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Formulation and Invitro Evaluation of Gastroretentive Drug Delivery System of Ciprofloxacin Hydrochloride

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ABSTRACT

The present investigation concerns the development of Hydro dynamically balanced tablets of Ciprofloxacin Hydrochloride, are designed to prolong the gastric residence time after oral administration and thereby increasing drug bioavailability. Floating tablets of Ciprofloxacin Hcl were prepared by direct compression using HPMC K4M and HPMC K15M as polymers along with Sodium bicarbonate as gas generating agent. The tablets were evaluated for in-vitro buoyancy, dissolution studies and physical characteristic viz. Density, Hardness, Friability, Thickness and Weight variation. Further, tablets were evaluated for in-vitro release characteristic for 12 hrs. It is found that the hardness of the tablets affects the Buoyancy characteristic of the dosage form. All formulations possessed good floating properties with total floating time more than 12 hrs. The in-vitro release studies indicated that the floating tablets of Ciprofloxacin Hcl containing 200mg HPMC K15M (F4) showed sustained release when compared with the marketed product and provides a better option for controlled release action and improved bioavailability.

Key words: Gastric residence, Ciprofloxacin, Buoyancy, HPMC K4M, HPMC K15M.

INTRODUCTION

Oral route is considered as the most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process [1]. Ciprofloxacin is a broad-spectrum antibiotic that belongs to the family of fluoroquinolones. It is used for the

treatment of gram-negative infections of the skin, sinuses, bone, lung, ear, abdomen, and bladder. It can also be used to treat some sexually transmitted infections, some forms of infectious diarrhoea, mycobacterial infections, corneal ulcers, bacterial conjunctivitis, typhoid fever and bacterial infection of Respiratory tract, urinary tract infections (UTI) in females, chronic bacterial prostatitis, Immuno compromised patients, uncomplicated cervical and urethral gonorrhea and Joint Infections [2]. Ciprofloxacin is acid-stable, is rapidly and completely absorbed from the GI tract, peak serum Ciprofloxacin concentration is attained with in 1hr at the average of 9, 15, 32-39 µg/ml for 250mg, 500mg and 1gm dosage respectively [3]. It is highly potent against wide variety of aerobic and anaerobic gram-positive and gram-negative organisms such as Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus pyogenes, E.coil and klebsiella species [4]. The antibacterial action of Ciprofloxacin results from inhibition of DNA gyrase and topoisomerase IV, essential enzymes responsible for counteracting excessive super coiling of DNA during replication, transcription, and repair of bacterial DNA [5]. As the mechanism of action of ciprofloxacin is different from that of other antimicrobial agents such as beta-lactams, macrolides, tetracyclines or amino glycosides, the organisms resistant to these drugs may be susceptible to ciprofloxacin. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials.

Gastric emptying of dosage forms is an extremely variable process. The ability of a dosage form to prolong and control the gastric emptying time is a valuable asset for drugs acting on GIT. Drug absorption from the GIT is a complex procedure and is subjected to many parameters to become bioavailable. It is widely acknowledged that the contact time with the small intestinal mucosa is related with the degree of GIT drug absorption [6]. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. Gastro retention provides better availability of new products with new therapeutic possibilities and substantial benefits for patients [7]. Controlled release drug delivery systems that retain in the stomach for a long time have many advantages over sustained release formulations. Such retention systems (i.e. GRDDS) are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that act locally in the stomach. Gastric retention may increase solubility for the drugs which are poorly soluble in intestine due to alkaline pH before they get emptied from the stomach. These systems are also advantageous in improving GIT absorption of drug having narrow absorption windows and site-specific absorption limitations [8]. A controlled drug delivery system is usually designed to deliver the drug in order to maintain blood levels above its minimum effective concentration and below its maximum safe concentration [9].

The present study outlines a systematic approach for design and development of gastroretentive drug delivery system of Ciprofloxacin Hydrochloride using polymers such as HPMC K4M, HPMC K15M, which increases the gastric residence time, decreases the diffusion distance and allow more of the antibiotic to penetrate through the gastric mucus layer and act locally at the infectious site to enhance the bioavailability and therapeutic efficacy of the drug [10]. Formulations were evaluated invitro for its buoyancy, dissolution, physical characteristic viz. Density, Hardness, Friability, Thickness and Weight variation. Further, tablets were evaluated for

in-vitro release characteristics in comparison to marketed product and effect of hardness on floating lag time.

