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Formulation and Preparation of Metronidazole Floating Drug Delivery System [FDDS] for Peptic Ulcer

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Abstract: *Gastric fluids, allowing it to remain buoyant in the stomach for a prolonged period. This system is used to: Prolong gastric residence time (GRT) to improve drug absorption, especially for drugs that are absorbed in the upper part of the gastrointestinal tract. Provide a slow, continuous release of the drug at a desired rate. Better control fluctuations in plasma drug concentrations.*

These systems work by using effervescent reactions or low-density materials to remain buoyant in the stomach without affecting the normal gastric emptying rate.

A floating drug delivery system (FDDS) is a type of gastroretentive drug delivery system designed to have a bulk density lower than

While floating, the system slowly releases the drug at a controlled rate, which enhances the drug's bioavailability and therapeutic effect by increasing the time it stays in the upper gastrointestinal tract. FDDS have a lower density than gastric fluids (~1.004 g/cm³), so they float on the stomach contents.

While floating, the drug is released slowly, and the system gradually empties from the stomach once the release is complete. The development of Floating Drug Delivery Systems (FDDS) represents a promising approach to achieve prolonged gastric retention and controlled drug release..

Keywords: Floating Drug Delivery System (FDDS), Gastric residence time (GRT), Buoyancy, Upper gastrointestinal tract, Drug absorption

I. INTRODUCTION

A Floating Drug Delivery System (FDDS) is an advanced form of gastroretentive drug delivery engineered to prolong the gastric residence time of orally administered dosage forms by maintaining a buoyant, low-density state in the gastric fluid.

FDDS may achieve buoyancy either through effervescent mechanisms, where carbon dioxide is generated in situ by the interaction of acid and bicarbonate components, or through noneffervescent approaches employing low-density polymers and matrix-forming agents such as hydroxypropyl methylcellulose (HPMC), ethylcellulose, or polysaccharides.

Floating systems explains that the systems are having low density, having a greater property of buoyancy to float over the gastric fluids present in stomach and help in maintaining of longer action1.

Davis first identified floating systems in 1968. They are low-density systems with enough buoyancy to float over the gastric contents and stay in the stomach for an extended period of time2.

The drugs which are having short biological half-life, they can be sustained by floating drug delivery system and their efficacy can be increased and help in decreasing the dosing frequency. This aspect of feds is assisting in increasing patient compliance and improving pharmacological therapy1.

Based on granules, powders, capsules, tablets, laminated films and hollow micro spheres, several buoyant systems have been developed3.

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Floating drug delivery systems are intended to prolong the duration of the dose form in the gastrointestinal tract while also assisting in the enhancement of absorption. Drugs that are more soluble in acidic conditions and have a specific absorption location in the upper section of the small intestine are more suited to these mechanisms4.

Floating multi-particulate are gastro-retentive drug free-flowing protein or synthetic polymer powders, preferably smaller than 200 micrometres in size.

Floating multi-particulate are gastro-retentive drug delivery systems which are based on non-effervescent and effervescent approach. Gastroretentive systems will remain for several hours in the gastric region and thus significantly extend the drug's gastric residence time.

For dose forms that stay in the stomach longer than standard dosage forms, the ability to extend and control the emptying time is a crucial asset.

Gastric emptying of dosage forms is an incredibly varied process.

Designing controlled release systems for greater absorption and increased bioavailability presents a number of challenges.

Drugs stomach residency times can be greatly extended by floating delivery systems since they can stay in the gastric region for several hours.

For medications that are less soluble in a high pH environment, prolonged stomach retention increases bioavailability, lowers drug waste, and enhances Solubility.

It can be used to administer medications locally to the stomach and nearby small intestines.

Gastro retention aids in improving the accessibility of novel drugs with fresh therapeutic opportunities and significant patient advantages. Mucoadhesion, flotation, sedimentation, expansion adjusted shape systems, or the concurrent administration of pharmacological agents that delay stomach emptying can all be used to manage the gastric retention of solid dosage forms.

