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

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## ABSTRACT
Ciprofloxacin HCl is a widely prescribed antibiotic, but its oral bioavailability can be compromised due to its limited solubility and absorption in the stomach. Floating tablets offer a promising solution to this problem by prolonging the drug's residence time in the gastric region. This study aimed to design, evaluate, and optimize a floating tablet formulation of Ciprofloxacin HCl using the Design Expert software. full factorial design was employed, with two independent variables, namely, the amount of sodium bicarbonate and the concentration of HPMC K4M. The dependent variables included the tablet's floating lag time, total floating time, drug release at 12 hours, and drug release at 6 hours. The results indicated that sodium bicarbonate and HPMC K4M had significant effects on the tablet's floating behavior and drug release. By using the Design Expert software, an optimized formulation was generated, and the desirability function was maximized. The optimized formulation exhibited a short floating lag time, prolonged floating duration, and controlled drug release, which can enhance the drug's bioavailability and therapeutic efficacy. In conclusion, this study demonstrated the successful formulation design, evaluation, and optimization of Ciprofloxacin HCl floating tablets using Design Expert. The optimized formulation showed promising attributes for controlled drug delivery, suggesting its potential application in the treatment of gastric infections. Further in vitro and in vivo studies are needed to confirm the clinical effectiveness of the developed formulation.

**KEYWORD:** Floating Tablet, ciprofloxin HCl, and design expert.

## INTRODUCTION
Over the past few years, advancements in research and development have focused on controlled rate oral drug administration systems. Oral bioavailability of drugs with a window of absorption in the upper gastrointestinal tract is typically restricted with dosage forms like tablets, capsules, and granules. These drugs can be delivered ideally by slow release from the stomach, providing a localized effect at the site of action. However, traditional extended release dosage forms have been found to have suboptimal absorption due to the transit time of the dosage form in the GI tract. To improve absorption and enhance bioavailability, sustained drug delivery systems with a prolonged residence time in the stomach can be used. Gastro-retentive dosage forms (GRDFs) are designed to be retained in the stomach for a prolonged time and release their active ingredients in a sustained manner. These systems can be classified into bioadhesive systems, expandable systems, floating systems, and high density systems. Bioadhesive systems bond to stomach epithelial cells or mucus, increasing the intimacy and length of contact between the GRDDS and the biological membrane.

Expandable systems are easily swallowable and reach a larger size in the stomach due to swelling or unfolding processes. These systems are known as "plug type systems" and are designed for gastric retention and regulated medication distribution into the stomach cavity. They have a high rigidity of the dose form to withstand peristalsis and mechanical contractility of the stomach, improving gastrointestinal receptivity.

Floating drug delivery systems have a lower bulk density than gastric fluids and remain buoyant in the stomach for an extended period without influencing gastric emptying rate. They are divided into two types: non-effervescent and gas-generating systems. Non-effervescent systems swell uncontrollably after swallowing, absorbing gastric juice to the point that it stops it from exiting the stomach. They are created by combining medication with a gel, which swells when it comes into contact with gastric

fluid after oral administration and maintains relative shape integrity.

Non-effervescent systems include colloidal gel barrier systems, microporous compartment systems, and alginate beads. Colloidal gel barrier systems use a medication with gel-forming hydrocolloids to keep the drug buoyant on the stomach content. Microporous compartment systems encapsulate a drug reservoir inside a microporous compartment, allowing the delivery system to float above the gastric content for continuous absorption. Alginate beads are created by combining sodium alginate solution with calcium chloride, resulting in a porous system capable of maintaining a floating force for over 12 hours.

Hollow microspheres loaded with medicine in their outer polymer shell were generated using a new emulsion solvent diffusion process. The medication and an enteric acrylic polymer ethanol/dichloromethane solution were placed into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally regulated at 40oC. The gas phase is established in the dispersed polymer droplet by the evaporation of dichloromethane formed in the polymer's interior cavity with drug. For more than 12 hours, the microballoon floated continuously across the surface of an acidic dissolving media containing surfactant.

Various types of effervescent systems have been developed, including gas-generating (effervescent) systems, high density systems, multiple unit type floating systems, ion exchange resins, and osmotic regulated systems. Gas-generating systems use matrices made of swellable polymers and effervescent components, while high density systems use sedimentation to hold pellets in the stomach folds. Ion exchange resins have stomach retentive effects, with a coated ion exchange resin bead formulation loaded with bicarbonates.

