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SYSTEM FOR GENERATING ORAL *IN-SITU* RAFTS USING ALGINATE

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Abstract: Oral drug delivery is the most practical way and safest option for the administration of pharmaceuticals. liquid dosage forms, such as syrups and suspensions, are easy to swallow and show convenience to patient populations like pediatrics, geriatrics, and those with dysphagia but have the disadvantage of not being site-specific and having a limited gastric resident time. Alginate-based oral *in-situ* raft forming system approach can be used to overcome the disadvantages of conventional oral liquid drug delivery systems. The raft system is a type of gastro-retentive drug delivery system that improves the gastric retention time of the dosage form and improves the bioavailability of the drug. The formation of *in-situ* gel based on physiological stimuli, and physical, and chemical mechanisms from which the drug gets released in a sustained and controlled manner. Alginate is a natural hydrophilic polysaccharide polymer present in the cell wall of marine brown algae; the ion-responsive property of the alginate made it preferable in the selection of a gel-forming agent. This system involves in development of liquid dosage form either suspension or solution in the alginate solution along with inactive calcium ions. When the dosage form comes in contact with the acidic environment, the calcium ions get liberated from the system and react with alginate, leading to *in-situ* gelation. The resulting gel can be modified to float or perform muco-adhesion. This article will provide an overview of liquid oral sustained-release drug delivery systems, with a focus on formulations based on alginate.

Keywords **- Alginate, *in-situ* raft, gastro retentive, gastric retention time, bioavailability, sustained release, ion-responsive, calcium ions, float, muco-adhesion.**

1 INTRODUCTION

The *in-situ* gelling (Raft forming) system is a transitional state between liquid and solid components. A three-dimensional structure called a hydrogel has the ability to hold large amounts of water and allow biological fluids to swell **[1]**. *In-situ* gels are a type of hydrogel that exist in solution form and undergoes gelation when they come into contact with bodily fluids or once the pH or temperature changes. Before reaching the body, *in-situ* formulations are in the form of a sol, but when inside, they come in contact with the gastric fluid and transform into a gel. The created raft floats on the gastric fluids prolongs the gastric residence time of the drug and allows sustained release of the drug from the gel. When compared to traditional drug delivery methods, *in-situ* gels have a number of advantages. They can be taken by oral, ophthalmic, rectal, vaginal, injectable, and intraperitoneal routes. The preferred and most common medicine delivery method is oral administration **[2,3,4]**. New drug delivery methods using expandable, mucoadhesive, floating, and high-density gastro-retentive systems have been developed. They offer regulated drug delivery with an extended stomach residence duration. Gastro-retentive floating medication delivery devices float on gastric fluid because their bulk density is lower than that of the fluid **[5]**. Due to their fast elimination from the stomach, liquid oral medications have low bioavailability. Problems of immediate release and short gastrointestinal residence of liquids can be resolved by an oral *in-situ* raft-forming system. This strategy enhanced localization at the site of action, increased residence, and sustained release.

1.1 Principle of *In-situ* Gelation

The principle leading to *in-situ* gelation is to develop a liquid drug dispersion (suspension) that is capable of converting liquid into gel when it comes into contact with GI fluids (i.e., *In-situ* gelation technique), and the effervescent agent raises the gel onto the top layer of the gastric fluid. Sodium alginate solution contains calcium chloride and sodium citrate, which complexes free calcium ions and release them only in the acidic environment of the stomach **[6]**. Sodium alginate acts as an ion-responsive polymer, trapping free calcium ions in polymeric chains of sodium alginate, and inducing crosslinking of polymer chains to produce a matrix structure. This gelation involves the formation of a double helical junction and the reassembly of double helical segments to create a three-dimensional network via complexation with cations and hydrogen bonding with water **[7,8]**.

