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# "FORMULATION AND EVALUATION OF AN ANTIMICROBIAL DRUG LOADED HYDROGEL MATRIX TABLETS FOR CONTROLLED DRUG DELIVERY"

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## ABSTRACT

The objective of present study was to prepare Ciprofloxacin Hydrochloride (CPH) loaded controlled release matrix tablets using a new polymer combination of Methyl cellulose A4 and Polyox WSR 303 in varying ratios by direct compression technique. Differential Scanning Calorimetry (DSC) measurements were carried out on the drug polymer mix and pure polymers Methyl cellulose A4 and Polyox WSR 303. A $3^2$ Full Factorial design was employed to optimize the matrix tablet formulation of Ciprofloxacin Hydrochloride (CPH) by selecting amount of Methyl Cellulose and Polyox WSR 303 as independent variables and their effects were observed on $T_{50}$, $T_{90}$, and % Swelling index. The optimized batch was examined for *in-vitro* drug release and pharmacokinetics in animals. The antimicrobial activity against *B. subtilis* and *E. coli* was determined. The optimized batch gave desired results at 5 hrs as time for 50% drug release at 23 hrs as time for 90% drug release and % swelling index as 45%. The kinetic model fitting of the optimized batch showed Weibull distribution as mechanism of drug release having 0.966 $R^2$ value for CPH from the matrix tablet.Pharmacokinetics (Non- compartmental analysis) in animals revealed $C_{max}$= 3.08 µg/mL, $T_{max}$ = 6hr, $AUC_{24}$= 45.18 µg/mL*hr, MRT = 21.93 µg/mL*hr, $T_{1/2}$= 13.4 hr and $K_e$= $0.0154^{-1}$. Compartmental analysis showed as per the following $K_a$= $0.64^{-1}$, $T_{max}$ = 4.36hr, $AUC_{24}$= 45.63 µg/mL*hr, MRT = 19.58 µg/mL*hr, $T_{1/2}$= 1.15hr and $K_e$= $0.64^{-1}$.

**KEYWORDS:** Controlled release drug delivery, hydrogel tablet, Ciprofloxacin Hydrochloride, matrix tablet, Antimicrobial.

## INTRODUCTION

Basic rationale is to prepare a controlled release dosage form in the form of tablets using hydrophilic polymers which form polymeric network due to which drug release is controlled and extended. Direct Compression technique was employed to limit number of additives and steps in making process. This formulation composition is expected to improve the efficacy at the site maintaining uniform constant release of drug in a controlled manner, thereby decreasing undesirable side effects and better patient compliance due to reduced dosing frequency along with low cost therapy.

Ozeki and Co-workers have examined effect of complex containing Methyl Cellulose (MC) and Carboxyvinyl Polymer for controlled release of Phenacetin.[1,2] Different combinations of high molecular weight PEOs (3,000,000–7,000,000 Da) have been employed by several scientists as swelling agents for modulating release of drugs.[3,4,5] We thought of employing a new combination, such as a mixture of PEO WSR 303 and Methyl cellulose in a varying concentration to control and extend release of Ciprofloxacin Hydrochloride (CPH).

CPH is a broad spectrum fluoroquinolone antibiotic having half-life between 4 to 6 hours after oral administration. It is rapidly and well absorbed from gastro-intestinal tract. From the year 2000 onwards antimicrobial agents began to be employed in design of controlled release dosage forms and more work is yet to be done. Therefore we thought of formulating CPH in controlled release drug delivery system.

CPH is a broad spectrum antimicrobial agent that is used in various infections such as urinary tract, lower respiratory tract, complicated abdominal, bone and joint, nosocomial pneumonia, acute sinusitis, skin and skin structure, typhoid fever, uncomplicated cervical and urethral gonorrhea.[6,7] The prescribed dose varies from 250 mg to 750 mg based on the acute and chronic condition of the patient. Frequency of dosing is every 12 to 24 hours for a duration ranging from 3 to 7 to 14 days.[8]

CPH is the most frequently prescribed fluoroquinolone for UTIs because of its availability in oral and intravenous formulations. It is well absorbed from oral

doses and is rapidly excreted from the body under normal conditions.[6,7,8]

This dosage form is formulated in the form of matrix tablets using two different polymers Methyl cellulose A4 and Polyox WSR 303.[9] in which the drug was dispersed homogenously. CPH has proper biopharmaceutical characteristics for its controlled release; therefore it was selected for present study. The present system was expected to release the drug in a continuous manner as diffusion controlled mechanism. Microcrystalline Cellulose was used as direct compression vehicle.

The compositions of extended release matrix tablets containing lactose showed rapid release of the drug. MCC was selected as direct compression excipient to process the tablets. MCC acts as a weakly swellable filler therefore remained within the gel layer enabling slower drug release. Reports also showed that MCC could show greater binding capacity.[10,11]

A number of workers have their formulation developed by preparing pH responsive in-situ gel,[12] Ciplox effervescent tablets by direct compression and wet granulation,[13] floating tablets by dry granulation technique,[14] a sustained release formulation using various grades of HPMC,[15] Ciprofloxacin hydrochloride nanoparticles.[16]

## MATERIALS AND METHODS

CPH was a gift from Alkem Laboratories, Mumbai, India. Methyl cellulose A4, Microcrystalline cellulose (MCC), Magnesium stearate and Talc were obtained from S. D. fine chemicals, India; Polyox WSR 303 was gifted by Sun pharmaceuticals Ltd, Vadodara, India. All other chemicals and reagents used were of analytical grade.

### Characterization of Drug (CPH) and Excipients (Methyl cellulose A 4 and Polyox WSR303)

### Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) was performed using a Shimadzu Corporation (DSC-60), Japan. Drug, polymer, and the drug-polymer complex were subjected to the DSC study. Samples were heated at a scanning rate of 20 LC/min from 50 to 300 LC under nitrogen air. Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. DSC scans of about 5 mg; using an automatic thermal analyzer system performed accurately weighed drug, polymer and complex containing the same amount of drug.[17]

### Fourier Transform Infra-Red (FTIR) Spectroscopy[19]

Drug, polymer and drug polymer complex were subjected to IR spectroscopy to check the drug polymer interaction using FT-IR (SHIMADZU 8400 S).

### Preparation of Hydrogel Matrix Tablet

A hydrophilic polymer Polyox WSR 303 and a cellulose derivative Methylcellulose A4 were used in formulation. The other excipients used were Microcrystalline cellulose (MCC) as direct compression vehicle, Magnesium stearate as lubricant and Talc as glidant.

The polymers were accurately weighed and triturated with CPH and MCC which was passed through Sieve no 120#. Then Magnesium stearate and talc were added and directly compressed in rotary compression machine. $3^2$ Full factorial design was employed in preparing various batches shown in below table.

**Table 1: $3^2$ full factorial design of F1-F9 batches.**

| Formulation Ingredients | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| Ciprofloxacin Hydrochloride | (mg) | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| Methyl cellulose A 4 | Transformed | -1 | -1 | -1 | 0 | 0 | 0 | +1 | +1 | +1 |
| | Actual (mg) | 80 | 80 | 80 | 100 | 100 | 100 | 120 | 120 | 120 |
| Polyox WSR 303 | Transformed | -1 | 0 | +1 | -1 | 0 | +1 | -1 | 0 | +1 |
| | Actual | 80 | 90 | 100 | 80 | 90 | 100 | 80 | 90 | 100 |
| MCC | (mg) | 80 | 70 | 50 | 60 | 50 | 30 | 40 | 30 | 20 |
| Magnesium Stearate | (mg) | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Talc | (mg) | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Total weight of tablet | (mg) | 750 | 750 | 750 | 750 | 750 | 750 | 750 | 750 | 750 |

Our hypothesis contained two independent variables, namely

$X_1$ = Concentration of Methyl cellulose A 4 and $X_2$= Concentration of Polyox WSR 303 effects of which were investigated on dependent variables, namely, $Y_1 = T_{50}$ (time required to release 50% drug) in hrs, $Y_2 = T_{90}$ (time required to release 90% drug) in hrs and $Y_3$ = % swelling index at 3 hr. The results are shown in table 5.

