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Floating Microparticulate System: An Approcah for Gastroretentive Drug Delivery

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ABSTRACT:-*Sustained release systems are designed to release the drug in-vivo with prediction so as prolong the release in order to increase its efficacy and bioavailability of drugs. Floating drug delivery systems (FDDSs) is one the approach which is expected to remain buoyant in a lasting way upon the gastric contents. The various buoyant preparations include microparticles, hollow microspheres, powders, granules, tablets, capsules, pills and laminated films. Floating microparticles are gastro-retentive floating drug delivery systems based on non-effervescent approach. Floating microparticles are especially fast attention due to their wide applicability in the targeting of drug to the stomach. These floating microparticles have the advantage that they remain buoyant and distributed uniformly over the gastric fluid to avoid the vagaries of gastric emptying and release the drug for prolonged period of time. A sustain release system with extended residence time in the stomach can be of great practical importance for drugs with an absorption window in the upper small intestine. The main limitations are attributed to the inter- and intra-subject variability of gastro-intestinal (GI) transit time and the non-uniformity of drug absorption throughout the alimentary canal. Multiparticulate low-density particulate particles can successfully prolong the gastric retention time of drug.*

Keywords: *Floating microparticles, sustain release system, buoyant, Gastric retention time*

1. INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug at proper site in the body and then maintain the desired drug concentration.[1]The oral route is the most promising route of drug delivery. It's used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance.[2]Every patient would always like to have an ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and dosage form must release active drug directly at the site of action.

Controlled-release drug delivery systems provide drug release at a predetermined,

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Volume 05 Issue 20
September 2018

predictable, and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period.[3, 4]

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time by using gastro-retentive dosage forms (GRDFs). It remains in the gastric region for several hours and hence prolongs the gastric residence time of drug. It has several advantages over immediate release dosage form including the minimization of fluctuations in drug concentration in plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduce the side effect, reduction of total dose administered and reduction of administration frequency leading to improved patient compliances.[5,6]

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting the main goal of drug delivery systems is to achieve desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period. The pointing of the goal is towards the two main aspects regarding drug delivery, namely spatial placement and temporal delivery of a drug. Spatial placement means targeting a drug to a specific organ or a tissue while temporal delivery refers to controlling the rate of drug delivery to that specific organ or a tissue. An appropriately designed sustained or controlled release drug delivery system can be a solution towards solving these problems. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.[7, 8]

1.1 Basic gastro-intestinal tract physiology:-

The GI tract is basically a tube about nine meters long that runs through the middle of the body from the mouth to the anus. The wall of the GI tract has the same general structure throughout most of its length, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. Anatomically the stomach is divided into 3 regions: fundus, body and antrum (pylorus) [9] (**Figure 1**). Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50 ml and contains a small amount of gastric fluid and air. Gastric emptying occurs during fasting as well as

e-ISSN: 2348-6848
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Volume 05 Issue 20
September 2018

fed states. The GI tract is in a state of continuous motility consisting of two modes: - (i) inter-digestive motility pattern and (ii) digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectriccycle (MMC) and is organized in cycles of activity and quiescence[10]. Each cycle lasts 90–120minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases.[11]

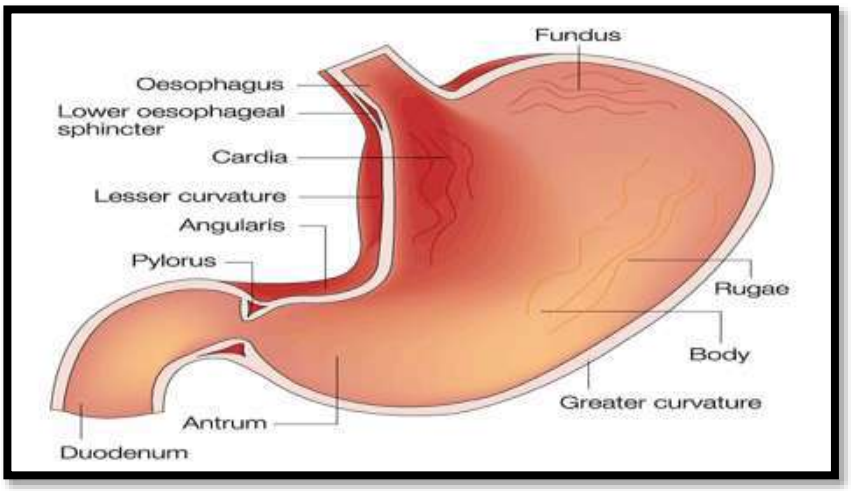


Figure no.1: Anatomy of stomach

1.2Gastro-intestinal motility pattern:-

The various phases are as below:

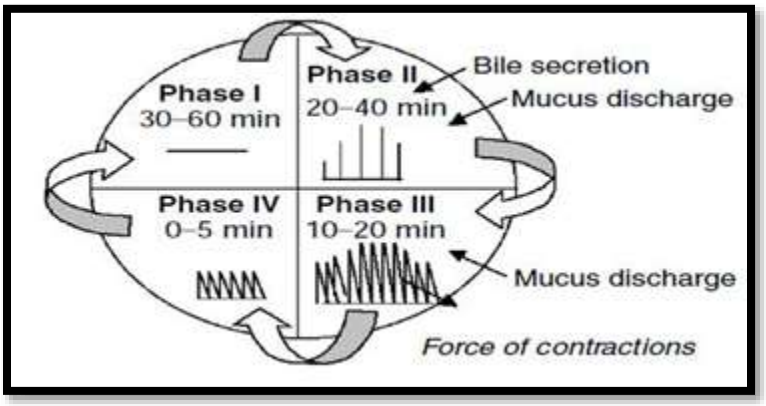
1. Phase I (basal phase)-Period of no contraction (30-60 minutes),

2. Phase II (preburst phase)-Period of intermittent contractions (20-40 minutes),

3. Phase III (burst phase)-Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave; includes intense and regular contractions for short period. It is due to this wave that all the un-digested material is swept out of the stomach down to the small intestine (10-20 minutes),