MATERIALS AND METHODS

Chemicals:

Ciprofloxacin Hydrochloride was obtained from Karnataka Antibiotics and Pharmaceuticals Ltd., Bangalore, India. HPMC K4M, HPMC K15M were gift samples from Dr**.** Reddy's Laboratories Ltd., Hyderabad, India. Lactose, Polyvinylpyrrolidone (PVP) was supplied by Nice Chemicals Pvt. Ltd., Bangalore, India. Sodium bicarbonate is supplied by Poona chemical Laboratory, Pune, India. Talc and Magnesium stearate was gifted by Loba Chemie Pvt. Ltd., Mumbai, Maharashtra, India. Hydrochloric Acid was supplied by S.D. Fine Chem. Ltd., Mumbai, Maharashtra, India. All other reagents and solvents used were of analytical grade [11].

Formulation of Floating Tablet of Ciprofloxacin Hcl:

Floating matrix tablets containing Ciprofloxacin Hydrochloride were prepared by direct compression method using variable concentrations of HPMC K4M, HPMC K15M with sodium bicarbonate. Accurate Quantity of drug, HPMC K4M, HPMC K15M for each formulation (F1 to F6) was calculated, which was shown in Table 1. All the ingredients except magnesium stearate and talc were mixed well using mortar and pestle uniformly and passed through sieve No.60 and mixed with Magnesium stearate and talc. Powders obtained were compressed with 9mm concave punches to obtain tablets (Mini Press I, Karnavati Engineering Ltd., Mumbai). The weights of the tablets were kept constant for all formulations (F1 to F6) [12].

Table 1: Composition of Floating Tablets of Ciprofloxacin Hydrochloride.

Ingredients(in mgs)	F1	F2	F3	F4	F5	F6
Ciprofloxacin Hcl	500	500	500	500	500	500
HPMC K4M	200	300	400	-	-	-
HPMC K15M	-	-	-	200	300	400
Lactose	15	15	15	15	15	15
Sodium Bicarbonate	50	50	50	50	50	50
Talc	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10
PVP	75	75	75	75	75	75

Evaluation of Ciprofloxacin Hcl floating tablets:

Physical evaluation:

The formulated floating tablets of Ciprofloxacin Hcl were evaluated for physical characteristic viz. Density, Diameter, Thickness, Hardness, Weight variation, Friability and Drug content uniformity [13-15]

Floating Evaluation:

The formulated Ciprofloxacin Hcl floating tablets were evaluated for Buoyancy lag time, total floating time, and effect of hardness on Buoyancy Lag Time [12, 16].

In-vitro Drug release & comparison with Marketed product:
The standard calibration curve of Ciprofloxacin Hydrochloride was plotted by plotting absorbance values against concentration (µg/ml) [17]. In-vitro drug release studies of the prepared floating tablets and marketed product of Ciprofloxacin were conducted for a period of 12 hrs using USP XXIII type II apparatus at 37± 0.5°C and at 50 rpm speed in 900ml of 0.1N Hcl (pH 1.2). After withdrawing at predetermined time intervals for 12 hours, the samples were analyzed by a UV Spectrophotometer (Shimadzu, UV 1601) at 262 nm using dissolution medium in reference cell. The cumulative amount of drug release was calculated and compared with that of marketed product (Cipro® XR 500mg, Bayer HealthCare Pharmaceuticals) [18].

RESULTS AND DISCUSSION

Physical evaluation, Drug content uniformity:
The formulated floating tablets of Ciprofloxacin were evaluated for Density, Diameter, thickness, hardness, friability, weight variation and Drug content uniformity for all the batches [19]. The density for the all formulations range between 0.82 to 0.99 g/cm^3. The diameter of all tablets range between 8.98mm to 9.09 mm. Tablets mean thickness were uniform in F1 to F6 formulations and found to be in the range of 5.12 mm to 5.18mm. The hardness of tablets of each batch ranged between 4.5 to 9.1 kg/cm^2, which ensures good handling characteristics of all batches. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. All the formulated (F1 to F6) tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ±5% of the weight [20]. The percentage of drug content for F1 to F6 was found to be 97.4% to 99.5% of Ciprofloxacin, which complies with official specifications [19]. All values are expressed as mean ± SD (n=3) and the results are shown in Table 2.

