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# Gastricretentive Raft Forming Drug Delivery: A Novel Expansion

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**ABSTRACT**

The oral drug delivery is the most preferable and convenient route of drug delivery due to the ease of administration of a drug, patient compliance, and flexibility in the formulations but has some drawbacks of non-site specificity and short gastric resident time. To avoid these drawbacks, several technical advancements have led to the development of a gastro retentive drug delivery system. Gastro retentive drug delivery system plays a vital role among the novel drug delivery systems. The retention of oral dosage forms in the upper gastrointestinal tract causes prolonged contact time of drug with the gastrointestinal mucosa, leading to higher bioavailability, and therapeutic efficacy thus improves patient compliance. Gastroretentive drug delivery system walls facing many challenges which can be overcome by upcoming newly emerging approach i.e. raft forming system.

## INTRODUCTION

Oral drug delivery is considered as the most desirable and preferred route for administering therapeutic agents to the systemic circulation to produce their systemic and local effects, due to their ease of administration, patient compliance, flexibility in formulation and handling of these forms [1, 2]. The conventional oral route of administration suffers from certain drawbacks mainly short residence time of the dosage form in the GI tract, an unpredictable gastric emptying, and degradation of the drug due to highly reactive nature of GI contents [1].To defeat the drawbacks of conventional oral drug delivery systems, several technical advancements have led to the development of a gastro retentive drug delivery system [2].

Gastroretentive drug delivery system ensures that dosage forms can remain within the gastric region for a longer duration of time. This fact improves gastric retention time for such a drug compared to conventional dosage form and further minimum effective concentration of drug maintained in systemic circulation for a 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[3]. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects[4].

### Merits of GRDDS [2]

- To deliver the drugs with a narrow absorption window in the small intestine region.
- Provide longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example, treatment of peptic ulcer disease.
- Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, ranitidine, amoxicillin, captopril, etc.
- Patient compliance improved by making a once a day therapy.
- Improved therapeutic efficacy

**Factors Affecting Gastroretentive Drug Delivery System**

Their various factors are to be considered for the development of gastroretentive dosage forms for prolongation of the dosing interval of formulation and thus improves patient compliance. They are given below[3].

**Physicochemical Factors**

- Size of dosage form: Dosage forms having a diameter, greater than the diameter of pyloric sphincter escape from gastric emptying and remain within the gastric region [3, 5].

- The shape of dosage form: Round or Ring-shaped dosage form are considered better in comparison to other shapes [3, 5].

- Density: Location of the particular gastro retentive dosage form in the gastric region depends on the density of the system. Those with low density tend to float on the gastric fluid surface while high-density systems sink to the bottom of the stomach [3, 4].

**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 [3, 4].

- Gender: Gastric retention time in male (3-4 hours) is less than the female (4-6 hours) [3].

- Fed or Unfed state: Gastric motility is higher in fasting conditions which depicts lesser gastric retention time [3,4].

- Feed frequency: Higher the frequency of taking food, the longer will be the gastro retention time[3].

- Nature of meal: High amount of fatty acids and other indigestible polymers generally decreases the gastric retention time by altering gastric motility [3].

- 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 [3].

- Disease state: Gastro retentive time is altered during the various gastric diseases like Crohn's disease etc [3].

**Approaches to Achieve Gastric Retention [4]**

1. Low-density approach (floating drug delivery)

2. High-density approach.

3. Mucoadhesive approach

4. Expansion by swelling approach

5. Raft forming system.

**Raft Forming Systems**

Raft forming systems are also known as floating *in situ* gel. The *in situ* gel system which provides a controlled drug delivery system. As compared to the oral liquid dosage form some problems associated with the solid oral unit dosage forms it cannot take as halves and swallow as the whole dosage form. Pediatric and geriatric patients have difficulty in swallowing the tablet/capsule and also in case of a life-threatening disease like dysphasia, certain cancer disease has difficulty in swallowing solid oral unit dosage form. In the case of liquid dosage form, different strength can be formulated to overcome the problems related to the solid oral unit dosage form [5]. Formulation of Rafting drug delivery systems is a useful approach to avoid this variability with an increased gastric retention time of the drug delivery system. Systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period. While the system is rafting on the gastric contents, the drug is released slowly at the desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This will result in increased gastric residence time and better control of the fluctuation in plasma drug concentration [1]. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft [Figure I]. This formed raft floats on the gastric fluids because of low bulk density created by the formation of $CO_2$. Usually, this system contains a

gel-forming agent and alkaline bicarbonates or carbonates which responsible for the formation of $CO_2$ to make the system less dense and float on the gastric fluids [2].

