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FORMULATION AND EVALUATION OF ARCHIMEDES BASED NOVEL FLOATING CAPSULE THROUGH FILM FORMATION AND RETENTION FOR DRUG DELIVERY OF LEVOFLOXACIN

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ABSTRACT: The study objectives were to develop a unique expandable integrated floating film to be filled in capsule dosage form, which combines hydrophilic and hydrophobic polymers. The developed film was totally free from the concept of gas generating system or the low-density system, which floats merely due to Archimedes principle. A 3² full factorial design was used in the study with HPMC K100M (X1) and ethylcellulose cp10 (X2) as independent variables and time required for dissolution of drug and swelling as dependent variables. FTIR and DSC studies were carried out to investigate any drug excipient interaction. The XRD studies of formulation showed decreased crystallinity of the drug levofloxacin. Steady slow gel formation and the higher concentration of ethylcellulose, resulted in sustained drug release. The hydrophilic polymer readily expands the polymeric network within two hours. The predicted value of 90.419 and the actual drug release from the polymeric film were closely related to each other.

INTRODUCTION: Polymers have played a crucial role in different sectors of engineering. They play a central role in extra corporeal devices, from contact lenses to kidney dialyses, and are essential components of implants, from vascular grafts to cardiac pacemakers. There is tremendous application of polymer in the designing of the new dosage form for drug delivery. Among such new pharmaceutical sector is targeting or restricting the delivery of drugs into the stomach only.

It has been observed that gastrointestinal disorders are common among all the people. ¹ With the objective of retention, one could ponder gas producing system, mucoadhesive system or the high-density systems. The pharmaceutical scientist often ignores the abdominal pain associated with movement of dosage form within the GIT, especially with high-density systems during stomach ulcers. The literature reports that some specific foods are prone to transient impaction, and results in pain. ²⁻³ If the ideal tablet dosage form stays over the stomach ulcer region due to its high-density, it could elevate the pain during its movement.

The gas producing system for drug retention in stomach often shows a remarkable pain within the

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abdomen region, showing the symptoms of tightness, knotted feelings and swelling of the abdomen.⁴⁻⁶ With the mucoadhesive system there has also been reports of pain, due to removal of mucus by the sticky starch. There by resulting in weak defensive action against acid-pepsin, and further leading to ulcer.⁷

So to overcome such problems, there is a need to develop suitable dosage form, which has least contact with the mucosal layer, and should have a soft nature to reduce pain. Among such novel concept the integrated film, apatented technology could be an example of such development⁸, where in first most general idea of floating behavior by the Archimedes principle was adopted.

Similar patented technology was a ring concept⁹. The intent of such technologies was to provide a suitable delivery system which retains within the stomach, that may release a drug associated with that over a controlled, predictable and for an extended period of time. The present study aim was to provide a novel film in capsule, where in the expandable film should retain by the Archimedes floating theory.

This can be fabricated by preparing multilayered film using different polymers, which should contain a release retardant polymer such as ethylcellulose (EC), and an elasticity providing polymer such as HPMC. Finally, the device being adapted to unfold in the subject's stomach to release the drug for a prolong period of time.¹⁰

1. Principle design of formulation system: The Novel floating expandable film was developed by first preparing the film with HPMC and part of the drug, followed by placing another layer of polymer EC with drug and drying it over it. Then again, HPMC layer was added over it and dried (**Fig. 1**). The film so existed was cut into appropriate size and was folded in a zigzag pattern, followed by insertion into the hard gelatin capsule body. There after gelatin cap was joined over the body. After ingestion of the capsule, the acidic environment quickly dissolves the gelatin shell; as a result, the film formulation get expands. The Archimedes principle accounts for the buoyant behavior of the expanded film.

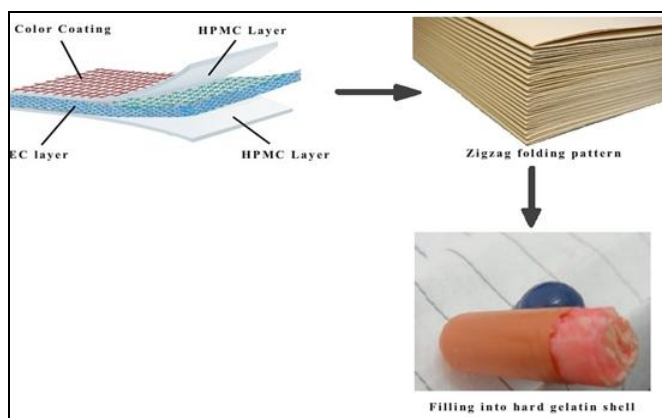


FIG. 1: SCHEMATIC PRESENTATION OF EXPANDABLE FILM, AND ITS INCORPORATION INTO HARD GELATIN SHELL

2. MATERIALS AND METHOD:

2.1 Materials:

Levofloxacin was supplied by Wockhardt Research Ltd. (Aurangabad, India). Hard gelatin capsules (#00) were obtained from Concept Pharmaceuticals Ltd. (Associated Capsules, Mumbai, India, Lot No: DKR10387). Hydroxypropyl methylcellulose (HPMC, Lot No.: GA228766) Mol. Wt. 15000 with viscosity of 100,000 mPa s was purchased from Colorcon, IndPvt. Ltd, Goa. Ethylcellulose was obtained from Shreya Life Sciences, Aurangabad. Glycerine was purchased from Thermo fisher Scientific Ind Pvt. Ltd, Mumbai. All other reagents used were of analytical grade.

2.2 Preparation of expandable film: To prepare expandable film, the HPMC K100M polymer was dissolved in hydroalcoholic solution with the aid of a mechanical stirrer (**Table 1**). Based on the area of petridish (38.5cm²) amount of drug added for each formulation was 1.6 g of levofloxacin. Each 2×3 cm² area contains 250 mg of the drug, respectively.

The drug levofloxacin was divided into three parts, from which two parts were added to the above hydroalcoholic solution with glycerin. To prepare first layer the half of above solution was poured to the petridish, and was kept in an oven at 37° C for overnight.

The second solution was prepared by dissolving the ethylcellulose polymer in ethanol followed by dispersing the remaining amount of the drug with glycerin. The second layer was prepared by the addition of second solution over the first HPMC polymer layer.

It was again kept in the oven at 37° C for overnight. The third layer was prepared by pouring the first HPMC solution over the second layer and was

again kept overnight in an oven. After complete drying, the film was peeled off and was subjected to the further process.

