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A REVIEW ON FLOATING TABLET, A NOTE ON THERMOPLASTIC GRANULATION TECHNIQUE

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ABSTRACT

The main aim of any drug delivery system is to attain appropriate concentration of the drug in system or tissue, which is therapeutically effective and non toxic for a prolonged period. One novel approach in this area is GRDDSs (Gastro Retentive Drug Delivery System), can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site. Various attempts have been made to develop gastro-retentive delivery systems such as such as floating drug delivery systems (FDDS), swelling and expanding systems, bio-adhesive systems, modified shape systems, high density systems or other delayed gastric emptying devices have been discovered till now. The purpose of writing this review was to investigate, compile and present the recent as well as past literatures in more concise way with special focus on approaches which are currently utilized in the prolongation of gastric residence time. These includes floating system, swelling and expanding system, bio/muco-adhesive system, high density system and other delayed gastric emptying devices. The present review addresses briefly about the classification, formulation consideration for GRDDS, factors controlling gastric retention, merits, demerits, applications of gastro-retentive drug delivery systems. The review also includes details about FDDS and a brief note on granulation technique.

KEYWORDS: Gastro Retentive Drug Delivery System, floating drug delivery systems, granulation technique.

INTRODUCTION

Oral administration is the most convenient and desirable mode of drug delivery and is associated with high patient compliance as compared to other modes of drug intake.

However, oral route of administration has only restricted use for some important drugs, from various pharmacological categories.[1] Even though oral drug delivery is that the most convenient and desirable route of drug administration, there are still challenges to beat. Due to incomplete absorption or degradation in the gastrointestinal (GI) tract those drugs shows poor oral bioavailability. Some of these drugs are characterized by a narrow absorption window (NAW) at the upper part of the gastrointestinal tract. Bioavailability of active pharmaceutical ingredients (APIs) is subject to vary, counting on their chemistry properties, as well as pH-dependent solubility and stability, and a narrow absorption window.[2]

Gastro-retentive drug delivery

Drugs which are absorbed easily from the GIT and have short half-lives are eliminated rapidly from the systemic circulation. Repeated dose is required to achieve suitable therapeutic activity. To improve gastric residence time, many approaches are available. Gastro-retentive drug delivery system is one of those approach to enhance contact time of drug with stomach region. There by targeting site specific drug release in the stomach for local or systemic effects. Hence this dosage form can last in the gastric region for long periods and thereby significantly enhance the gastric retention time of the drugs. It will release the drug in stomach in a controlled manner, so that the drug could be supplied continuously to absorption site in GIT i.e. stomach.[3]

Varied approaches are investigated to extend the retention of oral dose type within the abdomen, as well as floating systems, swelling and increasing systems, bio-adhesive systems, changed form systems, high density systems, and different delayed internal organ emptying devices.[4]

Merits of gastro-retentive drug delivery system

1. The GRDDS has the following advantages:

a. Increased bioavailability: The bioavailability of drugs can be significantly enhanced markedly for those which get metabolized in the upper GIT by this gastro- retentive drug delivery.[5]

2. Improved patient compliance: For drugs with relatively short half life, sustained release may result in a change pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.

3. Increased gastric retention: It can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is less than that of the gastric fluids.
4. Sustain release: Gastro-retentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine.
5. Site specific drug delivery: The controlled, slow delivery of drug form gastro-retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This will reduces undesirable effects of side effects.
6. Adverse effects are reduced: Gastro-retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be reduced. This feature is of special importance for drug with a narrow therapeutic index.[6]
7. High efficiency: Gastro-retentive drug delivery can diminish the counter activity of the body leading to higher drug efficiency.
8. Improved selectivity: Reduction of fluctuation in drug concentration makes it possible to obtain better selectivity in receptor site.
9. Increased therapeutic effect: The sustained mode of drug release from Gastro-retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.[7]

LIMITATIONS OF GRDDS

1. The drug which are not stable in acidic environment, are not suitable.
2. It is not suitable for drug which are well absorbed in the lower part of the GIT.
3. They shows Poor *in vitro* and *in vivo* correlation.
4. Difficulty to achieve expected outcome and dose dumping may occur.
5. Factors like gastric motility, pH and presence of food are influencing the Gastric-retention. Hence the dosage form must have capability to withstand grinding and churning force of peristaltic wave of stomach.
6. Higher cost of formulation.
7. In case of toxicity, poisoning or hypersensitivity reaction, Retrieval of drug is difficult.[8]

