WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 7, 253-275 Review Article SSN 2277– 7105

FLOATING ORAL IN–SITU GEL: A REVIEW

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Article Received on
07 March 2023,

Revised on 28 March 2023,
Accepted on 19 April 2023

DOI: 10.20959/wjpr20237-27959

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ABSTRACT

Drugs with a restricted window of absorption in the gastrointestinal tract (GIT) are frequently constrained by poor bioavailability because of imperfect drug release and brief residence times at the site of absorption. In order to provide controlled drug delivery with an extended stomach residence period, new drug delivery systems in the form of gastro retentive systems, such as floating systems, mucoadhesive, high-density, expandable systems, have been created. Since they undergo rapid transit from the stomach/duodenum, liquid orals are more likely to have limited bioavailability since they are quickly removed from the stomach. Oral in situ gels offer an effective solution to overcome the challenges of early liquid release and short gastrointestinal residence, making them a promising option for addressing these issues. The in situ gel dosage form initially exists as a liquid before administration, but upon contact with gastric contents, one or more mechanisms trigger its transformation into a gel-like state, floats on gastric contents. This results in both increased residence and sustained release. This method is useful for both systemic and local effects of drugs. This review study provides an overview of the formation of floating oral in-situ gels, as well as a summary of research conducted by multiple scientists on a variety of drugs and polymers.

KEYWORDS: Floating drug delivery, gastric retention time, swelling polymers, cross-linking gelation, In-situ gel.

INTRODUCTION

One of the novel medication delivery systems is the floating drug delivery system (FDDS). Many dosage forms, including microspheres, microbeads, pills, capsules, films, etc., are created in the form of gastro retentive floating systems. A novel development in FDDS is the in-situ gelling system. A number of administration techniques, including oral, nasal, ocular, peroral, rectal, vaginal, and parenteral routes, utilise in-situ gelling systems.[1] Gastro retentive FDDS have a bulk density lower than gastric fluid and, as a result, float in the stomach without slowing down the rate at which the stomach empties. Drugs that are absorbed from the upper part of the stomach, or whose absorption window is located there, benefit greatly from this sort of delivery mechanism. It is also helpful for medications introduced at an alkaline gastrointestinal pH that do not dissolve or produce negative effects. The medicine is released slowly and at the correct rate from the produced gel when it floats on stomach fluid. The remainder of the medicine is expelled from the stomach once it has been liberated from the floating system. This might improve GRT and stabilise plasma medication concentration swings (PCD). This version may stay buoyant on stomach contents for 8 to 10 hours without slowing down the rate of gastric emptying. Floating medication delivery dosage forms employ a variety of polymer systems. In this cellulose, other polymers, particularly HPMC, are the most common. Some of these are polysaccharides, polymethacrylates, hydrocolloids, etc. In comparison to traditional drug delivery methods, the composition of floating in situ gelling solution may sustain and prolong pharmaceutical action, improve patient compliance, and reduce drug administration frequency. Higher density delivery systems initially sink to the bottom of the stomach where they collect water, expand, and eventually flounder as the density of the system decreases. But, before the floating begins, there may be a probability of stomach emptying with such a system. Low system density, which causes floating, can be achieved by the introduction of low density excipients or by providing a mechanism that causes air entrapment within the system.[2]

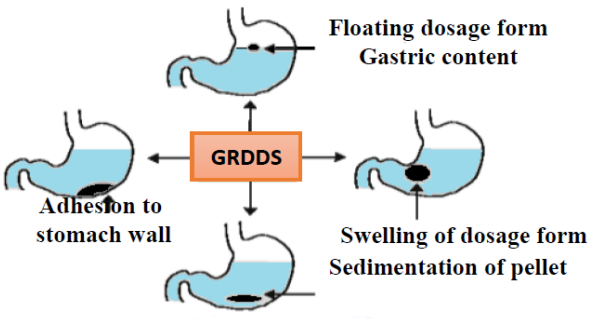

Fig. 1: Classification of GRDDS.

