JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Novel Approach In Floating Drug Delivery System: Raft Forming System

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ABSTRACT

The present review includes the floating drug delivery systems (FDDS) that are valuable approach to avoid this variability with increase the retention time of the drug-delivery systems in stomach. This review most focus on the novel approach in FDDS that are raft forming system including the design of raft system, polymer helpful in the formulation of raft system different approaches based on their mechanisms used for triggering the raft formation in the GIT and finally includes advantages and applications of the system.

Key-words; floating drug delivery systems, Raft forming system

1. INTRODUCTION

Tablet is solid unit compressed dosage form. Tablet is the most widely preferred oral solid dosage form. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration.[1]

Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.[2] It is widely accepted that gastric emptying of a conventional dosage form in humans is affected by numerous factors and the time taken shows wide inter- and intra-subject variation This variability, in turn, can lead to unpredictable times to achieve peak plasma drug levels and bioavailability, since many drugs are absorbed to the greatest extent in the upper part of the small intestine A drug that is released from a dosage form in a controlled manner in the stomach will empty together with fluids and have

the whole surface area of the small intestine available for absorption. Topical drug delivery to the gastric mucosa.[3]

1.1 Need for Gastroretentive Drug Delivery System

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for 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, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3 hours.[4] Mostly following types of drug are used in the GRDDS;

- Drugs acting locally in the stomach
  E.g. Antacids and drugs for H. Pylori viz., Misoprostol
- Drugs that are primarily absorbed in the stomach
  E.g. Amoxicillin
- Drugs that is poorly soluble at alkaline pH
  E.g. Furosemide, Diazepam, Verapamil, etc
- Drugs with a narrow window of absorption
  E.g. Cyclosporine, Methotrexate, Levodopa, etc
- Drugs which are absorbed rapidly from the GI tract.
  E.g. Metronidazole, tetracycline
- Drugs that degrade in the colon.
  E.g. Ranitidine, Metformin HCl.
- Drugs that disturb normal colonic microbes
  E.g. Antibiotics against Helicobacter pylori

1.2 Mechanism of floating systems

The system is floating on the gastric content the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach 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 has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to main submerged object. The object floats better if F 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 intragastric buoyancy capability variations.[5]

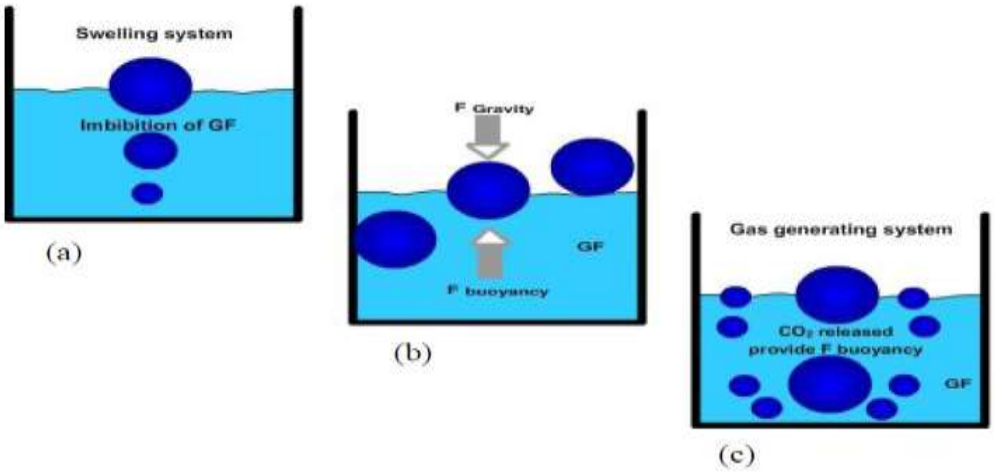

Fig. 8; Mechanism of floating systems

$F = F$ buoyancy $- F$ gravity $= (D\text{f} - D\text{s})\ g\ v$

Where, F = total vertical force,

Df = fluid density,

Ds = object density,

v = volume and

g = acceleration due to gravity

2. RAFT FORMING SYSTEMS

These systems have been made to retain the dosage form in the stomach as a way of increasing the retention time. Among the various attempts, the raft forming system is an advanced revolution in oral controlled drug delivery. Raft forming systems have received much attention for the delivery of the drug for gastrointestinal infections and disorders. The raft forming system is one of the approaches which involve the formulation of effervescent floating liquid with in situ gelling properties, which has been assessed for sustaining drug delivery and targeting. Moreover, the gels formed in situ remained intact for more than 48 h to facilitate sustained release of drugs.[6]