The difficulty to limit the dose form in the desired region of the gastrointestinal tract is one of these challenges

Without having any control over the drug delivery system, solid oral dosage forms like capsules and tablets supply a certain drug concentration in the systemic blood circulation and also generate significant changes in plasma drug concentrations.

The oral administration of any medicine is the most practical and preferable method of delivering it to the systemic circulation.

The oral controlled release drug delivery method has recently attracted more attention in the pharmaceutical industry in order to gain greater therapeutic advantages.

Such as case of dosage administration, patient adherence to the product, and adaptability in drug formulation. Drugs with short half-lives and easy absorption from the gastrointestinal tract.

CLASSIFICATION OF Floating Drug Delivery Systems (FDDS):-

1. Effervescent Systems:-
   - ✓ Mechanism: CO_2 generation for buoyancy
   - ✓ Subtypes: o Floating tablets o Floating capsules
   - ✓ Examples: o Metformin floating tablets o Ciprofloxacin effervescent tablets

2. Non-Effervescent Systems :-
   - ✓ Mechanism: Use of low-density polymers for floatation
   - ✓ Subtypes: o Hydrodynamically Balanced Systems (HBS) o Microballoons / Hollow microspheres o Alginate beads o Floating films o
   - ✓ Examples: Levodopa microballoons o Ranitidine floating beads.

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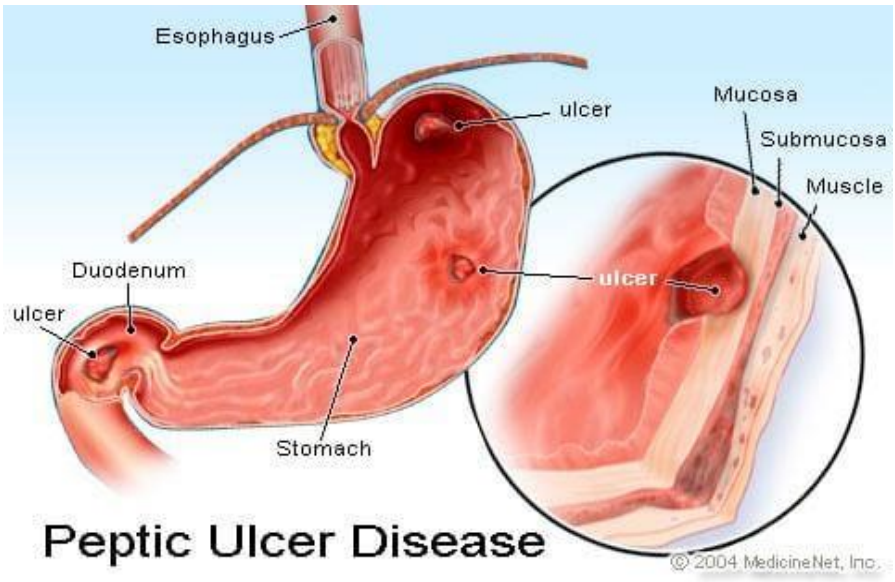

Fig no:-1 peptic ulcer

WHAT IS FDDS ?

Floating Drug Delivery System (FDDS) is a type of gastroretentive drug delivery system that floats on gastric fluid and releases the drug slowly for a longer time in the stomach to improve absorption and bioavailability.

Types:

1. Effervescent Systems – Use gas-generating agents to float.
2.Non-Effervescent Systems – Use low-density polymers to float.

