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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING BIOADHESIVE TABLETS OF TINIDAZOLE

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Abstract

Tinidazole is an Anti-amoebic, Anti-protozoal, Anti-bacterial, Antibiotic type of drug. That is practically active against amoebiasis, protozoa, trichomoniasis, giardiasis and bacteria. The purpose of this investigation is to improve bioavailability by preparing a gastroretentive drug delivery system. Floating tablets of Tinidazole were prepared by employing two different grades of HPMC K4M and HPMC E15M in different concentrations by effervescent granulation technique. These grades of HPMC K4M and HPMC E15M were evaluated for their gel forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. The tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy and dissolution studies. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The tablet swelled radially and axially during *in vitro* buoyancy studies. Among tablet formulations, formulation F3 gives best disintegration and dissolution profile compared with other formulations.

Keywords: Tinidazole, Floating tablets, Bioadhesive, HPMC K4M, HPMC E15M, FTIR.

Introduction

Amoebiasis is an infection of the large intestine caused by *Entamoeba histolytica*, called protozoan parasite. The current estimate is that *E. histolytica* causes between 34-50 million symptomatic infections each year and leading to the death of 40–100 thousands of people, which makes amoebiasis second to malaria as a cause of death resulting from protozoan parasite. The trophozoites of *E. histolytica* can invade the colonic epithelium,

causing amoebic colitis. Tinidazole, 1-(2-ethylsulfonylethyl)-2-methyl-5-nitroimidazole, is the drug of choice for intestinal amoebiasis and other colon infections which is a synthetic antibacterial, anti amoebic and anti protozoal agent of the nitroimidazole class, and it is used against protozoa such as *Trichomonas vaginalis*, Amoebiasis, Giardiasis and extremely effective against anaerobic bacterial infections. It is also used to treat Crohn's disease, antibiotic-associated diarrhoea, and rosacea. The oral bioavailability of

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Tinidazole is about 100 percent but there are some potential hazards such as peripheral neuropathy and convulsive seizures if the drug is given by conventional dosage form which provides minimal amount for local action in the colon, still resulting in the relief of amoebiasis. The amoeba mainly present in the intra intestinal lumen and the efficient treatment of amoebiasis and other colonic infections could be achieved by targeting drug to the colon and the best approach is a colon targeted specific drug delivery which would make the Tinidazole effective with low dose and prevent the potential hazards. Overall, there is less free fluid in the colon than in the small intestine. Hence, dissolution could be problematic for poorly water-soluble drugs. Moreover, the Tinidazole is showing good solubility in acidic environment. Therefore, incorporation of organic acids such as Citric acid, Tartaric acid, etc., in the formulation lowers the pH surrounding the system sufficient to effects the dissolution of the drug and enhance the soluble drug available for local and systemic action. *Helicobacter pylori* infection has been established as one of the major cause of gastric ulcer. The *H.pylori* induced gastric ulcer, if untreated, has been found to get turned into gastric cancer. *H. pylori* reside at the niche beneath the mucus lining of the stomach. They produce ammonia by urease enzyme to create a micro-environment of alkaline pH that help this bacteria to survive in acidic pH in stomach. Usually this infection is treated using combination of two drugs (one is among amoxicillin, tetracycline, clarithromycin etc. and another is from metronidazole, tinidazole and ornidazole group). These drugs were administered through conventional dosage forms such as tablets or capsules or solutions or suspensions in current therapy. However, these release the drugs quickly in g.i. tract and the drugs are absorbed in circulation and the drugs reach the site of infection in significantly low concentration that is not capable to eradicate the bacteria completely. This leads to recurrence of the disease and the development of drug-resistance. Different approaches have been reported to deliver the drugs to the site of infection from gastro-retentive devices for a prolonged period. This type of stomach specific delivery of amoxicillin, tetracycline, metronidazole have been reported.¹⁻⁶

Oral delivery of drugs

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of

administration, patient compliance and flexibility in formulation etc. From immediate release to site-specific delivery, oral dosage forms have really progressed. However, it is a well-accepted fact that it is difficult to predict the real *in vivo* time of release with solid.

