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RECENT ADVANCES IN THE DEVELOPMENT OF FLOATING MICROSPHERES FOR THE TREATMENT OF GASTRIC ULCERS

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ABSTRACT:- Peptic ulcer disease (PUD) constitutes a multifactorial and intricate pathology resulting from a dysregulation between protective and aggressive determinants (both endogenous and exogenous). Notwithstanding recent advancements, it continues to account for considerable morbidity and precipitating clinical challenges. In India The point prevalence of peptic ulcers was recorded at 4.72%, while the lifetime prevalence was documented at 11.22%. Gastroretentive Drug Delivery Systems (GRDDS) represent sophisticated pharmaceutical formulations engineered to prolong the duration a drug remains within the gastric environment, thereby augmenting its therapeutic effectiveness and bioavailability. Such systems are especially advantageous for compounds that exhibit suboptimal absorption in the distal gastrointestinal region or necessitate extended gastric retention to achieve maximal therapeutic impact.The bioavailability of gastroretentive floating microspheres that are sufficient buoyancy to float over gastric contents and remain in stomach due to low density systems that's why drug release is enhanced in the plasma drug concentration.Floating microsphere are solvent-evaporation method in that solvent – polymer ratio combination those characterizations of particle size analysis ,drug entrapment efficiency,scanning electron microscopy ,in-vitro release release,In- vitro buoyancy ,stability studies which shows better absorption ,increase the bioavailability and sustained release in the stomach.special categories of proton pump inhibitors ,antacids,antidiabetic,anti-fungal,anti-ulcer formulated into floating drug delivery system. These systems additionally offer significant prospects in the formulation of novel controlled and delayed release oral preparations, thereby pushing the boundaries of advanced pharmaceutical innovation.In that review pathophysiology of gastric ulcers , gastro retentive floating system approach ,advantages of preparation methods of floating microsphere,application are discussed.

KEYWORDS:-PEPTIC ULCERS.GASTRO RETENTIVE DRUG DELIVERY SYSTEM,FLOATING MICROSPHERE,IN -VITRO BUOYANCY.

INTRODUCTION :- The management of gastric ulcers has undergone considerable progress with the advent of floating microspheres, a unique category of gastro-retentive drug delivery systems (FDDS). These systems are engineered to prolong the gastric residence time of pharmaceutical agents, thereby enhancing their bioavailability and therapeutic effectiveness. Floating microspheres, distinguished by their low density and buoyant characteristics, can remain suspended within gastric contents for prolonged durations, which is essential for medications necessitating sustained release within the stomach to attain optimal therapeutic concentrations [1-3] [8]. Recent advancements in the formulation of these microspheres, notably via the emulsion-solvent diffusion technique, have facilitated the production of hollow microspheres capable of effectively encapsulating drugs, thus ensuring controlled and extended release [9]. Furthermore, the incorporation of hydrodynamic balance systems (HBS) and polymeric bioadhesive systems has significantly improved the retention capabilities of floating microspheres, effectively addressing issues associated with the variability of gastric emptying [4-7]. These innovations not only enhance patient adherence by minimizing dosing frequency but also promote superior therapeutic outcomes for drugs characterized by short half-lives [10]. The non-effervescent methodology employed in these systems facilitates a gradual medication release, which is particularly advantageous in sustaining therapeutic levels for the treatment of gastric ulcers [10]. Moreover, the capacity of these microspheres to remain buoyant over acidic media for extended periods, as evidenced by in vitro studies, accentuates their potential efficacy in maintaining drug availability in the stomach [11]. The characterization of drug release kinetics from these microspheres is crucial for comprehending their efficacy, as fluctuations in polymer concentration can profoundly impact release profiles [11]. In conclusion, the recent progress in the formulation of floating microspheres for gastric ulcer therapy underscores a comprehensive approach that merges inventive formulation methodologies with an intricate understanding of gastric physiology. This review intends to aggregate and analyze these advancements, concentrating on the mechanisms of flotation, the contributions of various delivery systems, and the ramifications for enhanced therapeutic strategies in the management of gastric ulcers [12] Peptic ulcer is a acid – peptic disease characterization of discontinuation in the inner lining of the gastrointestinal tract because of gastric acid secretion or pepsin.it usually occurs in the stomach and proximal duodenum less commonly,it occurs in the lower esophagus in the distal duodenum or in the jejunum as it can opposed hypersecretory states such as zollinger -ellison syndrome in ectopic gastric mucosa [13-20].