ADVANTAGES

1. Also at the alkaline pH of the intestine, floating drug types such as capsules or tablets will stay in the solution for an extended period.
2. The drugs which are absorbed through the stomach, for them the gastro- retentive system is advantageous. E.g., Ferrous salts, and antacids.
3. When an acidic substance like aspirin meets the stomach wall, it causes discomfort. As a result, HBS/FDDS formulations could be useful for administering aspirin and other comparable medications.
4. FDDS dosage forms are beneficial in cases of diarrhoea and vigorous intestinal movement because they keep the drug in a floating state in the stomach, allowing for a better response.
5. For drugs ingested through the stomach, the FDDS is beneficial, e.g.: ferrous salts, antacids. Improved drug Thakur et al Journal of Drug Delivery & Therapeutics. DDTAO absorption due to increased GRT and more time spent on its absorption site by the dosage type.
6. FDDS are advantageous for those drugs which provide local irritation to the stomach. eg: Antacids.
7. FDDS are having advantage for Treating the gastrointestinal disorders such as gastroesophageal reflux.
8. Ease of administration and patient compliance.
9. Reduces the frequency of dosing.
10. It enhances the bioavailability of drugs.
11. Increased bioavailability for medications that can be metabolised in the upper GI tract.
12 Because of the sustained release effect, floatability, and uniform release of the drug via the multi-particulate system, there is no gastric irritation

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13 It is useful in treating gastroesophageal reflux disorder (GERD).
14 Advantageous in case of diarrhoea.
15 Prolongs gastric residence time.
16. Improves drug absorption .
17. Provides controlled and sustained drug release.
18. Enhances bioavailability.

DISADVANTAGES

1. Various Factor like gastric motility, pH and presence of food influences the gastric retention and these are never constant. So, the buoyancy can't be predicted.
2. The drugs which cause irritation to the gastric mucosa are not suitable for formulating the floating drug delivery system
3. In sleeping subject, the gastric emptying of floating tablets may occur at random. Hence the patient should avoid the floating tablet dose just before going to bed
4. Drugs having solubility and stability problem in gastric fluids are not suitable for formulating floating drug delivery system
5. For the drug to float and work efficiently, it requires high level of field in the stomach
6. The drugs which undergo first pass metabolism are not suitable for preparing the floating drug delivery system.
7. The drugs which are unstable in the acidic environment of stomach are not suitable for formulating the floating drug delivery system.
8. In the case of children and unconscious patients, swallowing is a problem.
9.Not suitable for drugs unstable in stomach acid.
10. Requires sufficient gastric fluid.
11. May vary with gastric emptying time.
12. Not suitable for irritant drugs

MECHANISM OF FDDS

- ✓ FDDS have a lower bulk density than gastric fluid, so they stay buoyant in the stomach for a extended period of time without impacting the gastric emptying rate. While the systems are floating on the gastric material, the drug is slowly released from the system at the required rate.
- ✓ To keep the dose form buoyant on the surface of the meal, a minimum level of floating force (F) is necessary.
- ✓ A new apparatus for determining the resulting weight has been recorded in the literature for the calculation of floating force kinetics. The apparatus operates by continuously measuring the force that is needed to sustain the submerged object, equivalent to F (as a function of time)
- ✓ In order to avoid the disadvantages of unforeseeable variations in intragastric buoyancy performance, this system helps to optimize FDDS with regard to the stability and durability of floating forces generated.
- ✓ The drug is released slowly and at the optimal rate from the system while it is floating on the gastric material.

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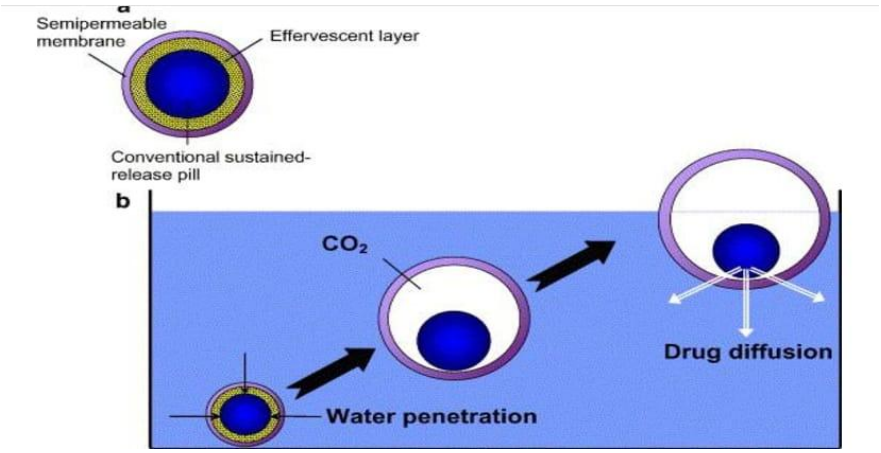

