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## SUSTAINED RELEASE TABLETS OF CIPROFLOXACIN FOR THE MANAGEMENT OF BACTERIAL INFECTIONS

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### ABSTRACT

Sustained release (SR) tablets were developed for prolonged release of Ciprofloxacin incorporating Hydroxypropyl methylcellulose (HPMCE5LV) as a controlled release polymer. The current research work was to formulate SR tablets of Ciprofloxacin. Based on various concentrations of HPMC four different batches of SR tablets of Ciprofloxacin are developed through wet granulation process. Pre-compression plus post-compression parameters of SR tablets are measured. Based on the highest drug release F4 was found to be the best among all batches. The % Cumulative drug release (CDR) for F4 was 98.484 % of Ciprofloxacin at the end of the 14 hours. The drug release was prolonged due to more amount of HPMCE5LV in F4. It is obtained from the results for all formulations that the release rate of active pharmaceutical ingredients can be controlled through the polymer of the core as well as following zero order kinetics. The Accelerated stability studies (ASS) confirmed that there were insignificant alternates in evaluated parameters at the end of 3 months of F4 batch. Hence the current technology for designing tablets can produce more advantages than conventional tablets.

**Keywords: Sustained Release, Controlled Release, Ciprofloxacin, Wet granulation**

### INTRODUCTION

Drug molecules may be developed into various dosage forms. It can be administered

to patients in the form of novel drug delivery systems (NDDS), and other drug delivery

systems [1]. Out of various NDDS sustained release (SR) systems mostly accepted in the market. It has ease of administration, constant release of drug to blood, and preferable patient compliance [2]. These dosage forms provide significant superiority over conventional dosage forms, including more effective, reduced side effects, reduced frequency of dosing, and greater patient convenience [3].

SR technology is used to obtain effective therapeutic concentrations of drugs in the blood throughout a longer duration of time. SR dosage form offers therapeutic benefits by decreasing side effects, increasing patient convenience and compliance as well as reducing the frequency of doses [4]. Mostly for sustained release action-controlled release polymers are incorporated to alter the release profile as well as obtain sustained action in the blood. Hydroxy propyl methyl cellulose (HPMC) is a hydrophilic polymer [5]. It is mostly utilized as a pH-independent gelling agent in the formulation.

Ciprofloxacin is a fluoroquinolone antibiotic [6]. It is used to treat several bacterial infections. The elimination half-life is 3.5 h. Ciprofloxacin bioavailability is 70 %. And protein binding is around 30%. 250 mg tablet every 12 h for conventional dosage forms [7]. The current research is to formulate SR matrix tablets of ciprofloxacin once daily of dose 500 mg.

## MATERIALS AND METHODS

### Materials

Ciprofloxacin is bought from Orin Laboratories Ltd, Hyderabad. Microcrystalline cellulose (MCC), and Avicel pH 101) were bought from Signet Pharma, Mumbai. HPMCE5LV is procured from SD Fine Chem Ltd, Mumbai. Other excipients utilized laboratory reagents. Analytical grade solvents and reagents are utilized in current research.

### Compatibility studies

#### Fourier Transform Infrared (FTIR) Spectroscopy Study

FTIR is utilized to find out characteristics peaks indicating compatibility between drugs and excipients. FTIR confesses distinguishing functional groups [8] in different excipients and drugs.

### Preparation of SR tablets

SR tablets are formulated through the wet granulation method [9]. Accurate weight of excipients mentioned in Table 1 except lubricant, and glidant passed across mesh size 30. Sieve No. 80 is used for the sieving of lubricant (magnesium stearate) and glidant (talc). Excipients other than the lubricant, and glidant were mixed homogeneously by a mortar and pestle. By geometric dilution the mixture was moistened using water. Then it was screened across mesh size 30 followed by drying in a hot air oven at 60°C for an adequate time (3-4 h). The dried granules were screened

across mesh size 30 followed by lubrication along talc and magnesium stearate. Then the granules were subduced to the evaluation of pre-compression parameters. The evaluated

granules were compressed along concave punches utilizing a rotary compression machine.

