THINK INDIA JOURNAL

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

AN APPROACH FOR THE TREATMENT OF PEPTIC ULCER BY RAFT FORMATION

Amneet Kaur[1], Kajol, Ashish Manocha, Liban Dahir, Sujit Bose*, Kalvatala Sudhakar

School of Pharmaceutical Science, Lovely Professional Univeristy , Jalandhar, Punjab.

*corresponding author: Sujit Bose, **Email id:** **sujit.19571@lpu.co.in**

ABSTRACT:

The most preferred and convenient route is an oral route for the delivery of a drug. The oral delivery of drugs is convenient but there is a partial release of drug due to the lesser residence time. To overcome this problem, a new approach came into light i.e. gastro retentive drug delivery system which includes raft formation. Raft formation is a novel approach for the delivery of oral dosage form. It is a liquid dosage form and has a density lesser than gastric content. So, remains floating over the gastric content. And once it gets interacted with gastric content, it changes to gel form. It is advantageous as it is patient compliance and is effective for an extended time period as it delivery of the drug from the dosage form is for more time. As the drug floats for a long time over the gastric content, it automatically leads to an increase in the local action of the drug and there is no need for frequent dosing. The conversion of solution to gel state is cation dependent or temperature-dependent. Various types of polymers which can be used in raft formation includes different approaches for gelation.

Keywords: Oral route, raft formation, patient compliance, gelation.

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1. Introduction:

The first and foremost step in designing any dosage form is to deliver it at the particular target site. And among all the routes for the management of the disease, the most preferred route is the oral route because of the most versatile, convenient path for the delivery of the medication for systemic action. The oral route is the ideal route because GI physiology shows further flexibility in the dosage form [1-2].

A peptic ulcer is the most gastrointestinal disorder. Peptic ulcers are the unbolted sores that occur on the innermost lining of gastrointestinal tract mainly in the stomach. Peptic ulcer arises because of an imbalance among the aggressive factor and defensive factor. Aggressive factors are like bile, pepsin, acid, and H.pylori and the defensive factors are like bicarbonate secretion, PGs, gastric mucus, innate resistance of the mucosal cells, nitric acid. Peptic ulcer includes symptoms like a burning pain, excessive bleeding, discomfort in the stomach, anemia, stomach cancer are very harmful to life [3-4].

The overall density of the floating drug delivery systems (FDDS) is less as compared to the gastric contents present in the stomach deprived of its effect on gastric emptying. The low density of the system helps in the slow delivery of the drug at a predetermined rate to control the variation in drug plasma concentration and eliminate the dosing frequency. To target the drug at a specific site it is very important to understand how to prolong the gastric residence time by using a floating drug delivery system. And it is the objective of the floating drug delivery system [5–7].

Due to prolong retention of the system in the stomach releases the drug slowly due to which there is less wastage of the drug and because of the slow release of the drug, there is an increase in bioavailability which is very beneficial for the patient. Drugs that are not soluble in high pH are suitable for the system. It is a local acting drug for the stomach. The

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reflux of the gastric content is prevented due to the raft present over the gastric content which acts a barrier between oesophagus and stomach. Following are the mechanisms used to attain gastric retention: [8-9]

- Sedimentation
- Mucoadhesion
- Floating

1.1 Advantages :

1. There will be an increase in drug absorption due to prolong gastric residence.
2. It is the site-specific drug delivery.
3. Gastro-intestinal disorders can be treated.
4. It is a very simple and convenient method.
5. The administration is easy.
6. More patient compliance.

1.2 Disadvantages :[10]

1. Drugs causing irritation to gastric mucosa are not suitable to be dispensed.
2. These systems are not possible for drugs with high stability and solubility problems in gastric fluids.
3. Many factors affect gastric retention such as pH, presence of food.

1. Basic anatomy and physiology of the stomach:

2.1 Anatomy:[11-12]

GIT is a long tube expanding from mouth to anus and is 9m in length. The main function of GIT is to absorb the nutrients and remove the residue by following processes like secretion, absorption, digestion, and elimination.

The three main parts of GIT are: Stomach, Small Intestine, Large Intestine

The shape of the stomach resembles J-alphabet. It has a resting volume of 25-30ml. Its location is on the leftward of the abdomen which is situated beneath the diaphragm.

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Storage of food is the main function of the stomach. The stored food is then ground and finally released into the duodenum.

