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Research Article

FORMULATION AND EVALUATION OF CIPROFLOXACIN HYDROCHLORIDE SUSTAINED RELEASE TABLETS USING HIBISCUS ROSA SINENSIS MUCILAGE

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ABSTRACT

Increased complications and costs of marketing of innovative drugs focused greater attention to the development of sustained release (SR) or controlled release (CR) drug delivery systems. Delivery systems extended release or controlled release rate can achieve predictable and reproducible, the extended duration of activity for the short time of life - drugs, reduced toxicity, and dose reduction request, the optimized therapy and better patient compliance. It is controlled primarily by the type and the proportion of the polymers used in the preparation. Ciprofloxacin hydrochloride is an extremely potent antibacterial agent with potent activity against most gram +ve and gram -ve bacteria. The objective of present work was to develop and evaluated oral sustained release matrix tablet of ciprofloxacin hydrochloride prepared by the method of wet granulation, using hydroxy propyl methyl cellulose (HPMC) and hibiscus rosa sinensis mucilage polymer alone and in combination at various concentrations. Pre-compression parameters were evaluated. The tablets were evaluated for post-compression parameters such as thickness, hardness, average weight, friability and In vitro release studies. No interactions were observed between ciprofloxacin hydrochloride and excipients from the Fourier transform infrared spectroscopy. The quantity of ciprofloxacin hydrochloride present in the tablets and the release medium were estimated by a simple, rapid and validated UV method. The swelling of the mixture of polymers was higher than that of any of the individual polymer containing formulations. The swelling index ranged from 51-211 % at the end of 10 h of study. It was observed that of all the formulations F1 and F4 could not sustain the release of ciprofloxacin up to 10 h. All other formulations were able to sustain the release of ciprofloxacin for 24 h duration. The formulations F5 and F7 exhibited almost similar release profiles with 64.96 and 67.18% drug release at 24 h. The results obtained from the study conclusively indicate that use of HPMC and hibiscus rosa sinensis leaf mucilage as the matrix forming substance could help in achieving sustained release over a longer duration and help in reducing the dose as well as frequency of administration of the medicaments.

Keywords: Ciprofloxacin hydrochloride, Hibiscus rosa sinensis, HPMC, Wet granulation method.

1. INTRODUCTION

Ciprofloxacin hydrochloride is an extremely potent antibacterial agent with potent activity against most gram +ve and gram -ve bacteria. Chemically, it is 1-cyclo-propyl-6-fluoro-1,4-dihydro-4-oxo-7- (1-piperazinyl)-3-quinoline carboxylic acid hydrochloride monohydrate. Ciprofloxacin hydrochloride is the most commonly used drug for the treatment of ocular infections and is the best alternative to more toxic drugs such as aminoglycosides [1]. Oral administration of drugs is generally preferred, especially over parenteral administration. Oral products are produced in a more cost-effective manner in comparison with parenteral products and account for approximately 60% of all prescription products worldwide [2]. Sustained-release oral drug products are designed to slowly release the active ingredient over an extended time following administration and offer significant advantages over conventional orally administered products, including reduce side effects, increase safety and patient compliance by reducing the frequency of dosing and decreased drug plasma-concentration fluctuations [3, 4]. Matrix formulations of hydrophilic and/or hydrophobic polymers have been used to control the release of drugs [5, 6] and can be

produced using conventional processing equipment. Formulation based on a hydrophilic matrix was chosen, since it is known to give robust formulae that can be manufactured by standard tabletting technology. In addition, it is possible to manufacture such formulations without using organic solvents; environmental risks associated with such solvents cause great concern and they often yield trace residues in finished products. To control and modulate drug release properties of tablets, retardant polymers including hydrophilic polymers such as HPMC have been utilized in solid dosage forms. For these reterdants, hydrophilic polymers control drug release from tablets by hydrogelation [7, 8]. The red flowered variety of hibiscus rosa -sinensis linn is used in medicine because its leaves and flowers have been proved to increase hair growth and improve wound healing. The leaves of hibiscus species contain a lot of water soluble mucilage, which when combined with water produces an aqueous colloidal suspension [9]. This mucilage can be employed as an excipients in a formulation when poorly soluble pharmaceuticals are included because it allows them to come into touch with water more quickly, enhancing drug solubility. Hence, in the present study, an attempt has been made to develop sustained release matrix tablets of Ciprofloxacin hydrochloride using the synthetic polymers like HPMC and natural polymers like hibiscus rosa-sinensis and fixed to retard the drug release up to 24 h.