**Table 1: Composition of SR Tablets of Ciprofloxacin**

Formulation code	Ciprofloxacin (mg)	MCC (mg)	Starch (mg)	HPMCESLV (mg)	Magnesium stearate (mg)	Talc (mg)	Total weight (mg)
F1	500	175	15	0	5	5	700
F2	500	125	15	50	5	5	700
F3	500	75	15	100	5	5	700
F4	500	25	15	150	5	5	700

## EVALUATION OF TABLETS

### Pre compression parameters

The angle of repose, tapped and bulk density and Carr's index (C.I) parameters were measured by specific procedures [10] for prepared granules. The fixed funnel technique was used for the measurement of the granular repose angle. Bulk density apparatus (Sisco, India) was used for the measurement of tapped and bulk density respectively.

For the determination of Carr's index [11, 12] the following formula was used.

$$\% \text{ C.I} = \frac{e_{\text{tap}} - e_{\text{bulk}}}{e_{\text{tap}}} \times 100$$

Where  $e_{\text{tap}}$  is the tapped density of granules and  $e_{\text{bulk}}$  is the bulk density of granules.

### Post-compression parameters [13-16]

#### Hardness

SR tablets hardness was measured by a Monsanto hardness tester (Sisco, India).

#### Friability test

The friability test of tablets is carried out using the Roche friabilator (Sisco, India). 20

tablets of initial weight ( $W_{\text{initial}}$ ) were noted. Subsequently tablets were kept in a Roche friabilator. 100 Revolutions were made. Afterwards the tablets weight is noted ( $W_{\text{final}}$ ). The friability percentage was determined.

#### Weight variation test (WVT)

Individual 20 tablets weight was taken of each batch by weighing machine. The average weight of tablets was measured. Subsequently, it was compared to the individual weight of tablets. The % WV was determined followed by a comparison along USP specifications.

#### Uniformity of drug content test

10 Tablets along a particular batch were reserved along with ground to make powder. Then one SR tablet weight equivalent to powder was taken. It is dissolved in a 100 ml volumetric flask filled with HCl buffer pH1.2 utilizing a magnetic stirrer for 24 h. Filtration was carried out by Whatman filter paper No.1 followed by dilution. Then the

sample solutions were undergone analysis by UV/Visible Spectrophotometer.

#### **Diameter of tablet**

Vernier caliper (Absolute digimatic, Mitutoyo Corp. Japan) is used for the diameter determination of tablets.

#### ***In vitro* dissolution study (IVDS)**

USP apparatus II was used for IVDS. The tablet was put in a dissolution medium of HCl buffer pH1.2 containing a volume of 900 ml. The stirrer was in rotation at 75 rpm. The temperature of dissolution media was maintained at  $37 \pm 0.5^{\circ}\text{C}$  for the first 2 h. Afterward, it was altered to a pH 6.8 phosphate buffer continuing similar conditions for the remaining h. At a specific time, a sample of 5 ml of solutions was taken out by 0.45- $\mu\text{m}$  CA filter from the dissolution apparatus by changing fresh fluid (5 ml) to dissolution medium. Absorbances of these solutions were determined at a particular  $\lambda_{\text{max}}$  of UV/Visible Spectrophotometer. The % CDR was plotted.

#### ***In vitro* drug release (IVDR) kinetic Study**

For the estimation of the IVDR kinetic study [17, 18] from SR tablets, the IVDR values were calculated. For the calculation of IVDR Korsmeyer and Peppas data, zero order, Higuchi, first order, and Hixson-Crowell equations were used.

