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FORMULATION AND EVALUATION OF EFFERVESCENT FLOATING TABLET OF CIPROFLOXACIN HYDROCHLORIDE AND RANITIDINE HYDROCHLORIDE

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ABSTRACT

The present study was aimed at developing gastro retentive bilayer drug delivery systems containing ranitidine HCl and ciprofloxacin HCl for the treatment of gastric ulcer to minimize the side effect, improve the prolongation of action, to reduce the frequency of drug administration. The formulation containing gastroretentive layer was designed using HPMC K 15, HPMC K4 and PVP K30 as floating agents, sodium bicarbonate and citric acid as gas-generating agent. Crospovidone, sodium starch glycolate and croscarmellose sodium was used as superdisintegrant for the preparation of immediate release layer. The prepared instant layer and gastroretentive layer was evaluated for their pre-compression parameters, physical characteristics like hardness, friability, uniformity of weight, uniformity of drug content, swelling index, *In-vitro* floating studies and *In-vitro* drug release. The release of the ranitidine from the immediate release layer was found to be 99.12% in 90minutes. The release of ciprofloxacin for the sustained release floating layer was found to be 99.74% in 12 hours. The present study revealed that ranitidine and ciprofloxacin bilayer tablets were successfully developed for the use against gastric ulcer.

Keywords: Ranitidine, Ciprofloxacin, Bilayer floating tab, Superdisintegrant, HPMC.

INTRODUCTION

Oral dosage forms of drugs are the main popular routes in spite of some disadvantages such as slow absorption and delayed onset of action. On the other hand, liquid forms of drugs are not stable enough and slow release dosage forms have longer routes for changing throughout the gastrointestinal tract. These two forms are thus limited in applications. Hence, effervescent tablets seem to be an appropriate alternative for oral dosage forms [1]. Effervescent tablets are designed to be dissolved or dispersed in

water before administration [2]. The tablet is promptly broken apart by internal release of CO_2 in water and the CO_2 reaction is created by an interaction of tartaric acid and citric acid with alkali metal carbonates or bicarbonates in the presence of the water. Effervescent tablets are uncoated tablets that usually consist of acids and bicarbonates or carbonates [3, 4]. Some products are useful for pharmaceuticals that damage the stomach or those which are susceptible to stomach pH. In addition, the drugs prescribed commonly in high doses may be used in the form of effervescent tablets [3, 5]. Moreover, since effervescent tablets are administrated in liquid form, they are easily swallowed so they are preferred over tablets or capsules with a difficult consumption for some patients. On the other hand, one dose of effervescent tablet is often dissolved in 3-4 ounces of water. Being previously dissolved in a buffer solution, effervescent products do not get in direct contact with the gastrointestinal tract. They can thus be tolerated in stomach and intestine well due to reduced gastrointestinal irritation. Another advantage relating to effervescent tablet is that when they are taken by the patient, exactly the taken amount enters the stomach. In fact, the CO_2 produced in an effervescence reaction increases the penetration of active substances into the paracellular pathway and consequently their absorption [6, 7]. Ranitidine is a potent histamine H_2 receptor antagonist extensively used in the treatment of conditions like duodenal and gastric ulceration, reflux esophagitis and Zollinger-Ellison syndrome. It is also used in postoperative prophylaxis and in the treatment of allergic and inflammatory conditions related to histamine receptors [8]. Ranitidine is more effective than omeprazole in treating gastric ulcer among the children who develop these condition two weeks after taking non-steroidal anti-inflammatory drugs (NSAIDs) [9]. Ranitidine has both oral (tablets, capsules and syrups) and injectables dosage forms. Ciprofloxacin is a broad-spectrum fluoroquinolone antibacterial agent. It is approved for use in the treatment of bone and joint infections, infectious diarrhea, lower respiratory tract infections, urinary tract infections, hospital-acquired infections and meningococcal prophylaxis [10]. Since the drug is freely soluble in water (1 g in 25 ml) and has an elimination half-life of about 4 h which is suitable to make a sustained-release dosage form aiming to enhance its antibacterial activity and provide a constant release of the drug without much fluctuation of plasma drug concentration in the blood. In the current scenario, the strategies for developing a fixed-dose combination (FDC) are primarily based on the therapeutic requirements. The present research was carried out with the aim of developing bilayer tablets of ranitidine and ciprofloxacin for the treatment of gastric ulcer.