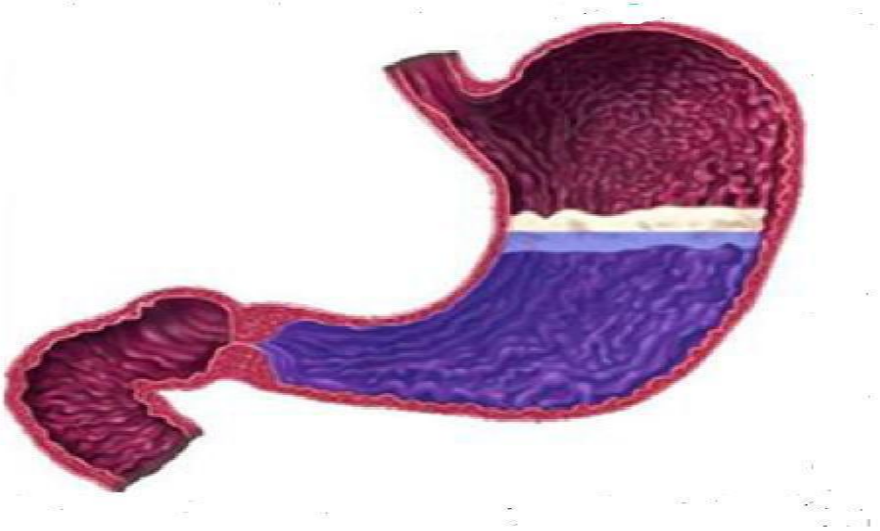

**Figure No. 1: Raft forming system**

**Advantages of Floating Raft Forming System [2]**

- Raft-forming system produces a low-density viscous layer on gastric contents and hence provides a more effective surface area than a tablet. This leads to more drug release and improvement of bioavailability.

- Floating of the raft is faster than the other floating dosage form.

- Improve patient compliance by making a once a day therapy.

- Improve therapeutic efficacy.

- Easy to administer to a patient. It increases the contact time of drug at the site of maximum absorption (stomach). It provides advantages such as the delivery of drugs with narrow absorption in the small intestinal region.

- Reduction in plasma level fluctuation

- Target stomach specific drug delivery system like *H. pylori*-induced gastric ulcer.

**Limitation of Floating Raft Forming System [2]**

- These systems are formulated in the form of solution which is more susceptible to stability problems. These are due to chemical degradation (oxidation, hydrolysis, *etc*.) or microbial degradation.

- The formulation must be stored properly because of the formulation is not stored properly it may cause stability problem. This is due to change in the pH of the system on prolonged storage or on storing inappropriate temperature conditions.

- Exposure of certain polymer to radiations (e.g. UV, Visible, electromagnetic, *etc*.) induces the formation of gel within the package.

**Approaches of Raft Forming System [4]**

Different approaches and mechanisms are utilized in the production of the *in situ* gel formation are as follows:

- Based on producing a physical mechanism
- Based on producing a chemical mechanism
- Based on physiological stimuli mechanism

**Raft formation based on the physical mechanism**

- Swelling:

Formation of the gel occurs when the liquid effervescent system comes in contact with gastric fluid. In situ formation of gel occurs when materials absorb water from the surrounding environment and expand to occur at the desired space. Swelling of the polymer occurs by the absorption of water which further lead to the formation of the gel. Certain biodegradable lipid substance such as myverol 18–99 (glycerol mono-oleate), is a polar lipid that swells in water to form lyotropic liquid crystalline phase structures [4, 5].

- Diffusion:

Diffusion is the method which involves diffusion of a solvent from a polymer solution into surrounding tissue, which further results in precipitation or solidification of the polymer

matrix. The solution of polymer that can be used for such a mechanism is N-methyl pyrrolidone (NMP)[4,5].

**Raft formation based on chemical mechanism**

- Ionic crosslinking:

In presence of the various ions present in the body fluids, like Na+, K+, Ca2+, Fe3+, etc., the ion-sensitive polysaccharides, e.g. carrageenan, gellan gum, pectin, etc., undergo transition in phase due to development of the polymer cross-linking, e.g. Sodium alginate undergoes gel formation in the presence of calcium chloride[4,5].

- Enzymatic cross-linking:

Enzymes present in the body fluids may also cause cross-linking to form a polymer network and is considered, as the most convenient mode of gel formation [4].

**Raft formation based on physiological stimuli mechanism**

- pH-dependent gelling:

Polymers, such as polyacrylic acid and its derivative (Carbopol), polymethacrylate, etc., undergo gel formation because of change in the pH, due to the presence of various ionizable groups in the chemical structure of the polymer. Polymer with anionicgroupsleads to increase in swelling with an increase in the pH, while polymer with cationic groups shows a decrease in the swelling [4].