APPROACHES TO DESIGN FLOATING DOSAGE FORMS

There are several approaches are used for enhancing gastric retention time of drug, they are

1. High-Density Systems.
2. Swelling and Expanding Systems.
3. Incorporation of Delaying Excipients.
4. Modified Systems.
5. Muco-adhesive or Bio-adhesive Systems.
6. Floating Systems.[9]

1. High-Density Systems

The density of the system should be higher than that the stomach fluid. It would be at least 1.50 g/ml. In this type, the drug can be coated or mixed with heavy, nontoxic materials such as barium sulphate, titanium dioxide, iron powder.[10]

2. Swelling and Expanding Systems

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus (Fig.1). These systems are sometimes referred to as plug type systems because they tends to remain loaded at the pyloric sphincter.[11] The polymer imbibes water and swells when they come in contact with the gastric fluid.

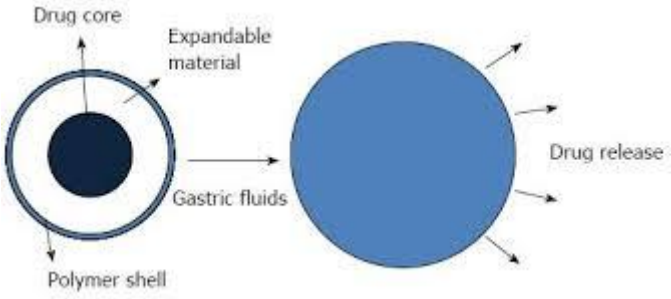

Fig.1: Swelling and expanding system.

3. Incorporation of Delaying Excipients

This is another delayed gastric emptying approach of interest which consists feeding of digestible polymers or fatty acid salts. This leads to changes in the motility pattern of the stomach to a fed stage thereby reducing the gastric emptying rate.[12]

Eg: tri ethanolamine myristate.

4. Modified Systems

These system extend the GRT depending on size, shape and flexural modules of drug delivery device.[13]

5. Muco-adhesive or Bio-adhesive Systems

The term bioadhesion is defined as adhesion of the delivery system to biological surface i.e. mucus and/or mucosal surface. Bioadhesive systems adhere to the mucosa of the stomach and remain in intimate contact with the membrane for longer period of time and hence retains in the stomach for its prolonged release. Bioadhesive polymers are used to formulate these systems.

These systems are essentially based on bio-adhesive polymers, which adhere to the mucin and / or epithelial surface. Bio-adhesive polymers can bind mucus as well as non-mucus membranes. If bio-adhesion is restricted to mucosal surface it is called muco-adhesion(fig.2). Non-specific bio-adhesive systems bind to mucin and epithelial surface by non-specific interaction between polymer particle and intestinal surfaces.[14]

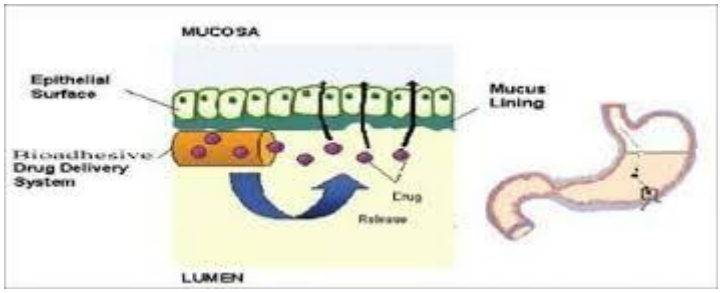

Fig. 2: Muco-adhesive or Bio-adhesive system.

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6. FLOATING DRUG DELIVERY SYSTEM

Floating Drug Delivery Systems (FDDS) have a lower bulk density than gastric fluids and therefore remain in the stomach for an extended period of time without affecting the rate of gastric emptying. While the device floats on the gastric contents, the drug is slowly released from the system at the required speed. The remaining system is removed from the stomach after the drug has been released. This leads to increased GRT and better control of plasma drug concentration changes. There are to two distinct categories of floating systems, effervescent and non-effervescent.[15]