1.2 Advantages

- Floating obtained faster than the other floating dosage form
- Increase patient compliance
- Enhance therapeutic efficacy
- Easy to administer to a patient

- It increases the contact time of the drug at the site of absorption (stomach)
- It offers benefits like the distribution of medications with restricted absorption in the small intestine area.
- less variation in plasma level.
- Target stomach-specific drug delivery systems like H. pylori-induced gastric ulcer

1.3 Disadvantages

- These systems are formulated in the form of a solution that is more susceptible to stability problems like chemical degradation (oxidation, hydrolysis, etc.) or microbial degradation
- The formulation must be stored properly because if the formulation is not stored properly, it may cause stability problems due to changes in the pH of the system on prolonged storage or on storing inappropriate temperature conditions
- Exposure of certain polymers to radiations (e.g., UV, Visible, electromagnetic, etc.). so induces the formation of gel within the package

1.4 Drugs Suitable for *In-situ* Gel Drug Delivery System

- Drugs that predominantly work in the stomach, such as misoprostol
- Drugs that are absorbed predominantly through the stomach, such as amoxicillin trihydrate
- Drugs that are poorly soluble at alkaline pH like verapamil HCl and diazepam
- Drugs with a narrow absorption window like levodopa and cyclosporine
- Drugs that are rapidly absorbed from the GIT like tetracycline
- Drugs that break in the colon, such as ranitidine and metformin
- Ampicillin and other antibiotics that disrupt natural colonic bacteria

1.5 Drugs Unsuitable for *In-situ* Gel Drug Delivery System

- Drugs that have limited acid solubility e.g. (phenytoin)
- Drugs that suffer instability (erythromycin) or solubility (phenytoin) problem in GIT
- Drugs designed for selective release in the colon, such as 5-aminosalicylic acid and corticosteroids
- Drugs that are absorbed along the entire GIT, which undergo first-pass metabolism e.g. (nifedipine, and propranolol)

2. APPROACHES OF DESIGNING ORAL *IN-SITU* RAFT FORMING SYSTEM

2.1 Raft Formation Based on Physiological Stimuli Mechanism

- Thermally Trigged System
- pH Triggered Systems

2.2 Raft Formation Based on Physical Mechanism

- Diffusion Controlled Mechanism
- Swelling Controlled mechanism

2.3 Raft Formation Based on Chemical Mechanism

- Enzymatic Cross-Linking
- Photo-Polymerization
- Ion Cross-linking

2.1 Raft Formation Based on Physiological Stimuli Mechanism:

- Thermally Trigged System: The principle involved in the thermal trigged system is temperature-induced-phase transition. These are hydrogels that are in the solution phase at room temperature (20ºC-25ºC) but when the temperature reaches body temperature (35ºC-37ºC) it converts into the gel phase. Some polymers exhibit abrupt changes in solubility in response to increasing environmental temperature (lower critical solution temperature, LCST) **[9,10]**. and the formation of negative temperature-sensitive hydrogels, in which hydrogen bonding between the polymer and water becomes unfavorable when compared to polymer-polymer and water-water interactions. Also, the solvated macromolecule rapidly dehydrates and transforms into a more hydrophobic structure. Some cross-linked polymers like N-isopropylacrylamide-co-butylmethacrylate show more micelle packing and gel formation due to polymer-polymer interactions when the temperature is increased.
- pH Triggered Systems: The principle involved in the Ph-triggered system is change in pH. This system uses pH-sensitive polymers for the generation of *in-situ* gel. The swelling of hydrogel increases with an increase in pH in the case of polymers containing weakly acidic groups and decreases in the case of polymers containing basic groups. Polymers such as PAA (Carbopol®, carbomer) or its derivatives, polyvinylacetal diethylaminoacetate (AEA), mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) show change from sol to gel with change of pH. Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) also have been used as a pH-sensitive system to achieve gelation4 **[11]**.

2.2 Raft Formation Based on Physical Mechanism:

- Diffusion-Controlled Mechanism: Diffusion is a process that involves the diffusion of a solvent from a polymer solution into surrounding tissue, resulting in the precipitation or solidification of the polymer matrix. N-methyl pyrrolidone (NMP) is a polymer solution that can be employed for such a mechanism **[12]**.
- Swelling Controlled mechanism: Water absorption induces polymer swelling, which leads to the creation of the gel. *In-situ* gel formation occurs when materials absorb water from their surroundings and expand to fill the appropriate space. Myverol 18-99 (glycerol monooleate), a biodegradable lipid molecule, is a polar lipid that swells in water to produce lyotropic liquid crystalline phase structures. It has bio adhesive characteristics and can be destroyed in vivo through enzymatic action **[13]**.

2.3 Raft Formation Based on Chemical Mechanism:

- Enzymatic Cross-Linking: Enzymatic cross-linking system is controlled by natural enzymes and the rate of gel formation depends on the amount of enzymes present in the system. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase

can swell in reaction to blood glucose levels, releasing the entrapped insulin.