2. MATERIALS AND METHODS

2.1. Materials

Ciprofloxacin hydrochloride were obtained as pure sample from Medreich Pharmaceuticals, Bengaluru, India as gift samples along with their analytical reports. HPMC was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Avicel PH102, Mannitol and Talc were purchased from SD Fine Chem. Limited, Mumbai. Magnesium stearate was purchased from Loba Chemie Pvt. Ltd, Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade. The fresh leaves of hibiscus rosa-sinensis were collected from the campus garden of the institute.

2.2. Methods

2.2.1. Preformulation studies

2.2.1.1. Organoleptic properties

Color: A small quantity of pure ciprofloxacin hydrochloride powder was taken in a butter paper and viewed in well illuminated place.

Taste and odor: Very less quantity of ciprofloxacin hydrochloride was used to get taste with the help of tongue as well as smelled to get the odour.

2.2.1.2. Solubility analysis

Solubility of ciprofloxacin hydrochloride was determined in methanol, ethanol, dimethyl fluoride, methylchloride, 0.1N hydrochloric acid. Solubility studies were performed by taking excess amount of ciprofloxacin hydrochloride in different beakers containing the solvent.

2.2.1.3. Melting point

The melting point of ciprofloxacin hydrochloride was determined by capillary method, using small quantity of ciprofloxacin hydrochloride was taken and placed in apparatus and determined the melting point and matched with standards.

2.2.1.4. Loss on drying

IT was determined by drying the pure drug in an oven at 100°C to 105°C for 3 hours. The percent loss of moisture was calculated by the difference between the initial and final weight of the drug.

2.2.1.5. Drug excipient compatibility studies by FT-IR

IR spectra of drug, polymer and drug and polymers, individual excipients, drug and polymers and excipients were obtained using FT-IR for study of compatibility.

2.2.1.6. Standard curve of ciprofloxacin hydrochloride

The maximum absorption of ciprofloxacin was observed at 276 nm. The calibration curve was obtained using different concentrations of the drug at the above wave length.

Preparation of stock and standard solution: The stock solution was freshly prepared by dissolving 100mg of ciprofloxacin hydrochloride in few ml of methanol (5ml) in a 100ml volumetric flask and then made up the solution upto the mark using 0.1N hydrochloric acid for obtaining the solution of strength 1000 µg/mL (stock I). 10ml of this solution is diluted to 100ml with 0.1N hydrochloric acid to obtain a solution of strength 100 µg/mL (stock II).

Preparation of various concentrations: 10 ml stock solution was taken from stock solution-2 and volume made up to 100 ml by using 0.1N hydrochloric acid to get 10 µg/ml concentrations. From this solution with

draw 2, 4, 6, 8, 10 ml of solution in to the 10 ml volumetric flask and volume made up to 10 ml by using 0.1N hydrochloric acid to get the concentrations 2, 4, 6, 8, 10µg/ml.

2.2.2. Extraction of Hibiscus rosa sinensis leaf mucilage

The fresh leaves of H. rosa sinensis Linn were collected from the campus garden of the institute. It was washed with water to remove dirt and dried. Then they were powdered and soaked in water for 5-6 h, boiled for 30 min, kept aside for 1 h for complete release of mucilage into water. The material was squeezed in an eightfold muslin cloth bag to remove the marc from the solution. Then, three times volume of acetone was added to filtrate, to precipitate the mucilage. The mucilage was separated, dried in an oven at a temperature less than 50°C, collected, dried, powdered, passed through sieve no. 80, and stored for further use in desiccator [10, 11].

