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RAFT FORMING SYSTEM – AN INNOVATIVE APPROACH OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

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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. Several technical advancements have led to the invention of a gastro-retentive drug delivery system, which has various therapeutic benefits, has the potential to revolutionize medication delivery and overcome the shortcomings of traditional oral drug delivery methods. Gastro retentive 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 a type of floating drug delivery system with low density. The present study provides valuable information and highlights advances in raft forming system. Additionally, a summary of the various smart polymer types utilized in their formulation has been provided. The review focuses on the mechanism, evaluation, formulation and development of the raft forming system. The study finally highlights advantages, disadvantages, and of the raft forming system.

Index Terms **- Raft forming system, Gastroretentive form, Gastric residence time, Absorption window, Floating.**

I. 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[8]. Unfortunately, there were a number of problems with conventional distribution, the most significant of which were the drug's rapid degradation due to the highly reactive nature of Gl contents, the dosage form's brief residence time in the Gl tract and irregular stomach emptying. 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[8]. The purpose of gastroretentive drug delivery systems (GRDDS) is to increase the medication's bioavailability by allowing it to remain in the stomach for a longer period of time. By constantly releasing the drug for a lengthy time prior to it reaching its absorption site, GRDDS can enhance the regulated delivery of medications with an absorption window and ensure optimal bioavailability[10]. This also improves the solubility of drugs which are less soluble at alkaline pH of intestine. Various controlled release gastro retentive drug delivery systems include high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, superporous hydrogel systems, magnetic systems[5].

Of all these technologies, the raft forming technique is the most commonly used since it is the most practical and favored way to achieve a continuous and prolonged drug delivery profile in the gastrointestinal tract. Through continuous drug molecule release, this approach can provide a rather stable plasma profile[5] . At room temperature, these hydrogels are liquid, but when they come into touch with body fluids or undergo a pH change, they gel & formation of a viscous layer called as Raft. Raft floats on gastric fluid due to low bulk density which is created by the origin of CO_2. The system already contains gel-forming alkaline bicarbonate or carbonate which are produced from CO_2 and the formation of the gel makes the system lighter from the upper surface of gastric fluid[9] . The purpose of this system's design is to either decrease the frequency of dosing or increase the effectiveness of the medication by localizing it at the site of action, lowering the dosage needed, or delivering the medication consistently. Additionally, the raft forming technology has various potential benefits such as easier manufacturing procedures, better patient compliance.

Potential Drug Candidates For Gastro retentive drug delivery system[4][12]

- Drugs acting locally in the stomach, e.g. Antacids and Misoprostol
- Drugs that have narrow absorption window in the upper gastrointestinal tract (GIT) e.g. L-DOPA, para amino benzoic acid, furosemide, riboflavin etc.
- Drugs those are unstable in the colonic environment e.g. captopril, ranitidine HCI,
- Drugs that exhibit low solubility at high pH values eg. diazepam, chlordiazepoxide, verapamil HCI Drugs that are primarily absorbed from stomach e.g. Amoxicillin
- Drugs that disturb normal colonic microbes

Drugs Those are unsuitable for Gastro retentive drug delivery system:

- Drugs that have very limited acid solubility e.g. phenytoin
- Drugs that suffer instability in the gastric environment eg: erythromycin Drugs intended for selective release in the colon. eg. 5- amino salicylic acid and corticosteroids.

Anatomy and Physiology of GIT

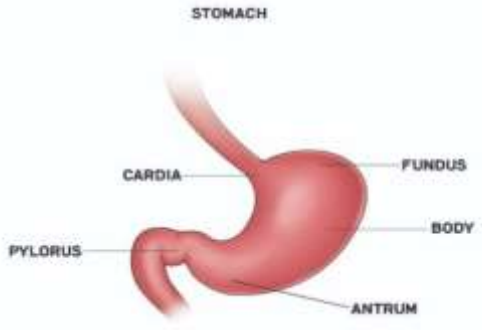

Fig 1: Anatomy of stomach

The gastrointestinal tract can be divided into three main regions namely:-

1. Stomach
2. Small intestine-Duodenum, Jejunum and Ileum
3. Large intestine

The GIT is a long, muscular tube that runs from the mouth to the anus. Its function is to absorb nutrients and expel waste through physiological actions like secretion, motility, digestion, absorption, and excretion. GIT is organized from stomach to large intestine[9]. The stomach is an organ with a capacity for storage and mixing.