Fig no 2:-Floating drug delievery system

FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM

1) Density of the dosage form.
   - ✓ Floating is dependent on density. The density of dosage form must be less than the gastric content (1.004 gm/ml).
   - ✓ So, density of less than 1gm/ml is required to show the floating property.
   - ✓ Therefore, dosage form having a density lower than the gastric content can easily float on the surface while higher density dosage forms sink to the bottom of the stomach.

2) Shape and size of dosage form
   - ✓ Increases in gastric retention time (GRT) relative to those with a diameter of 9.9 mm are recorded for dosage type units with a diameter greater than 7.5 mm.
   - ✓ With a flexural module of 48 and 22.5 kilo pounds per square inch (KSI), the dosage form of tetrahedron and ring shape designs was stated to exhibit better GIT for 90 to 100 percent retention at 24 hours compared to other shapes.

3) Food intake and its Nature
   - ✓ Feed intake, food viscosity and volume, caloric content and feeding frequency have a significant effect on the stomach retention of dosage types.
   - ✓ The presence or absence of food in the gastrointestinal tract influences the gastric retention time (GRT) of a dose type (GIT) Feeding indigestible polymers or fatty acid salts to the stomach may cause the motility pattern to shift to a fed state, resulting in a slower gastric emptying rate and longer medication release.

4) Caloric content
   - ✓ With a meal that is rich in proteins and fats, the gastric retention time (GRT) can be increased by 4 to 10 hours.
   - ✓ Due to the low frequency of migrating myoelectric complexes, floating will increase by over 400 minutes when successive meals are given compared to a single meal (MMC).

5) Effect of gender, posture and age:-
   - ✓ Females experience slower rates of gastric emptying than males.

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- ✓ The influence of posture does not vary much more in the meantime of gastric retention (GRT).
- ✓ Gastric emptying is slowed down in the case of elderly individuals, especially those over 70, who have a significantly longer GRT.

6) Fed or unfed condition

- ✓ Periods of intensive motor activity during fasting conditions or the migrating myoelectric complexes that occur every 1.5 to 2 hours characterise gastric motility
- ✓ The MMC sweeps undigested material from the stomach, and it can be predicted that the GRT of the unit is very short if the timing of administration of the formulation corresponds with that of the MMC. However, MMC is delayed in the fed state and GRT is slightly longer.

7) Concomitant drug administration

- ✓ Floating time can be affected by anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents such as metoclopramide and cisapride.

8) Single or multiple unit formulation.

- ✓ Leading to the failure of the units, multiple unit formulations are more predictable, allow coadministration of units with various release profiles or containing incompatible substances and allow a greater safety margin against failure of the dosage form compared to single unit dosage forms.

9) Biological factors

- ✓ Biological factors like Diabetes and Crohn's disease affect the floating drug delivery system.

10) Volume of liquids

- ✓ The stomach's resting volume is 25 to 50 ml. The amount of liquids given has an impact on the time it takes for the stomach to empty.

Benefits:

- ✓ Prolongs gastric residence time
- ✓ Improves drug absorption
- ✓ Provides sustained and controlled release
- ✓ Reduces dosing frequency
- ✓ Enhances bioavailability

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

1. Enhanced Bioavailability In contrast to the administration of non-GRDF CR polymeric formulations, riboflavin CR-GRDF has a substantially higher bioavailability.