Advantages of Floating Drug Delivery System[3-9]

1. Stable therapeutic level for a longer duration of time. Antibiotics such as beta lactams are one example.
2. Drug bioavailability is increased. E.g. Bioavailability of controlled release gastroretentive dosage forms (CR-GRDF) of riboflavin is improved as compared to non-CR-GRDF polymeric formulation.
3. By reducing dose frequency, gastroretentive dosage forms increase patient compliance.
4. Drug mucosal irritation is reduced by slowly releasing the medication at a regulated rate. NSAIDs, for example.
5. Treatment of gastrointestinal conditions such as gastroesophageal reflux disease, Helicobacter pylori infection, and so on.
6. For medications with low absorption in the gut, a floating drug delivery device is a viable option.
7. The floating medication delivery technique can reduce the body's counter-activity, resulting in increased drug efficiency.
8. For medicines having a short half-life, prolonged release may result in a pharmacokinetic flip-flop.
9. For medications that are absorbed through the stomach, floating drug delivery methods are useful. For example, ferrous salts, antacids, and so on.
10. Long-lasting drug delivery systems lessen the frequency with which medications with short half-lives must be dosed.
11. Despite the first pass effect, bioavailability improves because variations in plasma drug concentration are avoided; continuous drug release maintains a desired plasma drug concentration.
12. Controlled drug delivery of drugs.
13. Poor absorption is predicted when there is a forceful digestive movement and a short transit time, as may occur in some types of diarrhoea. In such cases, it may be preferable to keep the medicine floating in the stomach to obtain a significantly better reaction.

Disadvantages Or Limitation Of Floating Drug Delivery System[3,7- 9]

1. It is only helpful when the stomach fluid level is sufficiently high.
2. In supine patients, gastric emptying of floating dose forms might occur at random and is strongly reliant on diameter size. As a result, patients should not be given these formulations right before going to bed.

3. The standard dose forms of pharmaceuticals, which are absorbed throughout the gastrointestinal tract, are not significantly superior than these methods.
4. The dosage formed in swellable systems must remain larger than the resting pylorus aperture for the required time period.
5. The limitations of the floating drug delivery These technologies do not provide considerable advantages over traditional medication dose forms that are absorbed throughout the gastrointestinal tract .thud are violent gas production, dosage form disintegration, burst release, dose dumping, and an alkaline microenvironment.
6. Nevertheless, that once stomach empties and the dose form reaches the pylorus, its buoyancy may be limited.

Suitable Drug Candidates For In Situ Gel[1]

1. Small GI tract absorption window, such as for riboflavin and levodopa.
2. For example, calcium supplements, chlordiazepoxide, and cinnarazine are mostly absorbed from the stomach and upper section of the gastrointestinal system.
3. Stomach-specific medications, including as antacids and misoprostol.
4. Drugs that break down in the colon, such as metronidazole and ranitidine HCI.
5. Medications that alter the usual intestinal flora, such as amoxicillin rehydrate.

Ideal Characteristics of Polymers[1]

1. It should be biocompatible.
2. It should be capable of adherence to mucus. It should have pseudo plastic behaviour.
3. It should have good tolerance and optical activity. I influence the tear behavior.
4. Oral prolonged dosing of paracetamol in situ gelling pectin formulations Wataru Kubo, Yasuhiro Konno, Shozo Miyazaki, and David Attwood are among the cast members.

Classification of Floating Drug Delivery Systems[10-14]

Two unique technologies have been used in the creation of Floating Drug Delivery Systems, based on the mechanism of buoyancy.

1. Effervescent systems

These buoyant delivery systems employ matrices composed of swellable polymers such as Methocel or polysaccharides such as chitosan, as well as effervescent components such as sodium bicarbonate and citric or tartaricacid. Or matrices containing liquid chambers that

gasify when exposed to body heat. The effervescent reaction or the volatilization of an organic solvent (such as ether or cyclopentane). between organic acids and carbonate-bicarbonate salts can introduce gas into the floating chamber. As the matrices enter the stomach, the acidity of the gastric contents releases carbon dioxide, which is caught in the gellified hydrocolloid. This causes the dose form to rise and retains its buoyancy. A multi-unit form of floating pill that emits carbon dioxide gas was recently designed.

2. Non-effervescent systems

Non-effervescent floating drug - delivery methods are being developed. Polyacrylate, polycarbonate, polystyrene, and polymethacrylate are examples of gel-forming or highly swellable polysaccharides or matrix-forming polymers. In one way, the medication is intimately mixed with a gel-forming hydrocolloid, resulting ininteracting with stomach fluid during oral administration, retaining relative form integrity, and possessing a bulk density less than unity within in the gastrointestinal environment. The air contained by the expanded polymer gives these dose forms buoyancy. The most often used excipients in these systems include polyacrylates, polyvinyl acetate, carbopol, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonates.

Factors affecting the floating drug delivery system

Many attempts have been undertaken to keep the dose situ gel form in the stomach in order to increase retention. It's a difficult moment. The use of that dosage (e.g., forms (gas-generating systems and swelling or expanding poly systems), mucoadhesive systems, high-density systems, temper modified shape systems, gastric-emptying delaying devices, and administration of gastric-emptying IN S delaying drugs are among these attempts. A variety of variables influence the bioavailability and effectiveness of the gastro retentive system in the majority of these techniques.