2.2.3. Formulation of ciprofloxacin matrix tablets

The formulation of the matrix tablets was performed using wet granulation method by employing HPMC and Hibiscus rosa sinensis leaf mucilage as the matrix forming polymers (Table 1). Mannitol was used as the bulk forming agent for the matrix tablets. Ciprofloxacin hydrochloride and a 75% amount of HPMC and Hibiscus rosa sinensis mucilage were passed through sieve #40 and mixed thoroughly. The remaining amount of the polymers was dissolved in 30 mL of an isopropyl alcohol and dichloromethane (1:1) mixture. The resultant solution was used as a binding agent to prepare a wet mass. The wet mass was passed through sieve #12 to form granules. The wet granules were dried in a hot air oven at 45 ±5°C for 1 h. The dried granules were passed through sieve #20 and mixed with the remaining ingredients previously passed through #40 sieve [12, 13]. The matrix tablets were punched using single punch tablet compression machine using 8 mm diameter flat punch.

Table 1: Composition of matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Ciprofloxacin	200	200	200	200	200	200	200
HPMC	80	120	160	-	-	-	80
*Hibiscus rosa sinensis*mucilage	-	-	-	80	120	160	80
Avicel PH102	54	34	14	54	34	14	14
Mannitol	54	34	14	54	34	14	14
Magnesium stearate	4	4	4	4	4	4	4
Purified talc	8	8	8	8	8	8	8

2.2.4. Evaluation of ciprofloxacin SR matrix tablets

2.2.4.1. Pre-compression parameters

Angle of repose

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend were measured. The angle of repose was calculated using the following formula [14].

$$\tan \Theta = h/r$$

Where, "h" is the height of the heap and "r" is the radius of the heap of granules.

Bulk density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The BD of powder blends was determined using the following formula [15].

Bulk density = Total weight of powder/Total volume of powder

Tapped bulk density (TBD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of powder blends were determined using the following formula [16].

TBD = Total weight of powder/Total volume of tapped powder

Carr's compressibility index

The Carr's compressibility index was calculated from bulk density (BD) and tapped density of the blend. A quantity of 2 g of blend from each formulation, filled

into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25 ± 2/min to measure the tapped volume of the blend. The BD and tapped density were calculated by using the bulk volume and tapped volume.

Carr's compressibility index was calculated using the following formula [17, 18].

Carr's compressibility index (%) = [(Tapped density-Bulk density) ×100]/Tapped density

Hausner's ratio

It is the measurement of frictional resistance of the drug. The ideal range should be 1.2-1.5, it was determined by the ratio of tapped density and bulk density.

HR = Tapped Density/ Bulk Density

2.2.4.2. Post-compression parameters

Hardness test

The hardness of the formulated tablets was tested using Monsanto type hardness tester. Three tablets from each batch of formulation were randomly taken and the force required to break the tablets was measured using hardness tester.

Friability test

The friability test of the formulations was performed using a Roche type friability test apparatus. Twenty tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or runup to 100 revolutions. The tablets were weighed again (Wfinal). The percentage friability was then calculated by the formula.

% Friability = (W1 - W2) x 100/W1

Weight variation test

20 tablets were randomly taken and weighed to calculate the average weight of the tablets. Each of these tablets was individually weighed and the difference from average weight was calculated. The percent weight variation was calculated to determine the deviation from the average weight.

Thickness

The thickness of randomly selected tablets from each batch of formulation was measured using a digital vernier caliper.

In-vitro dissolution

The USP type II paddle apparatus with a paddle speed of 50rpm was used for dissolution testing for the formulated matrix tablets. The dissolution media used consisted of 900mL of 0.1 N HCl and distilled water. 5 mL of samples were collected at various time points until 24 h and the media was replenished with the same volume of fresh media. The free drug concentration was estimated using a UV spectrophotometer at a wavelength of 276nm.

Swelling index

One tablet from each formulation was kept in a Petri dish containing phosphate buffer pH 7.2. At the end of 2 h, the tablet was withdrawn, kept on tissue paper and weighed [19]. The weighing was continued for every 2 h till the end of 10 h. The % weight gain by the tablet was calculated by formula

$$S.I = \frac{Mt - Mo}{Mo} * 100$$

Where, S.I = swelling index, Mt = weight of tablet at the time (t) and M0 = weight of tablet at time 0.

