African Journal of Basic & Applied Sciences 3 (6): 300-312, 2011
ISSN 2079-2034

A Short Review on Gastro Retentive Formulations for Stomach Specific Drug Delivery: Special Emphasis on Floating *In situ* Gel Systems

Lovenish Bhardwaj, Pramod Kumar Sharma and Rishabha Malviya

Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology,
Delhi-Roorkee Highway, Baghpat Bypass Crossing, NH-58,
Meerut-250005, Uttar Pradesh, India

Abstract: Conventional oral dosage forms pose low bioavailability problems due to their rapid gastric transition from stomach, especially in case of drugs which are less soluble at alkaline pH of intestine. Similarly, drugs which produce their local action in stomach get rapidly emptied and do not get enough residence time in stomach. So, frequency of dose administration in such cases is increased. To avoid this problem, various efforts have been made to prolong the retention time of drug delivery system. In this review, we will discuss about the various approaches to produce gastro retention of drug delivery system, with special emphasis to floating *in situ* gel system for stomach specific drug delivery.

Key words: Gastro retention · Floating · *In situ* gel · Stomach specific drug delivery

INTRODUCTION

Recent development in technology has provided viable dosage alternatives that can be administered via different routes of administration. Various routes that are used these days include oral, parentral, topical, nasal, rectal, vaginal, ocular etc. But out of these routes, oral route of drug delivery is considered as the most favoured and practiced way of drug delivery, because of following reasons [1, 2]:

- Ease of administration,
- More flexibility in designing,
- Ease of production,
- Low cost.

Most of the drugs given via oral route are subjected to absorption throughout the gastrointestinal tract, with major absorption from stomach and intestine [3, 4]. Various processes occur after the drug release from the dosage form, which affect the absorption of drugs, e.g. degradation of drug by enzymatic or microbial action, precipitation etc.

Drugs, which get absorb from stomach or show local effect, should spend maximum time in stomach. This however, is found very difficult to occur, in case of conventional dosage forms like tablets and capsules, because of the gastric emptying.

Gastric emptying of a particular dosage form depends on various factors like volume and composition of the meal, temperature and viscosity of the meal, pH of stomach, body posture, emotional state of the individual, diseased state, gastric motility altering drugs etc. Parameters that affect the process of gastric emptying can be studied by various techniques viz. ã-scintigraphy, ultrasonology, endoscopy, radiotelemetry, radiology etc [5, 6]. Prolonged gastric retention of drug is required in the following conditions [1, 3]:

- Drug is best absorbed from stomach e.g. aspirin, phenylbutazone etc.
- Gastric fluids facilitate and improve the disintegration and dissolution of the drug,
- Dissolution and absorption of drug is promoted by the food e.g. griseoflvin,
- Slow dissolving drugs,
- Drug show local effect within stomach.

Corresponding Author: Lovenish Bhardwaj, Department of Pharmaceutical Technology,
Meerut Institute of Engineering and Technology, Delhi-Roorkee Highway,
Baghpat Bypass Crossing, NH-58, Uttar Pradesh, India,
Tell: +91-9808685705, Email: lovenish_bhardwaj@yahoo.com

In order to fulfill all these conditions, various approaches of the controlled drug delivery have been developed. One of these types of the approaches, which ensure that a particular drug or dosage form remains within stomach for longer duration of time, is Gastro retentive drug delivery system [7].

However, in certain condition gastro retention is considered undesirable [1]:

- For drugs which are gastro irritant, for e.g. diclofenac sodium, ibuprofen, acetyl salicylic acid etc.
- For acid labile drugs which are stable at gastric pH, e.g. macrolide antibiotics.
- Drugs which get absorbed throughout the gastrointestinal tract equally.

Gastro Retentive Drug Delivery System: Gastro retentive 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 [8]. 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.

Gastro retentive 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 [9].

Such systems also provide higher concentrations of drug released around gastric mucosa to efficiently treat the gastric diseases like ulcer, gastritis, oesophagitis etc. Drugs which can be given by gastro retentive drug delivery systems belong to various categories involving antibiotics (sulphonamides, cephalosporins), antivirals, antifungals, H_2 receptor antagonists (cimetidine, ranitidine and famotidine) etc. In addition to these, gastro retentive drug delivery systems may also be utilized for the oral delivery of proteins and peptides (calcitonin, erythropoietin, insulin, protease inhibitor, low molecular weight heparin etc.) [10, 11]. Various factors that should be considered during gastro retentive drug delivery formulations are included here [7, 10-15]:

Physicochemical Factors:

- *Size of dosage form*: Dosage forms having diameter greater than the diameter of pyloric sphincter escape from gastric emptying and remain within gastric region.
- *Shape of dosage form*: Round or Ring shaped dosage form are considered better in comparison to other shapes.
- *Density*: Location of the particular gastro retentive dosage form in gastric region depends on density of the system. Those with low density tend to float on the gastric fluid surface while high density systems sink to bottom of stomach.

