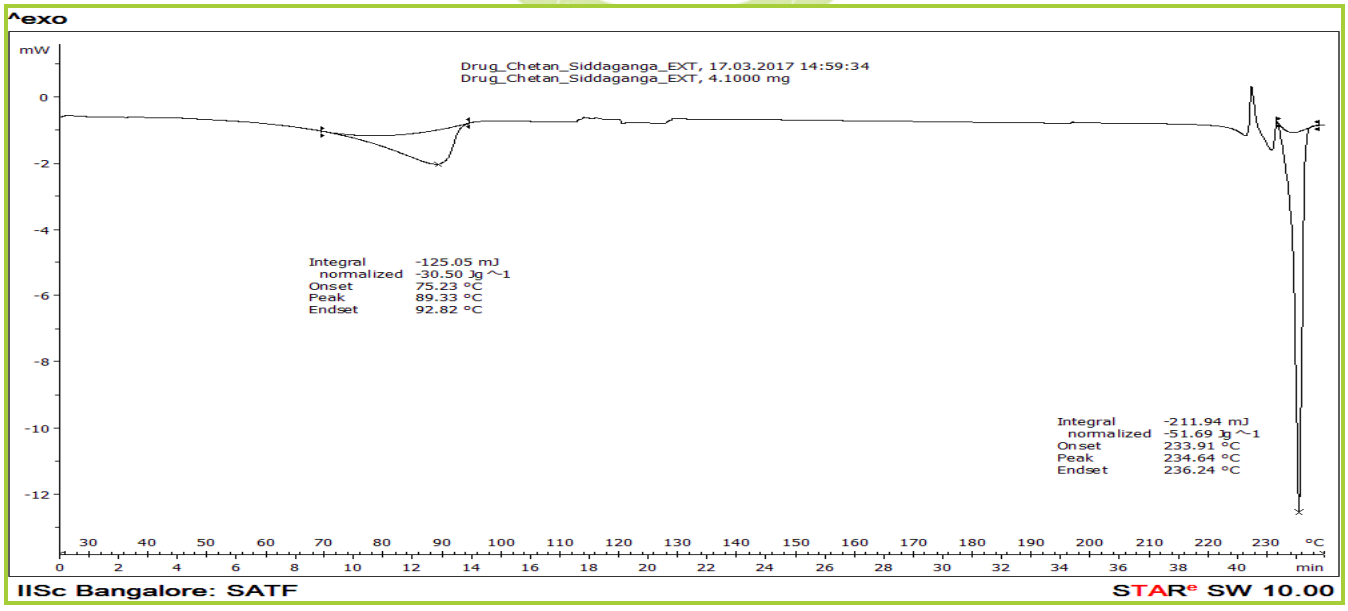

Figure No 8: Thermograph of pure drug Levofloxacin

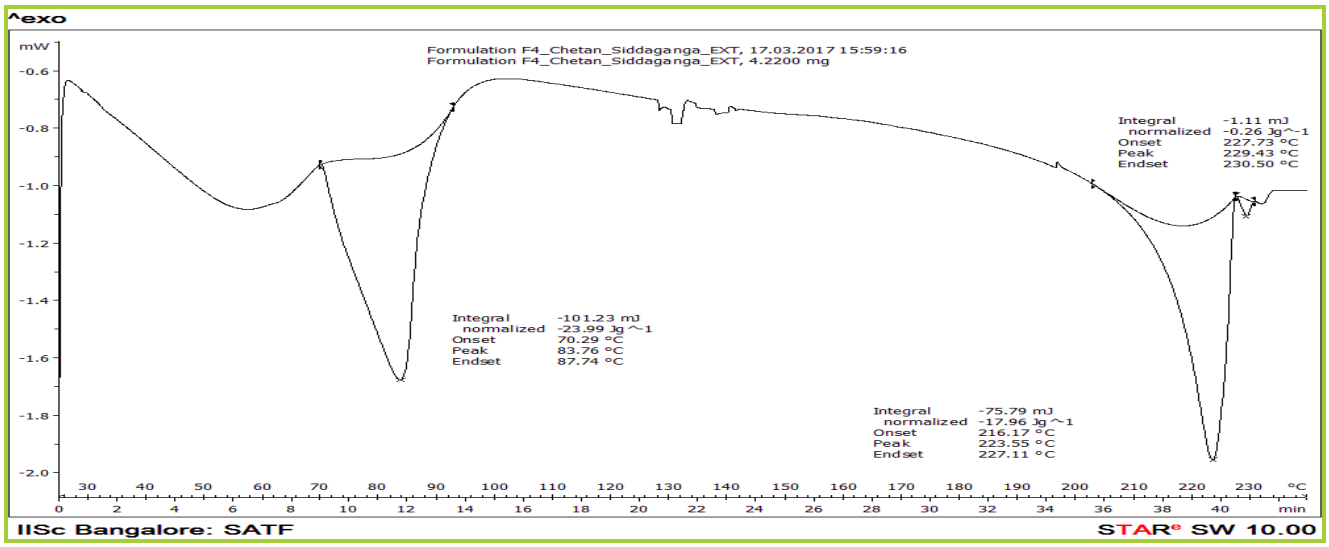

Figure No 9: Thermograph of Levofloxacin +HPMC K 100

Stability studies were carried out on selected formulation F-2 as per ICH guidelines. There was not much variation in matrix integrity of the tablets at all the temperature conditions. There was no significant changes in drug content, physical stability, hardness, friability and drug release for the selected formulation F-2 after 90 days at 25oC± 20C / 60% ± 5% RH, 300C ± 20C / 65% ±5% RH and 400C ± 20 / 75% ± 5% RH.

CONCLUSION

From the above observations, it was concluded that the formulation F-2 gave better drug release rate over a period of 12 hrs. Thus, formulation F-2 was found to be the most promising formulation from acceptable tablet properties and *in-vitro* drug release rate of 97.45%.It was found that increase in the polymeric concentration the drug release were decreased. Fillers are an important part of tablet formulation. The study of the effect of fillers on formulation F-2 concluded that filler solubility had a limited effect on release rate. It was found that increase in the fillers concentration increases the drug release. The kinetic treatment of selected optimized formulation shows that the regression coefficient for zero-order kinetics were found to be higher when compared with those of the first-order kinetics, indicating that drug release from all the formulations followed zero-order kinetics and then 'value lies between 0.729 to 0.948 (Korsmeyer-Peppa's model) demonstrating that the mechanism controlling the drug release was Anomalous (non-Fickian) diffusion. Therefore, the results of the kinetic study obtained permit us to conclude that an orally sustained Levofloxacin matrix tablet delivers the drug through a complex mixture of diffusion, swelling, and erosion. Based on the FT-IR studies, there appears to be no possibility of interaction between Levofloxacin and polymers / other excipients used in the tablets. The presence of all peaks indicates that all ingredients are compatible with Levofloxacin and there is no incompatibility between the selected ingredients. Stability studies were conducted for the optimized formulations as per ICH guidelines for 90 days which revealed that the formulations were stable. The results suggest that the developed sustained-release tablets of Levofloxacin could perform better than conventional dosage forms, leading to improving efficacy and better patient compliance.

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