GASTRO RETENTIVE INSITU GEL FORMULATION
– AN OVERVIEW

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ABSTRACT
Oral drug delivery is one of the simplest routes of delivery of drugs for systemic as well as local effect. Liquid oral dosage forms are easy to administer as compared to unit solid dosage forms but sustained effect are not achieved due to less residential time in gastrointestinal tract so due to this problem In-situ gel used to overcome the problems. The in situ gel dosage form is a liquid before administration and after it converts into gel by various mechanisms in gastric environment. By this way we can achieve sustained release effect. This approach is useful for systemic as well as local effect of drugs administered. This review gives a short idea about floating oral in-situ gel formation and future prospect on a number of drugs and natural and synthetic polymers.

KEYWORDS
Gastro retentive drug delivery system, in situ floating gel and apparoach, natural and synthetic polymer, appicalility in herbal formulation.

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INTRODUCTION

Gastro-retentive delivery is one of the site specific delivery for the delivery of drugs either at stomach or at intestine. It is obtained by retaining dosage form into stomach and drug is being released at controlled manner to specific site either in stomach, duodenum and intestine. there are some advantages like:

- Drugs acting locally in the stomach E.g. Antacids and drugs for H. Pylori.
- Drugs that are principally absorbed in the stomach.
- Drugs that are poorly soluble at the alkaline pH.
- Drugs with a narrow window of absorption E.g. Furosemide.
- Drugs absorbed readily from the GI tract.
- Drugs that degrade in the colon.

On the basis of Physiological consideration:

- Reduce fluctuation in drug effect.
- Improve selectivity in receptor activation.
- Reduce counter activity of the body.
- Extended time over effective concentration.
- Minimized adverse effect at colon.

1. Various Approaches of Grdds

   A) Low-density systems (Floating drug delivery)
   B) Expandable/Swellable systems
   C) Bio/Muco-adhesive systems
   D) High density systems
   E) Raft forming systems

Fig. 1: Approaches for Gastro Retentive Drug Delivery System.
2.1.1 Floating drug delivery system\textsuperscript{1,3,5}

- Floating drug delivery system (FDDS) have less density as compared to gastric contents so it will float over the gastric fluid due to this phenomena it will release drug without affecting gastric retention time.

- By this way the desire plasma concentration is achieved and prolong the drug release.

- It has longer residential time so it improve oral bioavailability of drug.

- Drug that may be absorbed from the upper portion of stomach is suitable for this delivery system.

  It has mainly two types of systems:
  - Effervescent system
  - Non effervescent system

2.1.1.1 Effervescent System

In this system there is acidic environment of stomach $\text{CO}_2$ is liberated from the dosage form and floats on the surface of gastric fluid.

Example of agent: Sodium bicarbonate, Citric acid, Tartaric acid, Calcium carbonate, Disodium glycine carbonate.

Various dosage form related to effervescent system:

\textit{Single Unit (monolithic unit)}

- matrix tablet
- matrix tablet with carbopol
- floating pills
- coated effervescent core
- programmable drug delivery

\textit{Multiple Unit}

- porous alginate beads
- ion exchange resin beads

2.1.1.2 Non Effervescent System

In this system the polymer have low density.

\textbf{Examples of Polymer}

1. More gel forming and highly swelleble, cellulosic hydro colloids (e.g. hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose).
2. Polysaccharides and matrix forming polymer (e.g. polycarbophile, poly acrylates, poly styrene).

Due to hydrophilic nature of polymer they absorbed gastric fluid and swell so that air trapped by swollen polymer and it lead to floating on GIT fluid.