Biological Factors:

- *Age*: Geriatric patients show a longer gastric retention time, while the neonates and children have low gastric retention time, in comparison to a normal adult.
- *Gender*: Gastric retention time in male (3-4 hours) is less than the female (4-6 hours).
- *Fed or Unfed st*ate: Gastric motility is higher in fasting conditions which depicts lesser gastric retention time.
- *Feed frequency*: Higher the frequency of taking food, longer will be the gastro retention time.
- *Nature of meal*: High amount of fatty acids and other indigestible polymers generally decreases the gastric retention time by altering gastric motility.
- *Concomitant drug administration*: Administration of certain drugs along with gastric motility enhancers (metoclopramide, cisapride) or depressants (atropine), greatly affect gastric retention time and hence absorption of stomach specific absorbing drugs.
- *Disease state*: Gastro retentive time is altered during the various gastric diseases like Crohn's disease etc.

Comparisons between conventional and gastro retentive drug delivery system are shown in table 1.

Table 1: Comparisons between conventional and gastro retentive drug delivery system [2]

Parameter	Gastro Retentive Drug Delivery System	Conventional Drug Delivery System
Risk of toxicity	Lower	Higher
Patient compliance	High compliance level	Less compliance level
Dose dumping	High risk	No risk
Drugs	Advantageous for drugs: • Having rapid gastrointestinal absorption • Degrade in colon • Showing local action in the stomach	Not advantageous for drugs: • Having low gastrointestinal absorption • Degrade in colon • Showing local action in the stomach

Advantages of Gastro Retentive Drug Delivery System [11, 12, 16, 17]:

- *Improved drug absorption*: Drugs, having absorption window in stomach show better absorption profile.
- *Better bioavailability*: Due to increased absorption with in stomach, bioavailability of drug is generally enhanced.
- *Drug delivery*: It is possible to control the delivery pattern of drug in to the stomach by proper designing of the drug delivery system.
- *Irritation*: Irritation of the intestinal mucous membrane can be minimized.
- *Gastro intestinal disease*: As the gastro retentive drug delivery system spent more time with in stomach, it is a perfect way for treating the gastrointestinal diseases with better cure rate, e.g. Crohn's disease.
- *Site specific drug delivery*: Drugs which are subjected to produce local action can be directly targeted to organ site.
- *Ease of administration*: Gastro retentive systems are similar in physical design to the conventional dosage forms like tablet, capsule, solution, suspension, which are easy to handle and administer.
- *Patient compliance*: Frequency of dose administration can be reduced remarkably; resulting in better patient compliance.

Disadvantages or Limitations of the Gastro Retentive Drug Delivery System [12, 16, 17]:

- *Stability*: Gastro retentive systems are not suitable for drugs which are degraded by gastric acid, gastric enzymes and gastric micro flora.
- *Lack of solubility*: Drugs which are less soluble at acidic pH of the gastric fluids are not suitable for such system.
- *Gastro-irritant drugs*: Drugs which irritate gastric mucosa should not be delivered by this type of system.
- *Absorption throughout the gastrointestinal tract*: Drugs which undergo equal absorption through all regions or sites of the gastrointestinal tract are not desirable candidate.
- *First pass metabolism*: Rate of first pass metabolism is higher with such system.

Approaches for Gastro Retention Systems: Different approaches, that have been developed, for formulating dosage form to produce adequate gastric retention and release within gastric region, are as follows [1, 2, 11, 18]:

- High-density drug delivery system
- Floating drug delivery system

- Hydrodynamically balanced drug delivery system
- Gas-generating drug delivery system
- Raft-forming drug delivery system
- Low-density drug delivery system

- Expandable drug delivery system
- Super porous hydrogels
- Mucoadhesive or bioadhesive drug delivery system
- Magnetic drug delivery system

High Density Gastro-retentive Drug Delivery System: It is a well known fact, that the density of the gastric content is approximately similar to water. So, when the density of the dosage form is higher than water, it tends to deposit or sink at the bottom of the stomach, near pyloric region. These sinked dosage forms, there, withstand against peristaltic contractions and do not get emptied from the stomach. Retarded gastrointestinal transit, in case of such dosage form has been reported to extend gastric retention time up to 6 to 24 hours.

