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Research Article

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Effect of cellulose and non-cellulose polymers on ciprofloxacin extended release tablets

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ABSTRACT

Sustained release delivery systems have shown to be of better significance in release rate for drugs [1]. The present study was an attempt to develop extended release tablets of Ciprofloxain HCl which on oral administration prolongs its release thereby increasing bioavailability, diminishing side effects and enhanced patient compliance. Ciprofloxacin HCl is used to treat a number of infections including: infections of bones and joints, endocardiasis, gasteroenteritis, prostatitis, anthrax and chancroid[5]. Ciprofloxacin extended release tablets were formulated using polymers HPMC (K4M, K15M, K100M) and Carbopol 71G by wet granulation technique [2]. The prepared formulations were evaluated with pre-compression parameters like bulk density, compressibility index, hausner ratio, angle of repose and post-compression parameters like weight variation, thickness, hardness, friability, in-vitro dissolution study. The in-vitro dissolution study of formulation CE10 shows drug release within 24 hours.

Key words: Ciprofloxacin HCl, HPMC, Carbopol 71G, extended release, *in-vitro* dissolution.

INTRODUCTION

Oral delivery of drugs is by far the most preferred route of drug delivery due to ease of administration, patient compliance and flexibility in formulation [1]. The design of extended drug delivery systems is primarily aimed to achieve more predictable and increased bioavailability. Gastric emptying time in humans, which is normally 2-3 hours through the main absorption area (stomach or upper part of intestine), can result in incomplete drug release from DDS leading to diminished efficacy of administered dose .

Ciprofloxacin Hcl is a broad-spectrum antibiotic active against both Gram-positive and Gram negative bacteria. The dosage is equivalent of 250 to 750 mg of ciprofloxacin twice daily (116 mg of ciprofloxacin hydrochloride is approximately equivalent to 100 mg of ciprofloxacin). The aim of the present study is to formulation and evaluation of extended release tablets of Ciprofloxacin Hcl using HPMC (K100M, K4M ,K15M and Carbopol 71G) in different ratio with sodium bicarbonate, magnesium stearate and talc by direct compression techniques.

EXPERIMENTAL SECTION

Materials:
Ciprofloxacin HCl was obtained from Sreepathi Pharmaceuticals Ltd., India. HPMC (K4M, K100M) was obtained from Taian Ruitai Cellulose Co. Ltd., China. Carbopol 71G was obtained from Yarrow Chem Products., Mumbai, India. Talc was obtained from Golcha Group., India. Magnesium steatite was obtained from Loba Chem Pvt. Ltd., India.

Flow properties:[5]
A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of sample granules is filled in funnel. Then funnel was opened to release the granules on the paper to form a smooth conical heap, is found by measuring in different direction. The height of the heap was measured by using scale. The value of angle of repose is calculated by using the following formula:

$$\mathbf{Tan\ \theta = h/r}$$
$$\mathbf{\theta = Tan^{-1}\ h/r}$$

Where, h- height of the heap
r- Radius of the heap

For most pharmaceutical granules, the angle of repose values range from 25 to 45, with lower values indicating better flow characteristics. Values of angle of repose ≤ 30 usually indicate a free flowing material and angle ≥40 suggest poorly flowing materials.

Bulk density:
A known quantity of granules was poured into the measuring cylinder carefully level the granules without compacting, if necessary and read the unsettled apparent volume (V), to the nearest graduated unit . Calculate the bulk density, in gm per ml, by the formula m / V.

Tapped density:
Cylinder dropping distance: 14± 2 mm at a normal rate of 300 drops / minute.
Unless otherwise specified, tab the cylinder 500 times initially and measure the tapped volume, Va, to the nearest graduated unit. Repeat the tapping an additional 750 times and measure the tapped volume, Vb, to the nearest graduated unit. If the difference between the two volumes is less than 2%, Vb is the final tapped volume, Vf. Repeat in increments of 1250 taps, as needed, unit the difference between succeeding measurements is less than 2%. Calculate the tapped density, in gm per ml, by the formula:

$$\textbf{Tapped Density} = \frac{m}{Vf}$$

Generally replicate determinations are desirable for the determination of this property.

