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### A REVIEW ON *IN-SITU* GELLING SYSTEM: NOVEL APPROACH FOR STOMACH SPECIFIC DRUG DELIVERY

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**Abstract:** The oral delivery of drugs with a narrow absorption window in the gastrointestinal tract. Because, Poor bioavailability with conventional dosage forms due to incomplete drug release and short residence time at the site of absorption. To overcome this disadvantage and to maximize the oral absorption of these drugs, novel drug delivery systems have been developed. Various gastroretentive systems such as floating systems, mucoadhesive, high-density, expandable and have been developed, since they provide controlled delivery of drugs with prolonged gastric residence time. Among all oral dosage forms, liquid orals are more prone to low bioavailability as far as stomach specific drug deliveries are concerned, since they subjected to faster transit from the stomach/ duodenum. To produce sustained release formulation of an oral liquid formulation could be successfully augmented substantially through a strategy of liquid in-situ floating gel system. This comprehensive article describe in-situ gel in brief.

**Keywords:** Gastroretentive System, In-Situ Gel, Sustain Drug Delivery System



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## INTRODUCTION

*In-situ* gel forming systems have been widely investigated as vehicles for sustained drug delivery. This interest has been sparked by the advantages shown by *in-situ* forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. *In situ* gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. So, *In-situ* gelling system via different route such as oral, nasal, ophthalmic etc. can be formulated. Various natural and synthetic polymers such as gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone are used for formulation development of *in-situ* forming drug delivery systems. Gastro retentive *in situ* gelling system helps to increase bioavailability of drug compared to conventional liquid dosage form. 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 bioadhesive nature of polymer and produce gastric retention of dosage form and increase gastric residence time resulting in prolonged drug delivery in gastrointestinal tract. This review attempts to discuss stomach specific *in-situ* gelling system in detail including formulation factors to be considered in the development of *in-situ* drug delivery.

## GASTRORETENTIVE DRUG DELIVERY SYSTEM

Gastroretentive system ensures that whole drug delivery system remains within the gastric region for longer duration of time. This improves gastric retention time for such drug in comparison to conventional dosage form and further minimum effective concentration of drug remains maintained in systemic circulation for longer duration. This also improves the solubility of drugs which are less soluble at alkaline pH of intestine and wastage of drug during the absorption process is reduced remarkably.

Gastroretentive drug delivery systems prolong the dosing intervals and thus improve patient compliance. Presence of drug in solution form is the most essential requisite for a drug to get absorbed. But, if the solubility of drug is poor then the time required for drug to get dissolve within stomach would be high and transit time becomes most stringent factor, which would in turn affect the absorption of drug. So, Dose of administration for such drugs should be kept at more frequent intervals in a single day. Gastro retentive drug delivery systems provide a support to reduce the frequent dosing of such drug by producing a controlled delivery within stomach for longer duration. Though, other formulations or novel dosage forms like nanoparticle, microspheres, liposome etc. can also be used for controlled release effect, but gastro retentive system are considered much better alternative for improved absorption through stomach.<sup>1</sup>

## BASIC ANATOMY OF STOMACH AND ITS PHYSIOLOGY OF STOMACH

During past 4 decades, the idea of gastro retention is known to researchers and is popularly cultured. Davis, in 1968, 1st described the concept of floating drug delivery systems. To understand the approaches for gastro retention, it is necessary to overview gastric physiology and gastric motility. Human stomach has a resting volume of 25-50ml, which can distend up to 1500ml following a meal. The stomach is a J-shaped organ. It is located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastria and left hypochondria region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Since the drugs are absorbed in the upper small intestine, it will be beneficial to develop the dosage forms that reside in that region.<sup>2,3</sup>

It is divided into 3 anatomical parts; Fig.1.

a) **Fundus:** also called proximal stomach, which acts as food reservoir.

b) **Body**

c) **Pylorus or antrum:** also called distal stomach, which acts as a site of mixing motions to propel gastric contents for emptying. Pyloric sphincter has a diameter of  $12.8 \pm 7$ mm in humans and serves as a sieve and stricture to passage of large particles.<sup>4</sup>

