Abstract

Conventional oral dosage forms having low bioavailability problems due to their rapid gastric transition from stomach, in case of drugs which are less soluble at alkaline pH of intestine. Further drugs which produce their nearby activity in stomach, get quickly emptied don’t get enough residence time in stomach. To avoid these problems, different endeavors have been made to draw out the the retention time of drug in stomach. The development of in situ gel systems has gotten impressive consideration in the course of recent years as it gives the most ideal approach to conquer problems of immediate release and short GI residence of fluids. In situ gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles. The in situ gel dosage form is a liquid before administration and after it interacts with gastric contents gets changed over to gel which floats on gastric contents. In situ gel formation happens because of one or combination of various stimuli like pH change, temperature modulation and ionic crosslinking. This accomplishes expanded residence as well as sustained release. It can be easily applied to the site of drug absorption where they swell to form a strong gel that is capable of prolonging the residence time of the active substance. This review gives a short thought regarding floating oral in situ gel formation and research done by different researchers on various drugs.

1 Introduction

Generally, oral drug administration has been the prevalent route for drug delivery. Amid the previous two decades, various oral delivery systems have been created to go about as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic perspective, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies c consistently the amount of drug expected to keep up consistent plasma levels once the steady state is reached1.

Although some significant applications, including oral administration of peptide and protein drugs, can be utilized to prepare colonic drug delivery systems, targeting drugs to the colon by the oral route. More often, drug absorption is unsatisfactory and highly variable among and between people, in spite of phenomenal in vitro release patterns. The explanations behind this are basically physiological and typically influenced by the gastrointestinal (GI) transit of the form, particularly its gastric residence time (GRT), which seems to be one of the significant reasons of the overall transit time variability2,3.

In the course of recent decades, the interest and investigation of devices designed to be retained in the upper part of the GI tract has progressed reliably as far as innovation and decent variety, encompassing a variety of systems and devices for example, floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. Stomach explicit (Gastric retention) will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Likewise, longer residence time in the stomach could be beneficial for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease4,5.
Gastric retention time can be drawn out by different techniques, for example, floating drug delivery system (hydro dynamically balanced system), swelling and expanding systems, polymeric boidhesive system, modified- shape system, high density system, and other delayed gastric emptying devices. Oral in situ gel forming system also known as stomach specific or raft forming systems have given an appropriate method for providing the controlled drug delivery inside stomach with improved gastro-retention.

2 Floating In-situ gel

In situ gel forming systems have been broadly examined, for their capability of producing the sustained and controlled drug delivery. In recent years, research has been completed in detailing in situ gel by means of prevalent routes like oral, nasal, ophthalmic and other routes like vagina. This demonstrated the promising outcome, for the utilization of system as a potential method of producing the controlled drug delivery. This system essentially uses polymers which undergo transformation from solution to gel like consistency, because of progress in their physicochemical properties. This system contains in situ gel forming polymers of synthetic or natural origin, e.g. gellan gum, alginic acid, xylolucan, chitosan, polycarolactone and so on. Addition of bicarbonates or carbonates to this system improves floating ability by producing effervescence by releasing carbon dioxide (air generation) will make the gel much lighter and in turn helps to float. Capacity of the gel for prolonged and controlled release may also be enhanced by raising its viscosity with the help of viscosity enhancers.6,8

2.1 Advantages of floating in situ gel

- Improved floating property contrasted with floating tablets
- Increase in bioavailability
- Production cost is low
- Reduced dosing frequency
- Improved patient compliance
- Method of preparation is easy compared to other floating drug delivery system (FDDS)

2.2 Limitations of floating in situ gel

- In situ gel forming systems are more susceptible to stability problems because of chemical or microbial degradation
- Change in pH may prompt to degradation

2.3 Benchmarks for the assortment of drug candidate for floating in situ gel

- Drugs, which undergo significant first pass metabolism may not be desirable candidate
- Drugs having solubility or stability problems in the highly acidic gastric environment or which are irritant to gastric mucosa cannot be formulated as FDDS
- Absorption from upper GIT: Drugs have a particular site for maximum absorption
- Drug having low pKa, which remains unionized in stomach for better absorption
- Drugs having a reduced solubility at higher pH
- Drugs that act locally in the stomach

