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FORMULATION, OPTIMIZATION AND *IN-VITRO* EVALUATION OF METRONIDAZOLE 500MG FLOATING TABLETS FOR THE TREATMENT OF *HELICOBACTER PYLORI* INDUCED GASTRIC INFLAMMATORY DISORDER

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ABSTRACT

One novel approach in gastro-retentive drug delivery system (GRDDS) is prolonging the gastric retention of the delivery system is some time desirable for achieving therapeutics benefits of drug that are absorbed from the proximal part of the gastro-intestinal tract (GIT) or that is less soluble in or are degraded by the alkaline pH or they encounter at the lower part of the GIT. GRDDS are thus beneficial for such drugs by improving their bioavailability, therapeutics efficacy and possible reduction of the dose. Apart of these advantages, these systems offer various pharmacokinetics advantages like maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels. Dosage forms that can be retained in stomach are called gastro retentive drug delivery systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability. Gastro retentive dosage forms (GRDFs) are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or heir therapeutic outcome. This research article focus on the simple method for formulation

and development of laboratory scale metronidazole 500 mg tablets and evaluated by all quality control parameters.

KEYWORDS: *GRDDS, Buoyancy tablets, Floating drug delivery systems.*

1. INTRODUCTORY NOTES

Oral controlled release dosages forms are the most commonly formulated but still offer highest attention in the area of novel drug delivery systems.[1] An ideal drug delivery system should possess two main properties

- It should be a single dose for the whole duration of the treatment.
- It should deliver the active drug directly at the site of action.[2]

Gastrointestinal retention depends on many factors such as density of the dosage forms, fasting and fed condition, nature of the meal taking, sleep, posture etc. It also depends strongly on a complicated and unpredictable gastric emptying with migrating myoelectric complex motility of stomach.[3]

Classification of GRDDS[4.5,6]

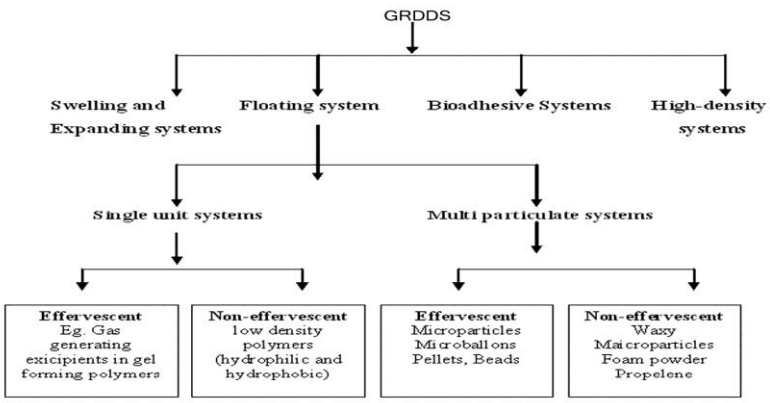


Figure 1:-Flow chart enlisting classification of GRDDS

1. Floating Drug Delivery System (FDDS) - Floating drug delivery systems (FDDS) have a bulk density less than gastric fluid and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floats on the gastric contents, the drug is released slowly at the desired rate from the system.[7]

2. Bio-adhesive systems- Bio/Muco-adhesion is defined as attractive interactions at the interface between a pharmaceutical dosage form and a mucosal membrane. Various

administration routes, such as ocular, nasal, buccal and gingival, gastrointestinal (oral), vaginal and rectal, make muco-adhesive drug delivery systems attractive and flexible in dosage form development. The advantages associated with the use of muco-adhesives in drug delivery include increased dosage form residence time, improved drug bioavailability, and reduced administration frequency, simplified administration of a dosage form and termination of a therapy as well as the possibility of targeting particular body sites and tissues.[8]

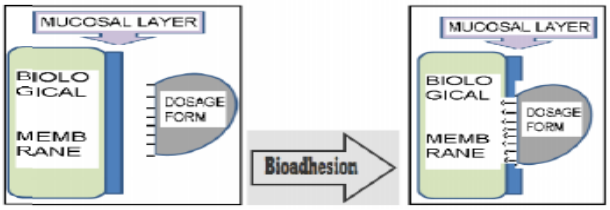


Figure 2: Bio-adhesive systems

3.Swelling/ Expanding Systems -These systems are such that after administration they swell to that extent which prevents their exit from stomach from pyloric sphincter. As a result the dosage form is retained in stomach for long period of time.[4]

