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A Review of Formulation Floating Drug Delivery System: Based Technique by Solid Dispersion

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Abstract

The present study aimed at development of Tinidazole floating tablets to enhance drug solubility and bioavailability. Tinidazole, a BCS Class-II drug with poor aqueous solubility, faces challenges in achieving predictable *in vivo* correlations and suffers from low and variable bioavailability due to extensive first-pass effects. Solid dispersions using PEG6000, PVP K30, and PXM 188 were prepared and characterized. The batch (SD9) with PXM 188 (1:3) showed better release profiles and was selected for effervescent tablet formulation. Drug free effervescent tablets (F4) were optimized using Box behnken response surface design and demonstrated optimal floating characteristics. Granules were found to be within acceptable ranges for bulk density, tap density, and angle of repose. Floating tablets of tinidazole were made by direct compression and subjected to a battery of tests. Formulation A3, which had a 1:1.5% ratio of HPMC to carbopol, showed promising results in terms of floating time, drug content, and drug release profile. After 12 hours, the drug release rate was around 91.56%, and the floating time was 7 hours, making formulation (A3) the best option. The research found that a combination of sodium bicarbonate as a gas producing agent and HPMC: Carbopol may be effectively employed to create Tinidazole sustained release floating tablets.

Keywords: Tinidazole, box behnken design, solid dispersions, PEG6000, carbopol, floating tablets

Introduction

Most people agree that taking medication orally is the most effective and safest way to do it. There are a number of variables that must be considered for oral medication delivery to be effective. These include stomach emptying time, dosage form transit time through the GI tract, drug release from the dosage form, and absorption location. When it comes to how they interact with the body, several oral dose forms have limits. Among these restrictions is the fact that stomach emptying is not always predictable, leading to irregular gastrointestinal transit. Consequently, the medicine may not absorb evenly, its release into the bloodstream may be partial, or the dose form may not remain in the stomach for an extended period of time [1].

Because of this, medications with a narrow absorption window, especially in the first portion of the small intestine, do not absorb fully. There is no further absorption of the medicine once it has passed the absorption site. Dosage type gastric emptying in humans may vary greatly from one person to the next due to a number of variables. Unpredictability and non-uniform absorption of medications might occur as a result of differences in absorption rates in the upper gastrointestinal tract. Consequently, for optimal medication delivery to the absorption location (more precisely, the upper portion of the small intestine), the ideal system would be able to control and prolong the time it takes for the stomach to empty [2].

Floating Drug Delivery System

There are a number of FDDS available today, built with various technologies that have their own set of pros and cons. hydrodynamically balanced systems (HBS) with one or more units, gas generation systems with one or more units, hollow microspheres, and raft-forming systems are all part of this category. To keep itself afloat in the stomach contents, the medication formulation 4 FDDS makes use of gel-forming hydrocolloids. By controlling the dissolution and release of the medicine from the dosage form, the stomach's pH maintains a controlled environment [3].

The gastric retentive characteristic of floating devices makes them an important class of medication delivery methods. Furosemide, cyclosporine, allopurinol, ciprofloxacin, and metformin are a few medications that could be helped by gastric retention. The small intestine has a higher pH than the stomach, which makes it less soluble for certain drugs. A few examples of these medications include captopril, which acts locally in the stomach, and chlordiazepoxide and cinnarizine,

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which are broken down in the intestinal pH. The development of dosage forms that retain food in the stomach provides a solution to this problem. One possible dose form for antibiotics, catecholamines, sedatives, analgesics, anticonvulsants, muscle relaxants, antihypertensive drugs, and vitamins is FDDS [4].