Various dosage form related to non-effervescent system:

**Single unit (monolithic unit)**
- HBS\textsuperscript{TM} Capsule
- Matrix tablet - single layer
- Non matrix bilayer system
- Tablet with agar and mineral oil
- Tablet with cylinder
- Coated hallow globule shell

**Multiple unit**
- Calcium alginate / pectinate beads
- Alginate beads with air compartment
- Floating powder
- Oil entrapped gel beads

2.2 Floating in Situ Gel\textsuperscript{6,7,8}

Floating in situ gel also known as raft forming system which provides controlled drug delivery system. The problem with solid oral unit dosage forms that it cannot taken as halves and swallow as whole dosage form as compared to oral liquid dosage form. Pediatric and geriatric patients have difficulty to swallow tablet/capsule and in case of life threatening disease like dyspasia, certain cancer disease. In case of liquid dosage form different strength can be formulated.

2.2.1 Various Approach for in Situ Gel Formation

There are various mechanism for the in gel formulation: physiologically changes (temperature and pH), Chimically stimulate (ionic cross linking), physical change in biomaterial (diffusion of solvent and swelling).

2.2.1.1 In Situ Gel Formation Based on Chemical Stimulation\textsuperscript{9,10,11}

Ion sensitive polymer (sodium alginate, calcium alginate, gellan gum, pectin) undergo phase transition in present of various monovalent and divalent cation (ca\textsuperscript{2+}, mg\textsuperscript{2+}, Na\textsuperscript{+}, k\textsuperscript{+}) for the formation of gel. For e.g: gelation of low methoxypectin in present of divalent cation (ca\textsuperscript{2+}). Alginate contain molecule (sodium alginate) under go gelation in presence of di/poly valent cation e.g. ca\textsuperscript{2+} interact with guluronic acid block in alginate side chain.

E.g: formulation evaluation and optimization of stomach specific in situ gel Ranitidine hydrochloride\textsuperscript{11}.
2.2.1.2 In Situ Gel Formation Based on Physiologically Changes:

(a) pH dependent gelling

Another formation of in situ gel based on pH dependent. For these purpose various pH sensitive polymers are use such as PAA(carbomer) or its derivatives,polyvinyl acetyl dimethylamino acetate(AEA),mixture of poly(methylacrylic acid)(PMA), and poly(ethylene glycol)(PEG) shows change from sol to gel when changes in pH,at higher pH range wickly acidic group shows gel formation and vice-versa.

E.g: strategy for development of pH triggered floating in situ gel of levetiracetam.

(b) Temperature Dependent Gelling

Dosage form are solution at room temperature (20 – 25 °c) but when in contact with body temperature (35 – 37 °c) they convert into gel. some of the polymer have drastic changes in solubility in respond to increase in environmental temperature (lower critical solution temperature)LCST. At the LCST the interaction between polymer and water is unfavourable as compared to polymer-polymer and water-water. so molecule becomes dehydrated and produce hydrophobic structure polymer such as pluronic(poly(ethyleneoxide)-poly(propyleneoxide)-poly(ethyleneoxide)(PEO-PPO-PEO)triblock), polymer network of poly(acrylic acid)(PAA) and poly acrylamine (PAAM) or poly (acrylamide-co-butyl methoacrylate). Below the upper critical solution temperature(UCST) hydrogel contracts upon cooling they form hydrogel this called positive temperature sensitive hydrogel. Polymer used such as poly acryclic acid, poly acryl amide and co-butyl methacrylate.

E.g: in situ gelling formulation based on the methylcellulose / pectin system for oral sustain drug release to dysphagic patient.

2.2.1.3 Physical Change in Biometrics:

Mainly bases on the Swelling and diffusion property of polymer. Some of the polymer that can absorb water and formation of gel like structure due to swelling.certain polymer use such as myverol 18-99 (glycerol mono oleate). In some condition gel formation can be occur due to diffusion of water this phenomeno called diffusion polymer us such as N- methyl pyrrolidone.

