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**Review Article**

# FORMULATION, CHARACTERIZATION, APPLICATION OF FLOATING TABLETS

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**A B S T R A C T**

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 which includes floating drug dosage systems (FDDS), effervescent and non effervescent system, swelling or expanding systems, mucoadhesive systems magnetic systems, modified-shape systems, high density system and other delayed gastric emptying devices. Among these systems, FDDS have been most commonly used.



## INTRODUCTION

### *Oral dosage forms*

A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules. Among the various dosage forms oral solid dosage forms have greater importance and occupy a prime role in the pharmaceutical market. Oral route of drug administration is widely acceptable and drugs administered orally as solid dosage form represents the preferred class of products. Over 90% of drugs formulated to produce systemic effects are produced as solid dosage forms. Because of these reason whenever new chemical entry (NCE) has discovered, which shows a sufficient pharmacological action, first the pharmaceutical company asks whether the drug is successfully administered by oral route or not. The oral route of administration still continues successfully administered by oral route or not. The oral route of administration still continues to be the most preferred route due to its manifold advantages including:

- Tablets and capsules represent unit dosage forms in which the accurate dose of drug to shows sufficient pharmacological action can be administered, in case of liquid oral dosage forms such as syrups, suspensions, emulsions, solutions and elixirs the patient is asked to administer the medication of 5-30 ml. such dosage measurements are typically error by factor ranging from 20-50%, when the drug is self administered by patient.
- Solid dosage forms are less extensive to shipping and less prone for the degradation when compared to liquid dosage forms.

### *Floating tablets*

- Floating systems (or) hydro-dynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.
- While the system is floating on the gastric contents, the drug is slowly released at a desired rate from the stomach.
- After the release of drug, the residual system is emptied from the stomach.
- This result in an increase in the gastric retention time and better control of fluctuations in the plasma.

### *FDDS*

- Floating drug delivery systems were first described by Davis in 1968.
- It is possible to prolong the gastric residence time of drugs using these systems.
- The gastric emptying time in humans which normally averages 2-3 hours through the major absorption zone (stomach and upper part of intestine) can result in incomplete drug release from the drug delivery system leading to reduced efficacy of administered dose.
- Lower dosing and less side effects.
- Beneficial in the treatment of gastric disease.

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- Suitable dosage forms for the drugs those are primarily absorbes in the stomach.
- Several techniques are used to design gastro retentive dosage forms. These include floating, swelling, inflation, adhesion, high-density systems and low density systems that increase the gastric residence time.
- Gastric retention is useful for drugs which

1. Act locally
2. Have narrow absorption window in the small intestinal region.
3. Unstable in the intestinal environment.
4. Low solubility at high pH environment.

Various dosage forms developed for gastric retention include, floating tablets, floating beads, pellets, floating granules, floating microspheres.

***Advantages***

- Enhanced solubility
- Enhanced first-pass biotransformation
- Sustained drug delivery/ reduced frequency of dosing
- Targeted therapy for local ailments in the upper GIT.
- Reduced counter-activity of the body.
- Extended time over critical (effective) concentration
- Minimized adverse activity at the colon.
- Site specific drug delivery.

***Disadvantages***

- Floating systems is not feasible for those drugs that have solubility or stability problem in the G.I. tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- The drugs that are significantly absorbs throughout the gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
- some drugs present in the floating systems causes irritation to the gastric mucosa.

***Floating agencies***

- hydrochlorides: HPMC1000, HPMC4000, βcyclodextrin, sodium alginate, HPC-L,$CPC_{934}$P,HPC,HPMC, $MetoloseS.M._{100}$,pvp, HPMC $K_{15}$,HPMC $K_4$,Acrylic polymer,Carbopol.
- Inert fatty materials: bees wax, fatty acids, long chain fatty alcohols,
- Effervescent agents: sodium bicarbonate, citric acid, tartaric acid, Di-SGC(di-sodium Glycine carbonate, CG(citroglycine).
- Release rate accelarants (5%-60%):e.g.lactose, mannitol.
- Release rate retardants (5%-60%):e.g.dicalcium phosphate, talc, magnesium sterate.
- Buoyancy increasing agents (upto 80%):e.g. ethyl cellulose.

***Tablet additives***

In addition to active ingredients, tablet contains a number of inert materials know as additives or excipients, different excipients are.

***Diluents***

Diluents are fillers used to make required bulk of the tablets when the drug dosage itself in inadequate to produce the bulk. Secondary reason is to provide better tablet properties such as improve cohesion, to permit use of direct compression manufacturing or to promote flow.