These elements are as follows

a. Density: Gastric retention time (GRT) is determined by dosage form buoyancy, which is affected by density.

b. Size and Shape: Dosage urit with a size more than 7.5 mm had a higher GRT when compared to those with a diameter of 9.9 mm. As compared to other shapes, dosage forms with a flexural modulus of 48 and 22.5 kiloponds per square inch (KSI) are claimed to have superior GIT for 90 to 100% retention at 4 hours.[15]

c. Fed or Unfed State: When someone is fasting, their gastrointestinal tract's motility is characterised by bursts of vigorous motor activity or migrating myoelectric complexes (MMC), which happen around every 1.5 to 2 hours. If the formulation is delivered concurrently with the MMC, which eliminates undigested material from the stomach, the unit's GRT should be quite brief. MMC is delayed and GRT takes a lot longer in the fed condition, however.[16]

d. Meal mixture: Feeding indigestible polymers of fatty acid salts can shift the stomach's motility pattern to a fed state, slowing gastric emptying and extending medication release.[17]

e. Caloric Content: GRT can be increased in 4 to 10 hours with a high protein and fat diet.

f. Feed Frequency: Due to the low frequency of MMCI, the GRT can increase by almost 400 minutes when multiple meals are provided instead of a single meal.

g. Gender: The average ambulatory GRT in meals (3.440.4 hours) is lower in men than in women of the same age and race (4.61.2 hours), independent of weight, height, or body surface area.[18]

h. Age: Older adults, particularly those over the age of 70, have significantly longer GRT.[19-20]

i. Posture: GRT can differ between the patients' supine and upright ambulatory states.[21]

j. Concurrent medication administration: includes anticholinergic substances such as atropine and propentheline, opiates such as codeine, and prokinetic agents such as metoclopramide and cisapride.

Polymers in Gel-Floating in Situ[22]

In floating drug delivery systems, polymers are frequently employed to transport medication to a particular part of the gastrointestinal tract, such the stomach. Both synthetic and natural polymers have been intensively researched in the development of medication delivery methods. Despite the introduction of various synthetic polymers, the usage of natural polymeric materials in drug administration has grown significantly during the last two decades.

Natural polymer incorporation in various drug delivery methods appears to be an active area of study and development for apparent reasons of compatibility, low cost, and accessible availability.

Natural polymers used in In-situ gel Preparation

1. Xanthan Gum

Xanthan gum is a high molecular weight extracellular polysaccharide derived by pure culture aerobic carbohydrate fermentation using Xanthomonas campestris bacteria.[22] Xanthan is a polysaccharide with a long chain and a lot of trisaccharide side chains. The primary chain is made up of b-(1,4)-linked D-glucose units. Two mannose units and one glucoronic acid unit make up the side chains. In water, this gum forms a fragile structure, resulting in high viscosity solutions at low concentration. From 0°C to 100°C, the viscosity remains relatively constant.[23]

2. Gum Gellan

Gellan gum is a deacetylated extracellular linear polysaccharide with an anionic molecular weight that contains glucuronic acid, rhamnose, and glucose. A pure colony of Pseudomonaselodea produces it as a fermentation product. Gellan gum, commonly known commercially as Phytagel or Gelrite. It can gel in the presence of monovalent and divalent ions. It comes in two varieties (high or low acyl content). This gum provides outstanding taste release, high gel strength, excellent stability, process flexibility, high clarity, good film forming, and thermally reversible gel properties.[24,25] Rajnikanth et al used the ionotropic gelation process to create and test gellan-based floating beads of acetohydroxamic acid. As powerful urease inhibitors, the prepared beads demonstrated good antibacterial action. They came to the conclusion that an oral dosage form of floating gellan beads carrying this medicine might be a beneficial stomach site specific drug delivery method for treating H. pylori infection.[26]

3. Gum Karaya

Karaya gum is a vegetable gum generated as an exudate by Sterculia trees. Gum karaya is a polysaccharide made up of the sugars galactose, rhamnose, and galacturonic acid. Gum is the least soluble of the commercial plant exudates, yet even at low concentrations (1%), it absorbs water quickly and swells to create sticky colloidal solutions. The presence of acetyl groups in the structure of karaya gum determines its swelling behaviour. Using natural hydrophilic polymers such as guar gum, xanthan gum, and karaya gum, Eaga et al created and tested sustained release floating matrix tablets containing atenolol and S-atenolol. The results show that each gum has a varied ability to hydrate and expand when exposed to water.