3. RESULTS AND DISCUSSION

Ciprofloxacin hydrochloride samples are examined and it was found to be soluble in water and slightly soluble methanol, soluble in dimethyl formamide. It was also found to be soluble in dilute alkali and in dilute acids. The melting point of ciprofloxacin hydrochloride was determined by capillary method, ciprofloxacin hydrochloride started melting at 257°C and completely melted at 262° C. Melting point compared with USP standards that showed that drug is pure. Loss on drying observed for ciprofloxacin pure drug was found to be 0.42%. Calibration curve of ciprofloxacin hydrochloride was determined by plotting absorbance (nm) versus concentration (µg/ml) at 276 nm (Fig. 1).

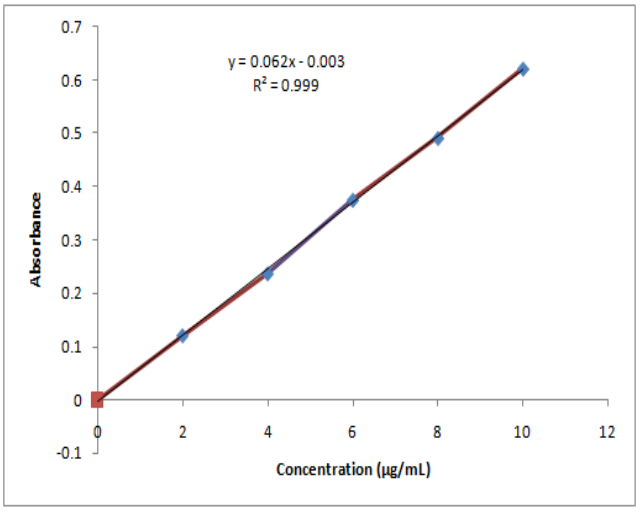

Fig. 1: Calibration curve of ciprofloxacin

The FTIR spectra of the pure drug and physical mixture of drug and excipient were recorded in between 400-

4000 wave number (cm-1). No peaks are observed which interfere with the main drug peaks. There was no appearance of new peak or disappearance of already existing peaks. Hence drugs were found to be compatibles with excipients (Fig. 2 & 3). The extracted mucilage powder was brownish colour with a characteristic odour.