- Photo-Polymerization: The *in-situ* synthesis of biomaterials frequently employs photo-polymerization. It is possible to create gel by injecting a solution of monomers, reactive macromers, and an initiator into a tissue site. When an appropriate photo initiator is present, acrylate or other polymerizable functional groups quickly undergo photo-polymerization, hence they are frequently utilized as the polymerizable groups on the individual monomers and macromers. Usually, visible and long-wavelength UV radiation is employed. Because it can only penetrate a small amount of tissue and is biologically damaging, short-wavelength UV is not frequently used.

Ion Cross-linking: In the presence of different ions such as k+, Ca2+, Mg2+, and Na+, certain ion-sensitive polysaccharides such as iota carrageenan, pectin, gellan gum, and sodium alginate undergo a phase shift **[14,15]**. Aqueous liquid solutions must be provided beforehand in order for an *in-situ* gel to develop. Under some conditions, a gelling agent must be utilized to generate an *in-situ* gel capable of holding the distributed medication and other excipients. This method gels by using polymer solutions activated by ionic complexation, such as gellan gum and sodium alginate. These solutions contain divalent ions complexed with Na-citrate, which degrades in the stomach's acidic environment to release free divalent ions (Ca2+) due to a pH change **[16]**. Orally administered substances gel *in-situ* as a result of free Ca2+ ions becoming trapped in polymeric chains and causing cross-linking to produce matrix structure.

3 ALGINATE-BASED RAFT-FORMING SYSTEM

Alginate is a natural edible hydrophilic polysaccharide polymer obtained from brown seaweed (Phaephyceae). Alginate biopolymer is biodegradable, biocompatible, and non-immunogenic **[16]**. Alginates are isolated by treating the seaweed with the dilute alkali which solubilizes the alginic acid present in it.

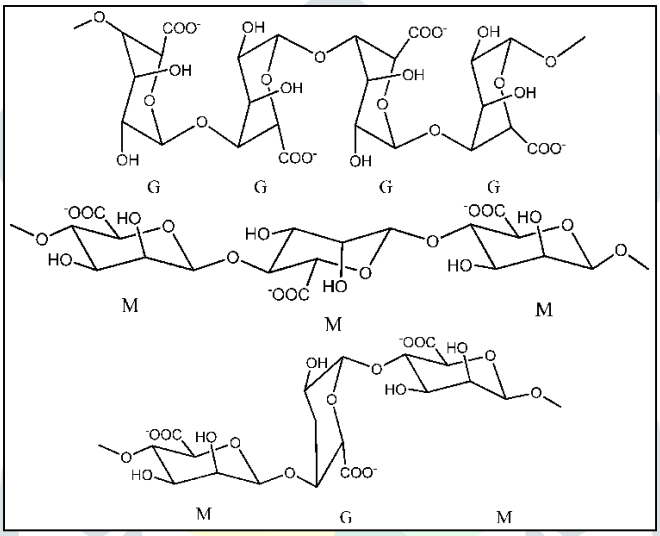

Figure 1 Chemical structure of alginate

Chemically alginate is a salt of alginic acid, alginic acid is a linear polymer consisting of D-Mannuronic acid and L-Guluronic acid are organized in polymer chain blocks. They are arranged in a copolymer form i.e., M-M-M-M/G-G-G-G or in alternate form M-G-M-G. The chemical composition and arrangement of polymers depends on the source, location, extraction process and season of collection **[17]**.

Alginates can undergo proton-catalyzed hydrolysis. Hydration of alginates leads to the formation of hydrogels of high viscosity due to intermolecular binding. Due to the presence of a lot of free hydroxyl and carboxylic groups, they provide a polyelectrolyte nature to the alginate **[18,19]**.

Monovalent ions form salt with alginates while divalent ions or multivalent ions forms gel with the alginate. Alginate with a high content of guluronic portion gives gel with high strength this is due to high affinity towards divalent ions. The gelling capacity and viscoelasticity of the gel are highly dependent on the M/G ratio **[20,21]**.