It has also been determined that gums can provide zero order drug release via a diffusion process.[26]

4. Psyllium Husk

Psyllium husk is a swellable, biocompatible, affordable, inert, environmentally acceptable, and easily accessible polymeric product derived from dried seed coats of Plantago ovate. The seed includes 5-10% lipids, sterols, proteins (15-18%), traces of cyclopentanopyridine-type alkaloids, aucubin, and carbohydratesplanteose, a trisaccharide, and 10-12% heteroxylan mucilage. 73 Psyllium husk also possesses anti-release characteristics. The features indicate that psyllium husk is most likely to be a feasible gastroretentive medication delivery strategy. Chavan Patil et al created ofloxacin continuous release floating tablets using various combinations of psyllium husk, HPMC K100M, and crospovidone. The buoyancy lag time, length of buoyancy, dimensional stability, drug content, and in vitro drug release profile of the formulations were also investigated.[27]

5. Pectin[28]

They are anionic polysaccharides of plant origin that are extracted from the cell walls of most plants and mostly consist of -(1-4)-D-galacturonic acid residues. Pectin gels in the presence of divalent ions (e.g., Ca), which induces galacturonic acid units to cross link (ionic cross linking), as well as in the presence of H ions (pH dependent gelling).

6. Xyloglucan[29]

It is a plant-based polysaccharide derived from tamarind seeds. This polysaccharide is chemically formed of a chain of (1-4)- D-glucan with (1-6)- D xylose units as branches that contain partial (1-2)-D-galactoxylose substitution. While xyloglucan does not gel, dilute solutions partially digested by galactosidase display gelling qualities when heated (temperature dependent gel formation).

7. Chitosan[29]

Chitosan is a natural and multifunctional polymer that is produced by the alkaline deacetylation of chitin. It possesses advantageous biological features such as non-toxicity, biocompatibility, and biodegradability. This polymer is a great agent for site-specific medication administration since it is bioadhesive and antimicrobial. The molecule of chitosan is a copolymer of N-acetyl-D-glucosamine and D-glucosamine. Chitosan is a high molecular weight polycationic weak base with a pKa value of roughly 6.2-7.0 for the D-glucosamine

residue and is thus insoluble at neutral and alkaline pH values. The drug release rate was reduced by increasing the thickness of the chitosan membrane. The development of medication delivery strategies that decrease the impact of gastrointestinal transit time may benefit from the usage of chitosan granules and chitosan-laminated formulations.

Synthetic polymers used in In-Situ Gel

The system's foundation consisted of three polymers with distinct roles, including GG, a polymer capable of gelling in the presence of ions, MC, a polymer with a gelation temperature close to 50 °C, and HPC, a polymer capable of interacting with mucin/mucosa. The three polymers work in concert to create a protective gel coating with long-lasting permanence on the mucosa.[30]

1. Alginate[31]

Alginic acid is a polysaccharide composed of D-mannuronic acid (M) and L-guluronic acid (G) residues linked by a 1,4-glycosidic bond. When di- and trivalent metal ions are added to diluted aqueous alginates, a co-operative mechanism involving subsequent guluronic residues in the G blocks of the alginate chain results in firm gels. This characteristic has been widely used in the development of vehicles for the continuous administration of bioactive compounds, most often as matrix devices.

2. Hydroxypropyl Methyl Cellulose (HPMC)

The limitations for the different forms of HPMC are shown in Fig. 18, and hydroxypropyl methyl cellulose (HPMC) is an O-methylated (OCH3) and O-(2-hydroxypropylated) (OCH2CH (OH) CH3) cellulose that complies with these limits. It comes in a number of grades with different viscosities (50–100,000 cps) and molecular weights (about 1000–1,500,000).[32]

3. N-Propyl acrylamide Copolymers

The LCST of the non-biodegradable polymer Poly (N-isopropylacrylamide) (pNiPAAm), at which cross-linked gels of this substance collapse, is 32 ℃ in water. Recently discovered applications for pNiPAAm-based hydrogels include medication delivery, cell encapsulation and delivery, and surfaces for cell culture.[33]

4. Carbopol

It is a well-known pH-dependent substance that, at acidic pH, remains in solution form but, at alkaline pH, transforms into a low viscosity gel. Increase the viscosity of the carbopol solution while lowering its acidity when combined with HPMC.[34]

5. Poloxamer

These polymers are PEO (A) and PPO-based triblock copolymers of the ABA type (B). The molecular weights and ethylene oxide-propylene oxide weight ratios of the poloxamer series' assortment of liquids, pastes, and solids range from 1100 to 14,000 and 1:9 to 8:2, respectively. Thermoreversible gels are created using poloxamer concentrated aqueous solutions. Poloxamer 407 (Pluronics F127) was discovered to gel at a lower concentration than the other poloxamer series members, 20% wt at 25 ℃. The solution acts as a viscous mobile liquid at ambient temperature (25 ℃), changing to a semi-solid translucent gel at body temperature (37 ℃).