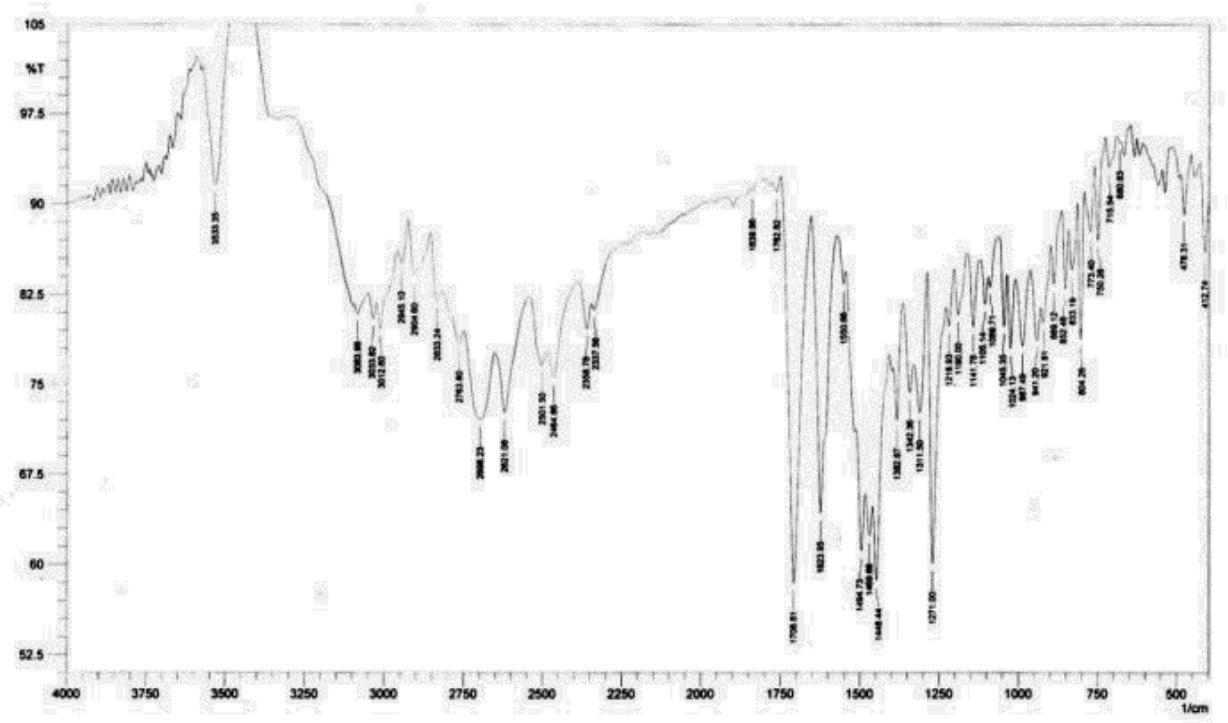

Fig. 2: FTIR spectra of ciprofloxacin

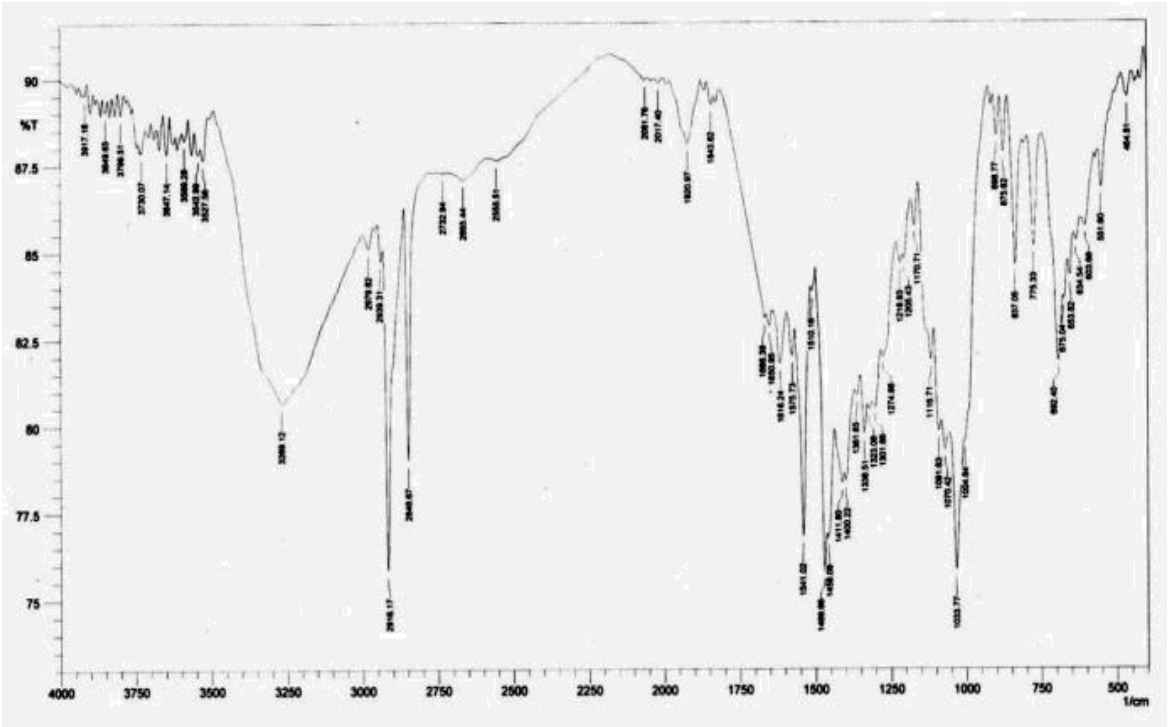

Fig. 3: FTIR spectra of physical mixture (ciprofloxacin+HPMC+mucilage)