Advantages of Floating Drug Delivery System (FDDS)

- The FDDS are advantageous for stomach-absorbed medications such ferrous salts and antacids, as well as for stomach-localized medications used to treat peptic ulcer disease.
- The site of absorption for some drugs does not impact the efficacy of those delivered utilizing the sustained release concept of FDDS.
- The medicine will dissolve in stomach fluid when a floating dose form tablet or capsule is given in an extended release form.
- The small intestine is the site of medication absorption once the stomach has emptied. If a medicine remains soluble even in the acidic intestinal pH, it is expected that the floating dosage form will be absorbed entirely.
- Absorption of medications may be inadequate in situations when the digestive activity is strong and the transit time is quick, such in some forms of diarrhea. Keeping the medicine in a free-floating form in the stomach could help in these cases to have a better reaction.
- One advantage of gastric retention is that it enables the administration of medications with poor small intestine absorption rates.
- The suboptimal absorption of several once-daily-dosage medications has been linked to their reliance on the dose form's transit time. This complicates the process of creating conventional extended release formulas. Consequently, the small intestine has a longer window of opportunity to absorb drugs when a system is designed for protracted stomach retention [5].

Disadvantages of Gastroretentive Drug Delivery System

- In designing gastroretentive systems, it's crucial to stay away from pharmaceuticals that can irritate the stomach lining or aren't stable in the acidic environment.
- In addition, a gastric retention system will not improve the absorption of other medications, including isosorbide dinitrate, which are equally absorbed throughout the gastrointestinal tract.
- A number of variables, such as stomach motility, pH levels, and meal content, might influence gastric retention. Due to the dynamic nature of these variables, accurate buoyancy prediction is currently unattainable.
- A key factor affecting the unpredictability of floating form emptying in supine patients is the diameter. Consequently, taking medicine in a floating form just before going to bed is not a good idea.
- Because the emptying process varies from person to person, the length of time it takes for the stomach to empty varies widely [5].

Types of Floating Drug Delivery Systems

Two separate technologies have been used in the creation of FDDS, which is based on the buoyancy mechanism [6-8].

a) Effervescent System

- Gas generating systems
- Volatile liquid/vacuum systems

b) Non-Effervescent System

- Single layer floating tablets
- Bilayer floating tablets
- Alginate beads
- Hollow microspheres

c) Raft-forming Systems

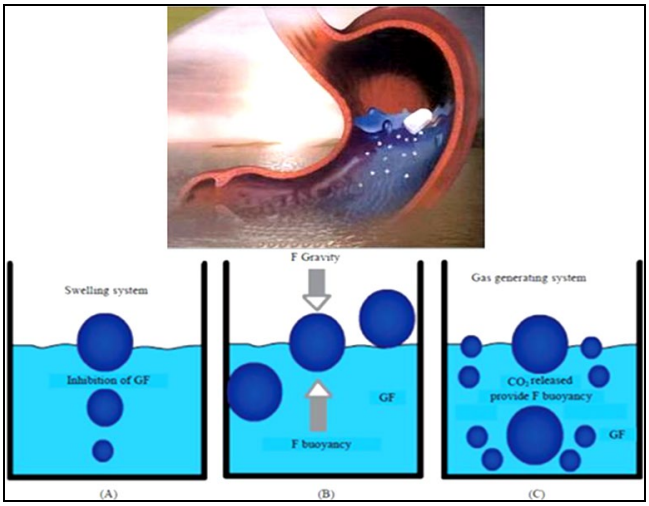

Fig 1: Floating Drug Delivery Systems and its types

a) Effervescent System

The matrix structure is the basis for this system's operation. Formulated using a variety of effervescent chemicals and swellable polymers such as methylcellulose and chitosan. Acids such as citric acid, tartaric acid, and sodium bicarbonate are examples. The formula is engineered to emit carbon dioxide gas upon interaction with gastric acid. Once the hydrocolloid swells, it traps the CO_2, making the dose form buoyant. Swellable asymmetric triple-layer tablets were the basis for the delivery system's design [6].

i). **Gas Generating Systems:** When the FDDS come into touch with bodily fluids, they release carbon dioxide, which is their operating gas. The materials are engineered to react in the stomach's acidic environment, releasing carbon dioxide gas. The dose form rises and stays buoyant because of the gel-like hydrocolloid. The dose form floats atop the chyme due to the reduction in specific gravity. It is possible to create either a single-layer or bilayered tablet by fully mixing the CO_2-generating components inside the tablet matrix. In one layer, a hydrocolloid houses the gas-generating mechanism, while in the other, the medicine is designed for a sustained-release action [7-8].

