INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Research Article

FORMULATION AND EVALUATION OF SUSTAINED-RELEASE FLOATING TABLETS OF CIPROFLOXACIN

Mudgal Vinod kumar*, Kheri Rajat, Saraogi G.K., Singhai A.K., Sharma Dharmendra

Lakshmi Narain College of Pharmacy Raisen Road, Bhopal, M.P., India

Article Received on: 20/05/12 Revised on: 01/07/12 Approved for publication: 03/08/12

*Email: Vinodmudgal6785@yahoo.com

ABSTRACT

The aim of this study was to develop a sustained-release floating system that is able to float over an extended period of time. Ciprofloxacin was used as a model drug. The system consisted of a 3 mm drug-containing gas-generating core, prepared by direct compression, and coated with a flexible polymeric membrane. Eudragit RL30D and ATEC were used as a film former and a plasticizer, respectively. The coating level was fixed at 20% (w/w). The floating lag time decreased as the proportion of effervescent agents increased. The optimized coated floating tablets could float within 20 min and remained buoyant for more than 13 h. In addition, a sustained release of ciprofloxacin for more than 20 h was observed. The time to flotation could be controlled by the composition (type of filler, concentration of effervescent agents) and hardness of the tablet core and the composition (type of polymer and plasticizer) and thickness of the coating.

KEYWORDS: Multiple unit systems; Sustained release**;** Eudragit RL30D; Floating; ciprofloxacin.

INTRODUCTION

Gastric retention has received significant interest in the past few decades as most of the conventional oral delivery systems have shown some limitations connected with gastric emptying time. In fact, variable and too rapid gastrointestinal transit can result in incomplete drug release above the absorption zone. This leads to diminished efficacy of the administered dose, especially for drugs that are absorbed to the greatest extent in the upper part of the small intestine. Because of this, ciprofloxacin was chosen as a model drug for the development of a floating sustained release (SR) delivery system with prolonged gastric residence time (GRT). Moreover, as ciprofloxacin is characterized by a relatively short elimination plasma half-time ($t_{1/2}$= 4 h). A slow-release formulation could reduce fluctuations in the therapeutic effect and so improve its clinical efficacy. Among the various attempts made to increase the retention of an oral dosage form, it seems that floating systems offer the most effective and rational protection against early and random times of gastric emptying[1]. In comparison to the single-unit systems, which are characterized by an all-or-nothing process, the multiple-unit dosage forms have been shown to reduce inter- and intra-subject variability. Moreover, they have also shown a more reproducible GRT and have offered a better dispersion throughout the gastrointestinal tract, lowering the possibility of mucosal damage.

The present study relates to the development of ciprofloxacin SR granulates prepared by wet granulation and compressed into tablets. These tablets, comprising only Metronidazole Precirol ATO and effervescent compounds were then coated with a water-insoluble acrylic polymer, Eudragit RL30D in order to obtain FT. Both the wet granulation and the fluidized-bed coating processes are very easy, short manufacturing processes that can be easily scaled up[2].

The objective of this work was to investigate the effects of manufacturing parameters such as the core diameter, the core composition and the level and formulation of the coating on the CFT floating capability and the ciprofloxacin release rate in order to design the most suitable form for a future in vivo study. The aim was to optimize and select a dosage form that would be able to provide a low floating lag time value, long floating duration and a constant sustained release of ciprofloxacin.

MATERIALS AND METHODS

Ciprofloxacin were obtained as a gift sample from Zim Laboratories pvt ltd. Nagpur, HPMC 100M, Glyceryl palmitostearate (Precirol ATO 5) and the insoluble polymer used to make the gas-trapping membrane was Eudragit RL30D supplied by Zydus cadila (Ahmadabad), sodium bicarbonate, talc from Loba Chemi pvt ltd. Mumbai and CMC were obtained from SD fine chem. pvt ltd Mumbai, Magnesium stearate, talc, ethanol, carbapol and all other chemicals are of analytical grade.