Ex:-microcrystalline cellulose, dibasic calcium phosphate dehydrate, calcium sulphate, mannitol, sorbitol, sucrose, dextrose.

***Binders & adhesives***

These materials are added either dry or in wet-form to form granules or to form cohesive compacts for directly compressed tablet.

Ex:-acacia, tragacanth solution, cellulose derivatives-methyl cellulose, HPMC, HPC.

Gelatin, glucose, PVP, starch paste, sodium alginate, sorbitol.

***Disintegrants***

Added to a tablet formulation to facilitate its breaking or disintegration when in contact in water in the GIT.

Ex:- starches, cellulose, aligns, gums and cross linked polymers.

Superdisintegrants:

Swells up to ten fold within 30 seconds when contact water.
Ex:- sodium starch glycolate.

***Lubricants & glidants***

Lubricants are intended to prevent adhesion of the tablet materials to the surface of dies and punches.
Ex:- stearic acid, magnesium stearate, talc, PEG, surfactants.
Glidants:

Glidants are intended to promote flow of granules or powder material by reducing the friction between the particles.
Ex:- corn starch, talc, silica derivative.

***Colouring agent***

The use of colors and dyes in a tablet has three purposes.

1. Masking of color drugs
2. Product identification
3. Production of more elegant product.

Ex:- FD&C yellow 6-sunset yellow, FD&C yellow 5-tartrazine, FD&C green 3 – fast green, FD&C blue 1 – brilliant blue.

1. Flavouring agents:

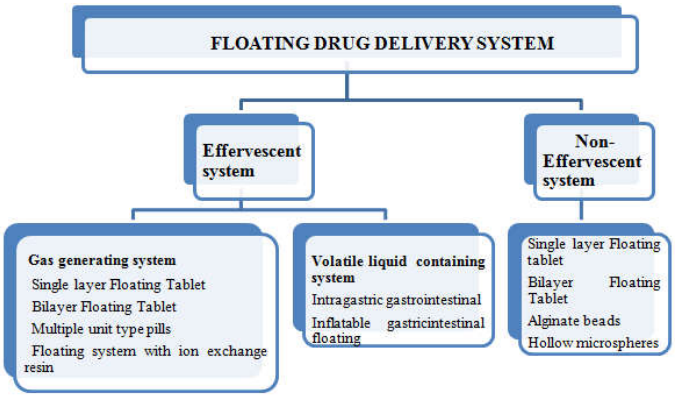
For chewable tablet – flavour oil are used.

2. Sweeting agents:

For chewable tablets: sugar, mannitol.

***Typies***

1. non-effervescent system
2. effervescent system.




## METHODOLOGY

- direct compression technique
- melt granulation technique
- melt solidification technique
- spray drying technique
- wet granulation technique

### *Direct Compression*

- tablets are compressed directly from powder blends of the active ingredient and suitable excipients.
- No pretreatment of the powder blends by wet or dry granulation procedures is necessary.
- Some granular chemicals like potassium chloride possess free flowing as well as cohesive properties that enable them to be compressed directly in a tablet machine without need of either wet or dry granulation.
- In the direct compression method the tablet excipients used must be materials with properties of fluidity and compressibility.

### *Melt Granulation*

- Melt granulation or thermoplastic granulation is a technique that facilities and agglomeration of powder particles using melt able binders, which melts or softens at relatively low temperature (50-90˚C).
- Cooling of the agglomerated powder and the consequent solidification of the molten or soften binder complete the granulation process.
- Low melting binders can be needed to the granulation process either in the form of solid particles that melt during the process.
- Melt granulation is an appropriate alternative to other wet granulation techniques which are used for water sensitive materials.

### *Melt Solidification*

- A melt granulation process has been investigated which efficiently agglomerates pharmaceutical powders for use in both immediate and sustained release solid dosage forms.
- The process utilizes materials that are effective as granulating fluids when they are in the molten state.
- Cooling of the agglomerated powders and the resultant solidification of the molten materials completes the granulation process.
- Both the molten agglomeration and cooling solidification were accomplished in a high shear collettegral mixer equipped with a jacketes bowl.
- Hence, the melt granulation process replaces the conventional granulation and drying operations which use water or alcohol solutions.

### *Spray Drying*

- This technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization/dispersing them in an organic/aqueous phase before spray drying.
- The liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions.
- such particles can be further prepared into tablets or capsules.