PATHOGENESIS OF PEPTIC ULCER :- The pathogenesis of peptic ulcers involves the paracrine binding of histamine to H2 receptors in parietal cells, which is initiated by histamine release from gastric acid (HCl). Gastrin is primarily produced in the antral G cells. The release of gastrin is regulated by central neural influences, the chemical composition of gastric content, and local distension. The release of histamine from mast cells and ECL cells from the effect of gastrin . This process elevates intracellular calcium levels through cyclic AMP and acetylcholine/gastrin, leading to increased acid secretion. The final stage of acid secretion is stimulated by H+/K+ ATPase, commonly referred to as the gastric proton pump. The pathophysiology of peptic ulcers involves the activation of cAMP or calcium ion-dependent pathways, as well as the activation of H+/K+ ATPase in parietal cells (**21**). The three proposition secretion is recommended to be stimulated secretagogues histamine , acetylcholine and gastrin for acid secretion. Histamine is unleashed from specialized mast cells because the receptors on the surface of the parietal cells include H2 receptors . The unleashed of histamine of Ecl cells due to the muscarinic gastric acid secretion **(22).**The main mechanism of NSAIDS inhibition of expected (cox -1),that's why reduced mucosal blood flow, responsible for prostaglandin synthesis ,the conc regimen of external cox -2 selective nsaids reduce mucosal damage and risk of ulcer **(23).**

ETIOLOGY OF PEPTIC ULCER [24-34] :-

DEFINITION:- peptic ulcer disease occurs mucosal break of the upper gastrointestinal tract due to acid peptic

digestion most commonly occurs in the stomach first part of small intestine (duodenum) and jejunum. The etiology of PUD involves several factors that contribute to the development of these ulcers:-

HELICOBACTER PYLORI INFECTION :- The most significant cause of peptic ulcer is with the bacterium helicobacter pylori affecting approximately 42% of patients .This bacterium can damage the protective lining of stomach and duodenum and is often associated with chronic gastritis and significant risk factors for developing ulcers.

NSAIDS:-The use of NSAIDS such as ibuprofen ,aspirin is another significant contributor to the development of peptic ulcer .These medication can inhibit the production of prostaglandins which helps the maintaining the protective mucosal lining of the stomach when this lining is compromised it can lead ulceration and more susceptible to damage from gastric acid .

ANATOMIC PREDISPOSITION:- The study indicates that in a despite of a full stomach any individuals who can change their body position left or right side after meals that can affect blood flow of crucial areas enhance the risk of ulcers .

ISCHEMIA AND ULCER FORMATION :-It can lead to tissue damage due to reduced blood flow ,this research significance in certain body positions can cause local ischemia due to the repeated occlusions of blood vessels ,that's why enlargement of peptic ulcers .

PSYCHOSOMATIC ULCERS :-The theory emphasizes accentuates chronic stones and emotional issues can decompose working of the nervous system causing ulcers. This discompose can be distinct as enlarged acid products and difference in stomach lining.

OTHERS FACTORS:-Additional factors that may provide the pathogenesis of peptic ulcers included the smoking ,stress ,Excessive alcohol consumption ,unhealthy lifestyle choice, caffeine intake use of analgesics .They can aggravate the condition of healing .

CONCLUSION:-The etiology of peptic ulcer disease is a multifactorial, combination of infectious agents NSAIDS,anatomic predispositions ,ischemia, ulcer formation ,psychosomatic ulcers, addressing these elements holistically can lead to more effective prevention and treatment strategies for individuals at risk of developing peptic ulcer disease .

PATHOPHYSIOLOGY OF PEPTIC ULCER: The Term peptic assumed from the hormone Pepsin that's responsible key role of breakdown of mucosal lining [41].According to the data in the global population 10% are affected chronic condition for the patient of peptic ulcer [38],[41],[46],[47].The three phases of development of peptic ulcers are Early phase, intermediate phase, Late phase.In that early phase physiological changes are occurred, Intermediate phase gastric acid secretion ,In that late phase effects of gastric acid for that the ulcer formation [8].In the most of the cases peptic ulcer formation the significant role is Helicobater pylori [35-45].Range of that 0.12%-1.5 % are primarily caused due to the H.pylori infection[52] and also H.pylori negative ulcers are the 12% -20% patient for structure within the ulcer scars [58].The factors are included Pathogenesis of peptic ulcer bacterial infection certain medication lifestyle factors such as stress smoking there is a cause of ulcer formation[45-55].There are four different factors are the cause of pathogenesis of peptic ulcers aggressive factors (like acid secretion and peptic activity),Defensive factors of the gastric mucosa ,influenced by both endogenous factors (such as bile secretion),and endogenous factors such as bile secretion),and exogenous factors (including H.pylori infection ,Non steroidal anti inflammatory drugs, and the effects of hyperplasia and hypertrophy gastrin and Parietal cells due to the chronic stress that's why development of duodenal ulcers[44],[41].