Commonly used excipients in such dosage forms are barium sulphate, titanium oxide etc., which raises the density of system up to 1.4 to 2.5 gram per cubic centimeter.

Such type of system has shown promising results in the animals, but no system has been in the market for human consumption [19].

Floating Delivery System: Floating drug delivery systems meant for gastric retention, float on the surface of the gastric fluids, due to their low density and produce prolonged effect by showing the release, while being buoyant on gastric fluid surface [20]. This type of delivery system is of great value for drugs which get absorbed from upper part of the stomach i.e. their absorption window resides in upper part of stomach [18].

Though, immediate floating of the delivery system can only be achieved if the density of the delivery system is on lower side [8]. Delivery system with higher density, initially settle down in stomach and then tend to float with decrease in the density of the system. But, with such system, there may be a possibility of gastric emptying of system, before the floating starts. Low density of system, which leads to floating, rendered either by incorporation of low density excipients or by providing a mechanism which leads to air entrapment within the system [21, 22].

Different types of floating systems have been developed, which may involve generation of gas (effervescent) or non effervescent. Approaches for producing floating systems are as follows:

- *Hydro-dynamically balanced system*: These systems consists of hydrophilic gel forming polymers like HPMC, hydroxy ethyl cellulose, hydroxy propyl cellulose, agar, alginic acid etc. and are generally designed for single unit dosage [23]. In this approach, hydrophilic polymer is mixed with drug along with other excipients and encapsulated in gelatin shell. Gelatin, being hygroscopic in nature dissolves rapidly in the gastric fluid and exposes the hydrophilic polymer and drug content to the fluids [7]. Polymer fraction present on the surface then undergoes hydration and swelling, to produce a floating mass.
- *Gas generating systems (Effervescent systems)*: Floating to a system can also be produced by the gas bubble generation. For this, carbon dioxide is generated within the system by incorporating bicarbonates and carbonates, which on reaction with gastric content (gastric acid) produce gas [7]. System utilizes the presence of swellable polymers like methocel, chitosan etc. along with effervescent components like bicarbonates with citric or tartaric acid for gas generation [2]. General approach for preparation of such system involves preparation of core with drug, swellable polymer along with effervescent system and coating with hydrophobic polymer like ethyl cellulose, which acts as semi-permeable membrane to regulate the inflow of the gastric content and keep the system intact within the polymer coating for complete gastro retention period.
- *Raft forming system [2, 16]*: In this type of system, a gel forming solution is prepared that swells on coming in contact with gastric contents and form viscous gel like layer which resemble same as a raft in river. This, raft like layer of gel, has a very low bulk density due to the generation of carbon dioxide within system, which makes the layer to float on the surface of gastric content. Raft forming system consists of a gel forming polymeric agent and carbon dioxide producing agents like bicarbonates and carbonates [24]. Gel forming agents that are being widely utilized for the formation of the raft like consistency are from the alginate category e.g. alginic acid. Such formulations also include antacids such as aluminium hydroxide, calcium carbonate etc. for reduction of the gastric acidity. As the solution after gel formation floats on the surface of the gastric fluids, such systems are used for the treatment of the gastro-esophageal reflux [18].
- *Low density systems*: Major limitation in case of effervescent delivery system is the time lag before floating on the gastric contents. In this time period, it may be possible that the delivery system may get evacuated, before floating and drug release. So, in order to overcome this limitation, low density systems (lesser than 1000 mg per cubic centimeter) have been developed, which show immediate floating and release of drug on the gastric content surface. System is basically consists of low density materials which entrap oil or air [18].

Expandable Systems [18, 25]: A dosage form, which is bigger in size than the diameter of the pyloric sphincter can withstand with the gastric transit and escape the evacuation from the gastric region. But while designing such system, it should be kept in mind that the dosage

form should be of adequate size, so that it can be easily swallowed and should not cause gastric obstruction. It should also be considered, that after complete drug release from system, it can be evacuated easily from the gastric system. The concept of designing such expandable system is to prepare a carrier (e.g. capsule) and to incorporate in it, a compressed system which expands, as it comes in contact with the gastric contents. As, the size of the system increases and reaches to diameter or dimensions, greater than the size of the pyloric sphincter, it cannot leave the stomach while gastric emptying process.

