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RAFT-FORMING IN-SITU GEL SYSTEMS: A NOVEL GASTRO-RETENTIVE APPROACH FOR ENHANCED DRUG DELIVERY AND REFLUX MANAGEMENT

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ABSTRACT

Raft-forming in-situ gel systems are innovative gastro-retentive drug delivery systems designed to enhance gastric residence time and improve therapeutic efficacy. These formulations are administered as liquids and undergo rapid gelation in the acidic environment of the stomach. The mechanism involves ionic cross-linking of polymers such as sodium alginate in the presence of calcium ions, along with carbon dioxide generation from gas-forming agents like sodium bicarbonate. The released gas becomes entrapped within the gel matrix, forming a low-density floating raft that acts as a physical barrier against gastric reflux and provides sustained drug release. Due to their prolonged gastric retention, controlled release behavior, and improved patient compliance, raft-forming systems represent a promising approach for the management of acid-related disorders and localized gastric drug delivery.

KEYWORDS: Raft-forming system, In-situ gel, Gastro-retentive drug delivery, Sustained drug release.

1. INTRODUCTION

Raft forming in-situ gel is a liquid oral drug delivery system that undergoes sol-to-gel transformation upon contact with gastric fluid to form a low-density, viscous and cohesive gel structure known as a “raft.” This raft floats on the surface of the stomach contents due to the entrapment of carbon dioxide generated by gas-forming agents within the gel matrix. The formed gel acts as a physical barrier that prolongs gastric residence time and provides sustained release of the incorporated drug, thereby improving therapeutic efficacy and enhancing bioavailability in gastro-retentive drug delivery systems. Improved drug delivery and the creation of restricted substances have drawn more attention during the past three decades. Since in situ gel systems have shown benefits such ease of application, decreased frequency of

use, and enhanced human pain compliance and comfort, their development has drawn a lot of attention in recent years. Before being administered, gel dosage forms are liquid, but they become a gel that floats on the stomach when they come into touch with stomach contents. One or more mechanisms, including physiological cues (like temperature and pH), physical alterations in the biomaterial (like solvent transport and swelling), and grafts (like vaccinations), are responsible for this gel shift. Numerous production challenges affect the biodegradable polymers used to create in situ gels, In contrast to natural polymers, there are occasionally batch differences, explosive effects, non-reproducible drug release kinetics, operational problems, and the utilization of organic solvents.[1]

Patient adherence and therapeutic effectiveness. To address these limitations, controlled-release formulations have been extensively explored to enhance bioavailability and maintain therapeutic levels. Gastroretentive drug delivery systems (GRDDS), particularly In-Situ raft-forming gels, have shown promise by increasing gastric residence time—especially advantageous for drugs that are absorbed primarily in the upper gastrointestinal tract. These systems undergo sol-to-gel transition in gastric conditions, forming a floating "raft" that offers both sustained release and prolonged retention in the stomach Key components of these raft systems—such as sodium alginate and natural gums like isabgol—gel in response to gastric ions, while gas-generating agents (e.g., sodium bicarbonate, calcium carbonate) ensure immediate buoyancy by producing carbon dioxide7–9.[2]

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 . 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. 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. 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.[3]

Current technological advancements have made feasible dose alternatives available through a variety of administration methods. Nowadays, there are many other ways that can be employed, such as oral, parentral, topical, nasal, rectal, vaginal, ophthalmic, etc. out of these delivery methods the oral route is said to be the most popular and commonly used approach for the reasons that follow:

- Simple to administer
- Greater adaptability when designing
- Production simplicity
- Inexpensive

The term GRDD refers to dosage forms that are capable of being kept in the stomach.[4]

Oral delivery of drug molecules is generally preferred when compared to other administration routes; however, it has certain limitations, including primary hepatic metabolism, drug degradation by alimentary canal enzymes, and GI toxicity, which limits oral administration of some drugs, mainly proteins and peptides. There are several drawbacks to the fact that most pharmaceutical dose forms are designed for quick release. For instance, medications with short half lives require frequent administration, patient compliance is poor, and adverse effects from drug level variations are more likely, particularly for medications with small therapeutic indices. Numerous technological advancements have increased the capacity to administer medications in a controlled manner, potentially updating drug therapy. offer several therapeutic benefits and solve the short comings of traditional medication delivery techniques. Limited gastric residence times (GRTs) restrict the oral sustained medication delivery strategy. Since most medications are absorbed in the stomach or upper portion of the small intestine, rapid GI transit can impede full drug release in the absorption zone and lower the effectiveness of the prescribed dose.[5]