4. Phase IV-Period of transition between phase III and phase I (0-5 minutes).[12]

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 20
September 2018



Figureno.2: Gastro-Intestinal Motility Pattern

1.3Approaches for the gastric retention:-

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include:-

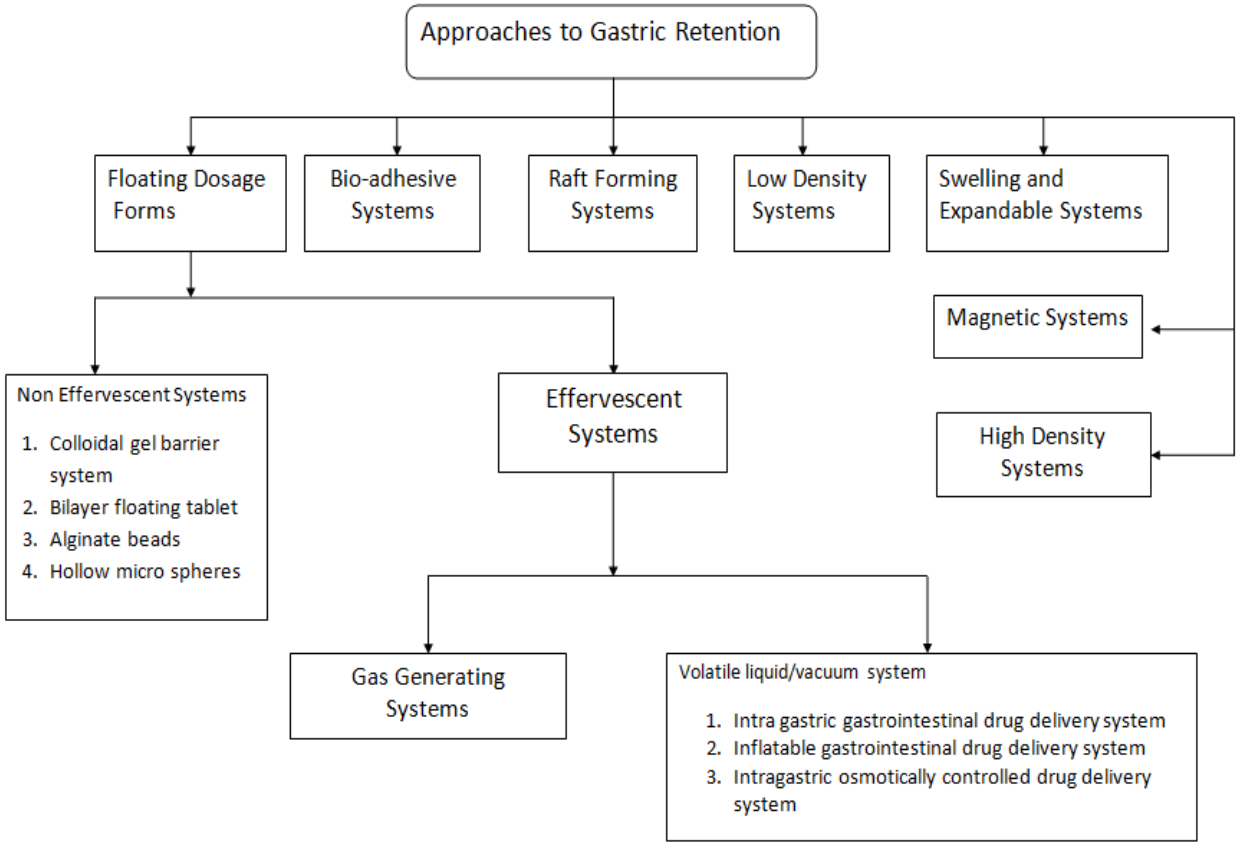


Figure no.3: Approaches to gastric retention

1.3.1. Floating Systems:-

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, on-effervescent and effervescent systems.[13]

1.3.2. Bio/Muco-adhesive Systems:-

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mainland serve as a potential means of extending the GRT of drug delivery system (DDS) in the Stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.[14]

The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are:-

1) The wetting theory.
2) The diffusion theory.
3) The absorption theory.
4) The electron theory.

Binding of polymers to the mucin/epithelial surface can be divided into three categories:-

a. Hydration-mediated adhesion.
b. Bonding-mediated adhesion.
c. Receptor-mediated adhesion.[14, 15]

1.3.3. Swelling and Expanding Systems:-

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as “plug type system”, since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.[16]

1.3.4. High Density Systems:-

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 20
September 2018

These systems with a density of about 3 g/cm3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium18.sulphate, zinc oxide, titanium dioxide, iron powder etc.[17]

1.3.5. Incorporation of Passage Delaying Food Agents:-

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C10-C14.[18]

1.3.6. Ion Exchange Resins:-

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.[19]

1.3.7. Osmotic Regulated Systems:-

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components-drug reservoir compartment and osmotically active compartment.[20]

1.4. Needs for gastric retention:-

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or are degraded by the alkaline pH they encounters at the lower part of GIT.
- Drug that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain condition.

- Particularly useful for the treatment of peptic ulcers caused by H. Pylori infection. [21]

1.5Drugs unsuitable for GRDDS:-

Drug which are unsuitable for GRDDS are as follows-

1. Drug that have very limited acid solubility.e.g. phenytoin etc.
2. Drug that suffer instability in the gastric environment e.g. erythromycin etc.
3. Drug intended for selective release in the colon, e.g. 5-amino salicylic acid corticosteroids etc.[22]

1.6 Rationale for the use of GRDDS:-

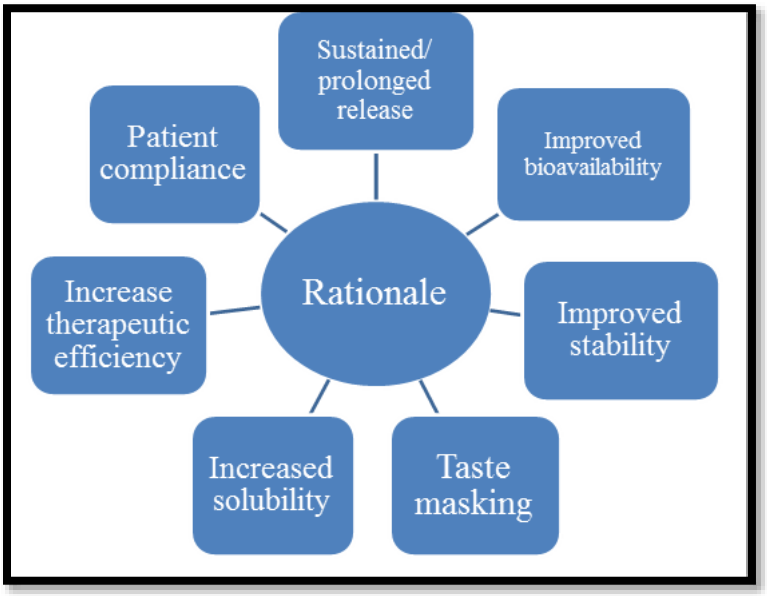


Figure no.4: Rationale for the use of GRDDS

2. FLOATING DRUG DELIVERY SYSTEM:-

The Concept of Floating Drug Delivery system was first described by Davis in 1968, when Davis discovered a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicinal pills.

2.1. Definition-Floating system or dynamically controlled system are low-density systems that have sufficiently 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. This result in an increased gastric retention time and a better control of the fluctuation in plasma drug concentration. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow microsphers.[23]

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 20
September 2018

While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system and the residual system is emptied from the stomach. This results in an increased Gastric Residence Time (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. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW). The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra-gastric buoyancy capability variations.[24]

F=F buoyancy-F gravity= (Df-Ds)/ gv

Where, RW/ F= is total vertical force, Df= is fluid density,

Ds= is object density, V = is volume, and g = is acceleration due to gravity.

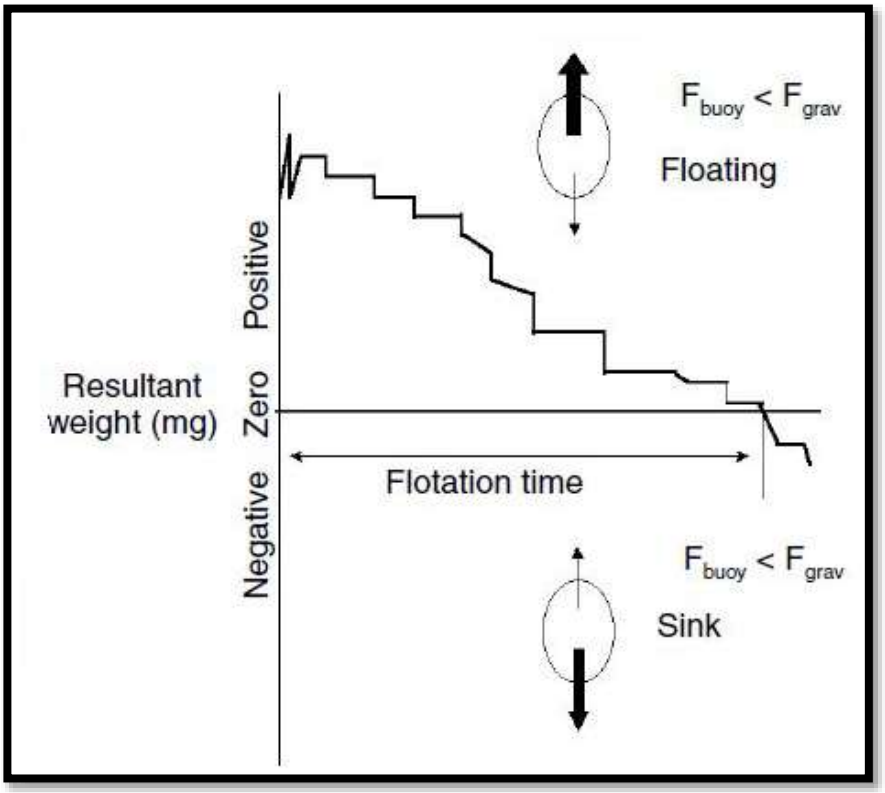


Figure no.5: Effect of resultant weight during buoyancy on the floating tendency of FDDS