### Characterization of Pre compression and Post compression[20]

### Characteristics of Pre compression

The following characteristics of controlled release CPH formulation were evaluated:

1. Bulk density
2. Tapped density
3. Hausner's ratio
4. Carr's Index or % Compressibility

5. Angle of Repose

**Characteristics of Post compression**

The following characteristics of controlled release CPH tablets were evaluated:

1. Weight variation
2. Tablet Thickness and diameter: Thickness and diameter was measured by Vernier calipers.
3. Tablet Hardness: It was measured by using Monsanto hardness tester.
4. Friability: It was measured by using Roche friabilator.
5. Swelling Index
6. *In-vitro* dissolution study[21]

The content of drug in the tablets was estimated by using UV/Visible spectrophotometric method. The measurement of absorbance at $\lambda_{max}$ of 277 nm in 0.1 N HCL at pH 1.2 for 2 hours and in pH 6.8 phosphate buffer solutions at 271 nm for 16 hours.

*In vitro* release studies of formulations were carried out in the USP dissolution apparatus type II (Paddle). The tests were carried out using 900 ml of dissolution media at 75 rpm at 37 ± 0.5℃, Aliquots of 5 ml, from the dissolution medium are withdrawn at 1 hr time interval and same was replaced by fresh dissolution medium to maintain sink condition. The sample collected was filtered and suitable dilution was carried out by analyzing for % drug release by measuring its absorbance at suitable λ max using dissolution medium as blank. The percentage drug release was calculated and graph was plotted of cumulative percentage drug release versus time (hrs).

**7. Antimicrobial study[22]**

Microbiological assay was performed using *B. subtilis* and *E. coli* under aseptic conditions. The results are shown in the table 15.

**8. Pharmacokinetic study[23]**

The pharmacokinetic study was performed in Adult wistar albino rats as per the guidelines of committee for the purpose of control and supervision of experiments on Animals (CPCSEA), Ministry of social justice and Empowerment, Government of India. Prior permission of experiments on animals was taken from the Institutional Animal Ethics Committee. Adult wistar albino rats, either sex having weight of 250-300mg were selected for experimental purpose. All the animals were housed at ambient temperature (22±1℃), relative humidity (55±1%) and 12 h light and dark cycles. Animals had free access to standard pellet diet and water ad libitum.

Treatment protocol

| Group no. | Treatment | No. of Rats |
|---|---|---|
| 1 | Control (saline solution) | 6 |
| 2 | Test (CPH controlled release tablet) | 6 |
| Total | | 12 |

**Methodology**

Rats were divided into 2 main groups, Control and test groups, each group contained 6 animals. Control group was given normal saline. Test group was given controlled release Ciprofloxacin hydrochloride dosage form.

**Drug Assay**

Under light ether anesthesia, blood samples were collected from retro-orbital vein at 0 (predose), 1, 2, 3, 4, 24 hours post dose into heparinized tube. Plasma samples were prepared by centrifugation for 15 minutes at 2500 RPM at room temperature. Plasma concentrations were determined by using UV/Visible Spectrophotometer at λ max 277nm.

**RESULTS AND DISCUSSION**

**Characterization of Drug (CPH) and Excipients (Methyl cellulose A 4 and Polyox WSR303)**

**Differential Scanning Calorimetry**

Obtained DSC thermograms of pure drug CPH in Fig.1, Polyox WSR 303 and Methyl cellulose A4 and the mixture of all ingredients in the proportion 1:1 are compiled in Fig.2. Summary of thermal parameters of DSC study of CPH in combination with each of the formulation excipients and the changes that occurred with characteristic endothermic peak of CPH is provided in Fig. 2. From DSC thermogram (Fig.2.) it is clear that the thermograms of the mixtures containing CPH in combination with Polyox WSR 303 and Methyl cellulose A4 exhibit all the thermal features of the individual components. The DSC analysis shows no change in endothermic peak of CPH indicated that there was no drug excipient incompatibility/interaction.[18]

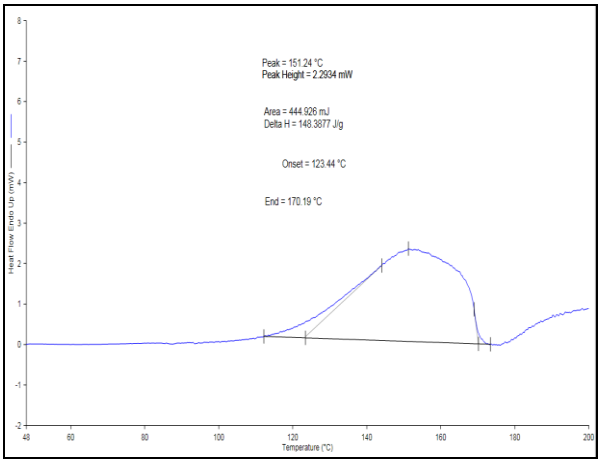


**Fig. 1: DSC of Ciprofloxacin Hydrochloride.**

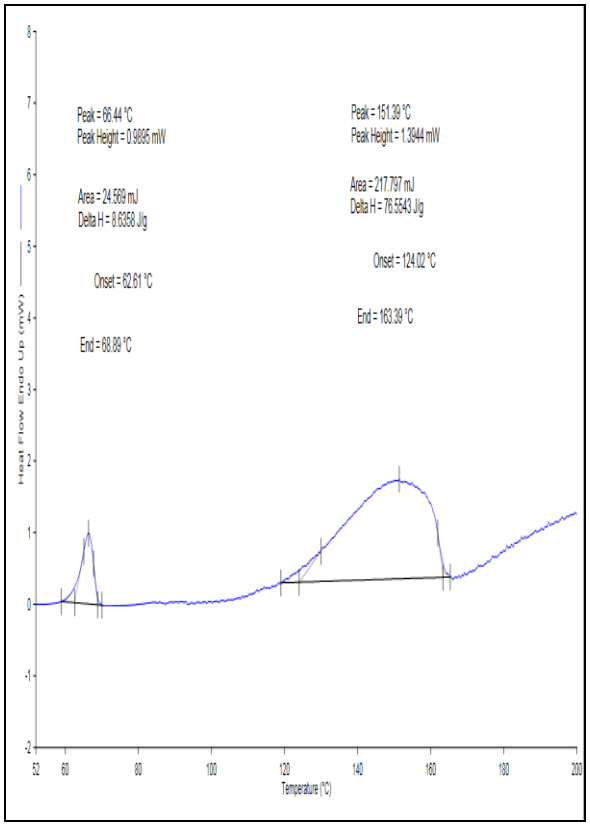


**Fig. 2: DSC of drug (CPH) with Excipients (Methyl cellulose and Polyox WSR 303).**

**Fourier Transform Infrared-Red Spectroscopy**

Fig.3. shows the FTIR spectrums of the pure drug CPH, physical mixture of CPH individually with Polyox WSR 303 and with Methyl Cellulose. No predominant drug interaction was detected. 3500-3450 (3521.78 cm-1) OH-group, 3000-2950 (2923.88 cm-1) Aromatic group, 1750-1700 (1731.96 cm-1) C=O group, 1650-1600 (1604.66 cm-1) Quinolines, 1450-1400 (1446.51 cm-1) Carbonyl group, 1300-1250 (1271.0 cm-1) Hydroxyl group, 1050-1000 (1035.70 cm-1) Flourine group.[18]