ii). **Volatile Liquid Containing Systems:** One component of this state-of-the-art floating system is a gadget that can transform from its collapsed state into a hollow deformable unit. The two-chambered housing is specifically engineered to connect to a deformable unit. A pressure-sensitive and impermeable moveable unit separates these compartments. It is common practice to place an active medicinal ingredient in the first chamber and a volatile liquid that evaporates at body temperature in the second. The gas produced by this vaporization makes it possible for the medication reservoir to float. A bioerodible stopper permits the vapor to escape when the unit is discharged from the stomach [7-8].

b) Non-effervescent FDDS

After consumption, this kind of system swells without

restriction as a result of stomach fluid absorption. Because of their enlargement, they may be unable to pass through the stomach. One method for making these dose forms involves mixing the medicine with a gel. After oral administration, this gel expands upon contact with gastric acid. Encased in a gelatinous shell, it aids in keeping the dosage form's shape and solidity. These dosage forms float thanks to the air contained by the inflated polymer. A variety of excipients are used in these systems, including but not limited to: polycarbonates, sodium alginate, agar, polyacrylate polymers, polyvinyl acetate, Carbopol, and hydroxyl propyl methyl cellulose (HPMC)[6-8].

c) Raft-forming Systems

The feasibility of raft-forming devices as a delivery mechanism for antacids and other medications used to treat gastrointestinal infections and diseases has attracted a lot of interest. The swelling and formation of a thick, sticky gel containing CO2 bubbles occurs when a solution comes into touch with stomach fluid. By coating the gastric fluid with this gel, the medicine may be released slowly into the stomach [9].

Drug Candidates Suitable for FDDS [10-12]

- Some medications have a limited ability to be absorbed in the gastrointestinal tract. Examples of these drugs include L-DOPA, p aminobenzoic acid, furosemide, and riboflavin.
- Some drugs have a localized effect in the stomach, such as misoprostol and antacids.
- Some drugs can be unstable in the intestinal or colonic environment. Examples include captopril, ranitidine HCl, and metronidazole.
- Medications that disrupt the balance of bacteria in the colon, like antibiotics used to treat Helicobacter pylori, such as tetracycline, clarithromycin, and amoxicillin.
- Some drugs, such as diazepam, chlordiazepoxide, and verapamil, have low solubility when exposed to high pH levels.

Mechanism of FDDS

Because they are less dense than gastric fluids, floating medication delivery devices are able to float in the stomach and not slow down the emptying process. The buoyancy may be sustained for a long time. Floating on top of the stomach contents, the device releases the medication at a predetermined pace. The stomach empties itself once the medicine has been released. As a result, the variability in plasma medication levels is better managed, and GRT is increased [13].

Nevertheless, for the buoyancy retention principle to be successful, there must be just the right quantity of stomach contents. Additionally, the dose form must have a minimum degree of floating force (F) to reliably stay buoyant on top of the meal. The device functions by continuously measuring the force needed to keep the submerged object in place. The object achieves optimal buoyancy when the value of F is increased on the positive side. This device assists in enhancing the performance of FDDS by focusing on the stability and durability of the floating forces generated, thereby mitigating the issues arising from unpredictable variations in intra gastric buoyancy capability [14].

$$F = F_{buoyancy} - F_{gravity}$$
$$= (Df - Ds)\, gv$$

Where, F= total vertical force, Df = fluid density, Ds = Object density, v = Volume and g = acceleration due to gravity.