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. A simple meaning of Raft is a flat structure, typically made of planks, logs, or barrels, that floats on water and is used for transport or as a platform for swimmers. Here also we are considering something that floats on gastric content of stomach. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of carbon dioxide. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of carbon dioxide to make the system less dense and float on the gastric fluids. The system contains a gel forming agent (e.g. Alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.[7]

The composition contained in the raft system drug, Alginic acid, sodium bicarbonate, calcium carbonate, mannitol and a sweetener. These ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float. When the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of the drug, the residual system is emptied from the stomach. This results in an increased gastro retention time and a better control of the fluctuations in plasma drug concentration.[8]

Fig. 10; Demonstration Report of Raft Forming System

2.1 The design of the raft forming system

The formulation of the raft forming system depends on the physicochemical properties of the drug molecule, the diseased condition for which treatment is required, the patient population and the marketing preference. Physico-chemical factors include molecular weight, lipophilicity and molecular charge, an anatomical and physiological factor includes membrane transport and pH of tissue fluid; formulation factors include pH, gelation temperature, viscosity, osmolarity, and spreadability.[9]

To achieve the gastric retention of the dosage form, the dosage form must be able to satisfy the following criteria. They are as follows;

- The drug should be released slowly from the system.
- The dosage form must be able to survive the force exerted by peristaltic waves in the stomach and the constant contractions, grinding and churning moments.
- They should maintain specific gravity lower than gastric contents i.e. 1.004–1.01 g/cm3.
- The dosage form must remain in the stomach for a prolonged period of time.
- Better patient compliance.
- Easy for administration to the patient.
- After the release of the drug the device should be easily evacuated from the stomach.

2.2 Polymer used in the formulation of the raft forming system

A variety of polymers are effective in floating drug delivery systems so as to target the delivery of the drug to a specific region in the gastrointestinal tract i.e. stomach. Various natural and synthetic polymers are used in the formulation of the raft forming drug delivery system. Natural polymer such as Alginic acid,

guar gum, gellan gum, Xyloglucan, pectin, chitosan etc. and synthetic polymer such as poly (DL lactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone, HPMC etc. are used for formulation development of the raft forming drug delivery system.[10]

A polymer used for in situ gels should have the following characteristics

- ❖ It should be biocompatible.
- ❖ It should have pseudo plastic behavior.
- ❖ The polymer should be capable of increasing the viscosity with increasing the shear rate.

2.2.1 Alginic acid

Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1, 4-glycosidic linkages. These are unbranched polysaccharides found in brown seaweed and marine algae such as Laminaria hyperborea, Ascophyllum nodosum and Macrocystis pyrifera. [11] Many different alginate salts and derivatives are also commercially available including sodium alginate, ammonium alginate, calcium alginate, magnesium alginate, potassium alginate etc. Out of these, sodium alginate is most commonly and widely used in the floating drug delivery systems. Alginic acid can be chosen for gastroretentive formulations since it exhibits favorable biological properties such as biodegradability and nontoxic. Formulation containing alginic acid not only has the ability to form gel, but also have its Mucoadhesive properties. It is hydrophilic, nontoxic, biodegradable, and biocompatible.[12] it was found that alginates form compact structure when ionic radical of the cation are lower. Dilute aqueous solutions of alginates form firm gels on addition of di and tri valent metal ions by a cooperative process involving consecutive glucuronic residues in the α-L-glucuronic acid blocks of the alginate chain Thus sodium citrate is added in the preparation to form complexation with the free Ca2+ ions and release them only in the highly acidic environment of the stomach.[13] The formulation thus remains in liquid form until it reaches the stomach, where gelation is instantaneous Sodium alginate has been employed in the preparation of gels for the delivery of biomolecules such as drugs, peptides and proteins.[14]