Gastro retentive delivery systems are increasingly being studied for their potential to improve oral drug absorption in the stomach, reducing dose frequency and increasing patient compliance.

## MATERIAL AND METHOD

**MATERIAL –** Eudragit, Guar Gum, Hydroxy Propyl Methyl Cellulose, Sodium Bicarbonate, Citric Acid, Ciprofloxacin HCl, HPMC K4M, Magnesium Stearate, Starch.

## METHOD

***Formulation of ciprofloxacin hcl floating tablet***

The proposed formulation of Montelukast sodium was prepared using Design expert 10 using HPMC K4M, Eudragit 100S and Guar gum as variable and the formulation design is given in the figure 1 and table1.

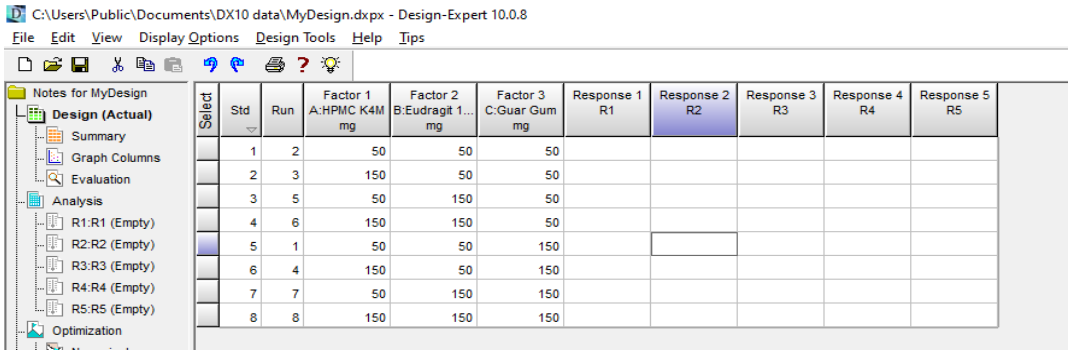


**Figure 1: Design Expert 10 Reponses of Formulation Design.**

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

| Formulation (mg) | CF1 | CF 2 | CF 3 | CF 4 | CF 5 | CF 6 | CF 7 | CF 8 |
|---|---|---|---|---|---|---|---|---|
| Ciprofloxacin HCl | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| HPMC K4M | 50 | 150 | 50 | 150 | 50 | 150 | 50 | 150 |
| Eudragit 100S | 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 formulation is given in formulation table no - 1. Totally Eight batches of granules were prepared

1. Ciprofloxacin Hcl is passed through sieve no.20,

2. HPMC K4M, Eudragit 100S, Guar gum, sodium bicarbonate, citric acid passed through sieve no.40.
3. Magnesium stearate is passed through sieve no 60.
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. The formed coherent mass was sieved manually through sieve no.16 to form granules.
7. Then the granules are collected and dried in hot air oven at 40ºC ± 2ºC for 2 hours.
8. The dried granules were passed through sieve no.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.

**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 be in the range of 90-110%. The result showed 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.

**Table 2: 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 |

**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.2 The buoyancy lag time values were found in the range of 134-172 sec.

**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.

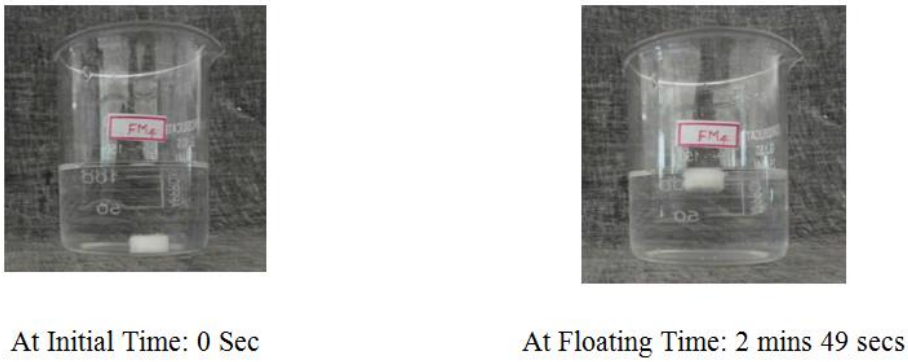


***Figure 2: Floating Studies for Optimized formulation (CF4).***

***In-vitro dissolution***

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile. 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. The dissolution studies of all eight formulation of Ciprofloxacin HCl floating tablets were shown in following tables no 3 and figure 3. 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 3: *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 |

