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FLOATING ORAL IN-SITU GEL A COMPREHENSIVE APPROACH FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM: AN OVERVIEW

Vaishnavi J. Patil[1*], Sulbha G. Patil[2], Amruta M. Patil[3], Puja C. Patil[4], Nishant M. Patel[5] and Jayesh A. Patil[6]

[1-6]Department of Pharmaceutics, P.S.G.V.P. Mandal's, College of Pharmacy, Shahada-425409, Dist.-Nandurbar, (MH) India.

***Corresponding Author: Vaishnavi J. Patil**

Department of Pharmaceutics, P.S.G.V.P. Mandal's, College of Pharmacy, Shahada-425409, Dist.-Nandurbar, (MH) India.

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ABSTRACT

The drugs having a confined absorption window in the gastrointestinal tract (GIT) when administered by oral route are often limited by poor bioavailability due to insufficient drug release and short residence time at the site of absorption. Liquid orals are more susceptible to low bioavailability because they are removed rapidly from the stomach since they are subjected to faster transit from the stomach/ duodenum. The issues of immediate release and short gastrointestinal residence of liquids are removed by formulating as oral in situ gels as they provide the best means to overcome these problems. The in situ gel dosage form is a liquid before administration and after it comes in contact with gastric contents due to one or more mechanisms gets converted to gel which floats on gastric contents. This accomplishes greater residence as well as sustained release. This approach is useful for both systemic and local effects of drugs administered. This review gives a brief idea about floating oral in-situ gel their merits and demerits, mechanism, applications, approaches and various factors affecting floating drug delivery system.

KEYWORDS: Floating gel, Gastric retention, Bioavailability, In-situ gel.

INTRODUCTION

Floating Drug Delivery System is one of the novel system of drug delivery. Floating drug delivery system (FDDS) was first described by Davis in 1968. FDDS is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. Floating drug delivery systems meant for gastric retention, float on the surface of the gastric fluids, due to their low density and produce prolonged effect by showing the controlled release. This type of delivery system is of great value for drugs which get absorbed from upper part of the stomach i.e. their absorption window resides in upper part of stomach. It is also useful for drugs which are inserting at alkaline pH of intestine and remains unabsorbed or causes side effects due to insolubility. The FDDS are particularly useful for drugs required for their local effect in stomach.[1, 2, 3]

Various dosage forms are formulated in the form gastro retentive floating systems such as microspheres, micro beads, tablets, capsules, films etc. In-situ gelling system is a new trend in floating DDS. In-situ gelling system have its application in different routes of administration like oral, nasal, ophthalmic, peroral, rectal, vaginal and also parenteral route. In situ forming polymeric drug delivery systems has many advantages such as ease of administration, increased local bioavailability, reduced dose frequency, improved patient compliance and has less complex method of production and so is cost effective. Gastro retentive FDDS have bulk density lower than gastric fluid and hence remain buoyant in stomach without affecting the gastric emptying rate for a long period of time. When the gel so formed float on gastric fluid the drug get released slowly at desired rate from the floating gel. After drug is released from floating system, the residual part is emptied from stomach. This may increase gastric retention time (GRT) and also control the fluctuations in plasma drug concentration.[4, 5, 6]

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of Floating Drug Delivery Systems.[7, 8, 9, 10]

1] Effervescent systems

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. Gas can be introduced into the floating chamber by the volatilization of an

organic solvent (e.g., ether or cyclopentane) or by the carbon dioxide produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed.

2] Non-effervescent systems

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxyl-propyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

MERITS[11]

- Ease of administration and good patience compliance.
- Increased gastric retention with slow drug release.
- Reduces dosing frequency.
- It shows a local action and site specificity by acting directly onto the targeted site.
- It shows less adverse effects compared to other pharmacological dosage form.
- Flexibility in formulation.
- Production is easy.

DEMERITS[12]

- In-situ gel forming systems are more susceptible to stability problems because of chemical or microbiological degradation.
- Change in pH may prompt to degradation.
- It requires high level of fluids.
- It leads to degradation due storage problems.

FACTORS AFFECTING THE FLOATING DRUG DELIVERY SYSTEM.

1] Density: gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.

2] Fed or Unfed State: Under fasting conditions, the gastro intestinal motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.[13]

3] Nature of the meal: Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.[14]

4] Caloric Content: GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

5] Size and Shape: Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GIT for 90 to 100% retention at 24 hours compared with other shapes.[15]

6] Posture: GRT can vary between supine and upright ambulatory states of the patients.[16]

7] Age: Elderly people, especially those over 70 years have a significantly longer GRT.[17]

8] Frequency of feed: The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.[18]

9] Gender: Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

MECHANISM OF FLOATING ORAL IN SITU GEL[19, 20]

The release of the drug gradually at the preferred controlled rate while it is floating just on stomach. After the drug is released, the residual system is emptied from the stomach. In addition to a minimal gastric content needed to implement the buoyancy retention principle, a minimal level of floating force (f) is also required to keep the dosage from becoming realistically buoyant on the meal's surface. If F is on the positive side, the item floats better.

$$F = F_{buoyancy} - F_{gravity}$$
$$= (Df - Ds)\, gv$$

Where, F = total vertical force
Df = fluid density
Ds = object density
v = volume
g = acceleration due to gravity

DIFFERENT APPROACHES FOR PREPARATION OF IN SITU GEL.

Various approaches for an in-situ gelling system is as follows.

A] In situ gel formation based on the physical mechanism.