Super Porous Hydrogels: These also come under the category of expandable or swellable system. Super porous hydrogels tends to swell and enlarge in size within a minute, due to rapid water uptake from gastric contents by capillary action via numerous interconnected pores and have sufficient mechanical strength to withstand pressure during gastric contractions. This can be achieved, by incorporating hydrophilic particulate materials, e.g. croscarmellose sodium [18].

Mucoadhesive and bioadhesive systems [25]: Mucoadhesive systems adhere to gastric mucosa and remain in the gastric region for prolong time. Adherence occurs due to hydration and swelling of the adhesive polymer on contact with gastric contents. Materials that are commonly used for imparting the mucoadhesive or bioadhesive property to the whole system include carbopol, chitosan, tragacanth, PEG, HPMC etc. However, it is very difficult to maintain the system adhered within the gastric region, due to rapid turnover rate of the gastric mucus. Such systems also pose another problem that it is very difficult to control the specific adhesivity of system to gastric mucosa and it may also adhere to other surfaces, e.g. esophagus.

Magnetic Systems: Magnetic systems involves the incorporation of the small magnet inside the core or matrix of the system and application of the another magnet on the abdomen region, externally. This system, however, provide satisfactory results, there is a problem of placing the magnet externally at the right position with great accuracy and precision [18].

Stomach Specific Floating *In situ* Gel: *In situ* gel forming systems have been widely studied, for their capability of producing the sustained and controlled drug delivery. Such systems offer the advantage of easy administration along with improved patient compliance [26, 27]. In recent few years, lots of work on development of *in situ* gelling formulation has been done and delivery of drug via popular routes like oral, nasal, ophthalmic along with other routes like vagina has been studied, which has shown the promising result, for the use of system as a potential way of producing the controlled drug delivery [20, 26, 28]. The system basically utilizes polymers which undergo transformation from solution to gel like consistency, due to change in their physicochemical properties. *In situ* gel formation can be stimulated by change in the temperature, change in pH, change in the solvent medium, by radiation exposure or by combination of any of these [29].

Gastro-retentive *in situ* gel forming system have provided a suitable way of providing the controlled drug delivery within stomach where an environment specific gel forming solution, on conversion to gel, floats on the surface of the gastric fluids (due to less density than gastric contents). In this technique, a solution of low viscosity is used which on coming in contact with the gastric fluids, undergo change in polymeric conformation and a viscous gel of density lower than the gastric fluids is produced. This low density gel formation not only provide the much desired gastro retention to prolong the contact time, but also produce the continuous and slow drug release [8]. System is basically comprises of *in situ* gel forming polymers of synthetic or natural origin, e.g. gellan gum, alginic acid, xyloglucan, chitosan, polycarolactone etc [29]. Floating ability of the gel may also be improved by the addition of effervescence producing system like bicarbonates or carbonates, with or without citric or tartaric acid, where the release of carbon dioxide (air generation) will make the gel much lighter and in turn helps to float. Ability of the gel to produce more prolong and controlled release may also be enhanced by raising its viscosity (by adding viscosity enhancers, e.g. HPMC) [30].

Advantages of floating *in situ* gel forming gastro-retentive drug delivery system over other gastro-retentive drug delivery system:

- *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.
- Floating obtained is faster than the floating tablets.

Limitations of floating *in situ* gel forming gastro-retentive drug delivery system:

- *In situ* gel forming systems are basically formulated in the form of solutions which are more susceptible to stability problems due to chemical degradation (oxidation, hydrolysis etc.) or microbial degradation.
- If such system is not stored properly than it may pose instability problems, due to change in the pH of system on prolonged storage or on storing in inappropriate temperature conditions. Exposure of certain polymers to radiations (e.g. UV, Visible, electromagnetic etc.) may also induce the gel formation, within the package, it is stored.

Approaches to Produce *In situ* Gel: Different approaches and mechanisms utilized or involved in producing the *in situ* gel formation are as follows [30]:

- Based on producing physical changes
- Based on producing chemical changes
- Based on physiological stimuli

***In situ* Gel Formation by Physical Changes [27]:** This approach involves either swelling or diffusion phenomenon. In swelling, polymer in the system absorbs water from the surrounding environment and swells to form a viscous gel (e.g. glycerol mono-oleate). In diffusion, solvent in which the drug and polymer is dissolved or dispersed, diffuse into the surrounding tissues causing the precipitation of the polymer to form gel (e.g. N-methyl pyrrolidone).