3 Various approaches to produce in situ gel

Floating in situ gels can be produced by by different methodologies given beneath

3.1 Physical change

By this methodology physical change like swelling or diffusion may happens. In swelling, polymer in the system absorbs water from the surrounding environment and swells to shape a viscous gel. In diffusion, solvent in which the drug and polymer is dispersed or dissolved, diffuse into the surrounding tissues making the precipitation of the polymer to form gel.

3.2 Chemical change

Change in chemical environment prompts polymeric cross linking thereby formation of gel.6

3.3 Change in temperature

Change in temperature prompts change in the solubility of polymer, thereby polymer- polymer interaction takes place to form a macromolecule of hydrophobic nature.

3.4 Change in pH

Polymer with anionic groups leads to increase in swelling with increase in the pH, while polymer with cationic groups shows a decrease in the swelling.

3.5 Dilution-sensitive

A polymer that undergoes phase transition in presence of higher amount of water may lead to formation of gel. eg; Lutrol F68

3.6 Electrical signal sensitive

Hydrogels sensitive to electric current undergo shrinking or swelling in the presence of an applied electric field.

3.7 Light-sensitive

Light-sensitive hydrogels can be utilized in the improvement of in situ forming gels for cartilage tissue engineering. eg; Quinone can be injected into a tissue and applied electromagnetic radiation is used to form a gel by enzymatic processes. For that long ultraviolet wavelengths are used.9
3.8 Glucose-sensitive

Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been explored. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Another methodology depends on competitive binding of insulin or insulin and glucose to a fixed number of binding sites in concanavalin A, where insulin is displaced in response to glucose stimuli, subsequently functioning as a self-regulating insulin delivery system.

4 In-situ gelation mechanism

These are fluids before administration and gel under physiological conditions. In-situ gel arrangement is possible by various frameworks like ionic cross-linkage, pH change and temperature regulation. Polymers that contain divalent particles eg; sodium alginate can shape a complex with sodium citrate, in this way breakdown of complex happens in acidic condition to discharge Ca\(^{2+}\) which prompts in-situ gelation. Complexation with cations and hydrogen holding with water prompts in-situ gelation\(^{10,13}\).

5 Floating in situ gel mechanism

At the point when this framework floats in the gastric region, medicate discharges progressively at a perfect rate. Floating force (F) is required to keep the measurements structure dependably light on the outside of the dinner. So as to gauge the coating power, a novel device is utilized for the assurance of resultant weight. This mechanical assembly works by estimating consistently the power equal to ‘F’ (as a component of resultant weight). The dosage form floats better if “F” is high. This contraption helps in advancing FDDS concerning security and strength of dosage form floats in situ gelation.\(^{14,15}\)

\[
F = F_{buoyancy} - F_{gravity} = (D_i - D_o)g\nu
\]

Where,

\(F = \) total vertical force, \(D_i = \) fluid density, \(D_o = \) object density, \(\nu = \) volume, \(g = \) acceleration due to gravity

6 Commercial formulations of in-situ gel

6.1 Regel depot technology

Regel is one of the Macromed’s restrictive medication conveyance framework and dependent on triblock copolymer, made out of poly (lactide-co-glycolide)- poly (ethylene glycol)- poly(lactide-co-glycolide). It is a group of thermally reversible gelling polymers created for parenteral conveyance that offers a scope of gelation temperature, debasement rates and discharge qualities as an element of sub-atomic weight, level of hydrophobicity and polymer fixation. Following infusion, the physical properties of polymer experience a reversible stage change bringing about arrangement of a water insoluble, biodegradable gel stop. Oncogel® is a solidified detailing of paclitaxel in Regel. It is a free streaming fluid underneath room temperature which upon infusion frames a gel in situ because of body temperature. hGHD-1 is a novel injectable terminal detailing of human development hormone (hGH) using Macromed’s Regel medicate conveyance framework for treatment of patients with high lack\(^{16}\).