Measurement of Granules Compressibility:
The compressibility Index and Hausner Ratio are measures of the propensity of granules to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing power, such interactions are generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility Index and the Hausner Ratio Calculated by the formula:

$$\textbf{Compressibility index:} = 100\,\frac{(V_0 - Vf)}{V_0}$$

$$\textbf{Hausner Ratio:} = \frac{V_0}{Vf}$$

Formulation of extended release tablets:
Extended release tablets were prepared by wet granulation method[2]. Tablets of Ciprofloxacin hydrochloride were prepared by using polymer HPMC K100M, HPMC K15M, Carbopol 71G in formulations. The ingredients given in table, except glidant and lubricant were thoroughly mixed in mortar and pestle. Wet granulation was done with a solution of sufficient quantity of polymer .The wet mass was passed through sieve no.16 and dried at 60 c for 30-45 min .granules thus obtained were compressed into tablets on a 8-station single rotary Rimak machine using 6mm standard punches.

EVALUATION OF EXTENDED RELEASE TABLET [3],[4].
A) Weight variation:
Twenty tablets were weighed individually and the average weight was determined. The percentage deviation was calculated and checked for weight variation.

B) Tablet thickness:
The thickness of the tablets of 10 tablets of each formulation was measured using digital vernier caliper in mm.

C) Hardness:
It is determined using a Monsanto hardness tester. Pressure required to break the tablet is determined in kg/cm^2.

D) Friability:
Weighed amount of 20 deducted tablets were subjected to rotating drum of friability test apparatus. The drum is rotated at 25 r.p.m. The apparatus was operated for 4 min and reweighed the tablets. Friability was calculated using formula

$$\mathbf{F= \frac{wo-w1}{wo} \times 100}$$

In-vitro release studies:
a) Procedure for standard curve:
The first stock solution was prepared by dissolving 100mg of Ciprofloxacin HCl in 100 ml 0.1N Hydrochloric acid in a 100 ml volumetric flask (1mg/ml). From the stock solution 5, 10, 15, 20, 25, and 30 µg/ml dilution were prepared. The absorbance of each sample was measured at 276 nm. Standard curve of concentration Vs absorbance was plotted.

b) Dissolution Study:
The dissolution test apparatus (USP II) is used. The whole assembly is kept in a jacketed vessel of water maintained at 37 ± 1^0 C. Tablet5 is placed in to the bottom of the flask. The beaker is filled with 900ml of0.1N HCl. The vessel is maintained at 100 rpm under stirring conditions by means of a paddle fabricated for the purpose in a dissolution apparatus. At various time intervals samples of dissolution medium are withdrawn and filtered through Whattmann filter paper no: 42. It is replaced immediately with an equal amount of fresh buffer. The samples are then analyzed UV spectrophotometrically at 276 nm. Absorbance measured and % drug release is determined.

RESULTS AND DISCUSSION

Evaluation of tablets:
Physicochemical parameters:
A) Uniformity of weight test:
All Individual weight of all formulation batches are complies with in the limit. The percentage weight variation range found for various batches of tablets is as shown in table 2. As none of the formulation show deviation of more than ±5% for any of the 20 tablets tested, the prepared formulations comply with the weight variation test as prescribed in the IP

B) Tablet thickness:
The average thickness of various batches of tablets is as shown in table 3.

C) Hardness:
The average hardness of the tablets of various batches is shown in table 4.

D) Friability:
% Friability was determined for 20 tablets from each batch and was found to lie within limited range of less than 1%. So all tablets complies for the test for friability.

E) *In Vitro* Drug Release Studies:
The *in-vitro* dissolution study was performed for all the formulated tablets of Ciprofloxacin HCl and the result is given in the table 7.

In-Vitro Study of CE1 to CE5:
The formulations CE1, CE2, CE3 were studied by drug with HPMC K 4M, K15M, K100M and Carbopol .In this CE1, CE2 and CE3shows the drug release 98.17% , 97.18% and 93.18% in 15 hrs, and CE4 and CE5 shows 80.47% and 84.25% in 24 hours

In-Vitro Study of CE5 to CE10:
The formulations CE5 to CE10 were studied by drug with HPMC K4M, K15M, K100M and Carbopol. In this CE6, CE7 and CE8 shows the drug release 89.18%, 91.24%, 94.87% in 24 hours and CE9 shows 97.36%, in 24 hrs, CE10 shows 99.89 % in 24 hours respectively.