Various formulated drug in research activities:

<table>
<thead>
<tr>
<th>Author Name</th>
<th>Drug</th>
<th>Category</th>
</tr>
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<tbody>
<tr>
<td>Jayswal et al17</td>
<td>Cimetidine</td>
<td>Anti histaminic</td>
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<tr>
<td>Patel et al11</td>
<td>Ranitidine</td>
<td>Anti histaminic</td>
</tr>
<tr>
<td>Itoh et al13</td>
<td>PCM</td>
<td>NSAID</td>
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<tr>
<td>Rajnikanth et al14</td>
<td>clarithromycin</td>
<td>Anti h.pylori</td>
</tr>
<tr>
<td>Bhimani et al15</td>
<td>clarithromycin</td>
<td>antibiotic</td>
</tr>
<tr>
<td>Lahoti et al16</td>
<td>Ofloxacin</td>
<td>antibiotic</td>
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Commonly Used in Situ Gel Formulation Polymer

<table>
<thead>
<tr>
<th>Natural</th>
<th>Synthetic</th>
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<tbody>
<tr>
<td>Sodium alginate</td>
<td>Pluronic F-27</td>
</tr>
<tr>
<td>Pectin</td>
<td>Carbopol</td>
</tr>
<tr>
<td>Tragacanth</td>
<td>Xanthangum</td>
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<tr>
<td>Gelatin</td>
<td>Malgum</td>
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<tr>
<td>Carrageenan</td>
<td>Taragum</td>
</tr>
<tr>
<td>Tamarind gum</td>
<td>Isapgulla</td>
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<tr>
<td>Guar gum</td>
<td>Locust gum</td>
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3. Evaluation of Floating Drug Delivery

3.1 Determination Of Drug Contain:

Accurately 10ml in situ gel formulation was taken (equivalent to 20mg drug) and transfer to 100ml volumetric flask. To this 0.1N HCL was added and sonicate the volumetric flask for 10 min to uniform distribution of gel in medium. To the above solution 10ml was taken and further with 0.1N HCL content of drug can be measure by using uv-spectoscopy at suitable wavelength.

3.2 pH Measurement:

In situ solution formulation pH measure by using calibrated digital pH meter at room temperature.

3.3 In Vitro Gelling Capacity:

Evaluation for gelling capacity can be measure by visualization method. In that method coloured solution of different formulations were prepared. In situ gelling formation was measured into 5ml of gelation solution (0.1 N HCL) in 15ml borosilicate glass tube at 37°C±1 °c. in situ formulation was added in such a way that tip of pipette touch to gelation solution and solution release slowly. during that time stiffness of gel and time duration to remain as such as a gel. color was added for the visualization purpose. In situ gelling capacity was categorized in three class based on gelation time and time period at they remain as such.

(+ ) gel after few minutes, dispersed rapidly

(++ ) gelation immediate, remain for 12hr.

(+++) gelation immediate, remain for more than 12hr.

3.4 In Floating Lag Time
In this parameter 10ml of in situ formulation was added into the 900ml dissolution vessel containing 0.1N HCL at 37°C. The time the formulation took to emerge on medium surface (floating lag time) and the time formulation constantly floated on surface of dissolution medium (duration of floating).

3.5 In Vitro Drug Release

The drug release was measured using USP dissolution apparatus I (basket covered with muslin cloth) at 50rpm. The speed of apparatus was maintain as slow as possible to avoid breaking of gelation formation and maintain mild agitation conditions to believe to exist in vivo condition. 900 ml dissolution medium (0.1N HCL) at 37°C ±1°C temperature. To that 5ml dissolution medium was pipette out at 1, 2, 4, 6, 8, 10 and 12hour interval. And measured absorbance at particular wavelength of drug using uv-spectrophotometer.

3.6 Measurement of Water Uptake

The water uptake of selected formulation were determine by simple method. In this study 40ml of in situ gel formed in 40ml 0.1N HCL. From all the formulation formed gel was separated and excess 0.1 NHCL was removed by tissue paper. Before transfer gel formulation to water initial weight was taken and then added to 10ml water after every 30 min water was decant and weight the gel formulation. the data was calculated and reported.

