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Optimization and Evaluation of Floating Drug Delivery System for Metronidazole.

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Research Article

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ABSTRACT

The present investigation concerns the development of Floating Drug Delivery System (FDDS) of Metronidazole, which are designed to increase the gastric residence time, thus prolonging the drug release with localized drug action. Hydroxy propyl methyl cellulose K_4M (HPMC) used as polymer and drugs to polymer ratio used to prepare FDDS by wet granulation technique. The prepared FDDS were evaluated as per Pharmacopoeia and other standard references. The drug-polymer ratio, HPMC, different diluents and gas generating agents were found to influence the drug release and floating properties of the prepared FDDS. The floating properties and drug release characteristics were determined for the prepared FDDS in 0.1N HCL as dissolution media. All the FDDS formulations showed good in-vitro floating properties with an optimum concentration of gas generating agents, sodium bicarbonate and citric acid. The rate of drug release decreased with increased polymer concentration. It was found that HPMC viscosity had a significant impact on the drug release from the prepared FDDS. The decrease in the release rate was observed with an increase in the polymeric system. HPMC K_4 M along with microcrystalline cellulose as diluents was found to be beneficial in improving the drug release rate and floating properties. Regression analysis of drug dissolution profiles on the basis of Higuchi's and zero order indicated that diffusion is the predominant mechanism controlling the drug release.

INTRODUCTION

Gastroretentive dosage form can remain in the gastric region for several hours and hence prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines [1]. Gastroretention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs of these drugs. The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in GRDFs that were designed, in large part, based on the following approaches. Low density form of the DF that causes buoyancy in gastric fluid [2]. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices [6,7].

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Metronidazole is a nitroimidazole antibiotic medication used mainly in the treatment of infections caused by susceptible organisms, particularly anaerobic bacteria and protozoa. Metronidazole is an antibiotic, amebicide, and antiprotozoal. It is well absorbed orally with a plasma elimination half-life ranging from 6–7 hours. Because of its short elimination half-life, the controlled release of Metronidazole from numerous matrix-type and polymeric-coated formulations has been widely investigated. The HPMC tablets of Metronidazole would more effective for patients as these characteristics would allow a rapid onset followed by prolonged antibiotic, amebicide, and antiprotozoal action. Hydroxyl propyl methylcellulose (HPMC) is used in the formulation for controlled release because of its hydrophilic gel-forming property, non-toxicity, cost effectiveness and its wide pharmaceutical applicability [3]. The objective of this study to prepare sustained release Metronidazole tablets using HPMC as polymer. Due to hydrophilic nature of HPMC it can be assumed that drug release may be sustained in terms of drug release profile and swelling behavior of polymer.

MATERIALS AND METHODS

Metronidazole was received as generous gift from Zydus-Cadila, Ahmedabad India. HPMC K_4M were received from Sun Pharma, Ltd, Ahmedabad, India. Sodium bi-carbonate, Gaur Gum, Microcrystalline Cellulose, Sodium Starch Glycolate were received from Loba Chemie Pvt. Ltd. Mumbai. Citric Acid And Isopropyl Alcohol Received From S. D. Fine Chem. Limited, Mumbai. All other chemicals used were of analytical reagent grade, available commercially and used as such without further processing.

Compression of Tablets

After evaluation of granules were then compressed into tablet using punch tablet machine.

Evaluation of Tablets

Post compression parameters

Weight Variation

20 tablets were selected at random and average weights were determined. Then individual tablets weighed and the individual weight was compared with the average.

Hardness

The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in kg / cm2.

Friability (F)

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). 20 tablets were initially weighed (Winitial) and transferred into the friabilator. The friabilator was operated at 25 rpm per min for 4 mins (100 revolutions). The tablets were weighed again (Wfinal). The % friability was then calculated by

$$F = Winitial - Wfinal / Winitial * 100$$

Content uniformity

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 5ml of Methanol and made up to volume with 0.1N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at a λmax of 273 nm using 0.1 N hydrochloric acid as blank.