TABLE 1: COMPOSITION OF LEVOFLOXACIN EXPANDABLE FILM

Formulation code	Levofloxacin (g)	X1 (g)	X2 (g)	Alcohol: Water (ml)	Glycerin (ml)
F1	1.6	0.25	0.375	20:30	5
F2	1.6	0.25	0.5	20:30	5
F3	1.6	0.25	0.625	20:30	5
F4	1.6	0.375	0.375	20:30	5
F5	1.6	0.375	0.5	20:30	5
F6	1.6	0.375	0.625	20:30	5
F7	1.6	0.5	0.375	20:30	5
F8	1.6	0.5	0.5	20:30	5
F9	1.6	0.5	0.625	20:30	5

X1 represents HPMC K100M

X2 represents Ethylcellulose

2.3 Coating of integrated film: The 6% ethylcellulose coating solution was prepared in acetone. To distinguish uniform coating and for visual observing during in vitro buoyancy studies, the colorant erythrosine was added to the coating solution. The above expandable film was coated employing dip coating technique. The coated film was then cut into the appropriate dimensions of 2×3 cm² area, which readily fits into the gelatin capsule shell. Finally, film was folded in zigzag pattern and was filled into an empty gelatin capsule body.

2.4 Thickness: The thickness range was determined for three integrated films of each batch. The thickness of film was expressed in mm. The thickness of the drug loaded film was measured at different points by using verniercaliper and determined the average thickness and standard deviation for the same to ensure the thickness of the prepared film.¹¹

2.5 Appearance: The appearance of each integrated device was determined by visual inspection for each trial.

2.6 Folding endurance: A strip of specific area was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.¹²

2.7 Drug content: Film is cut into pieces and put in 100 ml dissolution medium (0.1N Hcl) used and stirred continuously using a mechanical stirrer and the sample is withdrawn at the end of three

hours and the drug content is determined spectrophotometrically at 294 nm.¹³

2.8 In-vitro buoyancy studies: The *in vitro* buoyancy studies were carried out by observing the floating behavior as reported by Rosa.¹⁴ The capsules were placed into the beaker containing 100 ml of 0.1N HCL. The floating duration of a capsule along with the film expansion were noted by visual observation.

2.9 Drug release studies: The *in vitro* release of levofloxacin from the capsule filled expandable film were conducted using USP type II paddle dissolution apparatus (TDT-06T, Electrolab, India). The dissolution medium used was 900mL of 0.1N HCl at the rotation speed of 50 rpm, kept at 37° ±0.5°C. At the predetermined time intervals samples were withdrawn, and replaced with the same amount of pre-warmed fresh buffer mediums. The levofloxacin released to the medium was analyzed using a Shimadzu UV 1800 spectrophotometer at 294 nm. All release studies were performed in triplicate.

2.10 Mathematical drug release models: The different mathematical models may be applied for describing the kinetics of a drug release process from expandable films. The kinetics of levofloxacin release from capsule formulations were determined by finding the best fit of release data to zero order, first order, Hixson–Crowell, Higuchi, and Korsmeyer–Peppas plots, respectively.

2.11 Infrared spectroscopic studies: The spectra were recorded with a JASCO Fourier transform infrared spectrophotometer (Model 5300, Jasco Corporation, Tokyo, Japan).¹⁵ Infrared (IR) spectroscopic analysis was carried out on the mixtures to evaluate possible interactions between the drug and the carrier. Samples were prepared by KBR disc method (2 mg sample in 200 mg KBR) and examined in transmission mode. Individual polymer, levofloxacin and drug/polymer mixture were run as controls. The scanning range was 400–4000 cm⁻¹, and the resolution was set to 1 cm⁻¹. The recorded spectrum was further subjected to analysis by Essential FT-IR V 1.5 software, USA.

2.12 The DSC studies: Differential scanning calorimetry (DSC) analysis was performed using Mettler Toledo DSC instrument. The system was calibrated with a high-purity sample of Indium. The formulation consisting of drug and polymers were mixed thoroughly for five minutes in mortar, and then stored at 40°±1°C, 75% ±5% relative humidity for four weeks to accelerate the interactions between drug and polymers. The sample formulation was scanned in aluminum pan over the temperature range of 80°C to 300°C at the scanning rate of 10°C per min, and scans were performed in triplicate.

2.13 X-ray powder diffraction pattern: The crystal data were recorded on a Bruker AXS D8 advanced diffractometer (Massachusetts, USA) providing Cu radiation (wavelength 1.5406 Å) equipped with Si (Li) PSD detector. The sample was oscillated during the 31.2s period of data collection; data were integrated over a 2θ range from 3° to 45° with a resolution of 0.02° to yield the reported diffraction patterns. The structure was resolved using the program X-Shell.

2.14 Accelerated Stability Studies: The stability of formulation (F7) was studied for the period of 90 days, at the temperature of 40° ±2°C and 75% ±5% relative humidity. The film was then evaluated for various parameters viz. thickness, folding endurance, drug content and release studies.

3. RESULTS AND DISCUSSION:

3.1 Mathematics and the Laws of Nature: ¹⁶ Archimedes principle(Greek, lived-in Syracuse - Sicily - between 287 and 212 BC) provides a

particular formulation, the law of equilibrium of forces for the floating bodies. Every liquid exerts an upward force on the objects immersed in it. This upward force is referred as buoyant or up thrust force. Every object was added exerts some gravitational force, which pulls the object in downward direction. So to lift it, we should have an equal amount of upward force to that of the object. The equation can be derived for the rectangular box/film, where in the forces acting at sides of a body, tends to cancel each other.¹⁷

$$F_4 = L \int_0^T \gamma z dz + \rho_o LT = \frac{1}{2} \gamma LT^2 + \rho_o LT \dots\dots\dots \text{eqn (1)}$$

Similarly, the force on face 6 is

$$F_6 = -L \int_0^T \gamma z dz - \rho_o LT = -\frac{1}{2} \gamma LT^2 - \rho_o LT \dots\dots\dots \text{eqn (2)}$$

The only forces that remain are the bottom and the top face, i.e. faces 2 and 1, which is represented by eqn

$$F_1 = -\rho_o LB \dots\dots\dots \text{eqn (3)}$$

and the force on the bottom,

$$F_2 = \rho_o LB + \gamma LBT \dots\dots\dots \text{eqn (4)}$$

The resultant of F₁ and F₂ is an upward force given by

$$F = F_2 + F_1 = \gamma LBT + \rho_o LB - \rho_o LB = \gamma LBT \dots\dots\dots \text{eqn (5)}$$

The force *F* given by Eqn (5) is the weight of liquid volume displaced by the immersed body. The force γLBT is called buoyancy force.