Three major hypothesis the hyperactivity hypothesis, which involves disturbance in gastric acids ,histamine, gastrin, somatostatin the eicosanoid imbalance hypothesis,which focuses on changes in microcirculation due to the balance between vasoconstrictor eicosanoid like TXA2 and vasodilator cytoprotectant eicosanoids such as

PGE2 and infective hypothesis,which identifies as a significant pathogenic factor of ulceration [56].

Quality of ulcer healing is compromised due to incomplete regeneration of mucosal and submucosal structures with in ulcer scars ,leading to immature distorted tissue architecture.This poor QUOH is associated with the persistence of macrophages in the regenerated area which when activated by inflammation ,cytokines,attract neutrophils that release proteolytic enzymes ultimately resulting in ulcer formation [57].

The pathophysiology of peptic ulcer disease involves a complex interplay of neurogenic and genetic factors where the chronicity of ulcers is attributed to the combination of neurogenic influences and genetically modified reactivity of the gastroduodenal systems[58].

GASTRORETENTIVE DRUG DELIVERY SYSTEM AGAINST H.PYLORI INFECTION :

Recent advancement of floating microspheres in the gastro retentive drug delivery system playing vital role in the H,pylori infection for get cure of duodenal ulcers [62].Gastro Retentive drug delivery system can enhance drug retention time,improve bioavailability for drugs for poor solubility and low intestinal stability [59-62].To increase the capabilities of swelling and floating in the medications and absorbed in the stomach and also upper small intestine gastro retentive drug delivery systems design strategies for both single unit floating and multiple unit floating systems[63].The strategies of gastro retentive drug delivery system enhancing the therapeutic efficacy and bioavailability that have narrow absorption window in the upper gastrointestinal tract .The significance of swellable and floating systems the strategies such as hydrophilic polymers gas generating agents and superporous hydrogels.It also address the treating conditions of gastroesophageal reflux disease an peptic ulcer and also future trends in the field.

FLOATING DRUG DELIVERY SYSTEM:-The gastro retentive mechanism action of floating drug delivery system for extended period enhances the solubility and continuous release of active medication .This systems also work on developed the absorption and therapeutic effects .These system can also generated hydrophilic polymer that can float in the gastric fluid to get better sustained release and also improved the dissolution[65,66]

The application of floating drug delivery systems localized drug action such as Gastroesophageal reflux disease by maintaining drug in the stomach for sustained release and also beneficial the drugs having short half lifes and also poorly soluble drugs get optimized therapeutic outcomes [64].

(i)Hydrodynamically balanced systems:-

Hydrodynamically balanced systems release of drug in a controlled manner .There is a mechanism in this system also that low density systems that are the float in the gastric fluid and also higher density systems also can bottom of the stomach [67].The release mechanism are depends on the mechanism of diffusion that can throughout the hydrogel in the uniformity dispersed manner[68]

The components of the spheronization agents that can be highly porous matrix there can include a gas generating agent ,drug and sugar that can float in the gastric environment to get extended release of the drug [69].

(ii)GAS GENERATING AGENTS:- To increase the buoyant time in the stomach the significance role of gas generating system are plays a significant role in the floating drug delivery system.These systems also include the effervescent agents like sodium bicarbonate and citric acid that can also increase the buoyancy in the mechanism of that can react to gastric fluids to get produce carbon dioxide that can also help to float time and also increase the buoyancy .

the formulations overall design and also composition of effervescents agents to achieve the desired drug

concentration in blood or tissues,there by the improving the bioavailability of the drug that can help to get a optimal performance{70,71,72}

(iii)RAFT FORMING SYSTEMS:- Raft forming systems to create that the stable gastric residence time the agents are involved tragacanth gum,guar gum,xanthan gum,combined with the sodium alginate to create a prolong and predictable drug delivery system with in the gastrointestinal tract particularly in the stomach and intestine [73,74].In compared to the other methods the raft forming systems increased the bioavailability and also ensure the sustained drug release [75].These system also can enhance the bioavailability that are less soluble in high ph environment[76].