Approaches of In- Situ Gel Drug Delivery

Different approaches and mechanisms utilized or involved in producing the in situ gel formation are as follows:

1. Physiological Stimuli

A. Temperature.

B. pH

2. Physical Changes In Biomaterials

A. Solvent exchange

B. Swelling

3. Chemical Reactions

A. Enzymatic

B. Chemical

C. Photo-initiated polymerization.

1. In Situ Formation Based On Physiological Stimuli

A. Temperature

Temperature triggered in situ gel Temperatur: 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 In this system, and no need of iquid at room temperature (20-25°C) and undergo gelation when in to an increase of temperature thermo sensitive type Eg, Poly (Nisopropylacrylamide) positively thermo sensitive type Eg, polyacrylic acid thermally reversible In this system, thermo responsive or temperature responsive polymers are used that show a drastic and discontinuous change in easily applicable both in vitro and in vivo. gelation is caused due to body temperature external heat. These hydrogels are contact with body fluids (35-37 °C), du in temperature. There are three types induced systems. They are negatively type Eg: poloxamer, pluronics, Tetronics their physical properties with temperature. These polymers show a miscibility gap temperature an upper or lower temperature exists.[35-36]

B. pH

Gel forms in this system when the pH fluctuates. This approach employs pH sensitive polymers or pH responsive polymers. pH sensitive polymers include attached acidic or basic groups that may receive or release protons in response to environmental22 pH variations. Poly electrolytes are polymers with ionizable groups in vast quantities. The presence of poly electrolytes in the formulation raises the external pH, causing the hydrogel to expand and form an in situ gel. Polymers with anionic groups are particularly favourable for this method. CAP, carbomer and its derivatives, and polyethylene glycol are a few examples (PEG). Pseudolatexes and poly methacrilic acid (PMC), for example.

2. In situ formation based on Physical changes

A. Solvent exchange/ Diffusion[37-38]

The diffusion of solvent from the polymer solution into the surrounding tissue leads in the precipitation or solidification of the polymer matrix. N methyl-pyrrolidone (NMP) has been demonstrated to be a suitable solvent for such a system.

B. Swelling[39-40]

In situ formation can also occur when a substance collects water from its surroundings and expands to fill a desired region. Myverol 18-99 (glycerol mono-oleate), a polar 1400 lipid that expands in water to produce lyotropic liquid crystalline phase formations, is one such chemical. It possesses some bioadhesive characteristics and can be destroyed in vivo by enzymatic activity.

3. IN SITU GELLING BASED ON CHEMICAL STIMULI

Precipitation of inorganic solids from supersaturated ionic solutions, enzymatic activities, and photo-initiated processes are examples of chemical reactions that result in insitu gelation.

A. Enzymatic[41-42]

Enzymatic cross linking is the best way for forming an 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. An enzymatic method, for instance, can manage efficacy in physiological circumstances without the requirement for potentially harmful chemicals like monomers and initiators. Hydrogels are used in intelligent stimuli-responsive delivery systems that can release insulin have been investigated. Change the enzyme concentration while maintaining a reliable system for regulating the pace of gel formation, which permits the mixes to be injected prior to gel formation.

B. Chemical[43-44]

In the presence of different ions, polymers may go through phase transitions. Certain polysaccharides, including sodium alginate, rotacarrageenan, gellan gum (Gelrite®), and pectin, are ion sensitive and go through a phase change when exposed to ions including K+, Ca2+, Mg2+, and Na+. For instance, alginic acid gels when divalent or polyvalent cations, such as Ca2+, are present because of their interaction with the guluronic acid block in alginate chains. Where as icarrageenan produces elastic gels primarily in the presence of Ca2+, k-carrageenan creates stiff, brittle gels in response to tiny amounts of K+. Gelrite is the primary form of icarrageenan. It is an anionic polysaccharide that experiences in situ gelling in the presence of monovalent and divalent cations.