2.2. Suitable drug candidates for floating drug delivery systems:-

Sustained release in the stomach is useful as therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, where absorption occurs and contact time is limited, for example, material passes through the small intestine in as little as 1-3 hr as shown **(Figure no.6 (a) & (b)**

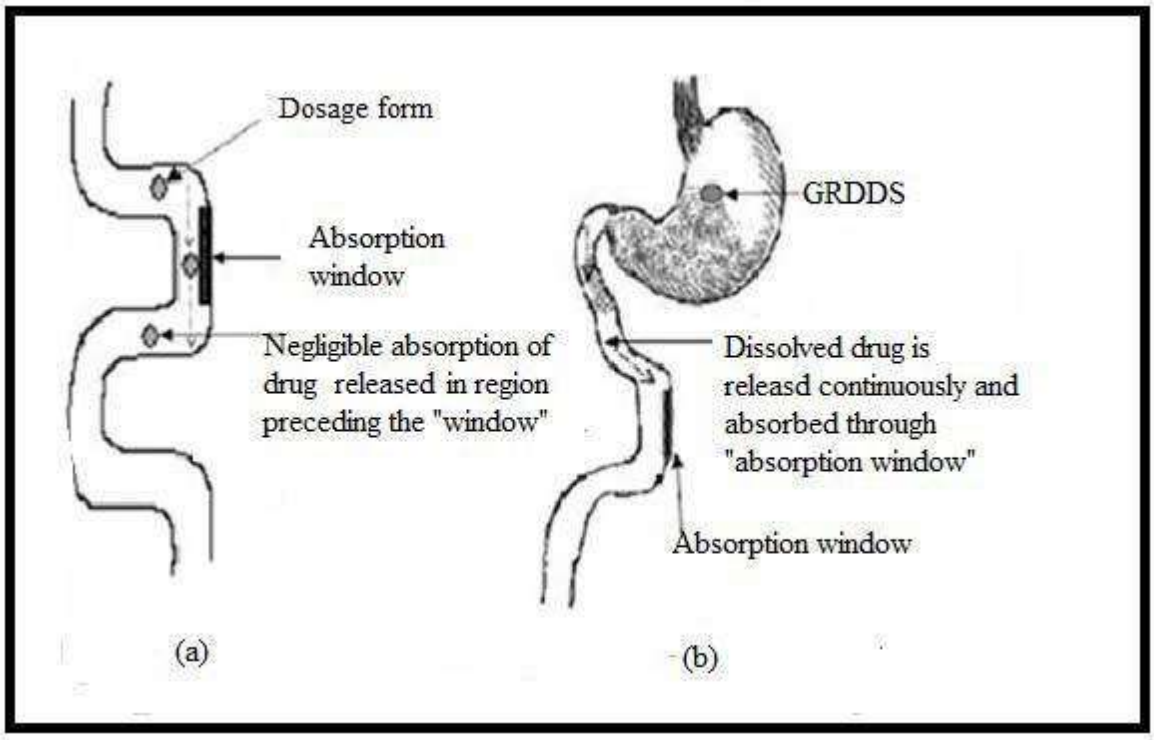


Figure no.6: Drug absorption in case of (a) conventional dosage forms (b) Gastro retentive drug delivery systems

In general, appropriate candidates for floating drug delivery system are the molecules that have Poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.[25]

1. Drugs with narrow absorption window in GI tract, e.g., Para amino benzoic acid, furosemide, Riboflavin in a vitamin deficiency and Levodopa.

2. Drugs which are primarily absorbed from stomach and upper part of GIT, e.g., Calcium

Supplements, Chlordiazepoxide and Scinnarazine.

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 20
September 2018

3. Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.

4. Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.

5. Drugs that disturb normal colonic bacteria, e.g. Amoxicillin trihydrate.

3. TYPES OF FLOATING DRUG DELIVERY SYSTEM:-

FDDS can be divided into two systems: [64]

3.1. Effervescent systems:-

3.2. Non-effervescent systems:-

3.1. Effervescent Systems:-

3.1.1. Volatile liquid containing systems:

3.1.1. a.Intragastric floating gastrointestinal drug delivery 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 Inflatationof the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, 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.[26]

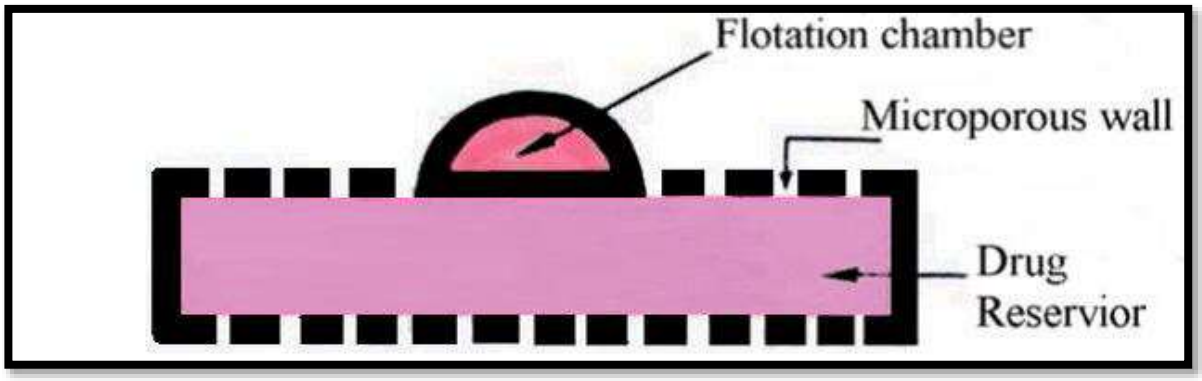


Figure no.7: Intra gastric floating gastrointestinal drug delivery device

3.1.1. b.Inflatable gastrointestinal delivery systems:-

In these system an inflatable chamber is incorporated, which contains liquids ether is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsuie. After oral administration, the capsule dissolves to release the drug reservoir together with the inflates and retains the

drug reservoir compartment released from the reservoir into the gastric fluid.[27]