The granules were slowly soluble in water and produced viscous solution. Fresh Hibiscus rosa-sinensis leaves produced 17.61 g of dried mucilage perkg. The percentage weight loss on drying is 11.43% and percentage moisture content is 13.21%. Angle of repose for all formulations was examined and the values were found to be within the range from 23°13' to 24°51'. This indicates that good flow property of powder blend. The bulk density and tapped density values were found to be within the range from 0.675 to 0.693 and 0.731 to 0.752 respectively. The Hausner's ratio values were found to be within the range from 1.08 to 1.10. All these parameters indicate that the powder blend had good flow property and is suitable for compression in to tablets (Table 2). All prepared batches of tablets were checked by visual inspection. The tablet had uniformly texture and structure. There were no oily drops and no pin holes on the surface. There were small variations in between thickness of all formulation but in a particular formulation there was no variation. The thickness of all formulation was ranged in between 4.7 to 4.8 mm. The hardness of the compressed tablets was determined by using hardness tester (Monsanto) indicates that the tablets are of adequate strength. Hardness of tablet of all formulation ranged from 4.5 kg/cm^2 and 6.2 kg/cm^2. The hardness of all formulation showed variation because of formulation combination and powder properties. The friability of all formulation was in the range of 0.17% to 0.65%. All formulation exhibited less than 1% friability and hence passed the test for friability. The weight variation of all formulation was in the range of 1.8 to 4.3 %. The weight variation test was performed according to the procedure in the pharmacopoeia. The individual deviation of all the tablets formulation was found to be within the limit and hence passed the test for uniformity of weight (Table 3). Swelling study was performed on all the formulation for 10 h. The results of swelling index were shown in (Table 4). As both the polymers used in the formulation of the matrix tablets were hydrophilic in nature and hence present a great ability to absorb water and swell up. Also it has been previously reported that *Hibiscus rosa-sinensis* has a higher swelling capacity in comparison to HPMC. The swelling behavior reflects that as the concentration of the polymer increases the swelling property increases. The swelling of the mixture of polymers was higher than that of any of the individual polymer containing formulations. The swelling index ranged from 51-211 % at the end of 10 h of study. The samples were withdrawn and estimated for the drug content at 2, 4, 6, 10, 18 & 24 hand the cumulative drug release was calculated. A plot of % cumulative drug release versus time for sustained release matrix tablet formulations is shown in Fig. 4. It was observed that of all the formulations F1 and F4 could not sustain the release of ciprofloxacin up to 10 h. All other formulations were able to sustain the release of ciprofloxacin for 24 h duration. The formulations F5 and F7 exhibited almost similar release profiles with 64.96 and 67.18% drug release at 24 h.

Table 2: Precompression characterization

Formulation code	Angle of Repose	Bulk density	Tapped density	Carr's Index	Hausner's Ratio
F1	24.13	0.681	0.742	8.22	1.09
F2	23.42	0.675	0.731	7.66	1.08
F3	23.57	0.693	0.749	7.48	1.08
F4	24.08	0.677	0.737	8.14	1.09
F5	24.36	0.675	0.734	8.04	1.09
F6	24.51	0.682	0.75	9.07	1.10
F7	23.46	0.681	0.752	9.44	1.10

Table 3: Quality parameters of matrix tablets of ciprofloxacin

Formulation code	Thickness (mm)	Hardness (Kg/cm2)	Weight variation (%)	Friability (%)
F1	4.8	4.9	2.2	0.65
F2	4.8	4.5	3.1	0.61
F3	4.7	5.7	4.3	0.52
F4	4.7	6.2	1.8	0.24
F5	4.7	5.5	4.1	0.21
F6	4.8	5.4	2.3	0.17
F7	4.8	6	3.2	0.42

Table 4: Swelling index of matrix tablets

Formulation code	Time					
	0	2	4	6	8	10
F1	0	51	101	108	121	137
F2	0	82	118	132	143	156
F3	0	108	157	171	197	211
F4	0	57	62	69	81	93
F5	0	52	71	83	89	97
F6	0	52	72	79	93	108
F7	0	91	132	148	159	174