2.2.2 Gellan gum

Gellan gum is an anionic deacetylated exocellular polysaccharide with a tetra saccharide repeating unit of one α-L rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. It is secreted by the Sphingomonas elodea (Pseudomonas elodea). The chemical structure of the polysaccharide has a tetra saccharide repeat unit consisting of two glucose residues, one glucuronic acid residue, and one rhamnose residue. These are linked together to give a tetra saccharide repeat unit, It has the tendency of gelation which is temperature dependent or cation induced.[15] This gelation involves the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water. The formulation consists of gellan solution with calcium chloride and sodium citrate complex, and when administered orally the calcium ions are released in the acidic environment of the stomach leading to gelation of gellan thus forming a gel in situ. Thus gellan gum undergoes gel formation due to change in temperature or due to presence of cations.[16]

2.2.3 Xyloglucan

Xyloglucan is a plant based polysaccharide obtained from seeds of tamarind. It is composed of (1–4)-β-D-glucan backbone chain, which has (1–6)-α-D xylose branches that are partially substituted by (1–2)-β-D-galacto xylose. Xyloglucan is composed of hepta saccharide, octa saccharide and nona saccharide oligomers, which differ in the number of galactose side chains, Although xyloglucan itself does not form gel, dilute solutions of xyloglucan which has been partially degraded by galactosidase exhibit a thermally reversible sol–gel transition on heating.[17] When xyloglucan is partially degraded by β-galactosidase, the resultant product exhibits thermally reversible gelation by the lateral stacking of the rod like chains. The sol–gel transition temperature varies with the degree of galactose elimination. It forms thermally reversible gels on warming to body temperature. Xyloglucan gels can be potentially used for oral, intraperitoneal, ocular and rectal drug delivery.[18]

2.2.4 Pectin

Pectin is a plant origin anionic polysaccharide extracted from the cell wall of most plants. Pectins are linear polymers mainly comprised of α-(1–4)-linked D-galacturonic acid residues interrupted by 1, 2-linked L-rhamnose residues. They have an average molecular weight of about 50,000 to about 180,000. It readily forms gels in an aqueous solution in the presence of divalent ions such as free calcium ions, which crosslink the galacturonic acid chains in a manner described by egg-box model.[19] The main advantage of using pectin for these formulations is that it is water soluble, so organic solvents are not necessary in the formulation. Divalent cations present in the stomach, carry out the transition of pectin to gel state when it is administered orally. Calcium ions in the complexed form may be included in the formulation for the induction of pectin gelation. Sodium citrate may be added to the pectin solution to form a complex with most of calcium ions added in the formulation. By this means, the formulation may be maintained in a fluid state (sol), until the breakdown of the complex in the acidic environment of the stomach, where release of calcium ions causes gelation to occur. The quantities of calcium and citrate ions may be optimized to maintain the fluidity of the formulation before administration resulting in gelation, when the formulation is administered in the stomach.[20]

2.2.5 Chitosan

Chitosan is a biodegradable, thermosensitive, polycationic polymer. It is obtained by alkaline deacetylation of chitin. Chitin is a natural component of shrimp and crab shell. Chitosan molecule is a copolymer of N-acetyl-D-glucosamine and D-glucosamine, Chitosan is a biocompatible, pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2, Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. On addition of chitosan granules in acidic media (pH 1.2) and neutral media (deionized distilled water) it immediately becomes buoyant in nature and provides a controlled release of the drug.[21]

2.2.6 Carbopol

Carbopol is a well known pH dependent polymer, which remains in solution form at acidic pH but forms a low viscous gel at alkaline pH. HPMC is used in combination with carbopol to impart the viscosity to carbopol solution. Various water soluble polymers such as carbopol system–hydroxyl propyl methyl cellulose system, poly (methacrylic acid) poly (ethylene glycol) can come under the category of pH-induced in-situ precipitating polymeric systems.[22]

2.3 Approaches used for the formulation of the raft forming drug delivery system

Raft forming drug delivery systems are a revolution in oral drug delivery. These have a unique property of temperature dependent and cation-induced gelation. Gelation involves formation of the double helical junction zones followed by aggregation of the double helical segments which form three dimensional networks by complexation with cations and hydrogen bonding.[23]