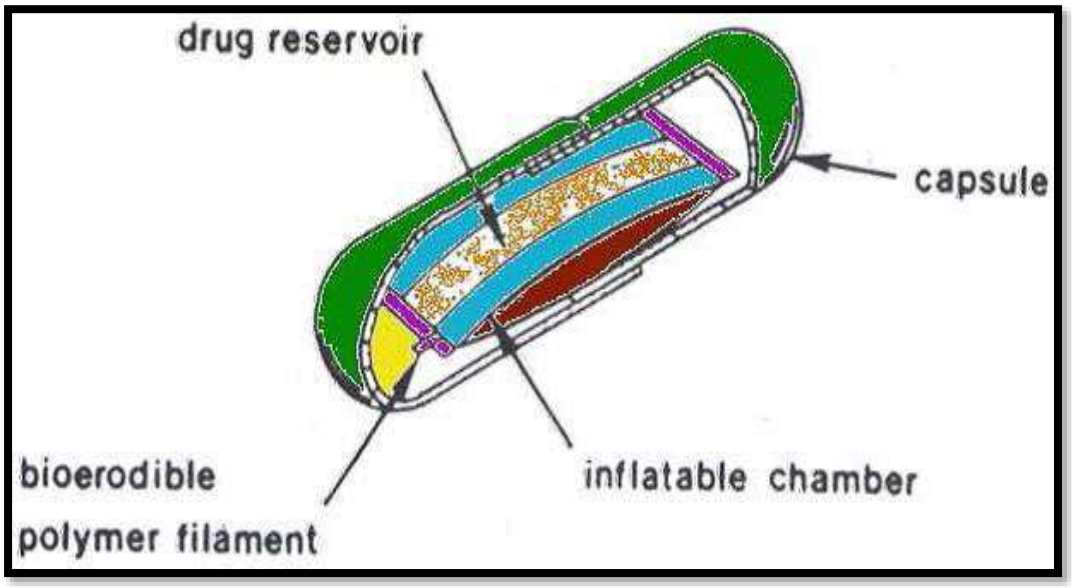


Figure no.8: Inflatable gastrointestinal delivery systems

3.1.1. c.Intragastricosmotically controlled drug delivery systems:-

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating Support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice [1].The floating support is also made to contain a bioerodible plug

that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.[28, 29] **(Figure9).**

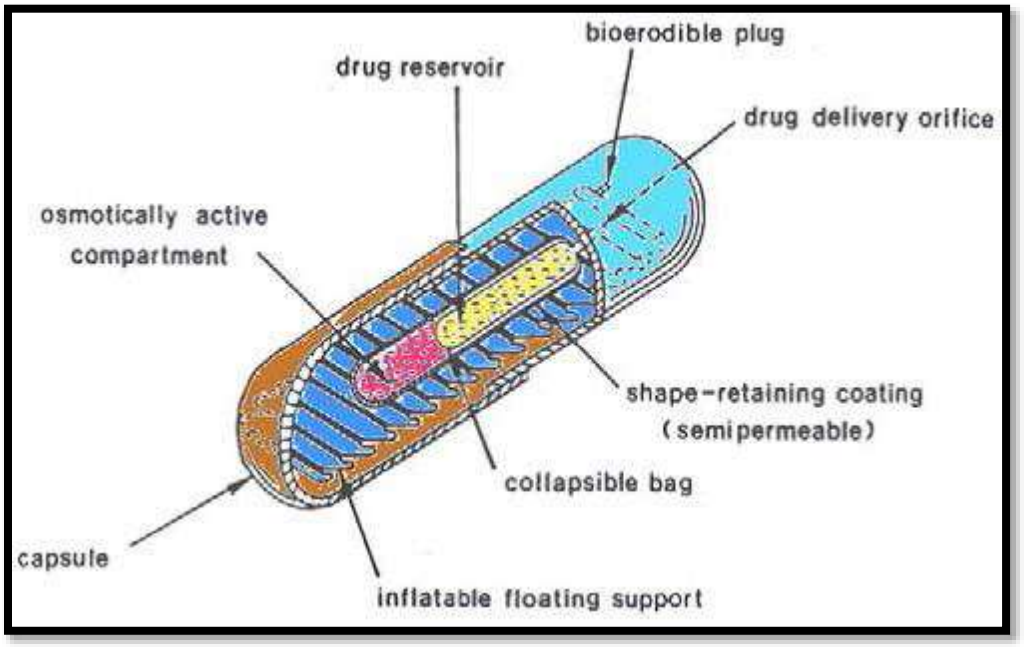


Figure no.9: Intragastricosmotically controlled drug delivery system

3.1.2. 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 chime [17, 18.]

These buoyant systems can be prepared by using swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach. Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 20
September 2018

that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc[30, 31].

3.1.2.a.Intra gastric single layer floating tablets or Hydrodynamically Balanced System (HBS):-

These are formulated by intimately mixing the co_2 generating agents and the drug within the matrix tablet**.** These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuation in plasma drug concentration.

3.1.2. b.Intra gastric bilayered floating tablets:-

These are also compressed tablets as shown in **Figure (10)** and contain two layers i.e. (i) Immediate release layer; ii) sustained release layer.

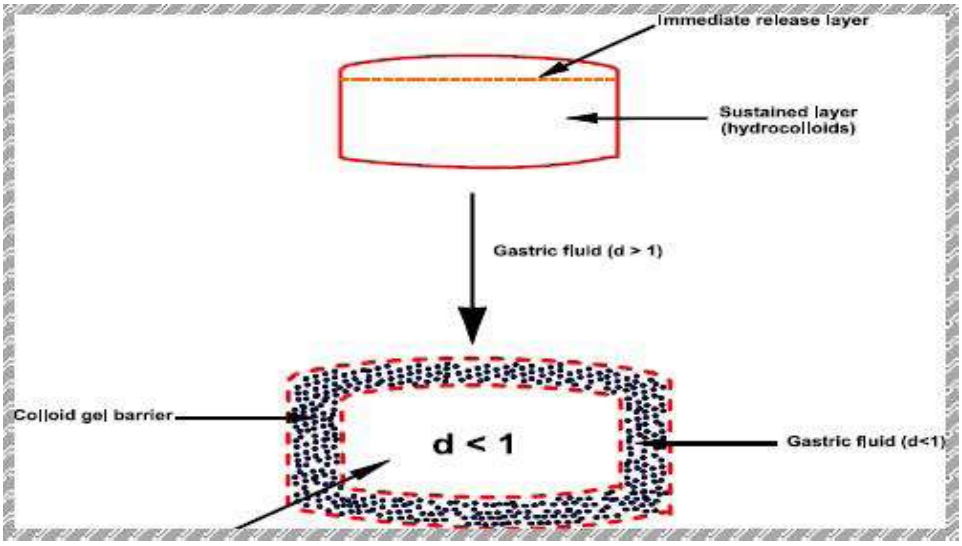


Figure no.10: Intra gastric bilayer floating tablet

3.1.2.c.Multiple Unit type floating pills:-

These systems consist of sustained release pill as ‘seeds’surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swrllable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density **(Figure 11 and 12)**

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 20
September 2018

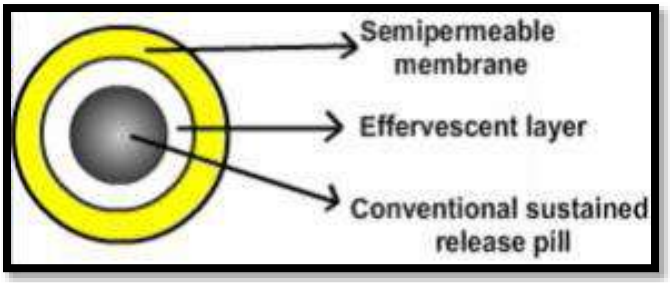


Figure no.11: Multiple Units of Oral FDDS

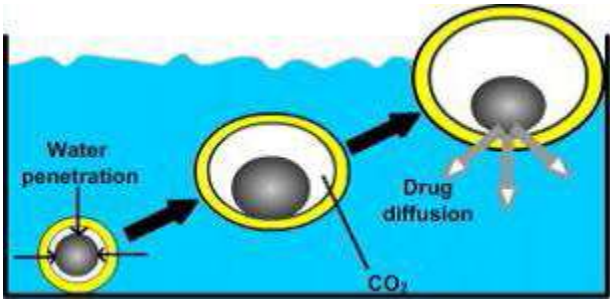


Figure no.12: Working Principle of Effervescent FDDS

3.2. Non-Effervescent Systems:-

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which Swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these system include gel forming or highly swrllable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polymethacrylate, polyacryalate, polystyrene as well as bioadhesive polymer such as chitosan, hydroxypropyl methyl cellulose (HPMC), carbopol ,sodium alginate, polyvinal acetate, agar, polyethylene oxide, calcium chloride.[32]

This system can be further divided into four sub-types:-

3.2.1. Colloidal gel barrier systems:-

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 20
September 2018

Hydro-dynamically balanced system (HBS) was first design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids e.g. HEC, HPMC, NaCMC, Polysaccharides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsules. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.