Oral drug delivery systems have dominated other drug delivery systems for human administration due to their various advantages including ease of administration, flexibility in formulation, cost effectiveness, easy storage and transport, and high patient compliance. Oral drug delivery systems face challenges such as low bioavailability due to the heterogeneity of the gastrointestinal system, pH of the commensal flora, gastric retention time of the dosage form, surface area, and enzymatic activity. GRDDs are a type of drug delivery system that is designed to prolong the residence time of a drug in the stomach.[1] This can be beneficial for drugs that are poorly absorbed in the small intestine, sensitive to stomach acid, or need to be delivered to the stomach. A system where gastric retention time coupled with the drug release for extended time has improved patients compliance. GRDDs can remain in gastric region for several hour and prolong the gastric residence time of drugs. Prolonging the gastric retention time with improve solubility, bioavailability and reduce the drug waste. GRDDs is an approach to prolong the GRT, targeting drug release in upper GIT for local and systemic effect. GRDDs can boost controlled delivery of drug with absorption window by releasing the drug for extended period of time before reached absorption site. The objective of a gastroretentive drug delivery system (GRDDs) is to prolong the residence time of a drug in the stomach.[1-2] This can be achieved by using a variety of techniques, such as:

- Floating systems: These systems are made of materials that are less dense than gastric fluid, so they float on top of the fluid and are not easily emptied by peristalsis.
- Mucoadhesive systems: These systems adhere to the lining of the stomach, making it more difficult for them to be moved by peristalsis.
- Magnetic systems: These systems contain magnetic particles that can be manipulated by an external magnetic field. This can be used to keep the system in a specific location in the stomach.
- Expandable systems: These systems expand in the stomach, making it more difficult for them to be emptied.[1-3]

GRDDs are used for a variety of drugs, including: − Drugs that are absorbed from the stomach (e.g., omeprazole, lansoprazole). − Drugs that are labile at alkaline pH (e.g., ranitidine, metformin). − Drugs that are poorly soluble at alkaline pH (e.g., furosemide, diazepam). − Drugs that have a narrow window of absorption (e.g., riboflavin, levodopa). GRDDs are feasible for drugs that have low absorption in the lower part of the GIT, are unstable and poorly soluble at alkaline pH, have a short half-life, and show local activity at the upper part of the intestine for eradication of Helicobacter pylori GRDDs are a promising technology for improving the delivery of drugs to the stomach. They offer

a number of advantages over conventional oral drug delivery systems, and they are being investigated for a variety of applications.[6]

Floating Drug Delivery System (FDDS) is one of the novel system of drug delivery In-situ gelling system is a new trend in FDDS. In-situ gelling system have its application in different routes of administration like oral, nasal, ophthalmic, peroral, rectal, vaginal and also Parenteral route. In situ forming polymeric drug delivery systems has many advantages such as ease of administration, increased local bioavailability, reduced dose frequency, improved patient compliance and has less complex method of production and so is cost effective. Gastroretentive FDDS have bulk density lower than gastric fluid and hence remain buoyant in stomach without affecting the gastric emptying rate for a long period of time. When the gel so formed float on gastric fluid the drug get released slowly at desired rate from the floating gel. A gel is a soft, stable, or solid-like material which consists of at least two components, one of them being a liquid, present in substantial quantity[7]

1.1 Advantages

1. To ease of administration
2. It administered to unconscious and old patients
3. It helps to extended or prolonged release of drugs
4. It allows more patient comfort and compliance
5. Due to the low dose, there will be no drug accumulation and minimize the drug toxicity
6. It offers more bio-availability
7. Improved Absorption: GRDDS can enhance the absorption of poorly water-soluble drugs by maintaining them in the stomach where absorption can occur.
8. Reduced Side Effects: Controlled release can also reduce fluctuations in drug levels in the bloodstream, potentially minimizing side effects.

1.2 Disadvantages

1. Requires a high level of fluids
2. The solution form of the drug is more susceptible to degradation
3. Due to chemical degradation, there is a chance of stability problems
4. Eating and drinking restricted for a few hours after placing the drug
5. Only small doses administered
6. Due to low mechanical strength, it may result in premature dissolution
7. Particularly for hydrophobic drugs, the quantity and homogeneity of drug loading into hydrogels may be limited.