The stomach is anatomically divided into three parts (Fig 1):
- fundus
- body
- antrum (pylorus)

Fundus and body are made by proximal part and work as reservoirs for undigested material, while the pylorus or antrum works as mixing and pump for gastric emptying by driving actions. Gastric emptying occurs during fasting as well as fed states.

During the fasting state an interdigestive series of electrical events occurs in cyclic manner both through stomach and intestine every 2 to 3 hours[5] .They are called as migrating myoelectric complexes(MMC) (Fig 2).

It is further divided into four phases[12]:

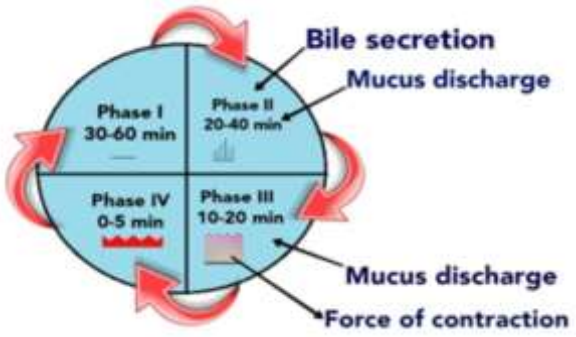

Fig 2: Gastric motility pattern

Phase I (Basal phase) the quiescent period, lasts from 40 to 60 minutes and is characterized by a lack of secretary, electrical and contractile activity.

Phase II (Preburst phase): lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses, the intensity and frequency also increases gradually.

Phase III Short periods of intense, large, regular contractions. This phase is termed as "housekeeper wave" as it enables all undigested materials to be swept out of the stomach and down to the small intestine. It lasts for 10-20 min with a frequency of 4-5/min.

Phase IV: transitional phase between phase III and I of two consecutive cycles. It lasts for less than 5min.

Factors affecting gastroretentive drug delivery system[5][8]

The development of gastroretentive dosage forms formulation should take into account a number of aspects in order to extend the dose intervals and enhance patient compliance. These are displayed below:

Factors related to dosage forms :-

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.

Size of dosage form:

Larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor affecting gastric retention.

Shape of dosage form:

Round or Ring-shaped dosage form are considered better in comparison to other shapes.

Food intake and its nature :-

Fed or unfed state:

Fasting conditions result in increased stomach motility, which indicates a shorter gastric retention time.

Nature of meal:

The stomach's motility pattern can be altered to a fed state by feeding indigestible polymers or fatty acid salts, which slows down the rate of stomach emptying and extends the time that drugs are released into the body.

Caloric content:
GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

Frequency of feed:
Higher the frequency of taking food, the longer will be the gastroretention time.

Patient related factors :-

Age:
Compared to a typical adult, elderly individuals exhibit a longer stomach retention time, whereas newborns and children have a lower gastric retention time.

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

Posture:
GRT can change depending on whether the patient is supine or upright and ambulatory.

Concomitant drug administration:
The co-administration of certain medications with gastric motility enhancers (cisapride, metoclopramide) or depressants (atropine) has a significant impact on gastric retention time and, consequently, the absorption of drugs that are specific to the stomach.

Disease states:
Different gastric disorders, such as Crohn's disease, Gastric ulcer etc., change the gastroretentive time.

Approaches to Achieve Gastric Retention[8]

1. Floating systems

2. High density systems

3. Bioadhesive systems

4. Swelling and expanding systems

5. Modified shape systems

6. Raft forming system

7. Superporous hydrogel

8. Magnetic systems

FLOATING SYSTEM

They have a bulk density lower than gastric fluids and thus remain floating in the stomach for prolonged period of time, unflattering the gastric emptying rate. The drug is released slowly at a desired rate from the floating system. Floating systems are divided into effervescent and non- effervescent systems. Non-effervescent systems are turned out by putting the drug with highly swellable cellulose derivatives or gel-forming polymers are used, while as in effervescent one's agents such as sodium bicarbonate, calcium carbonate, tartaric acid, and citric acid are used in combination with hydrophilic polymers. So that when they touch the gastric fluid, CO_2 is liberated and entrapped in a hydro-colloid matrix, thus influencing drug release[3]

