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# Formulation and Biopharmaceutical Evaluation of Gastro - Retentive Drug Delivery System of Anti -Ulcer Drugs (A Review)

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**ABSTRACT**

The floating drug delivery system or hydro dynamically balanced systems are among the several approaches that have been made developed in order to increase the gastric transit time of drug. The micro spheres are characteristically free flowing powders consisting of natural or synthetic polymers and ideally having a particle size lessthan200m.Microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of.Floating micro spheres to improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved. Enhanced absorption of drugs which solubilise only in stomach, Gastric retention time is increased because of buoyancy. Floating micro spheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. In the present review preparation, methods, characterization, advantages, mechanism of drug release from micro spheres, list of polymers, applications and list of the drugs formulated as floating micro spheres are discussed.

Famotidine is H2 receptor antagonist which is used for ulcers thus by formulating it in the form of floting microspheres it will not only shown targeted action but also shows sustainability and reduced dosing interval.Thus by formulating it as a floating microsphers the targeted action can be achieved. Famotidine is formulated as floating microsphers by Solvent evaporation method is the preparation technique that is widely preferred for the preparation of controlled release microspheres. To prepare emulsion by adding the dispersed phase consisting of drug, polymer and appropriate dispersion agent in organic solvent to dispersion medium which is immiscible with the dispersed phase and minimatrix forms are obtained by removing the solvent used at the dispersed phase from the droplets which are formed in the emulsion[5, 6].The obtained microsphers of famotidine were subjected to various analytical techniques like Particle size analysis, SEM analysis, invitro dissolution studies and stability studies.

**Keywords:** Floating micro spheres, Gastro Retention, Short half-life, Solvent diffusion.

## I. INTRODUCTION:

Oral drug delivery system is the most preferable system because of ease in administration, patient compliance and flexibility. To develop an oral drug delivery system, it is necessary to optimize both the residence time of system within the gastrointestinal tract and release of drugs from the system. Drugs that are easily absorbed from the gastrointestinal tract and have short half life are eliminated quickly from the blood circulation and require frequent dosing. To avoid these problems, the oral controlled release formulations have been developed in attempt to release the drug slowly into the gastrointestinal tract and maintain the constant drug concentration[1].

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery system. This drug delivery systems have a bulk density less than that of gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.[2] The gastroretentive drug delivery system (GRDDS) is of special interest in improving the bioavailability of drugs that are poorly soluble, unstable at higher intestinal $p^H$ or colonic environment and having absorption window in stomach[3].

Floating microspheres (Hollow Microspheres) are gastroretentive drug delivery systems based on non effervescent approach. Hollow microspheres are in strict sense, spherical

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empty particles without core, free flowing powders consisting of proteins or synthetic polymers, ideally having a size in the range 1-1000 micrometer. When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content is needed to allow proper achievement of buoyancy[4].

Peptic ulcer is a break in the inner lining of the esophagus, stomach, or duodenum. A peptic ulcer of the stomach is called a gastric ulcer. Acetylcholine and histamine is responsible for development of peptic ulcer leads to decrease in pH[5].

Drugs used in treatment of peptic ulcers are mainly classified into three categories:

1. Antacids
2. Anticholinergics
3. $H_2$ receptor antagonists[6].

The Aim of the present study is to formulate and evaluate Famotidine floating microspheres in a cost effective and simple technique.Famotidine is H2 receptor antagonist which is used for ulcers thus by formulating it in the form of floting microspheres it will not only shown targeted action but also shows sustainability and reduced dosing interval.Thus by formulating it as a floating microsphers the targeted action can be achieved,absorption of the drug can be monitored and increased thus showing effective absorption and better bioavailability, Thus showing effective action.

- **Peptic Ulcer**

Peptic ulcer constitutes a large scale problem in hyperacidity patients, which is due to infection of stomach or duodenal mucosal lining of the GIT. In the any part of the GIT peptic ulcer occurs which is discovered to pepsin and gastric acid i.e. the duodenum and stomach [12]. Generally acid secretion is nature in gastric ulcer. Acid secretion is large in divided of the patients in duodenal ulcer but normal in the rest. Acid build-up are either normal or even high, though it contributes to the ulcers, an invasive component whose contraction is the main method of ulcers treatment. An understanding of regulation of acid secretion and the mechanism will elucidate the targets of anti-secretory action as shown in Fig. 1 [13-15].