#### **Accelerated stability studies (ASS)**

As specified by ICH (The International Council of Harmonization) guidelines [19]

the developed batches were undergone ASS, stability chamber (Thermo Lab Scientific Equipment Pvt. Ltd., Mumbai, India) was used to keep packed SR tablets in a suitable container at  $75 \pm 5\%$  RH and  $40 \pm 2^{\circ}\text{C}$  for three months. SR Tablets were intermittently withdrawn along with the estimation of different parameters.

## **RESULT AND DISCUSSIONS**

### **FTIR Study**

The FTIR spectra of Ciprofloxacin and physical mixtures of additives were detected. The comparison was done between the drug, polymer and additives in formulation. The conclusion was made that there was no interference of peaks between Ciprofloxacin and the used excipients in the formulation.

### **Evaluation of SR tablets**

#### **Parameters of the pre-compression Ciprofloxacin SR granules**

Pre-compression parameters identify flow ability characteristics of granules. The parameters were represented in **Table 2**.

The angle of repose of all formulations ranged from  $24.08 \pm 0.11$  to  $29.12 \pm 0.17$ . From the evaluated value of the angle of repose, it showed good flow characteristics of developed formulations. The bulk densities of Ciprofloxacin batches were between  $0.462 \pm 0.17$  to  $0.483 \pm 0.11$  g/ml. The tapped densities were in the range of  $0.529 \pm 0.05$  to  $0.545 \pm 0.15$  g/ml. These results show that the granules had good

packing capacity. The values of Carr's index for all formulations of Ciprofloxacin ranged from  $9.07 \pm 0.05$  to  $15.22 \pm 0.14$ . The values of C.I shows good flow properties of granules. In all the formulations the values of Hausner's ratio ranged from  $1.09 \pm 0.04$  to  $1.17 \pm 0.16$  for granules of Ciprofloxacin. Overall, all the evaluated parameters were specified limits showing good flow characteristics.

### **The parameters of Ciprofloxacin SR tablets post-compression**

The parameters of different batches are evaluated and reported in **Table 3**.

Tablets were found to be white. The shape was circular, and concave. The texture of the tablets was smooth. The hardness of Ciprofloxacin SR tablets was between  $4.8 \pm 0.12$  to  $7.1 \pm 0.18$  kg/cm<sup>2</sup>. The % friability of developed batches was between  $0.14 \pm 0.02$  % to  $0.33 \pm 0.02$  %. Weight variation of the average weight of tablets was between  $1.28 \pm 0.16$  % to  $1.76 \pm 0.23$ %. The percentages of drug content for Ciprofloxacin SR tablets were found between  $100.0 \pm 1.32$  to  $100.96 \pm 1.4$ % which were inside acceptable limits of USP. The average diameters of all the formulations of Ciprofloxacin SR tablets ranged from  $12.11 \pm 0.03$  to  $12.14 \pm 0.09$  mm. It was within limits. Overall, evaluated post-compression parameters data were inside pharmacopeial specifications.

### **In vitro dissolution studies (IVDS) of Ciprofloxacin SR tablets**

IVDS of different formulations of Ciprofloxacin SR tablets were given in **Figure 1**. The % Cumulative drug release (CDR) for F1, F2, F3, and F4 was 60.34 %, 79.57%, 89.50 % and 98.484 % respectively of Ciprofloxacin at the end of the 14 hours. It claimed that the release of the drug release was increased in the F4 batch. The F4 batch had 150 mg of HPMC, as a result, it was sustained up to 14 h.

### **In vitro drug release (IVDR) kinetic studies of Ciprofloxacin SR tablets**

IVDR from developed formulations of Ciprofloxacin SR tablets were fitted in distinct kinetic models. The regression data and rate constants of developed batches were reported in **Table 4**. From the data, F4 shows zero order kinetics of drug release having non-Fickian diffusion mechanism.

### **ASS**

The different parameters are determined at different time intervals throughout stressed conditions of F4 formulation. The values were presented in **Table 5**. From the ASS it was confirmed that there were insignificant alternates in evaluated parameters at the end of 3 months.