1.3 Importance of in situ gelling system[4]

- Its unique "Sol Gel transition" aids in the drug's regulated and prolonged release.
- It aids in lowering the frequency of medicine delivery to the body.
- A small dosage of the medication is needed, and there won't be any side effects or drug accumulation.
- The medication will have a higher bioavailability.
- The drug's residence period will be extended as a result of gel formation

1.4 Need of Present Review

Although raft forming in-situ gel systems have been extensively investigated for their floating ability and sustained drug release characteristics, there is a lack of systematic understanding regarding their behavior under physiological gastric conditions. The stomach exhibits variations in pH, mechanical agitation and gastric emptying rate, all of which can significantly influence the gel formation, buoyancy and structural stability of raft systems. Conventional evaluation parameters such as floating lag time and total floating duration alone are insufficient to assess the actual performance of the raft system in the gastric environment. Parameters such as raft strength, density, erosion rate and reflux suppression capability play a crucial role in determining the effectiveness of these systems in providing prolonged gastric retention and therapeutic action. Hence, there is a need to review the influence of physiological factors such as gastric pH variation and motility on raft formation and stability to establish a better correlation between in-vitro evaluation and in-vivo performance of gastro-retentive raft-forming systems.

1.5 Objective of Review

The objective of the present review is to provide a comprehensive overview of raft forming in-situ gel systems as gastro-retentive drug delivery platforms with special emphasis on their performance under simulated physiological gastric conditions. This review aims to discuss the influence of gastric pH variation and mechanical motility on gel formation, buoyancy and structural integrity of the raft system. Additionally, the review focuses on evaluating the significance of parameters such as raft strength, density, erosion behavior and reflux suppression capability in determining the in-vivo effectiveness of these systems. By highlighting these critical yet underexplored aspects, the present review intends to bridge the gap between conventional in-vitro evaluation methods and actual physiological performance of raft forming gastro-retentive drug delivery systems.

2. Mechanism of Raft Formation in Raft Forming In-Situ Gel System

The mechanism of raft formation in raft forming in-situ gel systems involves a series of physicochemical interactions that occur when the liquid formulation comes into contact with the acidic environment of the stomach. Initially, the formulation is administered orally in a liquid state, which allows ease of swallowing and uniform distribution in the gastric fluid. Upon reaching the stomach, the formulation encounters the acidic pH of gastric fluid, which triggers the sol-to-gel transformation of the gelling polymer present in the system.

In the acidic environment, the gelling polymer such as sodium alginate interacts with divalent calcium ions released from cross-linking agents like calcium carbonate. This interaction leads to the formation of a three-dimensional cross-linked polymeric network through ionotropic gelation. As a result, a viscous and cohesive gel structure is formed at the surface of the gastric contents.

Simultaneously, the gas generating agent such as sodium bicarbonate reacts with hydrochloric acid present in the stomach to release carbon dioxide gas. The liberated carbon dioxide becomes entrapped within the gel matrix formed by the cross-linked polymer chains. This entrapment of gas bubbles decreases the density of the formed gel, making it lighter than the gastric fluid.

Due to its reduced density, the formed gel rises to the surface of the stomach contents and forms a floating raft-like structure. This raft remains buoyant for an extended period and acts as a physical barrier that prevents reflux of gastric

contents into the esophagus. Additionally, the gel matrix controls the diffusion of the drug from the raft system, resulting in sustained drug release and prolonged therapeutic action.

Thus, the combined effect of polymer gelation, gas generation and buoyancy leads to the formation of a stable floating raft that enhances gastric retention and improves drug delivery efficiency in gastro-retentive drug delivery systems.[1,2,8]

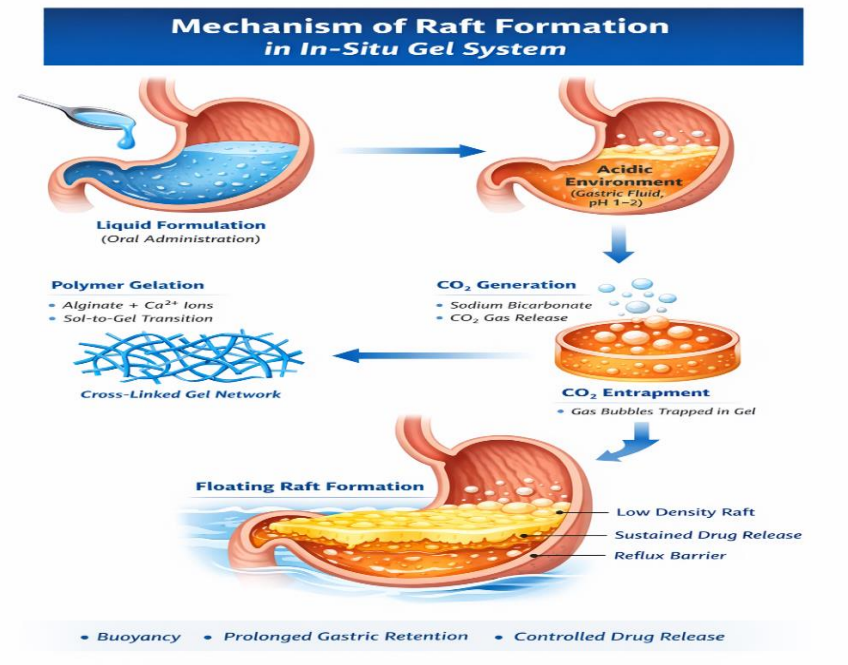

Fig no. 1: Mechanisms of Raft Forming nasal insitu gel.