3.7 Stability Study

Stability study of prepared formulation was done according to ICH (international conference on harmonization). To this method sufficient quantities of gel formulation was stored in dasicator containing saturated solution of sodium chloride which provide relative humidity 75±5%. The formulation was further put in hot air oven at 40±2°C temperature. Sample was withdrawn at 0, 30, 60 and 90 days interval for physical stability in terms of gelation or turbidity. and drug release and viscosity study was done at predetermined time interval.

4. Future Prospects With Respect To Herbal Drugs

Herbal drug delivery is the emerging field in the pharmacy. The use of FDDS for herbal medicament is the novel approach for the better delivery. For this purpose there is a great opportunity to work on GI transit profiles. This has given rise to new products with substantial benefits to the patients. Now with the advent of FDDS the products have been designed which could release drug for up to 24 hrs.

Some herbals that can be delivered as floating drug delivery systems:

**Black Myrobalan**

The aqueous extract of black myrobalan (familiar with Terminalia chebula Retz) has been shown to have uniform antibacterial activity against ten clinical strains of H. pylori.

**Ginger**

Ginger root (familiar with Zingiber officinale Rosc.) has been used traditionally for the treatment of gastrointestinal ailments such as motion sickness, dyspepsia and hyperemesis gravidarum, and is also reported to have chemo preventative activity in animal models. The
active constitute gingerols contain structurally similarity as polyphenolic compounds isolated from ginger.

**Turmeric**

Curcumin, a polyphenolic chemical constituent derived from turmeric (familiar with Curcuma longa L.), has been shown to prevent gastric and colon cancers in rodents. Various mechanisms had been proposed for the chemo preventative effects, although the effect of curcumin on the growth of *H. pylori* has not been reported.

**Licorice**

In a recent study at the Institute of Medical Microbiology and Virology, Germany, researchers found that licorice extract produced a potent effect against strains of *H. pylori* that are resistant against clarithromycin, one of the antibiotics typically used in the three antibiotic treatment regimens.

**Berberine**

Berberine is a plant alkaloid isolated from the roots and bark of several plants including golden seal, barberry, *Coptis chinensis* Franch. and *Yerba mansa*. Berberine-containing plants have been used medicinally in ayurvedic and Chinese medicine, and are known to have antimicrobial activity against a variety of organisms including bacteria, viruses, fungi, protozoans, helminths, and chlamydia. Now a day, berberine had been demonstrated to be effective against *H. pylori*. All these herbal drugs can be prepared as gastroretentive drug delivery system.

5. Recent Advancement In Stomach Specific In Situ Gel System

Gerhard Gröbner et al. developed a method for producing *in situ* gelation of poloxamer and mucoadhesive polymer chitosan by utilizing the property of poloxamer solution to convert in to gel at physiological temperatures and of chitosan to undergo ion responsive gelation in presence of Sodium tripolyphosphate. Differential scanning calorimetry and tube inversion techniques were used to study micellization and gelation of the poloxamer 407 in presence of chitosan. Mixture of poloxamer and tripolyphosphate was responsible to reduce the critical micellization temperature and critical gelation temperature of poloxamer solution in water. Poloxamer gel, so formed *in situ*, after the addition of chitosan and tripolyphosphate had shown decline in the dissolution rate and release characteristics of metoprolol, doxycycline and flufenamic acid. In addition to that, variation in the composition of both polymer components and tripolyphosphate had also shown the possibility to control the pH of system so that, it would enhance the solubility profile of drug.

Giuseppe Perale et al. developed a hydrogel which had shown the promising results in the spinal cord injury, when injected through 40 im needle in the solution phase, which converted in to gel inside the target tissue. Formulation was prepared by polycondensation, using two FDA approved polymer viz. Polyacrylic acid (Carbomer 947P) and Agarose, a common polysaccharide. Solution was injected in spinal cord of mouse and *in situ* gel formation was confirmed by magnetic resonance imaging that showed the presence of polymeric network at injection site. Hydrogel, so produced, had provided enough data to be considered as a new biocompatible tool that can be used as a local reservoir for *in situ* delivery of drugs.
Suvendu Bhattacharya et al. studied the textural characteristics like syneresis, opacity and fracture characteristics of gellan, agar and their mixed gels on application of uniaxial compression. Increase in the methacrylamide and N, N-dimethylacrylamide applied in the damage of mucous membrane due to drug. Hydrogel so formed were studied for the release rate at temperature 37°C and different pH values 2, 5 and 7 respectively. Dissolution of the ibuprofen from different formulation at different pH was studied. Results had shown that hydrogel were able to prevent crystallization of the ibuprofen at all pH.