Table 2: Pre-compression parameters of Ciprofloxacin SR granules

Formulation batches	Angle of repose ( $\theta$ ) <sup>a</sup> $\pm$ S.D	Bulk density (g/ml) <sup>a</sup> $\pm$ S.D	Tapped density (g/ml) <sup>a</sup> $\pm$ S.D	Carr's Index (%) <sup>a</sup> $\pm$ S.D	Hausner's Ratio <sup>a</sup> $\pm$ S.D
F1	29.12 $\pm$ 0.17	0.462 $\pm$ 0.17	0.545 $\pm$ 0.15	15.22 $\pm$ 0.14	1.17 $\pm$ 0.16
F2	25.13 $\pm$ 0.15	0.483 $\pm$ 0.11	0.536 $\pm$ 0.09	9.88 $\pm$ 0.06	1.10 $\pm$ 0.08
F3	26.32 $\pm$ 0.08	0.479 $\pm$ 0.01	0.534 $\pm$ 0.03	10.3 $\pm$ 0.04	1.11 $\pm$ 0.06
F4	24.08 $\pm$ 0.11	0.481 $\pm$ 0.04	0.529 $\pm$ 0.05	9.07 $\pm$ 0.05	1.09 $\pm$ 0.04

N.B.- Values are given as mean  $\pm$  S.D, <sup>a</sup> n = 3

Table 3: Post-compression parameters of Ciprofloxacin SR tablets

Formulation batches	Hardness (kg/cm <sup>2</sup> ) <sup>a</sup> $\pm$ S.D	%Friability (%) <sup>b</sup> $\pm$ S.D	%Weight variation (%) <sup>b</sup> $\pm$ S.D	%Drug content <sup>a</sup> $\pm$ S. D	Diameter (mm) <sup>a</sup> $\pm$ S. D
F1	4.8 $\pm$ 0.12	0.24 $\pm$ 0.03	1.76 $\pm$ 0.23	100.0 $\pm$ 1.32	12.13 $\pm$ 0.02
F2	5.5 $\pm$ 0.15	0.33 $\pm$ 0.02	1.51 $\pm$ 0.19	100.32 $\pm$ 1.41	12.11 $\pm$ 0.03
F3	6.6 $\pm$ 0.15	0.19 $\pm$ 0.03	1.28 $\pm$ 0.16	100.64 $\pm$ 0.98	12.13 $\pm$ 0.07
F4	7.1 $\pm$ 0.18	0.14 $\pm$ 0.02	1.52 $\pm$ 0.34	100.96 $\pm$ 1.4	12.14 $\pm$ 0.09

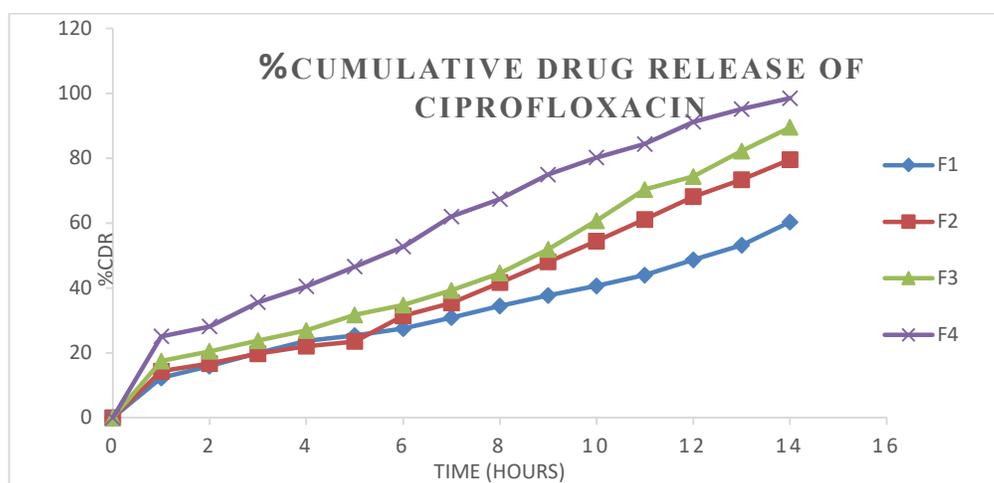
N.B.-Value expression in the form of mean  $\pm$  S.D, <sup>a</sup> n = 10, <sup>b</sup> n = 20