3. 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[3,9]

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

4.1 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)

5. Approaches of designing oral in-situ raft forming system

1. Raft Formation Based on Physiological Stimuli Mechanism

Thermally Trigged System

pH Triggered Systems

2. Raft Formation Based on Physical Mechanism

Diffusion Controlled Mechanism

Swelling Controlled mechanism

3. 3Raft Formation Based on Chemical Mechanism

Enzymatic Cross-Linking

Photo-Polymerization

Ion Cross-linking

5.1 Approaches To Produce In-Situ Gel

Various mechanisms have been reported to underlie the formation of in-situ gel:

1. Physical Changes[27]

- Swelling: Swelling occurs when a polymer in the system, such as glycerol mono-oleate, absorbs water from the surroundings and swells to produce a viscous gel.
- Diffusion: Diffusion occurs when a solvent, such as N-methyl pyrrolidone, dissolves or disperses a drug and polymer into the surrounding tissues, precipitating the polymer to form gel.

2. Chemical Changes

Gel formation may result from alterations in the systems chemical environment that create polymeric cross linking.

- Ionic cross-linking: When different ions, such as Na+, K+, Ca2+, Fe2+, etc., are present in body fluids, ion-sensitive polysaccharides like carrageenan, gellan gum, pectin, etc., experience phase transitions because the polymer cross-linking develop.[28]
- Enzymatic cross-linking: The most practical method of gel production is thought to be cross-linking, which creates a polymer network through the presence of enzymes in body fluids[27]
- Photo polymerization: When a gel producing system is injected into tissues, it can generate gels such as ethyl eosin, 2, 2 dimethoxy-2-phenyl acetophenone, and others within the tissues when exposed to microwave, UV, or electromagnetic radiation.[27,29]

3. Physiological Stimuli

The following physiological triggers can result in the development of gel:

- Change in temperature: This method shows a temperature-dependent phase transition from a relatively high viscosity gel to a less viscous solution. A sudden change in temperature causes the solubility of the polymer within the system to alter, and this interaction between the polymers results in the formation of a hydrophobic solvated macromolecule.[27,29]
- Change in pH: Polymers with different ionizable groups in their chemical structure, such as polymethacrylate, polyacrylic acid, and its derivative carbopol, undergo gel formation in response to pH changes. When the pH rises, polymers containing anionic groups cause swelling to increase, whereas polymers containing cationic groups exhibit decreasing swelling.[6]
- Dilution sensitive: In the presence of more water, a polymer found in this kind of hydrogel goes through a phase transition. More polymer can be utilized if the system is going through a phase change as a result of being diluted with water. Example, Lutrol F68.[15]
- Light sensitive: Light-sensitive hydrogels can be employed as in-situ forming gels for cartilage tissue engineering or in the creation of photo-responsive artificial muscle. In order to create a gel by enzymatic processes, polymerizable functional groups and theirinitiators, such as ethyl eosin and camphorquinone, can be injected into tissue and electromagnetic radiation applied.[15]
- Glucose sensitive: Insulin-releasing hydrogels have been used is intelligent stimuli responsive delivery devices. In reaction to blood glucose levels, cationic pH-sensitive polymers that contain glucose oxidase and immobilized insulin can swell, pulsatively release the trapped insulin.[15,16]

5.2 Approches of GRDDS

A. High Density Drug Delivery System: Gastric contents have an analogous viscosity as water (1.004 g/ cm3). Sedimentation has been used as a retention medium. A viscosity lesser than 2.5 g/ cm3 is needed to significantly extend GIT. Excipients that are generally employed include barium sulfate, zinc oxide, titanium dioxide, iron, and so on.