FLOATING DRUG DELIVERY SYSTEM

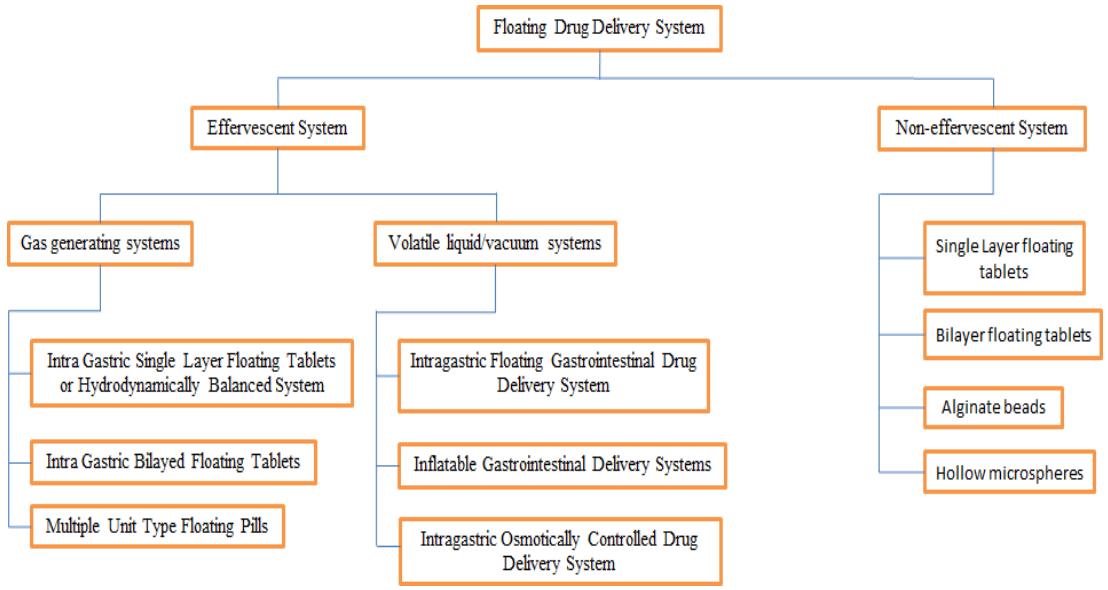

Fig. 3.

1. Effervescent System

In Effervescent system, gas generating agents are used, carbonates (example: Sodium bicarbonate) and another organic acid (examples: tartaric acid and citric acid) present in the formulation. Thus reducing the density of the system and making it to float on the gastric fluid. These effervescent systems further classified into two types.

i. **Gas generating systems**

ii. **Volatile liquid/vacuum containing systems**[16]

i. GAS GENERATING SYSTEM

These types of delivery systems use effervescence reaction between carbonate/bicarbonate salts and citric/tartaric acid leads to liberate CO_2. The liberated CO_2 gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over gastric fluid17(fig.4).

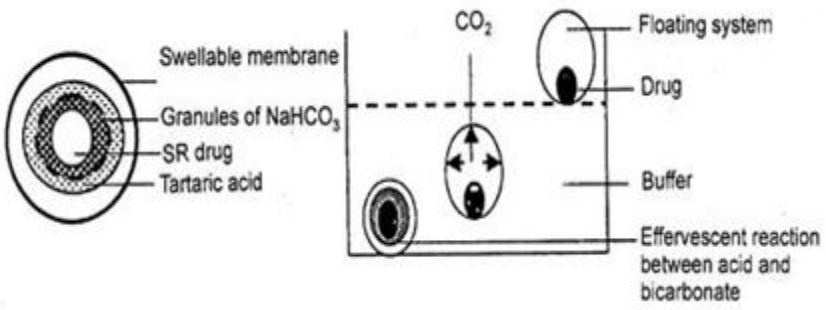

Fig. 4: Gas generating system.

a) Intra Gastric Single layer floating tablet

They also called as Hydro dynamically Balanced System (HBS). They are prepared by mixing the drug with carbon dioxide generating agent within the matrix tablet. The tablet remains floated for prolonged period due to the bulk density is lower than the gastric fluid without flattering the gastric emptying rate.[18] From the formulation the drug is released slowly at desired rate, and once the release is complete, the residual system get expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration[19](fig.5).

