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# FORMULATION DESIGN, EVALUATION AND OPTIMIZATION OF CIPROFLOXACIN HCL FLOATING TABLET USING DESIGN EXPERT®

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**ABSTRACT**

Floating drug delivery systems have a lower bulk density than gastric fluids and hence remain buoyant in the stomach for an extended period of time without influencing gastric emptying rate. While the system is floating on the gastric contents, the drug is slowly released from the system at the prescribed pace; after drug release, the remaining system is evacuated from the stomach. This leads in extended stomach retention time and better regulation of plasma medication concentration variations. There are two types of floating medication delivery systems. Non-effervescent and Gas-generating systems. Ciprofloxacin HCl floating tablets by using polymers like HPMC K4M, Eudragit 100S, guar gum. The prepared tablets are characterized by using different evaluation parameters like buoyancy lag time, floating time, *in-vitro* drug release, uniformity of drug content, hardness, friability etc. and it is optimized by factorial design using Design Expert Software. The *in-vitro* drug release of the optimized formulation is best fitted and found to follow Hixon crowell erosion kinetics with a higher $R^2$ value of 0.992.

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## INTRODUCTION

Over the past few years, scientific and technological advances have been made in the research and development of a controlled rate oral drug administration system. Oral bioavailability of drugs with a window of absorption in the upper gastrointestinal tract is generally restricted with dosage forms such as tablet, capsules and granules. These drugs can be delivered ideally by slow release from the stomach to give a localized effect at the site of action. Gastric emptying of dosage forms is an extremely variable process which depends upon various factors of the dosage form and the physiology of GIT, so the ability to prolong and control the emptying time is a valuable quality for dosage forms. The residence time is main factor which influence the absorption of drug in the stomach and upper intestine. It also modified *in vitro* &*in vivo* release profile of the oral conventional dosage form. To overcome these issues and to increase the bioavailability of these drugs, sustained drug delivery systems, with a prolonged residence time in the stomach, can be used. [1]

Gastro-retentive dosage forms (GRDFs) are designed to be retained in the stomach for a prolonged time and release their active ingredients in sustained manner and prolonged release of the drug to the upper part of the gastrointestinal (GI) tract. [2]

**Gastro retentive delivery system can be classified as follows.**

1. Bioadhesive Drug Delivery System
2. Expandable Drug Delivery System
3. Floating Drug Delivery System
4. High density systems

Floating drug delivery systems have a lower bulk density than gastric fluids and hence remain buoyant in the stomach for an extended period of time without influencing gastric emptying rate. While the system is floating on the gastric contents, the drug is slowly released from the system at the prescribed pace; after drug release, the remaining system is evacuated from the stomach. This leads in extended stomach retention time and better regulation of plasma medication concentration variations. There are two types of floating medication delivery systems: (i) Non-effervescent and (ii) Gas-generating systems. [3, 4]

## FLOATING SYSTEMS:

Floating Drug Delivery Systems (FDDS) have a lower bulk density than gastric fluids and hence remain buoyant in the stomach for a longer period of time without altering the gastric emptying rate. While the system is floating on the gastric contents, the medicine is gently released at the desired pace from the system. The residual system is discharged from the stomach once the medicine has been released. As a result, GRT increases and variations in plasma medication concentrations are better controlled. Non-effervescent and effervescent floating systems are the two types of floating systems. [5, 6]

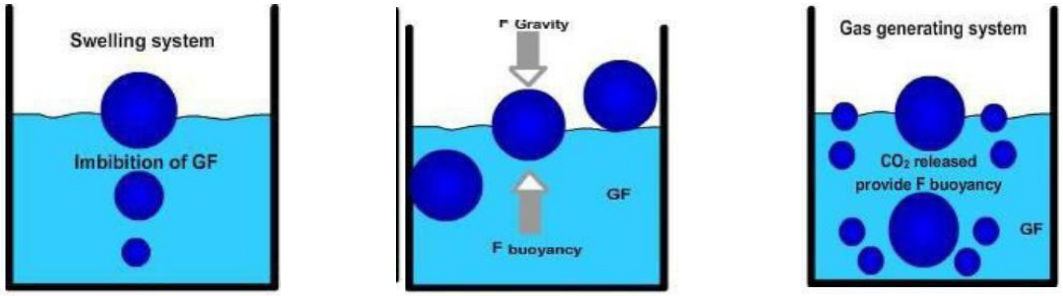


**Figure 1: Mechanism of Floating System.**

**Advantages of FDDS:**

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

- Improved drug absorption because of increased GRT and more time spent by the dosage form at its absorption site.
- Controlled delivery of drugs.
- Delivery of drugs for local action in the stomach.
- Minimizing the mucosa irritation due to drugs, by drug releasing slowly at controlled rate.
- Treatmentofgastrointestinaldisorderssuchasgastro-esophagealreflux.
- Simple and conventional equipment for manufacture.
- Ease of administration and better patient compliance.
- Site-specific drug delivery.[7]

**Ciprofloxacin:**

Ciprofloxacin is commonly known as broad spectrum antibiotic against both gram positive and gram negative bacteria. It is prescribed in treatment of respiratory and urinary tract infections. Conventionally Ciprofloxacin tablets have been used from the treatment of bacterial infections. It is an acidic drug which is majorly absorbed in stomach. The bioavailability of Ciprofloxacin is 69% and its half life is 4 hours. The Ciprofloxacin HCl floating tablets is proposed.

- To improve half life which shows prolongs action of drug in controlled manner for long period in stomach.
- To increase bioavailability of drug by increasing gastric residue time.
- Ciprofloxacin floating tablets are used to decrease dose frequency of drug also avoid fluctuations that cost by conventional tablets and also it helps to reduce the adverse effects caused by ciprofloxacin at higher doses.[8]

**Mechanism of Action:**

Ciprofloxacin HCl drug has *in vitro* activity against a wide range of gram negative and gram positive organism. Ciprofloxacin inhibits bacterial DNA gyrate, an enzyme Responsible for countering excessive super coiling of DNA during replication of transcription. But the mechanism action of Ciprofloxacin is different from other antimicrobial agents such as Beta lactum, tetracycline, amino glycosides therefore organism resistant to these drug may susceptible to Ciprofloxacin Hcl drug. [9]

**Factorial Optimization of Ciprofloxacin in HCl Floating Tablets**

To understand the influence of formulation variables on the quality of formulations with a minimal number of experimental trials and subsequent selection of formulation variables to develop an optimized formulation using established statistical tools for optimization. [10]

**METHODOLOGY**

**Preformulation Studies:**

The Preformulation studies are conducted to establish the physiochemical characteristics of the drug and its compatibility with the excipients used. The Preformulation studies are necessary to formulate drug into stable, safe and effective dosage form.

**Compatibility studies:**

The drug and excipients selected for the formulation are evaluated for physical and chemical compatibility studies.

**Drug–Excipients interaction study by FTIR:**

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of a mixture there by we can study incompatibility with two compounds. Compatibility in between both drug and excipients. The IR spectra of the test samples were obtained by Pressed Pellet technique using Potassium bromide. [11, 12]

**Construction of Calibration Curve Ciprofloxacin HCl:**

From the standard solution aliquots of2ml, 4ml,6ml, 8ml,10mlwerepipetteout to 100 ml standard measuring flask and made up to 100 ml with 0.1 N HCl. The absorbance of the above solutions was measured in UV-spectrophotometer at λmax 277 nm using 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-axis and Absorbance on Y-axis, which gives a straight line which indicates the drug, is pure and obeys the Beers lamberts Law.

**Formulation of Ciprofloxacin HCl Floating Tablet:**

The proposed formulation of Ciprofloxacin HCl was prepared using Design expert 10 using HPMC K4M, Eudragit 100S and Guar gum as variable and the formulate on design is given in the figure 7 and table.7.

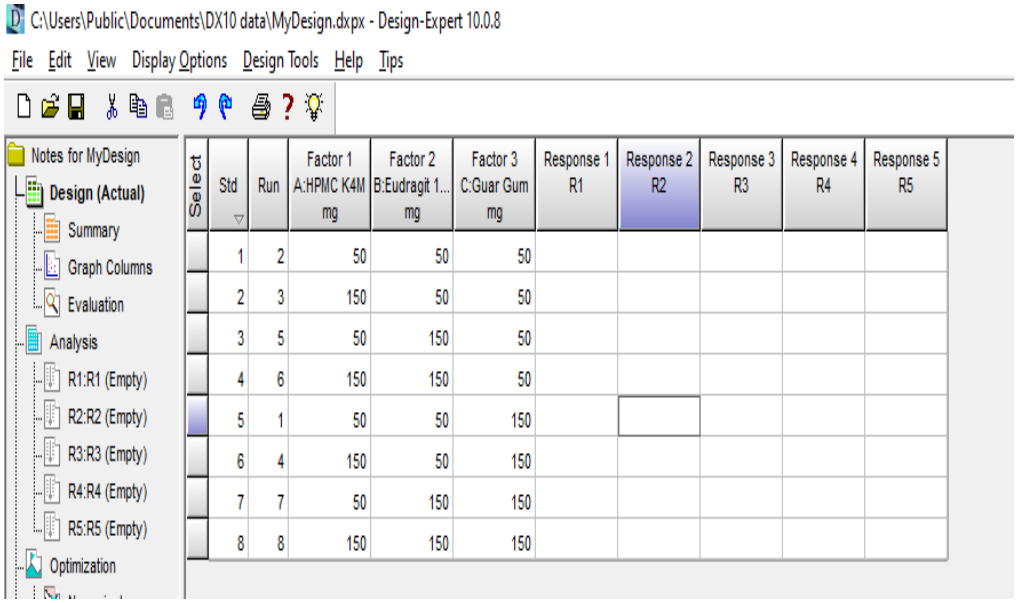


**Figure 2:DesignExpert10ReponsesofFormulationDesign.**

**Table 1: Formulation Design of Ciprofloxacin HCl Floating Tablet.**

| Formulation (mg) | CF1 | CF2 | CF3 | CF4 | CF5 | CF6 | CF7 | CF8 |
|---|---|---|---|---|---|---|---|---|
| Ciprofloxacin HCl | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| HPMCK4M | 50 | 150 | 50 | 150 | 50 | 150 | 50 | 150 |
| Eudragit100S | 50 | 50 | 150 | 150 | 50 | 50 | 150 | 150 |
| Guar Gum | 50 | 50 | 50 | 50 | 150 | 150 | 150 | 150 |
| Sodium bicarbonate | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Citric acid | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Starch mucilage | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Magnesium sterate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Lactose | 300 | 200 | 200 | 100 | 200 | 100 | 100 | 0 |