Factors affecting Floating Drug Delivery System [15-17]

a) **Density:** The dose form's density shouldn't be higher than the stomach contents' density (1.004gm/ml).
b) **Size and Shape:** According to certain research, the gastrointestinal transit time of dosage forms with a diameter more than 7.5 mm is longer than that of dosage forms with a diameter of 9.9 mm. There is some evidence that dose forms with tetrahedron or ring shapes and flexural moduli of 48 or 22.5 kilo-pond per square inch (KSI) have better GIT retention (90 to 100% at 24 hours) than other shapes.
c) **Fed or Unfed State:** In the absence of food, the gastrointestinal motility is defined by bursts of intense motor activity, called migrating myoelectric complexes (MMC),that happen every 1.5 to 2 hours. If the formulation is administered at the same time as the MMC, which removes undigested food from the stomach, the GRT of the unit should be quite short. On the other hand, MMC takes longer in the fed condition while GRT is much longer.
d) **Nature of the Meal:** To slow the stomach's emptying rate and extend the drug's release, indigestible polymers of fatty acid salts can induce a fed state in the stomach's motility pattern.
e) **Caloric Content:** GRT can be increased between 4 to 10 hours with a meal that is high in proteins.

Pharmacokinetic and pharmacodynamic aspects of FDDS

a) **Enhanced Bioavailability:** When it comes to medications having a short therapeutic window owing to poor GI absorption-caused by a number of factors-FDDS has investigated the topic with great competence, with the goal of increasing bioavailability. When it comes to medications with a narrow absorption window, FDDS has showed promise in improving chemical bioavailability to the target site. Riboflavin and levodopa administered via control release (CR) floating systems have a much higher bioavailability than the standard formulation. However, alendronate and other bisphosphonates in CR polymeric formulations are absorbed straight from the stomach. Even though bisphosphonate causes rats to retain it in their stomachs for an extended period of time whether administered experimentally or surgically, the size of this route is still moderate. It is reasonable to assume that the amount of drug absorption is affected by a combination of many processes that occur simultaneously throughout the gastrointestinal tract and are involved in drug absorption [19].
b) **Enhanced First-pass Biotransformation:** In contrast to a bolus injection, the studied compound's pre-systemic metabolism is greatly enhanced by prolonged drug delivery to the metabolic enzymes (cytochrome P450, particularly CYP3A4), resulting in FDDS. This is similar to how active transporters with restricted capacity activity are more effective [20].
c) **Improved Bioavailability Due to Reduced P-Glycoprotein (P-gp) Activity in the Duodenum:** Although CYP3A4 is more concentrated in the upper intestine, P-gp mRNA levels rise longitudinally from the beginning of the intestines to the colon, seemingly at odds with this trend. Digoxin is an example of a P-gp substrate that does not undergo oxidative metabolism; so, floating

systems may increase absorption relative to immediate and control release (CR) dose forms.

d) **Reduced Frequency of Dosing:** According to the various investigations, medications having a short biological half-life, sluggish input from sustained release, and control release floating system flip-flop pharmacokinetics were found to have reduced dose frequency. Better therapeutic outcomes are linked to this characteristic, which is related with higher rates of patient compliance.

e) **Targeted Therapy for Local Ailments in the upper GIT:** For targeted treatment in the small intestine and stomach, the medicine could be more effectively delivered over an extended period of time by floating systems to the stomach.

f) **Reduced Fluctuations of Drug Concentration:** On continuous medication input, the floating route of delivery maintains consistent blood drug concentrations within a shorter range than instant release dose forms. This way, the drug's effects are more stable, and the concentration-dependent side effects that occur at high doses are less likely to occur. This property is particularly useful for medications that have a small window of opportunity to have an effect [21].

g) **Improved Selectivity in Receptor Activation:** Because different medications activate different types of receptors at different doses, it is feasible to achieve some selectivity in the induced pharmacological response by minimizing changes in drug concentration.

h) **Reduced Counter-activity of the Body:** The pharmacological response often causes the body to engage in rebound activity, which reduces the drug's effectiveness, because it interferes with the body's natural physiological processes. It has been demonstrated that a slow drug injection into the body, like in the case of FDDS, reduces counter action and increases drug efficiency.

i) **Minimized Adverse Activity at the Colon:** The negative effect of FDDS retention, which mostly happens in the stomach when the medication is in a gastro retentive form, is reduced drug exposure in the colon. Thus, the colon is an area where the drug's unwanted effects may be avoided. Pharmacodynamic considerations justify the floating formulation of beta-lactam antibiotics because of their effect on microbial development in the colon and the fact that they are only absorbed in the small intestine [22].