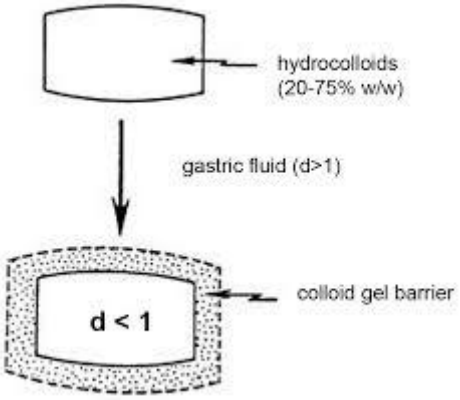

Fig 5: Intra Gastric Single layer floating tablet.

b. Intra Gastric Bilayer Floating Tablets

These are also compressed tablets, containing two layers(fig.6) i.e.

I. Immediate release layer

II. Sustained release layer.[20]

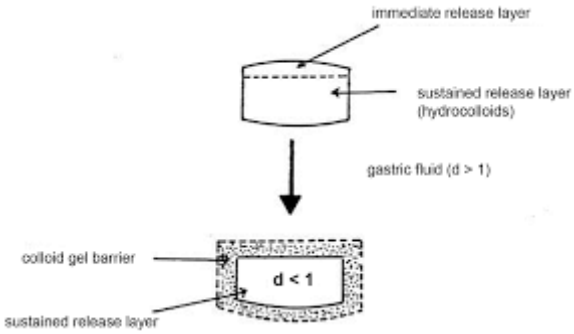

Fig.6: Intra Gastric Bilayer Floating Tablets.

c. Multiple Unit Type Floating Pill

These systems consist of sustained release pills surrounded by double layers as' seeds.' The inner layer is made up of effervescent agents, while the outer layer is a swellable layer of

membrane. When the device is immersed in dissolution at body temperature, it sinks immediately and then forms swollen pills like balloons and floats as the density reduces.[21]

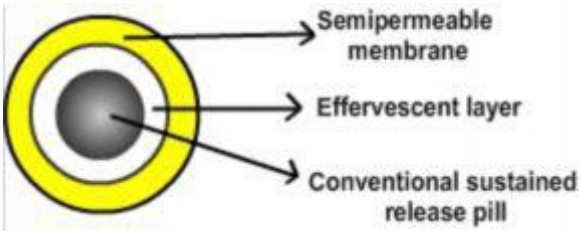

Fig. 7: Multiple oral floating dosage system.

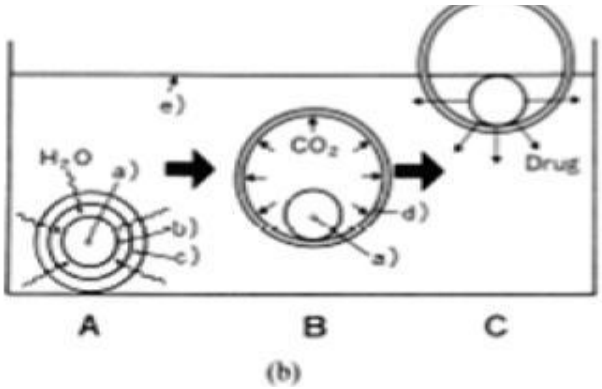

Fig. 8: Stages of floating mechanism.

a) A multi-unit type oral floating dosage system

b) Stages of floating mechanism.[22]

2. VOLATILE LIQUID /VACUUM CONTAINING SYSTEM

a) Intra-gastric Floating Gastrointestinal Drug delivery system

A gastrointestinal drug delivery system (GIDS) can be created to float in the abdomen by integrating a floatation chamber that may be a vacuum or filled with harmless gas.[23] A drug reservoir is encapsulated inside a microporous room with apertures along its top and bottom walls. There is a chance of direct contact of the stomach mucosal surface with undissolved drug, hence the peripheral walls of the drug reservoir compartment are completely sealed. The floatation chamber leads to GIDS to float on the gastric fluids in stomach. Through the apertures the fluid entered, dissolve the drug, and carry and drug solute out of the DDS for controlled transport to the intestine for absorption.[24]