**Preparation of Ciprofloxacin HCl Floating Tablet:**

Floating tablets of Ciprofloxacin HCl were prepared by wet granulation technique using various polymers like HPMC K4M, Eudragit100S, Guar gum with combination of sodium bicarbonate and citric acid as gas generating agent. The composition of each formulationis given in formulation table no - 7. Totally Eight batches of granules were prepared

1. Ciprofloxacin Hcl is passed through sieve no.20.
2. HPMCK4M, Eudragit100S, Guargum, sodiumbicarbonate, citricacidpassed through sieve no.40.
3. Magnesium stearateispassedthroughsieveno60.
4. The shifted materials of Ciprofloxacin HCl was geometrically mixed with polymer and sodium bicarbonate and citric acid and blended for 10 minutes.
5. Then starch mucilage was added slowly drop wise manner to form a coherent mass.
6. Theformedcoherentmasswassievedmanuallythroughsieveno.16toform granules.
7. Then the granules are collected and dried in hot air oven at 40ºC±2ºC for 2hours.
8. The dried granuleswerepassedthroughsieveno.20.
9. Magnesium stearate is added to the dried granules then subjected to pre compression studies.
10. After the completion of compression studies, the granules of all formulations were compressed into tablets by using tablets punching machine.

**Pre Compression Parameter:**

**Bulk Density (ρb):**

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder. This initial volume was called the 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 formula. [13]

$$\rho b = \frac{M}{Vb}$$

Where, **M** and **Vb** are mass of powder and bulk volume of the powder respectively.

**Tapped Density (ρt):**

Weighed powder sample was transferredtoa graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps (500). The tapped density was determined by the formula. [14]

$$\rho t = \frac{M}{Vt}$$

Where, **M** and **Vt** are mass of powder and tapped volume of the powder respectively.

**Angle of Repose (Θ):**

The flow properties were characterized in terms of Angle of repose, Carr's index and Hausner's ratio. For determination of Angle of Repose (Θ), the drug and the blends were poured through the walls of a funnel, which was fixed at a position such that its lower tip wasataheightofexactly2.0cmaboveahardsurface.Thedrugortheblendswere poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation. **[14]**

$$\theta = \tan^{-1}\frac{h}{r}$$

**Table 2: Flow Property.**

| FlowProperties | Angle of Repose(Θ) |
|---|---|
| Excellent | <25 |
| Good | 25-30 |
| Fair/Reasonable | 30-40 |
| Flow with difficulty | >40 |

**Carr's Index Or %Compressibility:**

It indicates powder flow properties. It is measured for determining the relative importance of interparticulate interactions. [14]

$$\text{CI} = \frac{\rho t - \rho b}{\rho t} X\ 100$$

**Hausner's Ratio:** Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula. [14]

$$\text{HR} = \frac{\rho t}{\rho b}$$

Where, **ρt** and **ρb** are tapped density and bulk density respectively.

**Weight Variation:**

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated.

**Hardness test:**

Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken.

**Friability test:**

Friability is the loss of weight of tablet in the container/package due to removal of fine particles from the surface. This test is applicable to compressed tablets and is intended to determine the physical strength of tablets. [15, 16]

**Estimation of Drug Content:**

20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of Ciprofloxacin Hydrochloride was transferred in to a 100 ml volumetric flask and volume made up with 0.1N HCl. Further 1ml of the above solution was diluted to 10 ml with 0.1N HCl and absorbance of the resulting solution was observed at λmax 277 nm. [17]

**Floating test:**

The tablets were placed in a 100ml beaker containing 0.1N HCl. The time between introducing of dosage form and its buoyancy on 0.1N Hcl and the time during at which the dosage form remain buoyant were measured. [17]

**Buoyancy lag time:**

The time taken for the dosage form to emerge on surface of medium is Called Floating lag time (FLT). Total duration of time during which the dosage form remains buoyant is called Total floating time (TFT). [18]

***In Vitro* Dissolution Studies of Tablets:**

900ml of 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°C + 0.5°C. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was continued from 0 to 12 hrs at 50 rpm.

At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at λmax 277 nm using UV-spectrophotometer. [19]

**Factorial Optimization of Ciprofloxacin HCl Floating Tablets:**

To understand the influence of formulation variables on the quality of formulations with a minimal number of experimental trials and subsequent selection of formulation variables to develop an optimized formulation using established statistical tools for optimization.

Mathematical modeling, evaluation of the ability to fit to the model and response surface modeling were performed with employing Design-Expert® software (Version 10). In full factorial design, all the factors are studied in all the possible combinations. Hence, $2^3$ factorial designs were chosen for the current formulation optimization study. Totally eight tablet formulations were prepared employing selected combinations of the two factors as per $2^3$ Factorial and evaluated to find out the significance of combined effects of the two factor to select the best combination required to achieve the desired sustained release of Ciprofloxacin HCl tablet.[20,21]

**Table 3: Experimental Design.**

| **Factors: Formulation Variables** | **Levels (mg/tablet)** | |
|---|---|---|
| | -1 | +1 |
| HPMCK4M | 50 | 150 |
| Eudragit100S | 50 | 150 |
| Guar gum | 50 | 150 |
| **Response** | **Goal** | |
| Time taken for drug releaseat 50% | Minimize | |
| Drugreleaseat12$^{th}$hour | Maximize | |

***In vitro* release kinetics**

To study the *in vitro* release kinetics of the optimized floating tablets, data obtained from *In vitro* dissolution study was plotted in various kinetic models. [22]

**Zero order equation:**

Time (The zero order release kinetics can be obtained by plotting cumulative % drug released Vs hours). It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$C=K_0t$$

Where, $K_0$=Zero order constant in Conc. /time

**First order equation:**

A graph was plotted with log% cumulative drug remaining Vs Time in hours.

$$Logic = logC_0 – Kt/2.303$$

Where, $C_0$= Initialdrugconcentration

K=Firstorderconstant

**Higuchi kinetics:**

A graph was plotted with %cumulative drug released Vs Square root of time.

$$Q= Kt_{1/2}$$

**Where,**

**K=** Constant reflecting design variable system (Differential rate constant)

**Hixson and Crowellerosion equation:**

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and Crowell erosion equation. A graph was plotted with cube root of % drug remaining Vs Time in hours. [23, 24]

$$Q^{1/3} – Q^{1/3} = KHC \times t$$

**Where,** $Q_t$=Amount of drug released at time t, Q0 = Initial amount of drug. **KHC=**Rate constant for Hixson Crowell equation

## RESULTS

### Preformulation Studies

### Physico Chemical Characterization of Ciprofloxacin HCl:

Ciprofloxacin HCl. raw material obtained from Hindustan chemicals pvt.ltd was tested as per in house specification and the results are listed in table 4. The drug source is identified and found complying with the specifications.

**Table 4: Characterization of Ciprofloxacin HCl.**

| S. No | Test | Specification | Results |
|---|---|---|---|
| 1 | Description | Faintly yellowish to light yellow crystalline powder | Complies |
| 2 | Solubility | Freely soluble in distilled water, Phosphate buffer pH 6.8 & 7.5 | Complies |
| 3 | Melting point | 255°C -257°C | 254°C -257°C |

### Chemical compatibility study by FTIR:

The physical and chemical state of polymers like HPMC K4M, Eudragit 100S, Guar gum and their admixture of polymer and drug used in Ciprofloxacin floating tablets prepared were studied by FTIR.

The samples for FTIR Spectral analysis were shown in table no.6 and peaks were shown in figure 8 to 15 and the interpretation of FTIR spectrum in table 14 to 21. The physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alterations of drug characteristics. From the result it was concluded that there was no interface of functional groups as principle peak of Ciprofloxacin Hydrochloride were found to be unaltered in the drug polymer physical mixture. The physical parameters of drug as well as excipients concluded that there was no change in peaks of admixture compared with drug which indicates that the drug and excipients are compatible.