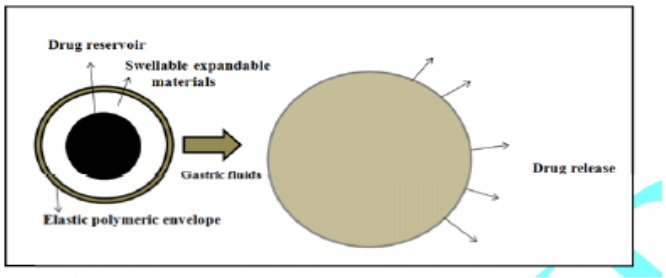


Figure 3:- Swelling/ Expanding Systems[4]

These systems are sometimes referred to as *plug type systems* because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical cross links in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross linking retards the swelling ability of the system

and maintains its physical integrity for a prolon- ged period. On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer. An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration.[9]

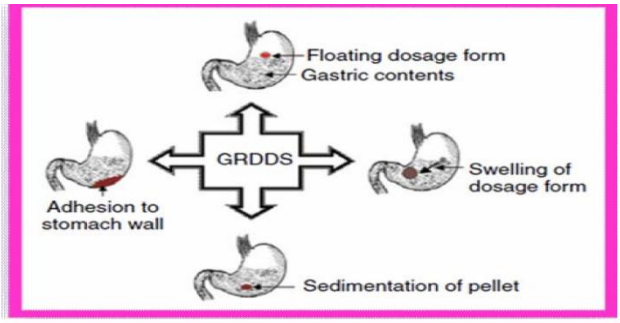


Figure 4: Classification of Gastro-retentive Drug Delivery Systems[9]

4. High Density Systems- High Density Systems remaining in the stomach for longer period of time, by sedimenting to the folds of stomach.[10] Gastric contents have a density close to water (1.004g/cm^3). When high density pellets is given to the patient, it will sink to the bottom of the stomach and are entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. Sedimentation has been employed as a retention mechanism for high density systems. A density ~3 g/cm seems necessary for significant prolongation of gastric residence time. Barium sulphate, zinc oxide, iron powder, titanium dioxide may be used to formulate such high density systems due to their high density. The only major drawbacks with this systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm^3.[9]

Floating Drug Delivery System (FDDS)

These systems are also known as hydro dynamically balanced systems (HBS) or floating drug delivery systems (FDDS).Floating systems was first described by Davis in 1968. FDDS is an effective technology to prolong the gastric-residence time in order to improve the bioavailability of the drug. FDDS are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the

system floats over the gastric contents, the drug is released slowly at the desired rate which results in increased GRT and reduces fluctuation in plasma drug concentration.[4]

Floating systems can be classified as effervescent and non-effervescent systems

(a) Non-effervescent systems[11]

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxyl propyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four sub-types

(i) Colloidal gel barrier system

Sheth and Tossounian first designated this 'hydro dynamically balanced system'. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxyl propylcellulose, hydoxyethyl cellulose, hydroxypropylmethyl cellulose (HPMC), polysacharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

(ii) Microporous compartment system

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the un-dissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

(iii) Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze dried at -40 ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

(iv) Hollow microspheres / Microballons

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The micro-balloon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours.

(b) Gas-generating (Effervescent) systems[11]

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating tablets with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxyl propyl methyl cellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

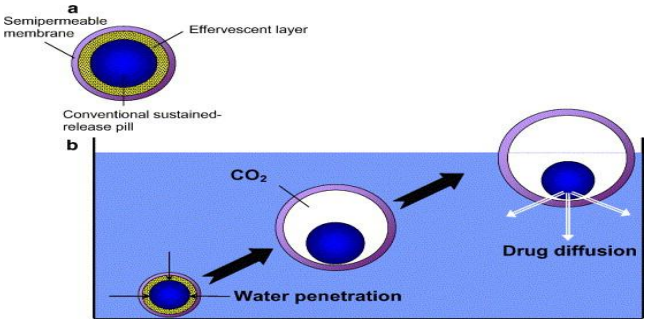


Figure 4:-Gas-generating (Effervescent) systems[11]

Factors Affecting Gastric Retention Time of the DosageForm[12]

1. Density: GRT is a function of dosage form buoyancy that is dependent on the density. The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm is required to exhibit floating property.

2. Size & Shape of dosage form: Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric.

3. *Single or multiple unit formulation*: Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

4. Fed or unfed state: under fasting conditions: GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

5. Nature of meal: feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

6. Caloric content: GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

7. Frequency of feed: the GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

8. Gender: Male: 3.4+ • 0.6hr to Female: 4.6+1.2hr.

9. Age: Elderly people, especially those over 70, have a significantly longer GRT.

10. Posture: GRT can vary between supine and upright ambulatory states of the patient.

11. Concomitant drug administration: Anticholinergic like atropine, propentheline-increase GRT and Metoclopramide and cisapride- decrease GRT.

12. Disease state: Gastric ulcer, diabetes, hypothyroidism increase GRT and Hyperthyroidism, duodenal ulcers decrease GRT.