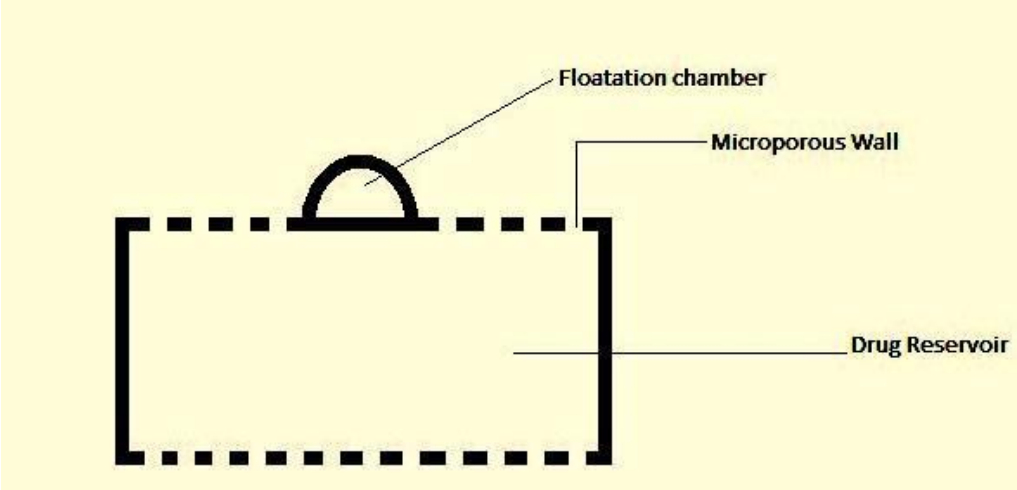

Fig 9: Intra-gastric Floating Gastrointestinal Drug delivery system.

b) Intra-gastric Osmotically Controlled Drug Delivery System.

It is incorporated with 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 intra-gastric 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.[25]

By the help of pressure responsive collapsible bag which encloses the drug reservoir compartment, which is impermeable to vapour and liquid and has a drug delivery orifice.

The osmotically active salt is present in the osmotically active compartment and is enclosed in semi-permeable housing. To dissolve the osmotically active salt in the stomach, the water in GI fluid continuously absorbed through the semipermeable membrane into osmotically active compartment. An osmotic pressure is created, this pressure acts on the collapsible bag and it turn forces the drug reservoir compartment to reduce its volume, activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. (fig.10) The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.[26]

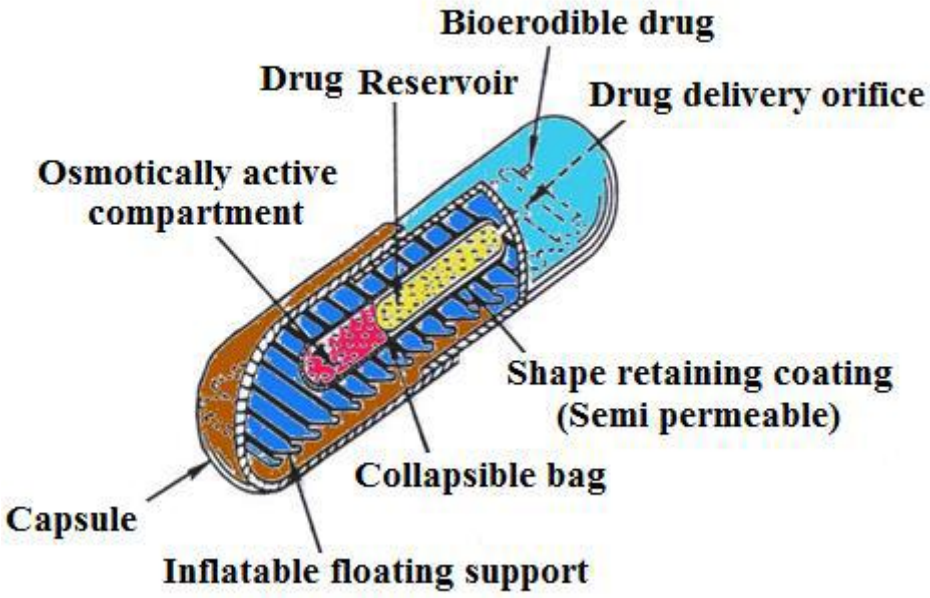

Fig. 10: Intra-gastric osmotic controlled drug delivery system.