Three parts of the stomach are-

Fundus, Body, and Antrum

The fundus is the proximal part of the stomach, then comes body which acts as a storage compartment for storing material which is left undigested & the last part is antrum that helps in the pumping of the material present in the stomach to duodenum part by propelling action. The antrum is the primary site of mixing of food but because of its small size, the absorption does not occur properly. Because of its small size, it also acts as a barrier for the small intestine.

2.2 Physiology of the stomach:[13]

Drug delivery is directly related to stomach physiology. The gastric emptying is can occur in both fed and fasted state and these two states decide the motility pattern.

A series of an electrical event occurs through the stomach and intestine during fasting state. This cycle occurs every 2 to 3 hours. This is called a migrating myoelectric cycle (MMC) or inner digestive myoelectric cycle.

MMC occurs in 4 phases:

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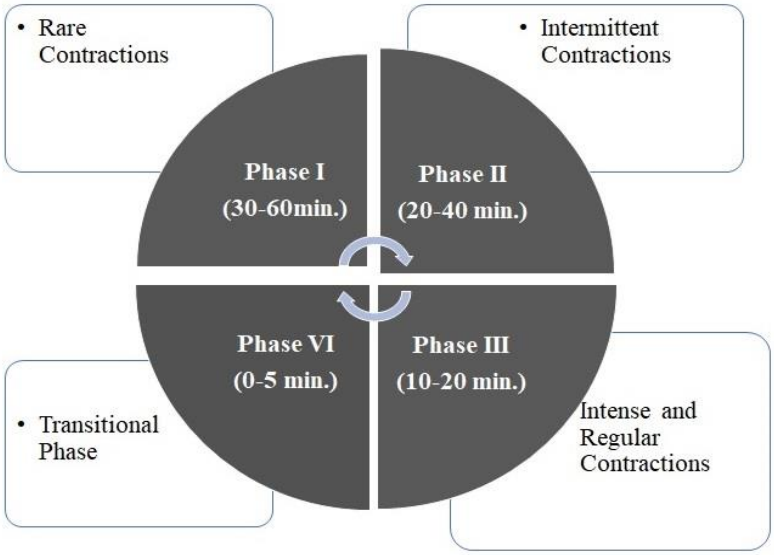

Fig.1: Different phases of MMC

Gastric emptying gets slowed down during the fed state because as long as the food is present in the stomach there will be an increase in the motor activity which leads to the delayed action of the MMC. Bioavailability is increased due to prolong gastric retention and also the solubility of the drug is increased. The increased time of fed activity is due to the type and amount of food ingested, with time spans of 2–6 h [14-15].

2. Peptic ulcer:

A peptic ulcer is a gastrointestinal disease. Peptic ulcer occurs due to an imbalance between aggressive factor and defensive factor. The most common cause of peptic ulcers is due to infection caused by H. pylori bacteria.

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3.1 Treatment of peptic ulcer:[3,6]

There are various approaches used in the treatment of peptic ulcer:

