# FORMULATION, DESIGN AND DEVELOPMENT OF CIPROFLOXACIN HYDROCHLORIDE FLOATING BIOADHESIVE TABLETS

**Sankha Bhattacharya[1]*, Bhupendra G. Prajapati[2]**

***1.*** *Assistant Professor, department of pharmaceutics B. Pharmacy college-Rampura, Godhra, Gujarat-389001, India.*
***2.*** *Associate Professor, Dept. of Pharmaceutical Technology, Ganpat University, Kherva, Mehsana, Gujarat-384012, India*
**Corresponding author: Mr. Sankha Bhattacharya (sankhabhatt@gmail.com) mobile: +91 7698067381*

## Abstract

Ciprofloxacin hydrochloride is a second generation antibiotic and a BCS class II drug. It was taken as a model drug to prepare floating bioadhesive tablet. This drug has maximum therapeutic window in the upper stomach, so controlled drug release with the optimum retentive formulation in the upper stomach would be an ideal formulation. Applying Placket and Burman design we tried to prepare floating bioadhesive tablets using three principal polymers, such as HPMCK15M (08%, 12% & 16%), carbopol 934P (06%, 09% & 12%) and CMC (03%, 06% & 09%). Total 13 formulations were designed (CF1 to CF13) and various evaluation parameters were studied. After a comprehensive analysis, it was confirmed that CF13 formulation was emerging out to be an optimum formulation. The various evaluation parameters of CF13 such as weight variation (500±0.35mg), average thickness (3.24mm), average diameter (12.53mm), %friability (0.94%), hardness (9.5kg/cm$^2$), wetting time (21seconds), drug content (97.36%), swelling index (2.801 after 12$^{th}$ hour), floating lag time (345second), total bouncy lag time (10 hour), bioadhesive strength (2.34gm), force of adhesion (0.229N), cumulative percentage drug release at 12$^{th}$ hour (92.45%), desirability factor (D=0. 920) shows satisfactory results. The CF13 formulations were further studied for kinetic behavior. It was found that CF13 maintained zero order kinetics ($R^2$=0.9886). The optimized formulation was then studied for similarity ($F_2$=57.083) and difference factor (F1=11.970) against Ciftran-OD tablet (Ranbaxy India Limited), which was within the specific limits. Further, the CF13 formulations were introduced into 6month stability studies as per ICH QIA (R2) guideline. The results were promising except dissolution (108.90% at the 12$^{th}$ hour), drug content (87.22%) after 6 months in a stability chamber. Finally, it can be concluded that CF13 formulation can be considered for industrial scaled up.

**Key words:** Placket and Burman design, ciprofloxacin hydrochloride, floating tablets, bioadhesive strength, carbopol 934P, desirability factor.

## Introduction

Desire therapeutic activity with minimizing dosing interval and minor adverse drug reaction is the ideal pre-request for making any controlled release formulation. Conventional dosage form has some critical problems like uncontrollable release pattern of drugs, sub or supratherapeutic drug concentration, forming deleterious effects, and limited delivery for short biological half-life containing drugs ($t_{1/2}$). To circumvent all associated problems a

proper designing of oral controlled drug delivery is incepted which can increase the bioavailability of drugs and challenges all physicochemical problems (variability, emptying, mobility etc) of drug released in Gastro Intestinal Track (GIT). In modern era increasing Gastric Resilience Timings (GRT) of formulations is a promising approach ie: Gastro Retentive Dosage Form (GRDF) [1]. The maximum absorption windows were present in upper to lower parts of the stomach, which makes it as a potential target site. Poorly soluble and sprightly soluble drugs has a paramount issue on dissolution as gastrointestinal transit time (2hours) can limit the drug absorption. To scrap all problems cohort with drug release, most eradicable Gastro Retentive Dosage Form (GRDF) was developed which increases drug concentration in GIT mucosa and also improve pharmacotherapy of stomach by local drug release.

The various concepts which have been used to increase the retention of dosage in the stomach are floating system, muco or bioadhesive system, osmotic regulatory system. Floating Drug Delivery System[2] is a promising approach where gastric juice density maintained higher than the formulation, due to which the formulation bayonet in the upper stomach for a longer period of time. This approach helps to decay fluctuation in plasma drug concentration and transition of released drug. Floating Drug Delivery System (FDDS) classified as an effervescent and non-effervescent system. On the other hand bioadhesive system releases the drug in site-specific manner. Polymer such as sodium carboxymethyl cellulose, acrylic acid copolymer (carbopol and polycarbophil), hydroxypropyl methyl cellulose, a copolymer of vinylpyrrolidone and vinyl acetate etc are used in formulating bioadhesive drug delivery system [3]. It was also observed that polymers containing carboxylic groups, such as carboxymethyl cellulose and polyacrylic polymers, shown a higher level of bio-adhesion [4]. Our target was to design a Floating-Bioadhesive tablet using ciprofloxacin hydrochloride as a model drug, which could bayonet for certain period of time in the upper stomach and further adhere in the fundus of the stomach. This approach is specifically designed to avoid Mio Electric Complex (MEC) which sweeps undigested food particles from the stomach in every 1.5 to 2 hours and to increase the residence time of the formulation in the upper stoma. From the literature review, it was confirmed that (Mukhopadhyay.S.et al 2010) HPMC & CMC can be used for controlled release dosage form [5]. It was also observed that carboxymethylcellulose & polyacrylic polymers, (e.g. Carbopol 940p) has good bioadhesive property, hence in the present investigation it was aimed to test, the bio adhesiveness [6] of the formulation taking Carbopol 940p as a principle polymer as well as optimised the floating nature of the formulation by changing the ratio of HPMC & CMC, by using PVP K-30 as a Binder

## Material and method

The model drug ciprofloxacin hydrochloride were gift sample from Bharat Coats; Chennai. HPMC-HV-145MPAS (LR), carbopol-940 was purchased from S.D fine chemicals; Vadodara. CMC, PVP-K-30, sodium bicarbonate, citric acid monohydride was purchased from Sisco-Research Laboratory; Mumbai. Microcrystalline cellulose, magnesium stearate, talc, was purchased from Loba chemical privet limited; Mumbai. Cifran-OD (ciprofloxacin floating tablets-manufactured by Ranbaxy, India limited) purchased from local medical store.

**The method of preparation**

Floating tablet containing ciprofloxacin hydrochloride as a model drug was prepared by direct compression method. As per $3^2$ factorial design, 13 batches were introduced (CF1 to CF13).Initially, drug (250mg) was mixed in a steel bowl with required quantities of microcrystalline cellulose (MCC). The varying concentrations of polymers[5] such as HPMC K15M (8%, 12% & 16%) carbopol 934P (6%, 9% & 12%), CMC (3%, 6% & 9%) combined with drug-MCC mixture, citric acid, sodium bicarbonate was mix together. The entire mixture was then pass through sieve number 40. All the ingredients except magnesium stearate and talc were blended in a polyethylene bag for five minutes. After sufficient blending remaining quantities of magnesium stearate and talc (previously sieved through mesh number 60) was admixture and again blended for 2-3minutes. The blended materials were punched by using 12 station punching machine (CEMACH: R&D-12MT, 6D/6B) in a die 13 mm diameter at 75 kg/cm$^2$ pressure for 2 minutes to obtain floating tablets containing individual 500mg of total tablet weight. The various weight of the tablets was checked periodically while performing the punching process (Table: 3).

**Table1: Factor and levels for Placket and Burman Design**

| Independent variable | Actual value (%) | | | Code value | | |
|---|---|---|---|---|---|---|
| | Low | Medium | High | Low | Medium | High |
| Concentration of HPMCK15M **(X1)** | 08 | 12 | 16 | -1 | 0 | +1 |
| Concentration of Carbopol 934P **(X2)** | 06 | 09 | 12 | -1 | 0 | +1 |
| Concentration of CMC **(X3)** | 03 | 06 | 09 | -1 | 0 | +1 |

**Dependent variables:**

1. Floating lag time **(Y1)**
2. Bioadhesive strength **(Y2)**
3. Cumulative percentage drug release at 12$^{th}$ hour **(Y3)**

**Evaluation parameters of floating tablets:**

**FTIR studies:** Fourier transform infrared spectroscopic studies were carried out on the pure drug, a physical mixture of the drug with excipients and finally with the finished optimized formulation. FTIR studies were carried out to find any confirmatory changes within the excipients and drug molecule. The various spectra's was taken within the range of 400-4000cm$^{-1}$. Sample and KBr (1:100) was punched to prepare pallet and was recorded in Shimadzu-IRTracer-100, Japan.

**Pre-formulation studies:** The various pre-formulation studies were carried out like bulk density, tapped density, Carr's index, Hauser's ratio, the angle of repose for pre compressible granules of various formulations. (Table: 4).