C) Inflatable Gastrointestinal Delivery System

These systems consist of an inflatable liquid ether chamber that gasifies at body temperature, causing the chamber to inflate into the stomach. A drug reservoir which is encapsulated in a gelatine capsule is present in the inflatable chamber. The capsule dissolves and releases the drug reservoir with the inflatable after oral administration.[27]

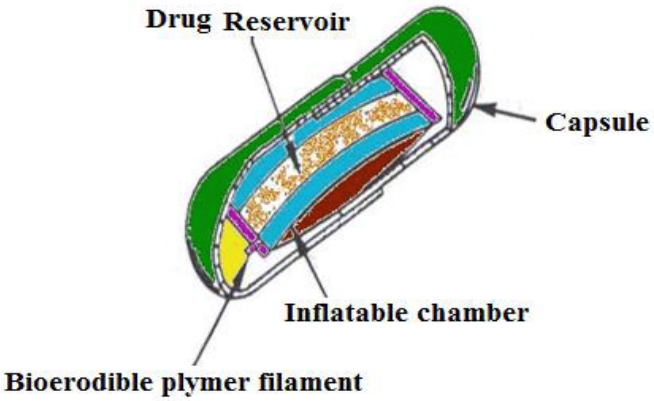

Fig. 12: Gastro- inflatable drug delivery device.

2. Non-Effeverscent systems

The non-effervescent FDDS is based on the mechanism of polymer swelling or bioadhesion in the GI tract to the mucosal layer. The most commonly used excipients in non-effervescent FDDS are hydrocolloids, polysaccharides, and matrix-forming materials such as polycarbonates, polyacrylates, polymethacrylates, polystyrene, etc.

The various types of these systems are

1. **Single Layer Floating Tablets**
2. **Bilayer floating tablet**
3. **Alginate Beads**
4. **Hollow Microspheres.**[28]

1. Single Layer Floating Tablet

In this type of Floating tablet, a gel forming hydrocolloid intimately mixing with drug, which leads to its swelling when in contact with gastric fluid and maintains bulk density of less than unity. The air trapped by the swollen confers buoyancy to this dosage forms.[29]

2. Bi layer Floating Tablet

This system consist of two layers, first layer which provide initial dose from the system called immediate release layer while the another is sustained release layer, absorbs gastric fluid forming an impermeable colloidal gel barrier on the surface. It helps to maintain the bulk density less than the unity and thereby it remains buoyant in the stomach.[30]

3. Alginate Beads

In this approach, precipitation of calcium alginate causing when the sodium alginate solution is dropped into aqueous solution of calcium chloride. In an another investigation, By the use of freeze dried calcium alginate with sodium alginate as the polymer and calcium chloride is the cross-linking agent ,Multiple-unit floating alginate beads have been formed. Then they are separated and dried by air convection and freeze drying, leads to form porous system which can maintain a floating force for over 12 hrs. These beads shows improve GRT more than 5.5 hrs.[31]

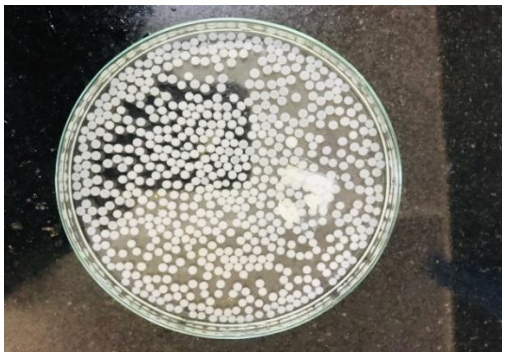

Fig. 13: Alginate beads.

4. Hollow Microspheres

Hollow microspheres or micro-balloons, Using Novel emulsion solvent diffusion method, the drug is incorporated in the outer polymer shell. The ethanol: dichloromethane solution of drug and enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 400ºC. There is generation of gas phase by the evaporation of dichloromethane in the dispersed polymer droplet created an inner cavity with drug in polymer microsphere.

For more than 12hrs *in vitro*, the micro-balloons floated continuously over the surface of acid dissolution media containing surfactant.[32] Fig(14)

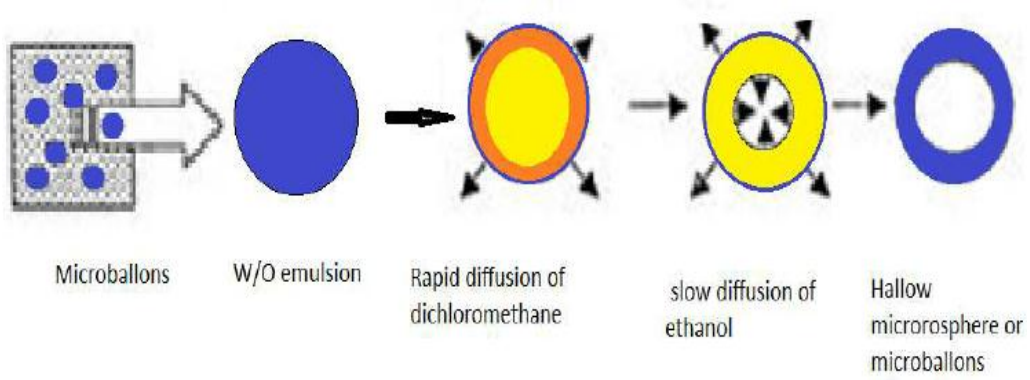

Fig. 14: Hollow microspheres.

