WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Review Article of Floating Drug Delivery System

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ABSTRACT

The practice school is a preliminary step for our project, and I opt for Pharmaceutics as domain. The objective for practice school was to encourage a partnership and intellectual exchange between academic and industry. Floating Drug Delivery system are retained in the stomach and are useful for drugs data poorly soluble or unstable in intestinal fluid . Module one deals with Introduction and GMP and GLP requirements. The second Module illustrated with preformulation, criteria for excipient selection, formulation and method of preparation. The third Module describes the evaluation and stability studies. The fourth Module includes storage, packaging, labelling.

KEYWORD: Floating tablet

INDRODUCTION

Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems (GRDDS). Generally, the drugs which gets easily absorbed in GIT exhibit short halflives and are eliminated quickly from systemic circulation and to achieve a suitable therapeutic activity of such drugs, it is necessary to give the dose frequently. To overcome these side effects, gastro-retentive drug delivery system were developed.

These systems were designed to prolong the residence time of a drug in GIT. Gastric retention can be prolonged by using mucoadhesive size-based and altered density systems. GRDDS continuously release the drug for a prolonged period before it reaches its site of absorption and thereby ensures optimal bioavailability of drugs having a low absorption window.

These systems are developed from the conventional release drugs by improving their bioavailability, therapeutic efficacy, possible reduction of dose and maintaining constant therapeutic levels for prolonged period thus decreasing the fluctuation in therapeutic levels, decreasing drug wastage and lastly improving the solubility of drugs with low solubility of drugs with low solubility at high pH environment such as weakly basic drugs (E.gs:Domperidone, papaverine).

During last few decades, various GRDDS approaches have been developed such as floating systems, high density systems, gastro adhesive systems, inflatable systems.

ADVANTAGES

1. Drugs with narrow absorption window gets delivered in the small intestine.
2. The longer residence time of the dosage form in stomach can be beneficial for local action in upper part of small intestine. eg: Treatment of peptic ulcer
3. Drugs that gets absorbed rapidly upon release in GIT shows improved bioavailability eg:ranitidine, amoxicillin, captopril, ciprofloxacin, cyclosporine etc.
4. The GRDDS improves patient compliance due to once a day therapy by reducing the dosing frequency.
5. It also improves the therapeutic efficacy of drugs.
6. Bioavailability of the drugs is improved due to reduction in p-glycoprotein activity in duodenum

DISADVANTAGES

1. It is not suitable for drugs that posses limited acid solubility. Eg : phenytoin
2. It is not suitable for drugs with unstable acidic environment of stomach. Eg: Erythromycin
3. It is not suitable for drugs that cause irritation and gastric lesion where they are released Slowly . E g : NSAIDS and aspirin.
4. It is not suitable for drugs that selectively gets absorbed in colon. Eg : corticosteroid

FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery system is also called the hydrodynamically balanced system (HBS).Floating oral drug delivery system are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating drug delivery system (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach.

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 fluctuations in plasma drug concentration.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

(A) Effervescent FDDS

1. Gas generating system.
2. Volatile liquid containing system

(B) Non – Effervescent FDDS

1. Colloidal gel barrier system.
2. Microporous compartment system
3. Floating microspheres / micro balloons
4. Alginate floating beads

(C)Raft forming system

ADVANTAGE

1.Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.

2. FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids 3. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response.

3.The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids

DISADVANTAGE

1.Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.

2.Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric empty-ing may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

3.One of the disadvantages of floating system is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.

METHOD OF PREPARATION

NON-EFFERVESCENT SYSTEMS

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming poly1mers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a

bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (1PMC) polyacrylates, polyv1ny! acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

EFFERVESCENT (GAS GENERATING) SYSTEMS

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid). The optimal stoicheometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. In this system carbon dioxide is released and causes the formulation to float in the stomach (Fig. 7.7). Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), and floating system based on ion exchange resin technology etc. Bilayer or multilayer system has also been designed. Drugs and excipients can be formulated independently and the gas generating material can be incorporated in to any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise belween elasticity, plasticity and permeability of the polymers.