Gastric emptying of dosage form is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage form.

In such circumstances, prolonged gastric retention is important in achieving control over the gastric retention time (GRT) because this helps to retain the CR system in the stomach for a longer and predicted time. In addition, this improves the bioavailability of the basic drug that has poor solubility in higher pH and drugs having narrow absorption window (Upper part of GIT).⁷⁻¹²

Various Approaches In Gastroretentive Systems¹³

Dosage forms with a prolonged GRT, i.e. gastro-remaining or gastroretentive dosage forms (GRDF) will bring about new and important therapeutic options. For instance, they will significantly extend the period of time over which drugs may be released, and thus prolong dosing intervals and increase patient compliance beyond the compliance level of existing controlled release dosage forms. Many of today's so-called "Once-a-day" formulations will become replaced by products with release and absorption phases of approximately 24 hours. Also, GRDF will greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at the gastric mucosa which are sustained over a long period of time. For example, the eradication of *helicobacter pylori*, which today requires the administration of various medications several times a day according to a complicated regimen and which frequently fails as a result of insufficient patient compliance, could perhaps be achieved more reliably using GRDF to administer smaller drug doses fewer times. Finally, GRDF will be used as carriers for drugs with so called absorption windows: these substances are taken up only from very specific sites of the gastrointestinal mucosa, often in a proximal region of the small intestine. Conventional controlled release dosage forms pass the absorption window while they still

contain a large and rather undefined portion of the dose which is consequently lost for absorption. In contrast, an appropriate GRDF would slowly release the complete dose over its defined GRT and thus make it continuously available to the appropriate tissue regions for absorption. The objective of the present work was to deliver tinidazole in stomach for a longer period of time from a floating controlled release tablet that may be capable of achieving higher concentration in the site of infection and may be potential for eradication of *H. pylori* when co-administered with an anti *H. pylori* antibiotic. Therefore, the major objective of the present investigation is to prepare formulate the sustained release with floating tablets of Tinidazole using different viscosity grades of HPMC i.e. HPMC K4m, HPMC E15 with different drug polymer ratio to reducing the dosing frequency and stability of the drug for more time and prolong action in the stomach and minimize the fluctuations of plasma drug concentration, evaluation has been done of the prepared formulation and compared with the standard.

Materials and Methods

Materials

Tinidazole Obtained as a gift sample from Emami Pvt.Ltd.Kolkata, Chloroform, Sodium bicarbonate and Ethanol Obtained as a Gift sample supplied Merck specialties Pvt. Ltd., Magnesium stearate and Poly vinyl pyrrolidone (k30) Obtained as a Loba chem. Pvt. Ltd, Mumbai, Hydroxyl propyl methyl cellulose (k4m) and Hydroxyl propyl methyl cellulose (E15m) Obtained as a Gift sample Loba chem. Pvt. Ltd, Mumbai

Methods

Preparation of Floating Tablets of Tinidazole:

The manufacture of granulation for tablet was prepared by wet granulation method. This is the most widely and general method used in the preparation of tablet. This method is popular because the granulation meets all the quantities required some good tablets. The step involved on the wet method are weighing, mixing, granulation, screening the damp mass drying, dry-screening, lubrication and compression.

Procedure

First an accurately weighed all quantity of drug, excipient, and polymers like (Drug Tinidazole, HPMC (K4m, E15m), NaHCO₃.) They were mixed

thoroughly with the help of mortar pastel. Then weighed magnesium stearate and pvp. PVP was taken in a small petridish and taken 3ml ethanol and putted into it and shaken. After mixed PVP and ethanol. Then all the ingredients were added with PVP and Ethanol in a small petridish. Then mixed all the ingredient thoroughly. After mixed all the ingredients were prepared the damp mass. Damp mass is then passed through sieve no- 1mm for granulation. Then dried the wet granules at 60⁰c for 30-45 minutes. After dried the lubricant (Mg. stearate) was added and mixed very well. After that granules were compressed by single punch cadmach tablet compression machine with 12mm punch.