Applications of Floating Drug Delivery Systems (FDDS)[10]

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

(1) Sustained drug delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of 1g as a result of which they can float on the gastric contents. An FDDS can remain in the stomach for several hours and therefore significantly prolong the GRT of numerous drugs. The assumed prolongation in the gastric retention is postulated to cause sustained drug release behavior and offers the advantage in having uniform and consistent blood levels of medication by administrating a single dose of medication, which releases active ingredient over an extended period of time.[10]

(2) Site-specific drug delivery

Targeting of drug to stomach appears to be useful for all substances intended to produce a lasting local action on the gastro duodenal wall. For instance, the eradication of *Helicobacter pylori* requires the administration of various medications several times a day resulting in poor patient compliance. A more reliable therapy can be achieved by using FDDS, which allows reduction of dosage and frequency of administration.[10]

***(3) Absorption Enhancement*[9,10]**

Drugs that have poor bioavailability because of sites specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. FDDS also serves as an excellent drug delivery system for the eradication of Helicobacter pylori, which causes chronic gastritis and peptic ulcers. The treatment requires high drug concentrations to be maintained at the site of infection that is within the gastric mucosa. By virtue of its floating ability these dosage forms can be retained in the gastric region for a prolonged period so that the drug can be targeted.

Advantages of Floating Drug Delivery Systems (FDDS)[12]

➢ Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide

➢ Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. E.g. b-lactam antibiotics (penicillin and cephalosporin)

➢ For drugs with relatively short half life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient Compliance.

➢ They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

➢ Gastro retentive drug delivery can produce prolongs and sustains release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

➢ The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable Effects of side effects.

➢ Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.

➢ Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.

➢ Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

➢ The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

Disadvantages of Floating Drug Delivery Systems (FDDS)[4,13,14,15,16]

➢ The floating system requires a sufficiently high level of fluid in the stomach for the system to float. This problem can be overcome by coating the dosage form with bioadhesive polymer which adhere to gastric mucosa or administering dosage form with a glass full of water (200-250 ml).

➢ Floating systems are not suitable for drugs that have stability or solubility problem in gastrointestinal fluid or that irritate gastric mucosa.

➢ Drugs which have multiple absorption site or which undergo first pass metabolism were not desirable candidate for FDDS.

➢ Floating dosage form should not be given to the patients just before going to the bed as gastric emptying occurs rapidly when the subject remains in supine posture.

➢ The single unit floating dosage form is associated with "all or none concept". This problem can be overcome by formulating multiple unit system like floating microsphere or microballons.

➢ Drugs like nifedipine, which is well absorbed along the entire GIT and which undergoes significant first pass metabolism may not be desirable candidates for FDDS since the slow gastric emptying may lead to the reduced systemic bio-availability.[4]

2. DRUG PROFILE

Metronidazole

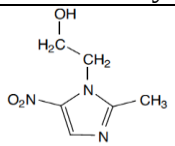
Use: It is primarily used for the treatment of Peptic ulcer caused by anaerobic bacteria i.e. *H. pylori.*[17]

Mechanism of Action[21]

Metronidazole is active against a variety of protozoa and bacteria. It enters the cell as a prodrug by passive diffusion and is activated in either the cytoplasm of the bacteria or specific organelles in the protozoa, whereas drug-resistant cells are deficient in drug

activation. The metronidazole molecule is converted to a short-lived nitroso free radical by intracellular reduction, which includes the transfer of an electron to the nitro group of the drug. This form of the drug is cytotoxic and can interact with the DNA molecule. The actual mechanism of action has not yet been fully elucidated but includes the inhibition of DNA synthesis and DNA damage by oxidation, causing single-strand and double-strand breaks that lead to DNA degradation and cell death. The activated reduced metronidazole molecule binds nonspecifically to bacterial DNA, inactivating the organism's DNA and enzymes and leading to a high level of DNA breakage, with immediate action of the drug but no cell lysis. Aerobic cells lack electron-transport proteins with sufficient negative redox potential; therefore, the drug is active against only bacteria with anaerobic metabolisms, even though the drug is effective against some microaerophils, such as *H. pylori.* In addition, reoxidation can occur in the presence of molecular oxygen and can convert the compound back to its original inactive form. Electron donors involved in the reduction process vary, depending on the organism. In anaerobic bacteria, the electron acceptors flavodoxin and ferredoxin, which receive electrons from the pyruvate-ferredoxin oxireductase complex, play important roles, although other enzymes and electron transfer components may also be involved in the process.