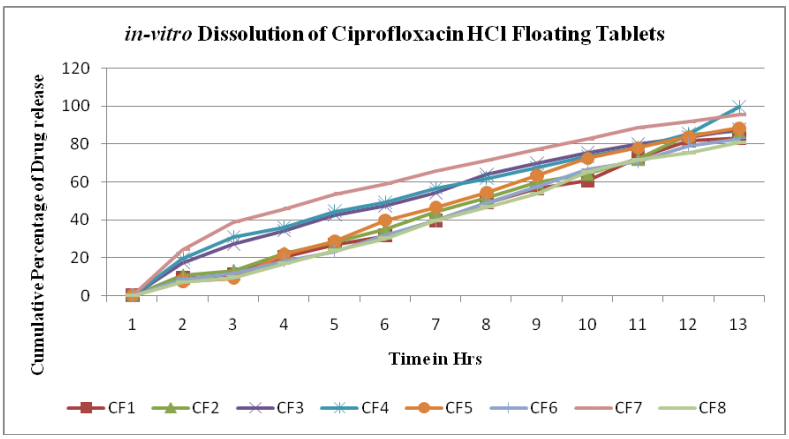


***Figure 3: In-vitro dissolution of Ciprofloxacin HCl Floating formulations.***

***Factorial Optimisation 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 a 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. 4.

**Table 4: Experimental Design.**

| **Factors: Formulation Variables** | **Levels (mg/tablet)** | |
|---|---|---|
| | -1 | +1 |
| HPMC K4M | 50 | 150 |
| Eudragit 100S | 50 | 150 |
| Guar gum | 50 | 150 |
| **Response** | **Goal** | |
| Time taken for drug release at 50% | Minimize | |
| Drug release at $12^{th}$ hour | Maximize | |

***Optimization by $3^2$ Factorial Design***

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 5: 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 | Time taken for 50 % 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**

