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INSITU GEL: AN OVERVIEW ON FLOATING INSITU GEL FOR ORAL DELIVERY

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ABSTRACT

Oral route technique is used over a decades. It is most common technique for oral administration of drug in the body, due to certain limitations drug targeting to particular organ can cause problem for administration through oral route. In order to overcome this problem a novel approach is developed i.e. Insitu Drug Delivery System. In-situ gel is a process in which solution form before administration in the body, but once administrated, it undergoes gelation in-situ, to form gel. The floating in situ gel forming systems are one of the most interesting systems in oral drug delivery. To prolong the gastric residence time and control the rate of drug release which can improve oral bioavailability and reduce frequency of dosing. The main aim of this review is to focus on insitu gel principle, mechanism, properties, advantages, and its formulation, evaluation, and applications as floating insitu gel system.

INTRODUCTION

Oral route is technique which is used over a decades. It is most preferred and common technique for oral administration of drug in the body, but due to certain limitation such as absorption of drug, drug targeting to particular organ can cause problem for administration through oral route. To overcome these types of problem as well as for improvement of drug safety and efficiency a novel approach is developed for delivery of drug i.e. floating in-situ drug delivery system.[1]

In situ is a latin phrase which can be translated literally as “In process.” In situ gels are drug delivery systems that are in solution forms before administration in the body, once administered they undergo gelation *in-situ* to form a gel. It is basically a polymeric drug delivery system. Administration routes for *in-situ* gels are oral, ocular, rectal, vaginal,

injectable, and intraperitoneal.

Oral *in-situ* gels are systems which are present as solutions and are capable of undergoing rapid sol-to-gel transformation triggered by external stimulus such as temperature, pH etc, on administration.[2]

The floating *in-situ* gel forming systems are one of the most interesting systems in oral drug delivery. They have been designed to prolong the gastric residence time and control the rate of drug release which can improve oral bioavailability and reduce frequency of dosing. When the system contacts with the gastric fluid, a gel is formed and floats on the surface of the stomach content. The drug then has a sustained release from the gel in the stomach. The floating *in-situ* gels have been shown to improve the efficacy and oral bioavailability of many compounds. The main components of such systems are the gelling agents that form a gel in the acidic environment and an agent to generate gas that makes the system float. The incorporated drugs in this *in-situ* gel forming system should be acid stable. *In-situ* gel forming systems are developed using different type of polymer base (alginate, pectin and gellan gum etc).[3]

Oral *in-situ* gel releases the drug uniformly throughout the GIT. *In-situ* gel forming tablets are a revolution in oral drug delivery. Gel-forming tablets provide a popular and convenient SR dosage form for delivering drugs over an extended time for 8-24 h. The drug is dispersed within a polymeric matrix, which controls the release rate. On contact with water or body fluids the outer surface swell by polymer hydration and chain relaxation, forming a hydrogel coat. When a poorly water soluble drug is dispersed throughout such a polymeric matrix, the swelling mechanism of the polymer results in wetting of the drug, due to sufficient contact between the drug and medium and thus enhancing the solubility of the drug. Many synthetic, semi synthetic and natural hydrophilic polymers are used in the formulation of oral *in-situ* gel. The most commonly used are natural hydrophilic polymers because they are compatible and economical to formulate.[4]

The oral *in-situ* gel drug delivery systems can be retained in the stomach and contribute in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract 7-9. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Gastro-retention is achieved by expandable systems, bio/mucoadhesive systems, floating drug delivery systems and combination of floating, mucoadhesion and swellable system**.** The *in-situ* gelling

system is a type of mucoadhesive drug delivery system principally capable of releasing drug molecule in a sustained manner affording relatively constant plasma profile.[5]

In-situ gelling system increases the bioavailability of drug as compared to conventional liquid dosage form. The gel formed *in-situ* being lighter than gastric fluids, floats over the stomach contents or adhere to gastric mucosa due to bio adhesive nature of polymer and produce gastric retention of dosage form.[6]

Gastro-retentive drug delivery[7]

Drugs which are absorbed easily from the GIT and have short half-lives are eliminated rapidly from the systemic circulation. Repeated dose is required to achieve suitable therapeutic activity. To improve gastric residence time, many approaches are available. Gastro-retentive drug delivery system is one of those approach to enhance contact time of drug with stomach region. Thereby targeting site specific drug release in the stomach for local or systemic effects. Hence this dosage form can last in the gastric region for long periods and thereby significantly enhance the gastric retention time of the drugs. It will release the drug in stomach in a controlled manner, so that the drug could be supplied continuously to absorption site in GIT i.e. stomach.

Merits of gastro-retentive drug delivery system[8]

1) **Increased bioavailability:** The bioavailability of drugs can be significantly enhanced markedly for those which get metabolized in the upper GIT by this gastro retentive drug delivery.[7]
2) **Improved patient compliance:** For drugs with relatively short half-life sustained release may result in a change pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.
3) **Increased gastric retention:** It can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time(GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is less than that of the gastric fluids.
4) **Sustain release:** Gastro retentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine.
5) **Site specific drug delivery:** The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This will reduce undesirable effects of side

effects.