C. Photo-initiated polymerization[45-46]

In the photo-polymerization procedure, electromagnetic radiations are employed to generate an in situ gelling system. The formation of gel can be accomplished by injecting a solution of reactive macromere or monomers and intruder into a tissue location. 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 Long-wavelength macromers are primarily utilised in the visible and ultraviolet spectrums. Short wavelength ultraviolet are not used often because they are limited penetration of tissue and biologically harmful. The initiator for UV

photopolymerization in this process is a ketone, such as 2,2 dimethoxy-2-phenyl acetophenone. camphorquinone and ethyl cosin initiators are used in visible light systems.

Mechanism of In-Situ Gelation

Before delivery, they are aqueous liquid solutions that gel under physiological circumstances. Ionic cross linking, pH change, and temperature modulation are three probable pathways that contribute to in-situ gel formation. Polymer solutions containing divalent ions complexed with sodium citrate, which are broken down in the acidic environment of the stomach to liberate free divalent ions (Ca+2), produce in-situ gelation of orally given solution. It entails the formation of double helical junction zones through the aggregation of double helical segments to create a dimensional network via cation complexation and hydrogen bonding with water.

Mechanism of Floating In-Situ Gel

The medicine is slowly removed from the system while the system is floating on the stomach at the correct rate. The stomach's residual system is emptied once the medication has been released. A minimum degree of floating force (F) is also necessary to maintain the buoyancy retention principle in place, in addition to the minimal stomach content that is necessary dosage form reliably buoyant on the meal's surface. A unique device for determining resultant weight has been published in the literature to quantify the floating force dynamics. The equipment works by continually measuring the force corresponding to F (as a function of time) necessary to lift a submerged item. If F is on the positive side, the item floats better. This device aids in improving the FDDS in terms of the stability and longevity of the floating forces generated in order to avoid the negative effects of unforeseen fluctuations in intragastric buoyancy capacity.

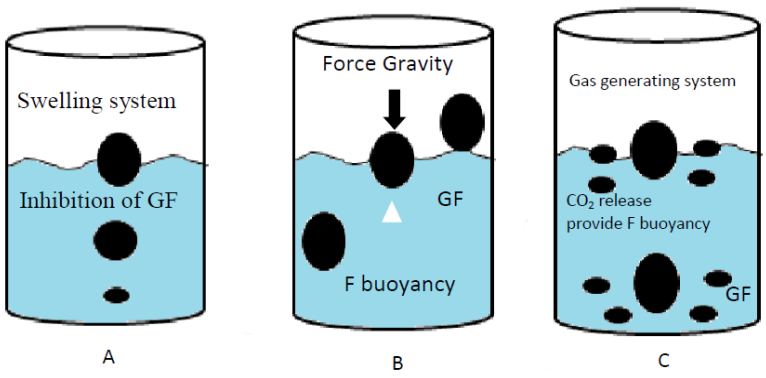

Fig. 2: mechanism of floating system.

F= F buoyancy - F gravity

= (Df-Ds) gv

Where,

F = total vertical force, Df = fluid density,

Ds = object density, v=volume and

G = acceleration due to gravity.

EVALUATION OF FLOATING ORAL IN-SITUGEL

A. Physical characteristics and pH

In situ solutions must be clear and free of any particles. In a buffer with a pH of 1.2, the amount of time needed for a solution to gel is monitored, and the gel's consistency is verified visually.[48]

One of the most crucial aspects of preparation is the clarity of the solution. By visually inspecting the answers on a black and white backdrop, the clarity of the solutions was established. At 25°C, the pH was determined using a calibrated digital pH metre.[47]

B. Viscosity

The viscosity of all formulations was evaluated using a Brookfield digital viscometer at 50 rpm on spindle number 2. The sample temperature was kept constant at 25 readings.[48] The viscosity of the solution is measured before and after gelling using a Brookfield viscometer or a cone and plate viscometer at an appropriate temperature (251) using 1 or 2ml sample aliquots.[47]

The formulation should have an optimal viscosity that allows for simple swallowing as a liquid, which subsequently undergoes a quick sol-gel transition due to ionic interaction and demonstrates shear dependency of the formulation the viscosity which reduced upon application of shear on the solutions, all polymer concentrations showed evidence of shear thinning behaviour, with the effect being more pronounced at higher concentrations. This shear thinning behaviour benefits the administration procedure since shaking the formulation enhances its fluidity and pour ability. The observed rise in viscosity with increasing concentration was previously seen for Gellan and was ascribed to increased chain interaction with polymer concentration. At all polymer concentrations studied, increasing the Calcium Carbonate component in the formulation enhanced the viscosity. Because the Calcium Carbonate is present in the formulations as an insoluble dispersion, increasing its

concentration increased the number of particles dispersed correspondingly, adding to increased viscosity.[49]