Result and Discussion

Flow properties

A. Angle of Repose

This was measured according to the fixed funnel method. A funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip 2.5 cm height (h), above graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. The mean diameter (2r) of the powder cone was determined and the angle of repose of the powder material was calculated using the formula.

$$\text{Angle of repose } (\theta) = \tan^{-1} h/r$$

Where, h is height of the pile, and r is radius of the pile. The test was repeated thrice.

Relationship between powder flow and angle of repose

Angle of repose	Type of flow
< 20	Excellent
20-30	Good
30-34	Passable
> 40	Very poor

B. Apparent Bulk Density

The bulk density, as a measure used to describe packing materials or granules, was determined by transferring the accurately weighed amount of agglomerates to the graduated cylinder (10 ml) with the aid of a funnel. The volume was noted and apparent bulk density was determined as the ratio of weight of the sample to the volume occupied. The test was repeated thrice.

C. Tapped Density

Weighed quantity of agglomerates, was transferred to a 10 ml graduated cylinder and tapped using tapped density apparatus for a fixed number of taps (100). The volume was noted and tapped density was determined as the ratio of weight of sample to tapped volume. Average of three determinations was taken.

$$\text{Tapped Density} = \frac{\text{Weight of powder taken}}{\text{Tapped volume}}$$

D. Hausner's Ratio

Hausner's ratio is an indication of the flowability of powder and the ratio is greater than 1.25 is considered to be an indication of poor flowability. Hausner's ratio was determined by the following equation. The test was done in triplicate.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

E. Carr's Index

Flowability of untreated and agglomerated samples was also assessed from Carr's Index (CI) The compressibility of sample blend was determined from their apparent bulk density and the tapped densities by using the following formula. The test was carried out in triplicate⁵⁵. Results are shown in Table 8A and 8B.

$$\% \text{ Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Flow Properties of Granules



The granules prepared for compression of floating tablets were evaluated for their flow properties (Table 3). Angle of repose, Bulk density, Tapped density and Hausner ratio ranged from granules of different formulations. These values indicate that the prepared granules exhibited good flow properties.

Table No. 01: Composition of floating tablets of tinidazole

Batch No	Drug	HPMC (K4M)	HPMC (E15M)	NaHCO ₃	Mag. Stearate	PVP	TOTAL
B1	250mg (50%)	100mg (20%)	50mg (10%)	50mg (10%)	10mg (2%)	40mg (8%)	500mg (100%)
B2	250mg (50%)	50mg (10%)	100mg (20%)	50mg (10%)	10mg (2%)	40mg (8%)	500mg (100%)
B3	250mg (50%)	15mg (3%)	135mg (27%)	50mg (10%)	10mg (2%)	40mg (8%)	500mg (100%)
B4	250mg (50%)	67.5mg (13.5%)	67.5mg (13.5%)	65mg (13%)	10mg (2%)	40mg (8%)	500mg (100%)
B5	250mg (50%)	135mg (27%)	---	65mg (13%)	10mg (2%)	40mg (8%)	500mg (100%)

Table No. 02: Micromeritic properties of precompressional powder blend

Code	Bulk density* (gm/cm ³)	Tapped density* (gm/cm ³)	Angle of repose*(θ)	Carr's Index* (%)	Hausner's Ratio*
F1	0.453±0.13	0.53±0.02	27.3±0.5	14.40±0.26	1.16±0.01
F2	0.453±0.02	0.53±0.01	27.84±0.49	15.5±0.37	1.18±0.02
F3	0.50±0.05	0.56±0.02	29.17±0.18	13.31±0.19	1.13±0.04
F4	0.46±0.18	0.53±0.01	26.24±0.41	14.26±0.23	1.16±0.01
F5	0.48±0.11	0.56±0.02	28.31±0.92	14.29±0.16	1.16±0.02