Mechanism of floating systems

Among these are the most frequently used floating dosage forms. Floating drug delivery systems (FDDS) have a bulk density lower than gastric fluids and therefore remain buoyant in the stomach for an extended period of time without affecting the gastric emptying rate. While the device floats on the gastric contents, the drug is slowly released from the system at the required speed (fig). The residual system is removed from the stomach after drug release. This leads to enhanced GRT and improved control of plasma drug concentration changes. Nevertheless, in addition to the minimal gastric content required to properly achieve the buoyancy retention effect, a minimum level of floating force is also required to maintain the buoyancy of the dosage form on the surface[33] (Fig15).

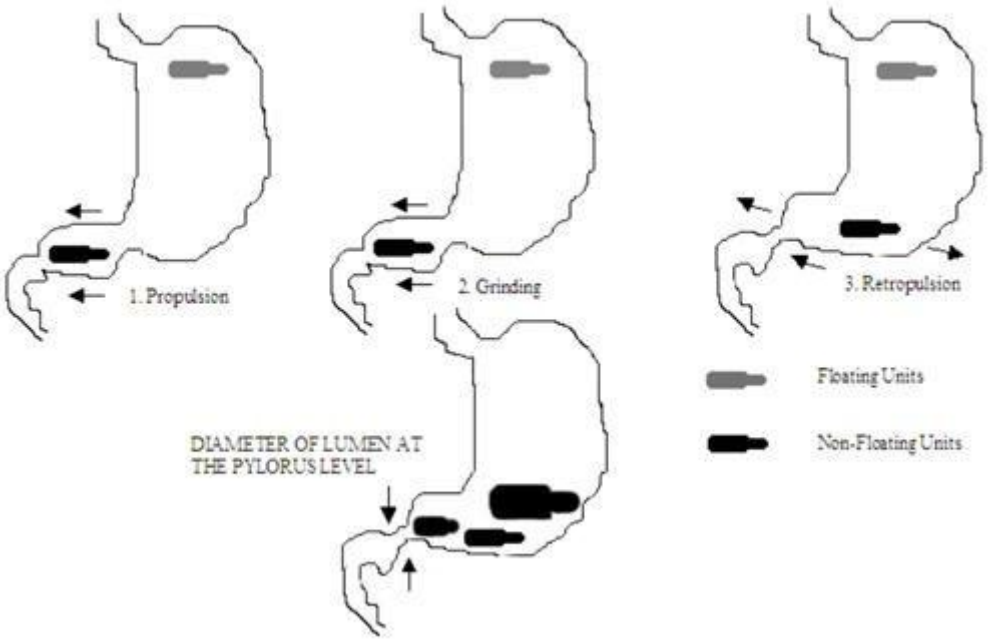

Fig. 15: Intra-gastric residence positions of floating and non-floating units.

Granulation

Granulation, the process of particle enlargement by agglomeration technique, is one of the most significant unit operations in the production of pharmaceutical dosage forms, mostly tablets and capsules. Granulation process transforms fine powders into free-flowing, dust-free granules that are easy to compress.[34]

Specialised Granulation Methods / Techniques

(i) Moisture activated dry granulation

(ii) Thermal adhesion granulation

(iii)Pneumatic dry granulation

(iv)Melt / thermoplastic granulation

(v) Fluidized bed granulation

(vi)Extrusion-spheronization granulation

(vii) Spray drying granulation

(viii) Freeze granulation

(ix) Foam binder granulation

(x) Steam granulation.[35]

Melt/Thermoplastic Granulation

Melt or thermo-plastic GT was also called melt agglomeration where granulation was achieved with meltable binder that was in solid state (at room temperature) but preferably melts in the temperature range of 50˚C-80˚C, and the melted binder acts like a binding liquid. Melt granulation was done either by.

