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A Review - Bilayer Floating Drug Delivery System

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ABSTRACT

In the recent years, scientific and technological advancements have been made in the research and development of novel drug delivery systems by overcoming physiological troubles such as short gastric residence times and unpredictable gastric emptying times. Several approaches are currently utilized in the prolongation of the gastric residence times, including floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices. This review entitled the detailed scenario related to Bilayer floating drug delivery system with their advantages over the conventional drug delivery system and also limitation, which are helpful in development of dosages form. Various types of techniques employed for development of this dosages form. Review focused on formulation aspect of effervescent floating drug delivery system with their evaluation techniques. The purpose of this comprehensive review is to compile the work going on this delivery system. Which provide the valuable information related to formulation aspect to achieve gastric retention and discussed the various factors affect and to overcome it

Keywords: Gastric residence time, Floating drug delivery system, Effervescent, Non-effervescent.

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FLOATING DRUG DELIVERY SYSTEM:-

Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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 released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal . Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres[1].

Drug candidates suitable for fdds:-

- Drugs that have narrow absorption window in GIT (e.g. L-DOPA, paminobenzoic acid, furosemide, riboflavin)[2]
- Drugs those are locally active in the stomach (e.g. misroprostol, antacids)[3]
- Drugs those are unstable in the intestinal or colonic environment (e.g. captopril, ranitidine HCl, metronidazole)[4]
- Drugs that disturb normal colonic microbes (e.g. antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin)[5]
- Drugs that exhibit low solubility at high pH values (e.g. diazepam, chlordiazepoxide, verapamil)[6]

Advantages of FDDS:-[6, 7]

1. The Floating systems are advantageous for drugs meant for local action in the stomach.
2. E.g. antacids
3. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
4. The Floating systems are advantageous for drugs absorbed through the stomach.
5. E.g. Ferrous salts, antacids.
6. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents.

7. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

Disadvantages of FDDS:-

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

TYPES OF FLOATING DRUG DELIVERY SYSTEMS:-

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS.

EFFERVESCENT FDDS

Volatile liquid containing system:

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach. [9]

Gas-generating Systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme. [9, 10]

NON-EFFERVESCENT FDDS [11,12]

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in noneffervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol.

The various types of this system are as:

Alginate Beads:

Multi-unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

Hollow Microspheres:

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.

Single Layer Floating Tablets:

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

Bi-layer Floating Tablets:

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

BRIEF DISCUSSION ABOUT BILAYER FLOATING TABLET:

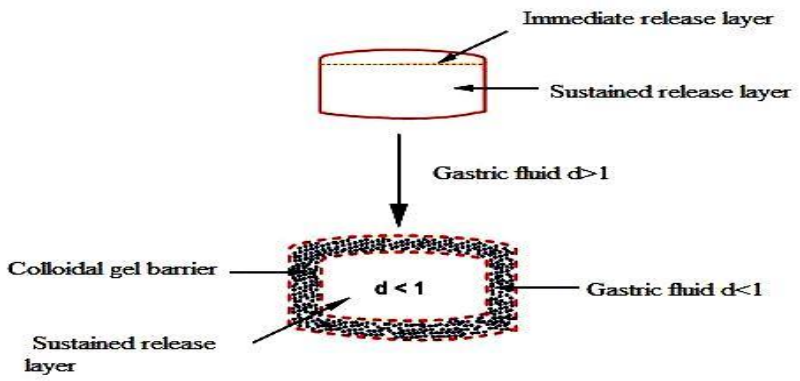

Figure. 1: Floating bilayer Tablet

TYPES OF BILAYER TABLET ON RELEASE PATTERN:-

Immediate release formulation

The release of drug from the conventional tablet dosage form and its absorption from the GIT depends upon two main processes. Firstly, the disintegration of tablet into granules and dissolution of these granules through the GIT into the blood. Disintegration is the rate limiting step in case of highly soluble drugs whereas dissolution is the rate limiting step in case of drugs with low solubility.