Table 2: Physical Properties of Tablets of Batch F1 to F6

Batch	Diameter (mm)	Tablet Density (g/cc)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)	content uniformity (mg)
F1	9.09 ±0.040	0.93±0.32	5.16±0.010	4.5±0.47	0.96±0.042	800.65 ±1.29	97.01
F2	9.08±0.006	0.82±0.46	5.14±0.012	5.4±0.32	0.72±0.056	801.50 ±1.74	99.5
F3	9.09±0.067	0.89±0.2	5.12 ±0.06	7.1±0.54	0.91±0.072	799.55 ±1.18	98.01
F4	9.08±0.070	0.99±0.62	5.16±0.011	8.3±0.42	0.86±0.054	800.05 ±1.37	97.4
F5	9.08±0.056	0.97±0.4	5.18±0.012	9.1±0.35	0.79±0.06	801.65 ±1.49	98.4
F6	9.05±0.043	0.96±0.7	5.17±0.010	9.0±0.32	0.79±0.04	799.89±1.25	97.5

Evaluation of floating properties:
Prepared floating tablets of Ciprofloxacin were evaluated for its floating behavior such as Buoyancy lag time, total floating time. Formulations had shown floating lag time in the range of 32-68 sec, and total floating time more than 12 hr. The results were shown in Table 3.

Table 3: Floating properties like Buoyancy Lag Time, Total Floating Time of F1to F6.

Batch	Buoyancy Lag Time (Sec)	Total Floating Time (hrs)
F1	32	>12
F2	68	>12
F3	24	>12
F4	40	> 12
F5	62	>12
F6	45	>12

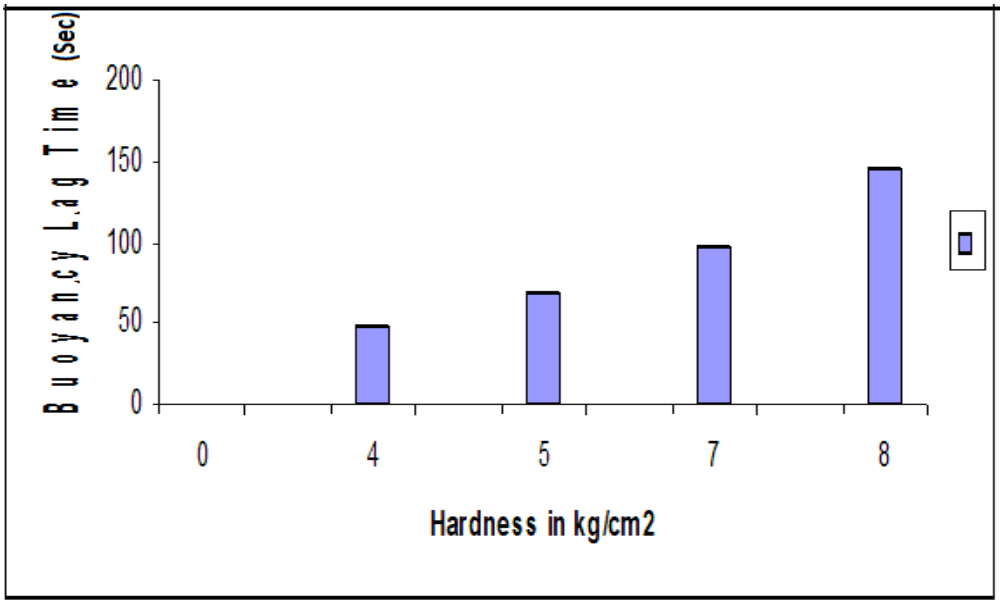
Effect of hardness on Buoyancy Lag Time:

The formulation F4 was evaluated for effect of hardness on buoyancy/ floating lag time, since it had sustained activity and good buoyancy lag time (40 sec). The results of floating lag time of tablets with hardness of 4 kg/cm^2 ,5kg/cm^2, 7kg/cm^2 and 8 kg/cm^2 were 49,68,97and 146 sec respectively and the results were shown Table 4. Floating lag time (sec) V/s hardness (kg/cm^2) plotted and shown in Figure 1. Batch F4 was selected for the study because it showed buoyancy lag time of 146 sec at maximum hardness of 8kg/cm^2. The results showed that the floating lag time increased as hardness increased.