B. Floating Drug Delivery System: Low-density devices known as floating drug delivery systems (FDDS) can float above stomach contents and stay in the stomach for extended periods of time without slowing down the rate at which the stomach empties. While the system floats above the gastric contents, the medicine is gently released at the desired rate. This leads to enhanced gastric retention time and greater control of changes in plasma medication concentrations.[14,15]

❖ Hydro-Dynamically Balanced System: These systems are often made up of hydrophilic gel-forming polymers such as HPMC, hydroxy ethyl cellulose, hydroxy propyl cellulose and alginic acid, and are intended for single-unit administration. Hygroscopic gelatin rapidly dissolves in stomach juice, exposing the hydrophilic polymer and medication contents to the bodily fluids. The polymer fraction existing on the surface is then hydrated and swollen, resulting in a floating mass.[7,16]

❖ Gas Generating System: Carbonate/bicarbonate salts and citric/tartaric acid react effervescently to release CO2 in buoyant delivery methods. The CO2 is then trapped in the jellified hydrocolloid layer, lowering its specific gravity and causing it to float above stomach fluid. The dosage forms are designed to create C02 when in contact with acidic gastric contents, which is then encapsulated in swelling hydrocolloids to offer floating properties.[17,18]

- ❖ Raft Forming System: Antacids and drugs for gastrointestinal diseases and infections have been administered using raft forming systems, which have attracted a lot of interest. This type of GRDDS is induced by the production of a viscous gel in contact with gastric fluids, which forms a continuous layer known as RAFT on top of the fluids due to low bulk density brought on by CO2 formation. Alkaline bicarbonates or carbonates that produce CO2 are typically included in this system's composition, along with a gel-forming substance (such as alginic acid) to help the system float on the stomach juices and become less dense.[19-21]
- ❖ Low Density System: The time lag before floating on the stomach contents is a major drawback of the effervescent delivery mechanism. Prior to floating and medication release, it is likely that the delivery system will be purged during this time. Hence, low density systems (less than 1000 mg/cm3) that demonstrate instantaneous drug floating and release on the stomach content surface have been created to get around this restriction. The system is essentially made up of low density materials that trap air or oil.[11]
- ❖ Expandable System: These systems can be mechanically expanded in size in relation to their initial dimensions. They are composed of biodegradable polymers. They come in a variety of geometric shapes, such as tetrahedron, ring, or planner membrane made of bio-erodible polymer that is squeezed inside a stomach-extending capsule. If a dosage form in the stomach is larger than the pyloric sphincter, it will not pass through the stomach.[22-24]

C. Super Porous Hydrogel: Conventional hydrogel absorbs water relatively slowly; it may take several hours to achieve an equilibrium condition. Super porous hydrogels (SPH) are porous hydrophilic materials that can absorb aqueous fluids up to a hundred times their own weight. They have a three-dimensional cross linked, network-like structure. Due to rapid water uptake through multiple linked open pores (average pores of 200 µm), maximum swelling is typically obtained in a fraction of a minute.[25,26]

D. Bio-Adhesive System: By sticking to the gastric mucous membrane of bio-adhesive system, the gastric retention time has increased. The adherence of the delivery system to the stomach wall increases bioavailability by extending residence duration. Nevertheless, the propulsion force of the stomach wall cannot be resisted by the gastric mucoadhesive force alone.[25,26]

E. Magnetic System: Using this procedure, a tiny magnet is incorporated into the dose form, and a second magnet is positioned on the abdomen above the stomach. Precise setting of the external magnet may result in less patient cooperation.[25]

- ❖ Stomach Specific Floating In-Situ Gel: An applicable system of delivering regulated drug delivery within the stomach has been made possible by gastro-forgetful in- situ gel forming systems, in which an environment-specific gel forming solution floats on the top of the gastric fluids (owing to its lower viscosity than the gastric contents) once it has gelated. This system uses a low density solution, when in contact with the stomach fluids, changes the polymeric conformation to produce a viscid gel with a viscosity that's lower than the gastric fluids. This low density gel conformation produces the continual and phased drug release in addition to the significant desired gastro retention to extend the contact period.[6]

6. Polymer used in Raft forming In situ gel

1. Sodium Alginate

Sodium alginate is the most commonly used natural polymer in raft forming in-situ gel systems due to its excellent ionotropic gelation property. It is an anionic polysaccharide that readily reacts with divalent calcium ions present in the formulation or gastric fluid to form a cross-linked gel network. Upon oral administration, sodium alginate undergoes rapid gelation in the acidic environment of the stomach, resulting in the formation of a viscous and cohesive raft

structure. This gel matrix helps in entrapping the carbon dioxide generated by gas-forming agents, thereby decreasing the density of the formulation and allowing it to float over gastric contents for an extended period. Additionally, sodium alginate provides mechanical strength to the raft and helps in sustaining the drug release by forming a diffusion barrier.