***In situ* Gel Formation Based on Chemical Changes or Stimuli:** Change in the chemical environment of system may lead to gel formation by producing polymeric cross linking.

- *Ionic cross linking [31, 32, 33]*: In presence of the various ions present in the body fluids, e.g. Na^+, K^+, Ca^{2+}, Fe^{3+} etc., ion sensitive polysaccharides, e.g. carragenan, gellan gum, pectin etc., undergo transition in phase due to development of the polymer cross linking, e.g. Sodium alginate undergoes gel formation in presence of calcium chloride.
- *Enzymatic cross-linking [27]*: Enzymes present in the body fluids may also cause cross linking to form a polymer network and is considered, as most convenient mode of gel formation.
- *Photo polymerization [27, 34]*:-Exposure of tissues, in which such gel forming system is injected, with microwave radiation, UV radiation or electromagnetic radiation leads to gel formation within the tissues, e.g. 2, 2 dimethoxy-2-phenyl acetophenone, ethyl eosin etc.

***In situ* Gel Formation by Physiological Stimuli:** Physiological stimuli that can induce gel formation include change in temperature and change in pH of the system.

- *In situ gel formation depending on change in temperature [27, 34]*: In this approach, temperature dependent phase transition from less viscous solution to comparatively high viscosity gel is seen. Change in temperature causes abrupt change in the solubility of polymer within system and polymer-polymer interaction occurs to form a solvated macromolecule of hydrophobic nature. Temperature sensitive polymers are the most studied class for producing the *in situ* gel characteristics, e.g. Polyacrylic acid, polyacrylamide etc.
- *In situ gel formation due to change in pH of system [8]*: Polymers, such as polyacrylic acid and its derivative (carbopol), polymethacrylate etc., undergo gel formation because of change in the pH, due to presence of various ionizable groups in the chemical structure of the polymer. 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.

Polymers Frequently Used for *In situ* Gelling for Gastro Retentive Reasons: *Sodium alginate [20, 31, 33]*: Sodium alginate is a widely used polymer of natural origin. Chemically, it is alginic acid salt, consisting of α-L-glucuronic acid and β-D-mannuronic acid residues connected by 1,4-glycosidic linkages. Solution of alginates in water form firm gels in presence of di-or tri-valent ions (e.g. calcium and magnesium ions). Alginate salts, specifically, sodium alginate is mostly used for preparation of gel forming solution, for delivery of the drugs and proteins. Alginate salts are considered most favourable because of biodegradable and non toxic nature, with additional bio-adhesive property.

***Pectin* [27]:** These are plant origin anionic polysaccharides isolated from the cell wall of most plants and basically consist of α-(1-4)-D-galacturonic acid

residues. Pectin undergoes gel formation in presence of divalent ions (e.g. Ca^{2+}) which causes cross linking of the galacturonic acid units (ionic cross linking) and also in the presence of the H^+ ions (pH dependent gelling).

Gellan gum **[31, 32, 34]:** Gellan gum (FDA approved) is secreted by the *Sphingomonas elodea (Pseudomonas elodea)* and chemically is anionic deacetylated polysaccharide with repeating tetrasaccharide units composed of β-D-glucuronic acid (1 unit), α-L-rhamnose (1 unit) and β-D-glucuronic acid (2 units) residues. Gellan gum undergoes gel formation due to change in temperature or due to presence of cations (e.g. Na^+, K^+,Ca^{2+}).

Xyloglucan **[27]:** It is a plant based polysaccharide obtained from seeds of tamarind. Chemically, this polysaccharide composed of a chain of (1-4)-β-D-glucan having (1-6)-α-D xylose units as branches which have partial (1-2)-β-D-galactoxylose substitution. Xyloglucan, itself, does not undergo gel formation but dilute solutions partly degraded by galactosidase exhibit gelling properties on heating (temperature dependent gel formation). Besides the use in oral drug delivery, it is also being used for ocular and rectal drug delivery. Xyloglucan has shown a very low gelation time of up to few minutes.