Peak Pick				
No.	P/V	Wavelength nm.	Abs.	Description
1		277.00	0.759	
2		242.00	0.367	

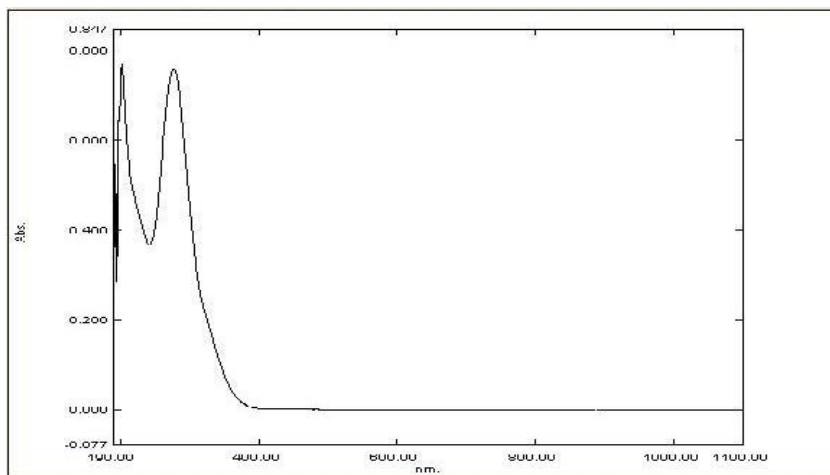


Fig. No. 01: UV absorbance spectra of Tinidazole in 0.1 N HCl

Table No. 03: Standard curve of tinidazole

Conc. in $\mu\text{g/ml}$	Abs. at 277.0 nm
2	0.05
4	0.1
6	0.155
8	0.204
10	0.255
12	0.31
14	0.356
16	0.407
18	0.458
20	0.504

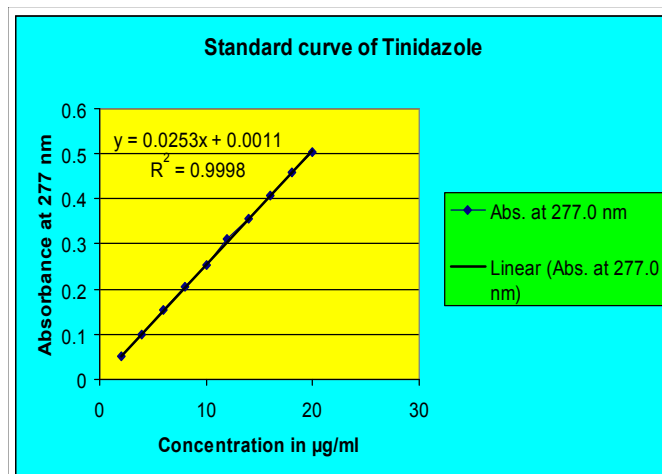


Fig. No. 02: Standard Curve of Tinidazole

Table No. 04: Physico-chemical Evaluation of Floating bioadhesive tablets of Tinidazole