MATERIALS AND METHODS

Ranitidine and ciprofloxacin were gifted by Aurobindo Pharma Limited, Hyderabad A.P, India. HPMC K4M, K15M, PVP K30 was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Sodium bicarbonate, citric acid, magnesium stearate and talc were obtained from Loba Chemical Pvt Ltd (Mumbai, India). Crospovidone, sodium starch glycolate, croscarmellose sodium obtained from Danmed Pharmaceuticals Pvt Ltd, Hyderabad. Hydrochloric acid was obtained from S. D. Fine Chem. 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.

Formulation development

Formulation of immediate release (IR) layer

Fast dissolving (Instant Layer) tablets of ranitidine were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60. The blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Nine different formulations of ranitidine were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 200mg, were obtained. Composition of tablets is mentioned in Table 1.

Method for preparation of ciprofloxacin hydrochloride floating tablets

Direct compression was followed to manufacture the floating tablets of ciprofloxacin hydrochloride. Eight different formulations (F1, F2, F3, F4, F5, F6, F7, & F8) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in Table 2 and all the formulation were used for further evaluations parameters.

Formulation development of bilayer tablet

Optimized formulation IF-7 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet.

Table 1 Composition of ranitidine fast dissolving tablets

Ingredients(mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Ranitidine	150	150	150	150	150	150	150	150	150
Sodium Starch glycolate	10	15	20	-	-	-	-	-	-

Croscarmellose sodium	-	-	-	10	15	20	-	-	-
Crospovidone	-	-	-	-	-	-	10	15	20
Microcrystalline cellulose	25	20	15	25	20	15	25	20	15
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weight	200	200	200	200	200	200	200	200	200

Table 2 various formulations of ciprofloxacin hydrochloride floating tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Ciprofloxacin hydrochloride	500	500	500	500	500	500	500	500
HPMC K4	50	75	50	75	-	-	-	-
HPMC K15	-	-	-	-	50	75	50	75
PVP K30	15	15	15	15	15	15	15	15
Sodium bicarbonate	10	10	10	10	10	10	10	10
Citric acid	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	50	25	50	25	50	25	50	25
Total Weight	650	650	650	650	650	650	650	650

Evaluation of Precompression Parameter

Angle of Repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation**.**

$$\theta = \tan^{-1}(h/r)$$

Where, h and r are the height and radius of the powder cone respectively.

Bulk Density/Tapped Density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index**.**

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula [11, 12].

Hausner's ratio = Tapped density/Bulk density.

Evaluation of post compression Parameter

Shape and color of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light [13].

Thickness

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach) and measured in terms of kg/cm^2.

Weight variation

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet.

Friability

A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche friabilator. The friabilator was operated for 4 min at a speed of 25 rpm. The tablets were removed from the friabilator, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,

%Friability= (Loss in weight/ Initial weight) x 100

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2**.**

Uniformity of drug content IR layer

The test is mandatory for tablets with 10mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml 0.1 N HCl (Simulated gastric fluid of pH 1.2 without enzymes) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 296nm for ranitidine.

Uniformity of drug content floating layer

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and reacts with dye and analyzed for drug content by UV spectrophotometer at a λ max of 270nm using of 0.1 N HCl as blank.

***In vitro* buoyancy studies**

In vitro buoyancy was determined by floating lag time as per the standard method. The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid, pH 1.2 as per USP. The time necessary for the tablet to increase to the outside and float was determined as floating lag time.

Dissolution rate studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50ºc and rpm of 75. One ciprofloxacin hydrochloride tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^0C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCl and take the absorbance at 270nm using spectroscopy.

RESULTS AND DISCUSSIONS

λ_{max} of ranitidine and ciprofloxacin was found to be 296 and 270nm by using U.V. spectrophotometer (Labindia-3000+). The powdered blends of different formulations of immediate and floating tablets

were evaluated for angle of repose, bulk density (BD), tapped density (TBD), compressibility index and Hausner's ratio was founds within the range, which shows good flow properties of the powdered blend Table 3 & 4. The prepared tablets were evaluated for different physico-chemical properties and the results are summarized in Table 5 & 6. The tablets were white, circular in shape and were found to be uniform with respect to weight variation, hardness; thickness, friability and content uniformity of different batch of tablets were found within acceptable range and the distribution of drug in all the formulations was uniform. The prepared bilayer tablets were evaluated for different physico-chemical properties and the results are summarized in Table 7 & 8. The tablets were found to be uniform with respect to weight variation and hardness (6.8 kg/cm^2). The thickness (5.1 mm) and friability (0.785%) of optimized batch of tablets were found within acceptable range. Content uniformity of formulations was found to be 99.85 and 99.95 %, where the distribution of drug in all the formulations was uniform. A dissolution study shows the release of Ranitidine and Ciprofloxacin hydrochloride. The Instant layer of ranitidine release approx 96.65 percent drug within 1.0 Hrs. and control layer ciprofloxacin shows release up to after 12 hours approx 99.74 percent. The release of bilayer tablet is shown in Table 9.