Table 4: Effect of Hardness on Buoyancy Lag Time of Batch F4

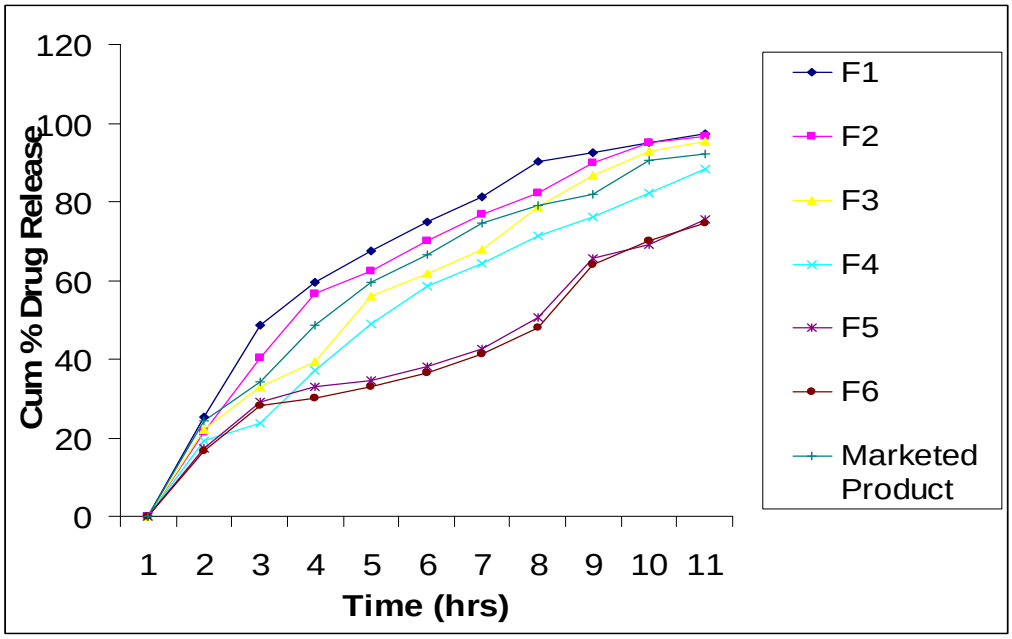
Hardness in kg/cm^2	Buoyancy Lag Time (sec)
4	49
5	68
7	97
8	146

Figure 1: Effect of Hardness on Buoyancy Lag Time of optimized formulation F4



In-vitro dissolution study of Ciprofloxacin floating tablets & Marketed Product:
In-vitro drug release studies of the all formulations of prepared floating tablets and marketed product were conducted for a period of 12 hrs using USP XXIII type II apparatus at 37± 0.5°C & 0.1N Hydrochloric acid (simulated gastric fluid, pH 1.2). Results were plotted as cumulative percent drug released V/s time, was shown in Figure 2.

Figure 2: In-Vitro Dissolution Profile for Tablets of Batches F_1 to F_6 and Marketed product.



From the in-vitro dissolution data it was found that formulation F1, F2 and F3 containing HPMC K4M released 97.2% , 96.54% and 95.47% of drug within 12 hr of the study indicating that the polymer amount is not sufficient to control the drug release. F4, F5 and F6 containing HPMC K15M released 88.42%, 75.50% and 74.56% of drug within 12 hr. So, the results indicate that Hydro dynamically Balanced Tablets of Ciprofloxacin Hcl containing only HPMC polymer showed good Buoyancy lag time (BLT) and Total floating time (TFT). Formulation F4 containing 200mg HPMC K15M showed good BLT of 40 sec, while the formulation containing HPMC K15M alone showed highest BLT and TFT of more than12 hrs. This may be due to the amount of polymer and gas generating agent, which were kept constant in the present study. The gas generated cannot be entrapped inside the gelatinous layer, and its escape leading to variation in BLT and TFT. So, F4 provides a better option for Controlled release action and improved bioavailability than the other formulations (F1-F6). The In-vitro drug release of F4 formulation was compared with marketed product, found that F4 had released 88.42% of drug after 12 hrs where as Marketed product was 92.3%. It concludes that the F4 had better controlled release than the marketed tablet of Ciprofloxacin Hydrochloride [21].

CONCLUSION

The principle of hydrodynamically balanced controlled drug delivery systems offers a suitable and practical approach to obtain controlled release of ciprofloxacin with enhanced bioavailability

and reduced dosing frequency. The ciprofloxacin floating tablets were prepared by using polymers such as HPMC K4M, HPMC K15M. Formulations were evaluated for floating behaviour, which showed floating lag time in the range of 32-68 sec, and total floating time more than 12hr. *In-vitro* drug release study was performed in simulated gastric fluid (1.2 pH), the optimized batch (F4) shows drug release in a controlled manner for 12 hr. From results it concludes that the floating lag time increased as hardness increased and F4 had better controlled release than the other formulations (F1-F6) and marketed product. So, formulation F4 provides a better option for Controlled release action and improved bioavailability of Ciprofloxacin Hydrochloride.

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