**Table2: Box–Behnken Design output:**

| Formulation code | Code value | | | Actual value (%) | | |
|---|---|---|---|---|---|---|
| **CF1** | 1 | 0 | 1 | 16.00 | 9.00 | 9.00 |
| **CF2** | 0 | -1 | 1 | 12.00 | 6.00 | 9.00 |
| **CF3** | 0 | 1 | 1 | 12.00 | 12.00 | 9.00 |
| **CF4** | 0 | 1 | -1 | 12.00 | 12.00 | 3.00 |
| **CF5** | 1 | 1 | 0 | 16.00 | 12.00 | 6.00 |
| **CF6** | 0 | -1 | -1 | 12.00 | 6.00 | 3.00 |
| **CF7** | -1 | 1 | 0 | 8.00 | 12.00 | 6.00 |
| **CF8** | 1 | -1 | 0 | 16.00 | 6.00 | 6.00 |
| **CF9** | -1 | 0 | 1 | 8.00 | 9.00 | 9.00 |
| **CF10** | -1 | 0 | -1 | 8.00 | 9.00 | 3.00 |
| **CF11** | -1 | -1 | 0 | 8.00 | 6.00 | 6.00 |
| **CF12** | 1 | 0 | -1 | 16.00 | 9.00 | 3.00 |
| **CF13** | 0 | 0 | 0 | 12.00 | 9.00 | 6.00 |

**Table 3: Factorial batch formula for floating tablets**

| Ingredient's | CF1 | CF2 | CF3 | CF4 | CF5 | CF6 | CF7 | CF8 | CF9 | CF10 | CF11 | CF12 | CF13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ciprofloxacin hydrochloride(mg)** | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| **HPMCK15M (mg)** | 80 | 60 | 60 | 60 | 80 | 60 | 40 | 80 | 40 | 40 | 40 | 80 | 60 |
| **Carbopol 934P (mg)** | 45 | 30 | 60 | 60 | 60 | 30 | 60 | 30 | 45 | 45 | 30 | 45 | 45 |
| **CMC (mg)** | 45 | 45 | 45 | 15 | 30 | 15 | 30 | 30 | 45 | 15 | 30 | 15 | 30 |
| **Sodium Bicarbonate (mg)** | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| **Citric acid monohydrate(mg)** | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| **MCC©(mg)** | 30 | 65 | 35 | 65 | 30 | 95 | 70 | 70 | 70 | 100 | 100 | 60 | 65 |
| **Talc(mg)** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Magnesium stearate(mg)** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

**Post compression parameters:** In-house post, compression parameters was performed. The hardness of floating tablets was measured by Monsanto (Model: MHT-20) hardness tester, which was expressed in $Kg/cm^2$. Friability test was carried out by using Panomex Inc. PX/FTA-2 Friability apparatus. The %friability lesser than 1% was considered acceptable. Various weight variations of tablets were estimated by using Fuzhou electronic balance (sensitivity 0.001g). As per Indian pharmacopeia for 500mg tablet, the % weight deviation must not excite 5 % (Table: 5).

**Floating studies**: *Ex vivo* Floating studies were carried out on CF1 to CF13 formulations (Figure: 4 & Table:7). One tablet each was taken from all the 13 formulations and individually kept in a 100ml glass beaker assimilating in simulated gastric fluid, maintaining 1-2 pH, as per united states pharmacopeia. The Floating Lag (FLT) time or bouncy lag time was calculated by measuring the time taken by tablets to rise above the surface of the medium. The total duration of time in which the tablets remain buoyant was considered as Total Floating Time (TFT) (Leena, Jagat S *at el*., 2011) [7].

**Determination of drug content in tablet:**

Weigh accurately 20 tablets of different formulations. Crush them all using glass motor and pastel. 0.25gm was taken and diluted to 100ml of sufficient 0.1N HCL. Further, the contents were sonicated for 20 minutes and filtered using 0.45µ membrane filter. From that filtrate again 1ml was withdrawn and diluted up to 100ml using 0.1 N HCL in a volumetric flask. The absorbance of the resultant solutions was estimated using SHIMADZU-1880UV-VIS Spectrophotometer at 278 nm where the A1%1cm value was considered as 878.

**Swelling index studies:**

Swelling of hydrophilic polymers such as HPMC, Carbopl, and CMC depends on contents of the stomach and osmolality of the medium. This provides outline about release pattern of drug and the residence time. The swelling index can be determined by placing the tablets in dissolution bowl containing 200ml of pH6.8 phosphate buffer maintaining 37±0.5° C. Each two hours interval (2-12hours) the swelled tablets were withdrawn and blotted with whatman filter paper to remove excess water (Figure: 3 and Table: 6). Further individual swelled tablet weight was estimated in Fuzhou electronic balance (Railkar, Anirudh *et al.*, 2001) [8].The swelling index can be determined by following formula:

$$\textbf{Swelling index (S.I)} = \{(W_t - W_O)/W_O\} \times 100$$

Where, S.I= swelling index $W_t$=weight of tablet at time t
Wo= weight of tablet before immersion.

**Bioadhesive strength:**

For measurement of the bioadhesive strength of the prepared formulations, everted pieces of fundus tissues of the goat was mandated. While transportation goat skin from the local slaughter house, it was stored in Krebs buffer solution (sodium chloride 6.9 mg/L, D-Glucose 2gm/L, monobasic potassium phosphate 0.16gm/L, magnesium sulfate 0.141 mg/L, potassium chloride 0.35 mg/L).While mounting in modified physical balance (Deshmukh, Jadhar and Sakarkar 2009) fundus skin was cleaned thrice with 0.1N HCL solution. The modified physical balance assembled with one upper vial (b) which was reversely connected with the balance (a) in one end (figure1). The vial (b) was prefilled with 0.1N HCL and its opening was fused with everted skin by using a rubber band. Another vial was prepared with the same method. The second vial was fused with everted skin (e) and prepared formulation (d) was fixed within using cello tape. The first vial (b) was reversely attached with formulation (d) along with skin (e) of the second vial for 2 minutes. After fusion of the

tablet was completed with skin (c) due to the viability of the fundus mucosa with tablet polymers, then gradually increase the weight

(g) on right hand weighing pan. Due to integrating weight, the skin (c) will detach the tablet surface. The minimum weight required for the detached bio-adhesive tablet from the skin (c) considered as bioadhesive strength. The following formula was used to determine the force of bio-adhesion (Figure: 1 & Table: 7) [9].

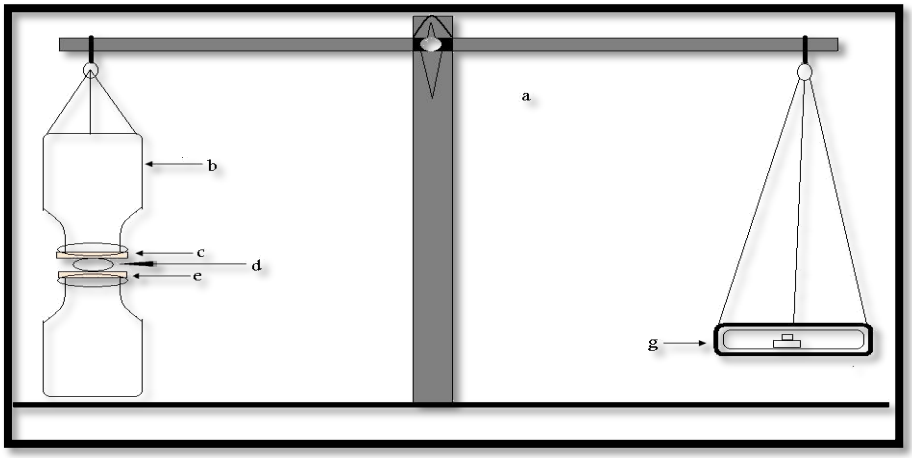



**Figure 1: Modified physical balance for bio-adhesive test on prepared formulations**

**In-vitro dissolution studies:**

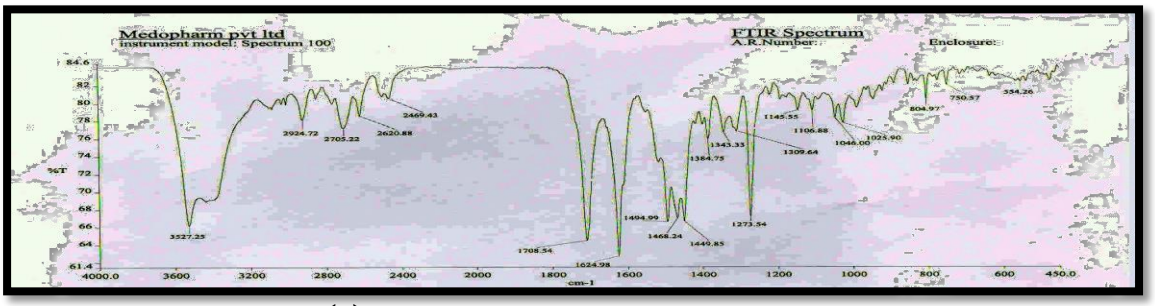
Dissolution of the tablet of each batch was carried out using USP type II apparatus using the paddle. Nine hundred ml of 0.1 N HCL (pH1.2) was placed in a dissolution vessel and the temperature of the medium was set at 37±0.5˚C. one tablet was placed in each dissolution vessel and the rotational speed of paddle was set at 50RPM.The 10 ml sample was withdrawn at predetermined time intervals for 10 hours and was replaced with same volume of fresh dissolution medium. The sample were taken at 0.5, 1,2,3,4,5,6,7,8,9,10,11 & 12 hours. The sample were filtered and diluted to suitable concentration with 0.1N HCL solution. The absorbance of the solution was measured at 278nm for ciprofloxacin with UV spectrophotometer (SHIMADZU-1880UV-VIS Spectrophotometer).Cumulative percentage drug release was calculated (Figure: 9 &Table: 16) (Mukhopadhyay. S. et al 2010) [5].