6.2 Cytoryn

This is one of the Macromed's items, which is a novel, peritumoral, injectable terminal plan of interleukin-2 (IL-2) for malignancy immunotherapy utilizing Regel sedate conveyance framework. It is a free streaming fluid underneath room temperature that in a flash structures a gel station upon infusion from which the medication is discharged in a controlled way. Cytoryn upgrades the immunological reaction by securely conveying multiple times the most extreme enduring portion permitted by regular IL-2 treatment. Cytoryn additionally initiates the foundational antitumor insusceptibility. Regel framework balances out and discharges IL-2 in its bioactive structure. The arrival of medications is constrained by the rate of dissemination from and debasement of the depot\(^{17}\).

6.3 Oncogel

Oncogel is an injectable detailing of paclitaxel in a biocompatible biodegradable gel (ReGel), gives controlled arrival of paclitaxel at the infusion site, bringing about high intralesional paclitaxel focuses and ceaseless radiosensitization without orderly fundamental toxicities. This portion acceleration examine assessed the poisonous quality, pharmacokinetics, and starter antitumor action of Oncogel infused intralesionally in patients with inoperable esophageal disease who were possibility for palliative outer bar radiotherapy (RT)\(^{18}\).

6.4 Timoptic-XE

It is a timolol maleate ophthalmic gel formulation of Merck and Co. Inc., This formulation is available in two dosage strengths 0.25% and 0.5% in market. The pH of the solution is approximately 7.0, and the osmolarity is 260-330 mOsm. Each ml of Timoptic-XE 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate), inactive ingredients include gellan gum, tromethamine, mannitol, and water for injection and the preservative used is benzododecinium bromide 0.012%. Timoptic-XE, when applied topically on the eye, reduces the elevated, as well as normal intraocular pressure, whether or not accompanied by glaucoma\(^{19}\).

6.5 AzaSite

AzaSite is an advertised result of InSite Vision. AzaSite is a topical ophthalmic arrangement of azithromycin figured in DuraSite (polycarbophil, edetate disodium, sodium chloride),
AzaSite is provided as a clean watery ophthalmic formulation intended for topical organization. The suggested introductory portion of the medication is in still 1 drop in the influenced eye(s) twice every day, eight to twelve hours separated for the initial two days and then in still 1 drop in the influenced eye(s) when day by day for the following five days.

6.6 Pilopine HS

Pilopine HS is a marketed product of Alcon Laboratories Inc. Pilopine HS (pilocarpinehydrochloride ophthalmic gel) 4% is a sterile topical ophthalmic aqueous gel which contains more than 90% water and employs Carbopol-940, a synthetic high molecular weight cross-linked polymer of acrylic acid, to impart a high viscosity.

6.7 Akten™

Akten™ is an HPMC-based gel of lidocaine hydrochloride for ocular surface anesthesia. Akten™ contains 35 mg of lidocaine hydrochloride per mL as the active ingredient. Akten™ also contains Hypromellose, Sodium Chloride, and Purified Water as inactive ingredients. The pH may be adjusted to 5.5 to 7.5 with Hydrochloric Acid and/or Sodium Hydroxide. The recommended dose of Akten™ is 2 drops applied to the ocular surface in the area of the planned procedure. Akten™ may be reapplied to maintain anesthetic effect.

6.8 Virgan

Virgan is an ophthalmic antiviral that is shown for the treatment of intense herpes simplex keratitis. The suggested dosing routine for Virgan is 1 drop in the influenced eye multiple times per day (around at regular intervals while alert) until the corneal ulcer mends, and after that 1 drop 3 times every day for 7 days. Virgan (ganciclovir) contains carbomer 974. The carbomers are polyacrylic corrosive subordinates that confer high viscosity to their fluid arrangements at nonpartisan pH (above their pKa estreems) because of ionization and hydration of the carboxyl gatherings.