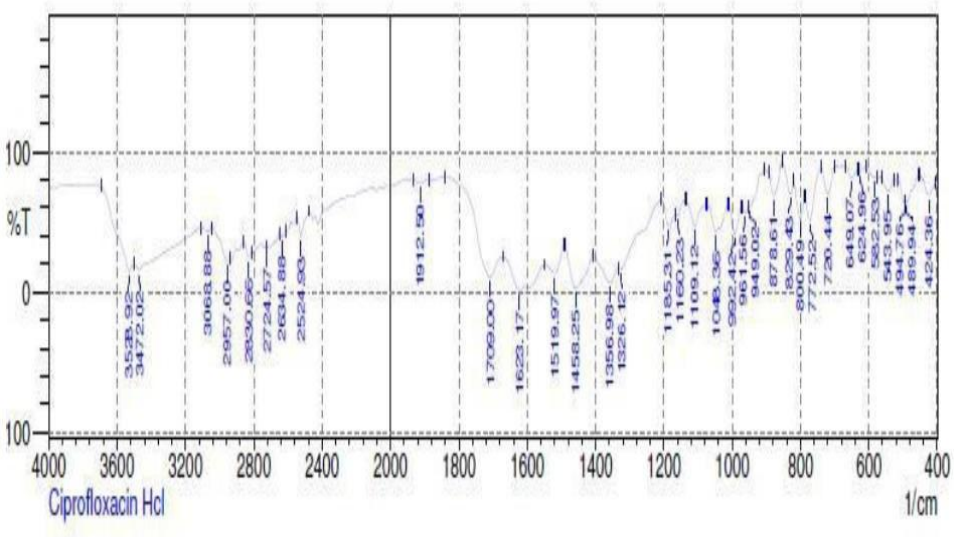


**Figure 3: FTIR of Ciprofloxacin HCl.**

**Table 5: FTIR Spectra Interpretation of Ciprofloxacin HCl.**

| S. No | Wavenumber$cm^{-1}$ | Interpretation |
|---|---|---|
| 1 | 1623.17$cm^{-1}$ | C=O carbonyl group |
| 2 | 1458.25$cm^{-1}$ | C-N Stretch |
| 3 | 3528.92$cm^{-1}$ | O-H Stretch |
| 4 | 3472.02$cm^{-1}$ | N-H Stretch |
| 5 | 2957.00$cm^{-1}$ | Aliphatic C-H Stretch |
| 6 | 2830.66$cm^{-1}$ | N-C Stretch |
| 7 | 1519.97$cm^{-1}$ | C=O Stretch of quinoline |

**Calibration curve of ciprofloxacin HCl:**
The calibration curve of Ciprofloxacin HCl in 0.1 NHCl.

**Table 6: Data for calibration curve of Ciprofloxacin HCl at λmax 277 nm.**

| Concentration(µg/mL) | AbsorbanceatλmaxnmCiprofloxacin HCl at λmax 277nm |
|---|---|
| 2 | 0.112 |
| 4 | 0.227 |
| 6 | 0.349 |
| 8 | 0.451 |
| 10 | 0.547 |

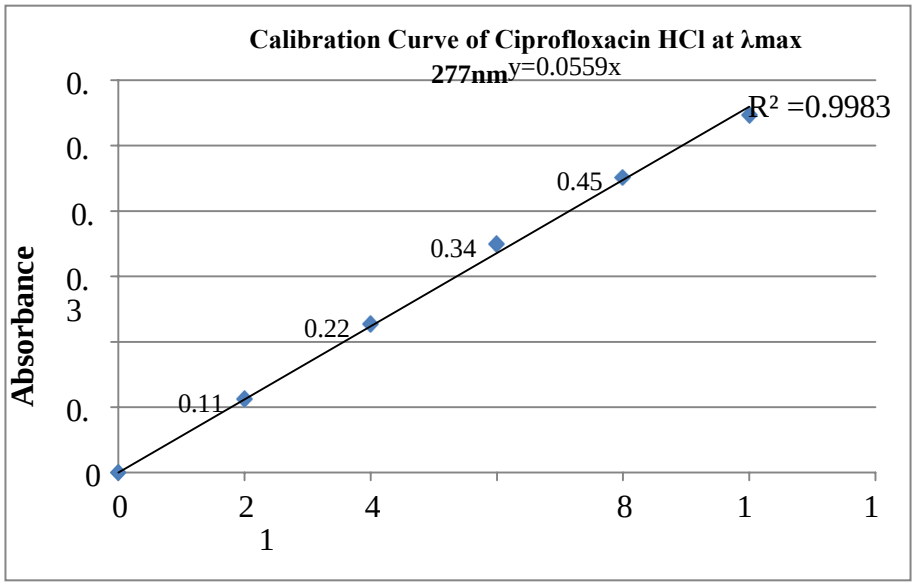


**Figure 4: Calibration curve of Ciprofloxacin HCl at λmax 277nm.**

It was found that the solution of Ciprofloxacin HCl show linearity ($R^2$ = 0.998) in absorbance at concentrations of 5 -25 (µg/mL) and obey Beer Lambert Law.

**Pre-compression study of ciprofloxacin HCl**
**Ciprofloxacin HCl Granules:**
The formulated blends of Ciprofloxacin HCl were evaluated for pre compression parameters.

**Table 7:Pre-compression of Ciprofloxacin HCl Granules.**

| Formulation | Bulk density (gm/ml) | Tapped density (gm/ml) | Compressibility index (%) | Hausner's ratio | Angle of repose(θ) |
|---|---|---|---|---|---|
| **CF1** | 0.314±0.012 | 0.342±0.013 | 14.54±0.62 | 1.11±0.01 | 22.13±1.02 |
| **CF2** | 0.329±0.018 | 0.352±0.012 | 15.39±0.71 | 1.12±0.01 | 21.27±1.03 |
| **CF3** | 0.374±0.011 | 0.392±0.009 | 15.47±0.79 | 1.16±0.02 | 26.44±0.74 |
| **CF4** | 0.393±0.009 | 0.421±0.012 | 14.39±0.72 | 1.17±0.02 | 24.37±0.81 |
| **CF5** | 0.367±0.013 | 0.392±0.016 | 15.74±0.45 | 1.15±0.01 | 26.42±1.45 |
| **CF6** | 0.392±0.012 | 0.417±0.009 | 15.82±0.51 | 1.18±0.02 | 23.15±1.32 |
| **CF7** | 0.314±0.019 | 0.365±0.011 | 15.14±0.47 | 1.16±0.02 | 25.33±1.12 |
| **CF8** | 0.390±0.021 | 0.411±0.017 | 14.87±0.82 | 1.15±0.01 | 24.72±0.78 |

The granules of Ciprofloxacin HCl floating tablets were prepared by wet granulation technique. The prepared granules are subjected to preformulation studies by following methods.

**Bulk density:**
Bulk density of all the granules was measured by using measuring cylinder method and the resultant values was found in the range of 0.314-0.393 g/cm. It showed that the bulkiness is within the acceptable limits.

**Tapped density:**

The tapped density of all granules was determined by tapping the Measuring cylinder for required times and the values were noted in table and the tapped density values were found in the range of 0.342-0.421 g/cm. The result proven that the tapped density values are within the acceptable limits.

**Compressibility index:**

The compressibility of granules are done by tapped density minus bulk density and divided with tapped density values and there values are in the range of 14.39-15.82. It indicates that the granules showed good flow properties.

**Hausner's ratio:**

It is the ratio of tapped density value to bulk density value and the resultant values of Hausner's ratio of all the formulations is between 1.11-1.18 which indicates that the granules shows good flow.

**Angle of repose:**

The granules of all seven formulations are subjected to angle of repose by funnel method. The value of angle of repose was found in the range of 21º27′-26º44′. The result proved that the granules of all formulations showed excellent flow properties.

**Post Compression Study of Ciprofloxacin HCl Floating Tablet:**

The formulated Ciprofloxacin HCl Floating Tablets were evaluated for post compression parameters. The results of weight variation, thickness, hardness, friability and assay.

**Table 8: Post Compression of Ciprofloxacin HCl Floating Tablets.**

| Formulation | Weight Variation (mg) | Thickness (mm) | Hardness (kg/cm$^2$) | Friability (%) | Assay (%w/w) |
|---|---|---|---|---|---|
| **CF1** | 798±2.0 | 3.38±0.11 | 3.17±0.13 | 0.32±0.12 | 97.14±0.31 |
| **CF2** | 811±5.0 | 3.40±0.15 | 3.44±0.11 | 0.41±0.11 | 100.10±0.14 |
| **CF3** | 823±7.0 | 3.38±0.13 | 3.43±0.18 | 0.36±0.13 | 99.13±0.43 |
| **CF4** | 794±4.0 | 3.35±0.17 | 3.38±0.17 | 0.40±0.11 | 101.12±0.15 |
| **CF5** | 813±8.0 | 3.40±0.16 | 3.24±0.12 | 0.49±0.09 | 100.34±0.27 |
| **CF6** | 794±7.0 | 3.41±0.15 | 3.44±0.14 | 0.42±0.07 | 98.22±0.17 |
| **CF7** | 816±5.0 | 3.35±0.22 | 3.37±0.16 | 0.41±0.05 | 99.61±0.31 |
| **CF8** | 820±4.0 | 3.43±0.17 | 3.32±0.14 | 0.42±0.12 | 101.11±0.12 |

**General appearance:**

The formulated tablets were evaluated for organoleptic characters. The tablets are circular in shape, yellowish in color, with no characteristic odor. All tablets showed elegance in appearance.

**Weight variation test:**

The weight variation of tablets was done by weighing the individual tablet weight and the average weight of 20 tablets which were selected randomly from each formulation batches. No more than two tablets should go more than the preferred deviation. The percentagedeviationis5%formorethan130mgtabletsandhereactual weight of tablet is 800 mg. So the acceptable deviation was 5%, thus all formulation passes the test.

**Thickness:**

The thickness of Ciprofloxacin HCl floating tablets were measured by using Vernier calipers. Thickness must be controlled to facilitate packaging. The result showed that the tablets of all the formulations show uniform thickness.

**Hardness test:**

The hardness of Ciprofloxacin HCl floating tablets were measured by Monsanto hardness tester and the values were tabulated in table. The hardness of all tablets in all formulations was within the range, So all formulated tablets passes the test.

**Friability test:**

The friability of Ciprofloxacin HCl floating tablets were performed by using Roche friabilator and the friability of all formulated tablets was within 1%. It proved that all formulations are within the acceptable limits.

**Drug content (%):**

The percentage of drug content were done by dissolving individual tablet in 0.1N HCl and transferred to a 100ml volumetric flask. The absorbance of the resulting solution is measured by Ultraviolet Spectroscopy at 277nm. As per IP, the content uniformity should beintherangeof90-110%.Theresultshowed that the percentage of Ciprofloxacin HCl in all formulations was ranging from 97.14-101.12%. It released that the drug is uniformly dispersed in the formulation and confirms the homogeneous mixing of the drug and the polymer. So all the formulated tablets passes the test.

**Buoyancy lag time:**

It is the time taken during which of dosage form remains buoyant on 0.1N HCl were measured and the values were listed in table.25 The buoyancy lag time values were found in the range of 134-172 sec.