2. Pectin

Pectin is a naturally occurring polysaccharide widely used in raft forming systems because of its ability to undergo gelation in the presence of calcium ions under acidic conditions. In the gastric environment, pectin interacts with calcium ions to form a stable gel network that enhances the integrity of the raft system. This polymer contributes to the viscosity and firmness of the formed gel, thereby preventing premature disintegration due to gastric motility. Pectin also plays a significant role in controlling drug release by forming a protective matrix around the drug particles, ensuring prolonged gastric residence time and improved therapeutic efficacy.

3. Gellan Gum

Gellan gum is an anionic polysaccharide known for its ability to form strong gels in the presence of cations such as calcium ions. In raft forming in-situ gel systems, gellan gum facilitates rapid gelation upon exposure to gastric fluid, forming a rigid three-dimensional network. This enhances the mechanical strength and stability of the raft structure, allowing it to withstand the dynamic environment of the stomach. Furthermore, gellan gum aids in maintaining the buoyancy of the system by supporting the entrapment of generated carbon dioxide within the gel matrix, thereby promoting prolonged floating behavior and sustained drug release.

4. Hydroxypropyl Methylcellulose (HPMC)

Hydroxypropyl methylcellulose is a semi-synthetic hydrophilic polymer commonly used as a viscosity enhancing and release controlling agent in raft forming systems. HPMC increases the viscosity of the formulation before administration, ensuring uniform dispersion of the drug and other excipients. Upon gel formation in the stomach, HPMC hydrates and swells to form a thick gel layer that acts as a barrier for drug diffusion. This helps in retarding the drug release rate and maintaining a sustained therapeutic effect. Moreover, HPMC contributes to the structural stability of the raft by reducing the erosion of the gel matrix over time.

5. Carbopol

Carbopol is a synthetic high molecular weight polymer known for its excellent mucoadhesive properties. In raft forming in-situ gel systems, Carbopol enhances the adhesion of the formed gel to the gastric mucosa, thereby increasing the gastric residence time of the formulation. It also improves the viscosity and gel strength of the system, which helps in maintaining the integrity of the raft structure under physiological conditions. Additionally, Carbopol aids in sustaining drug release by forming a dense polymeric network that controls drug diffusion from the gel matrix.

6. Xanthan Gum

Xanthan gum is a natural polymer that acts as a viscosity modifier and stabilizing agent in raft forming formulations. It enhances the rheological properties of the system by increasing its viscosity, which supports uniform gel formation upon contact with gastric fluid. Xanthan gum also contributes to improving the gel strength and elasticity of the raft, thereby preventing its rapid erosion in the stomach. This helps in maintaining the floating ability and ensures controlled drug release over an extended period.

7. Guar Gum

Guar gum is a natural galactomannan polymer widely used as a thickening and stabilizing agent in raft forming in-situ gels. It increases the viscosity of the formulation, which facilitates better gel formation in the gastric environment. Guar gum also supports the formation of a stable and cohesive raft by improving the mechanical strength of the gel network. In addition, it helps in controlling the release of the drug from the gel matrix by forming a diffusion barrier, thereby enhancing the gastroretentive properties of the system.

7. Formulation Components of Raft Forming In-Situ Gel System[12]

Raft forming in-situ gel systems are gastro-retentive liquid formulations that undergo sol-to-gel transformation upon contact with gastric fluid. The successful formulation of such systems depends upon the appropriate selection of polymers, gas-generating agents, cross-linking agents and other excipients that collectively contribute to gel formation, buoyancy, raft strength and sustained drug release. The major formulation components involved in the development of raft forming in-situ gel are described below.

1. Active Pharmaceutical Ingredient (API)

The active pharmaceutical ingredient is the therapeutic agent incorporated into the raft forming system to achieve the desired pharmacological action. Drugs selected for such systems are generally those that are locally active in the stomach, have a narrow absorption window in the upper gastrointestinal tract or exhibit pH-dependent solubility. Incorporation of the drug into a raft forming gel helps in prolonging its gastric residence time and maintaining a sustained release profile, thereby improving bioavailability and therapeutic efficacy.

2. Gelling Polymers

Gelling polymers are the primary components responsible for the formation of a viscous and cohesive gel structure upon contact with gastric fluid. These polymers undergo ionotropic gelation in the presence of divalent cations present in the formulation or gastric environment. Polymers such as sodium alginate, pectin and gellan gum form a three-dimensional cross-linked network that constitutes the raft structure. This gel matrix entraps carbon dioxide generated from gas-forming agents, resulting in a reduction in the density of the formulation and enabling it to float over gastric contents. Additionally, viscosity enhancing polymers such as hydroxypropyl methylcellulose (HPMC), xanthan gum and guar gum are incorporated to improve gel consistency, mechanical strength and control the drug release from the gel matrix.