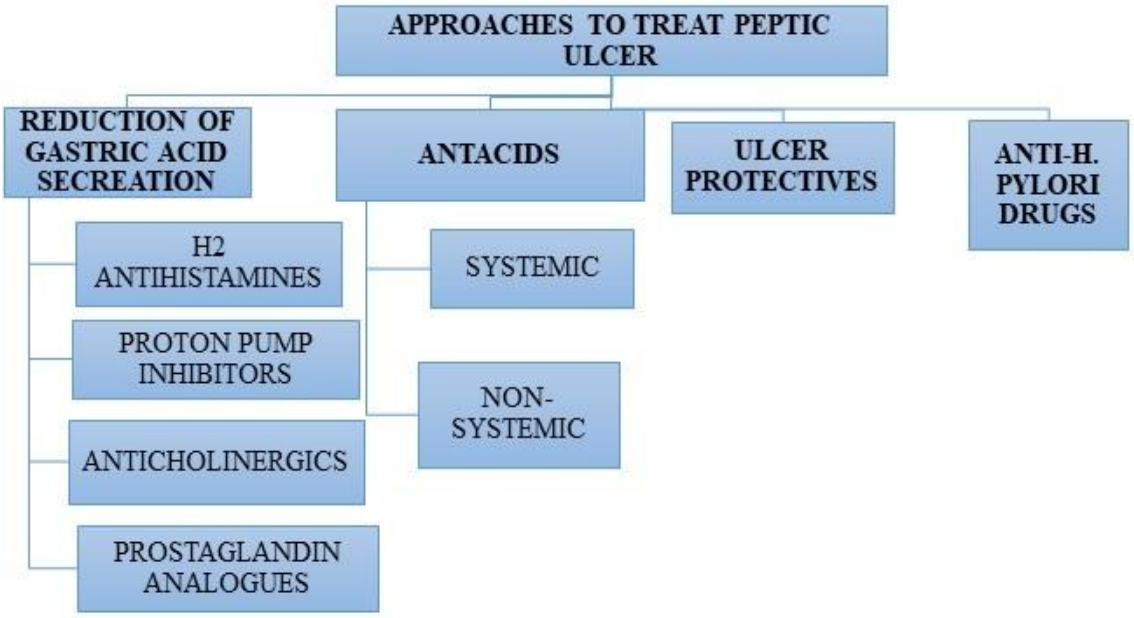

Fig.2: Approaches to treat peptic ulcer

3.2 Gastric acid secretion reduction:

3.2.1 H_2 antihistamines: It works by reducing gastric secretion in the parietal cells of the stomach. It inhibits the action of histamine at the H2-receptors. Example- Cimetidine, Ranitidine, Famotidine [16].

3.2.2 Proton pump inhibitors: It works by inhibiting the acid secretion. It also inhibits the H+/K+-ATPase enzyme of the gastric parietal cell. Example- Omeprazole, Esomeprazole, Pantoprazole, Rabeprazole, Lansoprazole [17].

3.2.3 Anticholinergics: It reduces the volume of gastric juice without raising its pH unless there is food in the stomach to dilute the secreted acid. Example- Pirenzepine, Propantheline [16].

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3.2.4 Prostaglandin analogues: Prostaglandins inhibit gastric acid secretion and increase the mucosal flow. Example- Misoprostol [3].

3.3 Antacids:[18]

3.3.1 Systemic antacids: They are completely absorbed into systemic circulation but may cause systemic alkalosis. Example- Sodium bicarbonate, Sodium citrate.

3.3.2 Non-systemic antacids: Non-Systemic antacids are insoluble in water. They are unabsorbed and do not produce systemic alkalosis. Example- Magnesium hydroxide, Aluminium hydroxide.

3.4 Ulcer protectives: These are cytoprotective agents. It uses the mechanism of protecting itself from the harmful effects of acid and pepsin. Example- Colloidal bismuth subcitrate, Sucralfate [19].

3.5 Anti-h.Pylori drugs: Example-Clarithromycin, Metronidazole, Amoxicillin, Tetracycline.

These are the various approaches that help in treating peptic ulcers. The formulations for the treatment of peptic ulcers are present in solid dosage forms as well as liquid dosage forms. The liquid dosage form is mostly preferred due to patient compliance. One such formulation is raft formulation which is liquid in the form.

4. Raft formation:

Raft formation is receiving much consideration for the delivery of antacids. Raft means flat surface usually made up of logs or planks and floats over the water surface which can also act as a support for the swimmers. Raft forming system is used for the treatment of gastrointestinal infection. The mechanism of raft formation is when the liquid dosage form meets gastric content, it gives rise to the formation of a layer of thick viscous gel. The liquid swells and forms the continuous layer over the gastric content. This continuous thick layer formed is called a raft. The density of this raft system is lower as compared to the gastric fluid. Due to which it starts floating over the gastric fluid due to the formation of CO_2. The formation of carbon dioxide is due to the presence of alkaline carbonates and bicarbonates and gel-forming agents that helps in making the system less dense resulting in its floating. The system of floating raft formation formulates of gel-forming agent, sodium

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bicarbonate acting as an antacid or acid neutralizer, which turns into gel upon getting in contact with gastric content. This raft formed is present in the stomach and acts as a blockade between oesophagus and stomach. It is also helpful in preventing the reflux action of the gastric contents. In the presence of gastric acid, sodium bicarbonate or potassium bicarbonate in the raft system gets converted into carbon dioxide. The carbon dioxide formed gets captured into the gel and starts floating over the surface. Calcium carbonate used also provides the strength to the raft. Calcium ions released by calcium carbonate when reacts with alginate, it forms a gel. There are different types polymers used for the formulation. Sodium alginate is the most commonly used. Anti-reflux raft forming system is a novel approach to treat the problem of acidity and other gastric problems. The formation of the gel is due to double-helical junctions which form a three-dimensional network by complex formation [20–23].