HIGH DENSITY SYSTEM

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~1.004 g/cm³). These formulations are prepared by coating drug on a heavy core or mixed with heavy inert materials such as iron powder, zinc oxide, titanium dioxide or barium sulphate. They are retained in the antrum of stomach[12]

BIOADHESIVE SYSTEM

Bioadhesive systems are usually exploited to localize a delivery device within the body to improve the drug absorption process in a site specific manner. In this approach bioadhesive polymers are used that can adhere to the epithelial surface of gastrointestinal tract. The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding, or receptor mediated.
In hydration mediated adhesion, the hydrophilic polymers become sticky and mucoadhesive upon hydration. Bonding mediated adhesion may involve mechanical or chemical bonding. Chemical bonds may involve covalent or ionic bonds or Van der Waals forces between the polymer molecules and the mucous membrane. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells.[10]

SWELLING AND EXPANDING SYSTEM

Swellable systems include the products that swell after swallowing to an extent that prevents their exit from the stomach through the pylorus. This results in retention of dosage form in stomach for prolonged period. These systems may be called 'Plug type systems' as they show a tendency to remain lodged at the pyloric sphincter[12] . Expansive gastroretentive dosage forms are capable of expanding in stomach. The expanded structure is trapped in stomach for prolonged period leading to sustained drug release and subsequent controlled absorption in stomach and intestine.
These systems are administered per orally in the form of capsule bearing the dosage form in folded and compact configuration. When exposed to gastric environment capsule shell breaks and the dosage form attains its expanded structure, which is retained in stomach for longer time.

MODIFIED SHAPE SYSTEM

Modified systems are geometric shapes made up of silastic elastomer or extruded from polyethylene blends, which prolong the gastric retention time, depending on size and shape.

SUPERPOROUS HYDROGEL

A superporous hydrogel is a 3-dimensional network of a hydrophilic polymer that absorbs water in large amount in a short period of time due to the presence of interconnected microscopic pores Superporous hydrogel have a pore size>100 um which swell to equilibrium size with in a minutes, due to rapid intake of water by capillary wetting through inter connected open pores[27] [7]. Superporous hydrogel do not have only fast swelling, but also properties like slipperiness, biodegradability, biocompatibility, high mechanical strength, and stability in acidic condition of the stomach.
A superporous hydrogel is filled into a capsule, so initial volume of this gastro-retentive dosage form is too small and easy to swallow. After oral administration, it swells rapidly in the gastric fluid to a large size, so that its emptying into the intestine is prevented.

MAGNETIC SYSTEMS

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. The real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision[10]

ION-EXCHANGE RESIN SYSTEMS

Drug is loaded into the resin to form the resin loaded drug complex, which can be combined with floating delivery or bioadhesive systems. They are designed to increase GRT, especially for low bioavailable drugs[3]

RAFT FORMING SYSTEM

Raft forming systems have drawn a lot of interest in the administration of medications for gastrointestinal infections and illnesses as well as antacids. 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. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2 [5][6] . The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a floating sodium alginate gel (raft) when in contact with gastric fluids[5][10]
The antacid components in formulations provide a relatively pH-neutral barrier. Calcium carbonate can act as an antacid as well as a raft strengthening agent. It releases calcium ions, which react with alginate and form an insoluble gel. Various polymers, especially different polysaccharides, have been used in various research works. Alginic acid, alginates and pectin are the most widely used raft-forming agents.
They are designed to be hydrogels at 25°C and then are transformed to gel when coming in contact with body fluids or with some changes in pH[3] .The idea is to function as a barrier between the stomach and esophagus to stop the reflux of stomach contents in to the esophagus[3] .
Thus it produces retention of dosage form and increases gastric residence time resulting in prolonged drug delivery in gastrointestinal tract. When the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of the drug, the residual system is emptied from the stomach. This results in an increased gastro retention time and a better control of the fluctuations in plasma drug concentration[28]

THE DESIGN OF THE RAFT FORMING SYSTEM

The formulation of the raft forming system depends on the physicochemical properties of the drug molecule, the diseased condition for which treatment is required, the patient population and the marketing preference. Physico-chemical factors include molecular weight, lipophilicity and molecular charge; an anatomical and physiological factor includes membrane transport and pH of tissue fluid, formulation factors include pH, gelation temperature, viscosity, osmolarity, and spreadability. [3][10]