Table 1: Physico-chemical Properties of Metronidazole

Drug	**Metronidazole**
Chemical Name	2-(2-methyl-5-nitro-1*H*-imidazol-1-yl) ethanol
Structure	
Category	Antibiotic (antiamoebic, antigiardiasis, and antibacterial)
Antibiotic class	Nitroimidazole
BCS Class	Class I (High solubility and high permeability)
Appearance	A white or yellowish, crystalline powder.
M.F & M.W	(M.F)Molecular formula $C_6H_9N_3O_3$ and molecular weight of 171.2
Melting point	158°C to 160°C
Solubility	The max solubility in water is 10 mg/ml at 20°C and 10.5 mg/ml at 25°C
PKa	2.62
Storage	Protect from direct sunlight and moisture

Pharmacokinetic Properties[18, 20, 23]

Metronidazole is administered orally, intravenously, intravaginally, and topically. Oral absorption of metronidazole is excellent. Food decreases the rate, but not the extent, of absorption. Intravaginally administered metronidazole is absorbed systemically; but peak

serum concentrations after intravaginal administration are < 2% of the levels achieved with 500 mg oral doses. Topically applied metronidazole products are only minimally absorbed; detectable serum levels are approximately 100 times lower than the peak concentrations of a single 250 mg oral dose.

Table 2- Pharmacokinetic Properties of Metronidazole.

Bioavailability	**Oral tablets is 93% to 95%**
$C_{ss\ max}$	6µg/mL for 250mg, 12µg/mL for 500mg, 20µg/mL for 750mg, 40µg/mL for 2000mg.
T_{max}	0.25 to 4 hr
Effective Permeability (P_{eff})	9×10^{-5} cm/s.
Protein Binding	Less than 20%
Volume of distribution	0.51 to 1.1L/kg (adults)
Elimination half life ($T_{1/2}$)	6 to 14 hr
Renal clearance	8-12ml/min
Elimination Route	Metronidazole and its metabolites are excreted principally in urine (60–80%) and to a lesser extent in feces (6–15%).
Absorption	Oral dose is absorbed from the GI tract
Metabolism	Metabolized in the liver by side-chain oxidation, producing 1-(β-hydroxyethyl)-2-hydroxymethyl-5 nitroimidazole (about 30%–65% of the activity of metronidazole) and 2-methyl-5-nitroimidazole-1-yl-acetic acid (not active), and by glucuronide conjugation.
Effect of Food	*Conventional tablets or capsules:* Food decreases the rate of absorption and peak plasma concentrations; total amount of drug not affected. *Extended-release tablets:* Food increases rate of absorption and peak plasma concentrations.

Each of these acceptors has a reduction potential lower than that of the metronidazole molecule and will thereby donate its electrons to the drug. In *H. pylori*, a separate mechanism seems to be involved in metronidazole susceptibility that includes a 2-electron transfer step in the reduction of the compound using an oxygen-insensitive nitroreductase (rdxA).

Drug Resistance[21]

Metronidazole-resistant clones are typically mutated in the *rdxA* gene.

Mechanism of resistance

- Reduced drug activation.
- Inactivation of the drug by alternative pathway for drug activation and/or reduction (nim genes).
- Prevention of entry of the drug or efflux.
- Altered DNA repair.

Adverse Effects[20, 22,23]

Table 3:- Adverse Effects of Metronidazole

Gastrointestinal	Abdominal discomfort, anorexia, nausea, vomiting, metallic taste, glossitis, hepatitis (rare), pancreatitis (rare).
Neurologic	Peripheralneuropathy, numbness, paraesthesia, ataxia, confusion, encephalopathy, tremors, seizures.
Hematologic	Reversible leukopenia, thrombocytopenia.
Hypersensitivity	Rashes, urticaria, pruritus, bronchospasm, serum sickness.
Other	Metallic taste.

Contraindications[20, 22, 23]

- First trimester of pregnancy.
- Hypersensitivity to metronidazole, or other nitroimidazole derivatives.

Precautions[20, 22, 23]

- CNS disease (possibility of seizures and peripheral neuropathy).
- Severe hepatic disease.
- Concomitant anticoagulant therapy.
- Concomitant alcoholic beverages (disulfiram effect).
- Evidence or a history of blood dyscrasias.

Drug Interactions[20, 22,23]

Table 4:- Drug-Drug Interactions of Metronidazole

Drugs	**Possible Interactions**
Warfarin	Increased risk of bleeding
Alcohol	disulfiram- like effect (violent retching, vomiting)
Disulfiram	Violent retching, vomiting, may be severe (psychosis, confusion, encephalopathy)
Lithium	Increased serum lithium levels (levels should be monitored when co-administered).
Phenobarbitol	Decreased metronidazole serum concentrations
Rifampin	Decreased metronidazole serum concentrations
Cyclosporine	Increased cyclosporine serum concentrations (monitor serum cyclosporine level)
Phenytoin	Increased phenytoin serum concentrations (monitor serum phenytoin level)
Cimetidine	Increased metronidazole serum concentrations
Carbamazepine	increased carbamazepine serum concentrations (monitor serum carbamazepine)