1**) PREFORMULATION**

Preformulation may be defined as a stage of the research and development process where the preformulation scientist characterizes the physical, chemical, biopharmaceutical and mechanical properties of a new drug substance, in order to develop stable, safe and effective dosage form.

PREFORMULATION FACTORS:

- pH /pka
- Solubility
- Thermal/heat effect
- Dissociation constant
- Compatibility studies – FTIR/DSC
- Oxidation and reduction
- Particle size

A) IDENTIFICATION AND CHARACTERIZATION METHOD OF DRUG

Physical appearance

- Organoleptic properties of the candidate drug molecule, E.g: colour, odour and taste.
- Bulk characterization. E,g: particle size and surface area, powder flow properties, density, compressibility, crystallinity, polymorphism and hygroscopicity.
- Solubility analysis E.g: ionization constant/ drug pka, partition coefficient, solubilization, thermal effect, common ion effect (Ksp) and dissolution.
- Stability analysis E.g: solution-state stability testing, solid-state stability testing and drug excipient compatibility study.
- Solubility study

Solubility study of a drug was prepared using 10ml of distilled water or any other organic solvent in 25ml volumetric flask. Precaution was taken so that the drug remains in medium in excess. Then by using mechanical shaker, the flask were for 24 hours. The sampling was done 24^{th} and 48^{th} hour. The sample withdrawn (1ml after filtration) was diluted with appropriate medium and was analyzed using UV spectrophotometer.

Melting point determination

Melting point of a drug was determined by taking a small quantity of drug in capillary tube sealed at one end and was placed in Thiel's melting point apparatus and temperature range at which the drug melted was noted. Average triplicate reading were noted.

Determination of λ_{max}

In order to ascertain the wavelength of maximum absorption (λ_{max}) of the drug, different solutions of the drug(10 µg/ml or 20 µg/ml) in organic solvent of 200-380nm against organic solvent as blank.

B) EXCIPIENT-DRUG COMPATIBILITY STUDY

Studied of actual pharmaceutical drug and active excipient suitability represents a major stage in the design or development of the improvement of all dosage forms or drug delivery systems, one of which is the actual pharmaceutical drug or active pharmaceutical ingredient (API). FTIR is another analytical technique used in compatibility assessment based on the same functional group change during drug-excipients interaction. If there is band shift and broadening in the functional groups as compared to spectrum of the pure active drug in the FTIR spectrum, there is an interaction between active drug and excipients. Fourier Transform Infrared Spectroscopy (FT-IR) Compatibility between the active drugs and worked excipients used were studied by using FTIR spectroscopy. The use of FTIR spectroscopy technique allows, demonstrating the subsumption of the different functional groups of re-existing and subsequent molecules by analyzing the prominently changes in the shape and position of the absorbance bands.

Method of estimation of Drug –Excipient Compactibility

Thermal method of analysis

A) Differential scanning colorimetry

DSC curves of pure components are curves obtained from 1:1 physical mixtures .A significant shift in the melting of the components or appearance of a new exo/endothermic peak and/or variation in the corresponding enthalpies of reaction in the physical mixture indicate incompactibility

B) Isothermal microcalorimetry

It allows determination of minute amounts of evolved or absorbed heat.The activity of API,excipient and their mixtures are measured individually in the calorimeter and the thermal activity at a constant temperature is monitored.

C) Hot stage microscopy (HSM)

HSM is a visual thermal analysis technique, which allows efficient monitoring of solid state interactions that could be erroneously interpreted as compactibility by DSC. This technique only requires very small quantity of sample of sample when performing compactibility studies.

C) CRITERIA FOR EXCIPIENT SELECTION

Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API).that have been appropriately evaluated for safety and are intentionally included in a drug delivery system.

EXCIPIENT SELECTION CONSIDERATION

Excipient play an important role in formulating a dosage form. This are the ingredient which allow with active pharmaceutical ingredient make the dosage form. Excipient act as protective agents,Bulking agent and can also be used to improve bioavailability of drugs in some instances.Regardless of why an excipient is selected, they must meet certain criteria in the formulation. These include the following:

A) They must be nontoxic and acceptable to the regulatory agents in all countries where the product is to be marketed.