The dosage form must be able to fulfill the following requirements in order to achieve gastric retention[10]

1. The drug should be released slowly from the system

2. The dosage form must be able to withstand the force exerted by peristaltic waves in the stomach and the constant contractions, grinding and churning moments

3. Should maintain specific gravity lower than gastric contents (1.004- 1.01 g/cm3).

4. The dosage form must remain in the stomach for a prolonged period of time.

5. Better patient compliance.

6. Easy for administration for the patient.

ADVANTAGES OF RAFT FORMING SYSTEM[5,9,10]

1) They are used for the symptomatic treatment of heart burn and oesophagitis. It can be used in LPR (Laryngopharyngeal Reflux), GERD etc.

2) It does not interfere with the activity of promotility agent, antisecretory agents such as cimetidine.

3) Rapid and Long-duration of action can easily achieved by raft formation. It may show its action within seconds.

4) It will not interfere with function of pyloric sphincter.

5) Better patient compliance can be achieved and it is well tolerated.

6) The raft forming system improves the solubility of drugs that are poorly soluble in the high pH of the intestine.

7) The system reduces plasma level fluctuation.

LIMITATION OF RAFT FORMING SYSTEM[5,8,9,10]

1. 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.

2. The formulation must be stored properly because if 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.

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

DRUGS SUITABLE FOR RAFT FORMING SYSTEM[5]

- Drugs with narrow absorption window in GIT, e.g., Riboflavin and Levodopa.
- Drugs that primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, chlordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- Drugs that degrade in the colon, e.g., Ranitidine HCI and Metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., Amoxicillin Trihydrate.

APPROACHES OF RAFT FORMING SYSTEM[8, 9,10]

In situ gel formation is produced using a variety of techniques and mechanisms, including the following ones:

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

Physical based raft system[9,10, 5,8,3]

These systems formed on a physical basis are divided into two mechanisms.

1. Swelling
2. Diffusion

Swelling

Here polymer absorbs water and then swells, forming the gel. So, the formation of the gel occurs when the liquid effervescent structure touches the gastric fluid. Also, in situ formation of gel takes place when materials absorb water from the surrounding environment and expand at the desired site of action.

Diffusion

Diffusion is the process by which a solvent from polymer solution diffuses in to the surrounding tissue, further results in precipitation or solidifying the polymer matrix.

Chemical-based raft system[5,8,9]

Ionic cross linking

There are various polysaccharides that undergo phase transition in the presence of various ions. Polysaccharides falling into the class of ion- sensitive ones are most widely used. In the presence of various ions such as K, Ca, Mg and Na, ion sensitive polysaccharides such as carrageenan, gellan gum (Gelrite®), pectin, and sodium alginate go through phase transitions. Alginic acid undergoes gelation in the presence of divalent/polyvalent cations like Ca2+ due to the interaction with guluronic acid block in alginate chains. K-carrageenan forms rigid, brittle gels in response to small amount of K. Gellan gum commercially available as Gelrite is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca2+, Mg2+, K and Na. Gelation of the low-methoxy pectin can be caused by divalent cations, especially Ca2+.

Enzymatic cross-linking

Body fluids contain enzymes that can also induce cross linking, which creates a polymer network and is thought to be the most feasible method by which gel is formed.

Physiological stimuli-based raft system[3,8,9]

pH dependent gelling

A change in the pH of the medium can also lead to gel formation. There are a lot of pH dependent polymer that are capable of composing in situ gel in the system. Numerous polymers including polyvinylacetal diethylaminoacetate (AEA), carbomer (PAA) or it's derivatives, mixtures of poly(methacrylic acid) (PMA) and poly(ethylene glycol) (PEG) show a change from sol to gel with change in pH. In case of anionic groups swelling of hydrogel increases as the external pH increases, but decreases if polymer contains cationic groups. In order to accomplish gelation, mixtures of poly(ethylene glycol) (PEG) and poly (methacrylic acid) (PMA) have also been utilized. pH sensitive polymers can be ionic or neutral in nature. Negatively charged moieties are found in anionic networks, positively charged moieties are found in cationic networks, both positive and negatively charged moieties are found in neutral networks.