**Stability study:**

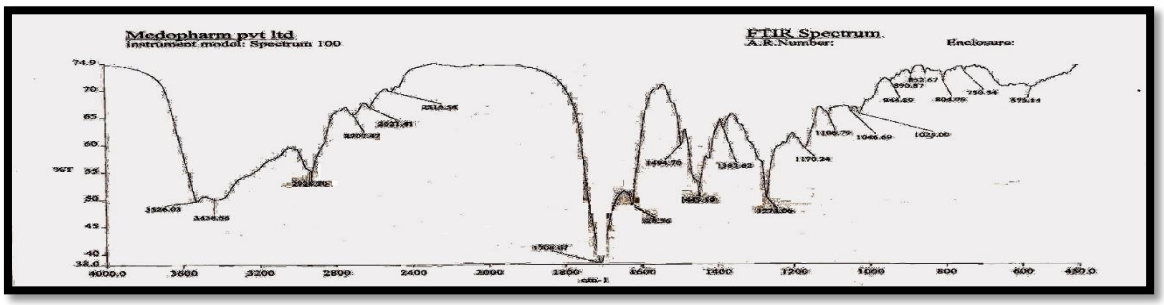
As per ICH guideline Q1A (R2) selected optimized batch (CF13) formulations were tested for accelerated stability studies. The selected tablets were wrapped in aluminum foils and kept in a humidity chamber (Lap Top, India) at 40°C ± 2°C/75% RH ± 5% RH for 6 months. Each one-month interval the various evaluation parameters of tablets were checked and reported (Table: 20 & 21).

**Pre-formulation studies output:**

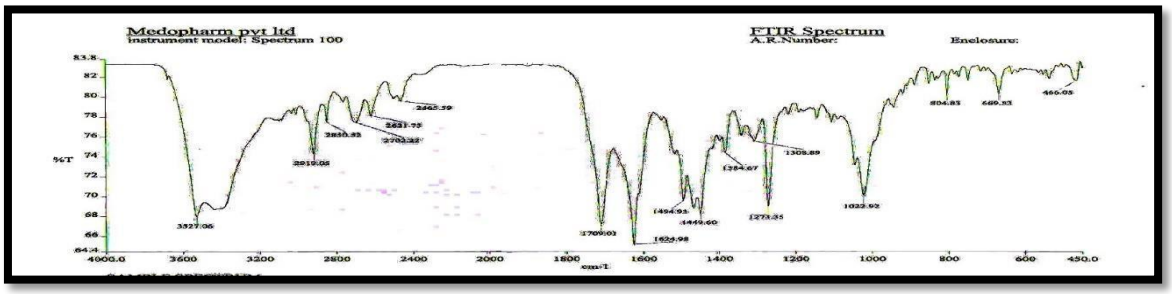
**FTIR results**: The various characteristic peaks were observed in ciprofloxacin pure drug such as at 3527.25 $cm^{-1}$ (N-H stretch), at 2924.72 $cm^{-1}$(O-H stretch), at 2705.22$cm^{-1}$(C-H stretch) at 1708.54$cm^{-1}$(C=O stretch). The IR spectra of a physical mixture containing drug, excipient and polymers give certain characteristic peaks at 35260.03$cm^{-1}$ indicating O-H stretch, at 2928.28 $cm^{-1}$(C-H stretching), at 1708.07$cm^{-1}$(C=O stretching). On the other hand IR spectra of ciprofloxacin, bio-adhesive floating formulations give certain characteristic peaks at 3435.11 $cm^{-1}$(O-H stretching), 2919.34$cm^{-1}$(C-H stretching), 1708.82 $cm^{-1}$(C=O stretching), Infrared absorption spectrum of a physical mixture of polymers and ciprofloxacin was studied and confirmed that there are no interactions with each other. The spectra showed all the prominent peaks of the drug as well as polymers. IR spectrum indicated characteristics peaks belongs to measured functional groups. There is no unexpected characteristic IR band shifts in formulation sample as well, hence it can be concluded that there is no significant changes and behavior in drug –polymer formulations (Figure: 2)




**(a)**




**(b)**




**(c)**

**Figure2: FTIR spectra of ciprofloxacin pure drug (a), drug and physical mixture of polymers (b) and finished formulation(c).**

## Results

The various evaluation parameters for the finished product (ciprofloxacin bio-adhesive floating tablet) were studied according to the specified methods. The output was tabulated and reported as bellow

**Table 4: Pre-compression characteristics of ciprofloxacin hydrochloride floating bioadhesive granules**

| Formulation code | Bulk density (gm/ml) | Tapped Density (gm/ml) | Compressibility index (%) | Hausner's ratio | Angle of Repose(∅) |
|---|---|---|---|---|---|
| **CF1** | 0.3607 | 0.4321 | 16.52 | 1.19 | 32.98 |
| **CF2** | 0.3828 | 0.4561 | 16.07 | 1.19 | 33.90 |
| **CF3** | 0.3256 | 0.4123 | 21.02 | 1.26 | 36.37 |
| **CF4** | 0.3461 | 0.4245 | 18.46 | 1.22 | 35.77 |
| **CF5** | 0.3123 | 0.4564 | 14.41 | 1.46 | 39.18 |
| **CF6** | 0.3190 | 0.4089 | 21.83 | 1.28 | 36.38 |
| **CF7** | 0.3345 | 0.4892 | 31.62 | 1.46 | 40.12 |
| **CF8** | 0.3219 | 0.4376 | 26.43 | 1.35 | 37.16 |
| **CF9** | 0.3432 | 0.4212 | 18.51 | 1.22 | 34.91 |
| **CF10** | 0.3381 | 0.4458 | 24.15 | 1.31 | 36.02 |
| **CF11** | 0.3456 | 0.4217 | 22.01 | 1.22 | 32.89 |
| **CF12** | 0.3469 | 0.4267 | 18.88 | 1.23 | 37.15 |
| **CF13** | 0.3347 | 0.4012 | 16.57 | 1.19 | 33.43 |

**Table 5: Post compression characteristics of ciprofloxacin hydrochloride floating bioadhesive tablets**

| Formulation code | Weight variation (mg) (n = 20) | Avg. Thickness (mm) | Avg. Diameter (mm) | Friability (%) (n = 10) | Hardness (kg/cm2) (n = 6) | Wetting time (seconds) | Drug content (%W/W) |
|---|---|---|---|---|---|---|---|
| **CF1** | 500±1.09 | 3.22 | 12.67 | 0.81 | 4.1 | 12 | 96.25 |
| **CF2** | 500±1.03 | 3.34 | 12.52 | 0.87 | 4.3 | 14 | 93.26 |
| **CF3** | 500±0.76 | 3.27 | 12.57 | 0.76 | 4.2 | 22 | 94.67 |
| **CF4** | 500±0.25 | 3.45 | 12.73 | 0.98 | 4.5 | 19 | 96.23 |
| **CF5** | 500±1.23 | 3.87 | 12.54 | 0.92 | 4.1 | 21 | 94.12 |
| **CF6** | 500±2.18 | 3.22 | 12.63 | 0.96 | 4.0 | 34 | 93.78 |
| **CF7** | 500±0.23 | 3.38 | 12.53 | 0.75 | 3.9 | 26 | 92.19 |
| **CF8** | 500±0.46 | 3.78 | 12.59 | 0.62 | 4.6 | 21 | 95.35 |
| **CF9** | 500±0.78 | 3.73 | 12.62 | 0.78 | 4.5 | 36 | 90.25 |
| **CF10** | 500±1.28 | 3.27 | 12.60 | 0.94 | 4.6 | 23 | 96.78 |
| **CF11** | 500±2.19 | 3.37 | 12.57 | 0.96 | 4.7 | 12 | 96.90 |
| **CF12** | 500±0.92 | 3.31 | 12.58 | 0.93 | 4.3 | 16 | 91.53 |
| **CF13** | 500±0.35 | 3.24 | 12.53 | 0.94 | 4.5 | 21 | 97.36 |

**Table 6: Swelling index studies**

| Formulation code | 2nd hour | 4th hour | 6th hour | 8th hour | 10th hour | 12th hour |
|---|---|---|---|---|---|---|
| CF1 | 0.834 | 1.139 | 1.367 | 1.678 | 2.389 | 2.825 |
| CF2 | 0.823 | 1.152 | 1.367 | 1.678 | 2.452 | 2.812 |
| CF3 | 0.813 | 1.103 | 1.256 | 1.682 | 2.356 | 2.782 |
| CF4 | 0.942 | 1.298 | 1.345 | 1.564 | 2.278 | 2.727 |
| CF5 | 0.810 | 1.169 | 1.312 | 1.634 | 2.290 | 2.672 |
| CF6 | 0.891 | 1.192 | 1.357 | 1.639 | 2.231 | 2.814 |
| CF7 | 0.891 | 1.110 | 1.335 | 1.659 | 2.298 | 2.721 |
| CF8 | 0.812 | 1.189 | 1.326 | 1.693 | 2.225 | 2.724 |
| CF9 | 0.890 | 1.178 | 1.387 | 1.634 | 2.231 | 2.782 |
| CF10 | 0.881 | 1.134 | 1.346 | 1.639 | 2.378 | 2.778 |
| CF11 | 0.879 | 1.145 | 1.356 | 1.645 | 2.301 | 2.762 |
| CF12 | 0.867 | 1.172 | 1.345 | 1.689 | 2.383 | 2.724 |
| CF13 | 0.812 | 1.142 | 1.356 | 1.645 | 2.356 | 2.801 |