Material and Method

Solid Dispersion Technique [22]

A class of solid goods called solid dispersions (SD) include a hydrophobic medication and a hydrophilic carrier, both of which are distributed in a physiologically inert matrix. Crystalline or amorphous carriers are both possible. A solid dispersion can improve the solubility or dissolution rate of medications that aren't very water soluble by dissolving the carrier and releasing the drug as small colloidal particles when exposed to water.

For medications that aren't very water soluble, using a hydrophilic carrier that contains the drug speeds up the dissolution process by decreasing particle size, increasing porosity, and putting the drug in an amorphous state. This, in turn, enhances wettability and, perhaps, bioavailability. Polymers made of low molecular weight materials, including sugars, are utilized, for example, PEG and PVP. In order to stabilize the formulations and prevent the recrystallization of the drugs while increasing their solubility, surfactants have been added recently.

Advantage of Solid Dispersion

- Many medications that are insoluble in water become more soluble.
- One advantage of quickly dissolving tablets in water is that they can be used as a substitute for parenteral therapy, allowing patients to self-medicate even when they don't have access to water.
- In order to hide the flavor of the medicine.
- For the purpose of making oral pills that dissolve quickly.

Disadvantages of Solid Dispersion [23]

- The bulk of polymers used in solid dispersions have the property of absorbing moisture, which means that they may undergo phase separation, crystallization, or a more stable structural change from an amorphous to a crystalline or metastable crystalline state when stored. This can lead to a decrease in both solubility and dissolution rate.
- The formulation into dose and reproducibility of its physicochemical qualities.

Materials Used in Preparation of Solid Dispersions

When making solid dispersions, there are a number of options for hydrophilic carriers.

- **Acids:** Citric acid, Tartaric acid, Succinic acid.
- **Sugars:** Dextrose, sucrose, sorbitol, Maltose, Galactose, Xylitol.
- **Polymeric materials:** PVP, PEG 4000, PEG 6000, HPMC, CMC, Guar gum, Xanthum gum, Sodium alginate, Cyclodextrin.[25]
- **Surfactants:** Poloxamer, Tween, Span, Gelucire 44/14, Deoxycholic acid, Polyoxyethylene stearate, Vitamin E TPGS NF.
- **Miscellaneous:** Urea, Urethane, Hydroxyalkyl xanthenes, Pentaerythritol.

Method of Preparation of Solid Dispersion

a) **Fusion Method:** A change has been made to the co-melting process. When the carrier is melted, it is placed in a porcelain dish and cooked over a steam bath. Gradually disperse the carefully measured medicine into the hot media using a glass rod. When the dish is no longer steaming, it is let to cool at room temperature until the contents harden, after which the medicine is completely dispersed throughout the carrier. The final step is to grind and filter the solid dispersion. Drugs can have their thermal degradation slowed down using this strategy. This strategy is more practical and cost-effective for medications that remain stable at temperatures below 1000°C. If the medication and carrier are soluble when heated together, the process becomes much simpler. Dispersions made using the melting approach dissolve far more quickly than those made using the solvent technique [26].

b) **Solvent Evaporation Method:** A common volatile solvent is used to dissolve the medication and carrier, and then the mixture is extracted using a vacuum. Pulverized and sieved is the produced solid dispersion. You can also use materials with a high melting point. It is possible to prevent the drug and carrier thermal breakdown that occurs during the fusion process.

c) **Kneading Technique:** The carrier is soaked with water and turned into a paste using this technique. A specific amount of time is then spent kneading in the drug. After kneading, the mixture is dried and, if needed, sieved.