**Table 9: Floating Lag time and Floating Time of Formulations.**

| S. No. | Formulation | Floating Lag Time (Sec) | Floating Time (hours) |
|---|---|---|---|
| **1** | **CF1** | 162 | 9.4 |
| **2** | **CF2** | 154 | 10.1 |
| **3** | **CF3** | 148 | 10.0 |
| **4** | **CF4** | 134 | 12.5 |
| **5** | **CF5** | 154 | 10.1 |
| **6** | **CF6** | 138 | 12.0 |
| **7** | **CF7** | 142 | 12.1 |
| **8** | **CF8** | 172 | 11.8 |

**Total floating time:**

It is the total duration of time during which the dosage form remains buoyant is measured and the values were ranges between 9.4-12.5 hrs which was noted in table.


At Initial Time: 0 Sec


At Floating Time: 2mins 49secs

**Figure 5: Floating Studies for Optimized formulation (CF4).**

***In-Vitro* dissolution:**

The dissolution studies of all eight formulation of Ciprofloxacin HCl floating tablets were shown in following tables no 26 and figure 18. The percentage drug release of all formulations after 12 hours using HPMC K4M, Eudragit 100Sand guar gum was found to be in the range of 80.85 to 99.69%.

From the *in-vitro* drug release, it was observes that the maximum drug release was found in formulation F4 is 99.69%. It shows that F4 formulation exhibits optimized drug release when compared with other formulation.

**Table 10:.In-vitro Dissolution of Ciprofloxacin HCl Floating Tablets.**

| Time (hrs) | CF1 | CF2 | CF3 | CF4 | CF5 | CF6 | CF7 | CF8 |
|---|---|---|---|---|---|---|---|---|
| 1 | 9.32 | 10.79 | 17.45 | 19.68 | 7.55 | 8.85 | 24.07 | 7.15 |
| 2 | 11.3 | 13.21 | 27.21 | 30.97 | 9.33 | 11.99 | 38.97 | 9.57 |
| 3 | 20.59 | 22.45 | 34.15 | 36.18 | 21.78 | 18.38 | 45.75 | 16.96 |
| 4 | 26.9 | 28.5 | 42.45 | 44.52 | 28.76 | 23.5 | 53.56 | 23.79 |
| 5 | 31.67 | 35.23 | 47.38 | 49.22 | 39.84 | 31.98 | 59.03 | 30.25 |
| 6 | 39.56 | 44.32 | 54.23 | 56.79 | 46.7 | 39.6 | 65.77 | 39.57 |
| 7 | 48.99 | 51.54 | 63.85 | 61.89 | 54.49 | 48.97 | 71.28 | 46.68 |
| 8 | 56.51 | 59.77 | 69.67 | 67.5 | 63.57 | 57.65 | 77.15 | 53.97 |
| 9 | 60.57 | 64.17 | 75.54 | 73.45 | 72.49 | 66.8 | 82.65 | 65.1 |
| 10 | 72.5 | 72.15 | 79.75 | 78.31 | 78.12 | 70.69 | 88.5 | 71.78 |
| 11 | 81.83 | 84.7 | 83.4 | 85.66 | 83.87 | 79.25 | 91.8 | 75.37 |
| 12 | 83.18 | 86.69 | 87.69 | 99.69 | 88.51 | 82.68 | 95.35 | 80.85 |

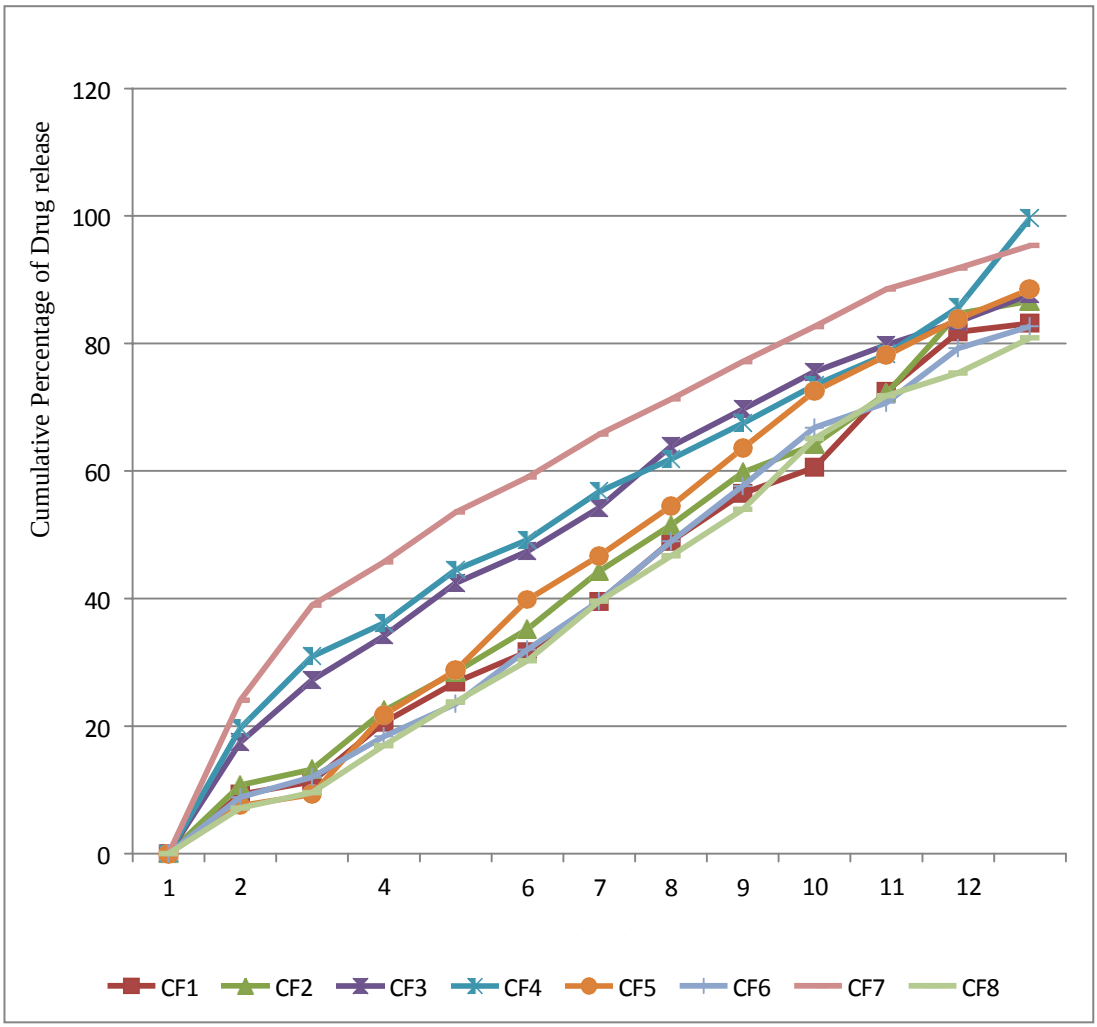


**Figure 6: .In-vitro dissolution of Ciprofloxacin HCl Floating formulations.**

**Optimizationby3$^2$FactorialDesign:**

On the basis of defined constraints for each independent variable, the Design Expert® Software version 10 automatically generated the optimized formulation. The experiments were performed and the responses were obtained.

**Table 11:.Result of Independent Variable and Dependent Variable according to 2$^3$ Factorial.**

| Run | Factor 1 | Factor 2 | Factor 3 | Response 1 | Response 2 |
|---|---|---|---|---|---|
| | HPMC K4M mg/tablet | Eudragit 100S mg/tablet | Guar Gum mg/tablet | Timetakenfor50 % drug release (minutes) | %Drug release at 12 hours |
| 1 | 50 | 50 | 50 | 445 | 83.18 |
| 2 | 150 | 50 | 50 | 414 | 86.69 |
| 3 | 50 | 150 | 50 | 342 | 87.69 |
| 4 | 150 | 150 | 50 | 312 | 99.69 |
| 5 | 50 | 50 | 150 | 388 | 88.51 |
| 6 | 150 | 50 | 150 | 456 | 82.68 |
| 7 | 50 | 150 | 150 | 212 | 95.35 |
| 8 | 150 | 150 | 150 | 437 | 80.85 |