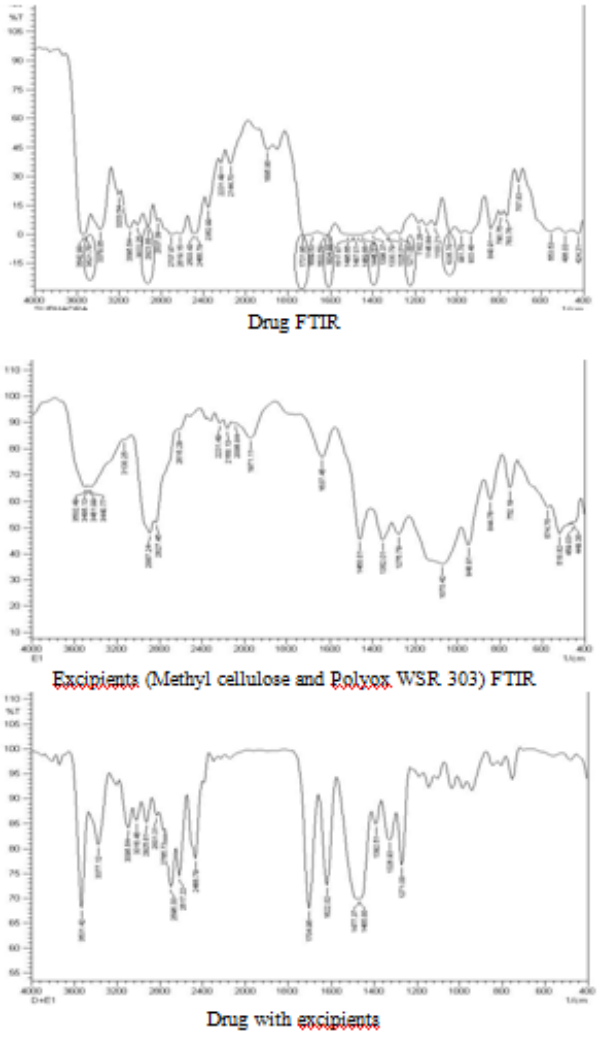


**Fig. 3: FTIR of drug (CPH), Excipients (Methyl cellulose and Polyox WSR 303) and Drug with Excipients.**

**Pre compression evaluation parameters of F1-F9.**

**Table 2: Pre-compression parameters of F1-F9.**

| Batches | Angle of repose ($\theta$) | Bulk density (g/cc) | Tapped density (g/cc) | Hausners ratio | Carr's Index |
|---|---|---|---|---|---|
| F1 | 37.86±0.20 | 0.31±0.00 | 0.40±0.00 | 1.27±0.01 | 22.18±0.03 |
| F2 | 36.08±0.04 | 0.28±0.00 | 0.41±0.00 | 0.14±0.00 | 29.90±0.07 |
| F3 | 29.15±0.28 | 0.28±0.00 | 0.36±0.00 | 1.26±0.01 | 19.91±0.07 |
| F4 | 24.50±0.05 | 0.28±0.00 | 0.36±0.00 | 1.41±0.01 | 19.13±0.74 |
| F5 | 32.57±0.15 | 0.28±0.00 | 0.41±0.00 | 1.24±0.00 | 15.25±0.38 |
| F6 | 34.89±0.05 | 0.27±0.00 | 0.38±0.00 | 1.37±0.01 | 27.40±0.07 |
| F7 | 35.51±0.13 | 0.26±0.00 | 0.37±0.00 | 1.36±0.00 | 27.15±0.09 |
| F8 | 25.46±0.11 | 0.29±0.00 | 0.38±0.00 | 1.25±0.00 | 19.70± 0.18 |
| F9 | 36.78±0.22 | 0.27±0.00 | 0.38±0.00 | 1.36±0.01 | 26.96±0.16 |

**Post-compression evaluation parameters of F1-F9 batches**

**Table 3: Post-compression parameters of F1-F9 batches.**

| Batches | Average Weight (mg) | Diameter (mm) | Thickness (mm) | Hardness (kg/cm$^2$) | %Friability | %Swelling Index at 3 Hr |
|---|---|---|---|---|---|---|
| F1 | 0.745±0.00 | 13 | 4.9±0.05 | 7.16±0.20 | 0.37±0.01 | 49.22±0.08 |
| F2 | 0.746±0.00 | 13 | 5.0±0.00 | 7.23±0.05 | 0.42±0.01 | 41.66±0.09 |
| F3 | 0.749±0.00 | 13 | 4.9±0.11 | 7.23±0.11 | 0.45±0.02 | 32.75±0.06 |
| F4 | 0.747±0.00 | 13 | 4.9±0.05 | 7.36±0.15 | 0.37±0.01 | 48.52±0.07 |
| F5 | 0.743±0.00 | 13 | 5.0±0.00 | 7.33±0.15 | 0.44±0.02 | 51.04±0.09 |
| F6 | 0.744±0.00 | 13 | 4.9±0.11 | 7.4±0.10 | 0.44±0.03 | 45.30±0.10 |
| F7 | 0.746±0.00 | 13 | 4.9±0.10 | 7.16±0.05 | 0.46±0.03 | 45.03±0.08 |
| F8 | 0.744±0.00 | 13 | 5.0±0.00 | 7.13±0.05 | 0.38±0.02 | 56.08±0.14 |
| F9 | 0.744±0.01 | 13 | 5.0±0.00 | 7.16±0.05 | 0.47±0.01 | 56.12±0.04 |

**Table 4: *In vitro* drug release data comparison of F1-F9.**

| Time (hr) | % Cumulative drug release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 1 | 5.82 ±0.04 | 5.72 ±0.02 | 2.61 ±0.03 | 5.28 ±0.01 | 10.82 ±0.01 | 9.29 ±0.02 | 7.61 ±0.02 | 6.49 ±0.01 | 3.17 ±0.01 |
| 2 | 17.33 ±0.25 | 17.26 ±0.03 | 11.27 ±0.06 | 17.23 ±0.02 | 15.59 ±0.01 | 21.90 ±0.01 | 23.94 ±0.03 | 22.37 ±0.01 | 15.40 ±0.01 |
| 3 | 27.85 ±0.03 | 30.90 ±0.02 | 18.39 ±0.02 | 31.02 ±0.06 | 32.26 ±0.05 | 35.47 ±0.01 | 35.63 ±0.02 | 33.18 ±0.02 | 29.25 ±0.02 |
| 4 | 35.87 ±0.03 | 47.28 ±0.05 | 25.65 ±0.03 | 48.41 ±0.06 | 41.11 ±0.02 | 46.06 ±0.02 | 48.27 ±0.03 | 37.97 ±0.01 | 41.86 ±0.02 |
| 5 | 60.95 ±0.03 | 56.66 ±0.04 | 41.31 ±0.02 | 61.62 ±0.01 | 51.28 ±0.03 | 49.39 ±0.01 | 50.86 ±0.02 | 49.60 ±0.03 | 46.30 ±0.02 |
| **Time (hr)** | **% Cumulative drug release** | | | | | | | | |
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| 10 | 74.45 ±0.03 | 67.10 ±0.02 | 61.77 ±0.02 | 67.18 ±0.03 | 66.75 ±0.04 | 63.91 ±0.02 | 62.09 ±0.07 | 66.03 ±0.02 | 62.35 ±0.04 |
| 14 | 80.46 ±0.04 | 72.42 ±0.02 | 66.19 ±0.04 | 72.41 ±0.05 | 75.56 ±0.05 | 72.90 ±0.01 | 69.82 ±0.03 | 72.45 ±0.03 | 68.35±0.02 |
| 18 | 84.60 ±0.02 | 77.28 ±0.07 | 70.57 ±0.02 | 79.92 ±0.03 | 80.06 ±0.03 | 79.29±0.01 | 79.21 ±0.02 | 79.46 ±0.01 | 73.83 ±0.02 |
| 22 | 91.44 ±0.03 | 81.63 ±0.02 | 78.95 ±0.02 | 86.47 ±0.02 | 84.79 ±0.01 | 85.68 ±0.03 | 86.81 ±0.02 | 85.45 ±0.03 | 79.83 ±0.02 |
| 24 | 91.44 ±0.03 | 96.60 ±0.02 | 90.85 ±0.01 | 91.95 ±0.02 | 96.52 ±0.05 | 94.50 ±0.02 | 97.06 ±0.02 | 96.07 ±0.02 | 90.07 ±0.01 |

***In vitro* drug release of F1-F9 batches**

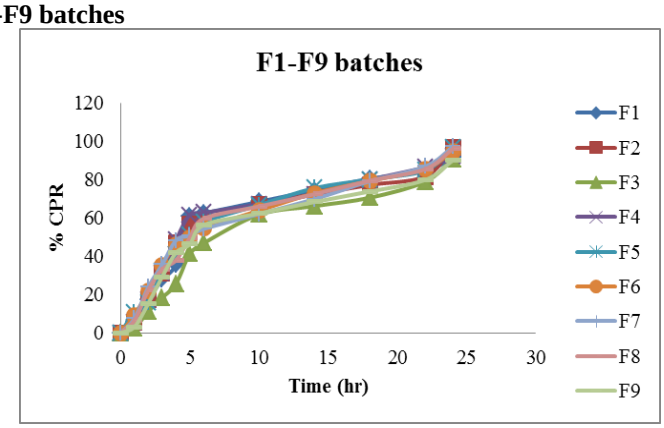


**Fig. 4: In vitro drug release profile of F1-F9.**

**Generation of full and reduced models for selected full factorial design**

**Table 5: Full factorial design with all polynomial terms.**

| Batches | $X_1$ | $X_2$ | $X_1X_1$ | $X_2X_2$ | $X_1X_2$ | $Y_1$ | $Y_2$ | $Y_3$ |
|---|---|---|---|---|---|---|---|---|
| **F1** | -1 | -1 | 1 | 1 | 1 | 4.50 | 23.70 | 49.26 |
| **F2** | -1 | 0 | 1 | 0 | 0 | 5.29 | 23.42 | 41.74 |
| **F3** | -1 | 1 | 1 | 1 | -1 | 6.47 | 23.83 | 32.8 |
| **F4** | 0 | -1 | 0 | 1 | 0 | 4.11 | 22.97 | 48.54 |
| **F5** | 0 | 0 | 0 | 0 | 0 | 4.87 | 22.78 | 45.04 |
| **F6** | 0 | 1 | 0 | 1 | 0 | 5.11 | 23.36 | 45.392 |
| **F7** | 1 | -1 | 1 | 1 | -1 | 4.66 | 23.18 | 51.06 |
| **F8** | 1 | 0 | 1 | 0 | 0 | 5.04 | 23.32 | 56.16 |
| **F9** | 1 | 1 | 1 | 1 | 1 | 5.30 | 23.99 | 56.16 |