### *Wet Granulation*

- In the pharmaceutical industry, granulation refers to the act or process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules.
- It is the process of collecting particles together by creating bonds between them.
- Bonds are formed by compression or by using a binding agent.
- Granulation is extensively used in for the manufacturing of tablets, pellets (or spheroids).
- The granulation process combines one or more powders and forms a granule that will allow tableting or spheronization process to be within required limits.

### *Examples of Derugs Involved In Floating Tablets*

| drugs | category | uses |
|---|---|---|
| glipizide | Anti-diabetic | Type 2- diabetes |
| domperidone | specific blocker of dopamine receptors | dyspepsia, heartburn, epigastric pain, nausea, and vomiting |
| captopril | Anti-hypertensive | Lowering high blood pressure |
| ofloxacin | antibiotic | Viral infections |
| verampamil | Calcium channel blocker | Hypertension,angina |
| acebutolol | Beta-blockers | hypertension |
| Lafutidine | Anti-ulcer | Gastric ulcer, deuodenalulcer,acutegastrities |
| cimetidine | H2 blockers | Certain types of ulcers and also used to treat gastroesophagal reflex disease(GERT) |
| cinnarizine | antihistaminic | Calcium channel blockers |
| flupertinemeleate | Non-steroidal analgesic, non-opioid | Alzheimer's disease, multiple sclerosis |
| ranolizine | Anti-angina | Chronic angina, blood pressure control |
| Salbutamol sulphate | B2-adrenergic agonists | Asthma, chronic bronchitis, breathing disorders |
| Merformin hydrochloride | Anti-diabetic | Type-2 diabetes |
| nateglinide | Anti diabetic | Type-2 diabetes |

### *Characterization*

- Micromeritic properties
  a. Angle of repose

b. bulk density
c. hausner's ratio
d. carr's index

- weight variation
- hardness
- friability
- in-vitro buoyancy studies
- drug content
- in-vitro drug release
- in vitro disintegration time
- drug release kinetics
- stability studies

***Angle of Repose***

The frictional force of granules can be measurement by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

**Tan(θ)=h/r**
Where, θ is the angle of repose,
h=height,
r=radius
**limits for angle of repose according to I.P**

| S.No | Angle of Repose | Type of Flow |
|---|---|---|
| 1 | <25 | Excellent |
| 2 | 25-30 | Good |
| 3 | 30-40 | Passable |
| 4 | 40 And Above | Very Poor |

***Bulk density***

Both loose bulk density (LBD) and tapped density (TBD) were determined. The accurately weighed amount of sample taken in a 25ml measuring cylinder of Borosil measurement/ recorded the volume of packing recorded and LDB and TBD calculated by following:

**LBD (LOOSE BULK DENSITY) =** mass of powder/ bulk volume of powder
**TAB(tapped bulk density)**= mass powder/tapped volume of powder
**Hausner's ratio:**
Flow properties of granules were determined by hausner's ratio calculated by following formula:

**H= tapped bulk density/lose bulk density**

A hausner ratio greater than 1.25 is considered of poor flowability.

**Limits of hausner's ratio according to IP**

| S.No | Hausner's ratio | Type of flow |
|---|---|---|
| 1 | <1.25 | Good flow |
| 2 | 1.25-1.5 | Moderate flow |
| 3 | >1.5 | Poor flow |

**Carr's index**

Percentage compressibility of granules was determined by carr's compressibility index, calculated by following formula
**Carr's index = TBD-LBD/TBD**

**Limits for carr's index according to I.P**

| S.No | Carr's index | Type of flow |
|---|---|---|
| 1 | 5-12 | Free flow |
| 2 | 12-16 | Good |
| 3 | 18-21 | Fair |
| 4 | 23-25 | Poor |
| 5 | 33-38 | Very poor |
| 6 | >40 | Extremely poor |

***Weight variation***

Contains the proper amount of drug. The test was carried out by weighing the 20 tablets individually using analytical balance, then calculating the average weight, and comparing the individual tablet weights to the average.