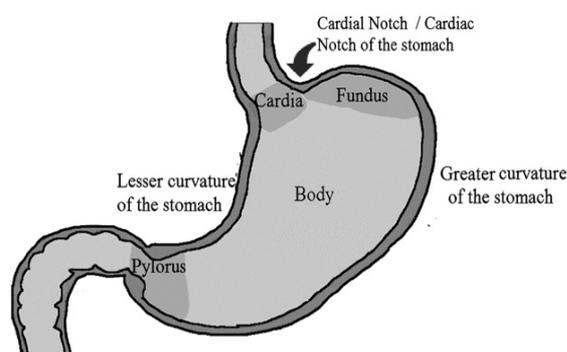


Fig. 1.1 Physiology of the stomach.

Gastric motility is also a key factor in stomach specific drug delivery. Thorough knowledge of motility is prerequisite for developing a retentive form of drug. Gastric motility differs in fasting and fed states. In fasting states, an Inter-digestive myoelectric motor complex (IMMC), a 2 hr. cycle of peristalsis is generated which progresses to ileocecal junction.

It consists of 4 phases.<sup>5</sup>

**Phase I:** also called quiescent period with rare low amplitude contractions, lasting for 30-60 min.

**Phase II:** it comprises of intermediate amplitude contractions with bile secretion, lasting for 20-40 min.

**Phase III:** also called Housekeeper waves, it forms of very high amplitude contractions offering maximum pyloric opening and efficient evacuation of stomach contents. It lasts for 10-20 min. with a frequency of 4-5/min.

**Phase IV:** Transitional phase between phase III and I of two consecutive cycles. It lasts for less than 5 min.

In fed states, motility is induced 5-10 min after ingestion and persists as long as food remains in stomach, typically 3-4 hr. Activity is same as phase II of IMMC. Gastro retentivity of drug was required to increase the bioavailability of drug and to reduce the undesirable effects caused by exposure of drug to other regions of GIT.

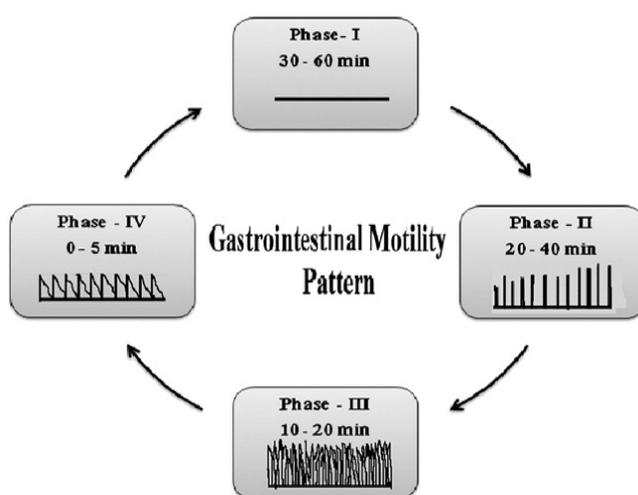


Fig.1.2 Schematic representation of the interdigestive motility pattern.

## APPROACHES OF GASTRORETENTIVE FORMULATION <sup>6</sup>

### A. Floating drug delivery systems (FDDS)

Floating drug delivery system (FDDS) was first described by Davis in 1968. FDDS is an effective technology which is prolong the gastric residence time in order to improve the bioavailability of the drug. FDDS are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. The single-unit floating dosage forms are associated with problems such as sticking together or being obstructed in the GIT,

which may produce gastric irritation. However, multiple-unit floating systems may be an attractive alternative since they have been shown to reduce inter and intra- subject availabilities in drug absorption as well as to lower the possibility of dose dumping Floating systems can be classified as effervescent and non-effervescent systems.