7 Present research in-situ gel

In situ gel of Ofloxacin was prepared by utilizing Calcium carbonate, 0.1N HCl, and trisodium citrate. It was seen that if the final concentration of CaCO₃ increases then it decreases the lag time for floating and if increase the concentration of sodium alginate and HPMC K4M the viscosity increases. It is demonstrated by observing the outcomes that ofloxacin in situ gel formulation has preferred execution over traditional formulation and furthermore improves consistence and improved efficacy.

The epic in situ gel of latidudine for gastroreteretive medication conveyance was set up by pH-activated ionic gelation procedure using different convergences of gelling polymer for instance, sodium alginate, gellan gum, and xanthum gum. In vivo examinations asserted the gastroretention of the plan in mice stomach for 8 h. The gastroreteretive in situ gel framework, delayed the gastric home time, in this manner focusing in the vicinity explicit medication discharge in the upper gastrointestinal tract.

The floating in-situ gelling arrangement of diltiazem hydrochloride was planned by using HPMC and calcium carbonate. The readied in situ gelling details of diltiazem hydrochloride could drift in the gastric conditions and discharged the medication in a continued way. The present plan was non-aggravation, simple to manage alongside great maintenance properties, better patient agreeable and with more prominent viability of the medication.

Sodium alginate based diltiazem hydrochloride floating in situ gelling systems were prepared. An attempt was made up a new raft forming oral in situ gelling system of metronidazole with improved residence time using sodium alginate as gelling polymer to eliminate H. pylori. The oral in situ gelling system of metronidazole can be formulated by use of sodium alginate as a gelling polymer and xanthan gum as release retardant to control the drug release for more than 10 hrs.

Formulation and evaluation of floating in situ gel of Ofloxacin for eradication of Helicobacter Pylori which undergoes pH dependent sol-gel transition at gastric pH, there by prolonging the retention of the system in stomach. The results substantiated that the optimized formulation revealed excellent floating characteristics and gastric retention.

The Sodium alginate based metronidazole floating in situ gelling systems were prepared. he prepared in situ gelling formulations of metronidazole could float in the gastric conditions and release the drug in controlled manner. The prepared formulations appear to be promising drug delivery system for localized delivery of metronidazole for better treatment of peptic ulcer disease caused by H. pylori.

The sodium alginate and HPMC based gliding oral in-situ gel of carbamazapine was planned for supported release. Thus consequences of the examination reasoned that valuable antiepileptic drugs like carbamazapine can be reformulated into increasingly understanding benevolent and restoratively useful definitions utilizing these sorts of oral in-situ floatable gel frameworks, which decreases producing cost and length.

Oral in-situ gelling framework for continued discharge sedate conveyance of famotidine was structured and assessed; in-vitro discharge examine uncovered that tranquilize discharged from the in-situ gel pursued non-fickian dissemination. In vivo examination for the sodium alginate was completed by pylorus legation strategy in rodents, which demonstrated gel arrangement in gastric juice and decrease in ulcer list. Security consider was additionally completed for a quarter of a year, which demonstrated no real transforms from their underlying state.
Thermo-responsive and bio adhesive in-situ gelling drug delivery system containing fluconazole, which can be used in oral thrush, was examined. Bio adhesive polymer was used as a thermo responsive material, because poloxamer18and carboxyethyl cellulose has thermal gellation properties at certain temperature. Sodium alginate based in-situ gel of clarithromycin and metronidazole benzoate was formulated, optimized and developed. Sodium alginate used as a polymer and CaCO3 was used as a cross-linking agent, this formulations exhibits good viscosity properties and sustained drug release and explained accelerated stability studies.

Mucoadhesive medication conveyance framework is a standout amongst the most intriguing and testing tries confronting pharmaceutical researcher. The ordinary buccal medication conveyance framework like mouthwash, flush, troches, creams and suspension show move back, for example, deficient destruction of candidiasis because of the short living arrangement time of antifungal medication in oral pit and debasement of antifungal specialists in the oral cavity. The improved details were assessed for gelling limit, thickness, gel quality, bioadhesive power, spreadability, tranquilize discharge and FTIR and DSC.