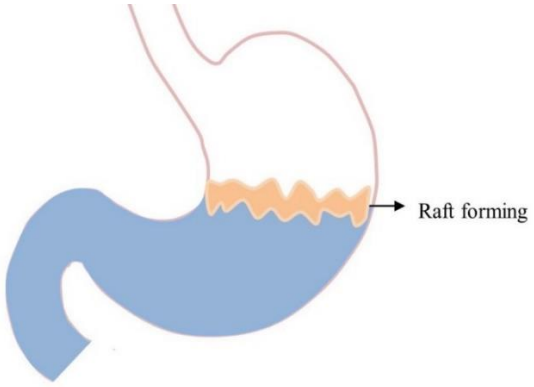

Fig.3: Schematic diagram of Raft formation using different polymers

4.1 Criteria for selection of polymers:

- Should ne non-toxic and biodegradable
- Should have optimum viscosity
- Should have ability to transforms into gel on getting in contact with gastric content

4.2 Polymers used in raft formation:

4.2.1 Alginic acid: Commonly used alginic acid is sodium alginate which is polysaccharide and hydrophilic also. It is found in marine algae and brown seaweed. Alginate salts and its derivates like sodium alginate, potassium alginate, calcium alginate is present. It is biocompatible and non-toxic. It has mucoadhesive properties and

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favourable biological properties also. It shows gelation property because of its arrangement of guluronic acid blocks of alginate chains. It is very commonly used and is slowly solubilize in water but in ethanol and chloroform, it is not soluble. Dilution of aqueous solution of alginate form gel due to adding of divalent and trivalent ions. The gel is formed with the help of a process having a sequence of glucuronic residues in an α-L-glucuronic acid blocks of an alginate chain. Complex formation occurs due to the addition of sodium citrate due to the reaction with free Ca^{2+} ions and then releases it in the stomach having high acidic environment [26–28].

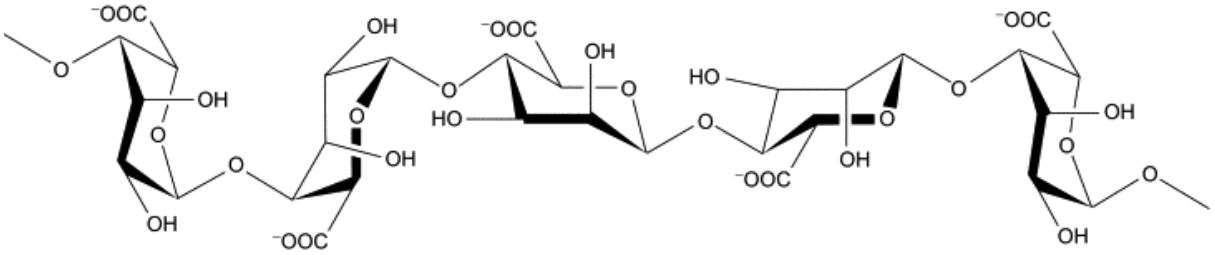

Fig.4: Chemical Structure of Alginic acid

4.2.2 Gellan gum: It is an anionic polysaccharide. It is biocompatible and has a long residence time. Gel formation is dependent on temperature and cations. Gelrite™ is commercially available gellan gum. The double-helical junction gives rise to the formation of the gel due to the formation of a complex three-dimensional network. The complex is formed with hydrogen bonding of cations with water. The formulation is orally administered when it contains a gellan solution with sodium citrate and calcium chloride. The gelation of the gellan gum is due to the acidic environment of the stomach which releases the calcium ions [29-30].

