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Floating Oral In-Situ Gelling System: A Review

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Abstract

Conventional oral dosage forms posses low bioavailability problems due to their rapid gastric transition from the stomach. Novel drug delivery systems in the form of gastroretentive systems such as floating systems, mucoadhesive, high-density, expandable have been developed as they provide controlled delivery of drugs with prolonged gastric residence time. Liquid orals are more prone to low bioavailability because they are eliminated quickly from the stomachsince they are subjected to faster transit from the stomach/ duodenum. The problems of immediate release and short gastrointestinal residence of liquids are eliminated by formulating as oral in situ gels as they provide the best means to overcome these problems In this review, we have discussed the various approaches to produce gastro retention of drug delivery system, with special discussion on floating *in-situ* gel system for stomach specific drug delivery. This achieves increased residence as well as sustained release. This approach is useful for systemic as well as local effect of drugs administered.

Keywords: Floating drug delivery, gastro-retentive time, In-situ gel.

INTRODUCTION

Floating Drug Delivery System (FDDS) is one of the novel system of drug delivery. 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 FDDS. In-situ gelling system have its application in different routes of administration like oral, nasal, ophthalmic, peroral, rectal, vaginal and also parenteral route. 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. 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 the upper part of the stomach. It is also useful for drugs which are inserted at an alkaline pH of intestine and remains unabsorbed or causes side effects due to insolubility. 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 GRT and also control the fluctuations in plasma drug concentration (PCD). This form may remain buoyant (8-10 hours) on gastric contents without affecting the rate of gastric emptying. Different polymer systems are used in floating drug delivering dosage forms. Among those some are polysaccharides, polymethacrylates, hydrocolloids etc. in this cellulose ether polymers are most popular, especially HPMC. The formulation of floating in situ gelling solution may sustain and prolong drug action, improve patient compliance and reduce frequency of administration of the drug in comparison to conventional drug delivery system Delivery system with higher density, initially settle down in stomach and then absorb water, swell and then float due to decrease in density of the system. But, with such system, there may be a possibility of gastric emptying of system, before the floating starts. Low density of system, which leads to floating, rendered either by incorporation of low density excipients or by providing a mechanism which leads to air entrapment within the system may have their own certain limitations.

ADVANTAGES

- 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.

DISADVANTAGES

- In-situ gel froming 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

SUITABLE DRUG CANDIDATES FOR IN SITU GEL

- Narrow absorption window in GI tract, e.g., riboflavin and levodopa.
- Primarily absorbed from stomach and upper part of GItract, e.g., calcium supplements, chlordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., antacids and misoprostol.
- Drugs that degrade in the colon, e.g. ranitidine HCl and metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

IDEAL CHARACTERISTICS OF POLYMERS

- It should be biocompatible.
- It should be capable of adherence to mucus.
- It should have pseudo plastic behavior.
- It should have good tolerance and optical activity.
- I should influence the tear behavior.
- The polymer should be capable of decrease the viscosity with increasing shear rate offering lowered viscosity during blinking and stability of tear film during fixation.

FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include the use of floating dosage forms (gas- generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and coadministration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastroretentive system. These factors are as follows:

- Density:- Gastric retention time (GRT) is an important factor that depends on the density. The density of the dosage form should be less than the gastric contents (1.004 gm/ml).
- Size and Shape:- Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
- Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have a better GRT at 24 hours compared with other shapes.
- Fed or unfed state:- Under fasting conditions, gastro intestinal motility is characterized by periods of strong motor activity that occurs every 1.5 to 2 hours and if the timing of administration of the formulation coincides with that of the MMC (migrating myoelectric complexes), 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.
- Nature of meal:- In the GI tract usually the presence of food and feeding of indigestible polymers or fatty acids can change the motality pattern of the stomach to a fed state. Thus, decreasing the gastric emptying rate improves the GRT of the dosage form and will increase absorption of drugs by allowing its stay at the absorption of site for a longer period.
- Caloric content:- GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.
- 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.
- Gender and Age:- Gastric emptying rate may differ in the males and females. Usually, the gastric emptying in males are faster than females.
- In the case of geriatric patients, especially those over 70years, have a significantly longer GRT.
- Body posture:- GRT can vary between supine and upright ambulatory states of the patients.
- Concomitant drug administration:- Anticholinergics like atropine and propentheline increase the GRT. Metoclopramide and cisapride decrease GRT.
- Disease state:- Gastric ulcer, diabetes and hypothyroidism increase the GRT. Hyperthyroidism and duodenal ulcers decrease the GRT.

DIFFERENT APPROACHES FOR IN SITU GELLING SYSTEM

There are different mechanisms used for triggering the in situ gel formation: physical changes in biomaterials (e.g., Diffusion of solvent and swelling), chemical reactions (e.g., enzymatic, chemical and photo-initiated polymerization) and Physiological stimuli (e.g., temperature and pH).