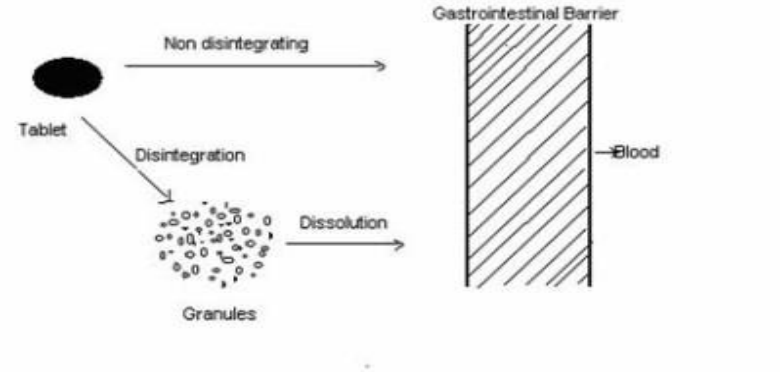

Figure. 2: Rate limiting steps in the absorption of drug from the GIT.

The release of drug from an immediate release dosage form can be achieved by

- Placing the drug in a layer or coating that is sufficiently thin to allow fast penetration by gastrointestinal fluid which then leaches the drug at a rapid rate.
- Incorporating the drug in a mixture that includes a supporting binder or other inert material that dissolves readily in gastrointestinal fluid, releasing the drug as the material dissolves.
- Using a supporting binder or other inert material that rapidly disintegrates into fine particles upon contact with gastrointestinal fluid, with both the binder particles and the drug quickly dispersing into the fluid.

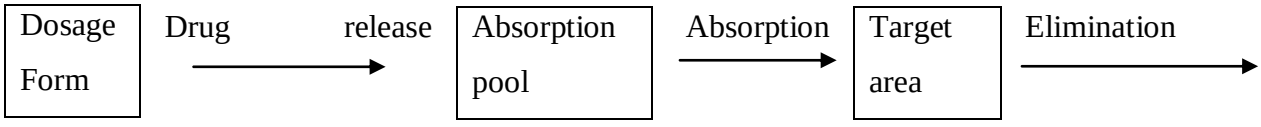

Figure. 3: Kinetic scheme of the release, absorption and elimination of drug from immediate release dosage forms

Conventional dosage forms can be considered to release their active ingredients into an absorption pool immediately. The absorption pool represents a solution of the drug at the site

of absorption, and the terms Kr, Ka and Ke are first-order rate constants for drug release, absorption and overall elimination, respectively. This is illustrated in the following simple kinetic scheme:

MECHANISM OF DISINTEGRANTS:-

1) High swellability

2) Capillary action and high swellability

3) Chemical reaction

The most popular Disintegrants are corn starch, soluble starch etc. which have been well dried and powdered. Starches have great affinity for water and swell when moistened thus facilitating the rupture of the tablet matrix, its disintegration action in tablets is due to capillary action. Spherical shape of starch increases the porosity of tablet thus promoting capillary action. Classification of "Superdisintegrants" may be organized into three classes based on their chemical structure. As shown in Table 1:

Table 1:- Classification of "Superdisintegrants"

Structure Type (NF Name)	Description	Trade Name
Modified starches (Sodium starch glycolate NF)	Sodium carboxy methyl starch, the carboxymethyl groups induced hydrophilicity and cross-linking reduces solubility.	Explotab Primojel
Modified cellulose (Croscarmellose NF)	Sodium carboxy methyl cellulose which has been cross-linked to render the material insoluble.	Ac-Di-Sol Nymcel Solutab
Cross-linkedpolyvinylpyrrolidone (Crospovidone. NF)	Cross-linked polyvinylpyrrolidone, the high molecular weight and cross-linking render the material insoluble in water.	Crospovidone Kollidon Polyplasdone

2. Extended release formulation:-

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in figure 5.

In general, the goal of a extended release dosage forms is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero – order release from the dosage forms. Zero – order release constitute drug release from the

dosage form that is independent of the amount of drug in the delivery system (i.e., a constant release rate). Enteric coated tablets are an example of this type of dosage forms.