3. Gas Generating Agents

Gas generating agents play a vital role in imparting buoyancy to the raft system. These agents react with gastric acid to release carbon dioxide gas upon administration. The liberated carbon dioxide becomes entrapped within the gel network formed by the gelling polymers, thereby decreasing the density of the system and allowing it to float on the gastric fluid. Commonly used gas generating agents include sodium bicarbonate, calcium carbonate and magnesium carbonate. The quantity of gas-forming agent significantly influences the floating lag time and total floating duration of the raft system.

4. Cross-Linking Agents

Cross-linking agents are incorporated to facilitate ionotropic gelation of the polymers. These agents release divalent calcium ions in the acidic environment of the stomach, which interact with the anionic polymer chains to form a stable

gel network. Calcium chloride, calcium carbonate and calcium gluconate are commonly used as cross-linking agents in raft forming systems. The presence of calcium ions enhances the gel strength and structural integrity of the raft, enabling it to withstand gastric motility and maintain prolonged gastric residence time.

5. Mucoadhesive Agents

Mucoadhesive agents are included in the formulation to enhance the adhesion of the formed raft to the gastric mucosa. This helps in increasing the retention time of the formulation in the stomach and prevents its premature elimination from the gastric environment. Polymers such as Carbopol and HPMC exhibit mucoadhesive properties and are often incorporated to improve the contact time between the formulation and the gastric mucosal surface. This results in improved drug absorption and therapeutic effectiveness.

6. Viscosity Enhancers

Viscosity enhancers are added to improve the rheological characteristics of the formulation prior to administration. These agents help in maintaining the uniform dispersion of drug particles and other excipients in the solution. They also contribute to the formation of a strong and stable gel upon contact with gastric fluid. Natural polymers such as xanthan gum and guar gum are commonly used as viscosity modifiers to enhance gel strength and prevent rapid erosion of the raft layer.

7. Preservatives

Preservatives are included in the formulation to prevent microbial contamination during storage and use. Since raft forming in-situ gel systems are generally aqueous in nature, they are susceptible to microbial growth. Preservatives such as methyl paraben and propyl paraben are commonly used to maintain the microbiological stability of the formulation and ensure product safety over its shelf life.

8. Sweetening Agents and Flavoring Agents

Sweetening and flavoring agents are incorporated to improve the palatability and patient acceptability of the formulation. These agents mask the unpleasant taste of the drug and enhance compliance, particularly in oral liquid dosage forms. Common sweetening agents include sodium saccharin and sucrose, while flavoring agents such as peppermint or fruit flavors may be added to improve the overall organoleptic properties of the formulation.

9. Solvents and Vehicles

Solvents or vehicles such as purified water are used to dissolve or disperse the formulation components uniformly. The vehicle provides a suitable medium for the hydration and dispersion of polymers and facilitates the uniform mixing of all excipients. It also aids in maintaining the desired viscosity of the formulation prior to administration.

10. Stabilizers

Stabilizers may be added to maintain the physical and chemical stability of the formulation. These agents prevent phase separation, degradation or precipitation of formulation components during storage, thereby ensuring consistent performance of the raft system.[10,12,13,18]

8. Evaluation Parameters of Raft Forming In-Situ Gel System

The developed raft forming in-situ gel formulations must be evaluated for various physicochemical and performance characteristics to ensure their suitability for gastro-retentive drug delivery. The important evaluation parameters are described below.

1. Physical Appearance

The prepared formulation should be visually inspected for:

- Colour
- Clarity
- Homogeneity
- Presence of particulate matter

The formulation should be clear and free from any visible particles or phase separation to ensure uniformity and stability.

2. pH Measurement[19]

The pH of the formulation is measured using a calibrated digital pH meter at room temperature. The pH of raft forming in-situ gel should be within an acceptable range to prevent irritation of gastric mucosa and maintain drug stability.

3. Viscosity Measurement

Viscosity of the formulation is determined using a Brookfield viscometer at a specified spindle speed and temperature. The viscosity should be low enough to allow easy administration but sufficiently high to facilitate rapid gel formation in the gastric environment.

4. In-Vitro Gelation Study

This test is performed to evaluate the ability of the formulation to undergo sol-to-gel transformation upon contact with gastric fluid.

A specific volume of the formulation is added to 0.1N HCl maintained at 37°C and visually observed for gel formation. The gelation capacity is assessed based on:

- Time required for gel formation
- Strength of formed gel
- Duration of gel integrity

5. Floating Lag Time

Floating lag time is defined as the time taken by the formed gel to rise to the surface of the dissolution medium after coming in contact with gastric fluid. It is measured by placing the formulation in 0.1N HCl maintained at 37°C.