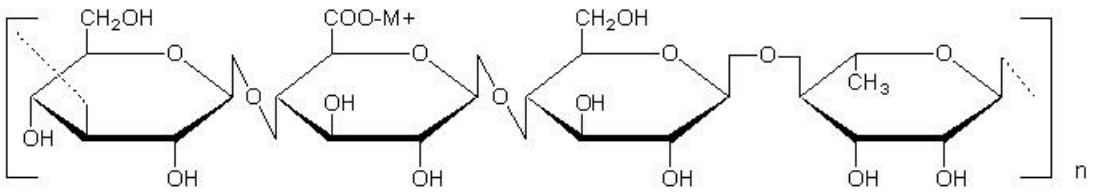

Fig.5: Chemical Structure of Gellan gum

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4.2.3 Chitosan: Chitosan is a natural polysaccharide. It is mainly derived from chitin. In neutral and alkaline solution, it is having low solubility. It is biocompatible and non-toxic. It is a cationic polymer and is dependent on pH. In aqueous solution up to pH 6.2, it kept on solubilized. But when the pH goes above 6.2 the hydrated gel-like precipitates form. The solution of pH-dependent polysaccharide directly gets converted into a pH-dependent gel-forming aqueous solution just by the accumulation of polyol salts like sorbitol, glycerol, fructose salts into an aqueous solution of chitosan. There is no chemical modification or cross-linking [31–33].

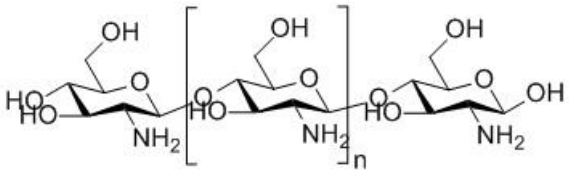

Fig.6: Chemical Structure of Chitosan

4.2.4 Carbopol: Carbopol is a polymer that is pH-dependent. As there is a change in pH, change in the state of Carbopol is observed. Solution form can be noticed at acidic pH and at alkaline pH the solution form gets changed into low viscous gel. To provide the viscosity to a Carbopol solution, it is always used in combination with HPMC. There are some water-soluble polymers of carbopol system. It is very helpful in increasing the mechanical strength of the polymer. Carbopol only confirms its solution to gel transition in aqueous solution when the pH of solution is above its pKa value which is 5.5 and before the phase transition of carbopol, an acidic ph is needed for its easy administration [34–36].

4.2.5 Pectin: Pectin is a second-most polymer used in raft formation. The cell wall of the plant is generally used to extract the pectin and also it is an anionic polysaccharide. In an aqueous solution, divalent ions are present which leads to the formation of a gel. Due to its ability to get solubilize in water organic solvents are not needed. Divalent cations are responsible for the conversion of pectin into the gel state in the stomach. Calcium ions are also required and are induced in the formulation to form a gel. To form the complex with

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calcium ions added, we can add sodium citrate. This complex formed gets broken in the stomach in an acidic environment [37-38].

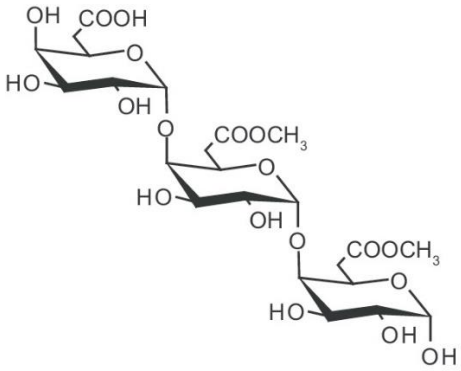

Fig.7: Chemical Structure of Pectin

4.3 Criteria for selection of drug:[24-25]

1. Drugs active locally in the stomach.
2. Drugs with low absorption in the gastrointestinal tract.
3. Drugs showing very low solubility at alkaline pH.
4. Drugs that remain unstable in the colon and disturb the normal colonic microbes.
5. Drugs getting rapidly absorbed from GIT.

4.4 Some of the drugs used in raft formation are:

4.4.1 Metronidazole: Metronidazole is used for treating H.pylori. It is also used to treat a variety of bacterial infections. Its activity does not depend on pH. Gastroretentive floating raft formulations can overcome the problems of bacterial resistance and other side effects associated with metronidazole. Youssef et al., 2015 prepared the raft formulation of metronidazole using sodium alginate as a polymer due to its high viscosity and stability. The formulation had an optimum viscosity for the easy swallowing of liquid solution and due to ionic interaction, it forms a gel in the stomach. The gel formed floats for a longer period of time and release the drug in a sustainable manner [39–42].

4.4.2 Gabapentin: It is an antiepileptic drug having a short half-life. Abouelatta et al., 2018 concluded that gabapentin is initially coated with Eudragit NE 30D, gellan gum, and LM pectin. Then to have various and different ratios of drug and polymer different

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formulations were prepared. The drug which was initially coated is then incorporated into the raft forming system. The polymer used in this formulation is helpful in maintaining the viscosity of the gel from its conversion from solution to gel form and maintain the controlled release for 12 hours of the drug and excellent floating nature of raft is observed [43].