Where *LBT* = length, breath and draught, *z*= depth, γ = fluid pressure, *F* =face, ρ_o = Atmospheric pressure. Finally, it can be said that when a body is partially or wholly immersed in a dissolution medium, it experiences an up thrust. This will be equal to the weight of fluid displaced by the immersed part of the body, thereby resulting in the floating behavior of film.¹⁸

So if an expandable film weighs 0.91gms, it will sink into the buffer media until it has displaced the same amount of water. Provided that the boat displaces 0.91 grams amount of water before the whole thing is submerged, the expandable film

floats. It is this upward water pressure pushing against the bottom of expandable film, which is causing the film to float. Each square centimeter of the expandable film that is under media has water pressure pushing it upward, and this combined pressure floats the expandable film. For the floating phenomena, shape of the formulation also plays a crucial role. The zigzag folded film within the hard gelatin capsule readily unfolds when the gelatin shell dissolves. This unfolded flat film provides extra force to pull it upwards and aids in floating.

The expandable film must float or retained within the gastric environment for at least 12 hours for better drug release and absorption profile. During our early studies carried out without an ethylcellulose coat, we found the expandable film floats for some duration and loses its dimension thereby readily sinks towards the bottom of a dissolution apparatus. This could be due to the rapid hydration of HPMC polymer with the buffer media. The liquid penetrates the spaces of the polymer resulting in hydration; chains gradually uncoil and extends. These events break polymer hydrogen bonds, making sites available for further hydrogen bonding with leftover water molecules.¹⁹

Thereafter partial dissolving loses its tensile strength thereby leads to the dimension changes. The tensile strength is considered to be an important property for the films, which are critical in protecting films.²⁰ During his study author reports that HPMC film becomes more flexible at 25°C, and suggests hydration temperature to be maintained at <10°C.

3.2 Calculation of area of petridish:

$$A = \pi r^2 = 22/7 \times (3.5 \times 3.5) = 38.5 \text{ cm}^2$$

3.3 Calculation of area of integrated film for the required dose of drug: We require 6 cm² area of integrated film to be folded and filled in capsule and it should contain 250mg of drug. Therefore

$$\begin{array}{ccc} 6 \text{ cm}^2 & \longrightarrow & 250 \text{ mg} \\ 38.5 \text{ cm}^2 & \longrightarrow & x \text{ mg} \\ & & x = \frac{250 \times 38.5}{6} \\ & & = 1604 \text{ mg} = 1.604 \text{ g} \end{array}$$

Therefore we required 1.6g of drug to be poured in each integrated film.

3.4 Development of Analytical Methods (UV Spectrophotometric):

3.4.1 Preparation of standard stock solution: Standard drug solution of levofloxacin was prepared by dissolving 200mg in methanol and the volume was made upto 100ml with 0.1N HCl, from this 1ml was taken and diluted upto 100ml with 0.1N HCl to obtain stock solution of 20µg/ml concentration. Ultrasonication was done to obtain a clear solution.

3.4.2 Determination of analytical wavelength: From the standard stock solution, 6 ml was pipette out into 10 ml volumetric flask. The volume was made up to 10 ml with 0.1N HCl. The resulting solution containing 12µg/ml was scanned between 200 and 400 nm.

3.4.3 Preparation of Calibration curve of levofloxacin: Aliquots of 01 to 06 ml portion of stock solutions were transferred to a series of 10 ml volumetric flasks, and volume made up to the mark with 0.1N HCl. The serial dilution of the range of 2, 4, 6, 8, 10, and 12µg/ml was prepared. The absorbance was measured at 294nm.

3.4.4 Preparation of Standard Calibration Curve:

Linearity and range: The linearity of the response of the drug was verified at 2 to 12µg/ml concentrations. The calibration graphs were obtained by plotting the absorbance versus the concentration data and were treated by linear regression analysis. The equation of the calibration curve for levofloxacin obtained. The linearity range of calibration curve and correlation coefficient (r²) of determination was obtained.

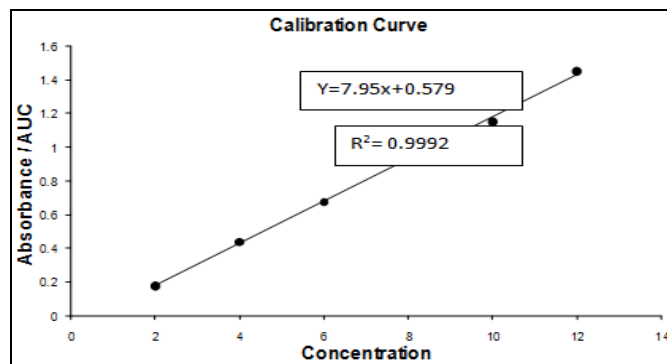


FIG. 2: STANDARD CURVE FOR LEVOFLOXACIN

3.5 HPLC method of analysis:

3.5.1 Selection of mobile phase: Different solvent systems were made and levofloxacin sample was injected into HPLC system. Different mobile phases containing phosphate buffer, methanol, acetonitrile were tried and finally sodium acetate buffer and acetonitrile was selected in a ratio of (60:40) respectively.

3.5.2 Preparation of mobile phase: Mobile phase comprising of sodium phosphate buffer and acetonitrile was adjusted to (3.5-4) pH and filtered

through watmann filter and kept for degasification in sonicator for 10 minutes. This mobile phase was pumped from the respective reservoir system to the column (flow rate 0.8ml/min. Eluents were observed at 295nm and data were acquired.

3.5.3 Preparation of calibration curve: Calibration curve was obtained by plotting AUC Vs conc. of levofloxacin and linearity range was obtained between 2 μ g-8 μ g/ml conc. of levofloxacin Solution.