medicines that are sensitive to moisture should not be used with this approach, however thermo labile medicines can be [27].

d) **Melt Solvent Evaporation Technique:** One method involves dissolving the medicine in an organic solvent before adding it to the melted carrier. The product is ground to the required size once the solvent is removed. Features the best features of solvent evaporation and fusing processes simultaneously. Benefits medications having a high melting point that are susceptible to thermal degradation.

e) **Co-melting Method:** This process requires physically mixing a medicine with a water-soluble carrier and then heating the mixture until it melts. A quick cooling in an ice bath solidifies the melted mixture. Crushing, grinding, and sieving produce the finished solid mass. A thin coating of the homogeneous melt poured over a ferrite or stainless steel plate and cooled by water or air on the other side of the plate is one way to alter the process. Applying the quenching approach to basic eutectic mixtures results in a substantially finer crystallite dispersion [28].

f) **Gel Entrapment Technique:** A transparent gel is formed when the carrier is dissolved in an organic solvent. After that, the gel is sonicated for a few minutes to dissolve the medication. Vacuum evaporation is used to remove organic solvents. Using a mortar and pestle and a sieve, solid dispersions are ground to a smaller size.

g) **Co-precipitation Method:** The carrier solution is then supplemented with the necessary dosage of medication. The system is shielded from light and maintained under magnetic agitation. The resulting precipitate is then allowed to dry at room temperature after being separated by vacuum filtration.[29]

h) **Spray Drying Method:** Dissolve the medication and its carrier in water as directed by the dosage form. The solutions are mixed using sonication or another suitable method, and then a spray dryer is used to dry them, resulting in a solid dispersion that looks like tiny, floating particles.

i) **Co-grinding Method:** The medicine and carrier are physically combined for a period of time using a blender set to a specific speed. The next step is to load the mixture into the vibration ball mill's chamber. Everything is ground into a fine powder. After that, the finished product is transferred to a glass vial with a screw lid and left to cool until needed.

j) **Electro Spinning Method:** Electro spinning is a process that uses a millimeter-scale nozzle to spin a polymeric fluid stream solution or melt into solid fibers. This process involves applying a strong electrostatic field via a conductive collecting screen to a polymer solution or melt in a reservoir that is held by a conducting capillary. When the electrostatic field intensity reaches a particular value, the charge species that have accumulated on the surface of a pendant drop become unstable, causing its hemispherical shape to transform into a conical one, also known as a Taylor cone. Nanofiber preparation and biomedical release control are two areas where this method shows promise.

k) **Supercritical Fluid (SCF) Method:** Carbon dioxide (CO2) is used in most of these treatments. It serves as both a solvent for drugs and matrix materials and an anti-solvent. An approach that has been subjected to temperatures and pressures beyond their critical values is one that uses a nozzle to introduce supercritical CO2 gas into a particle formation vessel simultaneously with a solvent that contains the drug and the carrier.

l) **Freeze-drying Method:** A common solvent is used to dissolve the medication and carrier, and then it is frozen in liquid nitrogen. The next step is to further lyophilize the frozen solution. Incorporating medicinal compounds into stabilizing matrices using this method is an attractive and appropriate strategy.

Benefits: The opportunity for phase separation is reduced, and the medication experiences little thermal stress while the solid dispersion is formed [30].

Conclusion

To improve the medicine's bioavailability, floating drug delivery devices lengthen the time the drug spends in the gastrointestinal tract. It floats on top of the stomach fluid due to its lower density than water. The stomach and upper small intestine are ideal sites for these drug delivery devices because of the limited absorption window. The rate limiting step in the absorption of this BCS Class-II medication is its limited dissolution from its dose forms. Problems with bioavailability and inability to achieve repeatable *in vivo*/*in vitro* correlations are exacerbated by poor water solubility and slow dissolution rate. Its poor and variable bioavailability is further caused by its large first pass impact.Drug free effervescent tablets were prepared and evaluated for floating time.

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