(iv)Mucoadhesive drug delivery system :-In the treatment of gastric ulcer there is a effective role plays a as a drug delivery system is a mucoadhesive due to be the also increased the drug bioavailability [79].These system prolonged the drug remain buoyant in gastric fluid due to the floating mechanism[9].These systems enhances the therapeutic effectiveness of drug due to the interact with the mucus layer on the mucosal epithelial surfaces that's why prolonged retention of the dosage form at the absorption site,that's why beneficial for the mucoadhesive drug delivery system[77].These systems specifically effective to the acidic environment of the gi tract due to the increased the gastric residence time that's why enhance the bioavailability and also therapeutic outcomes so effective in the gastric treatment [78].These systems also works on increased the residence time and also specifically increased the bioavailability that's why beneficial for the treatment of gastric ulcer[90].

MICRO SPHERES:-Microspheres are the spherical in shape the size are to be the 1 mm to 1000 mm in size made with the biodegradable protein and also the synthetic use of polymer plays a crucial role to a controlled release and to be a sustained release in the formulation dosage form[81].Microspheres are the two types of microspheres in that the microparticles and the microcapsules in a capsule wall the the systems are reservoir that's why microspheres distributed throughout the matrix [83,84].Microspheres are the different types that are to be bioadhesive microsphere ,magnetic microspheres ,biodegradable polymeric microspheres,to the enhance the bioavailability and controlled drug release [85].in that the biodegradable and bioadhesive to get a encapsulation to gets control over the drug release microspheres get a therapeutic substance[82].The methods are used in the microspheres solvent evaporation methods, ionotropic gelation methods,emulsion solvent diffusion methods,single emulsion technique ,double emulsion technique,polymerization techniques and the phase separation techniques [85].The characteristics of that the material ,methods and the techniques that are also useful to that the better therapeutic efficacy of microspheres[86].

Floating microspheres :-Floating microspheres are useful to get a reduce acid secretion of stomach to maintain a levels of gastric environment , to get increased the bioavailability ,increased the solubility that the reduce the patient compliance to get a better treatment of peptic ulcer[87].Floating microsphere are that the adjust the ph,also be a increased the gastric residence time ,increased the efficacy of drug absorption floating upper small intestine for get a better treatment of peptic ulcer [89}.Floating microspheres are mechanism of the polymer of a low density and low solubility that's are in the acidic environment of the gastric fluid increased the buoyancy that's why increased the gastric residence time and also controlled release of floating microspheres use as antibiotics ,nsaids,proton pump inhibitors [90].Floating microspheres are useful to get a less patient compliance and also that the decreased the dosing frequency to get a effective in a low solubility and the drugs are to be short half life so that the useful in that the floating microspheres to get a sustained drug action[91].Floating microsphere are to get a increased that the therapeutic efficacy and the increased the narrow absorption window, to get a polymer used Hpmc,Ec 100,and also the solubility and the bioavailability to get acid labile drugs[92].Floating microspheres are treatment of that reduce the antibiotic resistance to get a treatment of peptic ulcer so that the increased the limitation of the convenient dosage form to get a exterminating the H.pylori in bacteria[88].

ADVANTAGES OF FLOATING MICROSPHERES:- Floating microsphere are that used to that the increased the gastric residence time so that the more effective in the narrow absorption window ,so that the drug action are to be the more targeted way in that's way more effective in the treatment of peptic ulcer[93],[94].Floating microsphere are that the increase the bioavailability and also be the effective in the drug release time in a

controlled manner that's why for effective in the treatment of duodenal ulcer[94]. Floating microspheres that can be used as a various formulation in that the floating formulation films ,capsules ,less side effects and also prolong the drug actions and also less frequent dosing get easier to maintain a specific area of treatment(95). Floating microsphere acts as a various methods in that the single emulsion,double emulsion ,solvent evaporation methods according to that most effective way to get the solvent evaporation methods works on a effective manner that's why slow release of drug,increase the bioavailability to get better treatment of peptic ulcer [96]. Floating microspheres are useful to get those drugs are the less half lives are more effective to get a controlled release of drug in an effective manner to get better therapeutic outcomes for better results in the peptic ulcer treatment[97].

Mechanism actions of floating microspheres:- Floating microspheres are the best cure of peptic ulcer due to the mechanism of action in the extended release of drug in the upper area of stomach in the gi fluid for get better drug release and the remain buoyancy time in th egi fluid for get better action and also increased the half life of the therapeutic efficacy for the reduce the adverse effects and less patient compliance [98],[101].The preparation of floating microspheres are the like the drug have chosen proton pump inhibitors like rabeprazole,pantoprazole,ranitidine,famotidine and the polymer also ethyl cellulose and hpmc and the method is solvent evaporation method for get better outcomes of the treatment of peptic ulcer[98],[100].These kind of polymers are used to get a better for sustained and extended release of drugs and also for a better narrow absorption window for get better treatment of peptic ulcer [98],[99].Overall floating microsphere extended and also increased half life and also buoyancy time of stomach gi fluid for get better treatment of peptic ulcer [102],[103].