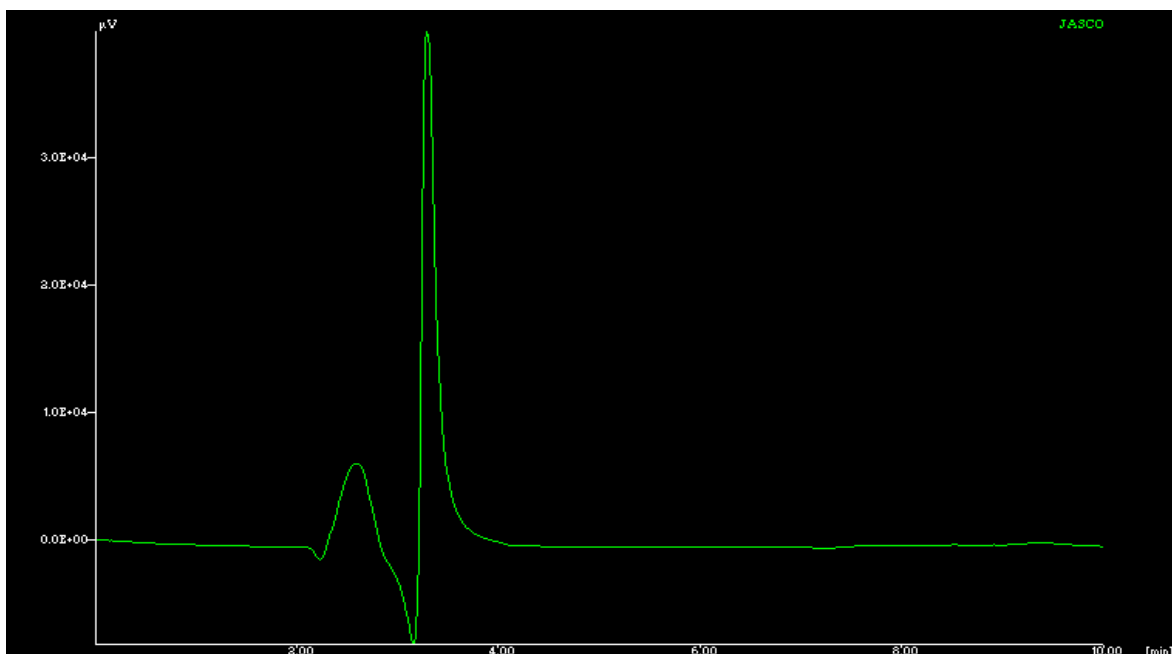


FIG. 3: HPLC TRIAL PEAK OF 6 μ g/ml OF LEVOFLOXACIN

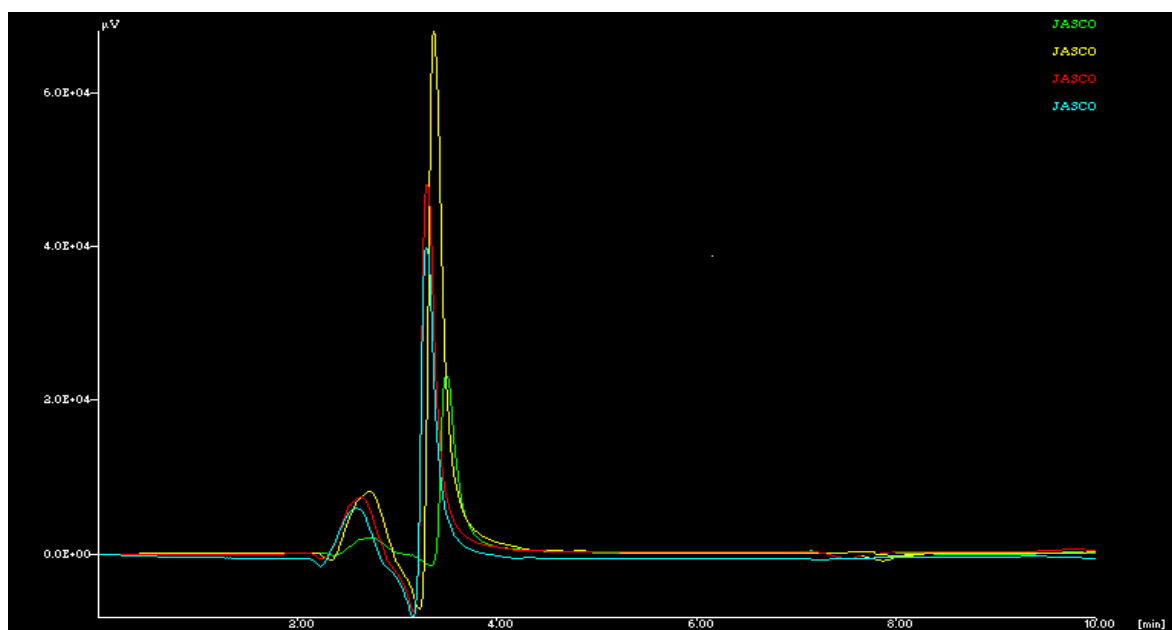


FIG. 4: OVERLAY OF PEAKS FOR CALIBERATION CURVE OF LEVOFLOXACIN

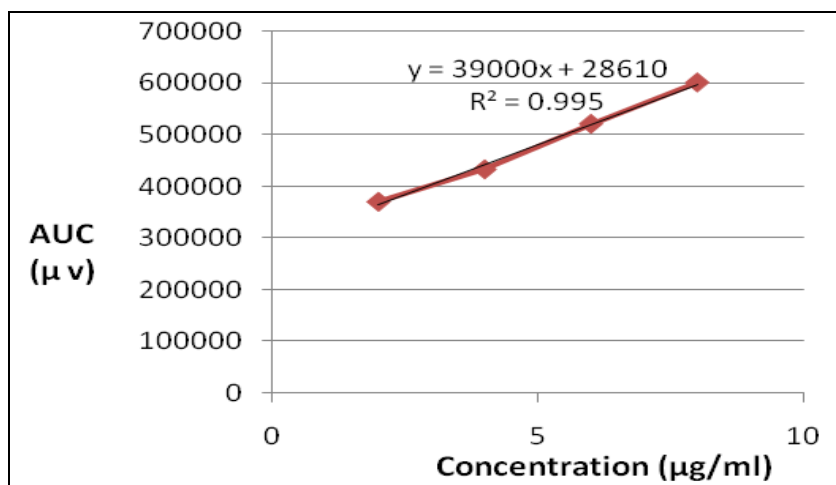


FIG. 5: CALIBRATION CURVE OF LEVOFLOXACIN BY HPLC

3.6 Evaluation of various parameters: The design were noted down. All the values of parameter like Thickness (mm), Appearance, Folding endurance, Drug content for factorial evaluation parameters are given below.

TABLE 2: EVALUATION PARAMETERS OF FORMULATIONS WITH 3² FULL FACTORIAL DESIGN

Formulation Code	Thickness (mm)	Appearance	Folding endurance	% Drug content
F1	1.2±0.03	++	10	98±0.076
F2	1.3±0.12	++	9	97.34±0.32
F3	1.2±0.66	++	8	99.11±0.098
F4	1.5±0.09	++	12	102.76±0.12
F5	1.3±0.03	++	10	97.97±0.76
F6	1.2±0.02	++	8	98.54±0.98
F7	1.2±0.12	++	14	101.92±0.86
F8	1.3±0.05	++	13	96.77±0.26
F9	1.3±0.07	++	12	99.45±0.83

Clear (No bubbles were observed)++

These batches show acceptable thickness, appearance and folding endurance. The drug content which does not much deviate from the theoretical value may be because of the constant surface area of petridish and constant temperature at which the film was dried. As these batches contain ethylcellulose in them, their folding

endurance is low as compared with other batches, which do not contain ethylcellulose in them. Because ethylcellulose is hydrophobic in nature and it provides brittleness to the film. With increased percentage of HPMC, folding endurance increases may be due to increase in the elasticity of the formed film.²¹