In-situ gel formulation by using 3 factorial design to retain in the stomach for extended period of time based on the three independent factors: concentrations of like gellan gum(x1), sodium alginate(x2) and anti-diabetic drug metformin(x3) and also considered five dependent variables are release exponents (Y1), dissolution efficiency (Y2), drug release at 30min (Y3), drug release at 210min (Y4), drug release at 480min (Y5). Three dimensional surface response plots were drawn to evaluate the interaction of independent variables on the chosen dependent variables. Three factorial levels coded for low, medium, and high settings (−1, 0 and +1, respectively) were considered for three independent variables.

In-situ framing polymeric medication conveyance frameworks had been defined and created by utilizing different kinds of polymers including gellan gum, alginate, xylene, gelatin, chitosan, poly caprolactone, poly(DL-lactic corrosive), poly(DL-lactide-glycoside) and so on were planned and created; and furthermore clarified determination of solvents (water, dimethylsulphoxide. N-methyl pyrrolidone,2-pyrrolidone and so forth.) relies upon the dissolvability of polymers.

Oral in-situ gel containing clotrimazole for oral candidiasis based on the pH triggerd and ion activated systems was formulated and evaluated. Triggered system consisting of carboxyethyl cellulose(0.2-1.4%w/v) and ion activated system using gellan gum(0.1-o.75%w/v) and hydroxyl propyl methyl cellulose E50LV for prolonged release of drug and carried out evaluation studies for gelling capacity, PDI, viscosity, clarity, gel strength and in vitro studies, microbial studies.

The gastric maintenance of an oral fluid plan has been effectively increased significantly through a methodology of fluid in-situ gelling framework. Characteristic polymers like alginate, gellan and chitosan can experience sol to gel change within the sight of either divalent cations or because of an adjustment in pH. The gel so framed, being lighter than gastric liquids, coasts over the stomach substance and is held there in for period's upto 24 hours.

Formulated in-situ gelling system for periodontal anaesthesia, and it contain chitosan (0.25%-w/v) and hydroxyl propyl methyl cellulose (0.25%-w/v) polymer. It has good gelling properties at 7.5 pH and provides prolonged action.

Another intra-gastric coating in situ gelling framework for controlled conveyance of amoxicillin for the treatment of peptic ulcer sickness brought about by Helicobacter pylori was created. Gellan based amoxicillin drifting in situ gelling frameworks were set up by dissolving shifting convergences of gellan gum in deionized water containing sodium citrate, to which fluctuating centralizations of medication and calcium carbonate, as gas-shaping operator, was included and broken down by blending.

8 Future prospects
Floating dosage form compromises distinctive future potential as evident from a few late productions. The decreased variances in the plasma dimension of medication results from deferred gastric exhausting. Medications that have poor bioavailability because of their restricted retention to the upper gastrointestinal tract can be conveyed productively in this way augmenting their assimilation and improving their outright bioavailability. Light conveyance framework considered as a supportive framework for the treatment of gastric and duodenal malignancies. The skimming idea can in like manner be utilized in the improvement of various enemy of reflux plans. The drug release profile has been an important focusing zone for the pharmaceutical research researchers as far back as two decades. The scientists are finding it an extraordinary chance to deal with GI travel profiles. This has offered climb to new items with liberal focal points to the patients. Currently with the presence of FDDS the items have been planned which could discharge medicate for upto 24 hrs.

9 Conclusion
Dosage forms with a drawn out GRT will acknowledge new and noteworthy healing decisions. It will fundamentally expand the time span over which medications may be discharged and subsequently drag out dosing interims and increment understanding consistence past the consistence dimension of existing FDDSs. The floating in situ gel approach is fitting for
medications having restricted retention window in stomach or medications showing close-by effect in stomach. These sorts of medications which are right now present in market as their strong dose frames (tablets or cases) will be accessible as their skimming in situ gels.

10 Conflict of interests
The authors have no conflict of interests.

11 Author’s contributions
RP, PKS and VS were equally participated in the preparation of manuscript. All authors read and approved the final manuscript.

10 References