Methods of floating microspheres:-

Single Emulsion Technique :- Single emulsion technique one of the best methods to get preparation of floating in that the aqueous environment solubilized are the natural polymers like alginate,gelatin ,chitosan,xanthan gum acacia in that creates non aqueous medium for that in a dispersion in a oil phase.These steps are crosslinked two distinct methodologies :-

Cross linking by heat :-Unsuitable for the thermolabile drugs that's are erythromycin,cephalosporins,penicillin by adding dispersion into heated oil.

Chemical cross linking agents:-In that preparation time the active ingredients to chemicals are the formaldehyde,glutaraldehyde,diacid chloride added in the preparation that get the next process centrifugation ,washing and separation.

Double emulsion Techniques :-Double emulsion techniques are one of the best methods of preparation of floating microspheres there after aqueous solution of polyvinyl alcohol pour into a W/O emulsion to get an W/O/W that can be done after that 30 min of contain was stirring microcapsule formation are done then filtered and collected and then dried in a vacuum .The natural polymers are that the chitosan,alginate ,gelatin ,starch are used.Semisynthetic polymers are the hydroxypropyl methyl cellulose,methyl cellulose,ethyl cellulose are used in that the technique for get better preparation of floating microspheres dispersion with in in the oil /organic phase is accomplished via homogenization of vigorous mixing,resulting in the creation of the initial emulsion which is subsequently integrated with the aqueous PVA of a multiple emulsion.

Spray Drying and spray congealing methods :- In that the process microspheres ranges are the ranges 1- 100 mium for that the drug in the amorphous state to the crystalline state in the polymer solution are in the homogenization because polymer are dissolved in that the other organic solvent of dichloromethane ,ethanol after that the microsphere formation are done after vacuum drying are the method are done.

Ionic gelation :-In that the techniques the electrostatic interactions of the nanoparticles and microparticles in specific conditions.At Least one polymer is required.

List of Drugs used as Anti-ulcer activity in the form of floating microsphere:-

SL NO	DRUG	METHOD	CARRIER	DISEASE	REFERENCE
1.	NIZATIDINE	SOLVENT EVAPORATION	FLOATING MICROSPHERE	GASTRIC ULCER	108
2	METRONIDAZOLE BENZOATE	OIL IN WATER EMULSION	FLOATING MICROSPHERE	GASTRIC ULCER	109
3	LAFUTIDINE	SOLVENT EVAPORATION	FLOATING MICROSPHERE	GASTRIC ULCER	110
4	ESOMEPRAZOLDE	NON AQUEOUS SOLVENT EVAPORATION	MICROSPHERE	GASTRIC ULCER	111
5	FAMOTIDINE	SOLVENT EVAPORATION	FLOATING MICROSPHERE	GASTRORETENTIVE	112
6	ROXATIDINE	ION TROPIC GELATION	MICROSPHERE	GASTRIC ULCER	113
7	CIMETIDINE	GASTRO RETENTION	FLOATING MICROSPHERE	GASTRIC ULCER	114

APPLICATIONS OF FLOATING MICROSPHERES :-Floating microsphere are that the increased that the gastric residence time and also stomach specific drug delivery system to get that the increased the bioavailability to get slow release of drug for get better treatment of gastric ulcer [115]Those drugs are such like famotidine ,ranitidine ,pantoprazole,rabeprazole,these kind of drugs are used to that the increased the half life of drugs ,increased therapeutic efficacy for get better treatment of peptic ulcer [116] [117].Floating microsphere are that the improved the narrow absorption window for the drug improved the bioavailability for get less the patient compliance so get better treatment of that the peptic ulcer [118].

CONCLUSIONS :- The comprehensive review of more than a 119 references that also defines that the various technologies of that the formulations of floating microsphere for the treatment of gastric ulcer .The method of preparation of floating microsphere and the drug to polymer ratios ,the preparation techniques, stirring speed ,the angle of dropwise added to the solvent in the surfactant these can improve the size,shape of floating microsphere, enhance the floating buoyancy ,increased the narrow absorption window ,also enhanced the therapeutic efficacy,reduce the patient compliance that can help to that the improved the better treatment of peptic ulcer treatment.

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