Temperature dependent gelling

At room temperature (20-25 °C), these hydrogels are liquid and they gel when comes in contact with body fluids (35-37 °C) due to rise in temperature. In drug delivery research, these hydrogels are likely the most commonly studied type of environment - sensitive polymer systems. Typical examples of this type of polymers are polyacrylic acid, poly acrylamide etc.

POLYMERS USED FOR RAFT FORMING SYSTEM

Pectin

These substances are derived from plant species that contain anionic polysaccharides, which are composed of residue of α -(1-4)-D- galacturonic acid and are extracted from cell walls of most plants. Pectin forms gel when divalent ions such as calcium was present. This leads to the cross linking of galacturonic acid units (ionic cross linking) and also in the presence of H ions, a process known as pH dependent swelling[8][10] . Pectin is mostly used in raft formulations since it dissolves in water, negating the need for organic solvent in the formulation. When divalent cations are present in the stomach they facilitate the oral transition of pectin in to a gel like form. The gelation property of pectin is induced by including a complexed form of calcium ions in the formulation. Commercial pectins are available in two varieties: high methoxy (HM) and low methoxy (LM)[8, 10] .

Gellan gum[8]

Chemically, gellan gum is an anionic deacetylated polysaccharide containing repeating tetrasaccharide units. It is an exocellular polymer released by Sphingomonas elodea(Pseudomonas elodea). In situ gels can be produced by combining gellan gum with Ca^{2+} ions as cross linking agent[29] .

Sodium alginate

Sodium alginate is a common in situ gelling ingredient in pharmaceutical formulations. Alginates are natural polysaccharide polymers isolated from brown sea weed (phaeophyceae). Chemically it is alginic acid

composed of α-L-glucuronic acid and β-D-mannuronic acid residues that connected by 1,4 glycosidic linkages[8]. When di or trivalent ions (such as calcium & magnesium ions) are present, the alginates in aqueous solution solidify into gels. Sodium alginate is mostly used in the production of gel forming solutions, for delivery of drugs and proteins. Alginate salts are considered to be most suitable for the gel formation because of biodegradable and non toxic nature. They also have bioadhesive property[8] .

Xyloglucan

This plant based polysaccharide is derived from tamarind seeds. This polysaccharide is chemically made up 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. When xyloglucan is partially degraded by β-galactosidase the resultant product exhibits thermoreversible gelation in dilute aqueous solution. Such gelation does not occur with native xyloglucan[8] [10] . They are usually utilized for rectal and ocular drug delivery as well as oral drug delivery. Xyloglucan has shown a very low gelation time of up to a few min[8].

Pluronic F-127[8]

The poloxamers Or pluronic composed of more than 30 different non ionic surface active agents. These polymers are polypropylene oxide(PPO) units(B) and polyethylene oxide (PEO) units (A) triblock copolymers of the ABA type. In ophthalmology, the most often used thermal setting polymer is poloxamers, which is marketed under the brand name pluronic R. Pluronic F-127 is the most widely used polymer in pharmaceutical technology because it produces translucent, colorless gels. In general poloxamer formulation prolonged the time of drug residence at application sites, improving the formulations bioavailability and activity. The solution acts like a mobile viscous liquid at room temperature (25°C), changing in to a semisolid transparent gel at body temperature (37°C). Pluronics or poloxamers also undergo in situ gelations by temperature change.

Carbopol[8]

It is a mucoadhesive polymer that will boost the mechanical strength of the formulation while simultaneously increasing surface contact and as a result contact time with ocular tissue. Carbopol in aqueous solution shows a solid-to-gel transition as the pH is raised above it's pKa of about 5.5, so it is a well known pH- dependent polymer that remains in solution at acidic pH but forms a low viscosity gel at alkaline pH.

Chitosan[8]

glucosamine and N- acetylated glucosamine copolymers. This is a naturally occurring polymer that is produced when chitin is deacetylated. Some of it's characteristics include being a non toxic, biodegradable polysaccharide with bioadhesive and antibacterial capabilities.