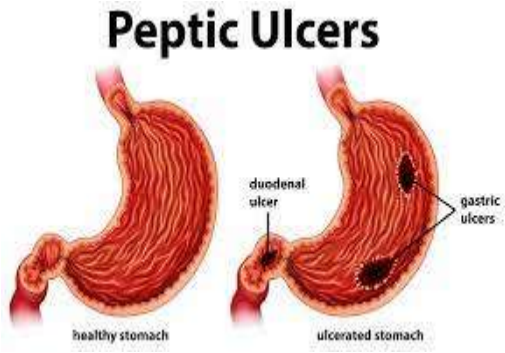


Fig. 1

- **Pathogenesis of Peptic Ulcer**

By H. pylori approximately half population of the world's is colonized, which ruins most important reason of peptic ulcers [16]. In developing countries, the occurrence of H. pylori is higher, especially in Central Asia, Africa, Eastern Europe and Central America [17]. In a free and crowded environment, this organism is cultivated in childhood and in countries where the socioeconomic conditions are low. By H. pylori epithelial cell degeneration and injury caused which is usually more severe in the antrum, by plasma cells, neutrophils, macrophages and lymphocytes accompanied by inflammatory response. The mechanism of development of various types of lesions induced by H. pylori in the gastro duodenal mucosa has not been fully explained. H. pylori infection can outcome in hyper chlorhydria. The main mediators of H. pylori infection is the cytokines that inhibit parietal cell secretion, but the activate calcitonin gene-related peptide (CGRP) can directly affected by H.pylori, sensory neurons are linked with somatostatin, H+/K+ ATPase α-subunit, and the production of gastric inhibited[18].

Different classes of drugs their mechanism of action with adverse effects are listed in table 1 [19-31] and Therapy combination type and efficiency of Helicobacter pylori elimination treatment options are listed in table 2 [32-37].

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Table 1. Mechanisms of action and adverse effects of the most commonly used Anti-ulcer treatment option

| Class of Drugs | Medicine | Mechanism of action | Adverse effect | Reference |
|---|---|---|---|---|
| Proton pump inhibitor | Omeprazole Lansoprazole Rabeprazole Esomeprazole Pantaprazole | Inhibition of the gastric H+/K+-ATPase (proton pump) enzyme system | Abdominal pain Diarrhea Nausea Vomiting Constipation Flatulence Vitamin B12 deficiency Osteoporosis | 32,33 |
| H2 Receptor Blockers | Cimetidine Famotidine Nizatidine Ranitidine | Blocking the action of histamine at the histamine H2 receptors of parietal cells | Headache Anxiety Depression Dizziness Cardiovascular events Thrombocytopenia | 34 |
| Antacids | Aluminum hydroxide Magnesium hydroxide | Increases gastric pH to greater than four, and inhibits the proteolytic activity of pepsin causes osmotic retention fluid | Frequency not defined: Nausea Vomiting Hypo phosphatemia Chalky taste Constipation Abdominal cramping Diarrhea Electrolyte imbalance | 35 |
| Potassium-Competitive Acid Blocker | Vonoprazan Misoprostol Sucralfate | Inhibits H+, K+-ATPase in gastric parietal cells at the final stage of the acid secretory pathway Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract | Nasopharyngitis Fall Contusion Diarrhea Upper respiratory tract inflammation Eczema Constipation Back pain Diarrhea Abdominal pain Headache Constipation | 36-42 |
| cyto protective Agents | | | | |

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Table 2. Types and efficiency of Helicobacter pylori (H. pylori) eradication treatment options

| Type | Duration | Efficiency | Reference |
|---|---|---|---|
| First line Standard triple therapy: PPI + two antibiotics (clarithromycin + metronidazole or amoxicillin | 7–14 days | 70-85 % | 43 |
| Second line Bismuth- containing quadruple therapy: PPI + bismuth salt + tetracycline +metronidazole Non-bismuth based concomitant therapy: PPI + clarithromycin + amoxicillin + metronidazole Levofloxacin triple therapy: PPI + amoxicillin + levofloxacin | 14 days<br>14 days<br>14 days | 77-93%<br>75-90 %<br>74-81 % | 44, 45 |
| Salvage regimens Rifabutin-based triple therapy: PPI + rifabutin + amoxicillin | 10 days | 60-70 % | 46 |

- **Gastro-retentive Drug Delivery Systems/ Gastro-retentive Dosage Forms (GRDF's)**

It has become clear from scientific and certification literature that the stomachs are becoming more interested in today's time. Educational and commercial research today has a long and sustained period [38, 39]. To get a long and predictable drug delivery plane in a GI system, running time of gastric habitation could be the most possible. Gastro retentive dosage form will award us with new and significant therapeutic options (Fig. 2).