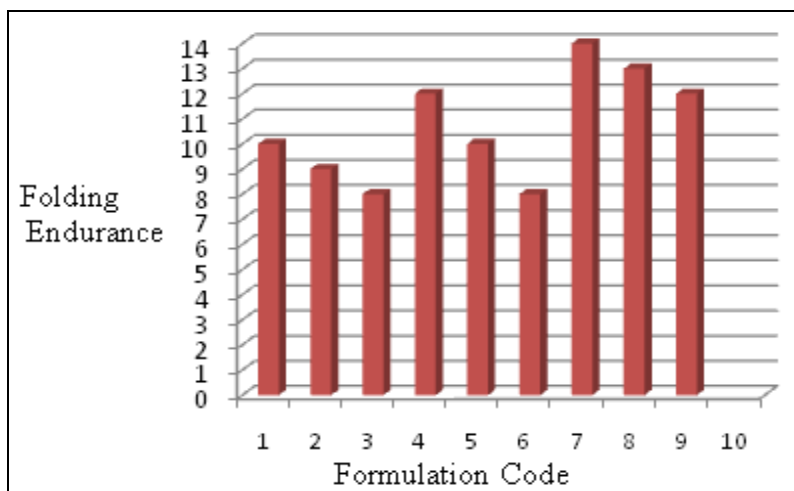


FIG. 6: FOLDING ENDURANCE OF VARIOUS 3² FACTORIAL BATCHES

3.7 In-vitro buoyancy studies: The *in vitro* buoyancy study was conducted at $37^{\circ} \pm 0.5^{\circ}\text{C}$, suggest increased flexibility to HPMC film either due to the temperature, and/or due to the turbulence created within the dissolution apparatus. To overcome this problem, we used different concentration of EC over the preformed film. The final coating was made with the optimized 6% ethylcellulose, which was made in acetone. Thereafter, all the coated film showed sufficient buoyancy time of 12 hours, as desired.

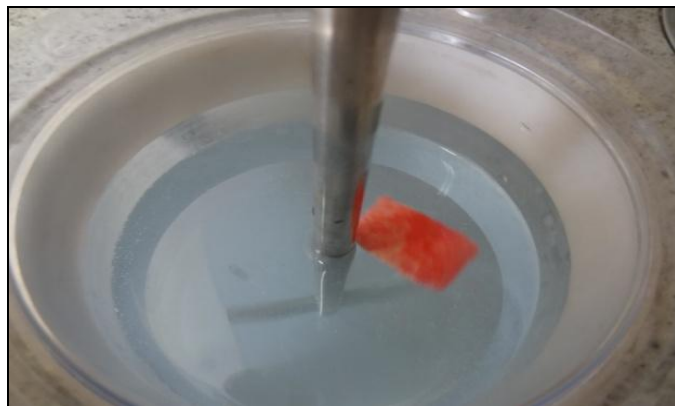


FIG. 7: INTEGRATED FILM AFTER 4 HRS IN DISSOLUTION APPARATUS



FIG. 8: INTEGRATED FILM AFTER 8 HRS IN DISSOLUTION APPARATUS

The floating behavior was observed in the final formulations due to the external ethylcellulose coat, which is hydrophobic in nature. The EC coat controls the water permeation and thereby its hydration rate. Unlike HPMC polymer, the EC polymer has high-tensile strength in the order of $7000\text{-}11000 \text{ lbs/in}^2$ and excellent flexibility over wide temperature range.²²

3.8 In-vitro drug release studies: Results of *in vitro* drug release of levofloxacin loaded capsules prepared using various polymer concentrations are

shown below. From the F1, F2 and F3 formulations, it is concluded that as the concentration of ethylcellulose increases, drug release decreases. The initial burst release was observed, which could be due to the presence of the drug within HPMC K100M polymer. This readily hydrates in contact with the acidic media and tends to expand polymeric network which thereby results in expulsion of drug material and provides higher drug release within two hours.²³ After 2 hours, the drug release tends to get decreased; this could be due to ethylcellulose polymer. The ethylcellulose polymer is known to have high-tensile strength and is hydrophobic in nature, which resist the entry of the water molecules to diffuse out of the drug molecule from the formulations. This eventually results in slow and sustained release for 12 hours.

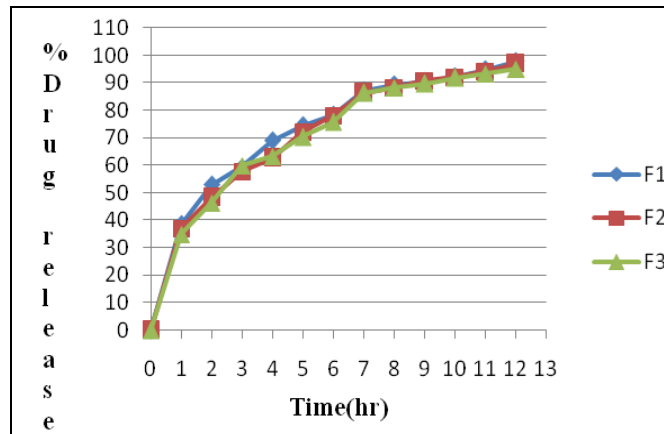


FIG. 9: COMPARATIVE RELEASE OF FORMULATION F1-F3

The F4, F5 and F6 formulations also showed a decrease in drug release due to increase in concentration of ethylcellulose, but these changes are not drastic may be due to HPMC K100M, which is not hydrophobic in nature. The both upper and lower HPMC K100M layers consisting of 66% of the drug, the drug releases to a higher extent during first hour due to its hydrophilic nature. The difference in the drug release profile of F4, F5 and F6 formulation is not much more, might be due to lower factorial space within the ethylcellulose polymer. This thereby suggests that high factorial space could lead to more difference in the drug release profile. The F7, F8 and F9 formulations also showed a decrease in the drug release with the increase in concentration of ethylcellulose polymer, respectively.