4.4.3 Amoxicillin: Amoxicillin is an orally absorbed and semi-synthetic antibiotic. It is having a wide spectrum of activity. It is helpful treating H.pylori infection. Rajinikanth et al., 2007 prepared a raft formulation of amoxicillin using gellan gum as a polymer having high gelling property. The formulation was able to get convert into gel form once it gets in contact with gastric content in the stomach and amoxicillin floating gel releases the drug for at least 8hr. and is sustain release. And the formulation prepared was helpful in treating the infection at a dose level. The pattern of release of drug is biphasic and follows the diffusion mechanism. First, there is bursting of the drug from the formulation and initially the drug released at a faster rate and then afterward the drug starts releasing in a sustained manner. The drug released for 8 hours from the gel and treats the H.pylori infection [44-45].

5. Approaches of raft formation:

4.5 Physical mechanism-based raft formation:

4.5.1 Swelling: After absorbing water from the adjacent environment, a substance tends to expand up to the desired place. Swelling occurs due to the intake of the water which then again forms a gel. So, upon getting in contact with gastric fluid, an effervescent system gives rise to a gel [46].

4.5.2 Diffusion: Diffusion is a process in which there is the dispersion of liquid solvent out from the polymer solution into the surrounding tissue. The solvent then precipitates or solidifies the polymer matrix. The commonly used polymer solution is N-methyl pyrrolidone (NMP) for this approach [47-48].

4.6 Chemical mechanism-based raft formulation:

4.6.1 Ionic cross-linking: Some polymers in the presence of ions undertake a phase transition. Polymers like pectin, sodium alginate, gellan gum experience transition of the phase-in presence of k+, Ca+, Mg+, Na+ ions. Gelation of alginic acid occurs due to

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divalent/polyvalent cations such as Ca^{2+}because of its interface with the guluronic acid block in alginate chains. Gelrite®, a commercial form of gellan gum is an anionic polysaccharide that experiences gelation due to monovalent and divalent cations like K^{+}, $Ca^{2+,}$ Na^{+}. Pectin undergoes gelation due to divalent cations mainly Ca^{2+} [49].

4.6..2 Enzymatic cross-linking: Hydrogel delivery system that release insulin was studied. In response to blood glucose level cationic pH-sensitive polymers comprising of restrained insulin and glucose oxidase get swelled and started releasing captured insulin in pulsatile manner. An enzyme is responsible for governing the formation of gel which made it possible to inject the mixture before it gets converted into gel [50-51].

4.6.3 Photopolymerization: Monomer solutions like acrylate and polymerizable functional groups & initiators such as 2,2 dimethoxy-2-phenyl acetophenone, camphor Quinone. After getting vaccinated at the tissue site, electromagnetic radiation is used to form a gel. These are designed in such a manner that they get persevered for a longer time in-vivo or get degraded immediately by enzymatic or chemical degradation. Generally, UV and visible wavelengths are used [6].

4.7 Physiological stimuli mechanism-based raft formation:

4.7.1 pH-dependent gelling: Change in pH is also a factor that is responsible for the formation of the gel. The pH-dependent polymers like polyethylene glycol (PEG), polymethacrylic acid (PMA), carbopol change from solution form to gel form due to pH change. Due to an increase in outside or external pH, there is an increase in the swelling of the hydrogel in anionic group but the swelling of the hydrogel decreases in cationic group. The nature of polymers is neutral or ionic. The cationic system has positive moiety and anionic system ahs negative moiety. And the neutral system has both the moieties i.e. negatively charged and positively charged moiety. In sulphonic acid and carboxylic acid group having anionic system ionization took place because pKa of that particular ionizable moiety is less than the pH of an external swelling medium [52].

4.7.2 Temperature-dependent gelling: Usually, at room temperature hydrogels are in liquid state but due to an increase in temperature, after getting in contact with body fluids gelation occurs. They make use of the temperature-induced phase transition. Sometimes due to an increase in environmental temperature there is change in solubility manner. This

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is lower critical solution temperature (LCST). At the LCST, polymer-polymer & water-water interaction is more appreciable when compared to the hydrogen bonding between the polymer and water. A sudden transition can take place if the solvated macromolecule quickly gets dehydrated and deviates to a more hydrophobic assembly. And amphiphilic show micelle packing and gel formation because of polymer-polymer interactions due to temperature increase. The positive temperature-sensitive hydrogel is an upper critical solution temperature (UCST). These types of hydrogels get packed on getting temperature below or cooling below UCST. Polymeric systems of polyacrylic acid and polyacrylamide have a positive temperature-dependent swelling [53].