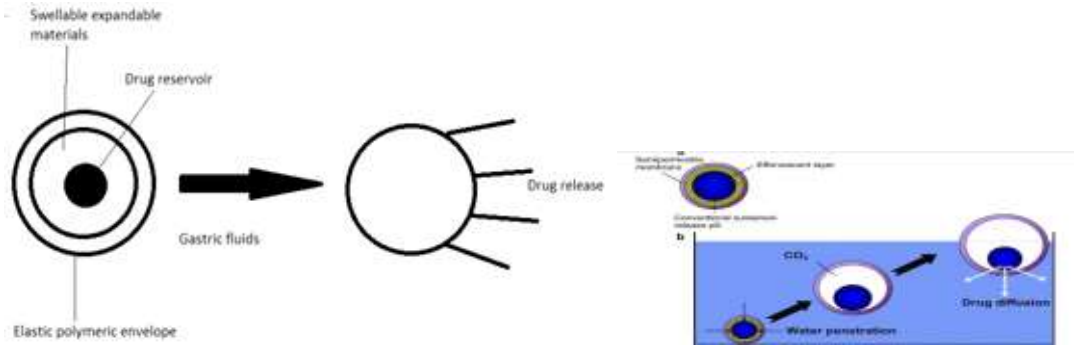


Figure 2. Gastro retentive drug delivery system

Therefore, GI method offers can have control over the placement of DDS in specific area, particularly as an absorption window in GI method for drug demonstration [40,41]. An intimate touch of DDS with the sucking interment and capable of more absorption of drugs has

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affected the rate of soaking the opinions, thus increasing the ability of oral controlled gastric perception. In these drugs, the gastro-intestinal system cannot be kept in equal proportion for the length of the gastro-intestinal system, because the dosage forms can be drawn from dry upper areas generally irregular and incompetent. In addition, some of the drugs are absorption from the upper point of small gut or belly [42]. The rate of drug absorption may not be regular even after taking this drug at regular rate to gastrointestinal fluid. The drug is sucked up only from distinct areas of the stomach or upper areas of the small gut in case when the drug has an apparent cut. Soaking window in the nearby intestine can bound the bioavailability of verbally governed modulates and can be a main difficulty to the progress of CDDS [43]. It is clean that for a drug having such an absorption window an emphatic oral restrained drug delivery system should be designed not only to convey the drug at a controlled rate but also to prevent the drug in the upper areas of the gastrointestinal system for a long duration of time. The actual problem of controlling the dosage form for the control of the dosage form is not only to increase delivery for 12 hours but also to prolong the dosage form in the upper area of the abdomen or intestine of breath. Requirement of gastro retention of dosage forms also stands up because of other causes in addition to these which are referred earlier in disadvantages of traditional oral controlled drug delivery system (OCDDS). To renovate bioavailability of drugs such as Cefuroxime, Ciprofloxacin, Cyclosporine etc. which are principally absorbed from upper area of GIT [44].

- **Advantages of gastro retentive systems**

Gastro retentive dosage forms change profitably the absorption outline of deadfall agent, so improving its bioavailability after instance a valuable increase in the bioavailability of furosemide from a floating dosage shape (42.9%) has been reported matched with commercially existing tablets (Lasix 33.4%) and intestinal products (29.5%) GRDFS most repairs pharmacotherapy of the abdomen via local medicine discharge leading to high drug concentrations of stomachic mucosa build up doable to cure belly and duodenal ulcers, gastritis, and esophagi is detect the hazards of carcinoma and manage non- systemic, controlled release antacid phasing (calcium carbonate).GRDFs can be used as takes away for drug with a called soaking window, these materials for instance antiviral, antifungal and antibiotics brokers (sulphonamides, Quinilones, Penicillin's, Cephalosporins, Aminoglycosides and Tetracyclines etc.) are taken up only from very unusual sites of the GI mucosa [45-49].