3.2.2. Microporouscompartment System:-

This technology is based on the encapsulation of drug reservoir inside a micro porous compartment compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric Mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

3.2.3. Alginate beads:-

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at - 40° for 24 h, leading to the formation of porous system, which can maintain a floating force over 12 h.[30, 31]

3.2.4. Hollow microspheres:-

Hollow microspheres (microballons), are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As, the system floats over gastric contents, the drug is resulting in increased gastric retention with reduced fluctuation in plasma drug concentration.[33]

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 20
September 2018

4. FLOATING MICROSPHERES:-

4.1. Definition- Floating microsphere can be defined as solid, approximately spherical particle ranging in size from 1 to 1000 um. The microspheres characteristically free flowing powder consisting of protein or synthetic polymers which are biodegradable in nature. Microspheres are small in size and therefore have large surface to volume ratio.[31-33] they are gastro-retentive floating drug delivery systems based on effervescent approach. and remain buoyant over gastric contents and for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.[2]

4.2. Mechanism of flotation of microspheres:-

While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system and the residual system is emptied from the stomach. This results in an increased Gastric Residence Time (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. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW). The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intra-gastric buoyancy capability variations.[24]

F=F buoyancy-F gravity= (Df-Ds)/ gv

Where, RW/ F= is total vertical force, Df= is fluid density,

Ds= is object density, V = is volume, and g = is acceleration due to gravity.

5.ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM:-

Floating drug delivery systems have numerous advantages listed below:

1. These systems are particularly advantageous for drugs that are specifically absorbed from Stomach or the proximal part of the small intestine, e.g. riboflavin and furosemide.

2. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.

3. The fluctuations in plasma drug concentration are minimized, and concentration--dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

4. Delivery of drugs for local action in the stomach.

5. The efficacy of the medicaments administered utilizing the sustained release principle of

Floating formulation has been found to be independent of the site of particular medicaments.

6. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.

7. Complete absorption of the drug from the floating dosage form is expected even at the alkaline pH of the intestine. The dissolution of the drug in gastric fluid occurs and then the dissolved drug is available for absorption in the small intestine after emptying of the stomach contents.

8. Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

9. Superior to single unit floating dosage forms such as microspheres releases drug uniformly and there is no risk of dose dumping.[30, 34.]

6. DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM:-

Following are the disadvantages of FDDS includes.

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

2. A high level of fluid in the stomach is required for drug delivery to float and work efficiently.

3. Drugs such as Nifedipine, which under goes first pass metabolism may not be desirable for the Preparation of these types of systems.

4. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.[12, 34]

7. MECHANISM OF DRUG RELEASE FROM THE MICROSPHERES:-

The mechanism of drug release from multiparticulates can occur in the following ways:

7.1. Diffusion: On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior[35].

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 20
September 2018

7.2. Erosion: Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

7.3. Osmosis: In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating[36].

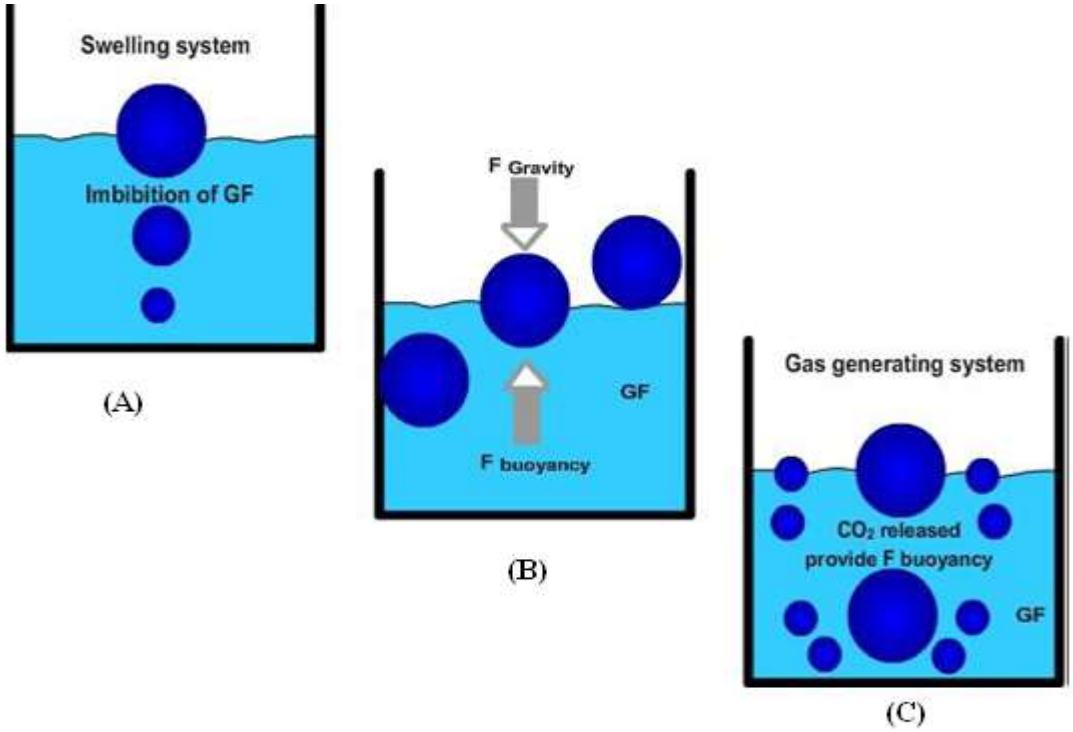


Figure no.13: Mechanism of floating systems (A) Swelling system (C) Gas generating System Formulation aspects

The design of novel controlled release dosage forms should take into account three important Criteria, viz., drug, delivery, and destination. The various aspects which have to be considered while formulating FDDS (floating microspheres in particular) [19,37]are;

a) Drug: the characteristics of the drugs which can be formulated as FDDS have already been discussed.

b) Polymer: low density polymers which have bulk density less than one, can be used for

Enhancing the buoyancy of the formulation is used in formulating FDDS.

c) Solvent: solvent system should be so chosen that it should yield good microspheres.

Generally, water miscible organic solvents are chosen. It should have good

volatile properties, so that it should easily come out from the emulsion leaving hollow microspheres. e.g. ethanol, dichloromethane (DCM), acetonitrile, acetone, isopropyl alcohol (IPA), dimethyl formamide(DMF).

d) Processing medium: the processing medium is used to harden the drug polymer emulsified droplets. It should be such that it should give spherical droplets when the drug-polymer solution is poured into it, should not interact with the former; mainly used are liquid paraffin, polyvinyl Alcohol and water.

e) Surfactant: these are used as stabilizers or emulsifiers play the role of hardening the

Microspheres as well. E.g. tween 80, span 80 and SLS.

f) Cross linking agent: chemical cross-linking of microspheres can be achieved using cross linking agents such as formaldehyde, glutaraldehyde or by using diacid chlorides such asterephthaloyl chloride. The method is limited to drugs that do not have any chemical interaction with the cross-linking agent.

g) Hardening agent: this helps to harden the microspheres formed in the processing medium. E.g.-hexane, petroleum ether (in case the processing medium is liquid paraffin).