Table 3 Results of pre-compressional parameters of ranitidine

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
IF1	0.365	0.472	22.669	1.293
IF2	0.347	0.483	28.157	1.392
IF3	0.358	0.465	23.011	1.299
IF4	0.359	0.467	23.126	1.301
IF5	0.362	0.473	23.467	1.307
IF6	0.348	0.453	23.179	1.302
IF7	0.374	0.483	22.567	1.291
IF8	0.362	0.459	21.133	1.268
IF9	0.341	0.447	23.714	1.311

Table 4 Result of pre-compression properties of ciprofloxacin floating tablets

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.358	0.468	30.73	1.307
F2	0.362	0.476	31.49	1.315
F3	0.378	0.469	24.07	1.241
F4	0.365	0.473	29.59	1.296
F5	0.369	0.483	30.89	1.309

F6	0.375	0.478	27.47	1.275
F7	0.373	0.476	27.61	1.276
F8	0.374	0.469	25.40	1.254

Table 5 Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
IF1	3.5±0.2	0.658±0.045	205±4	2.3±0.1	98.85±0.45
IF2	3.4±0.1	0.752±0.025	202±5	2.4±0.2	98.12±0.65
IF3	3.6±0.2	0.698±0.023	203±3	2.3±0.1	98.96±0.35
IF4	3.4±0.2	0.874±0.041	200±4	2.1±0.2	99.05±0.45
IF5	3.4±0.1	0.765±0.025	198±2	2.3±0.2	98.87±0.25
IF6	3.5±0.1	0.845±0.042	203±5	2.4±0.1	99.65±0.41
IF7	3.4±0.2	0.785±0.032	205±2	2.5±0.3	99.92±0.32
IF8	3.4±0.1	0.821±0.045	197±4	2.3±0.1	98.84±0.25
IF9	3.6±0.2	0.874±0.036	196±3	2.4±0.2	98.45±0.23

Table 6: Results of post compression properties of ciprofloxacin tablets

F. code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating lag time (sec.)	Total Floating Duration (Hrs.)
F1	3.6±0.2	5.6±0.1	652±5	0.758±0.045	98.65±0.32	45±3	MT 12
F2	3.7±0.3	5.5±0.2	655±7	0.658±0.032	99.45±0.25	52±4	MT 12
F3	3.8±0.4	5.7±0.1	658±6	0.885±0.025	98.78±0.12	56±5	MT 12
F4	3.8±0.6	5.5±0.2	648±2	0.785±0.065	98.56±0.14	47±2	MT 12
F5	3.7±0.4	5.6±0.3	655±4	0.735±0.045	98.78±0.23	48±4	MT 12
F6	3.9±0.4	5.7±0.4	658±5	0.865±0.025	98.98±0.25	51±1	MT 12
F7	3.7±0.3	5.5±0.5	653±8	0.745±0.032	99.45±0.36	33±2	MT 12
F8	3.8±0.2	5.8±0.2	657±2	0.658±0.024	98.98±0.32	49±3	MT 12

Table 7 Post-compression parameters of optimized formulation

Formulation	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	6.8	0.785	Passes	5.1

Table 8 Results of Drug content analysis

Formulation	Ranitidine (% Label Claim)	Ciprofloxacin hydrochloride (% Label Claim)
In-house Bilayer tablet	99.85	99.95

Table 9 Results of Dissolution rate studies of bilayer tablets

Time (Hour)	% Drug Release	
	Ranitidine	Ciprofloxacin hydrochloride
0.5	56.65	31.25
1	96.65	38.95
1.5	99.12	46.65
2	-	60.23
4	-	69.98
6	-	78.85
8	-	86.65
10	-	94.45
12	-	99.74

CONCLUSION

Present research work involve the development of a bilayer tablet of Ranitidine and ciprofloxacin using a super disintegrating agent for the fast releasing layer and HPMC K 15, HPMC K4 and PVP K30 as floating agents, sodium bicarbonate and citric acid as gas-generating agent for the floating layer. There was the initial burst effect from the formulations to provide the loading dose of the drug, followed by sustained release to provide maintenance dose of the drug. Ranitidine and ciprofloxacin bilayer tablets were found promising and as potential alternative to the conventional dosage form of the drug.

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