1] Diffusion

Diffusion is a type physical approach that is used in in situ gel formulation. In this method involves the diffusion of solvent from polymer solution into surrounding tissue which results in formation of precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been commonly used solvent which is useful for in-situ gelling system.[21, 22]

2] Swelling

Swelling is a type of physical approach that is used in in situ gel formulation. In this method the polymer are surrounding the polymer imbibe and the fluids that are present in exterior environment and swell from out to inside and drug releases slowly. The substance like myverol 18-99 (glycerol monooleate), which contain polar lipid that swells in water to make lyotropic liquid crystalline phase structures and It has some bioadhesive properties it may be degraded in-vivo by enzymatic action.[23]

B] Chemically Induced In-Situ Gelling System

1] Ionic cross linking

In this method, the ion sensitive polymers are used. Ion sensitive polymers may undergo phase transition in presence of various ions like Na^+, K^+, Ca^+, and Mg^+. These polymers categorize into the class of ion-sensitive ones. For example, Alginic acid undergoes phase transition in the presence of divalent cations example Ca2+ because of the interaction with a glucuronic acid block in alginate chains.[24]

2] Enzymatic cross linking

Enzymatic cross linking is the most suitable method used in formation of in situ gelling system. In this method, gel is formed by cross linking with the enzymes which are present in body fluids. In-Situ formation catalyzed by natural enzymes has not been investigated widely but this system has some advantages over other approaches. For example, an enzymatic process performs effectively under physiologic conditions without the need for potentially harmful chemicals like monomers and initiators.[25]

3] Photo-polymerization

In photo-polymerization method19 electromagnetic radiations are used during formation of in situ gelling system. A solution of reactive macromere or monomers and invader can be injected into a tissues site and the application of electromagnetic radiation used to form gel. In this method, ketone, such as 2, 2 dimethoxy-2-phenyl acetophenone, is used as the initiator for ultraviolet photo- polymerization. Camphorquinone and ethyl eosin initiators are used in visible light systems.[26]

C] Stimuli Responsive In-Situ Gelling System

1] Temperature induced in-situ gelation

Temperature is the most widely used stimulus in environmentally responsive polymer systems in in-situ gelling formulation. These in situ gelling systems are liquid at temperature (20˚-25˚C) and further undergoes gelation when it comes in contact with body fluids (35˚-37˚C) because of an increase in temperature. Polymers like poloxamers, HPMC and xyloglucan show temperature induced gelation.[23]

a] Negatively thermosensitive type

Example: Poly (N-isopropylacrylamide)

b] Positively thermosensitive type

Example: Polyacrylic acid (Carbapol)

c] Thermally sensitive type

Example: Poloxamer

2] pH induced in-situ gelation

The pH is also another important environment-sensitive parameter for drug delivery, because the change in pH occurs at many specific sites or pathologic body sites, like the stomach, intestine, endosome, vagina, blood vessels, lysosome, and tumor extracellular sites. In this system gel is formed due to pH changes. In this method pH sensitive polymers or pH responsive are used. The polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH-sensitive polymers. The polymers which show pH-induced gelation are cellulose acetate phthalate (CAP), polyethylene glycol (PEG) and poly methacrylic acid (PMC) etc.[27]

3] Ion induced in situ gelation

In this method, gelling of the solution is triggered by change in the ionic strength. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. The polymer which shows osmotically induced gelation is Gelrite or Gellan gum and Alginates, etc.[28, 29]

APPLICATIONS OF IN SITU GEL IN DRUG DELIVERY SYSTEM[30,31,32]

1] Oral drug delivery system

The pH-sensitive hydro gels have a potential use in site specific delivery of drugs to specific regions of the GI tract. The formulations of gellan and sodium alginate both contain a complexed calcium ion that undergoes a process of gelation by releasing of these ions in the acidic environment of the stomach.

2] Occular drug delivery system

In ocular delivery system natural polymers like alginic acid, inulin, & xyloglucan, inulin are most commonly used. For local ophthalmic delivery system different compounds such as autonomic drugs, anti-inflammatory agent & antimicrobial agent, are used to release intra ocular tension in glaucoma. Conventional delivery

system often result in poor availability & therapeutic response due to high tear fluid turn over & dynamics leads rapid elimination of the drug from the eye so, the overcome the bioavailability problem ophthalmic in-situ gel were developed.

3] Nasal drug delivery system

In nasal in-situ gel system xanthan gum and gellan gum are used as in-situ gel forming polymers Momethasone furoate used to evaluate for its efficacy for the treatment of allergic rhinitis.

4] Injectable drug delivery system

In this drug delivery system are also formulated as in situ gels which obtained over the last decade due to its uses as there is no surgical procedure is required and also patient compliance. Mostly synthetic polymers and block copolymers are used in the formulation of Injectable in situ gel.

5] Rectal drug delivery system

The rectal route may be used to deliver many types of drugs that are formulated as liquid, semisolid (ointments, creams and foams) and solid dosage forms (suppositories). Conventional suppositories often cause discomfort during insertion. In addition, suppositories are unable to be sufficiently retained at a specific position in the rectum, sometimes they can migrate up-wards to the colon that makes them possible for drug to undergo the first-pass effect

CONCLUSION

From the above review we concludes that the in situ gelling system helps for the sustained and controlled release of the drugs, improved patient compliance and comfort, reduced dosing frequency and also provide so many benefits. This floating in-situ gel approach is suitable for drugs having narrow absorption window in stomach or drugs showing local effect in stomach. These types of drugs which are currently present in market as their solid dosage forms (tablets or capsules) will be available as their floating in-situ gels. In situ gel system has emerged as one of the best novel drug delivery systems. There is great scope for research work on in situ gel system in order to provide technique advancement in drug delivery systems.

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