- Temperature-dependent gelling:

The temperature-dependent phase transition from a less viscous solution to comparatively high viscosity gel is seen. Change in temperature causes an abrupt change in the solubility of polymer within the system and polymer-polymer interaction occurs to form a solvated macromolecule of hydrophobic nature. Temperature-sensitive polymers are most studied class for producing the in situ gel characteristics, e.g. Polyacrylic acid, polyacrylamide, etc[4,2].

**Polymers Used for Raft Forming System [6]**

Materials which undergo sol to gel transition in aqueous solution at body temperature are used in the development of sustained-release vehicle with in situ gelation property. Some polymers are listed below which are used as in situ gelling agents [6]:

**Pectin**

These are the substance originated from plant species containing anionic polysaccharides which isolated from the cell wall of most plants and consist of α-(1-4)-D-galacturonic acid residues. Pectin which undergoes gel formation in presence of divalent ions (e.g. Ca ) which leads to the cross-linking of the galacturonic acid units (ionic cross-linking) and also in the presence of the H+ ions (pH-dependent gelling) gel formation will occur. The main purpose of using pectin for the raft formulations is that it is water-soluble, so organic solvents are not necessary for the formulation. The presence of divalent cations in the stomach, which help to the transition of pectin to gel state when it is administered orally. Pectin gelation property is induced by including a complexed form of Calcium ions in the formulation. Sodium citrate was added to the pectin solution to form a complex with the calcium ions that will be added in the formulation. By this way, the formulation will be maintained the fluid state (sol), until the breakdown of the complex in the acidic environment of the stomach, where the release of calcium ions causes gelation to occur[6,7].

**Gellan gum**

Gellan gum is an exocellular polysaccharide that secreted by the Sphingomonas elodea (Pseudomonas elodea) and chemically it is an anionic deacetylated polysaccharide with repeating tetrasaccharide units. This composed of β-D-glucuronic acid (1 unit), α-L-rhamnose (1 unit) and β-D-glucuronic acid (2 units) residues. Gellan gum undergoes sol to gel formation due to the change in temperature or due to the presence of cations (e.g. Na+, K +, $Ca^{+}$)[6,5].

**Sodium alginate**

Sodium alginate is the most widely used polymer of natural origin. Chemically, it is alginic acid salt, consisting of α–L-glucuronic acid and β-D-mannuronic acid residues that connected by 1, 4-glycosidic linkages. The solution of alginates in water form firm gels in the presence

of di-or trivalent ions (e.g. calcium and magnesium ions). Sodium alginate is mostly used for the preparation of the gel-forming solution, for delivery of the drugs and proteins. Alginate salts are considered most favorable for the gel formation because of biodegradable and nontoxic nature, with additional bio-adhesive property [6,4].

**Xyloglucan**

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). They used mostly in oral drug delivery and also being used for ocular and rectal drug delivery. Xyloglucan has shown a very low gelation time of up to a few minutes [6,8].

**Pluronic F127**

The Poloxamers or pluronic consist of more than 30 different non-ionic surface-active agents. These polymers are ABA-type triblock copolymers composed of polyethylene oxide (PEO) (A) and polypropylene oxide (PPO) units (B). Poloxamers, commercially available as PluronicR, is the most commonly used thermal setting polymers in ophthalmology. They are formed by the central hydrophobic part (polypropylene) surrounded by hydrophilic part (ethylene oxide). Depending on the ratio and the distribution along the chain of the hydrophobic and hydrophilic subunits, several molecular weights are available, leading to different gelation properties. Pluronic F-127, which gives colorless and transparent gels, so it is the most commonly used polymer in pharmaceutical technology. Poloxamer formulation generally increased drug residence time at application sites, that resulting in improved bioavailability and efficacy of the formulation. At room temperature (25°C), the solution behaves like a mobile viscous liquid, which is transformed into a semisolid transparent gel at body temperature (37°C). Pluronics or Poloxamers also undergo in situ gelations by temperature change[6,7].

**Chitosan**

Chitosan is a substance of cationic polysaccharide which consisting copolymers of glucosamine and N-acetyl glucosamine. This is a natural polymer obtained by deacetylation

of chitin. It has some properties like nontoxic, biocompatible, biodegradable polysaccharide and having bioadhesive, antibacterial activity. Chitosan aqueous solution forms a hydrated gel-like precipitate at the pH exceeding 6.2[6,8].