Figure 1: IVDS of ciprofloxacin release from different developed formulations

Table 4: Fitted IVDR values in different mathematical models

Models Batches	Zero-order		First-order		Higuchi		Korsmeyer-Peppas (KP)		
	R <sup>2</sup>	K <sub>0</sub>	R <sub>1</sub> <sup>2</sup>	K <sub>1</sub>	R <sub>H</sub> <sup>2</sup>	K <sub>H</sub>	R <sub>K</sub> <sup>2</sup>	K <sub>KP</sub>	n
F1	0.9756	3.6076	0.959	0.0548114	0.9753	29.434	0.917	17.298	0.514
F2	0.9809	5.3233	0.9159	0.101332	0.8925	23.404	0.923	19.769	0.503
F3	0.9753	5.7959	0.86	0.1328831	0.8901	21.405	0.904	22.855	0.460
F4	0.9761	6.4681	0.8497	1.9568591	0.9471	15.004	0.967	25.176	0.466

Table 5: Evaluated parameters of F4 formulation at hastened conditions

Sl.no.	Parameters	Initial	1 month later	2 months later	3 months later
1.	Physical appearance				
	Color	Pale white	unchangeable	unchangeable	unchangeable
	Shape	Circular, and concave	unchangeable	unchangeable	unchangeable
	Surface	Smooth	unchangeable	unchangeable	unchangeable
2.	Hardness (kg/cm <sup>2</sup> ) <sup>a</sup> $\pm$ S.D	7.1 $\pm$ 0.18	7.1 $\pm$ 0.18	7.1 $\pm$ 0.15	7.0 $\pm$ 0.14
3.	Friability (%) <sup>a</sup> $\pm$ S.D	0.10 $\pm$ 0.02	0.10 $\pm$ 0.02	0.09 $\pm$ 0.02	0.08 $\pm$ 0.02
4.	%Weight variation (%) <sup>b</sup> $\pm$ S.D	1.52 $\pm$ 0.34	1.62 $\pm$ 0.55	1.72 $\pm$ 0.34	1.58 $\pm$ 0.56
5.	CDR (%) <sup>c</sup> $\pm$ S.D	98.48 $\pm$ 2.06	98.48 $\pm$ 2.06	98.18 $\pm$ 3.05	98.08 $\pm$ 3.06
6.	Drug content (%) <sup>a</sup> $\pm$ S.D	100.96 $\pm$ 1.4	100.46 $\pm$ 1.4	100.32 $\pm$ 2.5	100.06 $\pm$ 2.6

N.B.-Expression of values in the form of mean  $\pm$  S.D, <sup>a</sup> n = 10, <sup>b</sup> n = 20, <sup>c</sup> n = 3

## CONCLUSION

The current research results show that the hydrophilicity of HPMC controls the Ciprofloxacin release effectively for 14 h. Hence incorporation of HPMC in SR matrix tablets of Ciprofloxacin is successful. Among all formulations, the F4 formulation has given the best dissolution studies at 98.484% at the end of 14h. The IVDS data of F4 formulation are fitted in different kinetic models. Among all the kinetic models  $R^2$  value was found to be maximum in the Zero order model showing 0.9761. Hence it follows Zero order kinetics. The KP model release exponent  $n$  for F4 is obtained, showing 0.466 ( $n > 0.45$ ). As a result of the  $n$  value, it shows a non-Fickian diffusion release mechanism. Hence the current technology for designing tablets can produce more advantages than conventional tablets.

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