### 1. Effervescent systems<sup>7</sup>

This delivery system is desirable for drugs with an absorption window in the stomach or in the upper small intestine. FDDS have a bulk density less than gastric fluids and so, remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time and the drug is released slowly as a desired rate from the system. After oral administration in the GIT, CO<sub>2</sub> is liberated from these drug delivery systems, which reduces the density of the system and making it float on the gastric fluid. Four Properties should possess by FDDS

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric Contents (1.004 - 1.01 gm/cm<sup>3</sup>).
- It must form a cohesive gel barrier.
- Effervescence Agents: Sodium bicarbonate, Citric acid, Tartaric acid, Calcium carbonate, Di-SGC (Di-Sodium Glycine Carbonate).

### 2. Non-effervescent systems

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In the non-effervescent system Excipients used most commonly in these systems include hydroxyl propyl methyl cellulose, polyacrylate, polyvinyl acetate, carbopol, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.<sup>8</sup>

#### B) Raft forming system

On contact with Gastric fluid A gel forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO<sub>2</sub> bubbles. This forms raft layer on top of gastric fluid which releases drug slowly in stomach. Such formulation typically contains antacids such as aluminum hydroxide or calcium carbonate to

reduce gastric acidity. They are often used for gastro esophageal reflux treatment as with liquid Gaviscon.

### **C). Bioadhesive System**

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

### **D). High density systems**

These dosage forms have a density(3g/ml) far exceeding that of normal stomach contents(1g/ml) and thus retained in rugae of the stomach and are capable of withstanding its peristaltic movements. The density of these systems should at least be 1.004 g/ml. This is accomplished by coating the drug with heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.<sup>12</sup>

### **E). Self-unfolding systems<sup>9</sup>**

The self-unfolding systems are capable of mechanically increasing in size relative to the initial dimension. This increase prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach. A drug can be either contained in a polymeric composition of the gastroretentive systems or included as a separate component. Several methods were suggested to provide for the self-unfolding effect.

1. The use of hydrogels swelling in contact with the gastric juice.
2. Osmotic systems, comprising an osmotic medium in a semipermeable membrane.
3. Systems based on low-boiling liquids converting into a gas at the body temperature.

### **ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM<sup>10,11</sup>**

1. The gastroretentive systems are advantageous for drugs absorbed through the stomach, e.g. ferrous salts, antacids.

2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence, HBS formulation may be useful for the administration of aspirin and other similar drugs.
3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
4. FDDS improves patient compliance by decreasing dosing frequency.
5. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.
6. Better therapeutic effect of short half-life drugs can be achieved.
7. Gastric retention time is increased because of buoyancy.
8. Enhanced absorption of drugs which solubilize only in stomach
9. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
10. Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.
11. The gastro retentive systems are advantageous for drugs meant for local action in the stomach e.g. antacids.

#### **DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM<sup>12</sup>**

1. There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
2. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems. Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract, drugs undergoing first pass metabolism will not benefit from incorporation into a gastric retention system.

3. It required sufficient high level of fluids in the stomach for the drug delivery to float. The dosage form should be administered with a full glass of water (200-250 ml)

However, this approach is not suitable for drugs having following characteristics.

- a) Drugs that have very limited acid solubility e.g. Phenytoin etc.
- b) Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
- c) Drugs intended for selective release in the colon e.g. 5- amino salicylic acid.
- d) Drugs that irritate gastric mucosa or cause lesions on slow release e.g. Aspirin, NSAIDS.

### ***IN-SITU* GELING SYSTEM<sup>13,14,15</sup>**

*In situ* gel forming drug delivery systems are a revolution in oral drug delivery. These hydrogels are liquids before administration but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependent and cation-induced gelation. This gelation involves formation of the double helical junction zones followed by aggregation of the double helical segments to form a three dimensional network by complexation with cations and hydrogen bonding. Various polymer are used which have specific characteristic

A. polymer used to prepare in situ gels should have following characteristics

- It should be biocompatible.
- It should be capable of adherence to mucus.
- It should have pseudoplastic behavior.
- It should have good tolerance and optical clarity.
- It should follow the bio-degradable behavior system. Also, different types of smart polymers, their mechanisms of gel formation from the sol forms.