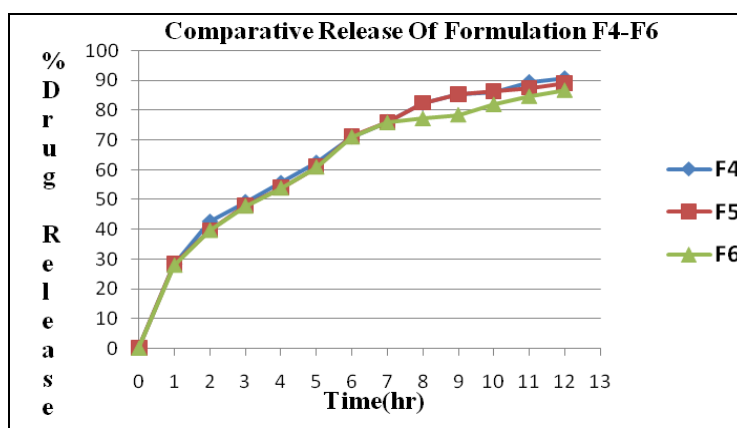


FIG. 10: COMPARATIVE RELEASE OF FORMULATION F4-F6

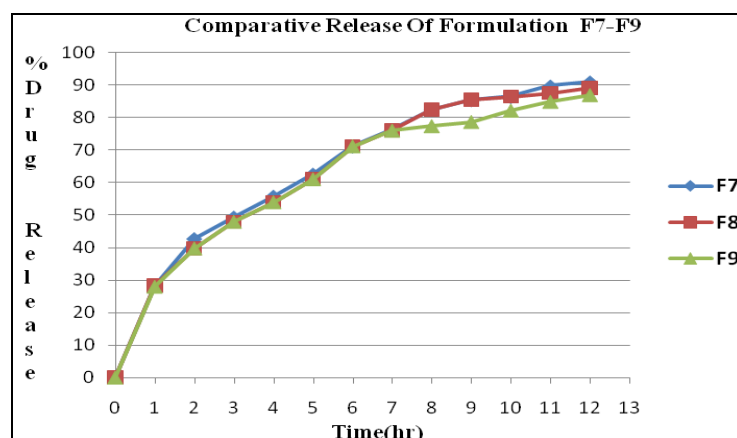


FIG. 11: COMPARATIVE RELEASE OF FORMULATION F7-F9

3.9 Surface response plot: The F-value of 73.14 implies the model is significant (Table 3). There is only a 0.01% chance that a "Model F-Value" can become large, which could occur due to noise. Values of "Prob> F" but less than 0.05 suggest model terms are significant. Values greater than 0.1 suggests the model terms are not significant. Both the factors A & B (HPMC K100 M and EC) shows a negative coefficient, which estimates that increase in concentration have an indirect effect on

drug release that is as concentration of A & B increases the drug release decreases. Actual drug release at 12th hour of F7 formulation was 90.920, and predicted value was 90.419 with a standard deviation of 0.813; so we can assume that F7 is the best formulation. From the surface response plot, it can be concluded that increase in concentration of HPMC K100 M and EC, decreases the drug release.

TABLE 3: ANOVA OF RESPONSE SURFACE LINEAR MODEL

Source	Sum of Squares	d.f	Mean square	F-value	P-value	Obtained R-Squared value	Predicted R-square value
Model	96.7542	2	48.377	73.1448	0.0001		
A-HPMC K100M	86.9442	1	86.944	131.457	0.0001	0.9606	0.9053
B-Ethylcellulose	9.8099	1	9.8099	14.832	0.0084		
Residual	3.9683	6	0.661	-	-	-	-

3.10 Mathematical Drug Release Kinetics: In order to develop an ideal kinetic model and to interpret *in vitro* drug dissolution rate data in terms of meaningful parameters, various kinetic models were applied to get the best fit of the data. It was found that release had been realized in accordance with Korsmeyer-Peppas for all the formulations.

The values of a release exponent for all formulations were between 0.3733 and 0.4654, which were less than 0.5, suggesting the drug release follows Fickian diffusion mechanism.²⁴⁻²⁵ The release profile of optimized formula F7, fitted best to Korsmeyer-Peppas model with R² value of 0.9951.

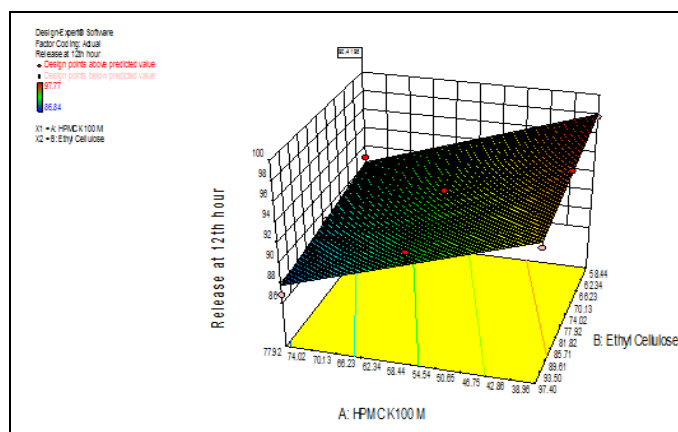


FIG.12: SURFACE RESPONSE CURVE

TABLE 4: RELEASE KINETICS OF BATCHES WITH 3² FACTORIAL DESIGN

Formulation	Release exponent (n)	Regression coefficient (R ²)				
		Zero order	first order	matrix	Kornsmayer-peppas(best fit)	Higuchi model
F1	0.3733	0.6292	0.9764	0.9731	0.9916	0.9554
F2	0.4026	0.7081	0.9910	0.9840	0.9948	0.9677
F3	0.4156	0.7105	0.9903	0.9831	0.9920	0.9568
F4	0.4608	0.8212	0.9916	0.9956	0.9960	0.9816
F5	0.4713	0.7670	0.9866	0.9849	0.9870	0.9558
F6	0.4644	0.7302	0.9820	0.9813	0.9821	0.9437
F7	0.4753	0.8121	0.9946	0.9948	0.9951	0.9714
F8	0.4841	0.8223	0.9899	0.9935	0.9941	0.9659
F9	0.4654	0.7880	0.9827	0.9915	0.9934	0.9478

3.11 Infrared spectroscopic studies: The infrared spectrums of fluoroquinolones are quite complex due to the presence of the numerous functional groups within the molecules. The Levofloxacin molecule contains 46 atoms, and it has 132 normal modes of vibration,²⁶ so their interpretations are based on the typical vibrations. The most important region in the IR spectrums of fluoroquinolones is

between 1800 cm⁻¹ and 1300 cm⁻¹. In levofloxacin, the carboxylic acid (COOH) band often appears within the range of 1725-1700 cm⁻¹. In the present study carboxylic acid COOH bands for pure compound were observed at 1724 cm⁻¹, while that in the formulation containing HPMC and ethylcellulose was observed at 1722 cm⁻¹ and 1700 cm⁻¹, which was in good agreement.

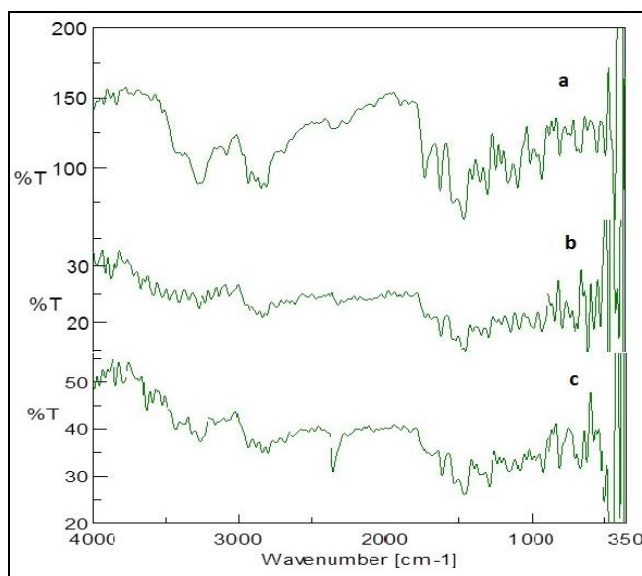


FIG. 13: FTIR SPECTRUM OF a) LEVOFLOXACIN, b) LEVOFLOXACIN WITH HPMC K100M, AND c) LEVOFLOXACIN WITH ETHYLCELLULOSE

The C-N stretching wave number is rather a difficult task since there are problems in identifying these wave numbers from other vibrations. Literature reports that C-N stretching absorptions in the region of 1391 cm^{-1} for 2-amino-5-iodopyridine.²⁷ In the present work, the band observed at 1346 cm^{-1} in FT-IR of pure drug has been assigned to C-N stretching vibrations, while the formulation showed a value at 1342 cm^{-1} and 1292 cm^{-1} , respectively.