   There are many mechanisms that function in concert to affect the degree of drug absorption, including drug absorption and transit in the gastrointestinal tract.
2. Sustained Drug Delivery Problems with gastric residence duration in the Gastrointestinal Tract (GIT) have been reported with oral controlled release formulations.

   These issues can be solved by HBS systems, which can stay in the stomach for long periods of time and have a high bulk density.

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3. Site –Specific Drug Delivery Systems These systems are especially useful for medications that are absorbed predominantly through the stomach or the proximal small intestine.The monitored, gradual delivery of the medication to the stomach ensures sufficient local therapeutic levels while limiting the drug's systemic exposure.
The drug's side effects in the blood supply are minimised as a result. Furthermore, a site guided delivery system's prolonged gastric availability can reduce dosing frequency. For instance, furosemide and riboflavin.

4. Absorption Enhancement Drugs having low bioavailability due to site-specific absorption from the upper part of the GIT may be formulated as FDDS to improve absorption.

5. Minimized Adverse Activity At The Colon
The amount of drug that enters the colon is decreased when the drug is stored in the Hydrodynamically Balanced system (HBS) systems at the stomach.
Hence, the drug's undesirable effects in the colon can be avoided. The justification for Gastro-retentive dosage form (GRDF) formulation for betalactam antibiotics that are absorbed only from the small intestine and whose presence in the colon contributes to the production of microorganism resistance is based on this pharmacodynamic aspect.

6. Reduced Fluctuations Of Drug Concentration In contrast to immediate release dosage types, continuous input of the medication after controlled release gastroretentive dosage form (CRGRDF) administration induces blood drug concentrations within a narrower range.
Thus, Drug effect variations are decreased, and concentrationdependent side effects associated with peak doses can be avoided. This is especially important for drugs with a small therapeutic index27.

✓ **DRUG:- Metronidazole and FDDS for Peptic Ulcer**

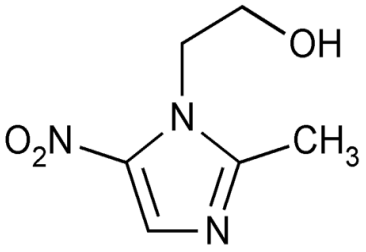

Fig no:-3 ***2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol***

1. About Metronidazole
   - Class: Nitroimidazole antibiotic Food intake, posture, and GI
   - Use: Effective against Helicobacter pylori infection and anaerobic bacteria; commonly used in peptic ulcer treatment.
   - Absorption: Rapidly absorbed in the upper gastrointestinal tract (stomach and proximal small intestine).
   - Half-life: ~6–8 hours
   - Limitations: Rapid gastric emptying can reduce residence time. o Conventional tablets may require frequent dosing for optimal effect.

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2. Rationale for Using FDDS with Metronidazole
   - Metronidazole's absorption is mainly in the stomach and upper intestine, making it ideal for gastroretentive delivery.
   - FDDS can: o Prolong gastric residence time (GRT) → keeps drug in stomach longer o Provide controlled/sustained release → reduces dosing frequency o Enhance bioavailability → better therapeutic effect against H. pylori o Targeted delivery → local effect in ulcer site.

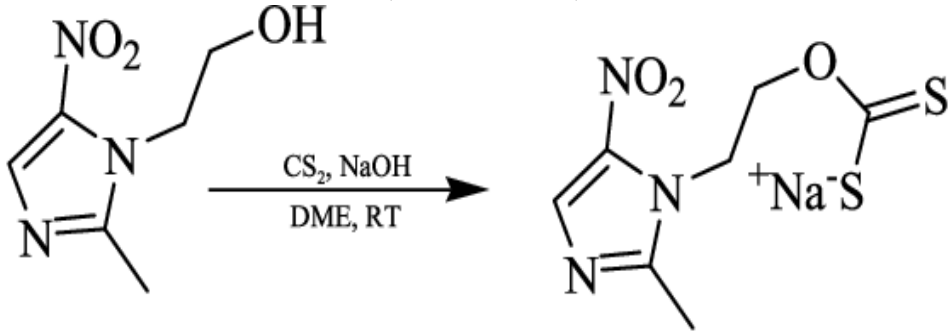
3. Types of FDDS Suitable for Metronidazole
   - Effervescent Floating Systems o Uses gas-generating agents like sodium bicarbonate + citric acid o Example: Floating metronidazole tablets.
   - Non-Effervescent Floating Systems o Uses low-density polymers such as HPMC, carbopol o Examples: Hydrodynamically balanced metronidazole tablets, floating microballoons