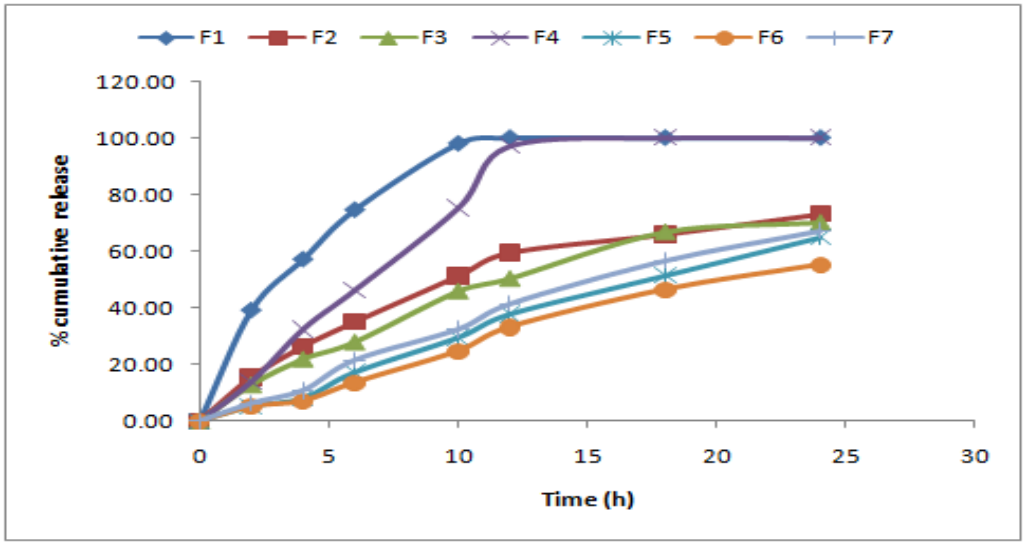

Fig. 4 Release of ciprofloxacin from formulations

4. CONCLUSION

The results obtained from the study conclusively indicate that use of HPMC and Hibiscus rosa sinensis leaf mucilage as the matrix forming substance could help in achieving sustained release over a longer duration and help in reducing the dose as well as frequency of administration of the medicaments. Further in vivo release studies are needed to support for the conclusion of the present investigation.

5. REFERENCES

1. Chambers HF. Sulfonamides, trimethoprim, and quinolones. In: Katzung BG, ed. Basic and Clinical Pharmacology. New York: McGraw-Hill; 2001:799.
2. Jain N, Jain R, Jain DK, Patel VK, Jain SK. *Int Res J Pharm.,* 2016; **7(6)**:91-95.
3. Charman, SA, Charman W. Oral modified-release delivery systems. In: Rathbone MJ, Hadgraft J, Roberts MS (Eds.). Modified-release drug delivery technology. New York: Marcel Dekker, 2002.
4. Moodley K, Pillary V, Choonara YE, Toit LC, Ndesendo VMK, Kumar P, et al., *Int J Mol Sci.,* 2012; **13**:18-43.
5. Jain SK, Jain N, Singhai P, Jain DK. *J Pharm Res.*, 2014;**13(2)**:50-56.
6. Qiu LY, Bae YH. *Pharmac Res.,* 2006; **23(1)**:1-30.
7. Fukuda M, Peppas NA, McGinity JW. *Int J Pharm.,* 2006; **310**:90-100.
8. Damien G, Barochez BH, Schiavi P. *Clin Pharmacokinet.,* 1999; **1**:13-19.
9. Amsa P, Mathan GK, Magibalan S, Velliyangiri EK, Kalaivani T, Priy S. *J Pharma Res Int.,* 2021; **33 (58B)**: 564-572.
10. Jani GK, Shah DP. *Drug Develop Indus Pharma.,* 2008; **34**: 807-816.
11. Deepika B, Sujatha K, ThangaThirupathi A, Chamundeeshwari D. *Res J Pharma Tech.,* 2021; **14(1)**: 245-248.

12. Khan R, Narwariya U. *J Pharmacol Biomed.,* 2021; **5(4)**:383-389.
13. Soumya P, Raghavendra Rao NG, Revathi K, Chawda B. *J Chem Pharma Res.,* 2013; **5(12)**:1398-1408.
14. Sakore S, Chakraborty B. *Int J Pharm Biomed Res*. 2013; **4**:21-6.
15. Udayakumar T, Suresh AG, Ubaidulla U. *Int J Res Dev Pharm Sci*., 2013;**2**:337-343.
16. Shashidhar P, Vidya Sagar G, Srikanth G. *Int J Pharm Chem Sci*.,013; **2**:780-792.
17. Sridhar Babu G, Vijay Kumar D, Aishwarya M, Malathy PS, Redya Naik R. *J Glob Trends Pharm Sci.,* 2014;**5**:2085-2092.
18. Saluja V, Garg C. *J Pharm Educ Res.,* 2013; **4**:92-97.
19. Wagh SC, Surya Kumar J, Banerjee S. *J Pharma Res.,* 2018; **5(4)**:2184-2190.