Thickness and diameter

The thickness and diameter of the tablets was measured by Vernier Calipers. It is expressed in mm.

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In vitro buoyancy study

In vitro buoyancy studies were performed for all the twelve formulations as per the method described by Rosa *et al* [5]. The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

In vitro dissolution studies

The release rate of Metronidazole from floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 75 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured by UV/Visible spectrophotometer.

Drug release kinetics

To analyze the mechanism of drug release from the prepared formulations, the data obtained from *in vitro* release studies were subjected to Higuchi's model, Zero order model and Korsmeyer's model.

RESULT AND DISCUSSION

Formulation of Metronidazole floating tablet

The matrix floating tablets of Metronidazole were prepared by wet granulation technique. All the powders were passed through 80 mesh sieve. The required quantity of drug, polymer and filler were mixed thoroughly, and granules were prepared by using isopropyl alcohol. The granules were dried at 60^{0}C in a Hot Air Oven. Sodium Starch Glycolate was finally added and the granules were compressed on rotary tablet machine.

Table 1: Composition of different floating formulations.

Sr.No.	Ingredients (quantity/tablet) mg.	Batch code FM1	FM2	FM3
01	Metronidazole	200	200	200
02	HPMC K_4M	135	150	175
03	Guar gum	35	35	35
04	MCC	10	10	10
05	SSG	25	25	25
06	Sodium Bi-carbonate	60	55	55
07	Citric acid	15	15	15
08	Lactose	20	10	-

Physical Evaluation, Drug Content and Floating Properties

The formulated matrix floating tablets of Metronidazole were evaluated for average weight, hardness, thickness, friability, floating lag time, buoyancy and drug content. The drug content of the prepared tablets was found between 97.1to 98.7 %. The floating lag time varies between 180 to 207 seconds and the buoyancy over 12 h.

Table 2: Formulations and their quality control tests.

Batch No	Hardness in Kg/cm^2	Friability loss in %	Drug Content (%)	Uniformity in weight (mg)	Thickness (cm)	Diameter (cm)
FM1	7.5±0.33	0.389±0.151	98.2±1.6	501±2.3	0.51±0.078	1.11±0.063
FM2	7.4±0.27	0.378±0.162	97.1±2.6	516±2.1	0.53±0.075	1.23±0.097
FM3	7.8±0.38	0.467±0.103	98.7±1.9	513±2.9	0.56±0.089	1.22±0.090

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In Vitro Buoyancy Studies

The in vitro buoyancy was determined by floating lag time, as per the method described by Rosa et al [5]. 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.

Table 3: Floating lag time and buoyancy time of different formulations.

Formulation	Floating lag time (Sec)	Buoyancy (h)
FM1	180	11
FM2	195	14
FM3	207	17

In Vitro Dissolution Study and Release Kinetics

The release rate of Metronidazole from floating tablets (n = 3) was determined using United States Pharmacopoeia (USP) 24 XXIV Dissolution Testing Apparatus 2 (paddle method). The *in vitro* dissolution study revealed that the formulation FM1 and FM2 released the drug faster as compared to formulation FM3. This variation in vitro dissolution profiles was due to the content of HPMC K_4M. The formulation FM1 and FM2 contains 135 and 150 mg of HPMC K_4M. During dissolution weak gel layer was developed around the tablet that results in 84.28% and79.59 % release of drug at the end of 10h and 12h receptively in case of FM1 and FM2. Whereas, in case of formulation FM3 as the content of HPMC K_4M was 175 mg, the drug dissolution was delayed due to formation of dense layer of HPMC K_4M around the tablet. This swollen layer controls the diffusion of Metronidazole in to the surrounding solution. Hence sustained release behavior of Metronidazole was observed up to 14h. The curve fitting results of the in vitro release data of formulations indicated that Higuchi model is the best-fit model to describe the release of the drug from matrix floating tablets and the mechanism of drug release was diffusion. The samples were filtered through a 0.45-µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 317 nm using a UV/Vis double- beam spectrophotometer (Shimazu ltd, Japan). Cumulative percentage drug release was calculated using an equation obtained from a standard curve [8,9]..