C. In-Vitro Gelation Study

To assess the gel forming solution's in vitro gelling capacity, a coloured solution of the formulation is prepared, and 15ml gelation medium (0.1N HCl, pH 1.2) is put in a test tube. After that, 1ml of coloured formulation is added. When the solution comes into touch with the gelation medium, it forms a rigid gel. Gelling capacity is governed by stiffness and the amount of time the gel remains stable.[48] Gelling capacity can also be evaluated using a visualisation approach. In this approach, 5ml of 0.1 N HCL was placed in a glass tube and kept at 37°C1°C. Several characteristics were measured, including the time required for in situ gel formation, the visual stiffness of the gel, and the length of time the gel remained intact.[47]

D. In Vitro Floating Study

The gel's floating ability is tested in a 500ml simulated dissolution equipment (type II). The dissolving vessel is then filled with 10ml of the produced mixture. The time it takes for the formulation to float (floating lag time) and the time it stays on the surface (floating time) are recorded.[48] The time it took for the formula to emerge to the medium's surface, as well as the duration of floating (DOF), the time the formula remained continually afloat on the medium's surface for each formula.

The in vitro gelling ability was classified into three groups based on FLT and DOF, as follows:

a. Low gelling capacity (+): FLT (immediate gelation) and DOF 12 h
b. Intermediate gelling capacity (++): FLT (immediate gelation) and 24 h > DOF > 12 h
c. High gelling capacity (+++): FLT (immediate gelation) and DOF > 24 h

This investigation was carried out by inserting an accurately weighed sample (1 g) of each formula in a test tube containing 10 mL of the simulated gastric fluid USP without pepsin enzyme and samples were then evaluated for their floating behaviour.[50]

E. In Vitro Drug Release

In vitro drug release is measured at 37 C using a USP dissolving equipment (type II) at 50 rpm in 900ml of 0.1N HCl and pH 1.2. 10ml of the formulation is placed in a Petri plate and

placed in the dissolving vessel. The dissolving media is then gently introduced into the dissolution vessel. At each predetermined time, a suitable sample is drawn and the medium is refilled. The dissolution research should last at least 8 hours.[48]

The in situ gel preparations were assessed using the USP dissolving test equipment (USP type II) with a paddle stirrer at 50 rpm, as reported by Zatz and Woodford (1987). This pace was slow enough to avoid gelled formulation breakdown and was consistent with the moderate agitation conditions thought to prevail in vivo. The dissolving liquid employed was 900 cc of 0.1 N HCl (pH 1.2), with the temperature maintained at 37°C. With the use of a pipette, 5 ml of formulation was brought up into the dissolution vessel containing dissolving media. The 5ml sample from the dissolving medium was extracted at various time intervals up to 8 hours while the sync condition was maintained. The samples were diluted before being analysed using a UV spectrophotometer at a maximum wavelength of 287nm.[47,51,52]

F. Stability Studies

The storage conditions for materials at room temperature were 25°C and 65% relative humidity, while the settings for accelerated stability tests were 40°C and 75% relative humidity. For 30 days, stability is to be assessed.[47]

F. Polymer Drug Interaction

The Polymer-Drug Interaction Can be evaluated by FTIR Instrument.

a. Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectroscopy is a method used to identify organic, polymeric, and certain inorganic materials, as well as to determine functional groups.

Interactions between drugs and excipients are critical in the release of drugs from formulations. The physical and chemical interactions between the medication and the excipients utilised have been studied using Fourier transform infrared spectroscopy. The pure amoxicillin and its mixtures with sodium alginate and HPMC K100 were mixed separately with IR grade KBr and scanned using an FTIR equipment (FTIR1700, Shimadzu, Kyoto, Japan) across a range of 400-4500 cm1. The ketonic, primary amine, secondary amine, and hydroxyl (broad) groups all contribute to the drug's peak.[53]

b. DSC (Differential Scanning Calorimetry)

DSC data give both qualitative and quantitative information on the drug's physicochemical state in formulation. An automated thermal analyzer system was used to investigate the drug polymer interactions in the DSC examination of the pure drug and drug-loaded in-situ gels (17). The experiment was carried out at a pace of 20o C min from 50o C to 300o C with a nitrogen flow of 25 mL/min.[54]