B) They must be commercially bioavailable in an acceptable grade in all countries where the product is to be manufactured.

C) Their cost must be acceptably low.

D) They must be physiologically inert.

E) They must be physically and chemically stable by themselves and in combination with the drugs and other tablet components.

F) They must be free of any unacceptable microbiological ‘load’.

G) They must be color compatible (not produce any off color appearance).

H) If the drug product is classified as a food, (certain vitamin products), the diluents and other excipients must be approved direct food additives.

I) They must have no deleterious effect on the bioavailability of the drugs in the product.

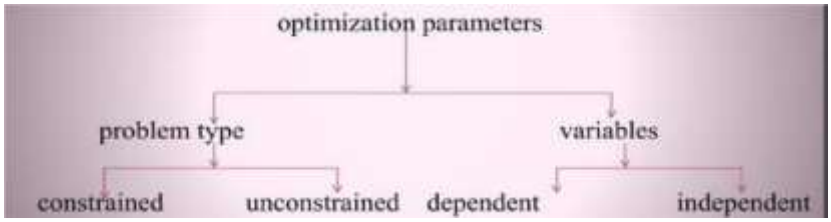
Formulators must also consider following physicochemical properties.

- Stability and compatibility issue.
- Pharmacokinetic attributes.
- Permeation characteristics.
- Segmented absorption behavior.
- Drug delivery platform.

D) FORMULATION OPTIMIZATION TECHNIQUES

Optimization term is defined as "to make perfect" which means to make the perfect anything using different techniques and processes. Optimization techniques are used in the different formulations of drugs which help to make good products.It involves in the various form of drug product and their process. Optimization technique are used in the finding solution of a slew of issues relating to the pharmaceutical process and product such as new drug development selection of excipients, formulation, manufacturing and other pharmacy-related problems. Due to the optimization technique we examine the various problems that occur during research.

Optimization technique are helpful to make easy the process and formulation of pharmaceutical products and processes .It provides diverse design quality of formulation and experiment design, as well as systemic and mannered strategies and performance, which are investigated by changing the experimental variable to assess the effect on the specific response.



(I) Unconstrained

In this system, the restriction is not based on physical limitations. For example, one might want to make an uncoated tablet possible for a specific pharmaceutical system.

(II) Constrained

In this system the restriction is based on physical limitations. As a result, the constrained challenge is to make the uncoated tablet but is should not be Disintegrate in the stomach.

(III) Independent variables

This type of variable are come under the supervision of a formulator like the force of compression, lubrication level, binder level etc.

(IV) Dependent variables

The formulator has no direct control over this type of variable. They are reliant on an unrelated variable. These are responses like hardness, flow property, and friability, among others

TABLET FORMULATION

Tablet Ingredients/ Excipients

In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients

Different excipients are:

	EXCIPIENT	**USE**	**EXAMPLES**
1	Diluent	Used to increase weight and improve content uniformity	Anhydrous lactose ,lactose monohydrate
2		Agents used to impart cohesive qualities to the powder material	Cellulose, methyl cellulose
3	Disintegrants	Used to promote the break-up of the tablet into smaller fragments in an aqueous environment	Carboxymethylcellulose (CMC), Hydroxypropylmethylcellulose(HPMC)
4	Lubricants	Lubricants reduce the friction between the tablet and the die metal surface	Stearic acid ,magnesium stearate
5	Glidants	Glidants are intented to promote flow of granules or powder material by reducing the friction between the particle	Corn starch, talc, silica
6	Colouring agent	Used to impart appearance to the pharmaceutical dosage form	Red ferric oxide, Titanium oxide
7	Flavouring agent	Give a tablet an additional taste or flavour	Grape, Cherry, Honey, Raspberry
8	Sweetening agent	Used to impart sweetness to the product	Sucrose, Fructose, molasses

EVALUATION OF FLOATING DRUG DELIVERY SYSTEM

1. Hardness

Tablet hardness and strength are the essential to see that the tablet can with the shock and stress during manufacturing packing and transportation, and while handled by the patient. To test the hardness of the tablet Monsanto tester, Strong-cobb tester, the Pfizer tester, the Erweka tester, the Schleuniger tester are used.