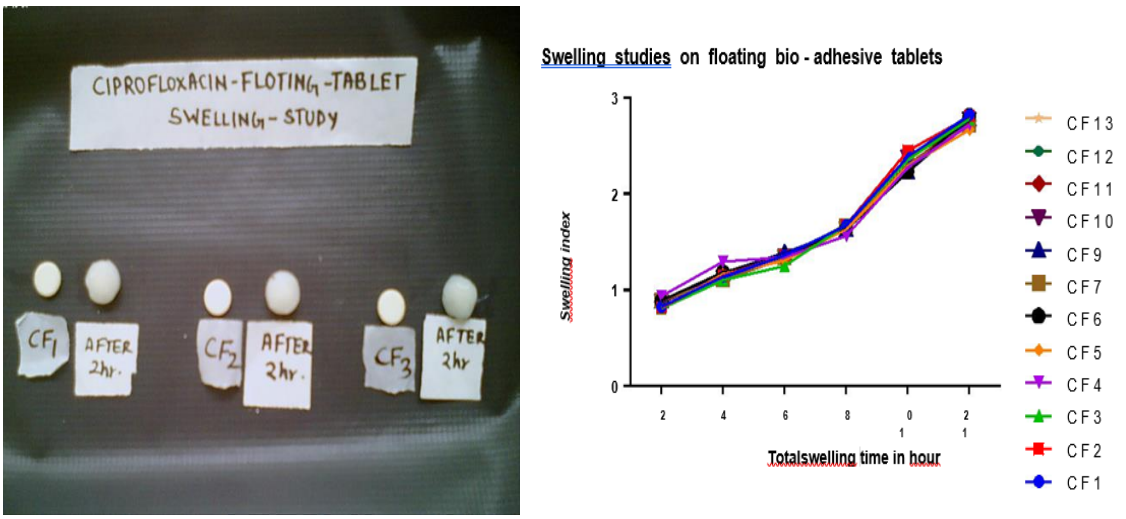



**Figure 3: (a) swelling study of prepared 3 formulations after 2 hour interval (b) swelling profile of all 13 formulation**

**Table 7: Floating and bio-adhesive studies on various formulations**

| Formulation code | Floating lag time (Seconds) | Total bouncy time (hours) | Bioadhesive strength(gm) | Force of adhesion (N) |
|---|---|---|---|---|
| **CF1** | 398 | 11 | 3.11 | 0.300 |
| **CF2** | 293 | 10 | 2.01 | 0.197 |
| **CF3** | 467 | >12 | 4.21 | 0.413 |
| **CF4** | 435 | >12 | 4.11 | 0.403 |
| **CF5** | 456 | >12 | 4.56 | 0.447 |
| **CF6** | 287 | 10 | 2.26 | 0.221 |
| **CF7** | 412 | >12 | 3.98 | 0.390 |
| **CF8** | 256 | 10 | 1.92 | 0.188 |
| **CF9** | 335 | 11 | 2.86 | 0.280 |
| **CF10** | 312 | 10 | 2.24 | 0.219 |
| **CF11** | 245 | 10 | 1.81 | 0.115 |
| **CF12** | 373 | 12 | 2.68 | 0.262 |
| **CF13** | 345 | 10 | 2.34 | 0.229 |

Box-Behnken design [10] output: Total of 13 batches were taken. The various dependent variables like floating lag time (Y1), bioadhesive strength (Y2), and cumulative percentage drug release at the 12th hour (Y3) were shown distinct results from 245 to 467 second, 1.81 to 4.56gm, 81.45 to 98.56% respectively.

**Effect on floating lag time:** After contour plot and 3D surface plot it was clear that all the independent variable has an effect on floating lag time. Hence design was established using expert design 7.0.0 software, after ANOVA studies, reduced quadric model was considered and the final polynomial equation was found to be:

**Floating lag time (Y1)** = $+342.80+22.37X_1+86.12X_2+10.75X_3+19.70X_3^2$ ..... (1)

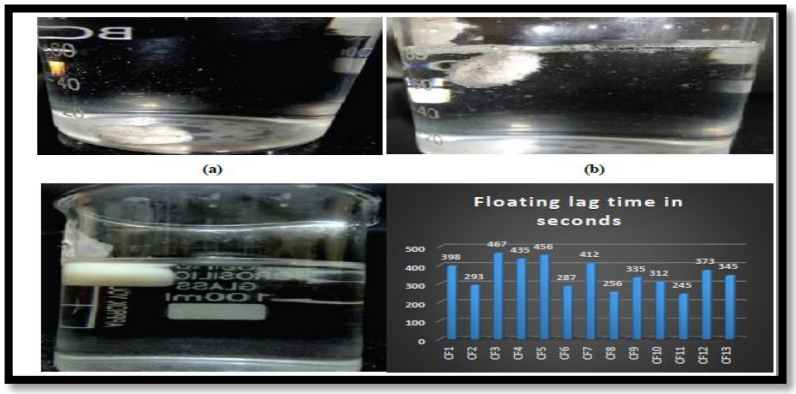



**Figure 4: The initial incorporation of the tablet in a beaker containing 0.1N HCL (a), mobilization of tablet towards water surface or floating lag time (b) and total buoyancy time (12 hours). Picture (d) indicates floating lag time profile of individual tablets.**

**Factorial study output:**

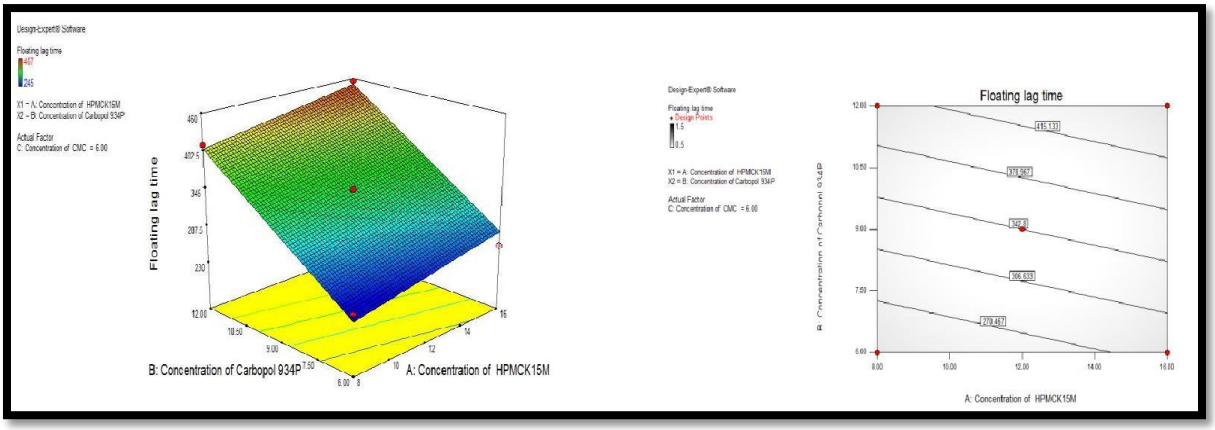



**Figure 5: At CMC (6%) actual factor concentration the various effect of HPMC K15M and Carbopol 934P on Floating lag time has shown by 3D surface and contour plot graphs.**

**Table 8: Estimation of significance factor of analysis of variance for response of floating lag time**

| ***source*** | ***df*** | ***SS*** | ***MS*** | ***F*** | ***Significance F*** |
|---|---|---|---|---|---|
| Regression | 3 | 64269.75 | 21423.25 | 63.94632914 | 2.16741E-06 |
| Residual | 9 | 3015.173077 | 335.0192308 | | |
| Total | 12 | 67284.92308 | | | |

**Table 9: Estimation of regression coefficient for reduced model of floating lag time using analysis of variance**

| **Factor** | **Coefficient** | **Standard error** | **P-Value** |
|---|---|---|---|
| Intercept | 342.80 | 6.75 | < 0.0001 |
| Concentration of HPMCK15M | 22.37 | 5.33 | 0.0030 |
| Concentration of Carbopol 934P | 86.12 | 5.33 | < 0.0001 |
| Concentration of CMC | 10.75 | 5.33 | 0.0786 |

**Effect on bioadhesive strength:** Bioadhesive strength was increased with increasing polymer concentration. Mainly Carabopol 934P was the main polymer which helps to increase bioadhesive strength. The reduced quadric model was considered and the final polynomial equation was found to be