8. POLYMERS USED IN FORMULATION OF FIOATING DRUG DELIVERY SYSTEM:-

8.1.Polymers: The following polymers used in preparations of FDDS -HPMC K4 M, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin,HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbonate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 M and Carbopol.

8.2. Inert fatty materials (5%-75%): Edible, inert fatty material having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires 39/01 and 43/01.

8.3. Effervescent agents: Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).

8.4. Release rate accelerants (5%-60%): eg. lactose, mannitol.

8.5. Release rate retardants (5%-60%): eg. Dicalciumphosphate, talc, magnesium stearate.

8.6. Buoyancy increasing agents (upto80%): eg. Ethyl cellulose.

8.7. Low density material: Polypropylene foam powder (AccurelMP 1000).[38]

9. METHODS OF PREPARATION OF MICROSPHERES:-

Wide ranges of developmental techniques are available for the preparation of gastro retentive Floating microspheres[39]. However, solvent evaporation method, and ionotropic gelation method have been extensively employed by large number of scientific investigators worldwide to explore the different vistas of floating microspheres. During the preparation of floating controlled release microspheres, the choice of optimal method has at most relevance for the efficient entrapment of active constituents. Selection of fabrication technique generally depends upon the nature of the polymer, the drug, and their intended use, [40, 41] Characteristic features of materials and the Process engineering aspects strongly influence the properties of microspheres and the resultant Controlled release rate. These techniques (i.e. solvent evaporation and ionotropic gelation).

9.1. Solvent Evaporation Method:-

This technique is widely employed by large number of pharmaceutical industries to obtain the controlled release of drug[42]. This approach involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and dissolved/dispersed drug in an excess amount of aqueous continuous phase, with the aid of an agitator. The concentration of the emulsifier present in the aqueous phase affects the particle size and shape. When the desired emulsion droplet size is formed, the stirring rate is reduced and evaporation of the organic solvent is carried out under atmospheric or reduced pressure at an appropriate temperature. Subsequent evaporation of the dispersed phase solvent yields solid polymeric micro particles entrapping the drug. The solid microparticles are recovered from the suspension by filtration, centrifugation, or lyophilisation[43]. For emulsion solvent evaporation, there are basically two systems which include oil-in-water (o/w) and water-in-oil (w/o) type.

e-ISSN: 2348-6848
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Volume 05 Issue 20
September 2018

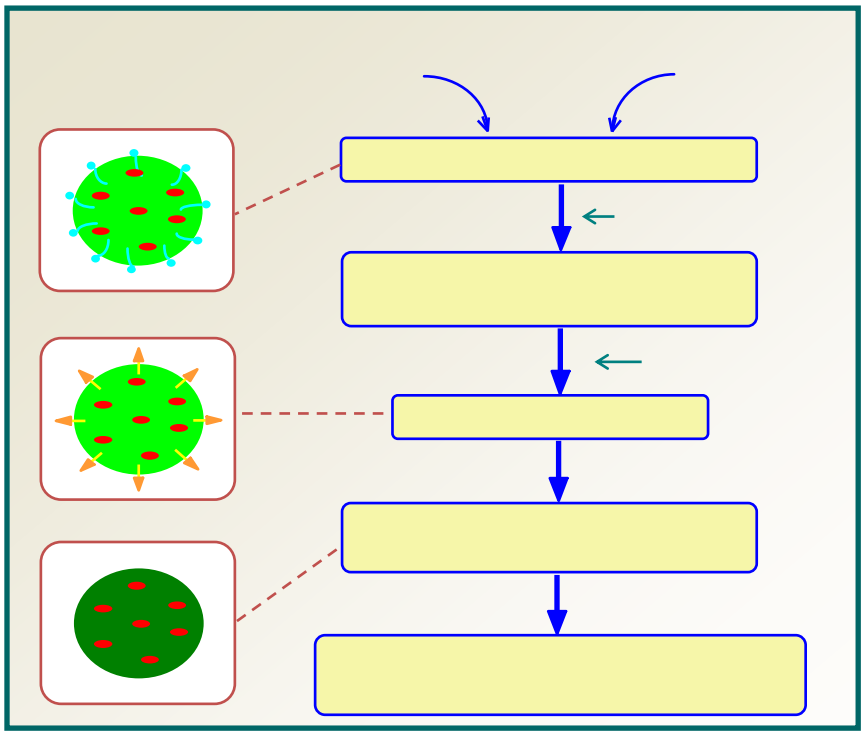

Figure no.14: Solvent Evaporation Method

9.1.1.Oil-In-Water Emulsion Solvent Evaporation Method:-

In this process, both the drug and the polymer should be insoluble in water while a water immiscible solvent is required for the polymer.[44]in this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform, or ethyl acetate, either alone or in combination. The drug is either dissolved or dispersed into polymer solution and this solution containing the drug is emulsified into an aqueous phase to make an oil-in water emulsion by using a surfactant or an emulsifying agent. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. Solvent removal from embryonic microspheres determines the size and morphology of the microspheres. It has been reported that the rapid removal of solvent from the embryonic microspheres leads to polymer precipitation at the o/w interface. This leads to the formation of cavity in microspheres, thus making them hollow to impart the floating properties.[45, 46] Oil-in water emulsions is widely used than water-in-oil due to simplicity of the

process and easy clean up requirement for the final product.[47]

9.1.2. Oil-in-Oil Emulsification Solvent Evaporation Method:-

This oil-in-oil (sometimes referred as water-in-oil) emulsification process is also known as non aqueous emulsification solvent evaporation. In this technique, drug and polymers are co dissolved at room temperature into polar solvents such as ethanol, dichloromethane, acetonitrile etc. with vigorous agitation to form uniform drug–polymer dispersion. This solution is slowly poured into the dispersion medium consisting of light/heavy liquid paraffin in the presence of oil soluble surfactant such as Span. The system is stirred using an overhead propeller agitator at 500 revolutions per minute (rpm) and room temperature over a period of 2–3 h to ensure complete evaporation of the solvent. The liquid paraffin is decanted and the microparticles are separated by filtration through a Whitman filter paper, washed thrice with n-hexane, air dried for 24 h and subsequently stored in desiccators. Span 60 is generally used which is non ionic surfactant. Span 60 has an HLB value of 4.3 and acts as a droplet stabilizer and prevents coalescence of the droplets by localizing at the interface between the dispersed phase and dispersion medium.[48, 49]

9.2. Ionotropic Gelation Method:-

In this method, cross linking of the polyelectrolyte takes place in the presence of counter ions to form gel matrix. This technique has been generally employed for the encapsulation of large number of drugs. Polyelectrolyte such as sodium alginate having a property of coating on the drug core and acts as release rate retardant contains certain anions in their chemical structure. These anions forms meshwork structure by combining with polyvalent cations and induced gelation. Microspheres are prepared by dropping drug loaded polymeric solution using syringe into the aqueous solution of polyvalentcations as depicted in**.**

e-ISSN: 2348-6848
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Volume 05 Issue 20
September 2018