- **Disadvantages of gastro retentive systems**

There are fixed circumstances where gastric retention is not pleasing. Aspirin and non-steroidal anti-inflammatory drug are known to reason gastric injuries and gently release of such drugs in the belly is unwanted therefore drugs that may irritate the stomach line or are unsteady in the acerb atmosphere should not be formulated in gastro retentive methods. Even further drugs such as Isosorbide dinitrate, that are sucked up equivalently well throughout the GI system will not advantage from illation into a gastric retention system. Also DRDFs have some ledges such as. Necessities of high scale of liquids in belly for the delivery system to float and work proficiently. Requirements the attendance of food to hold of gastric emptying. Drugs having solubility or durability problems in the highly gastric atmosphere or which are irritants to gastric mucosa cannot be formulated as GRDDs. In case of bioadhesive systems the acidic environment dense [50-55].

- **Floating System Approach of Gastric Retention**

A number of strategies were used to develop gastric retention of a dosage form are shown in fig. 3 by using a variety of concepts. These approaches are:

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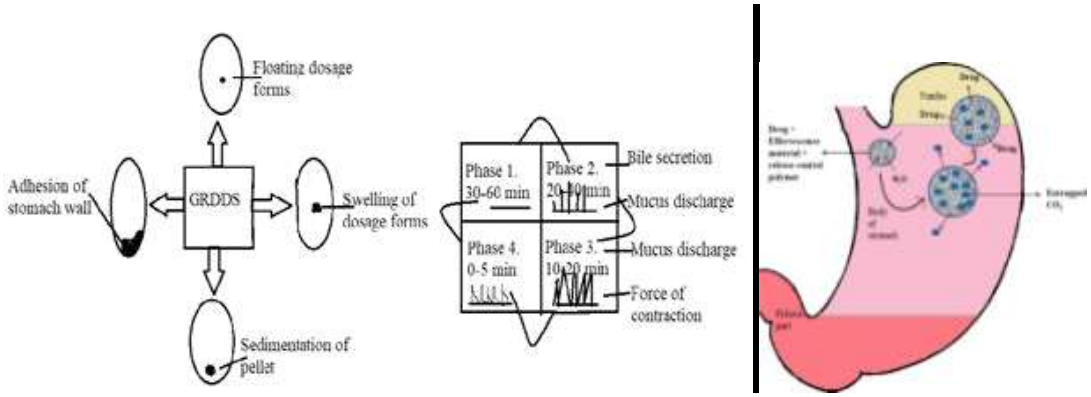


Figure. 3 Approaches of Gastric retention

- **Floating system**

Floating drug delivery system (FDDS) have a pile thickness lower than gastric liquids and so remain buoyancy in belly for a long duration of time without impression the gastric emptying speed. This method swims on the material, then after release of the drug it is slowly released from the system at the required rate. This increases the risk of bacterial infestation in the body and results in better control in the concentration of bacterial drugs. The floating system can be grouped into two separate ranges which are not backfiring and effluent systems. [56-60].

- **Microspheres**

Microspheres are loaded powders with protein or synthetic polymers ranging from 1-1000 micrometers to natural biodegradable.

- **Floating Microsphere**

These are the part of controlled drug delivery systems that have been designed to release the drug with predetermined rate with high effectiveness reduced adverse effects and enhances the bioavailability of drugs. Floating drug delivery system (FDSS) is likely to provide a permanent delighting on gastric ingredients. These catalytic factors include hollow micros, granules, powders, tablets, tablets, tablets, and laminated films [61, 62]. Gastroretentive floating microspheres are low density in which there is adequate buoyancy in the gastric contents for swimming and retained in the stomach for a longer period of time. It is gradually introduced by the favoured charge, resulting in a decrease in plasma drug awareness and elevated gastric level. To enhance patient compliance by floating microscope means of reducing dosing rate, better therapeutic impact of short half of-lifestyles capsules may be completed. More desirable absorption of drugs which solubilizes only in stomach, because of buoyancy gastric retention time is multiplied. [63].