**Bio adhesive strength (Y2)** $=+2.51+0.17\ X_1+1.11X_2+0.11X_3+0.51X_2^2+0.17X_3^2$. . (2)

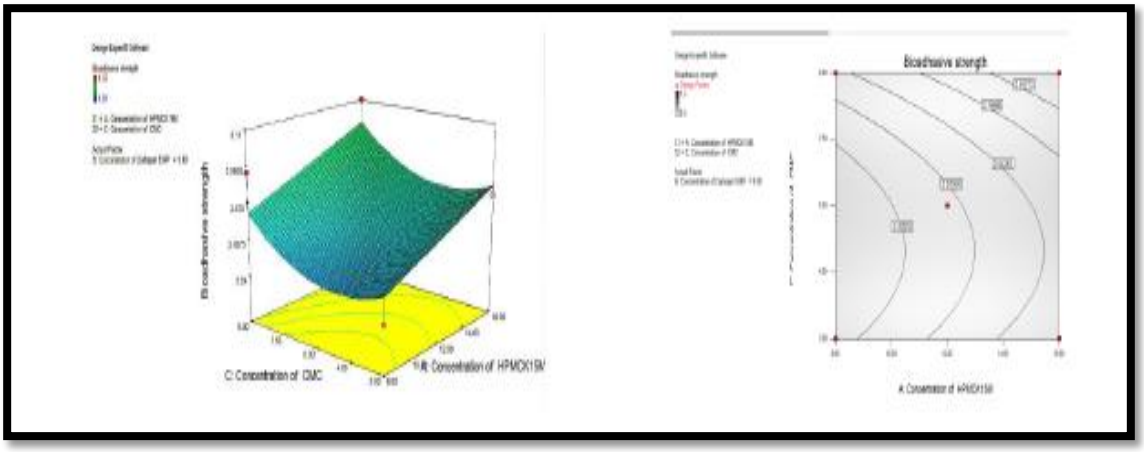



**Figure 6: At Carbopol 934P (9%) actual factor concentration the various effect of HPMC K15M, CMC, on bioadhesive strength has shown by 3D surface and contour plot graphs.**

**Table 10: Estimation of significance factor of analysis of variance for response of bioadhesive strength**

| ***Sources*** | ***df*** | ***SS*** | ***MS*** | ***F*** | ***Significance F*** |
|---|---|---|---|---|---|
| Regression | 3 | 10.15175 | 3.383917 | 26.89799 | 7.96E-05 |
| Residual | 9 | 1.13225 | 0.125806 | | |
| Total | 12 | 11.284 | | | |

**Table 11: Estimation of regression coefficient for reduced model of bioadhesive strength using analysis of variance**

| **Factor** | **Coefficient** | **Standard error** | **P-Value** |
|---|---|---|---|
| Intercept | 2.51 | 0.16 | < 0.0001 |
| Concentration of HPMCK15M | 0.17 | 0.084 | 0.0804 |
| Concentration of Carbopol 934P | 1.11 | 0.084 | < 0.0001 |
| Concentration of CMC | 0.11 | 0.084 | 0.2245 |

**Effect on cumulative percentage drug release at the 12$^{th}$ hour (Q12):** It was observed that increased concentration of polymers can cause a decrease in drug release on the 12$^{th}$ hour. Again reduced quadric model was considered and the final polynomial equation was established.

$$\textbf{Q12 (Y3)} = +93.29-1.96\ X_1-6.63X_2-1.01X_3-1.28X_1X_2-2.22X_2^2-0.033X_3^2 \ldots\ldots \quad (3)$$

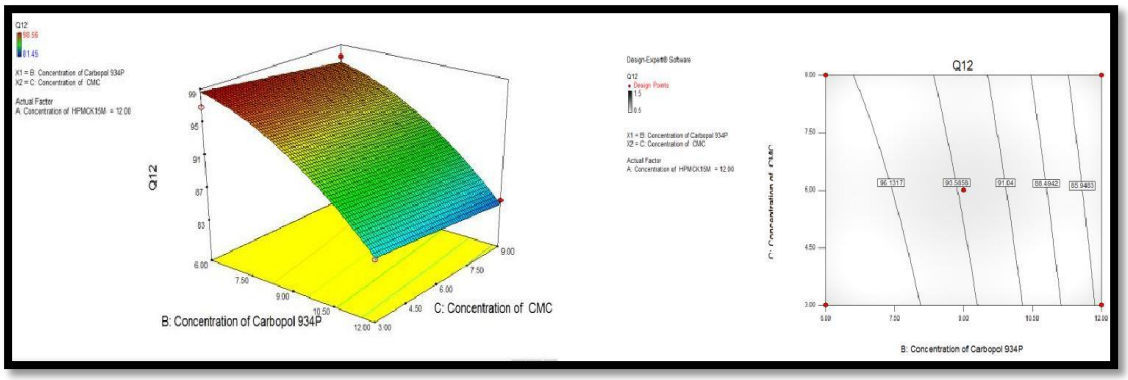



**Figure 7: At HPMC K15M (12%) actual factor concentration the various effect of carbopol 934P, CMC on cumalative percentage drug release at 12$^{th}$ hour (Q12) has showned by 3D plot and counter plot graph.**

**Table 12: Estimation of significance factor of analysis of variance for response of percentage cumulative drug release at 12$^{th}$ hour**

| ***Source*** | ***df*** | ***SS*** | ***MS*** | ***F*** | ***Significance F*** |
|---|---|---|---|---|---|
| Regression | 3 | 390.0147 | 130.0049 | 38.16639 | 1.91E-05 |
| Residual | 9 | 30.6564 | 3.406266 | | |
| Total | 12 | 420.6711 | | | |

**Table 13: Estimation of regression coefficient for reduced model of percentage cumulative drug release at 12$^{th}$ hour using analysis of variance**

| **Factor** | **Coefficient** | **Standard error** | **P-Value** |
|---|---|---|---|
| Intercept | 2.51 | 0.16 | < 0.0001 |
| Concentration of HPMCK15M | 0.17 | 0.084 | 0.0804 |
| Concentration of Carbopol 934P | 1.11 | 0.084 | < 0.0001 |
| Concentration of CMC | 0.11 | 0.084 | 0.2245 |

**Optimized batch analysis**

Contour plots of all dependents variables were overlapped to locate the area of common interest. The optimized batch was selected on the basis of following criteria: minimum floating lag time, maximum bioadhesive strength and optimum drug release after 12hour dissolution. The optimized batch was selected by using DESIGN EXPERT trial version

8.0.5 (Stat-Ease. Inc. Minneapolis, USA) and overlay plot was generated (Figure 8). To confirm the validity of design, the optimized batch was performed and % relative error was calculated which was found to be less than the 9% (Table 14) indicate goodness of fit in the model (figure 8).

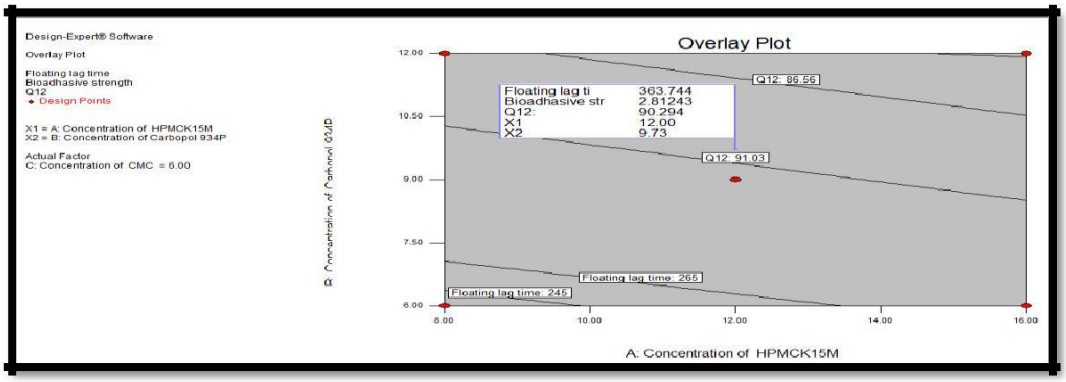



**Figure 8: Overlay plot on optimized formula**

**Table 14: Result of checkpoint batch**

| Response | Predicted value | Experimental value | Percentage relative error |
|---|---|---|---|
| **Floating lag time (Second)** | 363.744 | 341±0.23 | 6.25% |
| **Bio-adhesive strength** | 2.81243 | 2.74±0.29 | 2.49% |
| **Cumulative percentage drug releases at 12$^{th}$ hour** | 90.294 | 93.08±1.34 | 3.08% |

**Table 15: Response of experimental design formulations**

| Formulation code | Floating lag time(Second) | Bioadhesive strength (gm) | Cumulative percentage drug release at 12$^{th}$ hour (Q12) |
|---|---|---|---|
| **CF1** | 398 | 3.11 | 89.15 |
| **CF2** | 293 | 2.01 | 97.39 |
| **CF3** | 467 | 4.21 | 83.85 |
| **CF4** | 435 | 4.11 | 85.19 |
| **CF5** | 456 | 4.56 | 81.45 |
| **CF6** | 287 | 2.26 | 96.89 |
| **CF7** | 412 | 3.98 | 87.23 |
| **CF8** | 256 | 1.92 | 97.89 |
| **CF9** | 335 | 2.86 | 94.16 |
| **CF10** | 312 | 2.24 | 97.37 |
| **CF11** | 245 | 1.81 | 98.56 |
| **CF12** | 373 | 2.68 | 93.19 |
| **CF13** | 345 | 2.34 | 92.45 |