Evaluation of Stomach Specific Floating *In situ* Gel System: Stomach specific floating *In situ* gel forming system should be evaluated for following parameters:

- *Physical appearance [29]*: *In situ* solutions should be clear and free of any particulate matter. Time required for solution to convert in to gel in buffer pH 1.2 is measured and consistency of the gel formed is checked visually.
- *pH of system [29]*: pH of gel forming solution is measured using calibrated pH meter at 27°C.
- *Viscosity of in situ gelling system [20, 29]*: Viscosity of solution is determined before and after gelling by using Brookfield viscometer or cone and plate viscometer at suitable temperature (25±1°C), using 1 or 2ml of sample aliquots.
- *In vitro gelation study [32]*: To evaluate *in vitro* gelling capacity of gel forming solution, colored solution of the formulation is prepared and in a test tube 15ml gelation medium (0.1N HCl, pH 1.2) is taken. After that, 1ml of colored formulation is added. As, the solution comes in contact with gelation medium, a stiff gel is produced. The gelling capacity is determined on the basis of stiffness and time period for which gel remains, as such.
- *In vitro floating ability [20, 29, 32]*: *In vitro* floating ability of the gel is determined in 500ml simulated gastric fluid (0.1 N HCl, pH 1.2) at 37°C using USP dissolution apparatus (type II). After that, 10ml of prepared formulation is introduced in the dissolution vessel. Time taken by formulation to float (floating lag time) and duration for which the formulation floats constantly on the surface (floating time) is noted.
- *Water uptake by gel [29]*: Measurement of water uptake by gel is done by using thermo gravimetric analyzer. In this test, *in situ* gel formed in 40ml 0.1N HCl, pH 1.2 is used. Gel portion form the buffer is collected in a Petri dish and excess buffer is removed using tissue paper. Initial weight of the gel is taken and 10 ml distilled water is added. After every 30 minutes, water is decanted and weight of the gel is measured. The difference in the weight shows the water uptake by gel.
- *Uniformity of content*: Drug content is determined by a suitable quantitative technique as specified in particular monograph or as per the established standard testing procedure.
- *In vitro drug release [20, 32]*: *In vitro* drug release is determined using USP dissolution apparatus (type II) at 50 rpm in 900ml, 0.1N HCl, pH 1.2 at 37°C. 10ml formulation is taken in a Petri dish and kept in dissolution vessel. Then dissolution medium is introduced in the dissolution vessel without any disturbance. Suitable sample is drawn at each predefined interval and replenished with fresh medium. Dissolution study should be carried out for at least 8 hours.

Application of the Stomach Specific Floating *In situ* Gel [7, 10, 12, 17]:

- *Increased absorption*: Drugs which are mainly absorbed from upper part of stomach get prolonged contact time, at their site of maximum absorption. This causes increase in the extent of absorption.
- *Improved bioavailability*: As the absorption of the drug from stomach is increased, bioavailability of the drug enhanced, remarkably. Increase in the gastric transit time also causes an increase in the bioavailability of drug.

- *Less adverse effect of drug*: As, drug remains in the stomach till the complete release, frequency of the adverse effect on the colon decreases to greater extent.
- *Site specific drug delivery*: Drugs which are absorbed from the stomach get enough residence time for absorption; hence increase in the absorption rate occurs. Furthermore, local action of the drug in stomach is prolonged, so less amount of dose is required.

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 found 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 [35].

Giuseppe Perale *et al.* developed a hydrogel which had shown the promising results in the spinal cord injury, when injected through 40 ìm 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 [36].

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 concentration of colloids had shown to improve the opacity but reduces the syneresis. Syneresis was found to be at lower side, as 1.5% for mixed gel having 2% each of gellan and agar while opacity was found to be 30%, with even more values for opacity for the agar gel. Stress and energy for compression had improved the level of gelling agents [37].

S.G. Kazarian *et al.* had formulated pH sensitive hydrogels by morpholine derivatives utilizing homopolymers and copolymers of N-ethylmorpholine methacrylamide and N, N-dimethylacrylamide applied in the form of matrices for ibuprofen release, which prevent the damage of mucous membrane due to drug. Hydrogel so formed were studied for the release rate at temperature 37ºC 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 [38].

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 poly(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 [39].

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 [40].