4. Advantages of Metronidazole FDDS in Peptic Ulcer
   - Increases residence time at ulcer site → enhanced healing.
   - Reduces dosing frequency → improves patient compliance
   - Sustained drug release → maintains therapeutic plasma concentration
   - Minimizes side effects by localized delivery

5. Considerations/Challenges metronidazole in acidic PH:-
- Stability of Proper selection of polymers and effervescent agents to control floating lag time and drug release
- Individual variability in gastric emptying may affect retention.

✓ **Reaction of metronidazole:-**

Metronidazole is a small molecule antibiotic that is rapidly and almost completely absorbed in the upper gastrointestinal tract. Because of its short elimination half-life (6-10 hours), conventional oral formulation require multiple daily doses.
The reaction in an effervescent FDDS is a physical and chemical interaction within the dosage form itself to create buoyancy in the acidic environment of the stomach (0.1N HCL, Ph 1.2)



✓ **POLYMERS USED FOR FLOATING DRUG DELIVERY SYSTEM**
- ✓ Active drug :- METRONIDAZOLE
- ✓ Matrix forming polymer:- HPMC K4M
- ✓ Effervescent agent [gas formation]:-Sodium bicarbonate
- ✓ Acidic reactant for effervescent :-Citric acid

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- ✓ Diluent/compressibility aid :-Microcrystalline cellulose (MCC)
- ✓ Glidant :-Talc
- ✓ Lubricant :-Magnesium stearate

- **PROCEDURE OF FDDS METRONIDAZOLE TABLET**

✓ **Step 1: Sieving of Raw Materials**

1. Sieve Metronidazole, Sodium CMC, MCC, starch, sodium bicarbonate, citric acid through #40 or #60 mesh to ensure uniform particle size.
2. Collect sieved powders for mixing

✓ **Step 2: Preparation of Binder Solution**

1. Prepare a starch paste (binder) using 5–10% starch in water or suitable solvent.
2. Heat gently until gelatinized to form a uniform paste.

✓ **Step 3: Mixing of Dry Ingredients**

1. In a clean mortar or blender, mix the API (Metronidazole), polymer (Sodium CMC), effervescent agents ($NaHCO_3$ + citric acid), and MCC thoroughly.
2. Ensure uniform distribution of all powders before granulation.

✓ **Step 4: Granulation**

1. Gradually add the starch binder solution to the dry mixture while mixing continuously.
2. Form a wet mass with uniform consistency.
3. Pass the wet mass through a #40 or #60 sieve to form granules of uniform size.

✓ **Step 5: Drying of Granules**

1. Spread the granules on a tray and dry at 40–50°C in an oven until moisture content is reduced (granules should be free-flowing).
2. Avoid high temperatures to prevent decomposition of Metronidazole.

✓ **Step 6: Lubrication**

1. Sieve magnesium stearate and talc separately.
2. Blend dried granules with magnesium stearate (0.5–1%) and talc (0.5–1%) for 2– 3 minutes.
3. Do not overmix to avoid reducing tablet hardness.

✓ **Step 7: Compression / Tablet Punching**

1. Load the lubricated granules into the tablet compression machine.
2. Compress into tablets of desired weight and hardness using appropriate punch size. Ensure uniform thickness
3. weight for all tablets.