The percentage of weight variation is calculated by using the following formula.

$$\%\ \text{of wt. variation} = \frac{\text{Avg wt. of tablet} - \text{individual tablet wt}}{\text{Avgwt of table}} \times 100$$

Weight variation limits according to IP, BP, USP

| IP/BP | LIMITS | USP |
|---|---|---|
| 80mg or less | 10% | 130mg or less |
| >80mg or <250mg | 7.5% | 130mg to 324mg |
| 250mg or more | 5% | >324mg |

***Hardness***

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. Tablet hardness is defined as the load required crushing or fracture a tablet placed on its edge. Sometime it is also termed as tablet crushing strength. The hardness test was performed using Monsant type (Make: Singhla) hardness tester. The instrument measures the force required to break the tablet when the force generated by anvils to the tablet. The tablet was placed between two anvils; force applied to the anvils, and the crushing strength that just causes the tablet to break was recorded. The crushing strength test was performed on 20 tablets from each formulation.

***Friability***

For each formulation, the friability of 20 tablets was determined using Roche type friabilator. 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min. After removing of dusts, tablets were re-weighed and friability percentage was calculated using the following equation.

$$F = \frac{\text{initial weight} - \text{final weight}}{\text{Intitial weight}} \times 100$$

***In vitro buoyancy studies:***

The randomly selected tablets from each formulation was kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time.

***Drug content uniformity***

Twenty tablets had been weighed and overwhelmed in a mortar. Then weighed powder comprise equal to 100mg of drug transferred in 100ml of pH 6.8 . Its attention 1000 mcg/ml. 10ml from this stock solution taken and diluted to 100ml ofph 6.8. it makes hundred mg/ml. then 0.6ml of inventor solution and diluted to 10ml. absorbance degree at 276nm.

***In vitro dissolution studies***

Dissolution rate became studied via using USP kind-II apparatus (DR-6. Campbell apparatus, Dissolution test equipment at(50 rmp) using 900ml of zero.1 N HCl as dissolution medium [89-93]. Temperature of the dissolution mediumturned into maintained at 37± 0.5˚c, aliquot of dissolution medium turned into with draw at each 1 min interval and filtered. The absorbance of filtered solution changed into measured by way of UV spectrophotometric method at 276nm and attention of the drug was determined from fashionable calibration curve.

***In vitro disintegration time***

The process of breakdown of a pill into smaller particles is known as as disintegration. The in-vitro disintegration time of a tablet become determined using disintegration take a look at apparatus as per I.P. specifications I.P. specs: place one pill in every of the 6 tubes of the basket. upload a disc to each tube and run the apparatus the use of pH6.8 maintained at 37°±2°C as the immersion liquid . The meeting ought to be raised and lowered between 30 cycles consistent with minute inside the pH 6.8 maintained at 37°±2°C . The time in seconds taken for entire disintegration of the tablet and not using a palpable mass closing in the apparatus changed into measured and recorded.

***Drug release kinetics***

The cumulative amount of glipizide released from the tablets at different time interval was fitted to various kinetic drug release models like zero order, first order, higuchi, korsmeyerpeppas, weibul and hexon'scrowel.

***First order constant***

First order rate constant obtained by plotting log% dissolved versus time, the plot will be straight line and slope of the line (m) will be -K/2.303.

the slope of the line and the corresponding value of K can be calculated which is indicative of the release rate profile.

In Q-InQo=Kt

Where Q is the amount of drug release at time t. Qo is quantity of drug present intitially in the dosage form, and K is the first order release constant.

***Higuchi constant***

To investigate the mechanism of drug release the in vitro data were plotted as cumulative drug release versus square root of time as described by Higuchi, when the linearity was observed in the graph that indicated the diffusion controlled release.

$Q=K_H t^{1/2}$

Where Q is amount of drug release at time t, $k_H$ is Higuchi is square root of time release rate constant.

***Korsemeyer-peppas constant***

To understand the mechanism of drug release and to compare the differences among release profile of the floating tablets, the percentage drug release versus time profiles were fitted into the equation proposed by peppas.

$Mt/M\text{œ}=Kt^n$

Where Mt is drug release at time t, Mœ is the total amount of drug in the dosage form,Mt/Mœ is the fraction of drug release up to time t, K is the kinetic constant and n is the release exponent indicative of the release mechanism.

***Stability studies***

The best formulation was selected based on floating behaviour, physical properties and dissolution kinetic models was placed in stability chamber at 30˚c RH 75% for 3 months. They are evaluated for hardness, friability, floating behaviour, buoyancy time, drug content and dissolution.

***Applications***

- enhanced bioavailability
- sustained drug delivery
- site specific drug delivery system
- absorption enhancement
- minimized adverse activity at the colon
- reduced fluctuations of drug concentration

## CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number ofcompanies are focusing toward commercializing this technique.

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