6) **Adverse effects are reduced:** Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be reduced. This feature of special importance for drug with a narrow therapeutic index.
7) **High efficiency:** Gastro retentive drug delivery can diminish the counter activity of the body leading to higher drug efficiency.
8) **Improved selectivity:** Reduction of fluctuation in drug concentration makes it possible to obtain better selectivity in receptor site.
9) **Increased therapeutic effect:** The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

LIMITATIONS OF GRDDS

1. The drug which are not stable in acidic environment, are not suitable.
2. It is not suitable for drug which are well absorbed in the lower part of the GIT.
3. They show Poor in vitro and in vivo correlation.
4. Difficulty to achieve expected outcome and dose dumping may occur.
5. Factors like gastric motility, pH and presence of food are influencing the Gastric-retention. Hence the dosage form must have capability to withstand grinding and churning force of peristaltic wave of stomach.
6. Higher cost of formulation.
7. In case of toxicity, poisoning or hypersensitivity reaction, Retrieval of drug is difficult.[9]

FLOATING DRUG DELIVERY SYSTEM

Floating is the novel drug delivery system. Different dosage forms are developed in gastro retentive floating system 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, per oral, 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
- 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 gets 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).[10]

FDDS are widely explored for gastro retention purposes and have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on gastric contents, the drug is released slowly at a desired rate from the system. The gel formed from in situ gelling system, being lighter than gastric fluids, floats over the stomach contents or adhere to gastric mucosa due to presence of bio adhesive nature of polymer and produce gastric retention of dosage form and increase gastric residence time resulting in prolonged drug delivery in gastrointestinal tract. In situ forming gels are formulations, applied as a solution, which undergoes gelation after instillation due to physicochemical changes inherent to the biological fluids.[11]

IN-SITU GEL

In situ gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner and maintain plasma concentration in a stable manner. At room temperature, these gels are liquid in nature and when in contact with body fluids or undergoes change in pH they show gelation. They can be easily applied in liquid form to the site of drug absorption. They swell to form a strong gel that is capable of prolonging the residence time of the active substance at the site of drug absorption. In-situ gels can be produced by using both natural and synthetic polymers.[12]

Figure 1: In-situ gel formulation.

Principle of in situ gel formation

Formulation of gastro retentive in-situ gel system involves the use of gelling agent which can form a stable sol containing the dispersed drug and other excipients. The gelling of this sol system is to be achieved in gastric environment, triggered by ionic complexation due to change in pH. The formulation adopted is a sodium alginate solution containing calcium carbonate (as a source of Ca^{2+}) and sodium citrate, which complexes the free Ca^{2+} ions and releases them only in the acidic environment of the stomach. Sodium alginate acts as a gelling agent. The free Ca^{2+} ions get entrapped in polymeric chains of sodium alginate thereby causing cross linking of polymer chains to form matrix structure. This gelation involves the formation of double helical junction zones followed by re-aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water.

Sodium Citrate +Ca Carbonate (Ca^{2+}) ---□Ca Citrate Complex---$\xrightarrow{\text{acidic environment}}$-□($Ca^{2+}$) + COO^-

In this way, the formulation remains in liquid form until it reaches the stomach, where gelation of sodium alginate is instantaneous.[13]

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.

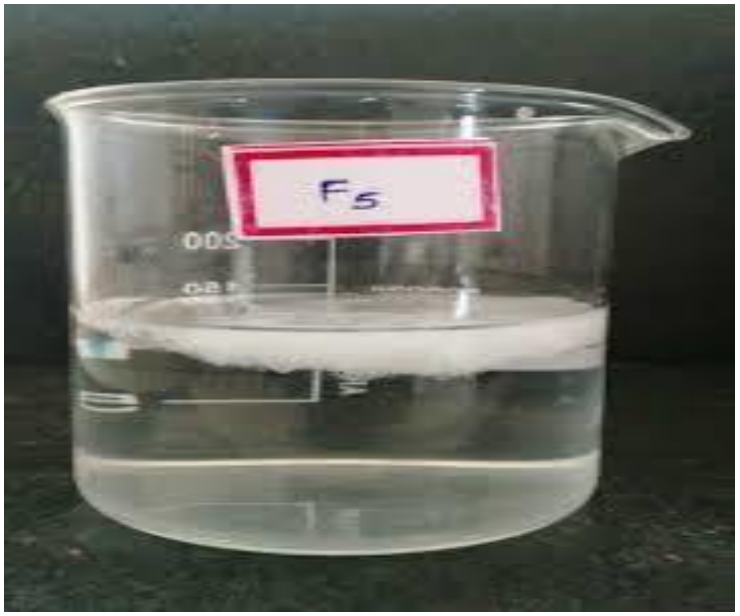
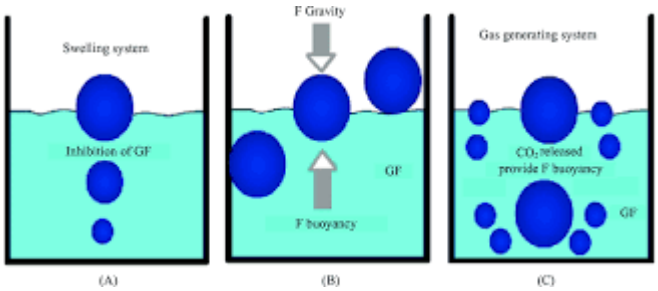


Figure 2: Floating behaviour of In-situ gel formulation.

