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Research Article

FORMULATION AND EVALUATION OF CONTROLLED RELEASE FLOATING TABLETS OF CEFIXIME USING HYDROPHILIC POLYMERS

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ABSTRACT

To prepare and evaluates controlled release floating tablets of Cefixime using hydrophilic polymers to increase the buoyancy time and release the drug in longer periods of time in the stomach. Nine batches (F1 to F9) formulation was prepared from active drug Cefixime trihydrate with different concentration of excipients; hydrophilic polymer polyvinyl alcohol, gas releasing excipients sodium bicarbonate and citric acid along with other excipients. All batches formulation was evaluated like in vitro buoyancy study; uniformity of drug content, disintegration, in vitro dissolution study, etc. among them selected F4 batch formulation conducted for stability study. *In vitro* buoyancy studied results revealed that, the floating lag time of all batches formulation were found to be in the range of 68 s to 82 s and total floating time were found to be 8 h to 11 h and the disintegration studied results was found to be 400±1 min to 577.6±2.59 min. The *in vitro* dissolution studied result of F4 batch's formulation was found to be maximum than other batches formulation, and it was found to be 98.48±0.98% at 12 h in 0.1 N hydrochloric acid medium. The stability studied results of selected F4 Batch's formulation indicated that the post compression parameters result were not much more different before and after the stability study (40±2°C at 75 % RH). So from the above studied results it concluded that to enhance the bioavailability and gastric residence time of Cefixime drug; F4 batches controlled release floating tablets of Cefixime is best choice.

Keywords: Cefixime, floating tablets, controlled release, hydrophilic polymers

INTRODUCTION

Almost in every developing country, infectious diseases are more common, among them bacteria are most responsible pathogenic microorganism[1]. Cefixime is a third generation cephalosporin group of drug which inhibits bacteria as well as other microorganism like *Mycoplasma* and *Chlamydia, E. coli, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes*, *Hemophilus influenzae, Salmonella, Shigella, and Neisseria gonorrhoeae*[2,3]. Cefixime attach to the protein that is penicillin-binding proteins which is responsible for the synthesis of peptidoglycan which will inhibit bacterial cell wall[4-6]. Polyvinyl alcohol is a water soluble synthetic, biocompatible and toxicologically safe polymer, sparingly soluble in ethanol and insoluble in most organic solvents. It was used to enhance the solubility of insoluble drugs[7,8]. Floating drug delivery systems are a buoyant state in the stomach for a long period of time and the drug is floating in less gastric fluid, as a result the drug will released in desire rate[9]. This is one of the best drug delivery system, as the drug that are easily absorbed from the gastrointestinal track without frequent dosing so, prepared formulation exhibit required therapeutic effect as well as better patient compliance[10-12]. The half-life of Cefixime about 3h and it has poor bioavailability, to overcome these problem we prepared controlled release floating tablets of Cefixime with hydrophilic polymer, viscosity enhancer such as polyvinyl alcohol, gas releasing excipients sodium bi carbonate and citric acid.

MATERIALS AND METHODS

Materials used in the development of controlled release floating tablets, Cefixime trihydrate was a gift sample from Divine Care Pharmaceuticals Haryana, polyvinyl alcohol, ethylcellulose, carbopol-934, beeswax, sodium bicarbonate, citric acid, talc, magnesium stearate, all were obtained from departmental store and all other chemicals and reagents used in the study were of analytical grade.

A direct compression technique was used for the preparation of controlled release floating tablets of Cefixime. Nine batches (F1 to F9) tablets were prepared from active drug Cefixime trihydrate along with different concentration of excipients by trial and error methods. Initially the drug Cefixime trihydrate was passed through Sieve #30, hydrophilic polymer polyvinyl alcohol, ethyl cellulose, carbopol-934, beeswax; sodium bicarbonate and citric acid were passed through Sieve #40. Talc and magnesium stearate were passed through Sieve #60. Required quantity of the drug and excipients were mixed homogeneously and compressed into tablets using a tablet compression machine (Madhur Industries, India) [13]. Each tablet contains 200mg Cefixime trihydrate and total weight was 560 mg. Composition of controlled released floating tablets of Cefixime was shown in Table: 1.

EVALUATION PARAMETERS OF PREPARED TABLETS

HARDNESS TEST

The hardness of all batches 06 tablets were measured by the Pfizer hardness tester. One tablet is vertically kept in two plungers of Pfizer hardness tester and applied the pressure until the tablet were broken down into small parts[14,15]. The reading was noted down in Kg/cm^2

DIAMETER AND THICKNESS

Diameter and Thickness of all batches 6 tablets were measured by Vernier caliper[16].