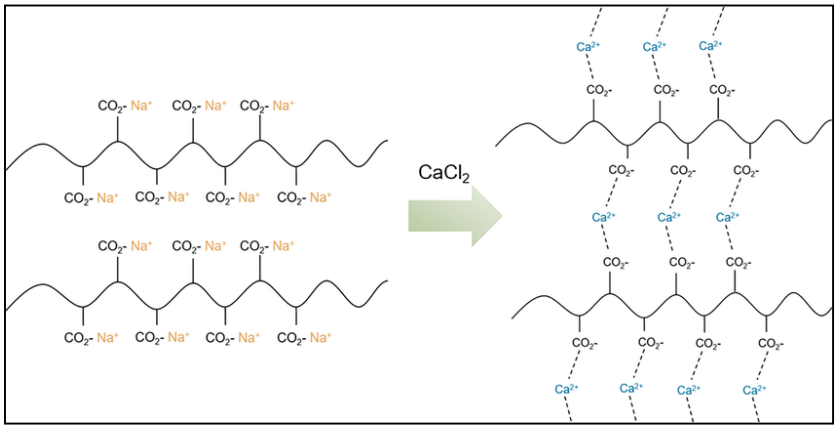

Figure 2 Reaction of sodium alginate with calcium ions

Alginic acid and its sodium salt are regarded as generally non-toxic and biocompatible **[22]** and Calcium ions are the most commonly used divalent ions due to their low toxicity and abundant availability at a reasonable cost. There are two ways for *in-situ* gelation using calcium crosslinking of alginate chains. A) Diffusion technique b) Internal setting mechanism. Calcium ions diffuse into the alginate solution from the

surrounding environment in the diffusion procedure. The calcium ion source is contained within the alginate liquid in an inactive state (i.e., calcium carbonate) in the internal setting method, and a trigger factor (i.e., pH of stomach juice) sets off the ions into the solution. To avoid premature gelation prior to administration, the divalent ions should be present in an inactive form. Internal setup is the most satisfying option when the ion source is located within the alginate solution **[16,23]**.

Sodium bicarbonate is typically added to the alginate liquid component to achieve raft forming system floating. When it interacts with the stomach's acidic environment, it produces carbon dioxide gas, which entraps in the produced gel, imparting low density and causing it to float above the gastric content **[24]**. The *in-vitro* floating lag time and total buoyancy time are critical properties that are commonly used to assess the system's success or failure **[25]**.

The rate of drug release is highly dependent on the composition as well as the concentration of liquid components.

Ranitidine, a locally active H2- antagonist, was studied as a floating gastro-retentive *in-situ* gelling liquid. The liquid system was created by combining different grades of sodium alginate (low, medium, and high viscosity) and calcium carbonate, in the presence or absence of calcium citrate complex (calcium source for alginate gelation *in-situ*). In the absence of calcium citrate, gelation and flotation rely primarily on the free availability of a sufficient amount of calcium ions and carbon dioxide gas produced by the interaction of calcium carbonate with gastric acidity. Changing the drug concentration, calcium carbonate, and alginate grade all had a significant impact on the drug release rate. It was determined that the existence of a calcium complex is required for the effective regulation of the ranitidine release rate **[26]**. Importantly, the presence of calcium carbonate revealed interior premature gelation after storage release **[27]**. As a result, the addition of a modest amount of sodium citrate would be advantageous in complexing with the potentially liberated calcium ions during the liquid's shelf life. Alternatively, sodium carbonate can be used in place of calcium carbonate. The pattern of drug release is greatly dependent on the mix and concentration of liquid components. For example, when the same components but different ratios were used, amoxicillin release followed Zero-order kinetics **[25]**. Pregabalin, on the other hand, demonstrated a Fickian diffusion mechanism **[28]**. This can be argued because the increased calcium citrate complex ratio in the pregabalin system resulted in the production of a more structured gel mass.

The combination of alginate with hydroxypropyl methylcellulose (HPMC) has been studied successfully. HPMC was utilized because it possesses high water swelling capabilities that are independent of pH **[29]**. (To facilitate fast flotation, the system also included sodium bicarbonate and calcium citrate complex. With zero order release kinetics, this floating device was able to sustain amoxicillin release for 12 hours [28]. Meloxicam was developed into a floating oral *in-situ* gelling liquid later on. Meloxicam's solubility was increased by creating a ternary solid dispersion with hydrophilic excipients. When compared to normal meloxicam, in vivo investigations revealed a considerable reduction in carrageenan-induced rat paw edema and a decreased ulcer genic effect in rats' stomachs **[30]**. A similar strategy of floating *in-situ* gel-producing oral alginate solutions was used for Nizatidine **[31]**, Ofloxacin **[32]**, and Losartan potassium **[33]**, making this approach an acceptable choice for many of the drawbacks associated with these drugs.