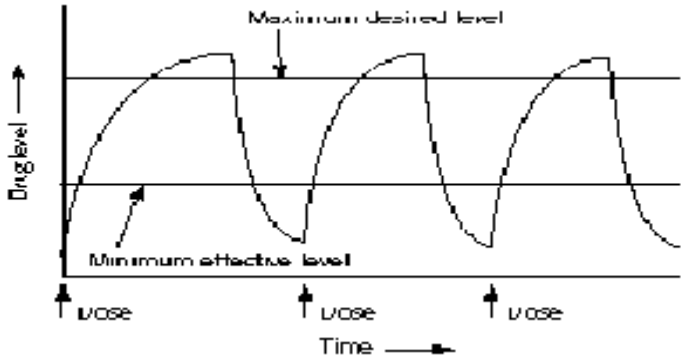

Figure. 4: Drug levels in the blood with Conventional drug delivery systems

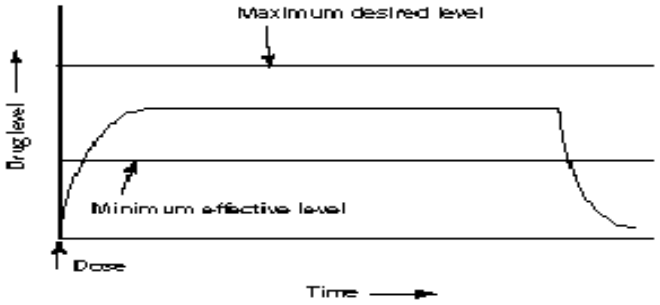

Figure. 5: Drug levels in the blood with extended drug delivery systems.

The delivery of drug at a rate for an extended period can be represented mathematically as;

$$\text{Rate in} = \text{rate out} = K_{elm} \times C_d \times V_d$$

Where, C_d is the desired drug level, V_d is the volume of distribution, and k_{elm} is the rate constant for drug elimination from the body. Often such exacting delivery rates prove to be difficult to achieve by administration routes other than intravenous infusion. Noninvasive routes (e.g.,oral)are obviously preferred.

Table 2: Various Types of Extended Release System

Type of system	Rate-control mechanism
Diffusion controlled Reservoir system Monolithic system	Diffusion through membrane
Water penetration controlled Osmotic system Swelling system	Transport of water through semi permeable membrane Water penetration into glossy polymer
Chemical controlled Monolithic system Pendant system Ion exchange resins	Surface erosion or bulk erosion Hydrolysis of pendent group and diffusion from bulk polymer Exchange of acidic or basic drugs with the ions