**Regression analysis for effect $X_1$ and $X_2$ on $Y_1$**

**Table 6: ANOVA (analysis of variance) of $Y_1$.**

| Source | Sum of Squares | df | Mean Square | F Value | P-value Prob > F |
|---|---|---|---|---|---|
| Model | 3.41 | 5 | 0.68 | 20.38 | **0.0160** |
| $X_1$-MC | 2.17 | 1 | 2.17 | 64.93 | **0.0040** |
| $X_2$-Polyox | 0.26 | 1 | 0.26 | 7.91 | 0.0672 |
| $X_1X_2$ | 0.44 | 1 | 0.44 | 13.22 | **0.0358** |
| $X_1^2$ | 3.472E-003 | 1 | 3.472E-003 | 0.10 | 0.7685 |
| $X_2^2$ | 0.53 | 1 | 0.53 | 15.76 | **0.0286** |
| Residual | 0.10 | 3 | | | |

**Results of ANOVA and Regression of $Y_1$**

The Model F-value of 20.38 implies the model is significant. There is only a 1.60% chance that an F-value this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case **$X_1$, $X_1X_2$, $X_2^2$ are significant model terms**. Values greater than 0.1000 indicate the model terms are not significant.

**The R square value of $Y_1$= 0.9714.**

**Full model equation**

Full model equation in terms of **coded factors**

$T_{50}$= +4.72 + 0.60* $X_1$ - 0.21* $X_2$- 0.33 * $X_1X_2$ - 0.042 * $X_1$ 2 + 0.51 * $X^2_2$

Final equation in terms of **actual factors**

$T_{50}$ = +29.18194 + 0.20054 * MC -0.77875 * Polyox - 1.66250E - 003 * MC * Polyox -1.04167E - 003 * $MC^2$ + 5.13333E-003 * $Polyox^2$

**Reduced model equation**

Reduced model equation in the terms of **coded value**

$T_{50}$ = +4.72 + 0.60 * $X_1$ - 0.33 * $X_1$ $X_2$ + 0.51 * $X_2^2$

Reduced model equation in the terms of **actual factors**

$T_{50}$ = +4.72 + 0.60 * MethylCellulose - 0.33 * Methylcellulose and Polyox + 0.51 * $Polyox^2$

**DISCUSSION**

From the regression analysis for effect on dependent variables of independent variables shows **$X_1$, $X_1X_2$, $X_2^2$ are significant. $Y_1$- $T_{50}$ (Time required to release 50% drug)** shows effect on Concentration of MC, Interactive effect on MC and Polyox and Interaction of Polyox.

**Regression analysis for effect $X_1$ and $X_2$ on $Y_2$**
**Table 7: ANOVA of $Y_2$.**

| Source | Sum of Squares | df | Mean Square | F Value | p-value Prob > F |
|---|---|---|---|---|---|
| Model | 1.24 | 5 | 0.25 | 104.77 | 0.0015 |
| $X_1$-MC | 0.29 | 1 | 0.29 | 124.38 | 0.0015 |
| $X_2$-Polyox | 0.03 | 1 | 0.03 | 14.88 | 0.0308 |
| $X_1X_2$ | 0.12 | 1 | 0.12 | 48.77 | 0.0060 |
| $X_1^2$ | 0.22 | 1 | 0.22 | 92.81 | 0.0024 |
| $X_2^2$ | 0.58 | 1 | 0.58 | 243.01 | 0.0006 |

**Results** of ANOVA and regression of $Y_2$

The Model F-value of 104.77 implies the model is significant. There is only a 0.15% chance that an F-value this large could occur due to noise. In this case **$X_1$, $X_2$, $X_1X_2$, $X_1^2$, $X_2^2$ are significant model terms**.

**The R square value of $Y_2$ = 0.9943**

**Full model equation**
Final equation in terms of **coded factors**

$T_{90}$ = +22.82 + 0.22 * $X_1$ -0.077 * $X_2$ + 0.17 * $X_1X_2$ + 0.33 * $X_1^2$ + 0.54 * $X_2^2$

Final equation in terms of **actual factors**

$T_{90}$ = +81.80889 - 0.23125 * MC - 1.05867 *Polyox + 8.50000E - 004 * MC * Polyox + 8.29167E-004 * $MC^2$ + 5.36667E - 003 * $Polyox^2$

**Reduced model equation**
Reduced model equation in terms of **coded factors**

$T_{90}$ = +22.82 + 0.22 * $X_1$ - 0.077 * $X_2$ + 0.17 * $X_1X_2$ + 0.33 * $X_1^2$ + 0.54 * $X_2^2$

Reduced model equation in terms of **actual factors**

$T_{90}$ = +81.80889 - 0.23125 * MC - 1.05867 * Polyox + 8.50000E - 004 * MC * Polyox + 8.29167E - 004 * $MC^2$ + 5.36667E - 003 * $Polyox^2$

**DISCUSSION**
From the regression analysis for effect on dependent variables of independent variables shows **$X_1$, $X_2$, $X_1X_2$, $X_1^2$, $X_2^2$** are significant. **$Y_2$- $T_{90}$ (Time required to release 90% drug)** shows effect on Concentration of MC and Polyox WSR 303, Interactive effect on MC and Polyox and Interaction of MC and Polyox.

**Regression analysis for effect $X_1$ and $X_2$ on $Y_3$**
**Table 8: ANOVA table of $Y_3$.**

| Source | Sum of Squares | Df | Mean Square | F Value | p-value Prob > F |
|---|---|---|---|---|---|
| Model | 412.39 | 3 | 137.46 | 49.03 | **0.0004** |
| A-MC | 35.09 | 1 | 35.09 | 12.52 | **0.0166** |
| B-Polyox | 261.10 | 1 | 261.10 | 93.13 | **0.0002** |
| AB | 116.21 | 1 | 116.21 | 41.45 | **0.0013** |
| Residual | 14.02 | 5 | 2.80 | | |

**Results** of ANOVA and regression of $Y_3$

The Model F-value of 49.03 implies the model is significant. There is only a 0.04% chance that an F-value this large could occur due to noise. In this case **$X_1$, $X_2$, $X_1X_2$ are significant model terms.**

**The R square value of $Y_3$ = 0.9671.**
**Full model equation**

Final equation in terms of **coded factors**
% Swelling index at 3 hr = + 47.35 - 2.42 * $X_1$ + 6.60 * $X_2$ +5.39 * $X_1X_2$

Final equation in terms of **actual factors**
% Swelling index at 3 hr = +242.62167 – 2.54642 * MC - 2.03533 * Polyox + 0.026950 * MC * Polyox

**Reduced model equation**
Reduced model equation in terms of **coded factors**
% Swelling index at 3 hr = + 47.35 - 2.42 * A + 6.60 * B + 5.39 * AB

Reduced model equation in terms of **actual factors**

% Swelling index at 3 hr = +242.62167 – 2.54642 * MC - 2.03533 * Polyox + 0.026950 * MC * Polyox

**DISCUSSION**
From the regression analysis for effect on dependent variables of independent variables shows **$X_1$, $X_2$, $X_1X_2$ are significant. $Y_3$ = % Swelling Index** shows effect on Concentration of MC and Polyox WSR 303, Interactive effect on MC and Polyox.