Table 1: Composition of prepared extended release tablets

Ingredients	CE1	CE2	CE3	CE4	CE5	CE6	CE7	CE8	CE9	CE10
Ciprofloxacin HCl	300	300	300	300	300	300	300	300	300	300
HPMC K4M	150	---	---	---	75	---	---	120	---	---
HPMC K15M	---	150	---	---	---	75	---	---	120	---
HPMC K100M	---	---	150	---	---	---	75	---	---	120
Carbopol	---	---	---	150	75	75	75	30	30	30
PVP	10	10	10	10	10	10	10	10	10	10

- Mg Stearate10 mg,Talc 5mg to each formulation. Total weight of tablet 475 mg

Table 2: Weight variation(n=3)

Batch no	WEIGHT VARIATION (mg) ± S.D
CE1	0.106 ±0.003
CE2	0.098 ±0.003
CE3	0.097 ±0.002
CE4	0.110 ±0.002
CE5	0.103 ±0.003
CE6	0.108 ±0.002
CE7	0.109±0.005
CE8	0.099±0.009
CE9	0.097±0.006
CE10	0.110±0.008

Table 3: Thickness of extended release tablets of Ciprofloxacin

Formulation code	Average thickness (mm)* ± S.D
CE1	2.90 ±0.015
CE2	3.09 ±0.026
CE3	2.93 ±0.015
CE4	2.95 ±0.036
CE5	3.09 ±0.026
CE6	3.18 ±0.025
CE7	3.09±0.018
CE8	3.15±0.021
CE9	3.05±0.054
CE10	2.99±0.078

** Average of 10 tablet (n=3)*

Table 4: Hardness of Ciprofloxacin extended release Tablets

Batch No	HARDNESS (kg/cm²) ± S.D
CE1	3.1 ±0.264
CE2	2.8 ±0.251
CE3	2.7 ±0.404
CE4	3.0 ±0.200
CE5	2.9 ±0.450
CE6	3.1 ±0.400
CE7	3.5 ±0.564
CE8	2.91 ±0.151
CE9	3.02 ±0.514
CE10	3.0 ±0.275

(n=3)

Table 5: % Friability of Extended release tablets:

Batch No	FRIABILITY (%) ± S.D
CE1	0.32% ±0.091
CE2	0.12% ±0.035
CE3	0.11% ±0.047
CE4	0.23% ±0.057
CE5	0.31% ±0.045
CE6	0.36% ±0.020
CE7	0.24%±0.021
CE8	0.29% ±0.417
CE9	0.31% ±0.405
CE10	0.46% ±0.120