2. Friability

Friability is the tested for a tablet to see weather the tablet is stable to abrasion or not, it is tested by using Roche friabilator. This is made up of a plastic drum fixed with a machine which rotated at 25 rpm for 100 revolutions. And then the twenty tablets which were weighed prior to the test are taken out of the drum and cleaned with a cloth and weighed once again, the weight variation must not be less than 0.5 to 1.0% for an conventional tablet.

3. Density of the tablet: Density of the tablet is a critical parameter for floating tablets. The tablet would float only when its density is less than that of gastric fluid (1.004). The density is determined utilizing following relationship.

$$V = r2\ h\ d$$

Where,

v = volume of tablet (cc)

r = radius of tablet (cm)

h = crown thickness of tablet

d = mass/volume

4. Floating test: The time between presentation of dose structure and its buoyancy on the reproduced gastric fluid and the time during which the dose structure remain were estimated. The time taken for dose structure to rise on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and all out term of time by which dose structure remain is called Total Floating Time (TFT)

5. In Vitro Methods

1) Floating lag time and floating time:

The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1 N HCl maintained at 37 0C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 N HCl as dissolution medium at 37 0C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. The system to check continuous floating behaviour contains a stainless steel basket connected to a metal string and suspended from a Sartorius electronic balance. A lotus- spread sheet could automatically pick up the reading on the balances. Test medium used in floating kinetics measurements was 900 ml simulated gastric fluid (pH 1.2) maintained at 37°C, data was collected at 30 sec interval; baseline was recorded and subtracted from each measurement

2. Swelling index

The prepared tablets were placed in a glass containing 200ml oh 0.1 N HCL at 37°C. The percentage of swelling at different time interval was calculated by the following equation.

$$(\mathbf{SI}) = (\mathbf{Wt\text{-}Wo})/\mathbf{WoX100}$$

Where,

SI is welling index

Wt is weight of tablet at time t

wo is weight of the dry tablet before placing in the glass.

3. Dissolution study

In vitro drug release of the formulation was carried out using USP dissolution apparatus type I paddle type under sink condition with rotating speed of 50 rpm and at temperature of37 ± withdrawn 0.5 °C. The dissolution medium used was 900ml 0.1NHCl. The samples were at pre determined time intervals for period of 6 hours and replaced with the fresh medium. suitably diluted and were analyzed using UV/Visible spectrophotometer.

6.Invivo methods 1) X-Ray method

X-Ray is a very popular evaluation parameter for floating dosage form now a day.54 It helps to locate dosage form in the g.i.t. and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio opaque material into a solid dosage form enables it to be visualized by Xrays51.

2) Gastroscopy

It comprises of peroral endoscopy, used with a fibre optic and video systems. It is suggested that gastroscopy may be used to inspect visually the effect of prolonged stay in stomach. Alternatively, FDDS may be drawn out of the stomach for more detailed evaluation.

STABILITY STUDIES

Stability studies of pharmaceutical products may be expressed as the time during which the pharmaceutical products retain its physical, chemical, microbiological, pharmacokinetic properties and characteristics throughout the shelf life from the time of manufacture. Shelf life of the product can be defined as the substance reduces to 90% of its original concentration.

TYPES OF STABILITY STUDIES ON DRUG SUBSTANCES

Physical stability

The original physical properties such as appearance, colour, dissolution, palatability, suspendability are retained. The physical stability may affect the uniformity and release rate, hence it is important for the efficacy and safety of the product.

Chemical stability

It is the tendency to resist its change or decomposition due to the reactions that occur due to air, atmosphere, temperature, etc.

Microbiological stability

The microbiological stability of the drugs is the tendency to resistance to the sterility and microbial growth. The antimicrobial agents used in the preparation retain the effectiveness within specified limits. This microbiological instability could be hazardous to the sterile drug product.

Therapeutic stability

The therapeutic effect (Drug Action) remains unchanged.

Toxicological stability

Toxicological stability has no significant increase in the toxicity occurs.

STABILITY TESTING METHODS

Stability testing is a procedure performed for all the pharmaceutical products at various stages of the product development.