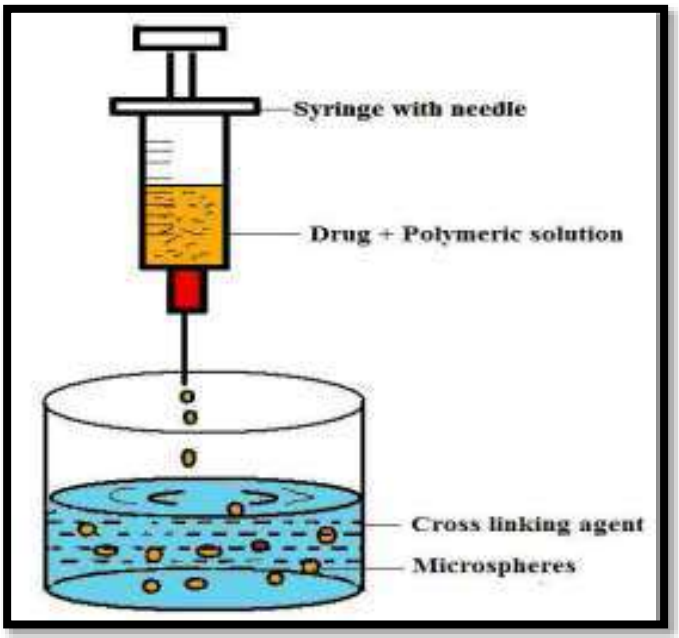

Figure no.15: Schematic representation of preparation of floating microspheres by ionotropic gelation.

The cations diffuses into the drug loaded polymeric drops, forming a three dimensional lattice of ionically cross linked moiety. Microspheres formed are left into the original solution for sufficient time period for internal gelification and they are separated by filtration. Natural polymers such as alginates can be used to improve drug entrapment and are widely used in the development of floating microspheres.[50, 51]

9.3. Emulsion Solvent Diffusion Method:-

In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible .The organic solvent diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase and the aqueous phase diffuse in to the droplets by which drug crystallizes.[33]

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 20
September 2018

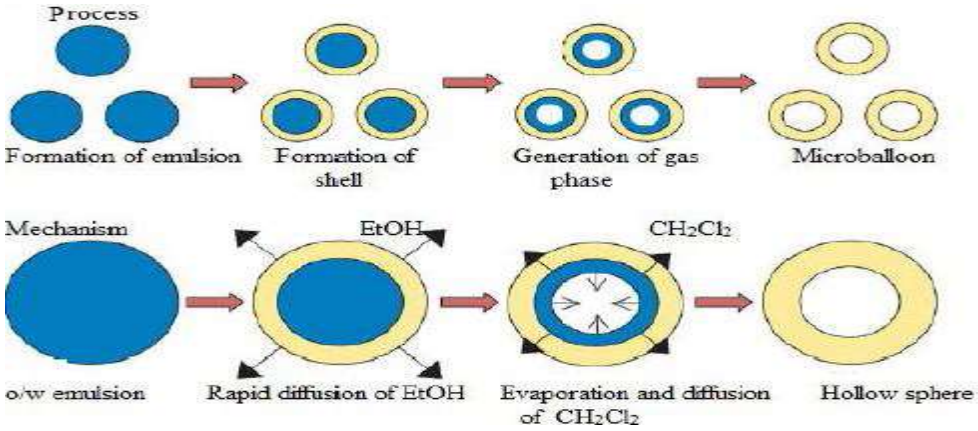

Figure no.16: Preparation technique (emulsion-solvent diffusion method) and mechanism of 'microballoon' formation.

9.4. Phase Separation Coacervation Technique:-

It is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase known as co-acervates. The drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer.[52]

9.5. Spary Drying and Spray Congealing:-

These methods are based on the drying of the mist of the polymer and drug in the air. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μm. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively.[41]

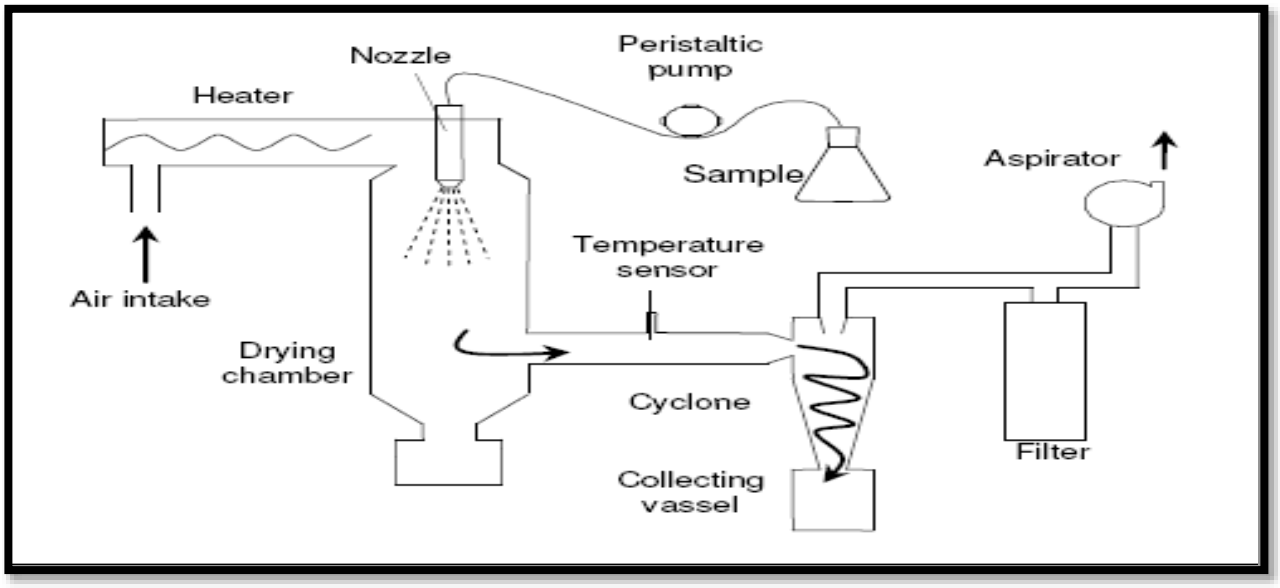

Figure no.17: Spray drying method for preparation of microspheres

9.6. Polymerization Technique:-

The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:

9.6.1. Normal Polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. Bulk polymerization has an advantage of formation of pure polymers.

9.6.2. Interfacial Polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed.[41]

10. CHARECTERIZATION/ EVALUATION OF MICROSPHERES:-

10.1. Micromeritic Properties-

10.1. a. Angle of repose (θ):-

The angle of repose is indicative of flow ability of the substance. Funnel was adjusted in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample powder was allowed to flow from the funnel, so the height of the pile just touched the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters. The angle of repose is calculated by using the equation no 1. (Values as given in Table 1).[53, 54]

$\tan \theta = h/r$ --- (1)

Where,

θ = Angle of repose

h = height of pile

r = Radius of pile

Table no.1: Relationship between angle of repose (θ) and flowability

Angle of Repose (θ)	Flowability
< 25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

10.1. b.Bulk density:-

Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed 10 gm sample of granules was placed into 25 ml measuring cylinder. Volume occupied by the granules was noted without disturbing the cylinder and the bulk density was calculated using the Equation (values expressed in gm/cm3).[53]

Bulk density = Weight of sample/Volume of sample--- (2)

10.1. c. Tapped density:-

Accurately weighed 10 gm of powder sample was placed in 25 ml measuring cylinder. The Cylinder was dropped at 2-second intervals onto a hard wooden surface 100 times, from a height of one inch. The final volume was recorded and the tapped density was calculated by the following equation (values expressed in gm/cm3).[53]

Tapped density = Weight of sample/Tapped volume--- (3)

10.1. d.Carr's index (%):-

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 20
September 2018

The Carr's index is frequently used as an indication of the flow ability of a powder. A Carr index greater than 25% is considered to be an indication of poor flowability and below 15% of goodflowability. Flow property of blend depends upon Compressibility index. The Carr's index is an indication of the compressibility of a powder. It is calculated by the formula. (Values given Table 2) [53], [56]

Carr′s index (%) = [(Tapped density − Bulk density)/Tapped density] x 100--- (4)

Table no.2: Carr's index as an indication of powder flow

Carr's index	Type of Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

10.1. e. Hausner's ratio:-

The Hausner's ratio is an indication of the compressibility of a powder. It is calculated by the Formula, [53]

Hausner′s ratio =Tapped density/Bulk density--- (5)

The Hausner'sratio is frequently used as an indication of the flowability of a powder. A Hausner'sratio greater than 1.25 is considered to be an indication of poor flowability. The Observations for the flow properties determinations were recorded.