ZhiYong Qian et al. had formulated a pH sensitive in situ hydrogel based on the macro monomer synthesized by heat initiated free radical polymerization of methoxy pol(ethylene glycol)-poly(caprolactone)-acryloyl chloride, poly(ethylene glycol)-methyl ether methacrylate and methacrylic acid. Macro monomer and hydrogels were characterized by utilizing NMR and FT-IR techniques. Other profile for the macro monomer produced was also studied like morphology, swelling behavior, in vitro drug release etc. and toxicity profile of the macro monomer. Hydrogel that showed the sharp changes in the different pH values were selected as most promising candidate for oral drug delivery of dexamethasone in the inflammatory bowel disease.

Antonios G. Mikos et al. examined the cytocompatibility of amphiphilic, thermoresponsive and chemically cross linkable macromer forming an in situ hydrogel, via in vitro studies. Macromers were synthesized by pentaerythritol diacrylate monostearate, N-iso propylacrylamide, acrylamide and hydroxyethyl acrylate using different molar ratios and changing molecular weights. The lower critical solution temperature was evaluated to determine the cytocompatibility with the fibroblast cell of rat. Cell viabilities of over 80% were observed after the incubation of cell for 24 hour, with molecular weight in range 1500-3000 daltons. Chemical modification of the macromers had also shown the time and dose dependent effect on cell viability. The data obtained had depicted that chemically modified macromers form a less cytotoxic physical gel, while phase separation increased the cytotoxicity.

6. Applicability Of In Situ Polymeric Drug Delivery System

Depending on the route of administration, these in situ polymeric systems may be classified as illustrated in following section.

6.1 Oral-delivery

There are various natural polymers used (such as pectin, gellan gum and xyloglucan) for in situ forming oral drug delivery systems. The purpose of an orally administered in situ gelling pectin formulation for the sustained delivery of paracetamol has been achieved in many formulation. The main benefit of using pectin for these formulations is that it is water soluble, so organic solvents are not necessary in the formulation. In situ gelling contain gellan formulation as vehicle for oral delivery of theophylline is formulated. The formulation consisted of gellan solution with calcium chloride and sodium citrate complex. When administered orally, the calcium ions are released in acidic environment of stomach leading to gelation of gellan thus forming a gel in situ. An increased bioavailability with sustained drug release profile of theophylline in rats and rabbits was observed from gellan formulations as compared to the commercial sustained release liquid dosage form.
6.2 Ocular- Delivery

For in situ gels based ocular delivery, natural polymers (such as gellan gum, alginic acid and xyloglucan) are most commonly used polymers. Local ophthalmic drug delivery has been used for various compounds such as antimicrobial agents, antiinflammatory agents and autonomic drugs used to relieve intraocular tension in glaucoma. When use of Conventional delivery systems result in poor bioavailability and therapeutic response because high tear fluids turn over and dynamics cause rapid elimination of the drug from the eye So, to overcome bioavailability problems, ophthalmic in situ gels were developed Much of the interest in the pharmaceutical application of gellan gum has concentrated on its application for ophthalmic drug delivery.25 Drug release from these in situ gels is prolonged due to longer precorneal contact times of the viscous gels compared with conventional eye drops. Miyazaki et al. attempted to formulate in situ gels for ocular delivery using Xyloglucan (1.5% w/w) as the natural polymer. These in situ forming polymeric systems were observed to show a significant mitotic response for a period of 4h when instilled into lower cul-de-sac of rabbit eye26. The formulation and evaluation of an ophthalmic delivery system for indomethacin for the treatment of uveitis was carried out. A sustained release of indomethacin was observed for a period of 8 h in-vitro thus considering this system as an excellent candidate with the water- soluble Carbopol system has been reported27.