**Plot for Response Y**
**Contour plot and response surface plot for $Y_1$ response**

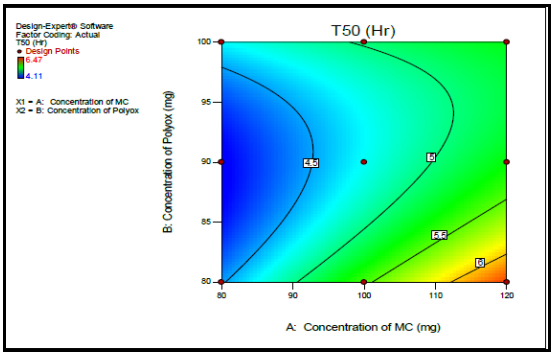


**Fig. 5: Contour plot for response $Y_1$.**

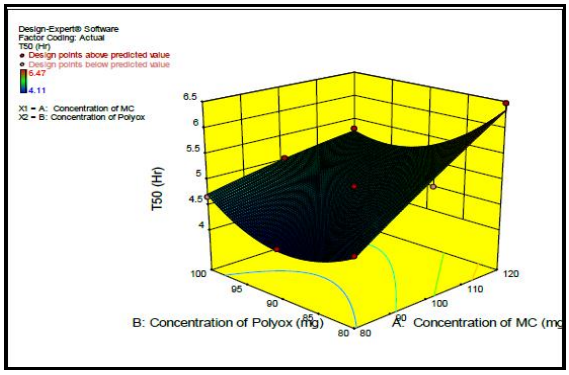


**Fig. 6: Response surface plot for Response $Y_1$.**

**Contour plot and response surface of $Y_2$ response**

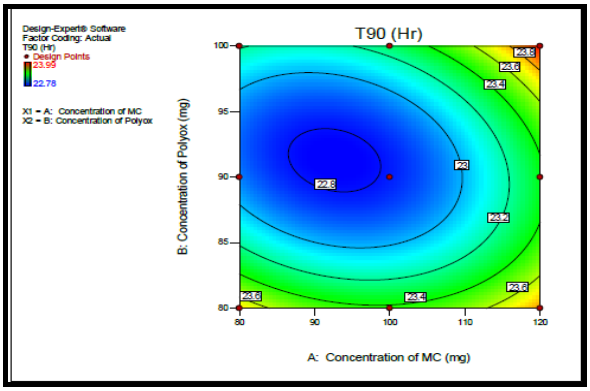


**Fig. 7: Contour plot for $Y_2$.**

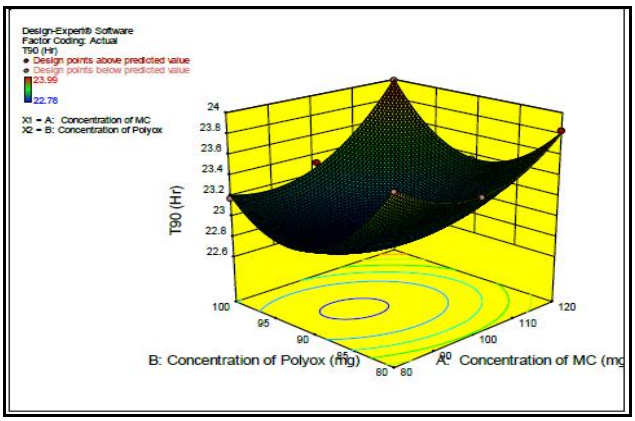


**Fig. 8: Response surface plot for $Y_2$.**

**Contour and response surface plot for $Y_3$ response**

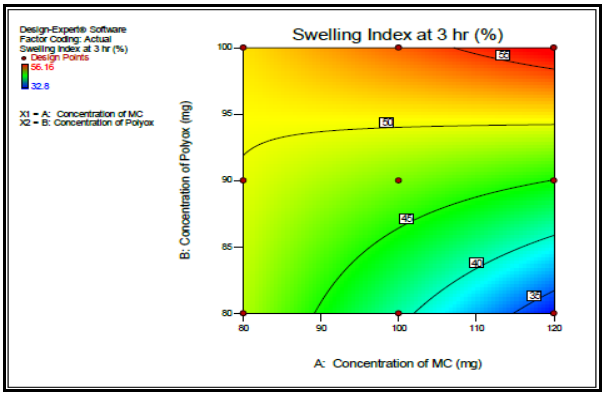


**Fig. 9 Contour plot for $Y_3$**

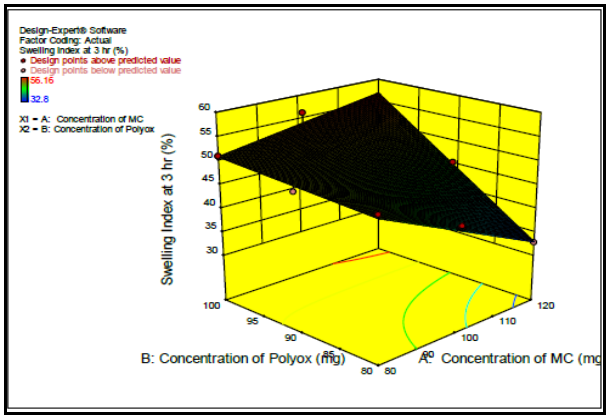


**Fig. 10 Response surface plot for $Y_3$**

**Development of the optimized batch based on response surface plot**

Optimization of the formula was carried out with the help of design of expert 10 by obtaining countour plots for the responses $Y_1$, $Y_2$, and $Y_3$, which shows two region of the optimal surface and from the middle region optimized composition was selected (as shown in fig.11.) Overlay plot of all the responses Y.

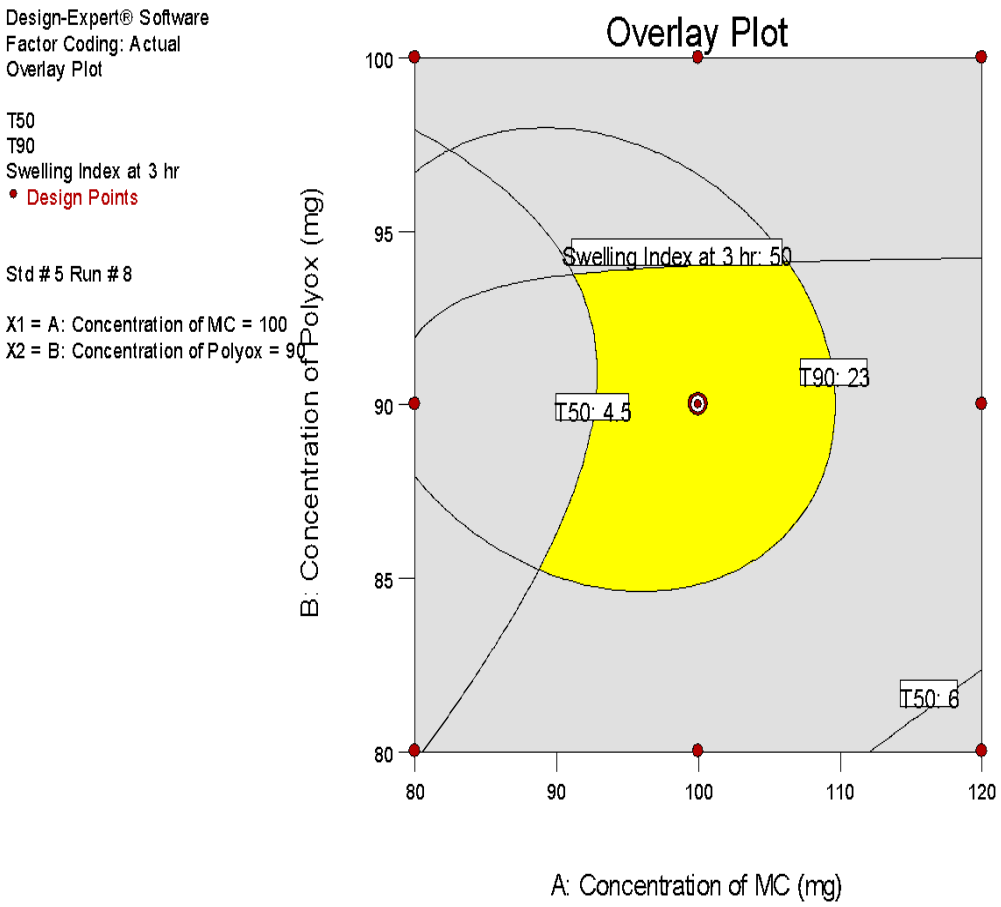


**Fig. 11: Overlay plot of Response Y.**

## DISCUSSION

From the overlay plot, different responses generated the optimized area as per requirement.

$Y_1$ response (time required to release 50% drug) was set in range as 4.5 to 6 hr, $Y_2$ response (time required to release 90% drug) was set in range as 22 to 23 hr, and $Y_3$ response (% Swelling Index at 3 Hr) was set in range as 32 to 50 %.

These requirements are satisfactory for controlled release of drug as per preliminary study and factorial design batches drug release. As shown from the overlay plot the optimized batch is found to be $X_1$ = Concentration of Methyl cellulose = 100 and $X_2$ = Concentration of Polyox = 90.