IN SITU FORMATION BASED ON PHYSICAL MECHANISM

- SWELLING

In-situ gel formation occurs when polymeric lipid absorbs water from the surrounding environment and expands to give the desired space. Example of substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form liquid crystalline phase structures. It has some bioadhesive properties, and it can be degraded *in-vivo* by the enzymatic action of the stomach.

- DIFFUSION

In this method the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of the polymer matrix. The solvent of N-methyl pyrrolidone (NMP) is useful for such a system.

IN SITU GELLING BASED ON CHEMICAL STIMULI

Chemical reactions that results in insitu gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

- IONIC CROSSLINKING

Polymers may undergo phase transition in resence of various ions. Some of the polysaccharides fall into the class of ion sensitive one such as sodium alginate, rotacarrageenan, gellan gum (Gelrite®), pectin undergo a phase transition in the presence of various ions such as K^+, Ca^{2+}, Mg^{2+}, Na^+.

For e.g., alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g.

Ca^{2+} due to the interaction with guluronic acid block in alginate chains.

While k-carrageenan forms rigid, small amount of K^+ are reply in brittle gels, elastic gels are forms in icarrageenam mainly in the presence of Ca^{2+}. Gellan gum mainly available as Gelrite.

It is an anionic polysaccharide, in the presence of mono and divalent cations that undergoes in situ gelling system.

- ENZYAMATIC CROSSLINKING

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 induce by natural enzymes and that are not been investigated widely but appear to have some advantages over chemical and photochemical methods. For example, an enzymatic process handles efficacy under physiologic conditions and no need for possibly destructive chemicals such as

monomers and initiators. Hydrogels are used in intelligent stimuli-responsive delivery systems that can release insulin have been investigated. Modify the amount of enzyme also maintain a suitable mechanism for controlling the rate of gel formation, which confess the mixtures to be injected before gel formation.

- PHOTO-POLYMERISATION

In photo-polymerization method 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. The most suitable polymers for photo polymerization are the polymers which undergo dissociation by polymerisable functional group in the presence of photo initiator like acrylate or similar monomers and macromers that are typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet are not used often because they are limited penetration of tissue and biologically harmful. 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.

IN SITU GEL FORMATION BASED ON PHYSIOLOGICAL STIMULI

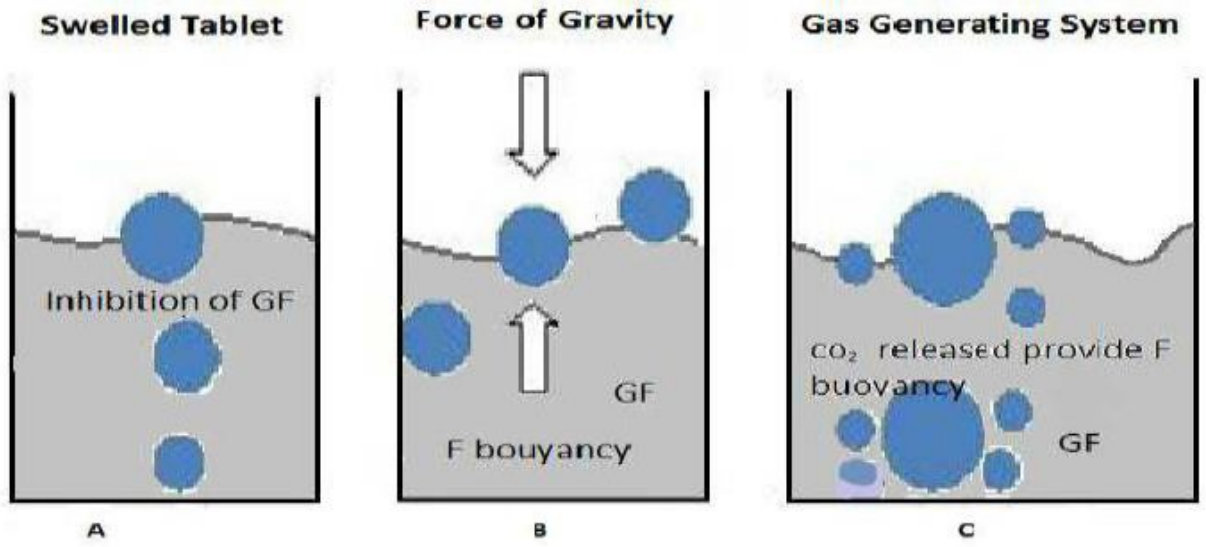
- TEMPERATURE DEPENDANT IN SITU GELLING

Temperature triggered in situ gel Temperature is the most widely used stimulus in environmentally responsive polymer systems in in-situ gelling formulation. The change of temperature used in easy to control, and also easily applicable both in vitro and in vivo. In this system, gelation is caused due to body temperature and no need of external heat. These hydrogels are liquid at room temperature (20–25°C) and undergo gelation when in contact with body fluids (35– 37°C), due to an increase in temperature. There are three types of temperature induced systems. They are negatively thermo sensitive type Eg: Poly (Nisopropylacrylamide) positively thermo sensitive type Eg: polyacrylic acid thermally reversible type Eg: poloxamer, pluronics, Tetronics. In this system, thermo responsive or temperature responsive polymers are used that show a drastic and discontinuous change in their physical properties with temperature.