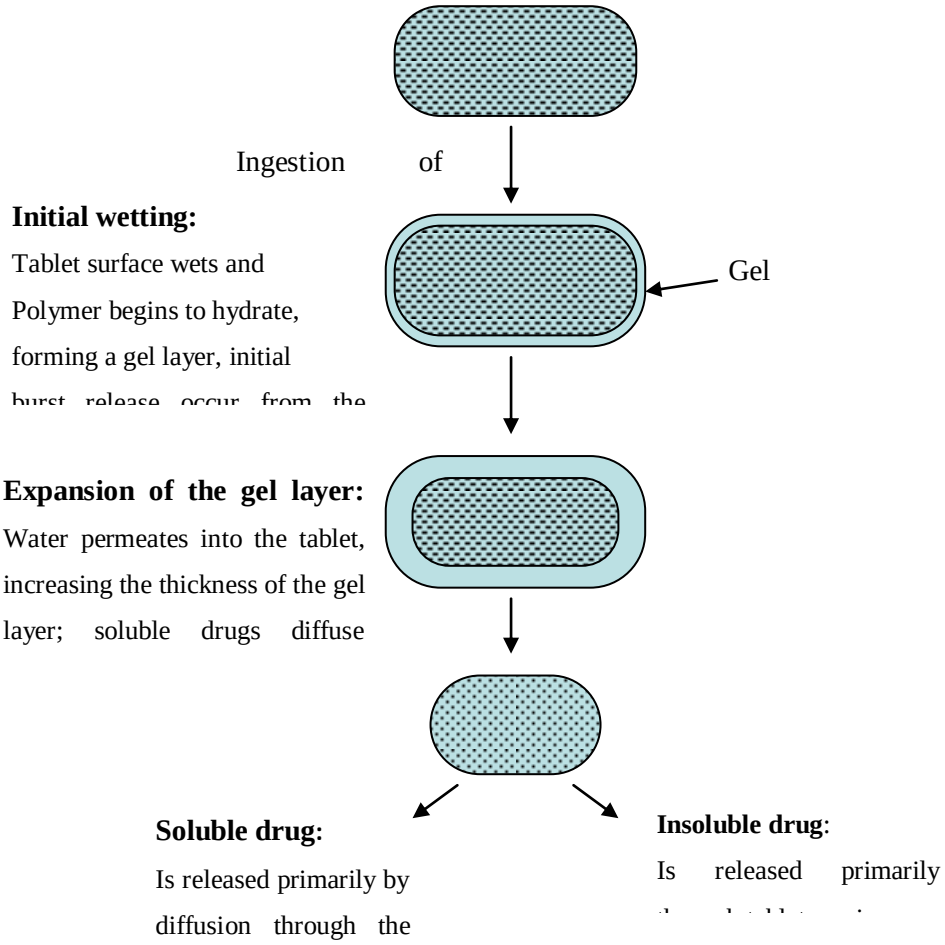

Figure. 6: Drug release from tablet matrix

By varying the coating thickness, or layering concentric sphere of coating material and Drug reservoir material, gives rise to different release times, Producing the repeat action dosage form.

Table 3: Types and mechanisms of Extended release system

Types	Mechanism
Matrix	Diffusion through a matrix or membrane
Reservoir/Membrane	Chemical reaction-erosion or cleavage
Osmotic pumps	Solvent activation

❖ **Mechanism Of Drug Release Through Hydrophilic Polymeric Matrices**[17]

Compressed hydrophilic matrices are commonly used as modified release dosage form for oral administration. These matrices incorporate hydrophilic polymers which swell rapidly, when in contact with water. The release of drug from the polymeric matrix depends upon the rate and extent of penetration of water into the core cavity, the thickness of the gel layer and the dissolution or diffusion of the drug through the swollen polymeric matrices. HPMC is most widely used in swellable matrix controlled systems because it tends to swell rapidly on absorption of water. HPMC being nonionic shows pH independent swelling. HPMC absorbs

water as it enters and passes through the upper digestive tract and substantially undergoes complete gelation (at least 70%). The structure of HPMC is linear and therefore soluble in water. As the preparation continues down the GI tract the cellulose ether dissolves, its surface gradually erodes maintaining a constant release of drug. HPMC when used alone shows an initial burst release. This may be controlled by combination with another polymer.