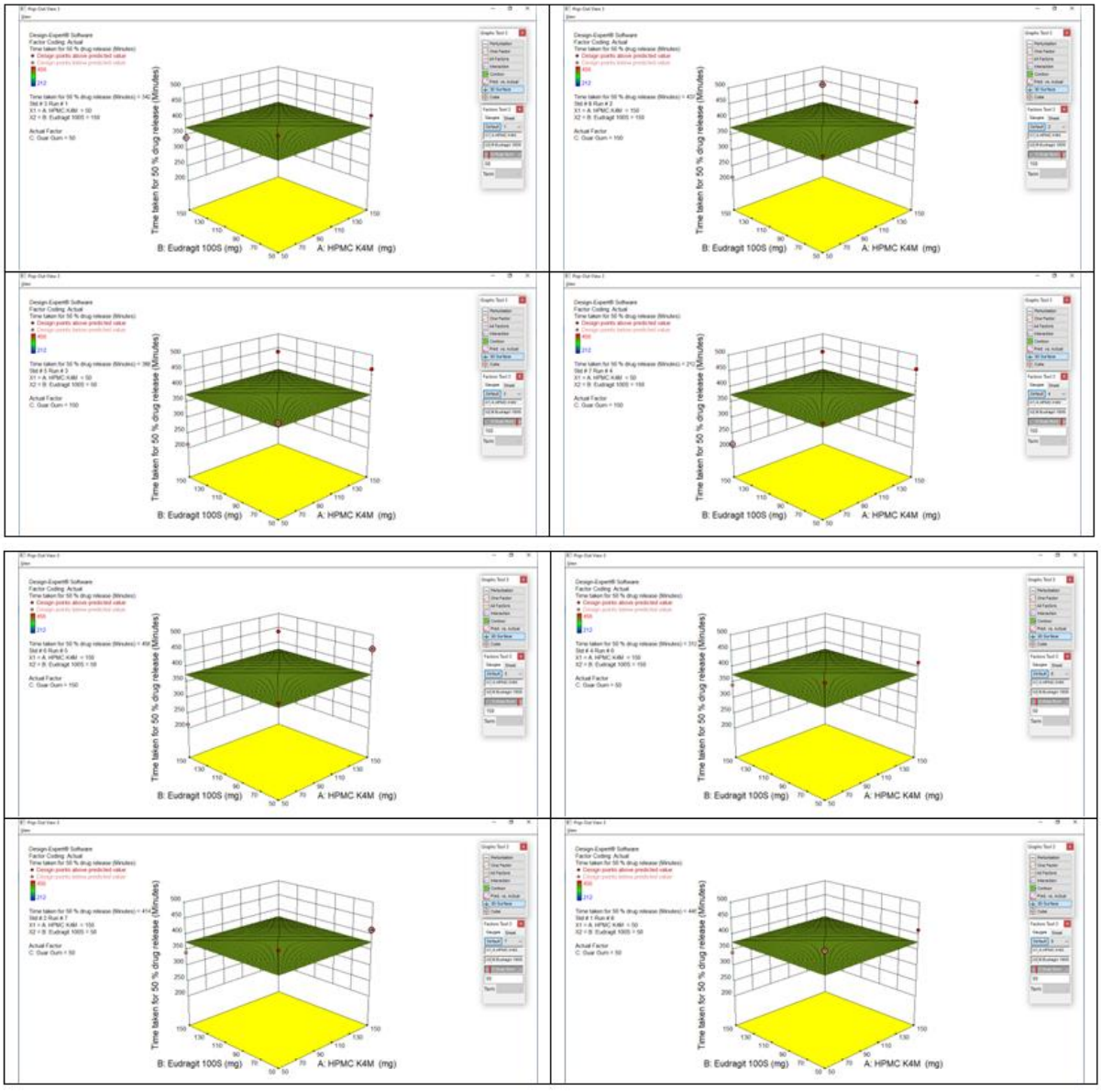


***Figure 4*: *Effect of HPMC K4M,Eudragit 100S and Guar Gum on time taken for 50% drug release presented by response surface plots.***

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 Guargum.