A. Makó *et al.* formulated a thermoresponsive and bioadhesive, *in situ* gelling system of drug delivery for treatment of esophageal pain and inflammation. Bioadhesive polymer used was Metolose, a cellulose derivative with thermoresponsive property. Thermal gelation temperature for the polymer was around 65-66°C. Alteration of pH between 2 to 10 and presence of alcohols had not influenced the gelation temperature but using water soluble salts and changing the concentration of polymer in solution (2-3%w/w) thermal gelation point can be reduced. Effect on the thermal gelation point, *in vitro* liberation and penetration was studied. Study showed that thermal gelation point did not vary but liberation and penetration of drug was changed. Morphological studies of esophagus had also shown that the system did not have any irritant effect or tissue damage effect on esophageal mucosa on exposure even after 12 hour [41].

Kunihiko Itoh *et al.* evaluated the gelation and release characteristics of physical mixtures of varying concentration of xyloglucan and pectin where xyloglucan had the thermally reversible gelation and pectin had the ion responsive gelation properties, in order to formulate an *in situ* gelling vehicle for sustained drug delivery via oral route. Rheological studies showed that inclusion of pectin (0.75% w/w) had increase the gel strength of the 1.5 % and 2.0% w/w xyloglucan and the resulting formulation produced. Plasma concentration studies in rats on oral administration the formulation had also shown the more sustained release and improved drug bioavailability was achieved by gel formed due to *in situ* gelation of this formulation, while the pectin (0.75%w/w) and xyloglucan (1.75%w/w) did not form any gel, under these condition. Visual observation of the gastric content of rat had shown that inclusion of pectin with xyloglucan had also reduced the erosion of gel formed [42].

B. Mishra *et al.* for treatment of gastric ulcers associated to H. pylori formulated a floating *in situ* gelling system of clarithromycin using gellan gum as gelling polymer and calcium carbonate as gas generating floating agent. *In situ* gelling system was prepared by dissolving different concentration of the gellan gum in water and uniformly dispersing the sucralfate. Formulation variables specially, gellan gum and sucralfate had shown significant effect on the *in vitro* release of drug. The resultant *in situ* gelling system in comparison to amoxicillin suspension had shown improved efficacy towards the clearance of the H. pylori. Prolonged gastric residence time, because of floating, had also shown to have improved efficacy of the drug towards peptic ulcer treatment [43].

B. Mishra *et al.* developed an intra gastric floating *in situ* gel system for controlled amoxicillin delivery in treatment of peptic ulcer disease caused by Helicobacter pylori (H. pylori). The system was prepared by, using different concentration of gellan gum in water containing citrate salt, to which varying drug and calcium carbonate (gas forming agent) was added. It had been shown, that concentration of calcium carbonate and gellan gum had significantly affected *in vitro* drug release. H. pylori clearance efficacy of the *in situ* gel forming system in reference to amoxicillin suspension had shown significant anti H. pylori effect when studied by polymerase chain reaction technique and microbial culture method. The results had also shown that *in situ* gel forming system of amoxicillin was more effective than the suspension due the prolonged gastro-retentive residence time [32].

David Attwood *et al.* compared the gelation and drug release characteristics of different formulation containing derivatized pectin which was methoxylated to different degree, i.e. high (31%) and low (9%) over a wide range of pH varying from 1.2 to 5.0. A source of calcium in complexed form was also added which released the Ca^{2+} on breaking under the acidic conditions. In presence of Ca^{2+} ions dilute pectin solution (1.5%w/w) undergo gelation due to cross linking of the galacturonic chain, at lower pH, but the gelating tendency of the pectin was reduced at the higher pH due to lack of Ca^{2+} ions released from complex. Gelation property of the formulation prepared by pectin with 9% degree of esterification was examined in presence of Ca^{2+} (1.6mM) over pH range of 2.5 to 5.0 and compared to the pectin with 31% degree of esterification. Pectin with low degree of esterification was found to produce the better gelation in comparison to pectin with high degree of gelation. A sustained delivery of the ambroxol was also shown by the formulation containing with Pectin low degree of esterification in gastric acidity controlled rabbits at pH 5.5-5.7 and *in situ* gelation was confirmed by visual examination. So, Pectin with low degree of esterification had shown to be a potential candidate for producing *in situ* gelling system for sustained delivery of drugs at gastric pH [44].