EVALUATION OF RAFT FORMING SYSTEM

***In vitro* evaluation parameter :-**

1. **Texture analysis:** The purpose of this text is to evaluate how cohesive and consistent the prepared formulation is. The text primarily determines whether the formulation sol can be effectively injected using a syringe fitted with proper needle. The adhesiveness of a gels is needed to be high to maintain intimate contact with surfaces like tissues[5]

2. **Sol-gel transition and gelling time:** Raft forming system involves the formation of viscous cohesive gel in contact with gastric fluids[5] .The temperature at which the phase transition of sol meniscus is first observed when allowed to remain at a particular temperature in a sample tube and subsequently heated at a predetermined rate is known as the sol-gel transition temperature[8][3][3] Gel formation is indicated by the lack of movement of meniscus on tilting the tube. Gelling time is the time for the first appearance of gelation[3] [8].

3. **Floating/buoyancy test:** It is measured to see how long it takes the dosage form to float on top of the dissolving medium after it has been inserted into it. SGF (simulated gastric fluid), which is kept at 37 °C, is typically used for testing. Measurements were made of how long the dose form remained buoyant after being introduced and how long it remained buoyant in the simulated stomach fluid. Floating time is defined as the time during which the dosage form remains buoyant and the time between. introduction of dosage form and it's buoyancy on stimulated gastric fluid known as the Floating Lag Time (FLT) or Buoyancy Lag Time

(BLT)[9] [10] and total duration of time by which the dosage form remains buoyant is called Total Floating Time (TFT)[5] .

4. **Gel strength:** This helps determine prepared formulation's gelling characteristics. Using a rheometer this parameter can be assessed[5] [9] . In this test a specified amount of gel is prepared in a beaker, from the sol form. After slowly inserting a rheometer probe in to the gel, gel containing beaker is lifted at certain rate. The changes in the load on the probe can be measured as a function of depth of immersion of probe below the gel surface[3].

5. **Viscosity and Rheology:** This is an important parameter to be evaluated for the raft forming system. The viscosity and rheological properties of polymeric formulations were determined with different viscometer. The viscosity can be determined with Brookfield rheometer or some other type of viscometers such as Ostwald's viscometer. Formulations should have a viscosity that does not cause problems for the patient to administer them[5].

6. **Drug-excipient interaction study:** Using Fourier transform infrared spectrocsopy, this test is carried out to investigate the compatibility of substances. With this method the nature of interactive forces can be assessed during the gelation process[5][3].Additionally Differential scanning calorimetry can also be used to observe if there are any changes in the thermograms as compared with the pure ingredients used thus indicating drug interactions.

7. ***In vitro* release studies:** The *in vitro* drug release of raft forming system is facilitated by a USP type-ll apparatus operating at 50 rpm in 0.1N HCl for a duration of 0-8 hrs. The temperature is maintained at 37±2°C and the dissolving medium employed is 900ml of stimulated gastric fluid (0.1N HCl, pH 1.2)[5]. A precisely measured sample of the dissolving media is pipetted out and replaced with fresh medium at each time interval. Spectrophotometric analysis can be used to ascertain the drug concentration in the aliquot[3] .

***In vivo* evaluation parameter :-**

Gastroscopy: Gastroscopy is a type of oral endoscopy that can be done using video frameworks or fiber optics. It is used to inspect visually the effect of dosage form for prolongation in the stomach. It can also give a detailed evaluation of the gastroretentive drug delivery system[9][5] [3] .

Radiology and scintigraphy: It makes use of markers that are radio opaque X-ray/Gamma Scintigraphy helps to locate the dosage form in the gastrointestinal tract, thus makes it possible to forecast and connect the time it takes for the stomach to empty and the passage of dosage form through the GIT. A common radio opaque marker is barium sulfate and it's inclusion in to a solid dosage form enables it to be visualized by X-rays at different intervals to determine gastric retention[3].In the same way the inclusion of γ-emission of radionuclide to a formulation permits indirect external observation through the use of a scintiscanner in which the γ-rays emitted by radionuclide are focused on a camera and allows the monitoring of dosage form situated in GIT [9] [5] .

Ultrasonography: Ultrasonic waves are employed in the ultrasonography procedure to create the images of the inside anatomy of body. Ultrasonic waves penetrate the tissues and are reflected back. An electronic device receives the reflected echoes and determines the tissue's position that is reflecting them as well as their intensity. The output might be shown as a moving image of the inside of the body or as static photos [9] [10] .

Magnetic marker monitoring: Iron powder is contained within the dosage form, which is magnetically tagged. The dosage form image can be captured using highly sensitive bio- magnetic measurement apparatus. This method uses no radiation and is less dangerous [5] [3] .