**Drug release at 12 hours**

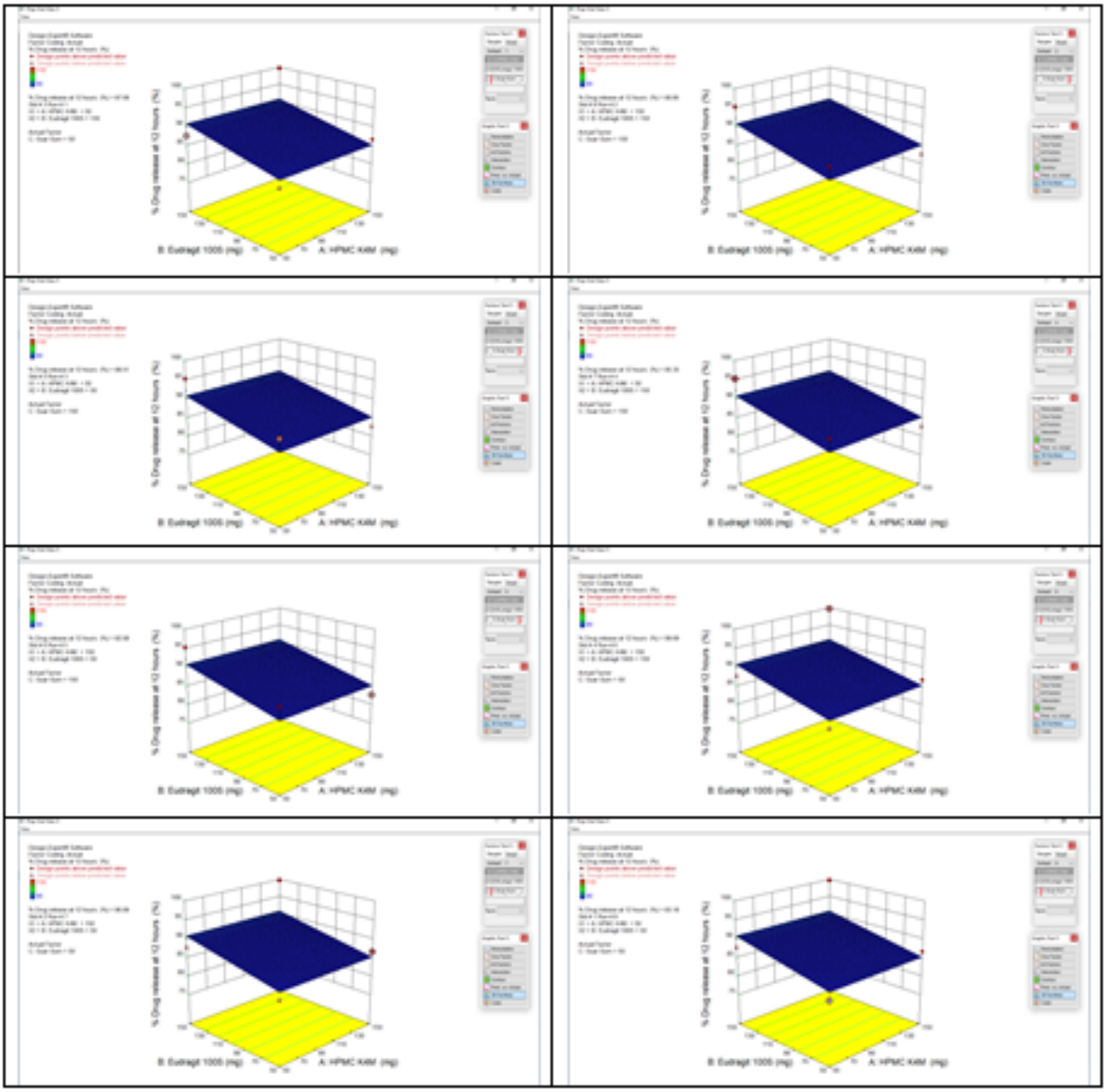

***Figure: 5. Effect of HPMC K4M, Eudragit 100S and Guar Gum on drug release at 12 hours presented by response surface plots.***

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 5.

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 6: Optimum Formulation Derived by Factorial Design.**