PREPARATION OF THE TABLETS

Granulates were made in a small vertical laboratory-scale high-shear mixer, Mi-Pro (Pro-C-EpT, Belgium), equipped with a transparent bowl and a heating jacket. The granulate compositions are listed in Table1. All experiments were started at an impeller speed (IS) of 1800 rpm and a chopper speed (CS) of 130 rpm while the temperature of the heating jacket was set at 60°C. When the product temperature reached sufficiently high values to soften the binder, the torque increased due to granule formation[3]. The IS was reduced to 600 rpm after the granule formation step in order to avoid any further product temperature increase, while the CS was increased to 1000 rpm to break any possible agglomerates. The massing time was kept constant at 5 min. The length of the whole granulate manufacturing process was around 20 min. At the end of the process, the granules were cooled at ambient temperature.

TABLETS PREPARATION

Prepared by direct compression

Granules were fed manually into the die of an instrumented single-punch tabulating machine (Korch, Germany) to produce tablets using concave-faced punches and dies.

Preparation of the coating dispersion

The different aqueous dispersions used for the coating of the tablets are given in Table 2. Talc was previously dispersed in water in the presence of an antifoam agent and mixed with the water-soluble additive using a T45 Ultra-Turrax (Janke & Kunkel GmbH, Staufen, Germany). Dispersions containing Eudragit RL30D require the addition of 20% (w/w) (relative to film former content) of plasticizing agent. The plasticizer was added to the polymer aqueous dispersions under gentle stirring. All the components of the coating dispersion were

then mixed under magnetic stirring for at least 1 h before starting the coating process[4].

Preparation of the coated tablets:

Tablets were transferred into a fluidized-bed coating apparatus (Uni-Glatt, Glatt GmbH, and Germany) equipped with a bottom-spray coating process in a Wu'rster column and coated with the coating dispersions until the desired film weight was deposited. During the coating operation, the aqueous dispersion was stirred continuously to prevent sedimentation of insoluble particles[5]. The conditions for layering were shown to be as follows: preheating temperature, 40±2°C, preheating time, 10 min; inlet and outlet temperatures, 40±2°C and 35±2°C, respectively; flow rate, 6g/min; pneumatic air pressure,1 bar. After coating, the coated tablets were further fluidized for 10 min and subsequently cured at 60°C for 8 h.

CHARACTERIZATION

Physical characterization[6]:

The fabricated tablets were characterized for weight variation (n=20), hardness (n=6, Monsanto hardness tester), thickness using a screw-gauge micrometer (Campbell Electronics, Mumbai, India) and % friability (n=20, Roche Friabilator, Electrolab, Mumbai, India

Assay of tablets:

Twenty tablets from each batch were weighed and powdered. Powder equivalent to 300mg of ciprofloxacin was accurately weighed and transferred into a 100ml volumetric flask and dissolved in a suitable quantity of 0.1N HCl. The prepared solution was diluted up to 100ml with 0.1N HCl and sonicated for 60 min. Five milliliters of the resulting solution was diluted to 100 ml with 0.1N HCl to get a concentration in the range of 15 µg/ml. A portion of the sample was filtered through 0.45µ membrane filter and analyzed by Shimadzu UV-1700 UV/Vis double-beam spectrophotometer (Kyoto, Japan) at 274 nm[7,11].

Floating capacity:

The in vitro buoyancy was determined by floating lag times as per the method described by Rosa. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time[8]. The experiments were conducted in triplicate. Total floating times were measured during in vitro dissolution studies.

In vitro dissolution studies: The release rate of ciprofloxacin from floating tablets (n=3) was determined as per British Pharmacopoeia (BP) using dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900ml of 0.1N HCl, at 37±0.5° and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 24 h, and the samples were replaced with fresh dissolution medium[9, 10]. The samples were filtered through 0.45µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 274nm using a Shimadzu UV-1700 UV/Vis double-beam spectrophotometer. Duration of time the tablet constantly float on dissolution medium were noted as total floating time