**Carbopol**

It is a Mucoadhesive polymer that will increase the formulation's mechanical strength, but also increases surface interaction with the ocular tissue and consequently contact time. Carbopol shows a solid-to-gel transition in aqueous solution as the pH is raised above its pKa of about 5.5, so it is a well-known pH-dependent polymer which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH [6,8].

**Evaluation Parameters of Raft Forming System [5]**

**Determination of Drug Content**

The accurately 10ml formulation was taken (equivalent to the 40mg drug) and it transferred to a 100ml volumetric flask. To this added 0.1N HCl and sonicate the volumetric flask for 10 min to the uniform distribution of gel in the medium. From the above stock solution, 10ml was taken and further diluted with 0.1N HCl. Content of drug can be measured by using UV-spectroscopy at suitable wavelength [5,9].

**pH Measurement**

*In situ* solution of formulation, pH is measured by using calibrated digital pH meter at room temperature [5,8].

**Measurement of the rheological property of sol and gel**

The viscosity of *in-situ* formulation can be measured by using Brookfield viscometer, Cone and plate viscometer, etc. Measurements were performed using appropriate spindle number and the temperature was maintained at 25 ± 1 °C. The viscosity of the gel can also be determined to estimate the gel strength [5, 9].

**Sol-gel transition temperature and gelling time**

Sol to gel transition temperature is determine the temperature at which the phase transition of sol meniscus is first noted when it kept in a sample tube at a specific temperature and then

heated at a specified time. Gel formation is indicated by the lack of movement of the meniscus on tilting the tube. Gelling time is the time required for the first detection of gel formation of sol formation [5, 8].

***In Vitro* Gelling Capacity**

Evaluations for gelling capacity can be measured by the visualization method. In that method colored solution of different formulations were prepared. *In situ* gelling formation was measured into 5ml of gelation solution (0.1 N HCl) in a 15ml borosilicate glass tube at 37±1°C. *In situ* gel formulation was added in a way that tip of the pipette touch to the gelation solution and solution release slowly to 0.1N HCl. During that time the stiffness of gel and time duration to remain as such as a gel will be noted. The color was added for the visualization purpose. *In situ* gelling capacity was categorized in three classes based on gelation time and period at they remain as such [5,8].

(+) gel after a few minutes dispersed rapidly.

(++) gelation immediate, remain for a few periods.

(+++) gelation immediate, remain for extended periods.

***In vitro* buoyancy test**

To determine this parameter 10ml of *in situ* formulations was added into the 900ml dissolution vessel containing 0.1N HCl at 37°C. The time for the formulation took to emerge on the medium surface (floating lag time) and the time for the formulation constantly floated on the surface of dissolution medium (duration of floating) can be noted [5, 9].

***In Vitro* Drug Release**

The drug release was measured using USP dissolution apparatus 2 (paddle type) at 50rpm. The speed of the apparatus was maintained as slow as possible to overcome the breaking of gelation formation and maintain mild agitation conditions to believe to exist *in vivo* condition. In this study 900 ml dissolution medium used is 0.1N HClat 37±1º C temperature. From that 5ml dissolution, the medium was pipette out at 1, 2,3,4,5, 6, 7 and 8, hour time interval and replace same amount fresh medium. Measured the absorbance at a particular wavelength of drug-using UV-spectrophotometer [5, 7].

**Measurement of Water Uptake**

The water uptakes of selected formulation were determined by a 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 N HCl was removed by tissue paper. Before transferring gel formulation to water initial weight was taken and then added to 10ml water after every 30 min water was decanted and weight the gel formulation. The data was calculated and reported [5, 7].

**Stability Study**

Stability study of the prepared formulation was done according to ICH (international conference on harmonization) guideline. To this method, sufficient quantity of gel formulation was stored in desiccators containing a saturated solution of sodium chloride which provides relative humidity 75±5%. The formulation was further put in a hot air oven at 40±2ºC temperature. The samples were withdrawn at 0, 30, 60 and 90 days interval for physical stability in terms of gelation or turbidity. And drug release and viscosity study were done at a predetermined time interval [5, 9].

## CONCLUSION

Gastro retentive drug delivery system developed to retain the drug in the gastric region for a prolonged time and release drug candidates at the sustained and prolonged manner at the upper part of the GIT thus improve its optimal bioavailability. Gastroretentive drug delivery system is facing many challenges which can be overcome by upcoming newly emerging approach i.e. raft forming system. Raft forming system is the most promising technique which undergoes sol to gel transition when coming in contact with gastric fluid or stomach pH. The raft system containing a gel-forming agent and alkaline bicarbonates or carbonates is the substance responsible for the formation of CO2 to make the system less dense and float on the gastric fluids.

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