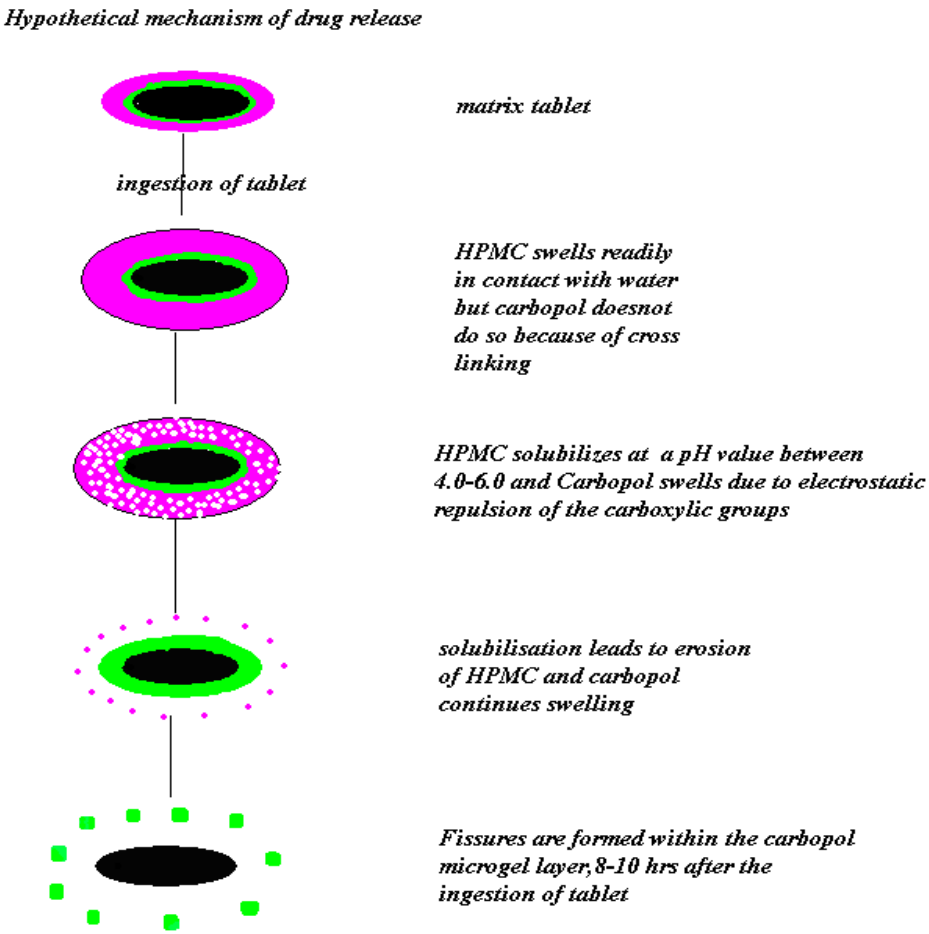

Figure. 7: Hypothetical mechanism of drug release through hydrophilic polymeric matrices.

SELECTION OF POLYMERES:-[19, 20, 21]

A. Gas generating agents

Alkalinizing agents and acidulent

Sodium bicarbonate, Calcium carbonates, Citric acid, Tartaric acid, Adipic acid

Rational behind the selection

Effervescent compound generally use for this purpose. Sodium bicarbonate, calcium carbonate with citric acid and tartaric acid. When these compounds come in contact with the acidic gastric contents, carbon dioxide is liberated and gets entrapped in swelled hydrocolloids, which provide

buoyancy to the dosage forms. Sodium bicarbonate induced CO2 generation in the presence of dissolution medium (0.1 N HCL). The gas generated trapped and protected within the gel, formed by the hydration of polymer, thus decreasing the density of the tablet as the density of the tablet falls below 1, the tablet become buoyant.

Acidulent is used;

since the pH of the stomach is elevated under fed condition (~3.5). Acidulent

(Citric acid, Tartaric acid, Adipic acid) was incorporate in the formulation to provide an acidic medium for sodium bicarbonate.

B. Viscolyzing agent

Sodium alginate, Carbopol 934

Rational behind the selection

They used to increase the viscosity in the system. Carbopol is being used in the controlled release solid dosage formulations since last four decades. The numbers of manufacturers commercializing controlled release tablets using carbomers are increasing considerably in recent period of development. Tablet formulations using Carbopol polymers have demonstrated zero-order and near zero-order release kinetics. These polymers are effective at low concentrations (less than 10%). Still they show extremely rapid and efficient swelling characteristics in both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The Carbopol polymers produce tablets of excellent hardness and low friability. These polymers can be successfully formulated into a variety of different tablet forms, including the traditional swallow able tablets, chewable tablets, buccal tablets, sublingual tablets, effervescent tablets, and suppositories; providing controlled-release properties as well as good binding characteristics. Carbomers show larger dissolution times at lower concentrations than other excipients. Because of these factors

Carbopol polymers have greater extent in formulating dosage forms. Because Carbopol polymers swell rapidly in water and absorb great quantities, to avoid the use of flammable solvents, roller compaction is being used as the method to prepare a new form of Carbopol polymer 71G NF. Carbopol polymer 71G NF is a useful and versatile controlled-release additive for tablet formulations in direct compression.

C. Swelling agent/Gel forming polymer

Hydroxypropylmethylcellulose (HPMC)

Rational behind the selection

Hypermellose powder is stable material, although it is hygroscopic after drying. Solution is stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypermellose

undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point 50-90°C, depending upon grade and concentration of material. Grades which are generally used in floating tablet are, which are highly viscous in nature like HPMC K 100, HPMC K 4, HPMC K 15.