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.[14]



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.

Approaches of in-situ gel drug delivery[15]

There are four broadly defined mechanisms used for triggering the in situ gel formation of biomaterials:

- Physiological stimuli
- physical changes in biomaterials
- chemical reactions

Characteristic properties of In-situ gel

- pH dependence
- Temperature dependence
- Cation induced gelation

Advantages of in situ gel system[16]

- Controlled and sustained release of the drug
- Ease of the drug administration
- It can be administered to unconscious patients
- More patient compliance and comfort
- Minimizing the dose frequency and drug toxicity
- Increased bioavailability
- Use of natural polymers provide biocompatibility and biodegradation
- Natural polymers have inherent properties of biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities
- Synthetic polymers usually have well-defined structures that can be modified to yield tolerable degradability and functionality.

- In situ gels can also be engineered to exhibit bio adhesiveness to facilitate drug targeting, especially through mucus membranes, for non invasive drug administration.
- In situ gels offer an important "stealth" characteristic in vivo, owing to their hydrophilicity which increases the in vivo circulation time of the delivery device by evading the host immune response and decreasing phagocytic activities. Disadvantages of in situ gel system.
- It requires high level of fluids.
- The sol form of the drug is more susceptible for degradation.
- Chances of stability problems due to chemical degradation.
- After placing the drug eating and drinking may become restricted up to few hours.
- The quantity and homogeneity of drug loading into hydrogels may be limited, particularly for hydrophobic drugs.
- Only drugs with small dose requirement can be given.
- Lower mechanical strength, may result into premature dissolution or flow away of the hydrogel from a targeted local site.

Evaluation of floating gel

1. **Appearance:** The developed formulation met all the pre-requisite to become an In- Situ gelling floating system, gelled and floated instantaneously at the pH condition of the stomach.
2. **pH:** The pH of the in situ solution of Loratadine was measured using calibrated digital pH meter at 37^0C. All measurement of pH was made in triplicate.[17]
3. **In vitro floating study:** Floating study of in situ gelling solutions was carried out in 900 ml of 0.1 N HCl (pH 1.2) in a Dissolution jar. Time required for floating on surface after adding solution (floating lag time) and total floating time were measured.[18]
4. **Viscosity of in situ gelling solutions:** The viscosity of the formulations increased with an increase in sodium alginate and pectin concentration. This phenomenon is a consequence of increasing chain interaction with an increase in polymer concentration. Calcium carbonate, which is the source of cations, increased the viscosity of the formulation. This change in viscosity is due to the proportional increase in the amount of dispersed calcium carbonate.[19]
5. **Determination of drug content:** Accurately, 1ml of in situ gelling solution was added to 53ml of purified water to yield solution containing strength of 1000µg/ml. From that

5µg/ml solution was prepared by diluting stock solution. The UV absorbance of the sample was determined at a wavelength of 294nm.[20]

6. **Gel strength:** This parameter can be evaluated using a rheometer. Depending on the mechanism of the gelling of gelling agent used, a specified amount of gel is prepared in a beaker, from the sol form. This gel containing beaker is raised at a certain rate, so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface.[21]
7. **In Vitro Floating Study**: Floating study of in situ gelling solution was carried out in 500mL of 0.1N Hcl (pH 1.2) in a beaker. Accurately measured 10mL of solution was added to Hcl with mild agitation. Time required for floating on surface after adding solution (floating lag time) and total floating time were measured.[22]
8. **Differential scanning calorimeter (DSC) studies**: DSC study was carried out to check the compatibility of drug and excipients. DSC analysis of pure drug and optimized formulation was performed with DSC 60 thermal analyser at heating flow rates of 100 C per minute between 50 0C -300 0C under static air using aluminium pans.
9. **Stability study**: Optimized formulations were placed in amber colored bottles and tightly closed with cotton plug and it should be capped and then stored for 1 month and then subjected to various evaluation parameters.[23]

Applications

- Antioxidation
- Stimulation of ribosomal RNA polymerase and subsequent protein synthesis, leading to enhanced hepatocyte regeneration.
- Enhanced liver detoxification via inhibition of phase I detoxification.
- Silymarin is also found to have immunomodulatory effects on the diseased liver.
- Amanita mushroom poisoning.
- Hepatitis
- Alcoholic liver disease and cirrhosis
- The chemopreventive action of silymarin helps it inhibit the carcinogenic action of many chemicals.

CONCLUSION

Based on literature survey it can be concluded that the drug release from the floating in-situ oral gel formulation can be modulated by the use of different amount of gel forming polymers.

Gels shows site specific drug delivery may be local or systemic delivery as it retains in stomach for long period of time by floating on gastric fluid. This reduces dosing frequency and hence patient compliance. In-situ gels are useful for sustained drug delivery and also beneficial for paediatric and gediatric drug delivery.

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