FRIABILITY TEST

All batches 20 tablets were placed in the friabilator and rotating vertically at 25 rpm for 4 min. After dusting the total remaining weight of the tablet was measured and calculated the % friability by the following formula[17].

$$\% \text{ Friability} = [(\text{Weight}_{\text{Final}} - \text{Weight}_{\text{Original}}) / \text{Weight}_{\text{Original}}] \times 100$$

IN VITRO BUOYANCY STUDY

In vitro buoyancy study was performed to determine the floating lag time and total floating time. In the study one tablet was placed in USP type II paddle apparatus. Dissolution basket was filled with 900 ml of 0.1N hydrochloric acid and maintained the temperature at 37 ± 0.5^{0}C. Floating lag time is the time taken for the tablet to rise to the surface of dissolution medium and total floating time is the time tablet float comfortably in dissolution medium[18,19].

UNIFORMITY OF WEIGHT

For the study, from each batch 20 individual tablets without dusting randomly selected and weight by electronic weigh balance. The resulted data were summarized with mean±SD [20,21].

DRUG CONTENT UNIFORMITY

Each batch 20 tablets were powdered and the blend equivalent to 200mg Cefixime was weighed and dissolved in 1000ml of 0.1N hydrochloric acid. The prepared solution was sonicated, filtered, and suitably diluted. After this, the drug content was determined with the help of Double Beam UV Spectrophotometer (UV-1800 Shimadzu) at 287.8 nm. Each sample was analyzed in triplicate. The resulted data were summarized with mean±SD [21,22].

SURFACE pH STUDY

The tablet (n=3) were made in contact 1 ml of distinct water and allowed to swell for 2h at room temperature. The pH is measured by electrode pH meter (Max 962-p) in contact with surface of the swell tablet and allowing it to equilibrate for 1 min [23,13].

DISINTEGRATION STUDY

The disintegration test apparatus (Electro lab disintegration test apparatus) was used to conduct the disintegration study. There was thermostat, which is provided to regulate the temperature of the fluid medium to the desired temperature. The test was carried out on 6 tablets in each batch formulation using disintegration media, 900ml 0.1N hydrochloric acid at temperature 37.5ºC± 2ºC. The time (min.) was calculated for the complete disintegration of the tablets, so that there was no mass remaining in the baskets of disintegration apparatus. The study was performed in triplicate and mean ± SD was calculated [24].

***IN VITRO* DRUG RELEASE STUDY**

USP- type II dissolution apparatus (paddle type) was used for the dissolution study of prepared controlled release floating tablets. The temperature of dissolution flask was maintained at 37± 0.5°C and filled 900ml 0.1N hydrochloric acid in the flask. The apparatus was allowed to run for 12h at 50rpm. 5ml sample solution was withdrawn after every 1 hour using a pipette and filtered the solution by 0.45µm syringe filter. The amount of sample withdrawn was replaced every time with the same quantity of the fresh dissolution medium. All samples were suitably diluted and analyzed by double beam UV Spectrophotometer (UV-1800 Shimadzu) at 287.8nm to determine the amount of drug content [16].

STABILITY STUDY

Stability study was conducted for F4 batch's formulation, as F4 batches formulation was best among the nine batches formulation (F1-F9) based on the buoyancy time, disintegration time, in vitro drug released study. Stability studies were performed over a period of 90 days at a temperature of 40±2°C at 75% RH. The samples were withdrawn at 30 days interval from the stability chamber and measured the drug content [24].

Table 1: Composition of controlled released floating tablets of Cefixime

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefixime trihydrate(mg)	200	200	200	200	200	200	200	200	200
Polyvinyl alcohol(mg)	83	77	69	60	69	64	66	73	77
Sodium bi carbonate (mg)	33	36	41	45	40	43	42	39	37
Citric acid (mg)	14	17	20	25	21	23	22	18	16
Ethylcellulose(mg)	70	70	70	70	70	70	70	70	70
Bees wax(mg)	80	80	80	80	80	80	80	80	80
Carbopol-934(mg)	52	52	52	52	52	52	52	52	52
Mag. stearate(mg)	15	15	15	15	15	15	15	15	15
Talc(mg)	13	13	13	13	13	13	13	13	13