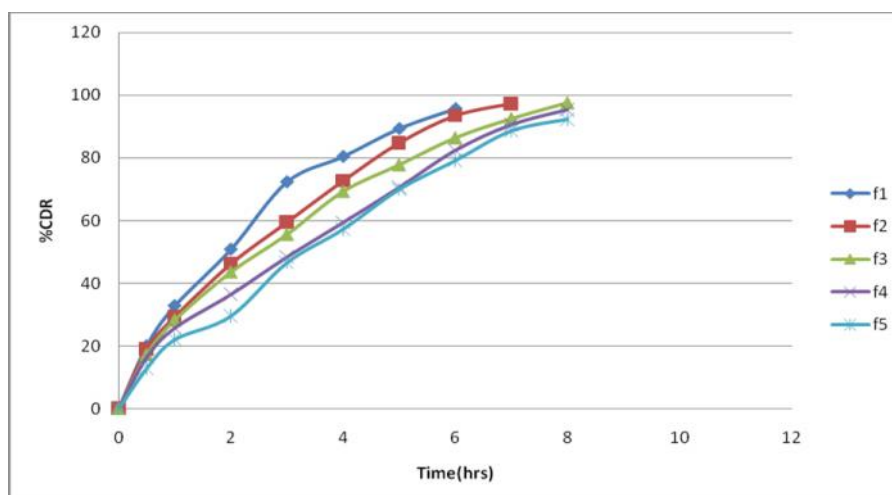
Code	Thickness (mm)	Hardness test(kg/cm^2)	Weight variation (%)	Friability	Drug content (%)
F1	3.11 \pm 0.03	5.9 \pm 0.33	passes	0.62 \pm 0.02	98.23 \pm 0.04
F2	3.12 \pm 0.01	5.7 \pm 0.25	Passes	0.74 \pm 0.03	97.12 \pm 0.05
F3	3.11 \pm 0.04	5.4 \pm 0.64	Passes	0.81 \pm 0.01	99.12 \pm 0.12
F4	3.10 \pm 0.06	5.2 \pm 0.30	passes	0.88 \pm 0.03	97.54 \pm 0.09
F5	3.13 \pm 0.02	5.1 \pm 0.28	Passes	0.44 \pm 0.01	100.1 \pm 0.06

Table No. 05: Physico-Chemical Evaluation of Floating Bioadhesive Tablets of Tinidazole

Code	Bioadhesive strength(gm)	Swelling index(%)	Floating log time(min)	Floating lag time(hrs)
F1	16.2	70	2	8
F2	18.7	79	2	8
F3	19.3	91	3	8
F4	20.4	101	2	8
F5	22.7	112	3	8

Table No. 06: Kinetic study of floating bioadhesive tablets of Tinidazole

Formulation code	Zero order r^2	First order r^2	Higuchi r^2	Korsmeyer peppas r^2	N
F1	0.924	0.978	0.986	0.988	0.623
F2	0.955	0.950	0.988	0.997	0.646
F3	0.954	0.969	0.992	0.996	0.624
F4	0.982	0.937	0.971	0.995	0.647
F5	0.979	0.959	0.97	0.988	0.717

**Fig. No. 03: In-vitro release profile of floating Bioadhesive tablets of Tinidazole****Fig. No. 04: Floating Photo of Tinidazole tablet****Evaluation of tablet** ^{14, 15}**Weight variation**

Twenty tablets were randomly selected from each batch individually weigh, the average weight and standard deviation of 20 tablet calculated.

Thickness

The thickness of the tablet was measured by using digital venire caliper, twenty tablets from each batch were randomly selected and thickness was measured.

Hardness

Hardness was measured using Pfizer hardness tester, for each batch three tablets were tested.

Friability

Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted and weighted.

Drug content uniformity

Ten tablets were randomly selected and allowed to equilibrate with HCl acid buffer of pH 1.2 overnight and the solution was filtered (0.22 μ , Millipore) after 24 hours. Suitable dilutions were made with HCl acid buffer of pH 1.2 to get the concentration in Beer's range. Absorbance of the solution was analyzed spectrophotometrically at 280nm against suitable blank using UV-visible spectrophotometer (1800, Shimadzu, Kyoto, Japan) and drug content per tablet was calculated.

In-vitro dissolution study

Dissolution study was carried out using USP dissolution test apparatus type II. The dissolution medium used was 900 ml of 0.1N HCl buffer at $37\pm 0.5^\circ$. The paddle speed was kept at 50 rpm throughout the study. Aliquot of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume. After each sampling suitably diluted with 0.1N HCl buffer and analyzed spectrophotometrically at 277nm against suitable blank using UV-visible spectrophotometer (1800, Shimadzu, Kyoto, Japan).

Conclusion

The effervescent-based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of gel-forming polymer HPMC (K4M and E15M) and gas-generating agent sodium bicarbonate along with Magnesium stearate was essential to achieve in vitro buoyancy. From the entrapment and dissolution study, it was concluded that batch F3 showed sustained release for 8 hrs.

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