- **Advantages of floating microspheres**

Improves affected person compliance by means of the use of decreasing dosing frequency. bioavailability enhances in spite of first bypass impact because of the fact variations in plasma drug concentration is prevented, a perfect plasma drug concentration is preserved with the aid of the use of continuous drug launch. Higher healing impact of brief half-life of drugs can be completed. Gastric retention time is elevated due to buoyancy. Drug releases in controlled manner for extended duration. Stronger absorption of drugs which solubilizes only in stomach. Superior to single forms as such microspheres releases drug uniformly and there can be no chance of dose dumping. Avoidance of gastric irritation, due to sustained launch impact, floatability and uniform launch of drug through multi particulate system. The go with the go with the flow characteristics and % potential of the following micro balloons are a good deal advanced when in evaluation with the uncooked crystals of the drug. Drug focused on to belly may be attractive for several different reasons. [64]. Different drugs used as Anti-ulcer in the form of floating microspheres are listed in table 3 [65-78].

- **Mechanism of flotation of microspheres**

When microspheres are come into contact with gastric fluid, the polysaccharides, polymers hydrate and the gel formers shape a colloidal gel barrier. By the hydration hydrocolloid layer, outer surface of the dosage form dissolves, while the gel layer is maintained. By means of the swollen polymer, air trapped which lowers the density and provide buoyancy to the microspheres. But to allow

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the process of floatation, a minimum volume of gastric content is needed [79].

- **Mechanism of drug release from the microspheres**

The mechanism behind the drug release from multi particulates can arise by the following approaches: -

- **Diffusion:** On contact with touch with gastric fluid, the water diffuses into the interior of the drug particles and dissolution takes place. The drug answers diffuse throughout the discharge coat to the outdoors [80].
- Erosion: In this mechanism the coating layers erode step by step with time and thereby liberating the drug covered under within the microspheres.
- **Osmosis:** The osmotic agents are used to develop such system. By using these agents osmotic stress can be built up inside the interior of the particle. The drug is exposed out of the particle into the outdoors via pressure [81].

- **Method of Preparation of Microspheres**

Single emulsion technique, double emulsion technique, polymerization approach, segment separation coacervation technique, spray drying and spray congealing, solvent extraction. Floating microspheres are gastro-retentive drug delivery structures based on non- effervescent technique. Floating microspheres are in strict enjoy, spherical empty debris without center. Those microspheres are also termed as "micro balloons" due to its function inner whole shape and super floatability in vitro. Gastro-retentive floating microtubules are low density with adequate buoyancy at the gastric contents glide and stay in the stomach for longer periods of time. As a gadget, this drug is operated slowly at the desired rate, resulting in an increase in gastric retention with fluctuations in the attention of the plasma drug. [82].

- **Solvent Evaporation Method**

To create the entire internal center through solvent diffusion and evaporation methods floating multi particulate dosage shape may be prepared. In a natural solvent, the polymer is dissolved and within the polymer solution the drug is either dispersed or dissolved. Then it emulsified containing suitable additive (surfactants / polymer) into an aqueous segment to shape o/w emulsion. The natural solvent is evaporated after the formation of a strong emulsion either by through non-forestall stirring or developing the temperature below pressure. After solvent removal at the o/w interface of droplets polymer precipitation occurs and to impart the floating homes hollow space develops. For the development of such systems the polymers studied are cellulose acetate, polyethylene oxide, eudragit, acrycoat, chitosan, methocil, carbopol, polyacrylates, polyvinyl acetate and polycarbonate [83].

- **Ion tropic Gelation Method**

This method is based on the ability of poly electrolytes to link with counter ions and to form beads. Because of the truth that, the usage of alginates, CMC and chitosan for the encapsulation of drug and even cells, ion tropic gelation method has been broadly used for this cause. the herbal poly electrolytes in spite, having belongings of coating at the drug center and acts as drug retardants, contains high quality anions on their chemical form. Those anions paperwork meshwork structure by way of combining with the polyvalent cations and prompt gelation by using binding especially to the anion blocks. The hydro gel beads are produced by means of way of dropping a drug-loaded polymeric answer into the aqueous answer of polyvalent cations [84].

- **Emulsion Solvent Diffusion Method**

This technique is more useful than other techniques. The medicament is dissolved within natural solvent. Polymers are dispersed in an aqueous solvent despite fact organic solvent is melting. Out of the emulsion droplets the natural solvent diffuse steadily in to the surrounding aqueous phase and in to the droplets the aqueous section diffuse through which drug crystallizes [84].