1.Real-time stability testing

Real-time stability testing is normally performed for a long duration of time to allow significant degradation of the product under the storage conditions recommended. The period of time for the test of the product depends on the stability of the product which clearly tells that the product is not degraded or decomposed for a long time.

2.Accelerated stability testing

This type of stability testing is done at higher temperatures and that decomposition the product is determined. The information is used to predict the shelf life or used to compare the relative stability of alternative formulations.

The accelerated stability studies are easily predicted by the Arrhenius equation

$$K = Ae^{-Ea/RT} \text{ Log where}$$

K= Specific rate constant

A= Frequency factor or Arrhenius factor

Ea= Energy of activation

R= Real gas constant 4.184 j/mol. k

T= Absolute temperature

In this method the drugs are stored at different temperatures such as 40°C, 60°C, 70°C, 80°C, 100°C etc.

3.Retained sample stability testing

These studies are to be done at room temperature and at refrigerator temperatures.

In this type of testing, the stability is done by selecting one batch for a year. If the number of samples exceeds more than 50 then they are divided into two batches. The samples stability studies help to predict the shelf life. The maximum shelf life of every product predicted could be 5 years which is conventional to the test samples at 3, 6. 9, 12, 18, 24, 36, 48 and 60 months.

This method of testing is also known as constant interval method

4.Cyclic temperature stress testing

This method is not so much used to the sampling of the products. In this method, cyclic temperature stress tests are designed knowledge of the product so as to mimic likely conditions in the market place storage. In this testing the sampling is considered to be conducted by a cycle of 24 hours which is known as the rhythm of the earth is 24 hours.

PACKAGING AND LABELLING OF TABLETS

PACKAGING

A Pharmaceutical Package container is an article or device which contains the Pharmaceutical Product and the container may or may not in direct contact with the product.

TYPES PF PACKAGES

Primary Packaging

Primary packaging are those package which are in direct contact with the Pharmaceutical formulation. The main aim of primary package is to protect the formulation from environmental, chemical, mechanical and/or other hazards.

Secondary Packaging

The package external to Primary package is known secondary package. This package provide additional protection during warehousing and also provide information about drug product for e.g Leaflets.

Tertiary packaging

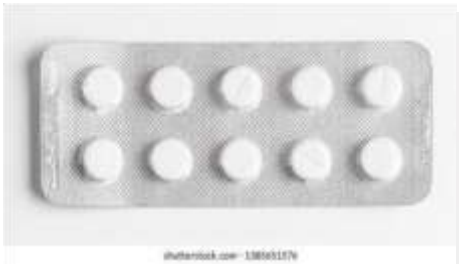
It is outer package of secondary packaging & prevents damage to the products. It is used for bulk handling and shipping. Examples: Barrel, crate, container, pallets, slip sheet.

TYPES OF PACKAGING MACHINES

- Strip paching machine
- Blister packaging machine
- Aluminium foil packaging machine
- Automatic pouch packaging machine
- Vertically tablet packing machine
- Economically tablet packaging equipment
- Fill and sealing machine

TYPES OF PACKAGING FOR TABLETS

- **Strip packing:**It is unit dose packaging in which a pharmaceutical product is enclosed between two webs of heat-sealed flexible film.
- **Blister packaging:**Blister packaging is a type of packaging produced by heating a sheet of plastic and molding it into shape to form a bubble or pocket the blister that completely covers the product.



LABELLING

LABEL:

Label means a display of written,printed or graphic matter upon immediate container or the wrapper of a drug package

LEGAL REQUIRMENTS OF A LABEL

- The name of preparation ✓ Strength and dosage form.
- Quantity.
- Instructions for the use.
- Precautions & warnings.
- Registration number.
- Batch number.
- Manufacturing & Expiry date.
- Price
- The name and address of pharmaceutical industry

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- STABILITY STUDIES OF PHARMACEUTICAL PRODUCTS Sneha Aashigari, Ramya Goud G., Sneha S., Vykuntam U. and Naga Raju Potnuri
- PHARMACEUTICAL PACKAGING TECHNOLOGY: A BRIEF OUTLINE Pratik Swarup Das*, Puja Saha, Krishan and Rumpa Das