Uses[17,20,23]

Metronidazole is used primarily as a drug for the treatment of infections by the parasitic protozoans *Entamoeba histolytica*, *Trichomonas vaginalis*, and *Giardia lamblia* . It has also been used to treat Vincent's infection (trench mouth) and acne rosacea. It has been prescribed for invasive intestinal amoebiasis and amoebic hepatic abscess, antibiotic-associated colitis,

balantidiasis, dental infection, gastritis or ulcer due to *Heliobacter pylori* and inflammatory bowel disease. It is also used as a trichomonacidal agent in veterinary medicine. Metronidazole may be administered orally (in capsules or tablets), vaginally (in creams, gels, or tablets), topically (in gels, creams, or lotions), or by intravenous injection.

Therapeutic dosage[24]

Table 5:- Therapeutic dose of Metronidzole

Route	Disease	Pediatric Dose	Adult Dose
Oral	Amoebiasis (Acute amoebic dysentery)	35 to 50 mg/kg daily in divided doses.	400 to 800 mg 3 times daily for 5 to 10 days.
	Amoebiasis (Amoebic liver abscess)	35 to 50 mg/kg daily in divided doses.	400 to 800 mg 3 times daily for 5 to 10 days.
	Trichomoniasis	15 mg/kg daily in divided doses for 7 days.	2 g in single dose, 250 mg 3 times daily for 5 to 7 days, 400 mg twice a day. 800 mg in the morn and 1200 mg at night, for 2 days.
Parenteral	Anaerobic infections	7.5 mg/kg every 8 hours.	800 mg initial dose, followed by 400 mg every 8 hours, for about 7 days.
	Giardiasis	15 mg/kg daily in divided doses for 3 days	2 g daily as a single dose for 3 days.
	Anaerobic infections	7.5 mg/kg as I.V infusion every 8 hours.	500 mg as intravenous infusion every 8 hours.
Rectal	Anaerobic infections	7.5 mg/kg every 8 hours for 3 days, then every 12 hours.	1 g suppository every 8 hours for 3 days, then every 12 hours.

3. OBJECTIVE OF THE STUDY

Metronidazole is a prototype nitroimidazole antibiotic, which is used for peptic ulcer. In conventional dosage, it has to take 500 mg twice daily given for 7 days. These conventional tablets are not suitable for the patient to take twice a day. So we are trying to make a dosage form which improves the patient compliance by decreasing dose frequency. Now a day's, increasing the patient compliance is also a great challenge for the pharmacist, which is continuously improving by the novel drug delivery system. The main objective of the research work is to formulate gastro-retentive dosage form of the drug are as follow

1. The main objective is to increase the bioavailability having a poor bioavailability of drug because of narrow absorption window in the upper part of GIT.
2. To remain in the stomach for prolonged period of time.
3. To increase patient compliance by decreasing the dose frequency.
4. To prevent the infection cause by *H. pylori* bacteria i.e. Peptic ulcer.

5. To reduce drug wastage.
6. To improve the solubility of drug.

4. REVIEW OF LITERATURE

Gastro-retentive dosage forms (GRDFs) are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome. The challenge to develop efficient gastro-retentive dosage forms began near about 20 years ago, following the discovery of *Helicobacter pylori* by Warren and Marshall. Many attempts have been made to devise an extended release GRDDS where the dosage form is small enough to ingest and then retained in the GI area for a long enough time for the active agent to be dissolved and eventually absorbed. For example, many swelling and expanding systems have been attempted. There are dosage forms that swell and change their size thereby floating to the surface. It is also reported that oral treatment of gastric disorders with an H2-receptor antagonist like ranitidine or famotidine, used in combination with antacids, promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion.[11]

The real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12 hours, but to prolong the presence of the dosage forms in the stomach or upper gastrointestinal (GI) tract until all the drug is released for the desire period of time. Novel oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups. One of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time (GRT).[25]

Dosage form with prolonged GRT or gastro-retentive dosage form (GRDF) provides an important therapeutic option. Dosage forms that can be retained in the stomach are called gastro-retentive drug delivery systems (GRDDS). The gastro-retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These

systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Various gastro retentive techniques were used, including floating, swelling, high density and bioadhesive system, has been explored to increase the gastro-retention of dosage forms. Floating systems having low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach without affecting the gastric emptying rate for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastric retentive time and reduces fluctuation in plasma drug concentration. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site of the body, to achieve promptly and then maintain the desired therapeutic drug concentration that elicits the pharmacological action and to minimize the incidence and the severity of unwanted adverse effects. To achieve this goal, it would be advantageous and more convenient to maintain a dosing frequency to once, or at most, a twice-daily regimen. An appropriately designed extended release dosage form can be a major advance in this direction.[26]

Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time and improves the oral bioavailability of the drugs that are having site-specific absorption from the stomach or upper part of the small intestine. Therefore different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems, swelling and expanding systems, floating systems and delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.[27]

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Gastro-retentive 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. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion modified shape systems or by the simultaneous administration of pharmacological agent that delay gastric emptying. This review focuses on the principal mechanism of floatation to achieve gastric retention.[28]

Gastro-retentive 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. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.[29]

In recent scientific and technological advancement have been made in the research and development of rate controlled oral drug delivery systems overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Furthermore, absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of controlled release formulations for important drugs. Methods to increase the residence of drug formulations at or above the absorption window are discussed. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery system (FDDS), also known as hydro dynamically balanced systems (HBS), swelling and expanding systems, modified shape systems and high density system. In this review, the current status of floating multiparticulate drug delivery systems including hollow

microspheres (micro balloons), low density floating micro pellets and floating micro beads (acrylic resin based), microcapsules etc.[30]

The relatively short gastric emptying time in humans, which normally averages 2-3 hrs through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the drug delivery system leading to diminished efficiency of the administered dose. Thus, localization of a drug delivery system in a specific region of the GIT offers numerous advantages, especially for drugs having narrow absorption window. The intimate contact of the dosage form with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have lead to the development of oral sustained release dosage forms possessing gastric or intestinal retention potential. The primary concern in the development of once daily oral sustained release dosage form is not just to prolong the delivery of drugs for 24hrs but also to prolong the presence of dosage forms in the stomach or intestine. Gastro-intestinal dosage forms through local drug release will greatly enhance the pharmacotherapy of the GIT leading to high drug concentrations at the gastric or intestinal mucosa, which are sustained over a long period of time enhance the pharmacotherapy of the GIT leading to high drug concentrations at the gastric or intestinal mucosa, which are sustained over a long period of time. Several times a day according to a complicated regimen and which frequently is unsuccessful as a consequence of insufficient patient compliance, could possibly be achieved more reliably using gastro-intestinal dosage form. Finally, gastrointestinal dosage form can be used as potential delivery system for drugs with narrow absorption windows. Conventional sustained release dosage forms pass the absorption window although they still contain a large fraction of the drug which is consequently lost and not available for absorption. In contrast, an appropriate Gastro-intestinal dosage form through local drug release will greatly enhance the pharmacotherapy the complete dose over its defined GRT and thus make it continuously available at the site of absorption.[8]

In recent years scientific and technological advancements have been made in the research and development of oral drug delivery system. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration. Oral sustained drug delivery system is complicated by limited gastric residence times (GRTs). To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract includes floating drug dosage

systems (FDDS), swelling or expanding systems, muco-adhesive systems, magnetic systems, modified-shape systems, high density system and other delayed gastric emptying devices. Among these systems, FDDS have been most commonly used.[9]

Technological attempts have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). It is known that differences in gastric physiology, such as, gastric pH, and motility exhibit both intra-as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behaviour. This triggered the attention towards formulation of stomach specific (gastro retentive) dosage forms. This dosage forms will be very much useful to deliver 'narrow absorption window' drugs. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed.[31]

The purpose of floating drug delivery systems (FDDS) was to compare with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.[32]

Management of illness through medication is entering a new era in which growing number of novel drug delivery systems are being employed and are available for therapeutic use. Oral sustained release gastro-retentive dosage forms (GRDFs) offer many advantages for drugs with absorption from upper parts of gastrointestinal tract and for those acting locally in the stomach, improving the bioavailability of the medication. Floating Drug Delivery Systems (FDDS) is one amongst the GRDFs used to achieve prolonged gastric residence time. The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation

variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems and their classification and formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems and applications of this system.[33]

5. MATERIALS AND METHODOLOGY

Materials: Metronidazole was obtained from Jackson Labs, Amritsar. HPMC (K_4m), Sodium bicarbonate, Citric acid, Light Magnesium carbonate, Starch (anhydrous), PVP (K_{30}), Magnesium stearate and Talc were procured from Mumbai fine chemicals, Mumbai. All other reagents and solvents used were of analytical grade.

Methodology employed: Weighed quantities of ingredients were triturated to fine powder individually in a mortar & pestle and passed through sieve no #44. The drug along with PVP (K_{30}), HPMC (K_4m), Starch powder, Citric acid, Sodium bi carbonate and Light Magnesium carbonate are uniformly mixed to which absolute alcohol is added to form a coherent mass. The wet mass was passed through sieve no #10 and wet granules were passed and dried at temperature of 40^{o}C for 50min.The dried granules were passed through sieve no #22 and blended with required amount of Magnesium stearate and Talc. Total 10 formulations (F1-F10) were developed by employing various quantities of excipients by the help of half factorial design method (3 factors with two levels). Then compressed into tablets of using flat circular die (8mm) in 24station multiple tablet compression machine.[34] Formulae is unable to discuss here due to applied for Intellectual rights.