**Table 16: *In vitro* drug release study of ciprofloxacin hydrochloride floating bio-adhesive tablet**

| Time | CF1 | CF2 | CF3 | CF4 | CF5 | CF6 | CF7 | CF8 | CF9 | CF10 | CF11 | CF12 | CF13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 0.5 | 14.35±1.0 | 19.67±0.23 | 10.28±0.27 | 12.71±1.23 | 09.16±0.13 | 12.09±0.36 | 12.06±2.19 | 18.92±0.201 | 12.10±0.12 | 19.27±0.25 | 12.29±1.09 | 11.87±0.12 | 10.22±0.91 |
| 1 | 21.45±2.12 | 27.28±0.21 | 16.21±0.29 | 18.32±0.26 | 16.72±0.11 | 19.05±0.36 | 18.39±0.55 | 26.37±0.72 | 18.29±0.13 | 28.42±0.27 | 20.17±0.48 | 20.19±1.08 | 19.25±0.27 |
| 2 | 29.89±0.56 | 35.21±0.17 | 22.87±0.16 | 26.21±0.65 | 23.19±0.27 | 27.92±0.35 | 25.11±0.11 | 32.11±0.43 | 27.17±1.24 | 34.25±0.25 | 29.08±1.25 | 28.17±0.25 | 26.26±1.65 |
| 3 | 36.18±0.24 | 43.67±1.11 | 30.27±2.101 | 31.83±0.25 | 29.25±1.78 | 37.51±0.25 | 30.22±0.45 | 39.21±1.55 | 34.29±2.63 | 41.76±2.11 | 37.11±0.35 | 36.14±0.27 | 33.16±0.11 |
| 4 | 43.89±0.21 | 49.71±0.102 | 36.15±0.22 | 38.56±0.45 | 36.14±0.36 | 45.11±0.35 | 36.75±0.43 | 45.72±0.43 | 41.76±0.05 | 49.11±0.53 | 44.19±0.25 | 42.11±0.98 | 39.04±0.45 |
| 5 | 48.32±0.18 | 56.89±0.11 | 42.27±0.19 | 44.11±0.27 | 40.82±1.36 | 49.92±0.54 | 40.16±0.76 | 51.11±0.17 | 48.21±0.28 | 57.18±0.28 | 51.74±0.37 | 48.17±0.36 | 44.52±0.19 |
| 6 | 53.91±0.12 | 60.37±0.23 | 49.29±2.01 | 50.15±1.83 | 47.22±1.045 | 54.91±0.27 | 47.24±0.73 | 59.26±0.33 | 53.14±0.55 | 64.11±0.36 | 59.15±0.39 | 56.19±0.64 | 51.27±0.45 |
| 7 | 60.19±0.17 | 69.28±0.36 | 56.35±0.36 | 57.19±0.76 | 53.61±0.86 | 61.78±0.33 | 55.14±0.35 | 66.27±0.75 | 59.06±0.39 | 71.86±0.55 | 66.18±0.22 | 63.13±0.27 | 58.91±1.23 |
| 8 | 68.74±0.11 | 75.82±0.26 | 60.12±1.05 | 64.19±1.09 | 59.19±0.16 | 71.29±0.26 | 62.15±0.28 | 71.34±1.26 | 66.27±0.35 | 79.21±1.11 | 72.17±2.17 | 70.24±0.28 | 66.23±0.36 |
| 9 | 74.23±0.77 | 80.79±0.74 | 66.38±0.76 | 69.98±0.56 | 65.38±0.28 | 79.29±0.48 | 69.18±0.33 | 79.25±0.56 | 73.18±0.35 | 84.29±0.33 | 79.15±0.56 | 78.14±0.87 | 72.14±0.65 |
| 10 | 80.29±0.28 | 88.27±2.13 | 71.81±0.32 | 75.82±0.54 | 71.85±0.54 | 84.67±0.15 | 74.84±0.11 | 85.81±0.26 | 81.24±0.17 | 89.64±0.53 | 86.57±0.25 | 82.32±0.34 | 79.29±1.86 |
| 11 | 85.27±1.65 | 94.83±0.04 | 76.39±1.08 | 81.09±1.58 | 76.31±1.36 | 90.56±0.26 | 81.65±0.13 | 92.58±0.39 | 89.33±0.56 | 94.11±0.29 | 92.16±0.36 | 87.11±0.37 | 85.21±0.65 |
| 12 | 89.15±0.17 | 97.39±0.27 | 83.85±0.56 | 85.19±0.36 | 81.45±0.98 | 96.89±0.85 | 87.23±1.75 | 97.89±0.36 | 94.16±0.21 | 97.37±0.36 | 98.56±1.28 | 93.19±1.28 | 92.45±0.25 |

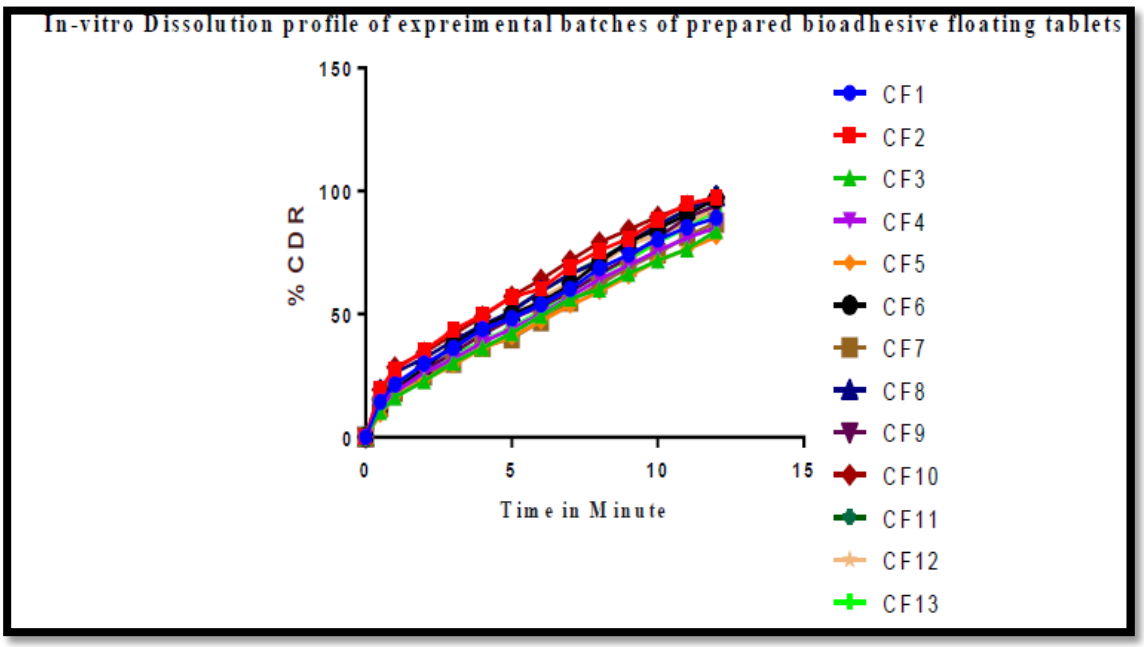



**Figure 9: In-Vitro dissolution profile of ciprofloxacin bio-adhesive floating tablets**

**Desirability function, used to determine optimized batch:**

Desirability study was carried out individually and finally, all responses were combined. The optimization parameters were floating lag time, bioadhesive strength, percentage cumulative drug release at 12$^{th}$-hour interval. The best part of this study is no need of specific total buoyancy time of formulations [11]. Our target is to find desirability for

minimum floating lag time hence following equations to be followed: **$d_1$= {(U-y) / (U-T)}…… (4)**

Where U = Upper limit of all formulation floating leg time 467 second) y= Individual floating lag time T= Targeted floating lag time, as per counter plot chart (363.744 seconds). When y<T, T≤ y ≤U, y>U

Our next target was to find desirability factor for maximum bioadhesive strength ($d_2$) and maximum dissolution profile at 12$^{th}$ hour ($d_3$), hence following equations has to be followed:

**Desirability factor for $d_2$ & $d_3$ = {(y-L)/ (T-L)}…… (5)**

When, y<L, L≤ y ≤T, y>T

L= Lower limit for bioadhesive strength and cumulative percentage drug release at 12$^{th}$ hour respectably (1.81 gm and 81.45%)

y= Individual bioadhesive strength and percentage cumulative drug release at the 12$^{th}$ hour

T= Targeted bioadhesive strength (as per counter plot, 2.81 gm) and targeted cumulative percentage drug release at the 12$^{th}$ hour (as per counter plot, 90.294%).

The overall desirability factors for all the 13 formulations was calculated by the following equation:

**The overall desirability (D) = (d1×d2×d3……dm) $^{1/m}$ …… (6)**

Where m is the number of responses. The overall desirability value should be below 1 as the range is within 0-1 if the value goes beyond 1 than formula must be rejected. But the maximum value (near 1) was to be considered for the optimizing batch. The optimized batch was found to be CF13 as it produces maximum D value (rejecting above 1 values) that is 0.920.Hence, optimized polymer concentrations are: HPMC K15M (12%), carbopol 934P (9%), CMC (6%) (Table: 17).