a) Spray congealing

b) Tumbling Melt Granulation[36]

Spray congealing

Also called spray chilling or spray cooling, is a unit operation in which aquid melt is atomized in to a cooling chamber. A sufficiently cold gas stream enters the chamber, typically in co-current configuration, i.e. flowing in the same direction, contacting the droplets and solidification takes place. This involves the transformation of molten droplets from liquid to solid state with removal of energy from the droplets. The transition of a melt from a soft or fluid state to a rigid or solid state by cooling is called congealing. Hence, the spray congealing process can be described by four events: i) atomization of the melt into droplets, ii) contact of the droplets with the cold congealing gas, iii) solidification of the droplets into particles and iv) separation of the particles from the congealing gas.[37]

A newer melt agglomeration technique, i.e., tumbling melt granulation, for preparing spherical beads has been reported. A powdered mixture of meltable and non-meltable materials is fed onto the seeds in a •uid-bed granulator.

Tumbling Melt Granulation

A newer melt agglomeration technique, i.e., tumbling melt granulation, for preparing spherical beads has been reported. A powdered mixture of meltable and non-meltable materials is fed onto the seeds in a fluid-bed granulator. The mixture adheres to the seeds with the binding forces of a melting solid to form the spherical beads. In preparing the spherical beads, both viscosity and particle size of the meltable materials should be kept at an optimum value.[38] The particle size of a meltable material should be 1/6 or lower than the diameter of the seeds. High-viscosity meltable materials should not be employed to avoid agglomeration of seeds and producing beads of low sphericity. In tumbling melt granulation, small meltable particles with sufficient viscous binding forces are obligatory for the production of spherical beads[39] (Fig.16).

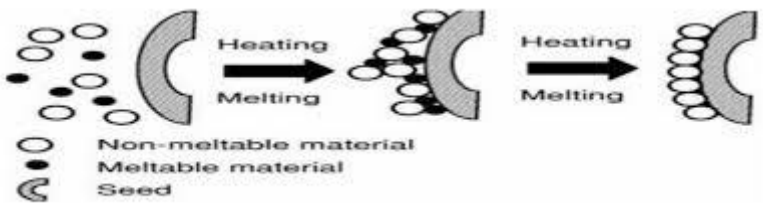

Fig. 16: Tumbling melt granulation.

Advantage

1. Both aqueous and non-aqueous solvent were not used,
2. Time and cost effective as involves fewer processing steps and eliminates drying step,
3. Uniform dispersion of fine particle occurs,
4. Release profile of drugs can be controlled and modified,
5. Suitable for enhancing dissolution profile and bioavailability of poorly water soluble drugs by forming solid dispersion
6. Product exhibit good stability at varying pH and moisture levels and;
7. Higher degree of regulatory compliance

Disadvantages

1. Thermo-labile materials were poor candidates, and
2. Meltable binders with melting point in the specific range can only be utilized.[40]

Requirements of MTG

1. Meltable binder at a level of 10–30% w/w with respect to solid particles was used,
2. Meltable binder should be solid at room temperature and melt between 400c and 800c,
3. Meltable binder should be physically and chemically stable,
4. Meltable binder should have suitable hydrophilic-lipophilic balance to ensure the correct release of the active substance, and.
5. The melting point of fine solid particles should be at least 20^{o}C higher to that of the maximum processing temperature.

A newer melt agglomeration technique, i.e., tumbling melt granulation, for preparing spherical beads has been reported. A powdered mixture of meltable and non-meltable materials is fed onto the seeds in a •uid-bed granulator (Fig. 2). The mixture adheres onto the seeds with the binding forces of a melting solid to form the spherical beads. In preparing the spherical beads, both viscosity a.

Meltable binders in MTG

There were two types of meltable binder namely hydrophilic meltable binders and hydrophobic meltable binders. The hydrophilic meltable binders were used to prepare immediate-release dosage forms while the hydrophobic meltable binders were preferred for prolonged-release formulations. Meltable binders should be selected basing upon their melting point range. Polyethylene glycol 2000/3000/6000/8000, gelucire 50/13, poloxamer 188, etc. was used as hydrophilic meltable binders while stearic acid, cetyl or stearyl alcohol, paraffin wax, microcrystalline wax, bees wax, carnauba wax, cetylpalmitate, glyceryl stearate, mono-/di-/tri- glycerides, etc. were used as hydrophobic meltable binders.[41]

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