B. The in situ gel forming polymeric formulations are having several advantages like

- Sustained and prolonged action compared to conventional drug delivery system,
- Ease of administration
- Deliverance of large dose as well as to prolong residence time of drug,
- Reduced frequency of administration, and improved patient compliance and comfort,

- This system suitable from the manufacturing point of view.

## DIFFERENT APPROACHES FOR *IN-SITU* GELLING SYSTEM<sup>16,17</sup>

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

### A. *In situ* formation based on physical mechanism

#### *Swelling*

*In situ* formation may also occur when absorbs water from surrounding environment and expand to occur desired space. One such substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some Bioadhesive properties and can be degraded in-vivo by enzymatic action.

#### *Diffusion*

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N- Methylpyrrolidone (NMP) has been shown to be useful solvent for such system.

### B. *In situ* formation based on physiological stimuli

#### *Thermally triggered system*

Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach *in-situ* formation. The ideal critical temperature range for such system is ambient and physiologic temperature, such that clinical manipulation is facilitated and no external source of heat other than that of body is required for trigger gelation. A useful system should be tailorable to account for small differences in local temperature, such as might be encountered in appendages at the surface of skin or in the oral cavity. Three main strategies are exists in engineering of thermoresponsive sol-gel polymeric system. For convenience, temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive, and thermally reversible gels. Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST) and contract upon heating above the LCST. Polymers with low critical temperature (LCST) transition between ambient and physiologic temperature is used for this purpose. one of the most extensively investigated polymers that

exhibit useful LCST transition is poly(N- isopropylacrylamide) (PNIPAAm). PNIPAAm is a water soluble polymer at its low LCST, but hydrophobic above LCST, which result on precipitation of PNIPAAm from the solution at the LCST. A positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST. Polymer networks of poly (acrylic acid) (PAA) and polyacrylamide (PAAm) or poly (acrylamide-co-butyl methacrylate) have positive temperature dependence of swelling. The most commonly used thermoreversible gels are these prepared from poly (ethylene oxide) -b- poly (propylene oxide) -b- poly (ethylene oxide) (Pluronics<sup>®</sup>, Tetronics<sup>®</sup>, poloxamer).

### ***pH dependent gelling***

Another formation of *in-situ* gel is based on Change in pH. Certain polymers such as polyvinylacetal diethylaminoacetate (AEA), Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) shows change from sol to gel with change of pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups.

### **C. *In-situ* gel formation based on chemical reactions**

#### ***Ionic crosslinking***

Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones. While k-carrageenan forms rigid, brittle gels in reply of small amount of K<sup>+</sup>, i-carrageenan forms elastic gels mainly in the presence of Ca<sup>2+</sup>. Gellan gum commercially available as Gelrite<sup>®</sup> is an anionic polysaccharide that undergoes *in situ* gelling in the presence of mono- and divalent cation, including Ca<sup>2+</sup>, Mg<sup>2+</sup>, K<sup>+</sup> and Na<sup>+</sup>. Gelation of the low-methoxy pectin can be caused by divalent cations, especially Ca<sup>2+</sup>. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca<sup>2+</sup> due to the interaction with guluronic acid block in alginate chain.

#### ***Enzymatic cross-linking***

*In-situ* formation catalysed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators. Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. 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. Adjusting the amount

of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation.

### ***Photo-polymerization***

A solution of monomers such as acrylate or other polymerizable functional groups and initiator such as 2,2 dimethoxy-2-phenyl acetophenone, camphor Quinone and ethyl erodin can be injected into a tissues site and the application of electromagnetic radiation used to form gel designed readily to be degraded by chemical or enzymatic processes or can be designed for long term persistence in vivo. Typically long wavelength ultraviolet and visible wavelengths are used. A photopolymerizable, biodegradable hydrogels as a tissue contacting material.

### **ADVANTAGES OF *IN-SITU* GEL<sup>18</sup>**

1. *In-situ* gel forms a low density viscous layer on the gastric contents and hence provides more effective surface area than a tablet. This leads to more drug release and improve the bioavailability.
2. Floating obtained is faster than the tablets.