**Time taken for 50% drug release:**

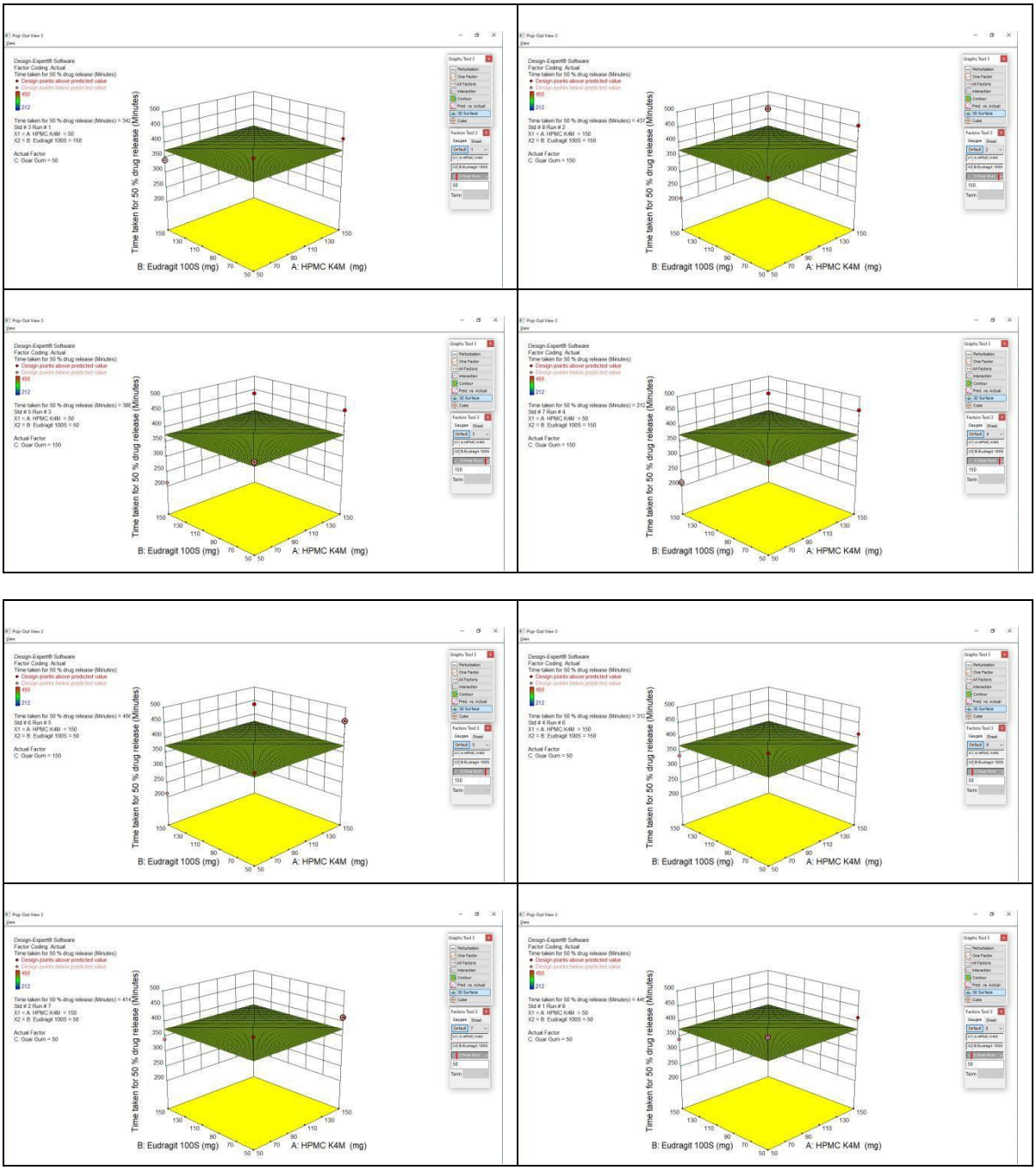


**Figure 7:.Effect of HPMC K4M, Eudragit 100S and Guar Gum on time taken for 50% drug release presented by response surface plots.**

The Fig illustrates, when the amount of HPMC increase, time taken for 50 percent drug release increased and time taken for 50 percent drug release increased when the amount of Eudragit 100S increase with respect to Guar gum.

**Drug release at 12hours:**

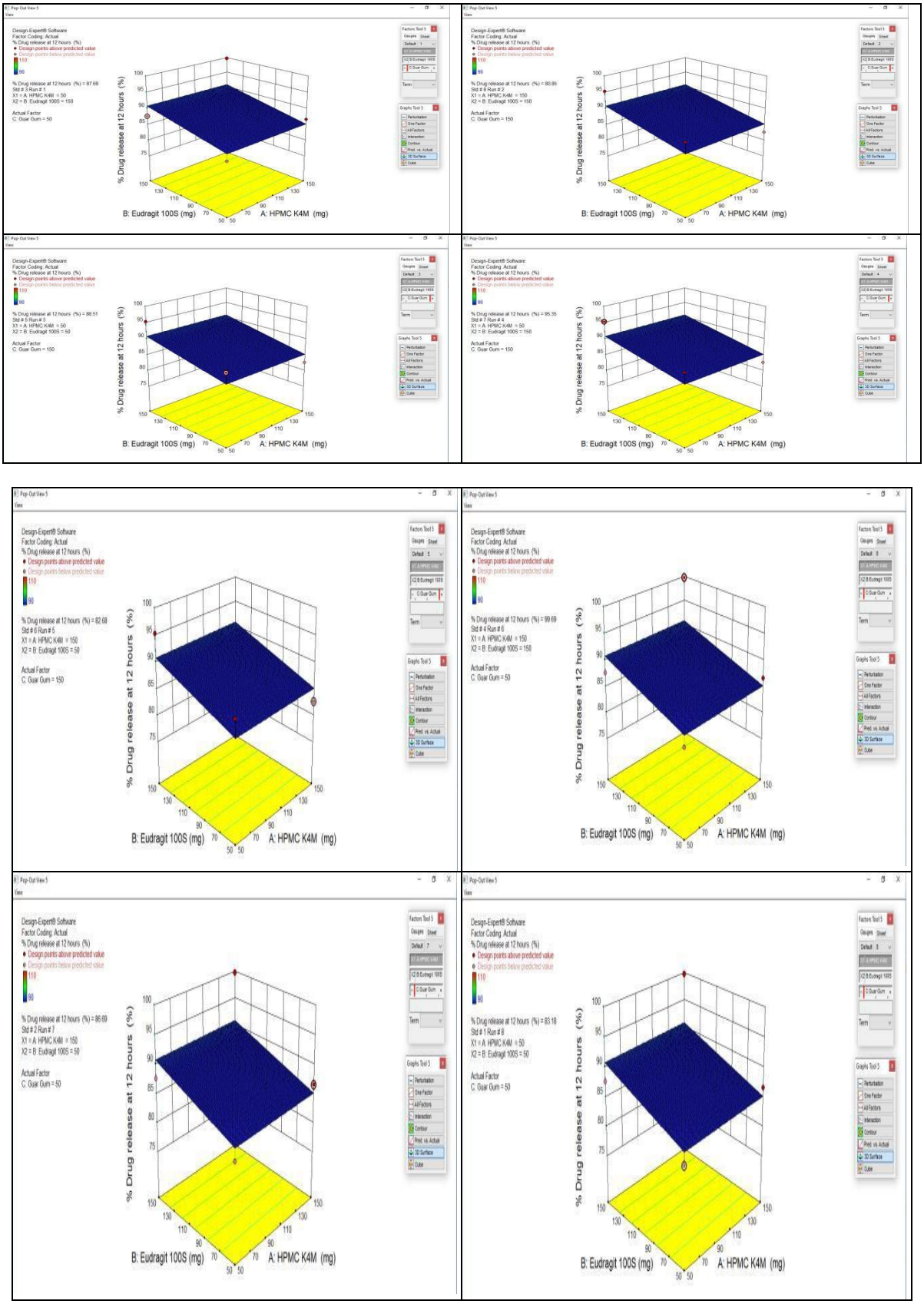


**Figure 8:.Effect of HPMC K4M, Eudragit 100S and Guar Gum on drug release at 12 hours presented by response surface plots.**

The Fig illustrates, when the amount of HPMC, increase, time taken for drug release at 12 hours release increased and time taken for drug release at 12 hours increased with when the amount of HPMC K4M,Eudragit 100S increase with respect to quantity of Guar Gum.

**Point prediction:**

The Ciprofloxacin HCl Floating tablets were formulated and responses were measured. The software generated the optimized formulation and predicts the response based on the constraint. Then batch was formulated based on the suggested formulation and responses were observed. The observed values of responses were compared to the predicted values of the response and % error was calculated to validate the method. The observed value of Y1 and Y2 were in a close agreement to the predicted one. By this the validity of optimization procedure was proven. The point prediction has been shown in the Table 29.

Desirability of optimum formulation was 0.946. When desirability value is between 0.8 and 1, the formulation quality is regarded to be acceptable and excellent. When this value is <0.53, the formulation quality is regarded as poor.

**Table 12.Optimum Formulation Derived by Factorial Design.**

| Factor | HPMC K4M | Eudragit 100S | Guar Gum | Desirability |
|---|---|---|---|---|
| **Optimum formulation** | 78.43 | 54.32 | 100 | 0.946 |

**Table 13: Point Prediction for Ciprofloxacin HCl Floating Tablets.**

| Point Prediction | Time taken for 50% drug Release | Drug release at 12 hours (min) |
|---|---|---|
| Predicted | 385.5 | 92.87 |
| Observed | 387.2 | 94.25 |
| %error | 0.44 | 1.48 |

% error= (observed value-predicted value) / predicted value 100

**Table 14: In-Vitro release of Optimized Ciprofloxacin HCl Floating Formulation.**

| Time | Optimized Formulation |
|---|---|
| 1 hour | 20.56 |
| 2 hour | 34.42 |
| 3 hour | 48.68 |
| 4 hour | 54.83 |
| 5 hour | 61.59 |
| 6 hour | 67.61 |
| 7 hour | 72.20 |
| 8 hour | 81.24 |
| 9 hour | 87.28 |
| 10 hour | 90.89 |
| 11 hour | 92.45 |
| 12 hour | 94.25 |