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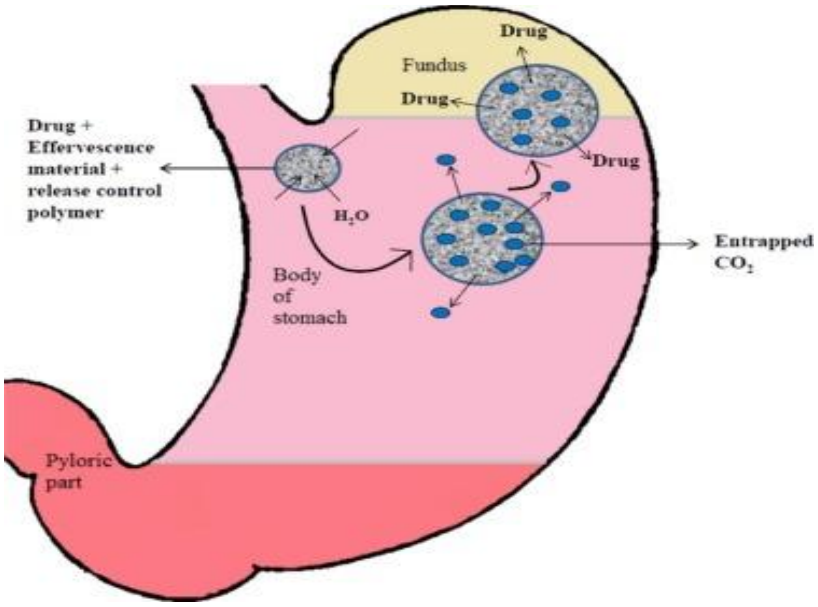

Fig no:-4 Gastro –retentive drug delivery system

- **EVALUATION OF FLOATING TABLET**

✓ **Weight variation**

test Twenty tablets were chosen at random from each batch and measured separately to see if there was any weight difference.

The USP allows for small variation in the weight of a tablet.

The percentage deviation in weight variance allowed is as follows.

The tablet weight was greater than 324 mg in all formulations, allowing for a maximum difference of 5%.

✓ **Hardness test**

The hardness of a tablet determines its ability to endure mechanical shocks while being treated.

The Monsanto tester was used to assess the hardness (kg/cm2) tablet.

The average of five replication determinations was used in all cases.

✓ **Friability test**

This was determined by weighing 26 pills after dusting, placing them in the Roche friabilator, and rotating the plastic cylinder vertically at 25 rpm for four minutes, according to Indian Pharmacopoeia (IP).

The total remaining weight of the tablets was reported after dusting, and the percentage friability was calculated using the equation below.

% Friability = Initial wt. of tablets – Final wt. of tablets / Initial wt. of tablets × 100 % The acceptable Friability of tablets= < 1%.

✓ **In vitro buoyancy study**

The period between the introduction of the dosage form and its buoyancy on the SGF, as well as the time the dosage form stays buoyant, were all measured.

The time it takes for the dosage form to appear on the medium's surface is known as Floating Lag Time (FLT) or Buoyancy Lag Time (BLT).

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the total time it takes for the dosage form to stay buoyant is known as Total Floating Time (TET).

Floating behaviour study were carried out in a USP XXIII dissolution Apparatus type II (Paddle) at a speed 50 RPM in 900 ml SGF at 37±0.50C for 12 hr to mimic in vivo conditions.

✓ **X-Ray method**

Nowadays, X-Ray has become a very common evaluation parameter for floating dosage forms.

It aids in the location of dosage forms in the GIT, as well as the prediction and correlation of gastric emptying time and dosage form passage in the GIT.

The incorporation of a radio-opaque substance into a solid dosage shape allows for X-ray visualisation.

✓ **Swelling index**

The weight assignment determines the swelling activity of the measurement device. When using a pH 6.8 buffer dissolution medium at 370.5 °C,

the tablet swelling index correlates to the tablet site in the dissolution tool basket (type 1).

At each time point, the trials were repeated three times.

✓ **Tablet dimension**

A calibrated vernier calliper was used to measure thickness and diameter. Three tablets of each formulation were chosen randomly, and their thicknesses were determined separately.