H. Swelling Index

A simple approach is used to calculate the gel swelling index of the specified formulation. An in-situ gel produced in 40 ml of 0.1N HCl (pH 1.2) was employed in this work. Remove the excess HCl solution using paper towels after separating the 0.1N HCl gel fraction from each formulation. Weigh the gel at the start, then add 50 cc of distilled water, wait 12 hours, record the weight of the gel, then calculate and report the weight difference.[53]

Applicability of In Situ Polymeric Drug Delivery system

1. Ocular Drug Delivery System

Natural polymers such as gallan gum, alginic acid, and xyloglucan are often employed in ocular delivery systems. To reduce intraocular tension in glaucoma, several chemicals including as antibacterial agents, anti-inflammatory agents, and autonomic medicines are employed in local ophthalmic administration systems. Because of the high tear fluid turn over and dynamics that cause fast clearance of the medication from the eye in conventional administration systems, ocular in-situ gel was created to solve the bioavailability problem.

2. Nasal Drug Delivery System

Gallan gum and xanthan gum are in-situ gel producing polymers utilised in nasal in-situ gel systems. The effectiveness of momethasone furoate in the treatment of allergic rhinitis was investigated. The impact of in-situ gel on antigen-induced nasal symptoms in sensitised rats was reported in an animal investigation utilising an allergic rhinitis paradigm. When compared to the marketed medication nosonex (Momethasone furoate solution 0.05%), in-situ gel was found to limit the rise in nasal symptoms.

3. Rectal Drug Delivery System

Gallan gum and xanthan gum are in-situ gel producing polymers utilised in nasal in-situ gel systems. The effectiveness of momethasone furoate in the treatment of allergic rhinitis was investigated. The impact of in-situ gel on antigen-induced nasal symptoms in sensitised rats

was reported in an animal investigation utilising an allergic rhinitis paradigm. When compared to the marketed medication nosonex (Momethasone furoate solution 0.05%), in-situ gel was found to limit the rise in nasal symptoms.

4. Vaginal Drug Delivery System

In addition to being an essential part of the reproductive tract, the vaginal canal may be used to provide drugs. To give sustained release of active components such as nonoxynol-9, progestins, estrogens, peptides, and proteins, formulations based on a thermo-plastic graft copolymer that undergoes in situ gelation have been created.

5. Injectable Drug Delivery System

One of the most apparent methods of providing sustained release medicine is to embed the drug in a delivery device and inject or implant it into bodily tissue. Thermoreversible gels made mostly of poloxamers are the most often utilised. The usefulness of poloxamer gel alone or in combination with hydroxyl propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (CMC), or dextran for epidural medication delivery was investigated in vitro.

6. Dermal and Transdermal Drug Delivery System

Pluronic F127 thermally reversible gel was tested as a carrier for percutaneous Indomethacin delivery. In-vivo investigations indicate that a 20% w/w aqueous gel may be useful as a basis for topical medication delivery. Poloxamer 407 gel was discovered to be useful for transdermal insulin delivery73. The combination of chemical enhancers with iontophoresis resulted in synergistic insulin permeation augmentation.

7. Oral Drug Delivery System

Natural polymers such as pectin, xyloglucan, and gellan gum are employed in the oral in situ gel delivery technique. A pectin formulation for continuous paracetamol administration has been described. Because pectin is water soluble, no organic solvent is required. Cross-linked dextran hydrogels with quicker swelling under high pH conditions were examined, as were other polysaccharides such as amide pectins, guar gum, and insulin, in order to build a viable colon-specific drug delivery system. W. Kubo et al. created gellan and sodium alginate formulations, both of which include complexed calcium ions that gelate by releasing these ions in the acidic environment of the stomach. The oral administration of paracetamol was investigated. Preparing silicone microspheres that released prednisolone in the stomach

media or displayed gastroprotective properties required hydrogels composed of different ratios of PAA derivatives and crosslinked PEG.

CONCLUSION

In conclusion, improving patient compliance is the main necessity of a successful controlled release solution, which is what in situ gels provide. Utilising polymeric in-situ gels for the controlled release of different medications has a number of benefits over traditional dosing forms. The in situ gel dosage forms are extremely dependable due to the drug's prolonged and sustained release, high stability, and biocompatibility properties. For the in situ gel formulations, the use of biodegradable and water soluble polymers can increase their acceptability and make them effective drug delivery vehicles. Liquid orals with continuous drug release have a lot of possibilities when it comes to in-situ medication administration. This floating in-situ gel method is appropriate for medications with a limited window of stomach absorption or medications with local effects. These medications, which are already accessible on the market in the form of pills or capsules, will also be offered as floating in-situ gels.

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