RESULTS AND DISCUSSION

Weight variation data of the prepared tablets indicated no significant difference in the weight of individual tablet from the average value. Hardness of the prepared tablets was observed to be within the range of 4.24±0.35 to 5.25±0.35 kg/cm^2. Thickness of all the tablets was found in the range of 2.80±0.42 to 2.92±0.46 mm. Friability of all the tablets was found below 1%. The drug content in all the batches of ciprofloxacin floating tablets was in the range of 95 to 105% (variation of ±5%).This ensured the uniformity of the drug content in the tablets (Table 2). Floating capacity of fabricated tablets was determined in 0.1N HCl, and the results are presented in Table 2.The tablets of all batches exhibited floating lag time less than 37sec (F-6). The tablets of HPMC K4 MCR batches exhibited more floating lag time compared to other batches. Tablets formulated from HPMC K4 MCR exhibited total floating time less then 5 h. In vitro dissolution studies showed that as the concentration of HPMC K4M was increased, drug release rate was decreased (fig.1). Tablets of batch F-4 not showed good dissolution profile and about 40% of drug was released in 1h, while tablets of batch F-6 released the drug in controlled manner at minimum level of HPMC content (30% w/w of tablet weight). Dissolution profiles of batch F-1 to F-3 were not good because high amount of drug release (30 to36%) at 1h. Fabricated tablets showed weight variation, hardness and uniformity of drug content within acceptable limits. A lesser floating lag time and desired total floating duration could be achieved by varying the amount of gas forming agent and using different polymer combinations.

ACKNOWLEDGMENTS

Authors are thankful to Zim Laboratories pvt ltd. Nagpur for providing gift sample of ciprofloxacin and Zydus cadila (Ahmadabad India) for providing HPMC K4M.

REFERENCES

1. Gorning R, Henum G, Oral dosage forms with controlled gastrointestinal transit, Drug. Dev. Ind. Pharma, 1984; 527-539.
2. Goddard A.F, Logan R.P, Diagnostic methods for Helicobactor pylori detection and eradication, Br. J. clin. Pharmacol, 2003; 273-283.
3. Schreiber S.M, Kondrait C, Groll P, Schield G, Hanauer S, the spatial orientation of Helicobactor Pylori in the gastric mucus, Proc. Natl. Acad. Scie. U.S.A. 2004; 5024-5029.
4. Dumbernet C, Arabian J, Vidon N, Les alienment dans le tube digestif, Doin, Paris, 1998; 2034 –2045.
5. Arora S, Ai Javed, Ahuja A, Khar K. R, Floating drug delivery a review, AAPS pharmascitech, 2005; 372-373.
6. Vakil N, Cutler A, Ten-day triple therapy with ranitidine, bismuthcitrate, amoxicillin and clarithromycin in eradicating Helicobacter pylori, Am. J. Gastroenterol. 1999; 1197–1199.
7. Gutierrez-rocca J, Omidian H, Shah K, Progress in Gastroretentive drug delivery systems, Business Briefing, Pharmatech, 2003; 152-156.
8. Seppala K, Farkkila M, Nuutinen H, Triple therapy of Helicobacter pylori infection in peptic ulcer, Scand J Gastroenterol, 1992; 973-976.
9. Iser J. H., Buttigieg J, Iseli A, Low dose short duration therapy for eradication of Helicobacter pylori in patients with duodenal ulcer, Med J Aust, 1994; 192-196.
10. Alfonso R, Grnnar, Remington the science and practice of pharmacy, brocardo publishern, Newyork, 1996; 903-910.
11. Singh B, Kim H, Floating drug delivery systems an approach to oral controlled drug delivery via gastric retention, J Control Release, 2000; 235-259.

Table No 1: Composition of prepared batches

Ingredients (mg/tablet)	F_1	F2	F3	F4	F5	F6
Ciprofloxacin	300	300	300	300	300	300
Precirol ATO5	12	12	12	12	12	12
HPMC K15MCR	150	150	150			
HPMC K4 MCR				150	150	150
Sodium bicarbonate	50	50	50	50	50	50
Citric acid	20	20	20	20	20	20
Colloidal silica	5	5	5	5	5	5
Purified talc	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5
Total weight	547	547	547	547	547	547

Table No.2: Some Physical Chemical properties of floating tablet:

Batch No.	Weight Variation	Average weight (mg)	Crushing strength (kg/cm^2)	Friability (%)	Drug content (mg/Tablet)
					Metronidazole
F- 1	0.020±0.15	897.5	4.24±0.35	0.57±0.10	298±0.45
F-2	0.028±0.16	891.6	5.00±0.25	0.54±0.13	299±0.79
F-3	0.032±0.28	894.3	4.25±0.35	0.75±0.07	298±0.46
F- 4	0.026±0.14	843.6	5.25±0.35	0.68±0.10	298±0.56
F-5	0.030±0.35	1034.4	5.25±0.35	0.45±0.15	299±0.15
F-6	0.034±0.48	985.4	4.25±0.35	0.63±0.73	298±0.75

Table No.3: Floating lag time and total lag time of all batches

Formulation code	Floating lag time(min)	Total floating time (hr)
F- 1	2.18±0.4	14.25
F- 2	2.45±0.3	11.15
F- 3	0.43±1.5	12:50
F- 4	1.34±1	10:22
F- 5	1.56±0.1	11:07
F- 6	2.49±0.3	9:22

Table 4. Cumulative % Drug Released from Tablet Formulations F1 to F6

Time(hrs)	F1	F2	F3	F4	F5	F6
1	18.64	20.81	20.90	21.92	18.95	21.09
2	30.40	33.68	34.65	25.35	32.29	37.87
4	53.08	55.33	57.63	56.49	49.26	58.80
6	59.85	66.44	65.06	65.72	61.44	70.65
8	70.33	71.83	72.29	71.79	68.06	76.52
10	76.89	77.78	78.57	77.64	76.48	81.60
12	86.09	84.75	85.43	85.69	81.14	88.44
24	94.29	94.70	96.45	96.96	95.34	97.87

Fig.1: Ciprofloxacin Tablets

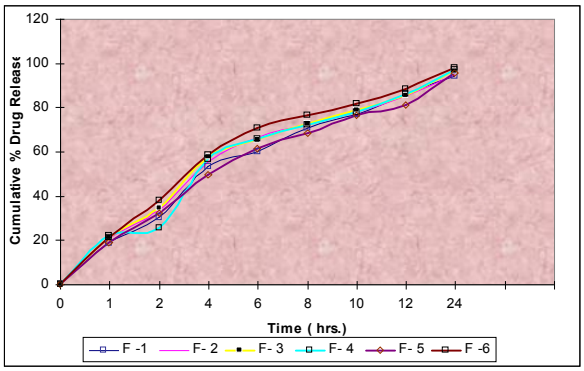
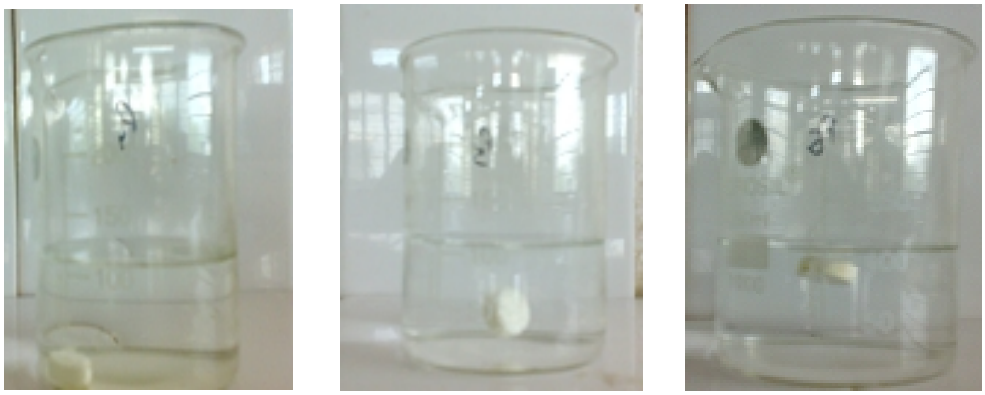


Fig. 3: Cumulative % Drug Released of F1 to F6



After 1 second After 5 second After 25 second

Fig.3: Ciprofloxacin floating tablet buoyancy time study

Source of support: Nil, Conflict of interest: None Declared