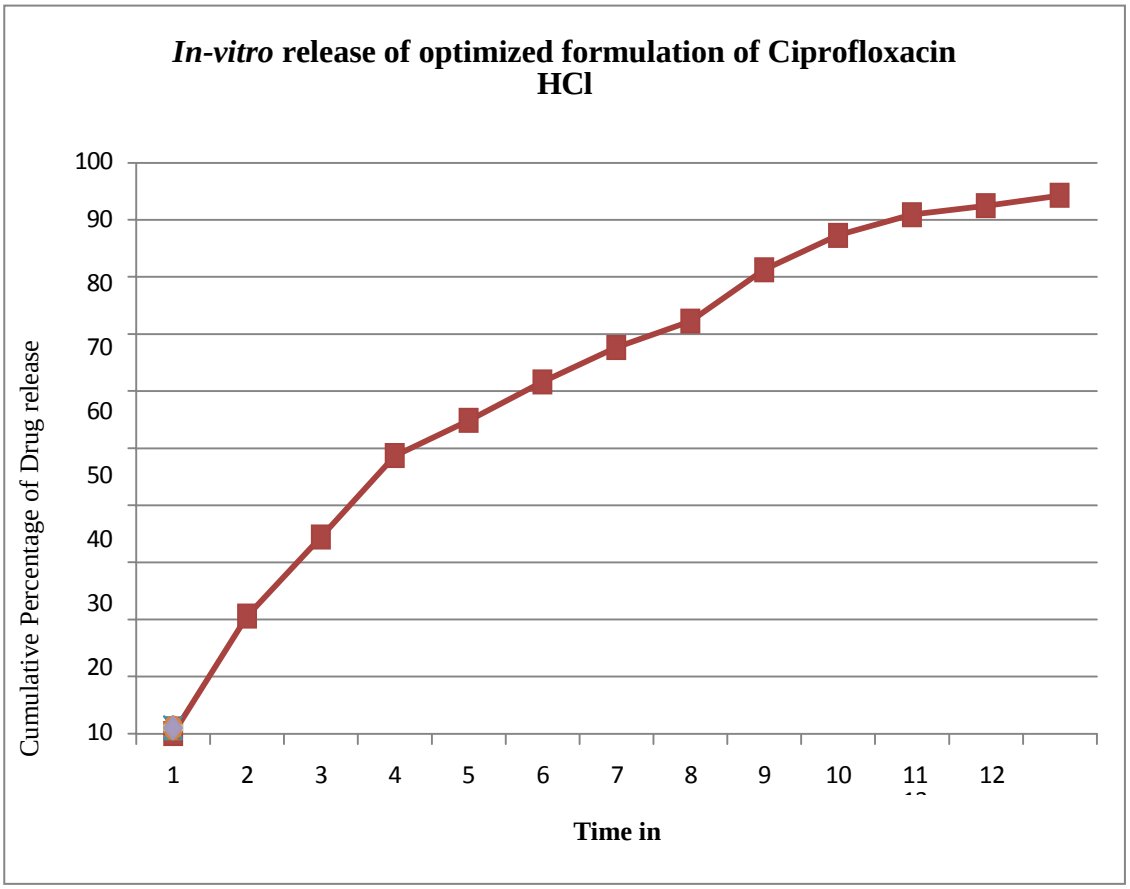


**Figure 9: In-vitro Release of Optimized of Ciprofloxacin HCl Floating Tablet.**

***In-Vitro* kinetics study of ciprofloxacin HCL floating Tablet**

The values obtained from *in vitro* dissolution of Ciprofloxacin HCl Floating tablets were fitted in various kinetics models.

**Table 15: In-vitro Release Kinetics of Ciprofloxacin HCl Floating Tablets.**

| Formulation | % Drug release | Zero order kinetics | First order Log % drug remaining | Higuchi Square root of Time | Pepas Log % of time | Hixon Cube root of drug Release |
|---|---|---|---|---|---|---|
| Optimized | 94.25 | 0.949 | 0.825 | 0.949 | 0.992 | 0.825 |