- **Single emulsion technique**

Micro particulate corporations of natural polymers occurs in this method i.e. By manner of single emulsion technique the ones of proteins and carbohydrates are prepared. In aqueous medium the natural polymers are dispersed or dissolved and exposed through dispersion in non-aqueous medium like oil with the assist of change in linking agent [85].

- **Double emulsion technique**

The formation of the more than one emulsions or the double emulsion entailed in this approach which consisting of multiple emulsion i.e. w/o/w. This method may be used with the natural as well as synthetic polymers [85].

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- **Polymerization technique**
- Normal Polymerization

With the use of tremendous strategies as suspension, emulsion, precipitation, bulk and micelles polymerization regular polymerization is performed. With the resource of bulk polymerization herbal polymers are formed [86].

- Interfacial Polymerization

On the interface it consists of the reaction of numerous monomers, to form a film of polymer contains most of the two immiscible liquid phases that basically envelops the dispersed [86].

- **Phase separation coacervation technique**

It's far based completely on the precept in organic segment, lowering the solubility of the polymer to have an influence at the development of polymer rich phase known as coacervates. In an answer of the polymer, the drug remains dispersed and to the system, an incompatible polymer is added which makes first polymer to phase separate and immerse the drug debris [87].

Table 3. List of Drugs used as Anti-ulcer activity in the form of floating microsphere

| Sr. No. | Drug | Method | Carrier | Disease | Reference |
|---|---|---|---|---|---|
| 1. | Nizatidine | Solvent Evaporation | Floating Microsphere | Gastric Ulcer | 81 |
| 2. | Lafutidine | Solvent Evaporation | Floating Beads | Gastric Ulcer | 82 |
| 3. | Metronidazole Benzoate | Oil in Water | Floating Microsphere | Gastric Ulcer | 83 |
| 4. | Esomeprazole | Non- aqueous Solvent Evaporation | Microsphere | Gastric Ulcer | 84 |
| 5. | Roxatidine | Ion tropic Gelation | Microsphere | Gastric Ulcer | 85 |
| 6. | Nimodipine | Solvent Evaporation | Floating Microsphere | Gastro retentive | 86 |
| 7. | Cimetidine | Solvent Evaporation | Gastro retentive Microsphere | Gastric Ulcer | 87 |
| 8. | Nizatidine | Solvent Evaporation and Spray drying | Floating Microsphere | Gastric Ulcer | 88 |

**Evaluation of microspheres:** Percentage Yield The prepared microspheres with a size range of 1µm to 1000µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres .

% Yield = Actual weight of product / Total weight of drug and polymer x 100

- **Application of Floating Microspheres**

Floating microspheres are very powerful method in shipping of drugs that has bad bioavailability because of their limited absorption

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within the better GIT. Those structures effectively maximize their absorption and enhance the bioavailability of numerous drugs.

E.g. furosemide, riboflavin and so on. The floating microspheres can be used as carriers for tablets with so-called absorption home windows, these materials, as an instance antiviral, antibiotic and antifungal agents (Aminoglycosides, sulphonamides, Quinilones, penicillin, Cephalosporins, and Tetracyclines) are taken up simplest from very particular web sites of the GI mucosa. Floating microspheres are very effective within the discount of fundamental unfavorable impact of gastric infection; which incorporates floating microspheres of non steroidal anti-inflammatory drugs i.e. Indomethacin are useful for rheumatic sufferers. Floating microspheres are mainly effective in transport of partial soluble and insoluble tablets [88].

Some more applications are in:

- Sustained Drug Delivery
- Site-Specific Drug Delivery
- Absorption Enhancement
- As carriers

## II. CONCLUSION

This comprehensive review of more than 85 references signifies the uses of various drugs in the formulation of floating microspheres for the treatment of peptic ulcer. The main focus was on the floating microspheres, their methods of preparation, evaluation and their applications. The various drugs, dosage form and methods used to prepare formulations have been described with all necessary details to treat peptic ulcers. These details are sufficient to the reader to understand the basic role of floating microspheres. Hence the researchers can use this review manuscript as ready reckoner to develop such type of formulation.

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