6. EVALUATION OF EFFERVESCENT FLOATING TABLETS

The flow properties of blends (before compression) were characterized in terms of Angle of repose, Bulk density and tapped density, Carr's index and Hausner's ratio.

Table-6: Pre-Compression parameters for the granules.

Formulations	Angle of Repose (Ɵ)	Carr's Index (%)	Hausner's ratio	Flow property
F1	24.07°	11.80	1.13	Excellent
F2	24.17^{O}	11.82	1.14	Excellent
F3	23.99^{o}	10.99	1.07	Excellent
F4	24.15^{o}	11.01	1.99	Excellent
F5	24.21^{o}	11.07	1.16	Excellent
F6	23.98^{o}	11.90	1.19	Excellent
F7	24.22^{o}	10.98	1.15	Excellent
F8	24.01^{o}	11.91	1.21	Excellent
F9	23.99^{o}	11.85	1.11	Excellent
F10	24.06^{o}	11.83	1.12	Excellent

Physical evaluation of metronidazole floating tablets

Two tablets from each formulation (F1-F10) were randomly selected and organoleptic properties such as color, odour, taste and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for weight variation using tablets, hardness (Monsanto tester) and friability using 10 tablets (Roche type friabilator).

The buoyancy lag time (BLT) and total floating time (TFT)

On immersion of tablets of different formulations in 0.1N HCl solution at 37±0.5°C, the tablets floated and remained buoyant without disintegration, the results of the buoyancy lag time (BLT) and total floating time (TFT) were noted.

***In vitro* dissolution studies:** The release rates of metronidazole from floating tablets (F1-F10) were determined using *United State Pharmacopeia* (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl at 37° ± 0.5°C and 50 rpm. An aliquot (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. Absorbance of these solutions were measured at 277 nm using a UV/Visible double beam spectrophotometer. The Cumulative percentage drug release was plotted against time to determine the release profile.

7. RESULTS AND DISCUSSION

Total 10 formulations (F1-F10) of Floating tablets of metronidazole were developed to increase the gastric residence time of the drug, so that they can be retained in stomach for longer time and help in controlled release of drug. The tablets were made using gel forming polymer HPMC along with effervescent agent Sodium bicarbonate to optimize the drug content, *in-vitro* buoyancy and *in-vitro* drug dissolution studies. Talc and Magnesium stearate was employed for their glidant and lubricating properties. The prepared tablets of all the formulations were evaluated for pre-compression parameters like angle of repose, bulk density, tapped density and physical characters like tablet hardness, friability, weight variation, buoyancy lag time, total floating time, *in vitro* drug release. The main aim was to control the release of drug up to 8 hrs.

Pre-compression parameters of Metronidazole granules

Among total 10 formulations, formulation (F1) showed good flow property and Carr's index. Angle of repose 24.07° Carr's index 11.80 and the Hausner ratio 1.13.

Post compression parameters of Metronidazole tablets

The shape of tablets of all formulations (F1-F10) remained white, smooth, convex faced circular with no visible cracks. The thickness of tablets was measured by digital vernier callipers and was ranged between 6.50 mm to 6.56 mm respectively. The hardness of the tablets was measured by Monsanto tester (Thermo Lab, Mumbai, India) and was in between 4 to 5.3kg/cm^2. The friability was measured by friabilator (Roche friabilator) and was found to be 0.653%, which is an indication of satisfactory mechanical resistance of the tablets. The drug content estimations showed values in the range of R^2 0.995 which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within Pharmacopoeial limits.

In-vitro **buoyancy studies:** All the tablets of (F1-F10) were prepared by granulation followed by compression. Sodium bicarbonate was added as gas generating agent. On contact with dissolution medium (0.1N HCl), carbondioxide gas was generated. It was observed that the gas generated is trapped and protected within gel, formed by hydration of polymer (HPMC), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. All the batches of tablets were found to exhibit short floating lag time due to presence of sodium bicarbonate. The tablets with HPMC with proportionate ratios of sodium alginate showed good floating time. Increase in HPMC level in formulations prolonged the floating lag time upto certain extent with proportionate increase in sodium alginate content. With reference to buoyancy studies results it can be concluded that the batches containing HPMC and sodium alginate showed good floating lag time (FLT) and Total floating time (TFT).