Table 2: *In vitro* buoyancy studied results, floating lag time and total floating time

Sr. No	Formulation batch code	Floating lag time (s)	Total floating time(h)
1.	F1	82	>10
2.	F2	81	>8
3.	F3	76	>9
4.	F4	68	>10
5.	F5	75	>9
6.	F6	78	>8
7.	F7	77	>9
8.	F8	79	>9
9.	F9	80	>9

Table 3: Evaluation parameters of controlled release floating tablets of Cefixime

Formulation batch code	Mean hardness Kg/cm²	Diameter and thickness (mm)	Friability % w/w	Uniformity weight (mg)	Mean drug content %±SD, n=3	Tablet surface pH	Disintegration time (min)
F1	11.05	12.1,4.1	0.53	560	99.6±0.81	6.9	400± 1.00
F2	10.23	12.1,4.2	0.52	559.9	98.8±1.05	7	436.6 ± 0.57
F3	9.72	12.3,4.1	0.56	560.2	100.6±0.7	7.1	494.6 ± 1.52
F4	9.58	12.2,4.1	0.51	560.1	100.3±0.8	6.9	577.6± 2.59
F5	9.89	12.1,4.2	0.58	560.4	101.2±1.0	7.2	457.0 ± 2.00
F6	9.62	12.1,4.2	0.4	560	101.1±1.0	7	519.3 ± 2.08
F7	10.20	12.1,4.2	0.54	560	101.5±0.8	7	452.3 ±1.52
F8	10.05	12.1,4.1	0.55	560	99.6±1.82	7.1	445.6 ±2.51
F9	9.95	12.1,4.2	0.57	560	99.0±1.00	7.1	439.6 ±2.08

Table 4: Cumulative % drug released of tablets in 900ml 0.1N hydrochloric acid medium

Time (h)	Cumulative % drug released of tablets in 900ml 0.1N hydrochloric acid medium								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	8.11±0.89	9.21±0.91	9.59±0.97	11.49±0.95	8.86±0.95	10.71±1.10	9.31±1.02	9.09±1.10	8.78± 1.34
2	12.23±0.80	13.67±0.84	16.51±1.11	22.63±0.97	16.56±1.05	16.65±1.00	16.78±0.69	15.35±1.05	14.42±0.92
3	20.86±1.24	20.63±1.11	24.46±1.06	31.52±1.06	23.63±1.00	27.70±0.90	23.26±1.00	22.44±0.95	21.58±1.15
4	27.52±0.94	30.31±1.33	35.49±0.79	40.45±0.98	34.56±1.20	34.53±0.95	34.45±1.01	32.64±1.06	31.37±1.01
5	39.01±1.20	40.44±0.98	47.53±1.01	49.56±0.91	46.60±1.05	48.68±0.82	46.70±0.90	44.65±1.01	42.34±1.22
6	46.78±1.16	46.60±1.00	53.33±0.99	58.59±0.90	52.36±1.11	55.64±2.05	53.30±1.07	50.45±0.90	48.50±0.76
7	53.04±1.72	55.42±1.27	59.59±1.00	66.60±1.23	58.55±1.12	65.67±1.06	57.71±1.11	57.20±1.11	56.33±0.92
8	56.73±0.98	57.50±1.14	64.64±1.32	71.40±1.07	64.40±0.86	71.38±1.06	64.90±1.73	61.30±1.15	59.30±1.21
9	60.49±1.06	61.37±0.99	69.49±0.92	77.72±0.76	68.57±0.92	77.55±1.25	67.41±1.48	64.33±1.05	62.46±1.49
10	61.60±1.11	67.49±1.05	73.61±0.99	82.57±1.11	73.19±0.82	81.67±1.07	72.35±1.17	70.27±1.00	68.28±1.04
11	66.66±0.87	71.69±1.12	78.56±1.05	90.51±1.15	77.50±1.10	87.91±1.44	77.37±0.99	74.49±0.83	72.55±1.27
12	71.26±1.01	73.61±0.85	84.46±1.26	98.48±0.98	83.68±1.15	93.48±1.22	81.56±1.05	77.35±1.11	75.09±1.56

Table 5: Stability studied results of F4 batch's controlled release floating tablets of Cefixime

Formulation	1st day	30th day	60th day	90th day
F4	99.948±0.0518%	99.913±0.0563%	99.620±0.0896%	99.693±0.0723%