David Attwood *et al.* studied the effect of the varying gastric pH over a pH range of 1-3 on gelation of the liquid formulation of pectin and *in vitro* and *in vivo* release of the paracetamol and ambroxol was studied from the resultant gels. Formulation was comprised of pectin with complexed Ca^{2+} in aqueous medium. When such complex came in the acidic medium Ca^{2+} were released which convert solution of pectin to gel. Gel (pectin 1-2%)

Table 2: Marketed formulations of Floating drug delivery system

Drug	Brand name	Manufacturer
Levodopa, Benserazide Hydrochloride	Madopar	Roche [49]
Cifrofloxacin	Cifran OD	Ranbaxy [50]
Aluminium Hydroxide, Magnesium carbonate	Liquid Gaviscon	Reckitt Benckiser [51]
Aluminium -Magnesium anatacid	Topalkan	Pierre fabre [52]
Folic Acid, Ascorbic Acid, Vit B12, Dried Ferrous Sulphate, Vit B6	Conviron	Ranbaxy [53]

suitable for the sustained delivery of paracetamol and ambroxol was formed at pH< 3 *in vitro*. While, very weak gels were produced at pH 3.0, leading to poor sustained release characteristics, in comparison to those, formed at pH 1.2, but no gelation at pH 3.5 was seen. Bioavailability for paracetamol and ambroxol from *in situ* formed gels were studied in gastric acidity controlled rabbits and visual observation for *in situ* gelation showed better gelation at both high and low gastric pH. Bioavailabilities for both drugs were found same for gels formed at low as well as high pH [45].

Alekha K. Dash *et al.* developed a chitosan-glyceryl monostearate based *in situ* gelling system to produce sustained drug delivery and site specific targeting. The system was prepared by using 3%w/v chitosan and 3% w/v glyceryl monostearate in 0.33M citric acid solution. Formation of *in situ* gel was performed at biological pH and *in vitro* release for drugs was performed in Sorenson's phosphate buffer (pH 7.4). Gelation of the system was characterized by studying effect of cross linker, determination of diffusion coefficient and water uptake by thermogravimetric analysis (TGA). Mucoadhesive property of gel was also studied using EZ-tester. Studies showed that cross linker had result in the decrease of the rate and extent of the drug release. Glyceryl monostearate had enhanced mucoadhesive property of chitosan to a great extent. This *in situ* gel system on the basis of study had been reported suitable for both oral as well as parentral sustained delivery of drugs [46].

David Attwood *et al.* evaluated the sustained delivery of paracetamol via two *in situ* gel forming formulations. Formulation was basically consists of aqueous solution of gellan gum (1.0% w/v) or sodium alginate (1.5%w/v) containing the calcium ion complex, which in acidic environment causes release of calcium ions. These calcium ions then caused the gelation of the gelling agents (gellan gum or sodium alginate). *In vitro* studies had demonstrated diffusion controlled release of paracetamol from *in situ* formed gels over a period of 6 hour. Bioavailability of paracetamol for *in situ* gel formulated was found to be similar to commercially available suspension of paracetamol [47].

Attwood *et al.* evaluated the gelling property for oral delivery of the cimetidine. Formulations prepared were dilute solution of the enzyme treated xyloglucan which form thermosensitive gel on body temperature along with gellan gum and sodium alginate. Complexed calcium ions were also added which on release in the acidic environment form gel on contact with the polymers gellan gum and sodium alginate. *In vitro* study for cimetidine release was conducted over a period of 6 hour. Plasma levels of cimetidine after oral administration to rabbits were compared with commercially available cimetidine/alginate suspension and *in vivo* release characteristics were found to be identical with commercial preparation [48].

Some of the marketed floating drug delivery systems are enlisted in table 2.

CONCLUSION

Development of an efficient gastro retentive dosage form for stomach specific drug delivery is a real challenge. So, in order to produce the desired gastro retention various approaches have been employed, out of which, floating drug delivery system has emerged as most promising technique. Floating *in situ* gelling system is one of the approaches of floating drug delivery system which undergo sol to gel transition in acidic stomach conditions and provide stomach specific release of drug for longer duration while being buoyant on the gastric fluid surface. Such systems provide the advantage of better absorption of drugs which are absorbed from the upper part of stomach. As the system remains in the stomach for longer duration local action of drug due to prolonged contact time to gastric mucosa is increased. This leads to less frequent dosing and improved efficiency of treatment. By understanding the floating and gel forming behavior of polymers we can look forward to improve the gastric retention and hence bioavailability improvement of various pharmacologically active agents. Similarly, good stability and better drug release than other conventional dosage forms make such system more reliable.

ACKNOWLEDGEMENT

The authors are thankful to Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Meerut for providing the necessary facilities to prepare manuscript in its current format.

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