** Average of 20 tablets* *(n=3)*

A. Standard curve:

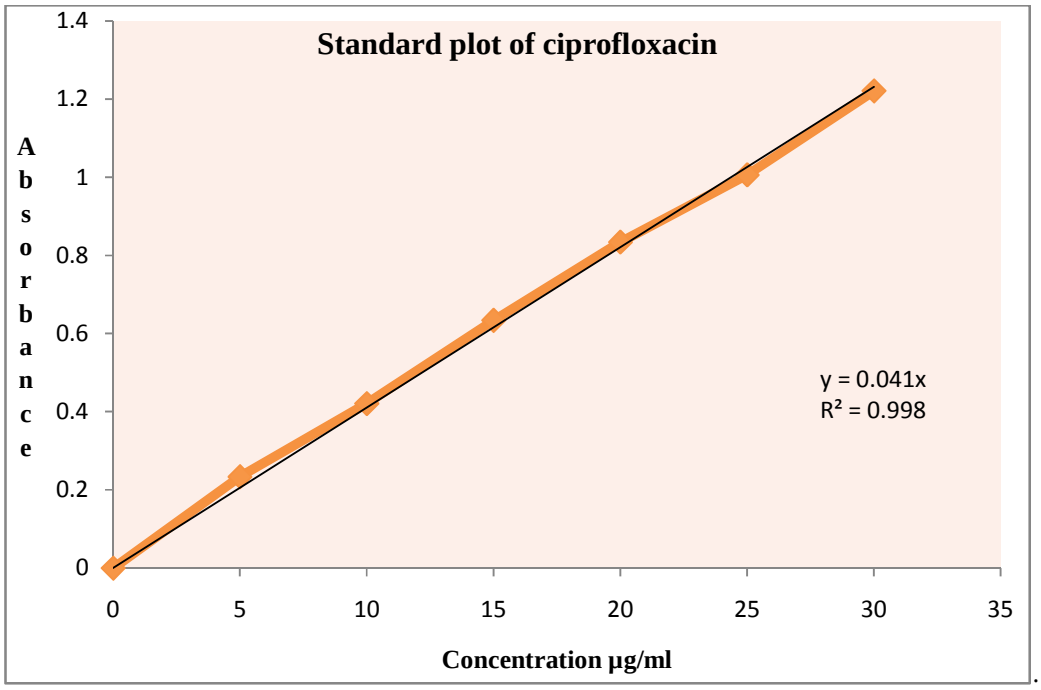
Table 6: Standard curve of Ciprofloxacin in phosphate buffer pH (7.4)

Sl no:	Concentration (µg/ml)	Absorbance
	0	0
1	5	0.234
2	10	0.421
3	15	0.634
4	20	0.834
5	25	1.006
6	30	1.221

Table 6: Dissolution study:

Batch no	1 hours	3 hours	6 hours	10 hours	15 hours	20 hours	24 hours
CE1	6.15	21.34	45.29	71.48	98.17	---	---
CE2	5.48	18.34	41.29	65.15	97.18	---	---
CE3	4.95	16.85	39.18	59.95	93.18	---	---
CE4	4.75	9.17	17.75	30.18	51.27	72.14	80.47
CE5	6.17	14.17	22.45	38.97	56.47	76.48	84.25
CE6	7.38	16.39	25.08	43.06	62.84	79.16	89.18
CE7	5.97	17.84	23.18	45.79	69.15	89.16	91.24
CE8	6.94	18.15	25.14	50.92	71.72	91.52	94.87
CE9	7.35	17.24	27.38	52.14	71.65	93.17	97.36
CE10	9.33	23.64	31.12	54.08	77.88	95.68	99.89

Graph:1



B. Dissolution study

The results of *in-vitro* drug release studies for all formulations are shown in table 6. The percentage amount of drug released is plotted against time to obtain the release profiles as shown in figures 1 and 2.

Figure 1: dissolution study of CE1 to CE5:

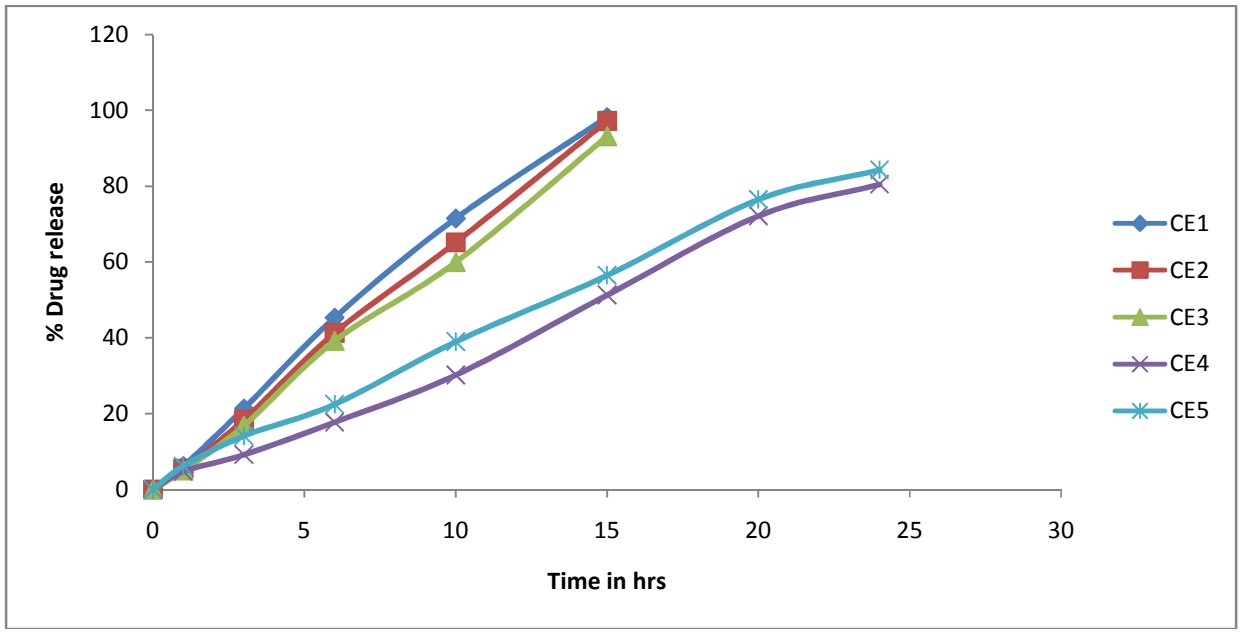
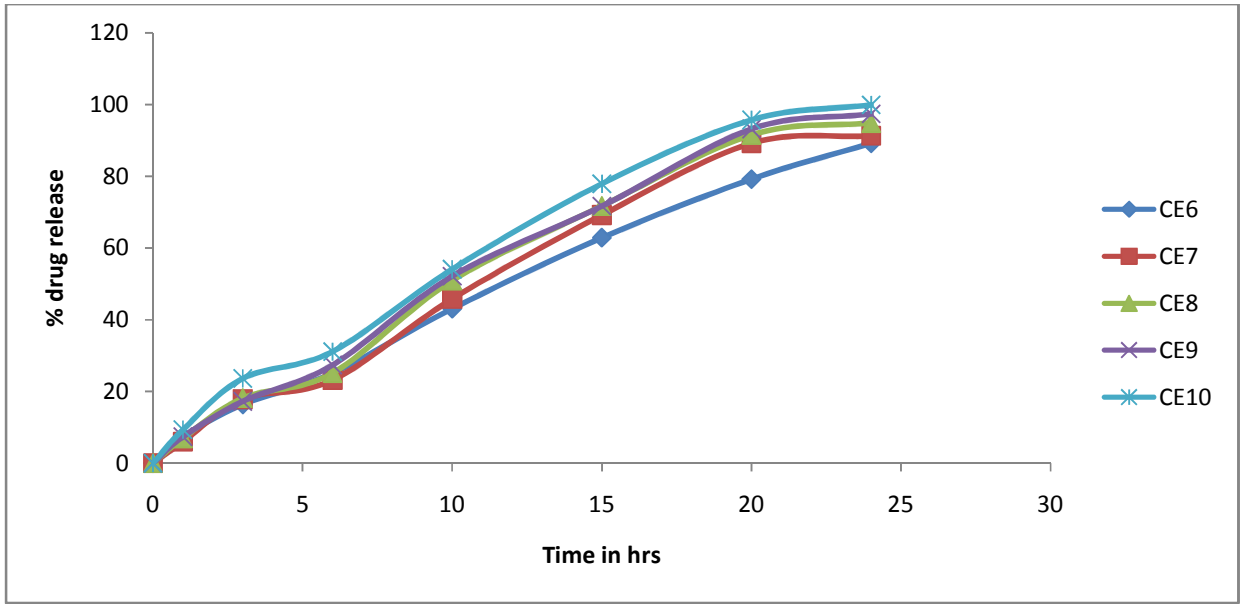


Figure 2: dissolution study of CE6 to CE10:



CONCLUSION

In the present study the effect of combination of cellulose derivative with non-cellulose derivative on extended release of Ciprofloxacin was studied. Formulations are made by the combination of cellulose derivative polymers like HPMC K4M, K15M, K100M and non-cellular derivative like Carbopol 71G in the ratio of 1:1 and 4:1. The best formulation in the present study was K100M and Carbopol 71G in the ratio 4:1.

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