**Table 17: Desirability studies on various formulations**

| Formulation code | $d_1$ | $d_2$ | $d_3$ | D |
|---|---|---|---|---|
| **CF1** | 0.668 | 1.300 | 0.870 | 0.910 |
| **CF2** | 1.685 | 0.200 | 1.802 | 0.846 |
| **CF3** | 0.000 | 2.400 | 0.271 | 0.000 |
| **CF4** | 0.309 | 2.300 | 0.422 | 0.669 |
| **CF5** | 0.106 | 2.750 | 0.000 | 0.000 |
| **CF6** | 1.743 | 2.450 | 1.745 | 1.953 |
| **CF7** | 0.532 | 2.170 | 0.660 | 0.913 |
| **CF8** | 2.043 | 0.110 | 1.858 | 0.749 |
| **CF9** | 1.278 | 1.050 | 1.437 | 1.241 |
| **CF10** | 1.501 | 0.430 | 1.800 | 1.050 |
| **CF11** | 2.149 | 0.000 | 1.934 | 0.000 |
| **CF12** | 0.910 | 0.870 | 1.327 | 1.016 |
| **CF13** | 1.181 | 0.530 | 1.243 | 0.920 |

K**inetic studies:** The obtained data from dissolution studies was fitted to various kinetic studies. The purpose of this study was to find the proper kinetic model for optimized batch (CF13) and rest of the others (Figure 10 & Table: 18).

**Table 18: Kinetics studies on drug released profiles of formulation batches**

| Formulation code | Zero | First | Higuchi | Peppas | $K_1$ | Best fit model |
|---|---|---|---|---|---|---|
| **CF1** | 0.9758 | 0.9607 | 0.9843 | 0.6015 | 0.166 | Higuchi |
| **CF2** | 0.9636 | 0.8813 | 0.9895 | 0.5515 | 0.250 | Higuchi |
| **CF3** | 0.9870 | 0.9685 | 0.9759 | 0.6618 | 0.133 | Zero order |
| **CF4** | 0.9846 | 0.9693 | 0.9769 | 0.6275 | 0.146 | Zero order |
| **CF5** | 0.9877 | 0.9744 | 0.9740 | 0.6693 | 0.128 | Zero order |
| **CF6** | 0.9842 | 0.8677 | 0.9762 | 0.6424 | 0.227 | Zero order |
| **CF7** | 0.9890 | 0.9403 | 0.9608 | 0.6349 | 0.150 | Zero order |
| **CF8** | 0.9755 | 0.8353 | 0.9785 | 0.5608 | 0.242 | Zero order |
| **CF9** | 0.9874 | 0.8914 | 0.9708 | 0.6417 | 0.196 | Zero order |
| **CF10** | 0.9622 | 0.9149 | 0.9901 | 0.5567 | 0.255 | Higuchi |
| **CF11** | 0.9844 | 0.8117 | 0.9801 | 0.6385 | 0.259 | Zero order |
| **CF12** | 0.9821 | 0.9378 | 0.9803 | 0.6368 | 0.192 | Zero order |
| **CF13** | **0.9886** | **0.9126** | **0.9689** | **0.6552** | **0.178** | **Zero order** |

After kinetic study it was confirmed that CF13 batch possessed best zero order modeling, hence it was confirmed that CF13 was best-optimized batch.

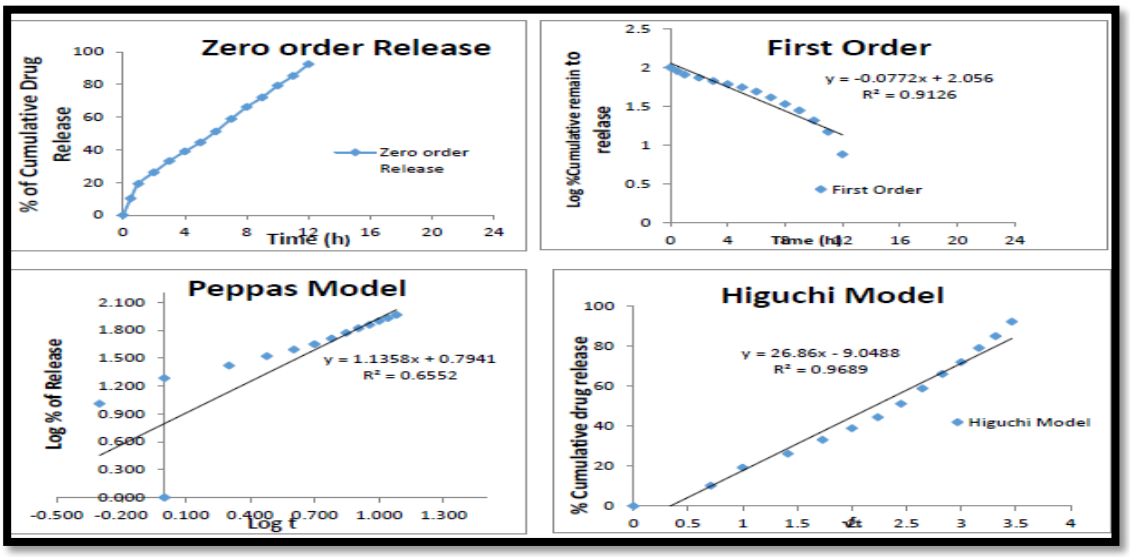



**Figure 10: Kinetic profile of CF13 formulation**

**Similarity and Dissimilarity study:** This approach uses a difference factor ($F_1$) and similarity factor ($F_2$) to compare the dissolution profile of optimized CF13 profile and along with marketed product; Cifran-OD (ciprofloxacin floating tablets) manufactured by Ranbaxy, India limited. The difference factor (F1) calculates the percent (%)

difference the two curves at each time point and is a measurement of the relative error between the two curves:

$$F_1 = \{[\sum_{t=1}^{n} |Rt - T1|] / [\sum_{t=1}^{n} Rt]\} \times 100 \ldots\ldots (7)$$

Where n= number of time point, Rt = dissolution value of the reference batch at time t
Tt= dissolution value of the test batch at time t
Similarity factor (F2) is a logarithmic reciprocal sequence root transformation of the sum of squared error and is the measurement of the similarity in the percentage (%) dissolution between the curve

$$F2 = 50.\log \left\{ \left[ 1 + (1/n) \sum_{t=1}^{n} |Rt - Tt|^2 \right]^{-0.5} \times 100 \right\} \ldots\ldots (8)$$

In order to calculate the difference and the similarity factor, first, the dissolution profile should be done. The difference factor (F1) and similarity factor (F2) can be calculated using the mean dissolution value from both curves at each time interval. If the value is more than 50 it is similar (F2) (Figure: 11 & Table: 19). If the value is less than 50 it is Dissimilar or difference (F1) [12].

**Table 19: Similarity and difference factor study result on CF13 and Cifran-OD formulation**

| Time in hour | %CDR of Cifran OD (Reference sample)-Rt | %CDR of CF13(Test sample)-Tt | Rt-Tt | $(Rt-Tt)^2$ | \|Rt-Tt\| |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 0.5 | 7.16 | 10.22 | -3.06 | 9.3636 | 3.06 |
| 1 | 21.48 | 19.25 | 2.23 | 4.9729 | 2.23 |
| 2 | 33.19 | 26.26 | 6.93 | 48.0249 | 6.93 |
| 3 | 40.28 | 33.16 | 7.12 | 50.6944 | 7.12 |
| 4 | 46.82 | 39.04 | 7.78 | 60.5284 | 7.78 |
| 5 | 52.92 | 44.52 | 8.4 | 70.56 | 8.4 |
| 6 | 59.92 | 51.27 | 8.65 | 74.8225 | 8.65 |
| 7 | 64.15 | 58.91 | 5.24 | 27.4576 | 5.24 |
| 8 | 71.73 | 66.23 | 5.5 | 30.25 | 5.5 |
| 9 | 79.12 | 72.14 | 6.98 | 48.7204 | 6.98 |
| 10 | 89.29 | 79.29 | 10 | 100 | 10 |
| 11 | 95.23 | 85.21 | 10.02 | 100.4004 | 10.02 |
| 12 | 101.9 | 92.45 | 9.45 | 89.3025 | 9.45 |
| **N=14** | **Summation of the Rt= 763.19** | **Difference factor(0-15) F1=11.97080675** | | **Summation of (Rt-Tt)$^2$= 715.0976** | **Sum of \|Rt-Tt\|= 91.36** |
| **Similarity Factor(50-100) F2=57.08355918** | | | | | |

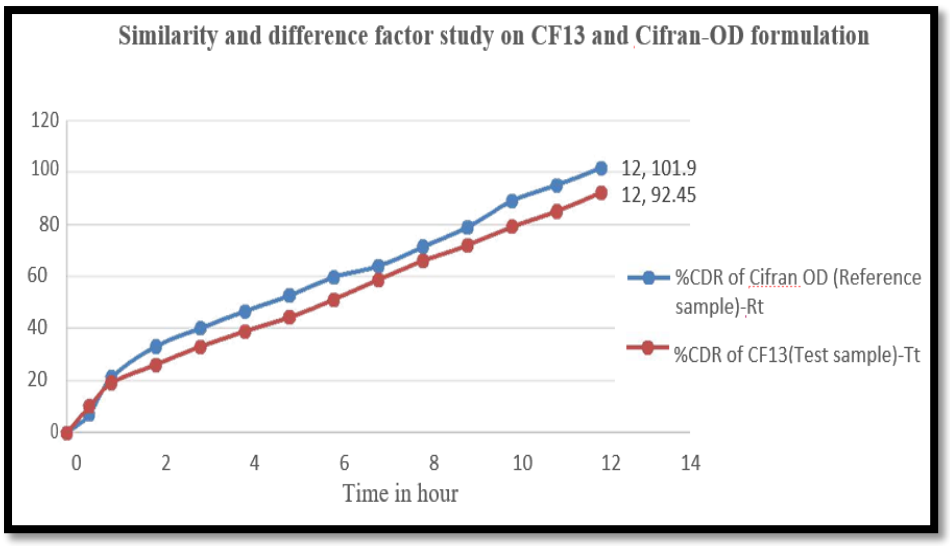



**Figure 11: Dissolution profile of CF13 and Cifran-OD tablets**

**Stability study report:**

Stability studies were performed on CF13 batches for 6month. The stability parameters such as hardness, drug content, *in vitro* dissolution, floating lag time, floating duration, matrix integrity, bioadhesive strength was recorded. The results were satisfactory up to a 5$^{th}$ month, but on 6$^{th}$ month the standard parameters start deviating and some kind of alteration took place. Which makes us conclude that after the 6$^{th}$ month of accelerated stability study [13] the formulation was started deteriorating (Figure: 12 & Table: 20).