^{13}C octanoic acid breath test: ^{13}C octanoic acid is incorporated in to the gastroretentive drug delivery system and the system is introduced in the stomach Octanoic acid causes a chemical reaction in the stomach that releases CO_2 gas which comes out in breath. The ^{13}C isotope takes the place of significant carbon atom that would eventually make up the CO_2 .Therefore, the gastric retention time of dosage form can be defined as the amount of time that CO_2 gas is observed in mouth. As the dosage form moves to the intestine there is no reaction and no CO_2 release[5] .

Accomplishments of raft system in gastroretention drug delivery systems

Since 1994, the raft system has been employed to raise the GRT of an antacid formula, with the floating antacid system confirmed by fabregas et. al. The authors employed sodium alginate as a polymer forming gel and acid neutralizer and sodium bicarbonate as agents that generated gas. The raft floats on the gastric fluid as a result of the release of CO_2 gas, which lowers the bulk density of the system. According to the findings the prepared raft antacid pharmaceutical formulation does in fact have a high antacid potency and a prolonged in vitro GRT that allows for the safe and sustained delivery of an antacid medication[14].

Frank C et al investigated another composition. The best option was an alginate /antacid composition that has been used to treat acid reflux disease. The formulation contained calcium carbonate and sodium bicarbonate with a minimal dose of Gaviscon (Low acid neutralizing capacity). Comparing the raft gel strength and resilience of the developed system to those of the other drugs evaluated, it demonstrated greater efficacy. GRT did not however appear to alter[15].

Another investigation on curcumin and Eudragit for the treatment of stomach ulcers was carried out in 2015. The study was carried out in Nattha et. al, sought to extend the GRT and have a regulated release of curcumin to treat gastric ulcers. The system that is created consist of Eudragit® EPO, calcium carbonate to release Ca^{++} ions, CO_2 to stabilize the floating characteristics and sodium alginate which is employed as a gelling polymer. Every formulation that was examined produced a gelled raft in one minute and maintained floatability for 8hrs, releasing 60-85% of curcumin. Compared to standard antisecretory drugs the curcumin prepared systems demonstrated a perfect curative effect on the stomach ulcer in terms of ulcer index and healing index[16].

Saowanee et. al conducted a second study comprising Eudragit® EPO and glycoside rich extract and the raft was used to acquire a prolonged sustained delivery of glycosides, asiaticoside and madecassoside in stomach, there by improving treatment of gastric ulcer. Calcium carbonate which produces CO_2 and serves as a calcium supply, alginate, HPMC K-100 and Eudragit EPO comprised the optimal formulation. Adequate strength, fast floating behaviour, and sustained release of glycosides over an 8hr period were identified as good qualities of the formulation. *In vivo* results in rats demonstrated a decrease in ulcer severity and improved curative efficacy compared to conventional antiulcer medications[17].

Nabarawi et. al created a Mebeverine HCl controlled release floating raft system, and assessed it's floating behaviour as well as *in vitro* controlled release with various excipients. The prepared formulation contained liquid solution of alginate with calcium carbonate as an effervescent agent. To slow down the rate of drug release alginate based formulations were combined with varying amounts of HPMC K 100M, Compritol® and Precirol ®. The optimized formula demonstrated a greater floating lag time and a total floating time of over 12 hrs, which encouraged the drug's prolonged release. In vivo studies demonstrated better oral bioavailability, a 3 hr T_{max} and a higher C_{max} compared to the marketed drug[18].

Pantoprazole sodium sesquihydrate is widely used in the treatment of peptic ulcer, and GERD. Alginate and pectin were used by the authors in a successful system that included the medication and additional excipients. The raft's strength and integrity were impacted by the presence of alginate and pectin, which also enables the raft to entrap antacid inside the gel. The hydroxyl groups found in pectin and sodium alginate facilitates the system's enlargement. Additionally HPMC K 100M forms viscous gel like properties around the raft, sustaining the drug's release. The *in vitro* release studies showed controlled release of drug up to 8hr with a marked increase in bioavailability[19].

One typical GIT issue is an infection caused by Helicobacter pylori. The purpose of this study was to treat the above infection using Metronidazole in raft formulation. The authors established the utility of employing ion-sensitive insitu gel forming polymers to raise GRT and Metronidazole release rate. Prepared formulations containing sodium alginate and gellan gum with sodium citrate and calcium carbonate, lipids such as glyceryl monostearate, compritol and precirol. Buoyancy, Gelation capacity and viscosity parameters were assessed. Drug kinetics and release were investigated[24] .