4 *IN-VITRO* EVALUATION PARAMETERS OF THE RAFT-FORMING SYSTEM

4.1 Texture Analysis:

Texture analysis is used to determine the formulation's firmness, consistency, and cohesion. This analysis primarily demonstrates the syringe ability of the sol, indicating that the formulation may be easily delivered in vivo. Gels with a higher adhesiveness value are required to maintain intimate contact with surfaces such as tissues **[34,35]**.

4.2 Gel Strength:

Gel strength is used to calculate the gelling property of a developed product. A rheometer can be used to assess this parameter. In this test, a predetermined amount of gel is made in a beaker from the sol form. A gel-containing beaker is lifted at a specific rate before slowly putting a rheometer probe through the gel. Changes in probe load can be assessed as a function of probe depth of immersion below the gel surface **[11,36]**.

4.3 Viscosity:

The viscosity and rheological parameters of the polymeric formulations were determined using a different viscometer, either in solution or in gel produced with fake tissue fluid (depending on the method of administration). The viscosity can be measured with a Brookfield rheometer or another form of viscometer, such as Ostwald's viscometer. The viscosity of formulations should be such that no issues during patient administration are anticipated **[36,37]**.

4.4 pH: The pH was measured in each of the solutions using a calibrated digital pH meter at 27°C**.**

4.5 Floating/Buoyancy Test:

It is calculated to estimate how long it takes the dosage form to float on top of the dissolution medium after being introduced in the medium. Typically, the test is carried out in SGF (simulated gastric fluid), which is kept at 37 °C. The time elapsed between the introduction of the dosage form and its buoyancy on the simulated stomach fluid, as well as the duration the dosage form remained buoyant, were measured. Floating time is the amount of time that the dose form continues to float on the dissolution media. The time required for the dose form to emerge on the medium's surface is known as Floating Lag Time (FLT) or Buoyancy Lag Time (BLT), and the total duration of time the dosage form is buoyant is known as Total Floating Time (TFT) **[38]**.

4.6 Sol to Gel Time:

In-vitro gelation time was determined by using USP (Type II) dissolution apparatus containing 500 mL of 0.1N HCl (pH 1.2) at 37±0.5ºC. It converted from sol to gel, when the formulation was coming in contact with 0.1N HCl, and time was measured. Gelling time is the time required for the first gelation of the *in-situ* gelling system. It was observed within seconds, the gel floated on buffer solution:

4.7 Fourier Transform Infra-Red Spectroscopy and Thermal Analysis:

Fourier transform infrared spectroscopy is used to investigate drug-excipient compatibility. Differential scanning calorimetry is performed to see if there are any differences between the optimized formulation and the pure substances used, indicating interactions **[39]**.

4.8 *In-Vitro* Drug Release Studies:

An *in-vitro* release investigation was performed using the USP Type II Paddle Method dissolution test apparatus. The drug release from the formulations was measured using a dissolution test device USP Type II with a paddle stirrer set to 50 rpm. The dissolution medium was 900 ml of (0.1N HCL, pH 1.2) solution, with the temperature kept at 37 0.2°C. At different time intervals, 1 ml of the sample solution was removed from this dissolution media and replaced with new medium. The drug concentration in the aliquot was measured using spectrophotometry **[40]**.

CONCLUSION:

Oral drug delivery of medicines with a narrow absorption window in the gastrointestinal system is frequently limited in conventional dosage forms by poor bioavailability due to limited drug release and a short period of residence at the site of absorption. The gastro-retentive floating delivery of drugs is quite challenging for prolonging gastric retention and physiological compatibility with the stomach. The *in-situ* gel formulation has been developed to improve patient compliance and reduce dose frequency. Based on the literature reviewed, it is possible to conclude that gastro-retentive drug delivery offers a variety of potential benefits for drugs with low bioavailability because absorption is restricted to the upper gastrointestinal tract (GIT), and they can be delivered efficiently, maximizing absorption, and increasing absolute bioavailability. Alginate-based raft-forming systems have been successfully formulated for various drugs. One of the most essential elements to investigate is the effect of food on the gelling capacity and drug release pattern of an alginate-chitosan-based system. The outcome of this research and how the results can help advancement in this field will be determined in the future.

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