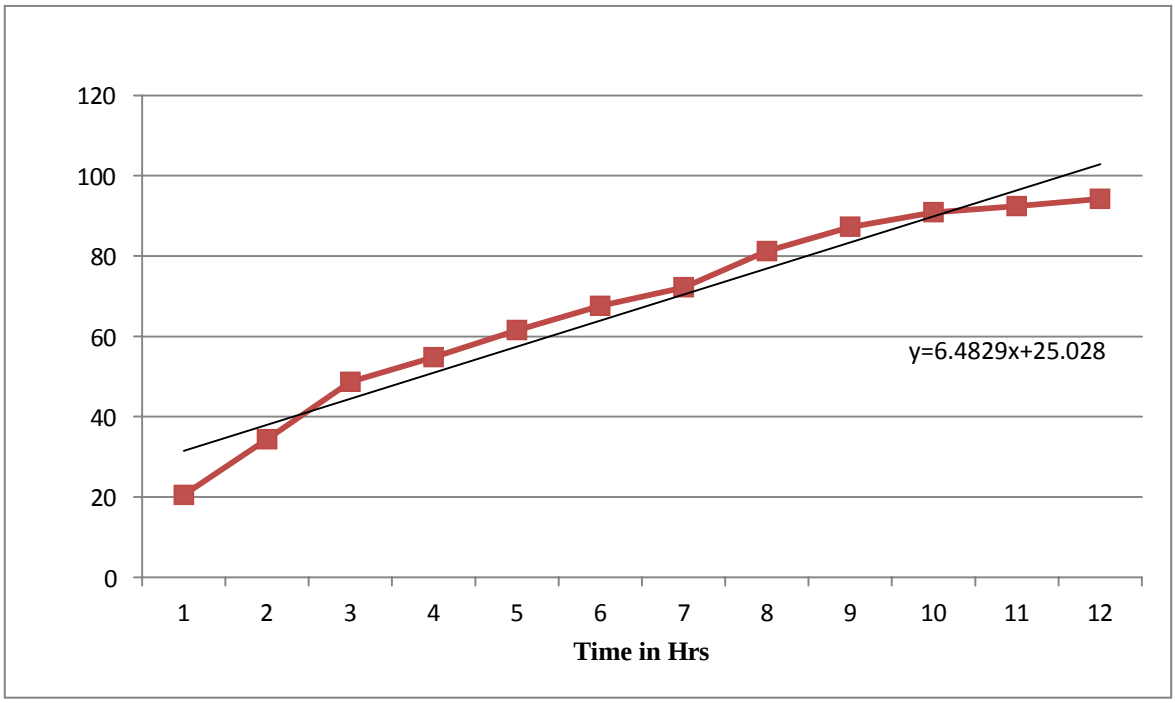


**Figure 10: Zero order Kinetics.**

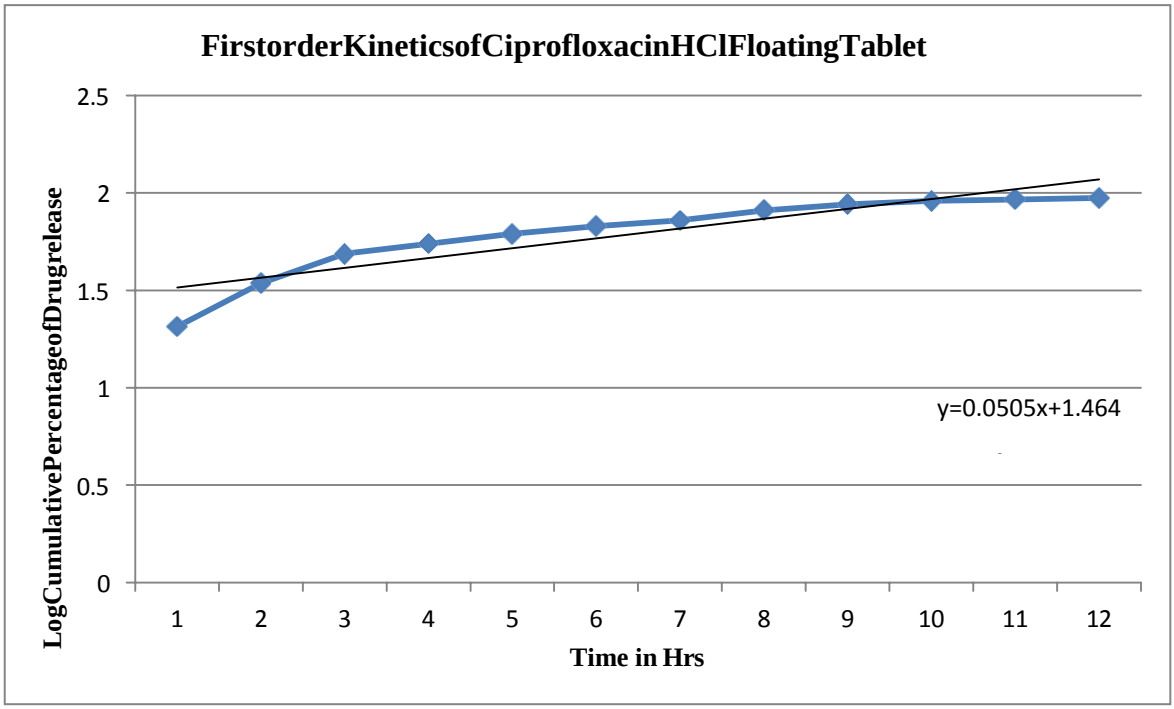


**Figure 11:.First Order Kinetic.**

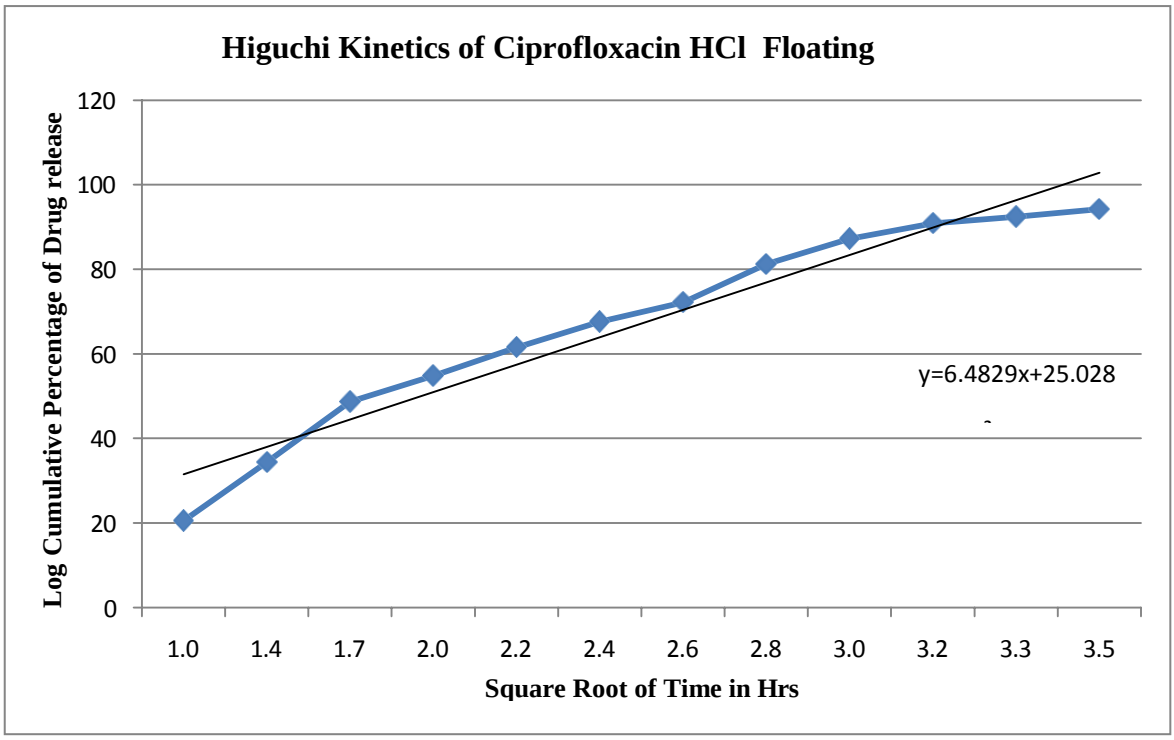


**Figure 12: Higuchi.**

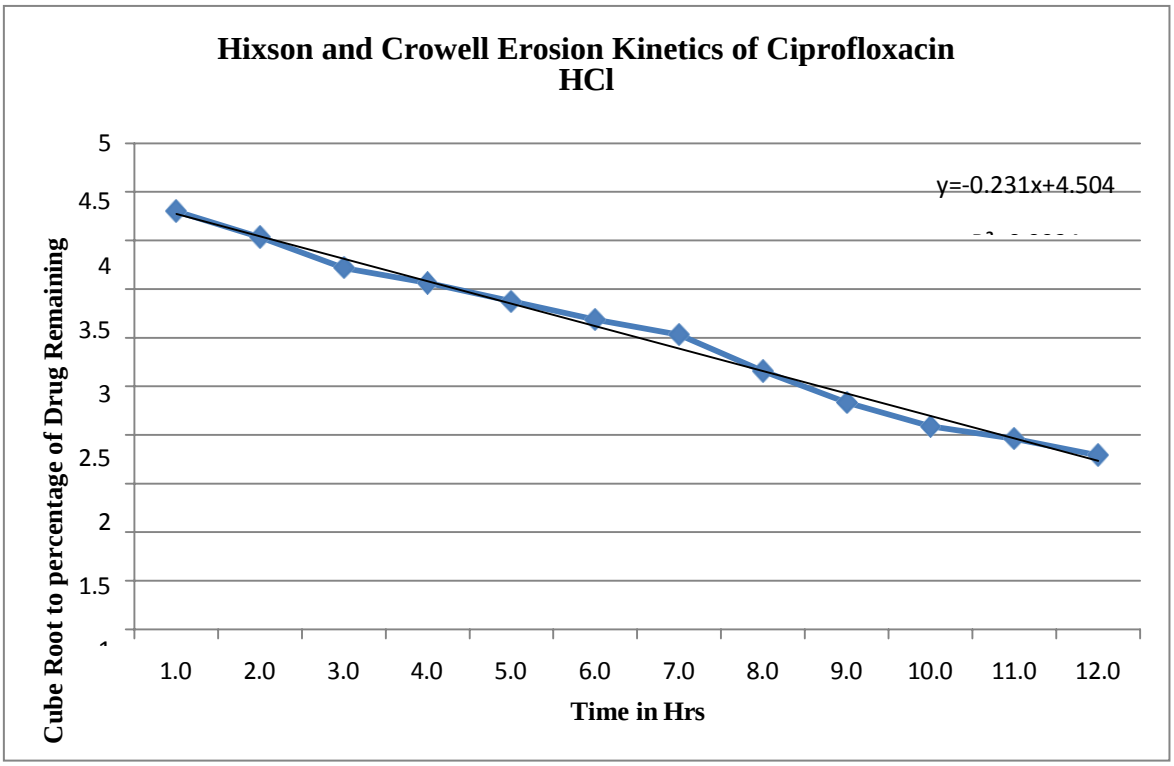


**Figure 13:.Hixoncrowell.**

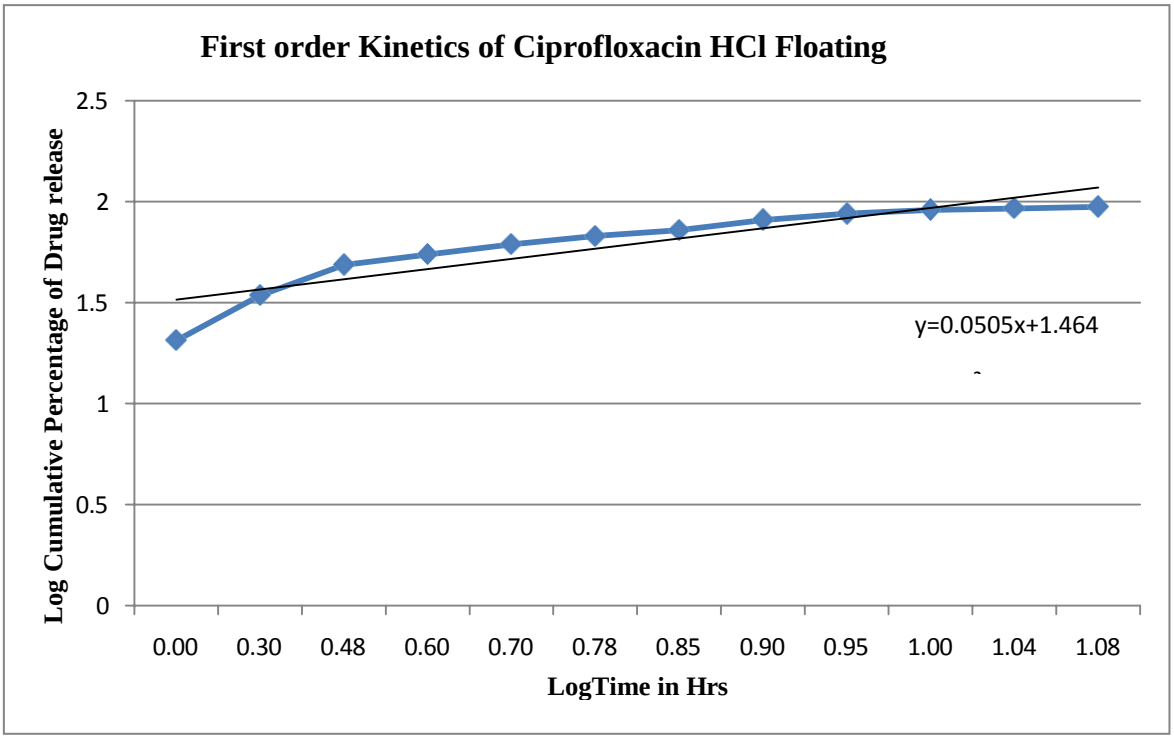


**Figure 14: Krosmeyar-Peppas.**

**Determination of drug release mechanism of optimized bilayer tablets**

- From the drug release kinetic study the results indicates that the in-vitro release of bilayer tablets is fitted with various models such as zero order kinetics, first order kinetics, Hixson crowell, krosmeyar- peppas .
- The models were evaluated based on the slope and regression ($R^2$) values, the respective $R^2$ and N values of models were given in the table 31.
- The in-vitro drug release of the optimized formulation is best fitted and found to follow Hixon crowell erosion kinetics with a higher $R^2$ value of 0.992.

## CONCLUSION

From the literature Ciprofloxacin HCl is an acidic drug and largely absorbed from the stomach, So the formulation of floating tablets of Ciprofloxacin HCl developed by using natural and synthetic polymer HPMC K4M, Eudragit 100S and guar gum with Sodium bicarbonate combination and citric acid as gas generating agent was achieve increased bioavailability. From the results of various formulations of Ciprofloxacin HCl floating tablet and it is optimized by 2 level factorial design. The optimized floating tablet prepared and the data obtained from in vitro release study for sustained release layer were fitted to various mathematical model like zero order, first order, Higuchi model and Peppas model. The results of mathematical model fitting of data obtained indicated that, the best fit model was Hixon crowell erosion kinetics.

## ABBREVATIONS

DOE : Design of Experiments;
API : Active Pharmaceutical Ingredients;
Vs : Versus; PBS: Phosphate buffer saline;
Pvt. Ltd. : Private limited; TEM: Transmission electron microscopy.

## AUTHOR'S CONTRIBUTIONS

This work is carried out in collaboration between all authors. Author Khushal managed the literature searches, designed the study and wrote the protocol. Author Dr. Revathi A. Gupta analysis of the study and approved the final manuscript.