Manal et. al carried out a study on chewable tablets that formed a raft. Sodium bicarbonate was used as a gas generating agent, calcium carbonate as an antacid and strengthening agent, and sodium alginate as the raft forming agent to create chewable tablets. X-ray scanning revealed that the object floated immediately after

ingestion and stayed whole for around 3hrs as a raft formed on stomach contents. This leads to improved absorption and immediate alleviation from acid burning symptoms[20].

Formation of a floating system by an antacid raft was explained by Jorgen et al. He used a gel forming agent, which is sodium alginate along with sodium bicarbonate and acid neutralizer. When the sodium alginate comes in contact with stomach contents it foams and floats on gastric fluids, which avoid the reflux of gastric content in to the esophagus[21]

Ahmad Bani-Jaber et al applied a raft system formation on ambroxol, a drug used to treat respiratory disorders. The objective was to create pharmaceutical formulation that would allow for sustained release using raft forming techniques. The system was built using calcium alginate ions. An initial burst release was followed by a continous release to achieve a biphasic release. The system was designed as suspension in aqueous vehicle of sodium alginate and calcium carbonate Compared to gaviscon liquid, the prepared suspensions formed rafts of similar strength and higher resilience[22].

Ibandronate is a low bioavailability osteoporosis medication that might irritate the stomach and esophagus. Oral bioavailability will be enhanced by the substances capacity to create raft in the stomach. Additionally the created raft prevents the esophageal and stomach from being inflamed. The systems have been successfully prepared from citrus pectin and have shown effective porous formation[23].

Neural treating drugs were applied to raft systems with some remarkable results. Their bioavailability might be enhanced by their important regulatory roles in membrane signaling to the nucleus, action potential propagation and synaptic transmission. Teaima et. al were able to manufacture the antidepressant medication bupropion in to floating system, using insitu gelling pectin and alginate. Bupropion has a high solubility in water, yet patient compliance is low due to frequent dosing. The authors formulate a system that has outstanding viscosity, allowing for a quick sol gel transformation in stomach, great floating behaviour and a controlled release profile with a comparable bioavailability. Patient compliance was enhanced and allowed to control bupropion rate release by the ideal raft forming technique[25] .

Gabapentin, an antineuropathic medication, has a short half life(5-7hrs), a restricted window for absorption. To prolong the GRT of Gabapentin, Samar et al investigated a raft forming system. Firstly the drug was coated by Eudragit NE. The coated drug was later incorporated in to the system. This floating systems ideal viscosity made it simple to swallow as a liquid dosage form, which then undergoes a rapid sol gel transition and floating due to ionic interaction. The pharmacokinetic analysis demonstrated a substantial rise in C_{max} and a 1.7 fold increase in relative bioavailability in contrast to immediate release formulations[26].

Patel et al also carried out a study on raft forming chewable tablet of lafutidine. The tablets were prepared using sodium alginate as raft forming agent, in combination with calcium carbonate (antacid) and sodium bicarbonate (gas generating agent). The optimized formulation has good raft strength, sufficient acid neutralization capacity and satisfactory *invitro* drug release. The formulation was also stable at accelerated conditions of temperature and humidity for one month[2]

Soni et al prepared and evaluated raft forming chewable tablet of Ranitidine HCl for the treatment of GERD. The system was built using pectin, sodium bicarbonate and calcium carbonate etc. The optimized formulation has sufficient raft strength to prevent reflux of gastric contents[13] .

CONCLUSION

A gastroretentive drug delivery system was created to improve the drug's optimal bioavailability by keeping the medication in the stomach area for an extended period of time and releasing drug candidates gradually and continuously in to the upper part of GI tract. The raft forming system has demonstrated it's suitability and potential for developing effective controlled release of a range of medications. Raft forming system undergoes sol to gel transition when comes in contact with gastric fluid and composed of a gel forming agent and alkaline bicarbonates or carbonate substances that are responsible for producing CO_2 to make the system less dense and float on gastric fluids. Therefore it can be concluded that these dosage forms serves the best in treatment of diseases related to GIT, GERD etc.

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