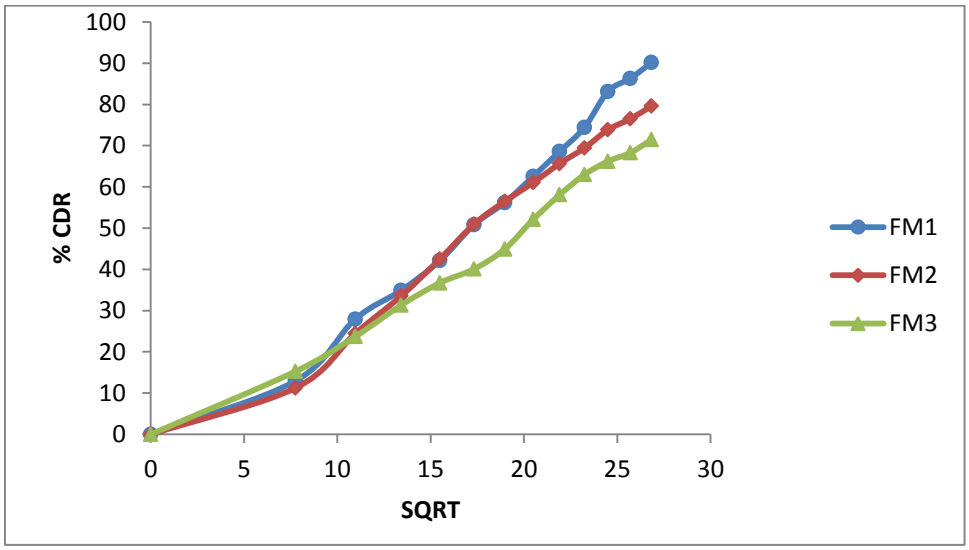

Figure 1:% Cumulative Release of FM1, FM2, FM3.

Table 4: Higuchi and zero order equation has been applied to all the formulations and the results shown below.

Formulation	R^2	
	Higuchi	Zero order
FM1	0.991	0.968
FM2	0.977	0.936
FM3	0.992	0.915

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Stability Study

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines [4]. Optimized formulation (FM3), sealed in aluminum packaging and various replicates were kept in the humidity chamber (LabTop, India) maintained at 40°C and 75% RH for 3 months. At the end of studies, samples were analyzed for the drug content, in vitro dissolution, floating behavior and other physicochemical parameters.

Table 5: Metronidazole released from formulation (FM3).

Time (Min)	% Metronidazole released (Initial)	% Metronidazole released (3 Months)*
0	0	0
1	15.93± 1.8	15.03± 2.9
2	28.23± 2.3	27.56 ± 4.7
3	36.27± 0.8	35.83± 4.3
6	52.77± 1.2	49.27 ± 3.4
8	59.25± 4.3	60.54 ± 0.8
10	66.19± 3.3	65.12 ± 1.6
12	71.44± 4.3	69.92 ± 2.4
14	73.76± 2.2	71.73 ± 3.9

*Storage at 40 °C/75% RH for three months.

Table 6: Characteristics of FM3 formulation.

	Drug (%)	Hardness (Kg/Cm2)	Floating lag time (sec)	Floating behavior Floating Duration(hr)	Matrix integrity
Before storage	98.7±1.9	7.8±0.38	207± 5	17 ± 0.5	Very good
3 Months at 40°C/75% RH	97.5 ± 1.2	7.9 ± 0.51	210 ± 4	13 ± 0.11	Very good

CONCLUSIONS

Sustained release matrix tablets of Metronidazole were prepared successfully using HPMC as polymer which retard the release and achieve required dissolution profile. The types and amounts of pharmaceutical excipients such as surfactant, binders and solubilizers in HPMC tablets were found to crucially control Metronidazole release characteristics. Release profiles were governed by water uptake, tablet erosion and diffusion in aqueous media. . It was also demonstrated that the release of drug Metronidazole from HPMC matrix tablets could be modified by changing the type and amount of polymer in the matrix tablets.

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