These polymers show a miscibility gap at high or low temperature an upper or lower critical solution temperature exists.

- pH TRIGGERED IN SITU GELATION

In this system gel is formed due to pH changes. In this method pH sensitive polymers or pH responsive are used. In pH sensitive polymers includes pendant acidic or basic groups that may accept or release protons in counter to changes in environmental22 pH. The large number polymers of ionizable groups are known as poly electrolytes. The poly electrolytes are present in the formulation causes increase in external pH that leads to swelling of hydrogel that forms in situ gel. Some suitable polymers for this approach those polymers having anionic groups. Some are cellulose acetate phthalate (CAP), carbomer and its derivatives, polyethylene glycol (PEG), pseudo latexes and poly methacrilic acid (PMC) etc.



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.

MECHANISM OF IN-SITU GELATION

These are aqueous liquid solutions before administration, but gel under physiological conditions. Several possible mechanisms lead to in-situ gel formation are: Ionic cross linkage, pH change and temperature modulation. Polymer solutions of gellan, pectin & sodium alginate, etc. contain divalent ions complexed with sodium citrate that are breakdown in the acidic environment of stomach to release free divalent ions (Ca+2) causes the in-situ gelation of orally administered solution. It involves the formation of double helical junction zones by aggregation of double helical segments to form dimensional network by complexation with cations and hydrogen bonding with water.

MECHANISM OF FLOATING IN-SITU GEL

While the system is floating on the stomach, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach 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 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.

APPLICABILITY OF IN SITU POLYMERIC DRUG DELIVERY SYSTEM

1. Ocular drug delivery system:-

In ocular delivery system natural polymers like gallan gum, alginic acid & xyloglucan are most commonly used. For local ophthalmic delivery system various compounds like antimicrobial agent, anti-inflammatory agent & autonomic drugs are used to relieve intra ocular tension in glaucoma. Conventional delivery system often result in poor availability & therapeutic response because high tear fluid turn over & dynamics which cause rapid elimination of the drug from the eye so, the overcome the bioavailability problem ophthalmic in-situ gel was developed.

2. Nasal drug delivery system:-

In nasal in-situ gel system gallan gum & xanthan gum are used as in-situ gel forming polymers Momethasone furoate was evaluated for it's efficacy for the treatment of allergic rhinitis. Animal study were conducted using allergic rhinitis model & effect of in-situ gel on antigen induced nasal symptoms in sensitizes rats was observed. In-situ gel was found to inhibit the increase in nasal symptoms are compared to marketed preparation nosonex (Momethasone furoate suspension 0.05%).

3. 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.

4. Vaginal drug delivery system:-

The vagina, in addition to being an important organ of reproductive tract, serves as a potential route for drug administration. Formulations based on a thermo-plastic graft copolymer that undergo in situ gelation have been developed to provide the prolonged release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins.

5. Injectable drug delivery system:-

One of the most obvious ways to provide sustained release medication is to place the drug in delivery system and inject or implant the system into the body tissue. Thermoreversible gels mainly prepared from poloxamers are predominantly used. The suitability of poloxamer gel alone or with the addition of hydroxyl propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (CMC) or dextran was studied for epidural administration of drugs invitro.

6. Dermal and transdermal drug delivery system:-

Thermally reversible gel of Pluronic F127 was evaluated as vehicle for the percutaneous administration of Indomethacin. In-vivo studies suggest that 20% w/w aqueous gel may be of practical use as a base for topical administration of the drug. Poloxamer 407 gel was found suitable for transdermal delivery of insulin73. The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation.

7. Oral drug delivery system:-

For the oral in situ gel delivery system pectin, xyloglucan & gellan gum natural polymers are used. Pectin formulation for sustained delivery of paracetamol has been reported. Advantages of pectin is water soluble so, no need to add organic solvent. Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amide pectins, guar gum and insulin were investigated in order to develop a potential colon-specific drug delivery system. W. Kubo et al. developed the formulations of gellan and sodium alginate both containing complexed calcium ions that undergo gelation by releasing of these ions in the acidic environment of the stomach. Oral delivery of paracetamol was studied. Hydrogels made of varying proportions of PAA derivatives and crosslinked PEG allowed preparing silicone microspheres, which released prednisolone in the gastric medium or showed gastroprotective property.

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