5. Applications:

1. Alginate rafts form a physical barrier on top of gastric content to protect it from reflux action. Gavison formulation was compared with alginate rafts and alginate raft was having better results like more raft strength and better buoyancy [54].
2. Clarithromycin raft formulation was prepared using gellan gum as a polymer. Various formulations were prepared and found that the formulation having a high concentration of calcium carbonate has low gelation time and the formulation with a low concentration of calcium carbonate has more gelation time [55].
3. The floating raft system of Mebeverine HCl using sodium alginate as a polymer was prepared. An increase in lipid polymer increases the floating ability. The cross-linking of the lipid further reduces the permeability and gelling property further increases the buoyancy [56].
4. Nizatidine raft formulation formulated of sodium alginate as a gelling agent, calcium carbonate used to make the raft firm and neutralizing effect and sodium bicarbonate as a gas generating agent and it showed the rapid onset of action indicating the lesser time required to obtain the highest concentration [57].
5. Gellan gum formulations exhibited promising potential for different modified release oral formulation, in situ ophthalmic and nasal mucoadhesive gel sprays, and a rapid permeation topical gel formulation [58].
6. A raft liquid delivery system using Gabapentin which is an anti-epileptic agent having a shorter half-life and narrow absorption window. Gellan gum and pectin were used as a

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polymer. Glyceryl monooleate was also added. It was found that the in-situ gel formed started floating immediately and this may be due to the addition of glyceryl monooleate as it forms a low dense mass because of its oily nature. This gel remained floating for more than 24hr [59].

7. The floating raft forming system for atenolol has been successfully developed with long buoyancy and controlled release profile from the hydrophilic matrices with better bioavailability for the treatment of hypertension. The system showed excellent floating properties coupled with extended drug release. The type and quantity of polymer played the main role in providing buoyancy and controlled release profile. As the concentration of polymer increases, lag time also increases. The best drug release profile was obtained for films based on gellan and xanthan gum combinations [60].

8. Metronidazole formulation of raft formulation of metronidazole and it was concluded that the drug is helpful in treating peptic ulcers by showing the results like increased gastric residence time and diffusion-controlled drug release mechanism. of metronidazole using sodium alginate as a polymer because of its high viscosity and stability. The formulation had an optimum viscosity for the easy swallowing of liquid solution and due to ionic interaction, it forms a gel in the stomach. The gel formed floats over the stomach for a longer time and slowly and steady release the drug in a sustainable manner.

Sr No.	**Method**	**Drug**	**Polymer**	**Reference**
1.	Solvent Casting Technique	Atenolol	Gellan gum, Xanthan gum	[58]
2.	Ionotropic Gelation Method	Lafutidine	Sodium alginate, HPMC K4M	[51]
3.	Floating hydrogel-based microsphere	Itopride hydrochloride	Alginate, HPMC	[61]
4.	In-situ gelling method	Metronidazole	Sodium alginate, Gellan gum	[39]
5.	In-situ gelling method	Amoxicillin	Gellan gum	[41]
6.	In-situ gelling method	Mebeverine HCl	Sodium Alginate	[62]

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6. Marketed formulations of raft formmulation

Formulation	Company	Active ingredient	Reference
Gaviscon	Glaxosmith kline, India	Magnesium hydroxide, Calcium carbonate	[1]
Topalkan	Pierre Fabre drug, France.	Aluminum and magnesium mixture.	[1]

7. Conclusion:

Due to incomplete drug release and short residence time, oral drug delivery has less bioavailability. So, the formulation of an effective dosage form that releases the drug at a target site and for prolong time is very challenging. Among the various approaches, the floating system is very promising which has longer residence time. Raft floating system is very effective as it is helpful in increasing the bioavailability. Polymers are selected very carefully for raft formation as it is responsible for maintaining the viscosity of the formulation. Various researches have been done using different types of polymers. Drugs having high solubility and stability problems are difficult to formulate in raft formation. Raft formation is very effective for increasing bioavailability.

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