**Formulation and evaluation of optimized batch**

**Table 9: Optimized formula.**

| Optimized formula | |
|---|---|
| **Ingredients** | **Quantity (mg)** |
| Ciprofloxacin Hydrochloride | 500 |
| Methyl cellulose A 4 | 100 |
| Polyox WSR 303 | 90 |
| Microcrystalline cellulose | 50 |
| Magnesium stearate | 5 |
| Talc | 5 |
| Total weight | 750 |

**Table 10: shows evaluation of optimized composition of controlled release CPH tablets derived from overlay plot.**

| Evaluation parameters | Results | Property |
|---|---|---|
| Carr's Index (%) | 15.250 ±0.38 | Good |
| Hausner's Ratio | 1.243±0.00 | Fair |
| Angle of Repose ($\theta$) | 24.510 ±0.05 | Excellent |
| Hardness (kg/cm$^2$) | 7.330±0.15 | - |
| Friability (%) | 0.443±0.20 | - |

***In-vitro* drug release data of optimized batch**

**Table 11: *In-vitro* drug release study data of optimized batch.**

| Time (hr) | % Cumulative drug release | | | |
|---|---|---|---|---|
| | I | II | III | Average± standard deviation |
| 0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 1 | 13.78 | 13.87 | 13.92 | 13.85±0.07 |
| 2 | 34.19 | 34.16 | 33.89 | 34.08±0.16 |
| 3 | 47.23 | 47.57 | 47.45 | 47.41±0.17 |
| 4 | 53.16 | 53.32 | 53.26 | 53.24±0.08 |
| 5 | 71.92 | 72.05 | 71.12 | 71.69±0.50 |
| 6 | 73.09 | 73.18 | 73.21 | 73.16±0.06 |
| 8 | 74.13 | 74.36 | 74.38 | 74.29±0.01 |
| 10 | 74.96 | 75.09 | 75.14 | 75.06±0.13 |
| 12 | 75.16 | 75.27 | 75.29 | 75.24±0.01 |
| 14 | 75.96 | 75.98 | 75.89 | 75.94±0.09 |
| 16 | 81.29 | 81.36 | 81.41 | 81.35±0.01 |
| 18 | 84.19 | 84.30 | 84.37 | 84.28±0.07 |
| 20 | 84.67 | 84.71 | 84.76 | 84.71±0.01 |
| 22 | 89.89 | 89.93 | 89.96 | 89.92±0.05 |
| 24 | 99.20 | 99.22 | 99.17 | 99.19±0.01 |

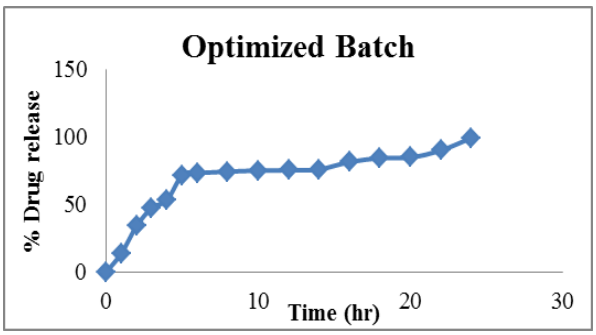


**Fig. 12: Percentage (%) drug release of Optimized batch.**

## DISCUSSION

Table 11 exhibits cumulative drug release of optimized batch from which it can be concluded that the combination of Methyl cellulose A4 and Polyox WSR 303 gives good controlled release of CPH tablet.

The drug release by combining high molecular weight of Polyox WSR 303 and Methyl cellulose is governed by the swelling of Polyox and MC rather than by erosion of the combination. When Polyox was used singly as a controlled release adjuvant 91.0 % of drug was released at 24 hour and MC alone would release the drug entire at 20th hour. Therefore optimized combination of both resulted in a successful controlled release of drug over 24 hours as shown in fig.12.

Fickian release of CPH might be due to strong hydrogen bond formation with 0.1 N HCl (pH 1.2). This was also observed by Maggi.[24] that high molecular weight Polyox showed greater swelling in comparison with low molecular weight PEO.

Sanjeevni et. al., have included Polyox WSR 303 in varying concentration with methocel K 15M, methocel K 100M they have shown retardation of release of drug up to 12 hours.[25]

**Kinetic model analysis of the drug release**

The drug release from the prepared hydrogel matrix tablets during *in-vitro* tests in pH 1.2 and Phosphate buffer pH 6.8 was determined and fitted using different kinetics model like zero order, first order, Higuchi and Korsmeyers Peppas, Weibull equation.

$(Mt/M\infty) = K\ t^n$

Where, K = Constant for the structural and geometric characteristics of the tablets,

n = Release exponent, indicate drug release mechanism and

$(M_t/M_1)$ = Drug dissolved fraction at time t.

Based on various kinetic models, the magnitude of the release exponent 'n' indicates the release mechanism of tablet. ([26])

**Table 12: Mechanism of drug release based on n value.**

| n value | Mechanism of Drug Release |
|---|---|
| <0.5 | Case I Fickian diffusion |
| 0.5-0.89 | Anomalous (Non Fickian Diffusion) |
| 0.89 | Case II Transport |
| >0.89 | Super Case II Transport |

Model fitting was done by DDsolver software.

**Results of kinetic model profile of optimized batch**

**Table 13: Results of drug release kinetic profile of optimized batch.**

| Kinetic model | Zero order | First order | Higuchi | Korsmeyer's Peppa's | Hixon crowell | Weibull |
|---|---|---|---|---|---|---|
| **K0** | 2.682 | 0.261 | 21.221 | 34.555 | 0.040 | - |
| **R2** | 0.692 | 0.950 | 0.807 | 0.914 | 0.736 | **0.966** |
| **MSE** | 180.179 | 30.426 | 108.471 | 50.438 | 148.274 | **21.984** |
| **AIC** | 212.236 | 168.658 | 198.613 | 180.406 | 206.428 | **161.371** |
| **MSC** | 0.561 | 2.304 | 1.106 | 1.834 | 0.794 | **2.596** |
| **n** | **0.318** | | | | | |

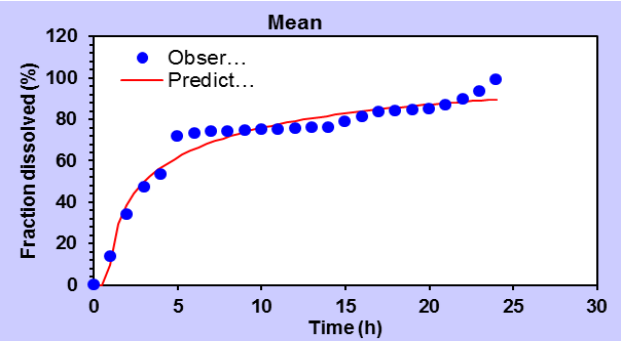


**Fig. 13: Weibull curve of drug release.**

The Weibull equation can be applied to almost all kinds of dissolution curves.[27,28,29] If applied to dissolution of pharmaceutical dosage form, this equation expresses the accumulation of fraction of drug in solution and is given by equation

M = M0 [1-e-(t-T/a) b]

Where, M is the amount of drug dissolved as a function of time t. M0 is total amount of drug being released. T accounts for the lag time measured as a result of the dissolution process. Parameter 'a' denotes a scale parameter that describes the time dependence, while 'b' describes the shape of the dissolution curve progression. For b = 1, the shape of the curve corresponds exactly to the shape of an exponential profile with the constant k = 1/a

M = M0 (1 – e-k (t-T)

If 'b' has a higher value than 1, the shape of the curve gets sigmoidal with a turning point, whereas the shape of the curve with 'b' lower than 1 would show a steeper increase than the one with b = 1.

The time, when 50% (w/w) and 90% (w/w) of drug being in each formulation was released, was calculated using the inverse function of the Weibull equation: t (50% resp. 90% dissolved) = (- a ln M- M0 / M0)1/b + T

The equation may rearrange into logarithmic form,
Log [-ln(1- m)] = b log (t- Ti) - log a

From this equation a linear relation can be obtained for a log–log plot of -ln (1-m) versus time, t.

The shape parameter (b) is obtained from the slope of the line and the scale parameter, a, is estimated from the ordinate value (1/a) at time t=1. The parameter, a, can be replaced by the more informative dissolution time, Td, that is defined by a= (Td) d and is read from the graph as the time value corresponding to the ordinate - ln (1- m) = 1. Since -ln (1 - m) = 1 is equivalent to m=0.632, Td represents the time interval necessary to dissolve or release 63.2% of the drug present in the pharmaceutical dosage form. To pharmaceuticals systems following this model, the logarithm of the dissolved amount of drug versus the logarithm of time plot will be linear ([30-31]).