**Table 20: Accelerated stability studies on CF13 formulation, as per ICH guideline Q1A (R2) at 40°C ± 2°C/75% RH ± 5% RH for 6 month**

| Stability parameters | 1$^{st}$ month | 2$^{nd}$ month | 3$^{rd}$ month | 4$^{th}$ month | 5$^{th}$ month | 6$^{th}$ month |
|---|---|---|---|---|---|---|
| **Hardness(Kg/cm$^2$)** | 4.3 | 4.1 | 4.1 | 3.7 | 3.4 | 2.8 |
| **Drug content (%)** | 97.01 | 96.28 | 95.19 | 92.25 | 89.31 | 87.22 |
| **Floating lag time(seconds)** | 340 | 334 | 331 | 324 | 312 | 282 |
| **Floating duration(Hours)** | <10 | <10 | >10 | >10 | >8 | >6 |
| **Bioadhesive strength(mg)** | 2.12 | 2.09 | 2.01 | 1.98 | 1.92 | 1.62 |

**Table 21: As per ICH guideline Q1A (R2) *in –vitro* dissolution studies on CF13 formulation**

| Time In hour | %CDR at 1st month | %CDR at 2nd month | %CDR at 3rd month | %CDR at 4th month | %CDR at 5th month | %CDR at 6th month |
|---|---|---|---|---|---|---|
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 0.5 | 11.22±0.12 | 13.34±0.22 | 15.29±0.23 | 16.87±0.12 | 16.38±0.91 | 18.25±1.23 |
| 1 | 19.25±0.23 | 21.98±0.11 | 20.21±0.18 | 21.23±0.23 | 25.13±0.29 | 30.13±1.21 |
| 2 | 29.21±0.11 | 30.13±0.34 | 34.12±0.91 | 37.23±0.34 | 33.16±0.27 | 44.17±1.24 |
| 3 | 37.66±0.45 | 39.29±0.46 | 40.19±0.29 | 43.81±1.23 | 43.14±0.28 | 50.26±1.87 |
| 4 | 40.00±1.02 | 43.38±0.34 | 47.13±2.01 | 49.19±0.13 | 52.09±0.25 | 58.34±0.96 |
| 5 | 48.11±0.23 | 50.14±0.02 | 54.19±1.03 | 55.19±0.23 | 60.11±1.08 | 65.21±0.23 |
| 6 | 57.34±0.35 | 56.34±0.45 | 59.28±1.93 | 64.10±0.22 | 65.23±1.09 | 70.12±0.08 |
| 7 | 64.11±0.98 | 63.98±0.32 | 65.29±0.13 | 70.23±0.21 | 74.12±1.22 | 78.19±1.23 |
| 8 | 69.24±0.34 | 70.25±0.45 | 73.15±0.25 | 75.22±0.34 | 79.28±1.34 | 84.98±1.03 |
| 9 | 78.18±0.93 | 76.81±0.21 | 79.26±0.20 | 81.23±0.19 | 87.18±1.34 | 90.25±1.97 |
| 10 | 80.30±0.11 | 83.98±0.34 | 86.26±2.93 | 89.13±0.25 | 95.29±1.25 | 96.24±0.97 |
| 11 | 88.27±0.45 | 91.81±0.22 | 93.29±1.90 | 94.19±0.01 | 99.25±1.34 | 103.17±0.23 |
| 12 | 96.29±0.22 | 98.23±0.14 | 99.14±0.15 | 101.27±0.24 | 104.89±0.14 | 108.90±1.34 |

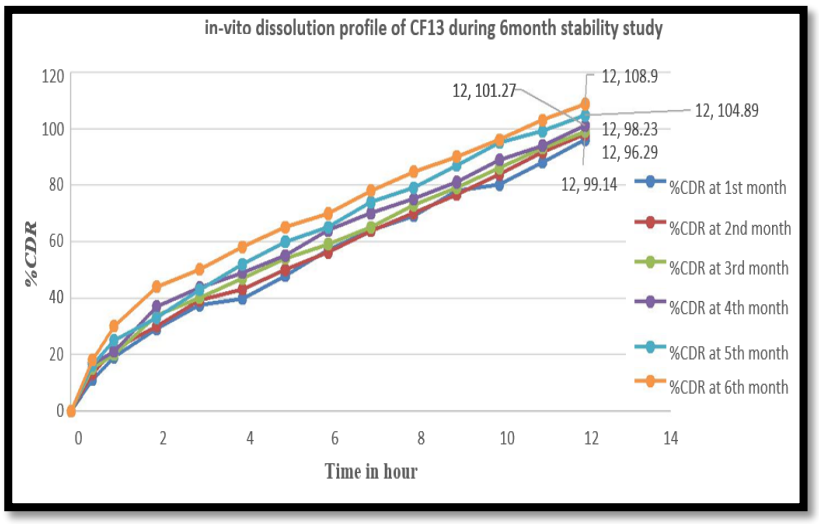



**Figure 12: Comparative dissolution profile of CF13 during 6 months accelerated stability study**

**Discussion:**

Ciprofloxacin hydrochloride was used as a model drug while developing floating bio-adhesive approach. In the modern era of controlled drug delivery system, new modification is mandated. Simple floating drug delivery for upper stomach targeting sometimes causes burst effect and toxicity. We try to figure out this prior art and developed floating bio-

adhesive tablet with an advanced approach to make it adhere after floating on the surface of the upper stomach. Based on Placket and Burman Design model we optimized 3 different polymers (independent variables) such as HPMC K15M (0-16%), carbopol 934P (06-12%), CMC (03-09%) used. The resulting output was monitored and optimization was done by taking dependent variables like floating lag time (245- 267seconds), bioadhesive strength (1.81-4.56gm), cumulative percentage drug release at the $12^{th}$ hour (81.45 -98.56%). Using design expert software (version 7.0.0) statistical regression analysis was done using a reduced model equation. 3D surface modeling and counter graphs were plotted against optimum concentrations of polymers and various dependent variables. ANOVA studies revealed that the F value of all the 3 dependent variables; floating lag time (F=63. 9463), bioadhesive strength (F= 26.897), cumulative percentage drug release at $12^{th}$ hour (F=38. 166) were much higher than the significant F value, respectively, hence it can be concluded that null hypothesis can be rejected and alternative hypothesis or design model for all 3 dependable variables can be selected. All the 3 polymers have significance at the floating lag time, bioadhesive strength, and cumulative drug release at the $12^{th}$ hour because all 3 intercept P value were < 0.0001.Finally by using overlay model predicted responses were recorded. The result of checkpoint batches shown <9% standard error which indicates well-optimized formulation. Further desirability studies were performed and it was assumed that CF13 possess a significant amount of desirability (D=0. 920), further to prove its desirability kinetic modeling studies were inspected. Again CF13 turns out to be the best formulation as it has zero order kinetics with an $R^2$ value of 0.9886. CF13 formulation was considered as optimized one and further studies were carried. For difference (F1) and similarity (F2) factor studies Cifran-OD tablets were taken as a reference and CF13 formulation was taken as a standard. F1and F2 value was found to be 11.9780 and 57.083 respectively, which indicates good dissolution profile against Cifran-OD tablet. As per ICH Q1A (R2), guideline accelerated stability studies were done. It was found that CF13 batch starts deteriorating after the $6^{th}$ month.

**Conclusion:**

Ciprofloxacin, a BCS classic III drug was used as a model while designing this approach. Ciprofloxacin basically a quinolone antibiotic, which has versatile uses. Ciprofloxacin has a maximum therapeutic window which is available in the upper stomach (fundus part). But commercial oral dosage form cannot target the desired site, hence floating bio-adhesive approach has incited. Since it is a BCS III drug, it has its own limitation on permeability. To tackle all this kind of obstacles, constant zero order release was targeted. By designing formulations using design expert (7.0.0) software, it was concluded that CF13 possess a good profile of drug release and stability. Hence present formulation can be considered for scaled up.

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