### **EVALUATION PARAMETER OF *IN-SITU* FLOATING GEL**

#### **Physical appearance**

The clarity of formulated solution and gel was determined by visual inspection under black and white background.

#### **pH**

The pH was measured of in situ solutions of cephalexin using a calibrated digital pH meter at 25°C. All measurements of pH were made in triplicate.<sup>19</sup>

#### **Viscosity measurement of in situ gels**

Viscosity of the in situ gelling solution was determined with a Brookfield viscometer (Model no RVT 6513476) using a 20 ml aliquot of the sample. Measurements were performed using spindle number 2 and the temperature was maintained at 25±10C. All measurements were made in triplicate.<sup>21</sup>

#### ***In-vitro* floating study**

Floating study was carried out in 500 ml of 0.1 N HCl (pH 1.2) in a beaker. Accurately measured 10 ml of solution was added to HCl. Time requires for immersed on surface after adding solution (floating lag time) and total floating time were measured.<sup>20</sup>

### Gel strength

The gel strength apparatus was fabricate in house using a measuring cylindrical of 1.2 cm radius and a bore of 0.1 mm at its base. A needle 2 cm in length was used to which a nylon threads was tied. Solution (10 ml) was taken in the cylinder with temporarily sealed bore followed by addition of 50 ml 0.1 N HCl for gelation. After gelation the HCl was drained off by opening bore leaving the gel mass formed. The needle was rested on to surface of the gel. At the free end of the thread a light weight pan was attached to which the weight were added. The gel strength was reported in terms of weight required to pass the needle probe through the formed gel mass. The gel strength is calculated using this formula.<sup>20</sup>

$$\text{Gel Strength} = \text{Mg/a}$$

Where, M = Weight at which needle passes through the formed gel mass.

g = Gravitational force, a = Area of surface.

### *In vitro* gelation study

To evaluate formulation for their gelling capacity by visual method, coloured solution of in situ gel was prepared. The gelling capacity was measured by placing 5 ml of gelation solution (0.1 N HCl, pH 1.2) in test tube and maintained at  $37 \pm 10^\circ\text{C}$ . one ml of coloured solution was added with pipette. The formulation was transferred in such a way that places pipette at surface of fluid in test tube and formulation was slowly released from pipette. As solution comes in contact with gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity was evaluated on basis of stiffness of formed gel and time period for which formed gel remained as such. The gelling capacity was graded in 3 categories on basis of gelation time and time period for which formed gel remain as such.<sup>21</sup>

+ = gels after few minutes, dispersed rapidly

++ = gelation immediate remains for few hour

+++ = gelation immediate remains for an extended period.

### Drug content

Accurately, 1 ml of in situ gelling solution (equivalent to 30 mg of Cephalexin) was added to 29 ml of purified water to yield solution containing strength of 1000  $\mu\text{g/ml}$ . From that 5  $\mu\text{g/ml}$

solution was prepared by diluting stock solution. The UV absorbance of the sample was determined at a wavelength of 257nm.<sup>19</sup>

### ***In vitro* drug release study**

The release rate of Cephalexin was determined using USP apparatus 2 at 50 rpm. This speed slow enough to avoid breaking of gelled formulation and was maintaining mild agitation condition exist *in vivo*. The dissolution medium used was 900 ml of 0.1 N HCl and temperature was maintained at 37<sup>0</sup>C. A sample was withdrawn at every 30 min time interval. The sample was analyzed and % cumulative release was calculated.<sup>20</sup>

### **CONCLUSION**

Dosages form with prolonged gastric retention and its compatibility with stomach physiology is the real challenge. So in order to achieve gastric retention various approaches have been done from several years. Out of which floating in situ drug delivery system is the most promising technique which undergo sol to gel transition in acidic medium of stomach and provide site specific release for longer duration of time by floating on the surface of gastric fluid, due to which its contact time with gastric mucosa is increased. In situ gels are not only helpful for sustained drug delivery but also become convenient for pediatric and geriatric patients. In situ gel have good stability and bio compatibility characteristics and better drug release which make it more reliable dosages form over the conventional one.

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