10.2. Percentage yield:-

Percentage yield of floating microspheres was calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of floating microspheres and is represented by following formula.[55]

% yield = [(actual weight of product)/ (total weight of drug and (Excipients)] ×100--- (6)

10.3. Drug entrapment efficiency (DEE):-

The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance is measured by spectrophotometer against appropriate blank. The amount of drug

entrapped in the microspheres was calculated by the following formula:-[25]

DEE = [(amount of drug actually present)/ (theoretical drug load expected)] × 100--- (7)

10.4. *In vitro* Buoyancy:-

Floating behavior of hollow microspheres was studied using a USP dissolution test apparatus IIby spreading the microspheres (50 mg) on 900 ml of 0.1 N HCl containing 0.02% Tween 80 as surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 hours, both the floating and the settled portions of microspheres were collected separately. The microspheres were filtered, dried and weighed. The percentage of floating microspheres was calculated using the following equation.[55]

% buoyancy of microspheres = [(weight of floating microspheres)/ (initial weight of floating Microspheres)] x 100--- (8)

10.5. Dissolution test (in *vitro*-drug release) of microspheres:-

In vitro dissolution studies can be carried out in a USP paddle type dissolution assembly. Microspheres equivalent to the drug dose are added to 900 ml of the dissolution medium and stirred at 100 rpm at 37 ± 0.5 ºC. Samples are withdrawn at a specified time interval and analyzed by any suitable analytical method, such as UV spectroscopy.[55, 56, 57]

10.6. Morphological Study using SEM:-

The external and internal morphology of the microspheres were studied by scanning electron microscopy (SEM). It provides vital information about the porosity microstructure of these drug delivery systems. The most common technique used is scanning electron microscopy (SEM). The sample prepared for this method should be dehydrated as vacuum field is necessary for image generation in SEM. Prior to loading the samples are coated with electron dense coating materials such as gold, palladium or a combination of both to take photomicrograph. The coating can be done by sputter coating or thermal vacuum evaporation. Franklin et.al attached microbeads samples to aluminum stages and coated with 10µm of gold/palladium using a Hummer sputter coater and captured the images electronically.[55]

10.7. Differential Scanning Calorimetry (DSC) Analysis:-

The DSC technique can provide qualitative and quantitative information about the physicochemical status of the drug in the Microspheres. This involves an endothermic or exothermic process and the related thermal transitions include melting, recrystallisation, and decomposition, out gassing or a change in the heat capacity of the listed material. DSC is used to monitor different samples of the same materials to assess their similarities/differences, or the effects of additives on the thermal properties of the material [58]

10.8. Particle size Analysis:-

Particle size characterization is an important study of ensure that the particle

size of the formulation lies in the optimal range. A wide variety of methods which employ different physical principles for the determination of size include:

(A) Manual:

a) Optical Microscopy

b) Electron Microscopy

(i) Transmission electron microscopy

(ii) Scanning electron microscopy

c) Sieving

d) Sedimentation (Andreason Pipette Method)

(B) Automated:

a) Particle counters – (i) Optical particle counting

(ii) The counter principle

(iii) Permeability

(iv) Impaction& inertial techniques

b) Light Scattering – (i) Dynamic light scattering

(ii) Enhance laser diffraction

c) Flow cytometry

d) Field flow fractionation

S.C.Lee et.al & H.Takahata et.al sized micro particles by laser diffractometry.[59]

10.9. *In vivo* Tissue Distribution Studies:-

In vivo studies are a key component of any study since they provide tangible evidence of the efficacy of microspheres, and because the properties exhibited by microsphere are crucial for understanding the functional characteristics of formulation in a biological system. To examine the appropriate properties of the formulation in vivo, adult albino mice/wiretap rats/ Rabbits, etc of certain specified weight can be used. A calculated dose of the drug is administered to each animal as dispersion in saline with 1% of tween 80. At predetermined time intervals, the animals are injected with the microsphere through the tail route vein and sacrificed by cervical dislocation. The organs like lungs, liver, kidneys, heart and spleen are extracted and studied for target action. The tissue samples are stored for 24 hrs at - 200c. Then the concentration of drug localized in each organ is determined quantitatively using the HPLC method.

Invivo tissue distribution studies in animal models are carried out to prove the hypothesis of targeting of microsphere/formulation to the organs and compare them with conventional dosage forms of the drug [57, 60, 61]

10.10 Stability Studies:-

Optimized formulation was sealed in aluminum packaging, coated inside with polyethylene. The samples were kept in the stability chamber maintained at 40°C and 75% RH for 3 months. At the end of studies, samples were analyzed for the physical appearance and drug content.[55, 62]

11. APPLICATIONS:-

11.1. Sustained Drug Delivery[64]

Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS system can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral controlled release formulation, hence, can be overcome with these systems. These systems have bulk density of <1, as a result of which they can float on the gastric contents.

11.2. Absorption enhancement[64]

Drugs that have poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.[44]

11.3. Site specific drug delivery[64, 65]

These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine e.g. riboflavin furosemide and misoprostal. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.

11.4. Maintenance of constant blood level

These systems provide an easy way of maintaining constant blood level with an ease of administration and better patient compliance.[63]

11.5. Minimized adverse activity at the colon

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This Pharmacodynamic aspect provides the rationale for GRDF formulation for betalactamantibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

11.6. Reduced fluctuations of drug concentration

Continuous input of the drug following crgrdf administration produces blood drug concentrations journal of current pharmaceutical research 2011; 7 (1): 6-20 within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.[45].

12. MARKETED PRODUCTS OF FDDS:-[65, 66]

Table 3: List of drugs explored for various floating dosage forms.	
Dosage form	**Drugs**

Floating Microspheres	Aspirin, Ibuprofen, Griseofuvin, Terfinadine, Tranilast.
Floating Granules	Diclofenac sodium, Indomethacin , Prednisolone
Floating Capsules	Diazepam, Furosemide, L-Dopa and Benserazide
Tablets/Pill	Amoxycillin Trihydrate, Ampicillin, Diltiazem, p - Aminobenzoic acid,

13. CONCLUSION

Formulation of floating drug delivery systems is an efficient, potential and cost effective approach for gastric retention of dosage forms to improve bioavailability and also to achieve the desired response for longer duration. Floating Microparticles have advantage of reducing dose frequency and patient compliance. Multiparticulate drug delivery systems provide several all the advantages including greater flexibility and adaptability of microparticulate dosage forms which gives clinicians and those engaged in product development powerful new tools to optimize therapy. Gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. FDDS have wide variety of applications in field of targeted and controlled drug delivery system .These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development.

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