**Applications:** The Weibull model is more useful for comparing the release profiles of matrix type drug delivery,[32,33]

## DISCUSSION

From the results shown in table.13, $R^2$ as **0.966 indicates that our optimized batch fits Weibull model**, wherein a = 2.084 which shows time dependence, b = 0.486 therefore curve in the fig. 13 shows steeper increase in drug release. Td at 4.5 hrs shows 63.2% of the drug release. The value of n from the same table 13 signifies release of drug as **fickian diffusion** process.

**Comparisons of optimized batch with marketed product**

**Table 14: Comparisons of optimized batch with marketed product in dissolution profile.**

| Time (hr.) | % Cumulative drug Release | |
|---|---|---|
| | Optimized batch | Marketed product |
| 0 | 0.0 | 0.0 |
| 1 | 13.856±0.07 | 48.450±0.13 |
| 2 | 19.890± 0.06 | 65.256±0.06 |
| 3 | 34.080±0.16 | 83.923±0.03 |
| 4 | 47.416±0.17 | 89.084±0.03 |
| 5 | 53.246±0.08 | 89.813±0.05 |
| 6 | 62.540±0.01 | 90.234±0.05 |
| 8 | 73.160±0.06 | 91.163±0.01 |
| 10 | 74.290±0.01 | 92.723±0.04 |
| 12 | 75.240±0.01 | 93.236±0.04 |
| 14 | 75.945±0.09 | 93.833±0.02 |
| 16 | 81.353±0.01 | 94.756±0.03 |
| 18 | 84.286±0.07 | 95.223±0.04 |
| 20 | 84.713±0.01 | 95.316±0.02 |
| 22 | 89.926±0.05 | 99.460±0.03 |
| 24 | 99.196±0.01 | 110.976±0.08 |

**Results:** The f2 (similarity factor) value of optimized batch by comparing with marketed product gives **28.54**. Therefore, it shows significant changes in optimized batch as compared to marketed product.

**Results of microbiological assay of optimized batch**

**Table 15: Zone of inhibition of microbiological assay of optimized batch and marketed product.**

| Time (hr) | Optimized Batch | | | Marketed product | | |
|---|---|---|---|---|---|---|
| | Zone of inhibition (mm) | | | | | |
| | Concentration (mg/ml) | *B. subtilis* | *E. coli* | Concentration (mg/ml) | *B. subtilis* | *E. coli* |
| 0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 2 | 170.0 | 33.7 | 27.2 | 326.0 | 57.2 | 43.0 |
| 4 | 264.0 | 36.6 | 46.8 | 419.0 | 64.2 | 43.8 |
| 10 | 366.0 | 35.0 | 64.6 | 456.0 | 72.2 | 46.6 |
| 16 | 406.0 | 43.3 | 80.4 | 485.0 | 75.0 | 53.4 |
| 24 | 494.0 | 43.2 | 80.2 | 571.0 | 69.2 | 48.3 |

Interpretation involves correlation of the diameter obtained in the agar cup plate method for ciprofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-mcg ciprofloxacin disk should provide the following zone diameters in these laboratory quality control strains.[34]

**Microorganism Zone Diameter (mm)**

*Escherichia coli* ATCC 25922 30-40

*Staphylococcus aureus* ATCC 25923 22-30

* In our study we have selected *B. subtilis* instead of *Staphylococcus aureus.*

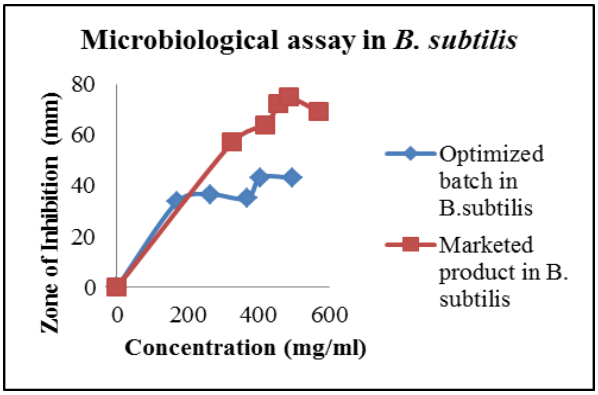


**Fig. 14: Microbiological assay of optimized batch and marketed in *B. subtilis.***

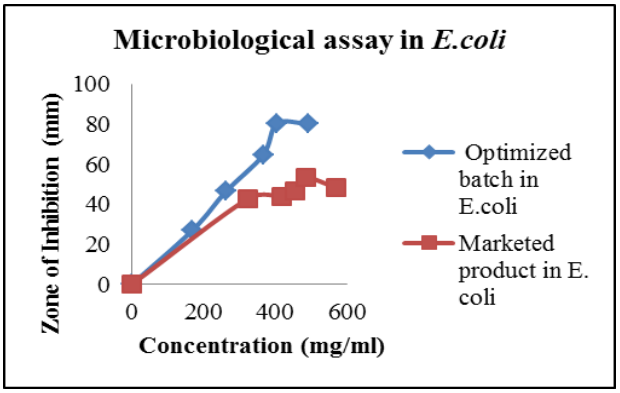


**Fig. 15: Microbiological assay of optimized batch and marketed product in *E. coli.***

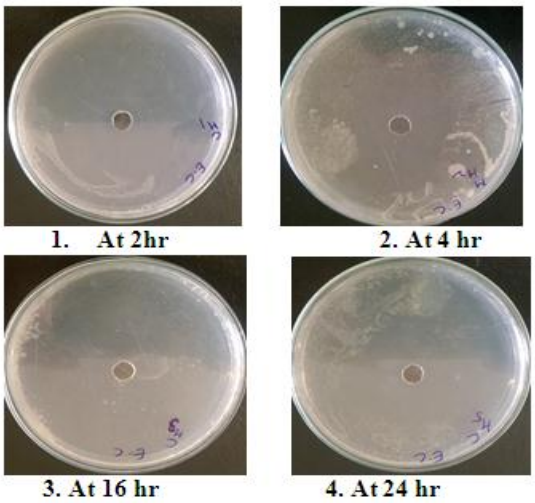


Fig.16 Microbiological assay of Optimized batch in gram negative organism *(E.Coli)*

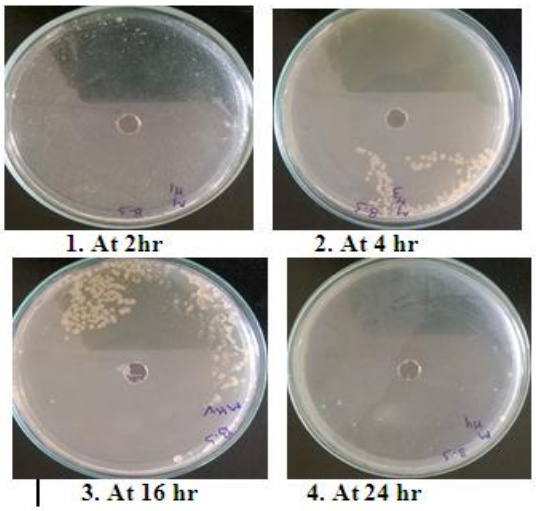


Fig.17 Microbiological assay of marketed product in gram positive organism *(B.Subtilis)*

**Pharmacokinetic Analysis**[35,36]

PK parameters were determined by using standard PK methods.218. Both non-compartmental and compartmental PK data analyses were performed with the software Program PKsoftware.