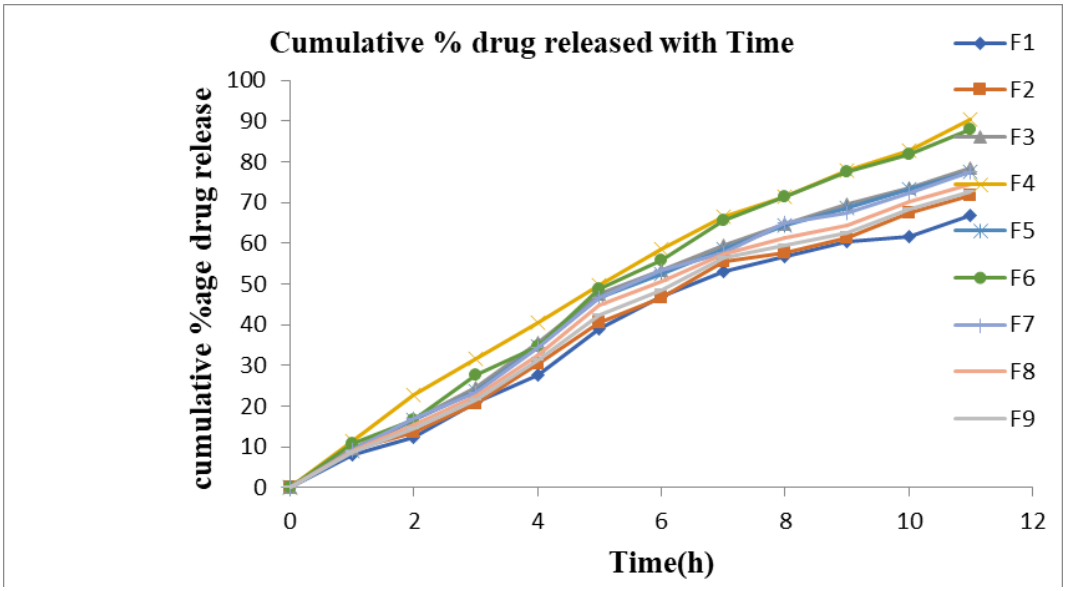

Figure 1: Cumulative % drug released with time in 900ml 0.1N hydrochloric acid medium

RESULTS AND DISCUSSION

The *In vitro* buoyancy studied results of controlled release floating tablet of Cefixime with hydrophilic polymer; revealed that the floating lag time (FLG) of all the nine batches formulation was in the range of 68 s to 82 s, among them F4 batch's tablets were found to be 68 s. The total floating time (TFT) of all the nine batches formulation was found to be in the range of 8 h to 11 h among them F4 batch's tablets were found to be 10.8 h. The resulted data were shown in Table 2.

The disintegration time of all nine batches formulation was found to be in the range of 400±1min to 577.6±2.59min and F4 formulation was found to be 577.6±2.59min. The resulted data were shown in Table 3.

The dissolution studied result of F4 formulation in 900ml 0.1N hydrochloric acid medium, cumulative % drug released of Cefixime was found to be 98.48±0.98 at 12h. The resulted data were shown in Table 4 and Figure 1.

The stability studied results of selected F4 Batch's formulation indicated that the post compression parameters like hardness, disintegration time, drug content uniformity, and friability studied results were not much more different before and after the stability study (40±2°C at 75 % RH). The resulted data were shown in Table 5.

The evaluation parameters of controlled release floating tablet of Cefixime with hydrophilic polymer polyvinyl alcohol results revealed that gastric residence time increased with increasing viscosity enhancing polymer polyvinyl alcohol and %drug release increased from the tablets with increasing concentration of gas releasing excipients sodium bicarbonate and citric acid.

CONCLUSION

The aim of the study was to formulate and evaluate controlled release floating tablet of Cefixime with hydrophilic polymers as well as viscosity enhancers such as polyvinyl alcohol and gas releasing excipients sodium bicarbonate and citric acid along with other excipients. Nine batches (F1 to F9) tablets were prepared and their quality control tests were performed like hardness, friability, *in vitro* buoyancy study, floating time, disintegration study, dissolution study, stability study etc. On the above studied results revealed that F4 formulation was the best formulation among F1 to F9 batches formulation. So from the above studied results concluded that prepared F4 batch's Cefixime controlled release floating tablets can be best choice to enhance the gastric residence time and bioavailability.

Prepared F4 batch's Cefixime controlled release floating tablets can be best choice to enhance the gastric residence time and bioavailability.

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