The ring stretching vibrations are important in the spectrum of pyridine and its derivatives, which are the highly characteristic of aromatic rings. The aromatic ring carbon-carbon stretching vibrations occur in the region of $1430\text{--}1625\text{ cm}^{-1}$. For levofloxacin, it was observed at 1619 cm^{-1} , while in the formulation containing HPMC and EC, it was observed at 1446 cm^{-1} and 1461 cm^{-1} , respectively. These vibrations are in good agreement with the literature values. No new observable peaks were noted, which implies that no significant differences between the pure drug and the formulations. This implies absence of significant chemical changes within the levofloxacin formulation process.²⁸

3.12 The DSC Studies: Active pharmaceutical ingredients are often processed under conditions that result in the formation of crystalline hydrates and solvates.²⁹ During the film drying, these hydrates and solvates can lose their solvent molecules, resulting in a desolvated material that can occur in either the same crystal structure (isomorphous desolvate), a different crystal structure (anhydrate), or as amorphous material. Earlier studies concluded that dehydration of hemihydrate form of levofloxacin leads to collapse of the crystal lattice, and produces a mixture of physical forms (α , β , and γ), including amorphous levofloxacin. This suggests a need for the DSC studies.

During the process of film formulation, if the levofloxacin gets converted into the levofloxacin hemihydrate form, then that should have shown the broad endothermic transition peak in the temperature range of $20\text{--}70^\circ\text{C}$. Apart from the levofloxacin peak, there was no additional peak observed in the DSC studies, which indicates the absence of levofloxacin hemihydrate formation during the film drying process.

The three anhydrous forms of levofloxacin which corresponds to the melting point are at α (225.4°C), β (229.6°C), and γ (232.7°C), respectively. In our present study, levofloxacin formulation showed a characteristic endothermic peak at 224.4°C , which indicates an anhydrous form of α -levofloxacin molecule. This study shows levofloxacin is compatible with the excipients, and with the formulation drying process.

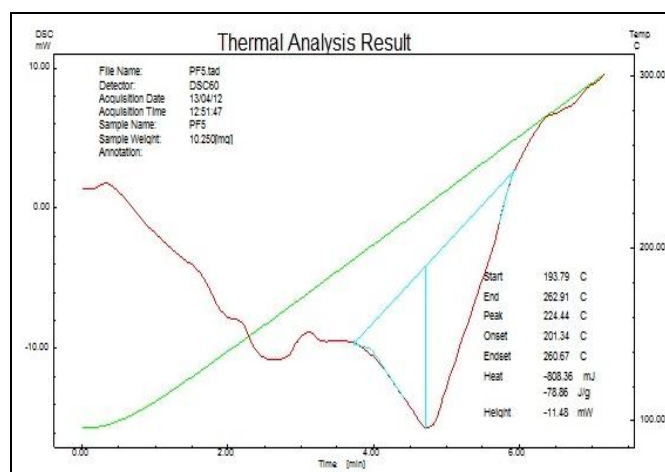


FIG. 14: DSC THERMOGRAM OF LEVOFLOXACIN FORMULATION

3.13 X-ray powder diffraction pattern: X-ray diffraction is a classic technique for exploring the orientation of crystalline materials, with particular applications in metallurgy.³⁰ The X-ray powder diffraction data of formulation showed that there was a significant change in the intensities of powder. The 2θ Values of levofloxacin drug when compared to pure drug, exhibits a drastic drop of levofloxacin crystallinity after incorporation into the formulations. The pXRD diffraction data of formulation explains its poorly crystalline nature.³¹

Further, a literature reports that when levofloxacin XRD was recorded at various temperature ranges ($47^\circ\text{C}\text{--}52^\circ\text{C}$); there were significant changes taken place in their intensities. This suggests dependence of intensities over the temperature range. Specific changes were observed at 6.91° , 13.34° , 19.68° , 20.24° , 26.66° , 29.02° , and at 31.62° 2θ . The decrease in the intensities in our formulation could suggest the presence of poor crystalline nature, which was also confirmed from DSC studies.