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

**Table 7: 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 x 100

**Table 8: *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 |

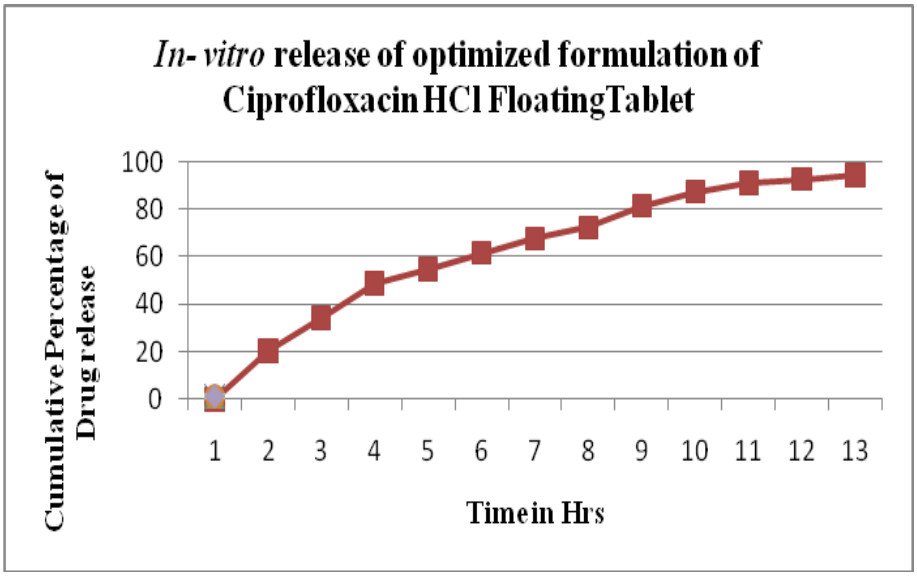


***Figure: 6 In- vitro Release of Optimized of Ciprofloxacin HCl Floating Tablet.***

***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. The results are given in the Table 7.

**Table 7: *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 |

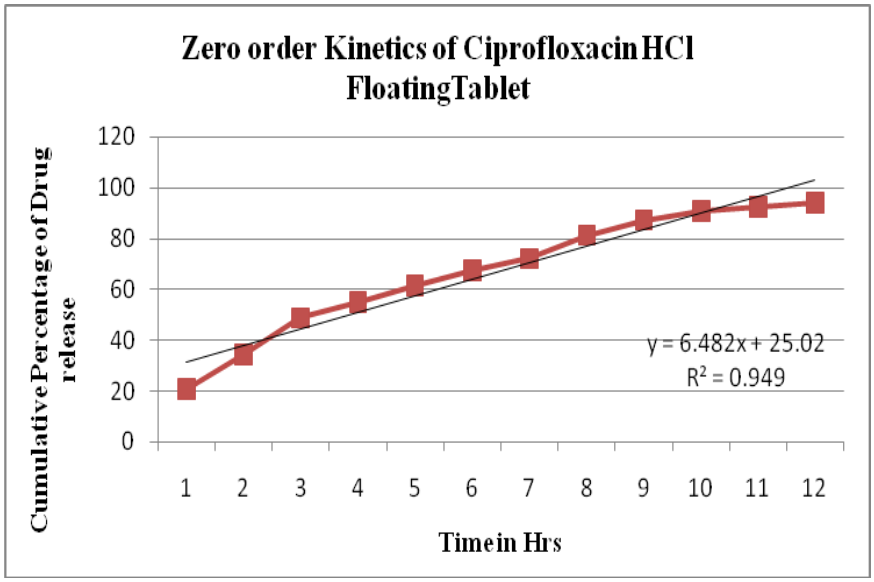


*Figure 7: Zero Order Kinetics.*

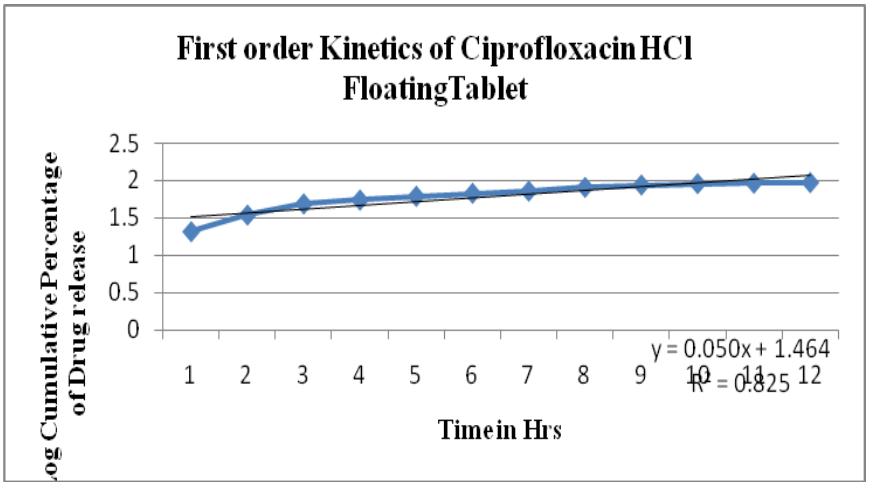


*Figure 8: First Order Kinectics.*

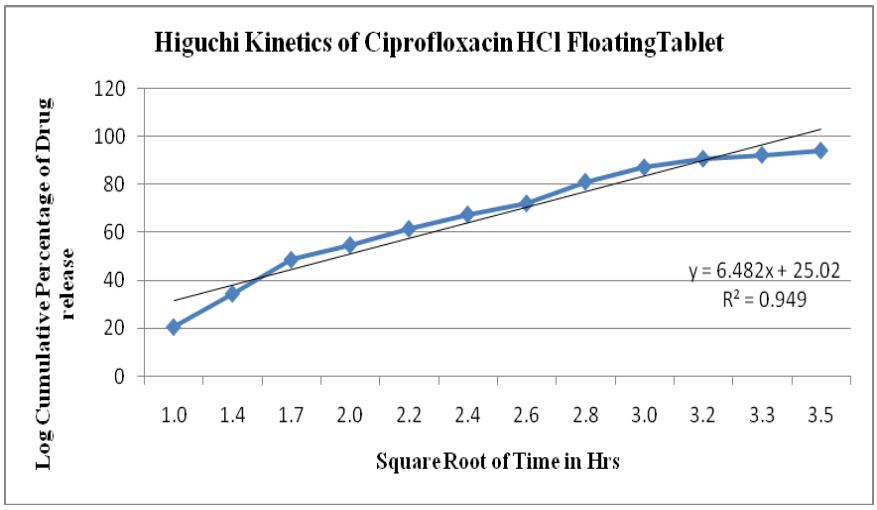


*Figure 9 Higuchi.*

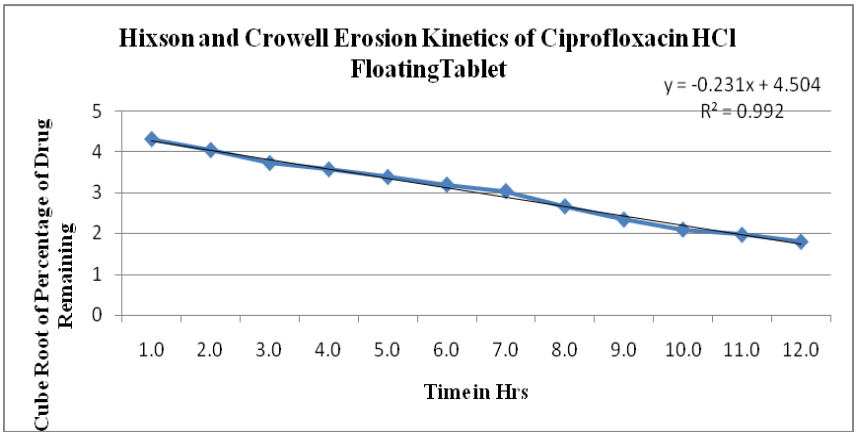


***Figure 10 Hixon crowell.***

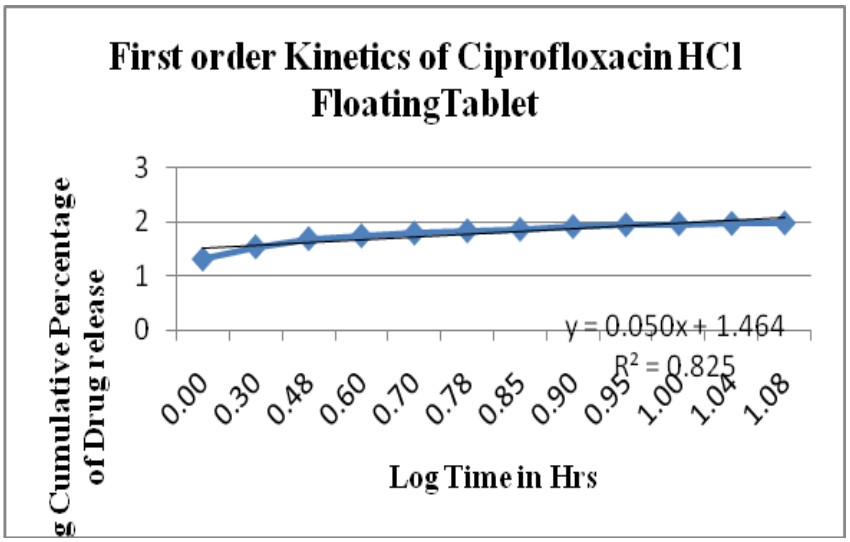


***Figure 11: Krosmeyar- Peppas.***

**SUMMARY AND CONCLUSION**

A hydrodynamically balanced floating tablet of Ciprofloxacin HCl has been formulated with anapproach to increase gastric residence and thereby improves drug bioavailability. Thefloating tablets of Ciprofloxacin HCl developed by using natural and synthetic polymer HPMCK4M, Eudragit 100S and guar gum with Sodium bicarbonate combination and citric acid asgas generating agent was prepared by wet granulation technique (CF1-CF8) was achieved.

- Using the Design Expert 10 Software the Polymers HPMCK4M, Eudragit 100S and guar gum were used as factors and 50mg and 150mg were used as two level. Based on this the formulation were designed to study the impact of the polymers.