## REFERENCES


1. Streubel A, Siepmann J, Bodmeier R. Drug delivery to the upper small intestine window using a stroretentive technologies. Curr Opin Pharmacol. 2006;6(5):501– 508.
2. WhiteheadL,FellJT,CollettJH.Developmentofagastroretentivedosageform. EurJPharm Sci. 1996; 4:182–182.
3. Hirtz J. The GIT absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol. 1985;19:77S–83S.
4. Larhed AW, Artursson P, Grasjo J. Diffusion of drugs in native and purified gastrointestinal mucus. J Pharm Sci. 1997;86(6):660–665.
5. Bardonnet PL, Faivre V, Pugh WJ. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. J Cont Release. 2006;111(1–2):1–18.
6. Hwang SJ, Park H, Park K. Gastric retentive drug delivery systems. Crit Rev Ther Drug Carrier Syst.1998;15(3):243–284.
7. Felipe JO, Varum HA, Merchant Basit AW. Oral modified–release formulations in motion:Therelationshipbetweengastrointestinaltransitanddrugabsorption. IntlJ Pharm. 2010;395(1–2):26–36.
8. Deshpande AA, Shah NH, Rhodes CT. Development of a Novel ControlledRelease System for Gastric Retention. J Pharm Res.1997;14(6):815–819.
9. Moes AJ. Gastroretentive Dosage forms. Crit Rev Ther Drug Carrier Syst. 1993;10(2):143–195.
10. Mahesh D, Chavanpatil Jain P, Chaudhari S, et al. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. Int J Pharmaceutics. 2006;316(1–2):86–92.
11. Klausner EA, Lavy E, Friedman M, et al. Expandable gastroretentive dosageforms. J Cont Release. 2003;90(2):143–162.
12. Singh BN, Kim H. Floating drug delivery system an approach to control drug delivery via gastric retention. J Controlled Release. 2000;63(3):235–259.
13. Arora S, Ali J, Ahuja A, et al. Floating Drug Delivery Systems: A Review. AAPS Pharm Sci Tech. 2005;6(3):372–390.
14. Desai S, Bolton S.. A Floating Controlled Release System: In–vitro and In–vivo evaluation. J Pharm Res. 1993;10(9):1321–1325.
15. Stockwell AF, Davis SS, Walker SE. In vitro evaluation of alginate gel system as sustained release drug delivery system. J Control Release. 1986;3(1-4):167–175.
16. Kawashima Y, Niwa T, Takeuchi H, et al. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci. 1992;81(2):135–140.
17. Choi BY, Park HJ. Preparation of alginate beads for floating drug delivery system: effect of $CO_2$gas forming agent. J Contolled Release. 2000;25(1-2):488–491.
18. Hilton AK, Deasy PB. In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxicillin trihydrate. Int J Pham. 1992;86(1):79–88.
19. Bhowmik D, Chiranjib B, Chandira M, et al. Floating Drug Delivery System: A Review. Der Pharmacia Lettre. 2009;1:199–218.
20. David SS. Theeffect of densityon the gastricemptyingon single and multipleunit dosage forms. J Pharm Res. 1986;3(4):208–213.
21. BechgaardH, Ladefoged K. Distribution of pellets in the gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets. J Pharm Pharmacol. 1978;30(11):690–692.
22. Seth PR, Tossounian J. The hydrodynamically balanced system, a novel drug delivery system for oral use. Drug Dev Ind Pharm. 1984;10:313– 339.
23. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patientswith gastritis and peptic ulceration. Lancet. 1984;1(8390):1311– 1315.
24. VakilN.HelicobacterpyloriEradication:SequentialandTraditionalTherapy. Gastroenterology&Hepatology. 2009;5:59–64.
25. ConwayBR.DrugdeliverystrategiesforthetreatmentofHelicobacterpylori infections.CurrPharmDes.2005;11(6):775–790.
26. Yang L. A New Intragastric Delivery System for the Treatment of H. pylori associated with gastriculcers. J of controlled Release.

1999; 57 (3) : 215–222.
27. Uma maheshwari RB, Jain S, Jain NK. A new approach in gastroretentive drug delivery system using cholestyramine. Drug Deliv. 2003;10(3):151– 160.
28. Uma maheshwari RB, Suman R, Jain NK. Anti Helicobacter pylori effect of mucoadhesive nanoparticle bearing amoxicillin in experimental gerbils. APPS Pharm Sci Tech. 2004;5(2):25–29.
29. Rajinikanth PS, Mishra B. Floating in situ gelling system for stomach site–specific delivery of clarithromycin to eradicate H. pylori. J Control Release. 2008;125(1):33–41.
30. Rajinikanth PS, Mishra B. Floating in situ gelling system of acetohydroxamic acid for clearance of H. pylori. Drug Dev Ind Pharm. 2008;34(6):577–587.
31. Katayama H,Nishimura T,Ochi S, et al. Sustained releaseliquid preparation using sodium alginate for eradication of Helicobacter pylori. Biol Pharm Bull. 1999;22(1):55–60.
32. Ruggiero P, Peppoloni S, Rappuoli R, et al. The quest for a vaccine against Helicobacter pylori: how to move from mouse to man? Microbes Infect. 2003;5(8):749–756.
33. Miller CJ, McChesney M, Moore PF. Langerhans cells, macrophages and lymphocyte subsets in the cervix and vagina of rhesus macaques. Lab Invest. 1992;67(5):628–634.
34. Mestecky J. The common mucosal immune system and current strategies for induction of immune responses in external secretions. J Clin Immunol. 1987;7(4):265–276.
35. Babiuk LA, Pontarollo R, Babiuk S, et al. Induction of immune responses byDNA vaccines in large animals. Vaccine. 2003;21(7-8):649–658.
36. Xie Y, Zhou NJ, Gong YF, et al. The immune response induced by H. pylori vaccine with chitosan as adjuvant and its relation to immune protection. World J Gastroenterol. 2007;13(10):1547–1553.
37. Van der Lubben IM, Verhoef JC, Borchard G, et al. Chitosan for mucosal vaccination. Adv Drug Deliv Rev. 2001;52(2):139–144.
38. Lin YH, Chang CH, Wu YS, et al. Development of pH–responsivechitosan/heparin nanoparticles for stomach–specific anti–Helicobacter pylori therapy. Biomaterials. 2009;30(19):3332–3342.
39. Jain P, Jain S, Prasad KN, et al. Polyelectrolyte coated multilayered liposomes (nanocapsules) for the treatment of Helicobacter pylori infection. Mol Pharm. 2009;6(2):593–603.
40. H.G.Sivakumar,FloatingDrugDeliverySystemforProlongedGastricResidence time: A review, Ind. J. Pharm. Edu., oct-dec-2004 P.311-316.
41. Roop K. Khar, Controlled Drug Delivery, Gastro retentive system 4th edn. P. 202- 203.
42. N.H Foda, S.M Ali, Gastro Retentive Drug Delivey System as a potential tool for enhancing the efficiency of antibiotics:AReviw, International Journal Of pharmaceuticals and Biosciences,(2011):P.94-104.
43. Rajinikanth PS, Blasubramaniam J, Mishra B, Development and evaluation of a novel floating insitu gelling system of Amoxicillin for eradicating of Helicobacter pylori; International journal of pharmacy, (2007) (335),P.114-122.
44. Whithead L, Collett JH, Fell JT; Amoxicillin release from a floating dosage form based on alginates, International journal of pharmaceutics,(2000) (210),P45-49.
45. Moes AJ. Gastro retentive Dosage forms. Crit. Rev. The Drug Carrier Syst. 1993; 10: 143-195.
46. S. J. Hwang, H. Park, K.Park, "Gastric retentive drug delivery systems." Crit. Rev.Ther.Drug Carrier Syst., 1998, 15, 243–284.
47. Gavin P. Andrews, Thomas P, laverty, David S. jones; Mucoadhesive Polymeric platforms for controlled drug delivery; Eur. J. Pharm. Bio-Pharm. (2008), doi:10.101016/j.ejpb.2008.09.028.
48. Talunkder R, Fassihi R: Gastro retentive drug delivey system; A mini Review, Drug Development and Industrial Pharmacy(2004);P(1019-1028.
49. TaleshVarshosaz, N.Tavakoli, F.Roozbahani; Formulation and invitro characterization of Ciprofloxacin and bioadhesive extended release tablets(2006),P.277-285.
50. AmitkumarNayak, RumaMaji, Biswarup Das,; Gastro retentive drug delivery system: A Review: Asian Journal Of Pharmaceutical and Clinical Research(2010),P. 2-10.
51. Mayavanshi A.V, Gajjar: Floating drug delivery system concept and advances: A Review,Research Journal of pharmacy and technology,(2008),1(4).
52. Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. Ciprofloxacin safety in paediatrics: a systematic review. Arch Dis Child. 2011;96(9):874-880. doi:10.1136/adc.2010.208843
53. Cipolla D, Blanchard J, Gonda I. Development of Liposomal Ciprofloxacin toTreat Lung Infections. Pharmaceutics. 2016;8(1):6. Published 2016 Mar 1. doi:10.3390/pharmaceutics8010006.
54. McShane PJ, Weers JG, Tarara TE, et al. Ciprofloxacin Dry Powder for Inhalation (ciprofloxacin DPI): Technical design and features of an efficient drug-device combination. Pulm Pharmacol Ther. 2018;50:72-79. doi:10.1016/j.pupt.2018.03.005
55. Schlender JF, Teutonico D, Coboeken K, et al. A Physiologically-Based Pharmacokinetic Model to Describe Ciprofloxacin Pharmacokinetics Over the Entire Span of Life. Clin Pharmacokinet. 2018;57(12):1613-1634. doi:10.1007/s40262-018-0661-6.
56. Santos VM, Carneiro MV, Cruz LR, Paixao GT. Drug-induced acute esophageal lesions and use of ciprofloxacin. An Sist Sanit Navar. 2012;35(1):127-131. doi:10.4321/s1137-66272012000100012
57. Nitzan O, Elias M, Peretz A, Saliba W. Role of antibiotics for treatment of inflammatory bowel disease. World J Gastroenterol. 2016;22(3):1078-1087. doi:10.3748/wjg.v22.i3.1078
58. Bassetti M, Vena A, Russo A, Peghin M. Inhaled Liposomal Antimicrobial Delivery in Lung Infections.Drugs. 2020;80(13):1309-1318. doi:10.1007/s40265- 020-01359-z

59. Singh I, Saini V. Formulation and optimization of floating matrix tablets of clarithromycinusingsimplex latticedesign. PakJ PharmSci.2016;29(2):511-519.
60. Fukuda M, Peppas NA, McGinity JW. Floating hot-melt extruded tablets for gastroretentive controlled drug release system. J Control Release.2006;115(2):121-129. doi:10.1016/j.jconrel.2006.07.018
61. Someshwar K, Chithaluru K, Ramarao T, Kumar KK. Formulation and evaluation of effervescent floating tablets of tizanidine hydrochloride. Acta Pharm. 2011;61(2):217-226. doi:10.2478/v10007-011-0015-5
62. Sathiyaraj S, Devi RD, Hari VB. Lornoxicam gastro retentive floating matrix tablets: Design and in vitro evaluation.J Adv Pharm Technol Res. 2011;2(3):156-162. doi:10.4103/2231-4040.85531
63. Bani-Jaber AK, Alkawareek MY, Al-Gousous JJ, Abu Helwa AY. Floating and sustained-release characteristics of effervescent tablets prepared with a mixed matrix of Eudragit L-100-55 and Eudragit E PO. Chem Pharm Bull (Tokyo). 2011;59(2):155-160. doi:10.1248/cpb.59.155.


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