✓ **Tablet density**

Tablet density is considered as an important parameter for floating tablets.

The tablet will float only when its density is less than that of gastric fluid (1.004).

We can determine the density using following formula32, V = r2 h d = m/v v= Tablet's volume (cc) r = Tablet's radius(cm) h = Tablet's crown thickness(g/cc) m = Tablet's mass

✓ **Density Study**

FDDS tablets must have density less than gastric fluid (< 1 g/cm³). Formulations showed apparent density < 1, confirming suitability for floatation.

✓ **In-Vitro Dissolution (FDDS Aspect)**

Drug release profile is important to confirm controlled release while tablet floats.

Metronidazole release was sustained over 8–12 hours, matching FDDS objectives.

Release mechanism followed diffusion + polymer relaxation, typical of floating matrices.

- **Considerations of FDDS**

1. For the drug delivery system to float and function well, the stomach needed to contain a high amount of fluid. Not suited for medications with GIT solubility or stability issues.
2. It might not be advisable to use medications like Nifedipine (a calcium channel blocker), which is well absorbed throughout the GIT and goes through first pass metabolism.
3. Drugs that irritate the stomach mucosa are also undesirable or inappropriate.
4. It is not advisable to use drugs that are unstable in the stomach's acidic environment.
5. Drink a full glass of water together with the dosage form.
6. A full glass of water (200-250 ml) should be consumed along with the dosage form.
7. Many substances, such as chlordiazepoxide, cinnarizine, and calcium supplements, are mostly absorbed from the stomach and upper GI tract.

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Drug properties:-

The drug selected should have a suitable dose, because high-dose drugs may lead to large tablets that do not disintegrate quickly. Its solubility and dissolution characteristics must support rapid drug release, and drugs with bitter or unpleasant taste require taste-masking. The drug should also be stable to moisture and heat, as FDDS formulations often use hygroscopic excipients.

excipients selection

Excipients must be chosen carefully to ensure fast disintegration and acceptable tablet strength. Superdisintegrants such as crospovidone, croscarmellose sodium, or sodium starch glycolate are critical and must be used at optimal concentrations. Diluents like mannitol improve mouthfeel and dissolve quickly, while sweeteners and flavors help mask bitterness. Lubricants should be used sparingly to avoid slowing disintegration.

Tablet Characteristics:

FDDS tablets should have adequate hardness to withstand handling but still possess high porosity and low density for rapid wetting. They must provide a pleasant mouthfeel, without grittiness, and should disintegrate in under 30 seconds or according to pharmacopeial requirements.

Manufacturing Considerations:

The chosen manufacturing method—whether direct compression, lyophilization, sublimation, or molding—must support fast disintegration and tablet integrity. Direct compression requires good flow and compressibility of powders, while lyophilized tablets offer very fast disintegration but are fragile and costly. Sublimation and molding improve porosity but may affect mechanical strength.

Observation

The prepared metronidazole floating tablets were uniform in size, color, and weight.

The floating lag time (time taken to start floating) was short, and tablets remained buoyant for a prolonged period, indicating good floatation characteristics.

The tablets maintained integrity throughout the floating duration without disintegration.

Drug release was observed to be sustained and gradual over the test period, suggesting effective controlled-release behavior.

Result:-

Successfully formulated Metronidazole Floating Tablets using effervescent agents (sodium bicarbonate and citric acid) and polymer (Sodium CMC).

II. CONCLUSION

The Metronidazole Floating Drug Delivery System (FDDS) was successfully formulated and showed good buoyancy, prolonged gastric retention, and controlled drug release.

This enhances the drug's absorption and bioavailability, making it an effective approach for the treatment of peptic ulcers.

The dosage form floated on gastric fluid for an extended time, confirming its buoyancy and gastroretentive property.

The formulation achieved controlled and sustained drug release, improving the potential for enhanced bioavailability and reduced dosing frequenc

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