D. Disintegrating agent

Povidone, Polyplasdone XL and XL-10

Rational behind the selection

PVP belongs to a class of compounds known as superdisintegrantes. When they comes in contact with the fluid media they provide the swelling properties to the system they used as highly active explosive agent and as an accelerating agent for disintegration of solid medications. In tabletting, povidone solutions are used as binder in the wet granulation processes.

EVALUATION TECHNIQUES OF BILAYER FLOATING TABLET:-

***In vitro* evaluation of floating tablets**

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

I. Pre-compression parameters

a) Angle of Repose [22]

$$\tan \text{Ø} = h/r$$

$$\text{Ø} = \tan^{-1}(h/r)$$

Where, Ø = angle of repose

h = height of the heap

r = radius of the heap

The relationship between Angle of repose and powder flow is as follows in table

Table 4: Relationship between angle of repose and powder flow

Angle of repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

b) Compressibility Index

Calculated by –

$$\text{Compressibility index (\%)} = \frac{\rho t - \rho o \times 100}{\rho t}$$

Where, **ρo** = Bulk density g/ml002E, **ρt** = Tapped density g/ml.

II) Post-compression parameters:-

Shape of Tablets

Compressed tablets were examined under the magnifying lens for the shape of the tablet.

Tablet Dimensions

Thickness and diameter were measured using a calibrated varniear caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

Hardness[23]

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It was expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability test[22]

The friability of tablets was determined by using Roche Friabilator. It was expressed in percentage (%). Ten tablets were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again

The % friability was then calculated by –

%F = 100 (1-W0/W)

% Friability of tablets less than 1% was considered acceptable.

Tablet Density[24]

Tablet density was an important parameter for floating tablets. The tablet would floats only when its density was less than that of gastric fluid (1.004). The density was determined using Following relationship.

$$V = \pi r^2 h$$

$$d = m/v$$

v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet (g/cc)

m = mass of tablet

Weight Variation Test[22]

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet by U.S. Pharmacopoeia. The following percentage deviation in weight variation was allowed show in table 5.

Table 5: Percentage deviation in weight variation

Average weight of a tablet	Percent deviation
130 mg or less	10 %
>130mg and <324mg	7.5 %
324 mg or more	5 %

Buoyancy / Floating Test

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Swelling Study

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent weight gain, as given by the equation.

$$WU = \frac{(Wt - W0) \times 100}{W0}$$

Wt = Weight of dosage form at time t.

W0 = Initial weight of dosage form.

***In vitro* drug release studies:-**

The test for buoyancy and *in vitro* drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37^{o}C. In practice, floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1 HCl as a testing medium maintained at 37oC. The time required to float the HBS dosage form is noted as floating (or floatation) time. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replenished with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started. A small, loose piece of non reactive material such as not more than a few turns of wire helix may be attached to the dosage units that would otherwise float. However, standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of *in vitro* performance for floating dosage forms [23, 24.]

DRUGS USED IN FDDS[10]

Table 7: List of drugs formulated as a single and multiple unit forms of floating drug delivery system.

Dosages forms	Drugs
Tablets	Acetaminophen, Acetylsalicylic acid, Amoxicillin trihydrate, Ampicillin, Atenolol, Ciprofloxacin, Captopril, Chlorpheniramine maleate, Cinnarizine, Diltiazem, Fluorouracil, Isosorbide mononitrate, Isosorbide dinitrate, Piretanide, Prednisolone, Riboflavin-5'-phosphate, Theophylline, Sotalol, Verapamil HCl.
Capsules	Chlordiazepoxide HCl, Diazepam (Valrelease®), Furosemide, L-Dopa, Misoprostol, Propranolol, Urodeoxycholic acid.
Powders	Several basic drugs.
Granules	Diclofenac sodium, Indomethacin, Prednisolone, Diltiazem.
Microspheres	Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Terfenadine, Tranilast, Verapamil.
Films	Cinnarizine
Liquids	Gaviscon® floating liquid alginate Preparations, Topalkan® aluminum magnesium antacid Preparation.

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