A shorter floating lag time indicates better buoyancy of the formulation.

6. Total Floating Time

Total floating time refers to the duration for which the formed raft remains buoyant on the surface of the gastric fluid. The raft should remain floating for an extended period to ensure prolonged gastric residence time.

7. Raft Strength Measurement

Raft strength is an important parameter that determines the ability of the formed gel to withstand gastric motility.

It is evaluated by placing the formed raft under a specified weight until it breaks. The force required to break the raft is recorded as raft strength. Higher raft strength indicates better integrity of the gel system.

8. Raft Thickness

The thickness of the formed raft is measured using a suitable measuring scale after gel formation. Raft thickness influences the drug release profile and mechanical stability of the formulation.

9. Raft Density Determination

Density of the formed raft is determined to ensure its buoyancy. The density should be lower than that of gastric fluid (approximately 1.004 g/cm³) to enable the raft to float effectively over the gastric contents.

10. Water Uptake Study

Water uptake study is carried out to determine the swelling behavior of the gel.

The formed raft is weighed initially and then at regular intervals after immersion in simulated gastric fluid. The increase in weight indicates the amount of water absorbed by the gel.

11. In-Vitro Drug Release Study

Drug release from the raft forming system is studied using a USP dissolution apparatus in 0.1N HCl maintained at 37°C.

Samples are withdrawn at predetermined time intervals and analyzed spectrophotometrically to determine the percentage of drug released over time.

12. Release Kinetics Study

The drug release data obtained from the dissolution study is fitted into various kinetic models such as:

- Zero order kinetics
- First order kinetics
- Higuchi model
- Korsmeyer–Peppas model

This helps in determining the mechanism of drug release from the gel matrix.

13. Raft Erosion Study

Raft erosion study is performed to evaluate the stability of the formed gel in the gastric environment.

The formed raft is weighed initially and after specified time intervals to determine the rate of erosion over time.

14. Stability Studies

Stability studies are conducted to evaluate the physical and chemical stability of the formulation under different storage conditions such as:

- Room temperature
- Refrigerated conditions

Parameters such as pH, viscosity, drug content and floating behavior are monitored periodically.[20,23,30]

9. Current Challenges

- Variation in gastric pH under fed, fasted and diseased conditions affecting gel formation
- Mechanical instability of formed raft due to gastric motility and peristaltic movement
- Premature erosion or disintegration of raft structure in dynamic gastric environment
- Difficulty in maintaining optimum viscosity for easy oral administration and rapid gelation
- Inconsistent floating behavior due to improper CO_2 entrapment
- Poor in-vitro–in-vivo correlation of raft performance
- Lack of standardized evaluation methods for raft strength and density
- Inadequate assessment of reflux suppression capability
- Difficulty in maintaining long-term stability of liquid formulation
- Challenges in scale-up and industrial manufacturing
- Variability in gastric emptying rate affecting retention time
- Limited evaluation under physiological gastric conditions

10. Future Directions

- Development of physiologically relevant in-vitro evaluation models
- Evaluation of raft performance under variable gastric pH conditions
- Simulation of fed and fasted gastric states during formulation testing
- Incorporation of gastric motility simulation studies
- Improvement in mechanical strength of raft structure
- Detailed investigation of raft erosion behavior
- Evaluation of reflux suppression capability of raft system
- Standardization of raft evaluation parameters and testing protocols
- Enhancement of formulation stability during storage
- Establishment of better in-vitro–in-vivo correlation
- Optimization of polymer concentration for improved performance
- Development of scalable and reproducible manufacturing techniques
- Exploration of patient-compliant liquid gastro-retentive formulations

11. Optimization Approaches

1. Trial and Error Method

Initial formulations are prepared by varying polymer and excipient concentrations. Each formulation is evaluated for floating behavior, gelation and drug release to identify suitable concentration ranges for further optimization.

2. Factorial Design Method

A statistical experimental design is employed to study the effect of multiple formulation variables simultaneously. Different combinations of polymer and excipient concentrations are prepared and evaluated to determine their influence on raft performance parameters.

3. Response Surface Methodology (RSM)

Response Surface Methodology is used to optimize formulation variables by analyzing the interaction between independent factors and dependent responses. It helps in identifying the optimal concentration of formulation components required to achieve desired raft characteristics.

4. Optimization Based on Desirability Function

This method is used to obtain an optimized formulation by combining multiple response parameters such as minimum floating lag time, maximum raft strength and sustained drug release into a single desirability function.

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