- The pre-compression studies such as angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio were performed of the prepared granules and the result showed that all the parameters are within the limits.
- The floating Tablets were prepared by wet granulation method and evaluated for general appearance, hardness test, friability test, uniformity in weight, drug content estimation. All the formulations were found to be good appearance without showing any chipping, capping and sticking defects and other parameters were also passed the test.
- FTIR Spectroscopic studies indicated that the drug is compatible with all excipients and there are no drug-polymer interactions.
- When comparing all formulation CF4 showed optimized drug release of 99.69%. at the end of 12 hours.
- These optimized CF4 formulation showed buoyancy lag time of 134 sec. and floatingtime of.12.5 hrs respectively.
- Based on the results obtained by the eight formulations, It is used as response factors for optimization using design expert and an optimized formulation was generated.
- The optimized formulation containing 78.43mg of HPMC K4M, 54.32mg of Eudragit 100S and 100mg of Guar Gum was used in the preparation and *in vitro* release shows 94.25% drug release in 12 hrs.
- Data obtained from kinetic treatment revealed Optimized formulations follow Hixon crowellerosion kinetics with a higher $R^2$ value of 0.992.

From the above study, it was concluded that Ciprofloxacin HCl can formulated as Floating drug delivery system which helps to increase gastric residence timethere by itincreases the bioavailability and half life of Ciprofloxacin HCl.

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