In-vitro **dissolution studies:** In vitro dissolution studies of all the formulations(F1-F10) of floating tablets of metronidazole were carried out in 0.1N HCl. The study was performed for 8 hours and cumulative drug release was calculated for every one hour time interval. In vitro dissolution studies of all the formulations are shown in Fig HPMC and Na-alginate were used to formulate the floating tablets. It was observed that the type of polymer influences the drug release pattern. All the formulation containing equal amount of sodium bicarbonate.

Analysis of drug release mechanism: The drug release data of metronidazole were fitted to models representing Zero order and Higuchi's kinetics to know the release mechanisms. The data were processed for regression analysis using MSEXCEL statistical function. The results are shown in Table no 8 and graphs in Fig no-5. Diffusion is related to the transport of drug from the dosage form in the *in-vitro* fluid depending on the concentration. In the present study, *in-vitro* release profiles could be best expressed by Higuchi's equation as formulation showed good linearity (R^2: 0.995) indicates that the diffusion is dominant mechanism of drug release with these formulations.

Table 7: %age Weight variation of formulation (F1-F10) randomly selected.

Sr No.	Weight of individual tablet W1 (mg)	Difference (W1-W)	% deviation
1	592	-11	4.9
2	587	-16	4.8
3	604	+1	5.0
4	601	-2	4.9
5	613	+10	5.08
6	606	+3	5.02
7	616	+13	5.10
8	597	-6	4.95
9	608	+5	5.04
10	609	+6	5.04
11	614	+11	5.09
12	611	+8	5.06
13	575	-28	4.6
14	590	-13	4.89
15	616	+13	5.10
16	589	-14	4.88
17	605	+2	5.01
18	618	+15	5.12
19	620	+17	5.14
20	599	- 4	4.96

Average weight (W) = 603mg. All the above mentioned tablets passed weight variation test, as % weight variation was in between pharmacopoeial limits i.e. $\pm$5%.

Table -8. Absorbance and standard plot of the optimized formula (F1)

Concentration(µg/ml)	Absorbance (At 277nm)
0.5	0.12
1.0	0.154
1.5	0.222
2.0	0.304
2.5	0.384
3.0	0.468

3.5	0.541
4.0	0.623
4.5	0.707
5.0	0.795

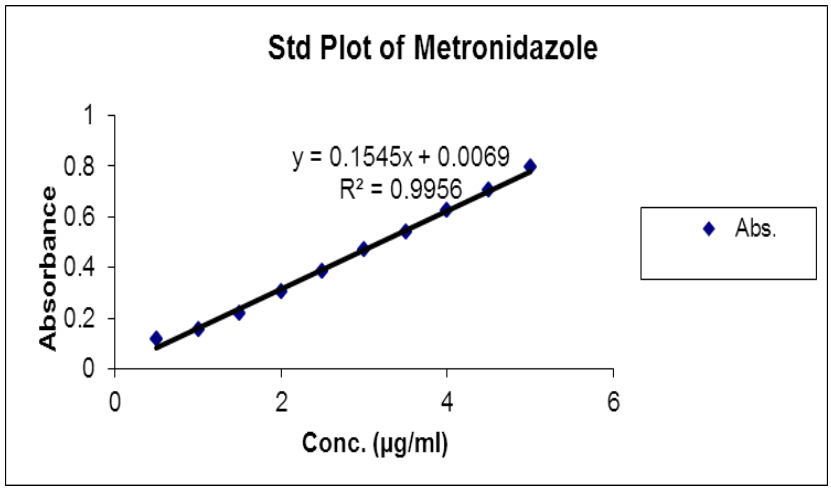


Figure 5:- Standard Plot of Metronidazole

Table-9: Destructive Evaluation of the tablets (F1-F10) Randomly selected.

Tablets	Thickness (mm)	Hardness(kg/cm2)
F1	6.52	4.5
F2	6.56	5.0
F3	6.49	4.5
F4	6.50	5.0
F5	6.53	5.0
F6	6.54	5.1
F7	6.55	4.7
F8	6.56	4.8
F9	6.44	5.3
F10	6.48	5.1

The test for friability was performed by using 20 tablets (F1) in (Roche friabilator) for 4mins at 25rpm and the result given below:-

Total weight of 20 tablets before friability test = 12.24gm

Total weight of 20 tablets after friability test = 12.16gm

The %age of friability was found to be 0.653%. Hence tablets passes the friability test as per pharmacopoeial limits (< 1%)

8. CONCLUDATORY COMMENTS

Gastro retentive dosage forms (GRDFs) are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This

technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome. In this above mentioned research article focus was implemented on a simplest method for formulation and development of laboratory scale metronidazole 500mg tablets and their various physico- chemical, organoleptics as well as pharmaceutical destructive methods of quantification with evaluation by all quality control parameters. Among 10 formulations designed and prepared, F-1 was found to be optimized formula.

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