**Results of Non-compartmental Analysis**

**Table 16: Results of Non-compartmental analysis with marketed product.**

| Non-compartmental pharmacokinetic parameter | | |
|---|---|---|
| **Parameters (units)** | **Optimized 500mg CR** | **Marketed 500mg XR** |
| $C_{max}$ (µg/ml) | 3.08 | 1.24 |
| $T_{max}$ (h) | 6.00 | 2.00 |
| $AUC_{0-t}$ (µg/ml*h) | 45.18 | 6.46 |
| $AUC_{24}$ (µg/ml *h) | 69.16 | 14.78 |
| $K_e$ (1/h) | 0.01 | 0.17 |
| $T_{1/2}$ (h) | 13.40 | 4.00 |
| MRT (µg/ml*h) | 21.93 | 6.00 |
| CL/F (L) | 72.20 | 67.60 |
| V/F (L) | 139.80 | 345.90 |

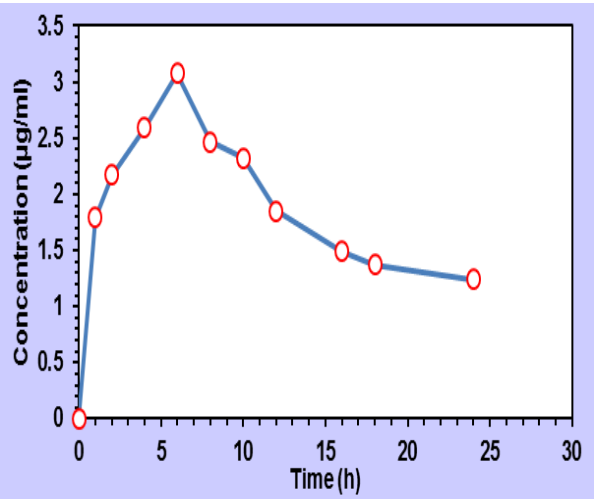


**Fig. 18: AUC Curve by linear Trapezoidal method.**

**Results of Compartmental Analysis**

**Table 17: Results of Compartmental analysis with marketed.**

| Compartmental pharmacokinetic parameters | | |
|---|---|---|
| **Parameters (units)** | **Optimized 500m CR** | **Marketed 500mg XR** |
| $K_a$ (1/h) | 0.60 | 1.17 |
| $K_e$ (1/h) | 0.60 | 0.19 |
| $T_{max}$ (h) | 4.36 | 2.00 |
| $T_{1/2}$ (h) | 1.15 | 3.65 |
| CL/F (L) | 77.90 | 69.18 |
| V/F (L) | 139.60 | 345.90 |
| AUC 0-t (µg/ml*h) | 45.63 | 6.46 |
| AUC 0-inf (µg/ml*h) | 64.16 | 14.78 |

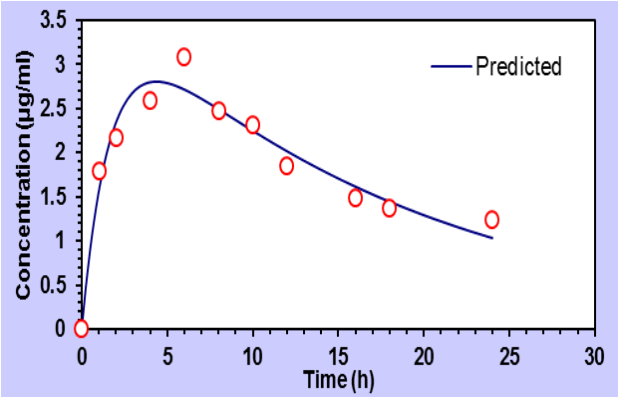


**Fig. 19: AUC curve by linear trapezoidal method.**

**Bioavailability**[37]

The relative bioavailability of optimized batch was obtained by equation,

$$F_r = \frac{AUC\ test * Dref}{AUC\ ref * Dtest} = \frac{45.18 * 500}{6.45 * 50}$$

**$F_r$ = 70.046 %**

The pharmacokinetic parameters such as maximum plasma concentration ($C_{max}$), time to reach peak plasma concentration ($t_{max}$), $t_{½}$, Area under the plasma concentration time curve $(AUC)_{(0-t)}$, $K_{el}$ and mean residence time (MRT) were calculated using software by PK summit solutions and results are given.

Proquin XR is a CPH extended release 500 mg tablets marketed by Depomed. The manufacturer has used povidone, polyethylene oxide and magnesium stearate in his formulation and tablets are film coated. The manufacturer showed steady state pharmacokinetics for CPH in plasma of healthy subjects (Day 3). The comparison of pharmacokinetics study has been given as per the following in table 18.

**Table 18: Comparison of pharmacokinetics parameters.**

| **Pharmacokinetic parameters** | **Compartmental analysis** | | **Non-Compartmental analysis** | | **Proquin XR** |
|---|---|---|---|---|---|
| **Parameters (Units)** | **Optimized 500m CR** | **Marketed 500mg XR** | **Optimized 500mg CR** | **Marketed 500mg XR** | |
| $C_{max}$ (mcg/ml) | - | - | 3.08 | 1.24 | 0.82 |
| $K_a$ (1/h) | 0.60 | 1.17 | - | -- | - |
| $K_e$ (1/h) | 0.60 | 0.19 | 0.01 | 0.17 | - |
| $T_{max}$ (h) | 4.36 | 2.00 | 6.00 | 2.00 | 6.1 |
| $AUC_{0-t}$ (µg/ml*h) | 45.63 | 6.46 | 45.18 | 6.46 | - |
| $T_{1/2}$ (h) | 1.15 | 3.65 | 13.40 | 4.00 | - |
| $AUC_{24}$ (µg/ml *h) | - | - | 69.16 | 14.78 | 7.67 |
| CL/F (L) | 77.90 | 69.18 | 72.20 | 67.60 | - |
| V/F (L) | 139.60 | 345.90 | 139.80 | 345.90 | - |
| MRT (µg/ml*h) | - | - | 21.93 | 6.00 | 7.67 |
| AUC 0-inf (µg/ml*h) | 64.16 | 14.78 | - | - | - |

**$C_{max}$ = maximum plasma concentration, $t_{max}$ = time to reach peak plasma concentration, AUC = area under the curve, AUMC = area under first moment curve, MRT = mean residence time**

The $T_{max}$ values in each case do not show marked difference $C_{max}$, $AUC_{24}$ and MRT show marked difference in our optimized formulation in comparison to Proquin XR in human subjects.[38]

## CONCLUSION

We have succeeded in formulating a controlled release tablet of CPH 500 mg for once daily regimen. Our formulation gets swollen in acidic pH 1.2 medium and alkaline pH 6.8 and release of 50% drug is shown at 5 hrs and 90% at 23 hrs in comparison with an ER tablet of Ciprofloxacin (500mg) formulation by Hou and his co-

workers.[39] who showed the 90% release of CPH over a 6 hour period.[40]

Our mechanism of delivery is compared with the currently marketed extended release CPH tablet, our optimized formula showed complete drug release within 24 hrs. The drug release of marketed extended release CPH showed complete release at 22 hrs.

Therefore we claim that our objective has been achieved in overcoming frequency of GI side effects such as nausea and diarrhea, and improving patient compliance by reducing frequency of administration and finally treatment costs.

Our controlled release profile results in approximately 95 mg out of the 500 mg dose released in the first 2 hrs in our *in vitro* study as compared to 325 mg of a 500 mg dose released within first 2hrs for marketed CPH extended release tablet.

The main aim of development of extended release CPH was to improve the pharmacokinetic and pharmacodynamic profile achieved with presently marketed immediate release twice daily CPH, in order to allow more convenient once daily dosing, while acknowledging bacteriological efficacy better than the conventional twice daily therapy. We obtained better response in terms of the area under the curve in comparison to the marketed preparation.

Such a formulation would provide an AUC/ MIC ratio equivalent to that observed with the marketed preparation.

A second criterion developed by us was achievement of $C_{max}$ (a maximum plasma concentration) higher than that observed with a corresponding regimen of marketed preparation.

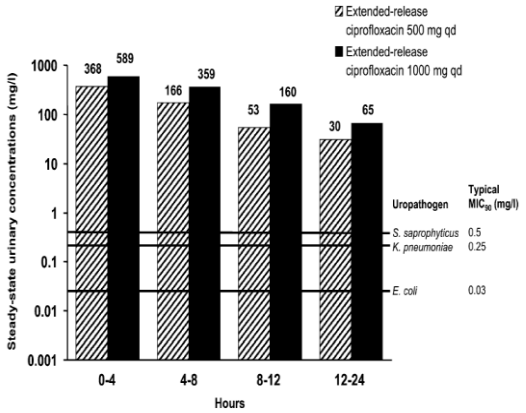


Fig. 20 Urinary drug concentrations at steady-state following administration of extended-release ciprofloxacin 500 and 1000 mg qd.[44,45,46] are far greater than the minimal inhibitory concentration (MIC90) values for common urinary pathogens, which are taken from Sahm et al.[47] and Woodcock et al.[48]

Attainment of both better AUC and higher $C_{max}$ values and equivalent $T_{max}$ was desired as bactericidal activity of CPH is concentration dependent and the AUC/MIC and $C_{max}$/MIC ratios are the key determinants in this respect.[41,42] Also, by achieving targeted AUC/MIC and $C_{max}$/MIC values, development of resistance may be prevented.[43]

Therefore we claim that the controlled release tablet dosage form of CPH developed by us can be successfully prescribed for both complicated and uncomplicated urinary tract infections.

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