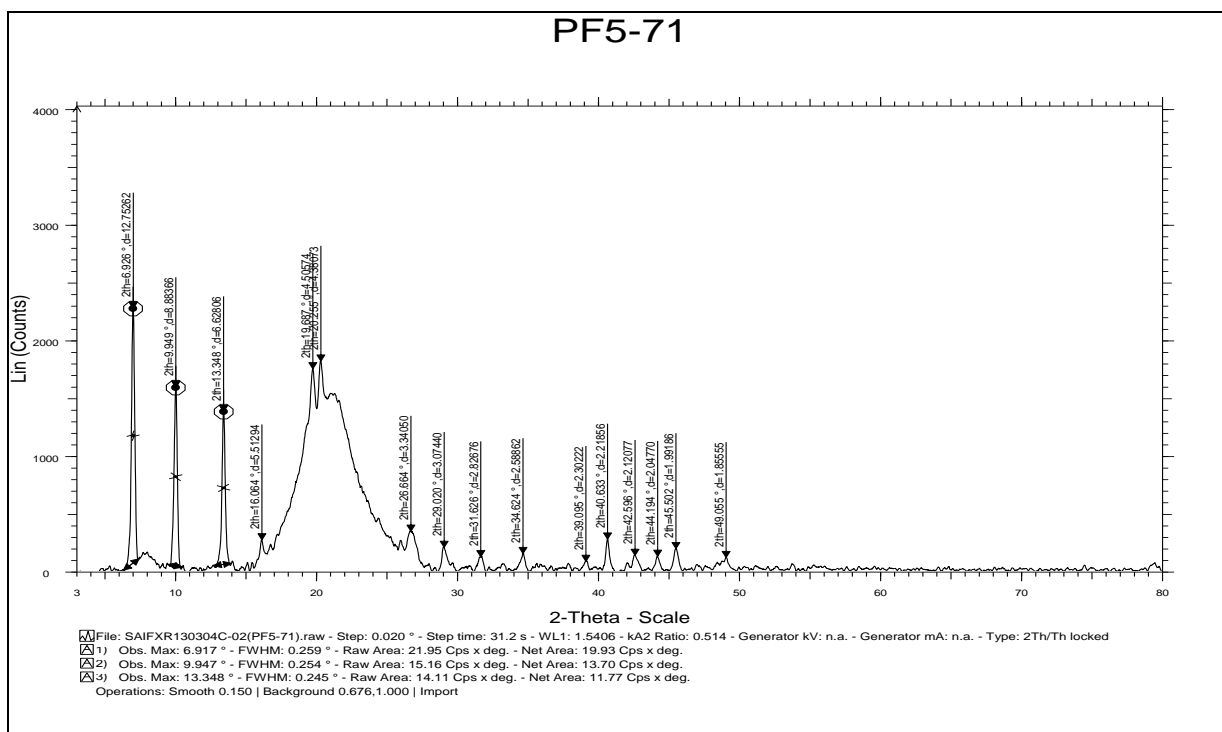


FIG. 15: XRD OF FORMULATION F5

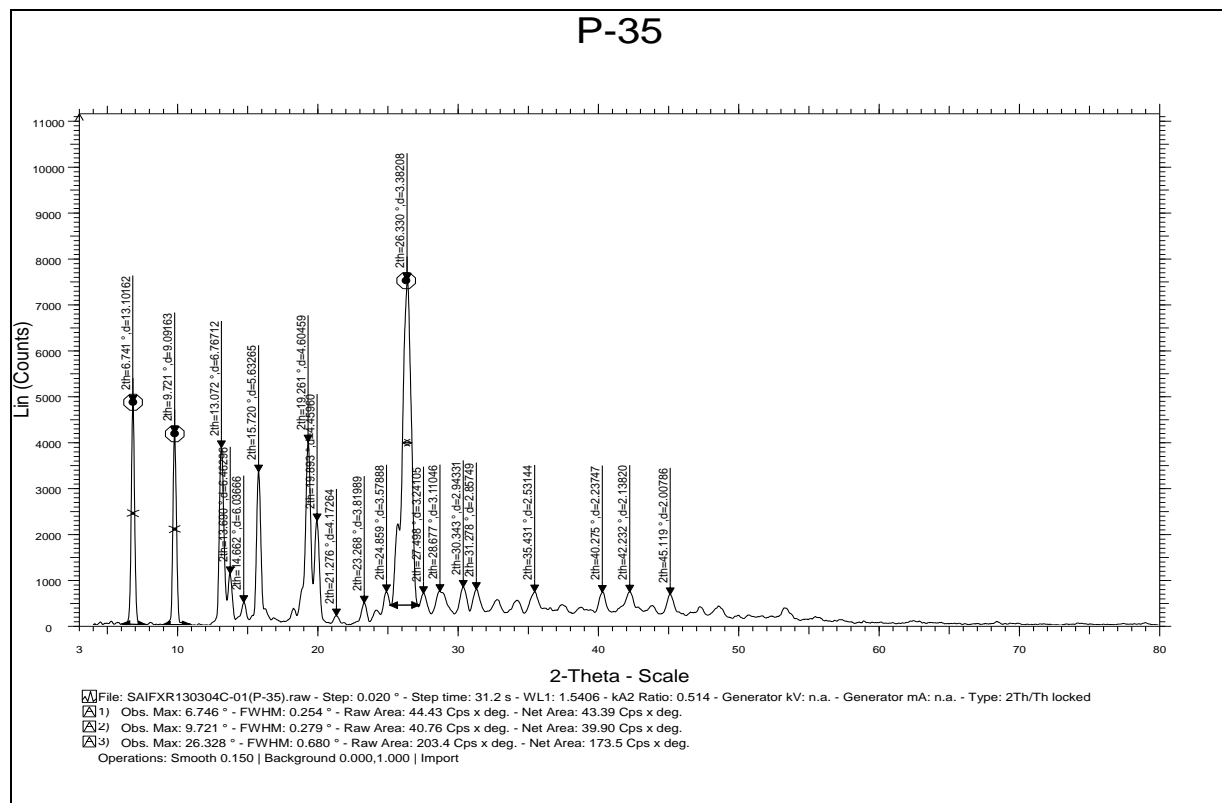


FIG. 16: XRD DATA OF LEVOFLOXACIN

3.14 Accelerated Stability Studies: After 3 months of storage of formulations at the mentioned temperature and relative humidity, visual examination of the film did not show any changes in appearance, thickness and did not show

significant variations in drug release pattern. The variation in drug release was found to be within the range of 0.69 to 3.99% after 90 days (Table 6). These results indicate the stability of drug and its dosage form.

From **Table 5** it can be seen that there is almost negligible changes taken place in the evaluation parameters of the film during 3 months. In **Table 6**

there is a slight decrease in drug release, but it is negligible. Hence, stability studies revealed that formulation F7 is stable for 3 months.

TABLE 5: STABILITY EVALUATION

Batch Code	Thickness (mm)	Folding Endurance	Percent Drug Content	Appearance
F7 (Before)	1.2±0.12	14	101.92± 0.86	++
F7(after 3 months)	1.2±0.02	15±1	100.92± 0.15	++

*All values are means ± SD, n=3

TABLE 6: DRUG RELEASE PROFILES OF F 7

Time (hr)	% Drug release	
	For 0 Days	For 90 Days
1	28.314±0.81	27.262±0.78
2	42.686±1.71	40.981±0.98
3	49.314±1.25	50.765±1.23
4	55.758±0.88	55.209±0.54
5	62.551±0.70	61.765±1.54
6	71.155±1.23	70.234±1.59
7	76.227±0.53	76.012±1.93
8	82.394±1.74	80.987±0.98
9	85.416±0.72	84.820±0.45
10	86.353±0.43	85.338±0.82
11	89.678±0.34	87.932±0.11
12	90.920±0.28	89.992±1.35

CONCLUSION: There were two principle objectives to this study, first to develop a novel concept in the form of expandable film and its insertion into a hard gelatin capsule shell. The data presented here have established that these prepared formulations concept were highly effective by floating phenomena to target drug into the stomach region, and to treat such *H. pylori* infections. The second objective was to assess the effect of formulation variables over different evaluation parameters. Such a simple new design may provide extended residence time, and improve the therapeutic efficacy. Optimization of floating phenomena for such expandable film filled capsules can be achieved by Archimedes principle through displacement behavior or by the proper coating of the formulation, or due to the swelling behavior of the dosage form.

Further, these formulations were shown to be free from any drug chemical interaction. The results of *in vitro* experiment studied demonstrated that such a new concept of polymeric film can be successfully applied for site specific delivery of drugs.

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