Different approaches based on their mechanisms used for triggering the raft formation in the GIT are as follows;

- ❖ Raft formation based on physical mechanism
- ❖ Raft formation based on chemical mechanism
- ❖ Raft formation based on physiological stimuli mechanism

2.3.1 Raft formation based on physical mechanism

2.3.1.1 Swelling

Formation of a gel occurs when the liquid effervescent system comes in contact with gastric fluid. In situ formation of gel occurs when materials absorb water from the surrounding environment and expand to occur at the desired space. Swelling of the polymer occurs by absorption of water which further causes formation of the gel. Certain biodegradable lipid substance such as myverol 18–99 (glycerol mono-oleate), is a polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded in-vivo by enzymatic action. [24]

2.3.1.2 Diffusion

This method involves diffusion of a solvent from polymer solution into surrounding tissue, which further results in precipitation or solidification of polymer matrix. [25]

2.4 Raft formation based on chemical mechanism

2.4.1 Ionic cross linking

There are various polysaccharides that undergo phase transition in the presence of various ions. Polysaccharides falling into the class of ion-sensitive ones are most widely used, Ion sensitive polysaccharides such as carrageenan, gellan gum, pectin, and sodium alginate undergo phase transition in the presence of various ions such as k+, Ca+, Mg+, and Na+ Alginic acid undergoes gelation in the presence of divalent or polyvalent cations like Ca2+ due to the interaction with glucuronic acid block in alginate chains.[26]

2.5 Raft formation based on physiological stimuli mechanism

2.5.1 pH dependent gelling

Formation of gel in the system also occurs due to change in the pH of the medium. Various pH dependent polymers are used which cause the formation of in situ gel in the system. pH sensitive polymer can be neutral or ionic in nature. The anionic networks contain negatively charged moieties, cationic networks contain positively charged moieties, and neutral networks contain both positive and negatively charged moieties. In the case of anionic polymeric network containing carboxylic or sulphonic acid groups, ionization takes place, as the pH of the external swelling medium rises above the pKa of that ionizable moiety. [27]

2.5.2 Temperature dependent gelling

These hydrogels are liquid at room temperature (20°C–25°C) and undergo gelation when in contact with body fluids (35°C–37°C), due to an increase in temperature. This approach exploits temperature-induced phase transition. Some polymers undergo abrupt changes in solubility in response to increase in environmental temperature Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. Polymers such as pluronics (poly (ethylene oxide)–poly (propylene oxide)–poly (ethylene oxide) polymer networks of poly (acrylic acid) and poly acrylamide or poly (acrylamide-co-butyl methacrylate) are commonly used for temperature sensitive hydrogels formation. [28]

3. ADVANTAGES [29-32]

1) Raft forming system forms a low density viscous layer on gastric contents these lead to more drug release and improve bioavailability.
2) Improve patient compliance by making a once a day therapy.
3) Improve therapeutic efficacy.
4) Easy to administer to a patient.
5) Rapid and Long-duration of action can easily achieved by raft formation.
6) It will not interfere with function of pyloric sphincter.
7) These are advantageous for drugs absorbed through the stomach.
8) Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
9) It does not interfere with the activity of promotility agent, antisecretory agents such as cimetidine.
10) Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

4. DISADVANTAGES [30-33]

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

5. APPLICATIONS

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follow**:**

5.1 Sustained Drug Delivery

FDDS can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.[34]

5.2 Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine .The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.[35]

5.3 Absorption Enhancement

Drugs that have poor bioavailability because of site- specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery. [36]

5.4 Bioavailability Enhancement

The bioavailability of controlled release gastroretentive drug formulation is significantly enhanced in comparison to the administration of non gastroretentive drug formulation controlled release polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption. [37]

5.5 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 Pharmacodyanamic aspect provides the rationale for gastroretentive drug formulation for betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.[38]

5.6 Reduced Fluctuations of Drug Concentration

Continuous input of the drug following for controlled release gastroretentive drug formulation administration produces blood drug concentrations 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.[39]

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