6.3 Nasal -Drug Delivery Systems

An in-situ gel system for nasal delivery of mometasone furoate was developed and evaluated for its efficacy for the treatment of allergic rhinitis.30 natural polymer (such as, Gellan gum and xanthan gum) were used as in situ gel forming polymers. Animal studies were conducted using an allergic rhinitis model and the effect of in situ gel on antigen induced nasal symptoms in sensitized rats was observed. In-situ gel was found to inhibit the increase in nasal symptoms as compared to marketed formulation nasonex (mometasone furoate suspension 0.05%). Intact ciliated respiratory epithelium and normal goblet cell appearance indicated from histopathology of rat nasal cavity proved that these formulations were safe for nasal administration. Wu et al. designed a new thermosensitive hydrogel by simply mixing N-[(2-hydroxy-3- methyl trimethyl ammonium) propyl]chitosan chloride and poly (ethylene glycol) with a small amount of α-β- glycerol phosphate; for nasal delivery of insulin. The formulation was in solution form at room temperature that transformed to a gel form when kept at 37°C. Animal experiments demonstrated hydrogel formulation to decrease the blood-glucose concentration by 40-50% of the initial values for 4-5 h after administration with no apparent cytotoxicity. Therefore, these types of systems are suitable for protein and peptide drug delivery through nasal route.28

6.4 Rectal and Vaginal -Delivery

In situ gels also possess a potential application for drug delivery by rectal and vaginal route. Miyazaki et al. investigated the use of xyloglucan based thermoreversible gels for rectal drug delivery of indomethacin. Administration of indomethacin loaded xyloglucan based systems to rabbits indicated broad drug absorption peak and a longer drug residence time as compared to that resulting after the administration of commercial suppository. For a better therapeutic efficacy and patient compliance, mucoadhesive, thermosensitive, prolonged release vaginal gel incorporating clotrimazole-β-cycloextrin complex was formulated for the treatment of vaginitis. In addition, a significant reduction of drug C max was observed after administration.
of in situ polymeric system thus indicating the avoidance of adverse effects of indomethacin on nervous system.  

7. Patentable Formulation

Various patentable formulation in US patent system

<table>
<thead>
<tr>
<th>S.No.</th>
<th>US patent</th>
<th>Formulation</th>
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<tbody>
<tr>
<td>1</td>
<td>US20020119941</td>
<td>In situ gel formulation on pectin</td>
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<tr>
<td>2</td>
<td>US20110082221</td>
<td>In situ gelling system as sustained delivery for eye</td>
</tr>
<tr>
<td>3</td>
<td>US20120009275</td>
<td>In situ forming hydrogel wound dressing containing antimicrobial agent</td>
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<tr>
<td>4</td>
<td>US20050063980</td>
<td>Gastric raft composition</td>
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<tr>
<td>5</td>
<td>US5360793</td>
<td>Rafting antacid formulation</td>
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</tbody>
</table>

CONCLUSION

In present scenario it’s a challenging task for prolonging the gastric retention and physiological compatibility with stomach.so, in various approach one of the most promising is in situ floating gel drug delivery system. Which form sol to gel formation in various physiological environment like pH, temperature and ionic condition .so, it proved as a site specific release formulation. Several biodegradable polymer are used for this formulation.in situ floating gel have a good biocompatibility, bioavailability ad stability.so, it become more reliable over conventional dosage form.

REFERENCES

4. Oral drug delivery. Gastroretentive drug delivery system Sanjay Garg and Shringi Sharma Associate Professor and Senior Research Fellow, Department of Pharmaceutics ,National Institute of Pharmaceutical Education and Research (NIPER) page no 160-166.


