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A REVIEW ON GASTRO-RETENTIVE FLOATING TABLETS OF BIODEGRADABLE POLYMERS

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Abstract: This present study describes of gastroretentive floating tablet, it was fabricating with different concentration of two polymers of different grades. The formulated tablets were evaluated in different parameters like hardness, friability, weight uniformity, buoyancy, swelling index and dissolution release profile. Oral drug delivery system is the most preferred route of administration for drug delivery. In the development of the drug delivery system many components play important role. Polymers are amongst those components which have evolved with the drug delivery system. Polymers are the macromolecule compound containing many monomer units joined to each other by bonds. The floating drug delivery systems (FDDS) become an additional advantage for drugs that are absorbed primarily in the upper segments of gastrointestinal (GI) tract, i.e., the stomach, duodenum and jejunum. The purpose of writing this review on floating drug delivery systems (FDDS) was to focus on the types of floating drug delivery systems, principal and mechanism of floatation to achieve gastric retention and polymers used in floating Drug delivery systems. Polymers used in the drug delivery system are of two types Natural and Synthetic based on their origin. Both types of the polymers have some advantages and disadvantages. This particular article gives information about the different types of natural and synthetic polymer used in the drug delivery system. Natural polymers like guar gum, chitosan, xanthan gum, Gellan gum and sodium alginate are mentioned in the article. Synthetic polymers mentioned are HPMC, Eudragit, and Ethyl cellulose.

Keywords Floating Drug Delivery System, Polymers, Natural gums, HPMC.

Introduction

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastro intestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug

absorption is related to contact time with the small intestinal mucosa[1] . In oral tablets can modify drug release and design to site specific drug release. In normal physiology the orally ingested drugs are push off to intestine after a specific period of 3-4 hours. The drug retardation technology the oral drug release possible up to 24 hours for many drugs, but if the drug should have to well absorb in entire gastrointestinal tract. A significant obstacle may arise if there is a narrow window drug absorption in the gastrointestinal tract[2]. In gastro retentive floating drug delivery system is most beneficial for narrow absorption window drugs and makes the drug candidate to prosperous and beneficial to patients. Prolongation of drug release in gastric part which improves bioavailability reduces drug waste and improves solubility for the drug that is less soluble in a high pH environment[3]. Gastric retention is achieved by making the drug release in controlled manner within gastro intestinal tract (stomach). Several approaches are currently used in the prolongation of the gastric residence times (GRT) by one of the methods is floating drug delivery systems (FDDS) with low- density polymer systems[4]. The bulk density of floating drug delivery system is lower than the gastric fluids, so it buoyant in upper part of stomach in longer period irrespective of gastric emptying rate influence. While the system is floating on gastric contents, drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This result is increase in GRT and a better control of fluctuations in plasma drug concentrations[5]. On the basis of buoyancy mechanism, two different technologies applied, i.e., non-effervescent and effervescent systems. Non-effervescent systems of floating use gel-forming or highly swell-able cellulose type hydrocolloids, polysaccharides and matrix forming polymers (polycarbonate, polyacrylate, polymethacrylate, and polystyrene) used. Effervescent systems matrices prepared with swellable polymers or chitosan and effervescent compounds, such as sodium bicarbonate and citric or tartaric acid[2]. Ciprofloxacin is a broad-spectrum antibiotic active against both Gram-positive and Gram-negative bacteria. The dosage is equivalent of 250 to 750 mg of ciprofloxacin twice daily. The objective of the present investigation is to prepare and evaluate gastro retentive Ciprofloxacin floating tablet which will help to retain the dosage form in the stomach and to increase gastric residence time, resulting in prolonged drug delivery in stomach using gel forming polymers such as hydroxyl propylmethyl cellulose (HPMC K4M, HPMC K 100M) in different ratio with microcrystalline cellulose, sodium bicarbonate and magnesium stearate by direct compression techniques.

Biodegradable polymers-

Biodegradable polymers can be defined as polymers that are degradable in vivo, either enzymatically or none enzymatically, to produce biocompatible or nontoxic by-products. These polymers can be metabolized and excreted via normal physiological pathways. They are classified into three groups, namely natural, semi synthetic, and synthetic, based on their sources. Examples of commonly used natural biodegradable polymers are gelatin, alginate, Biodegradable polymers are a newly emerging field.

Polymers Used In Floating Drug Delivery System

Polymers are used in floating system so as to target the drug delivery at specific region in the GI tract i.e. stomach. Both synthetic and natural polymers are used in the floating drug delivery. Natural polymers used in floating system are Guar gum, Chitosan, xanthan gum, Gellan gum, Sodium alginate, etc. Synthetic polymers used for the floating drug delivery are HPMC, Eudragit, ethyl cellulose, etc[20].

Natural Polymers

Natural gums (obtained from plants) are hydrophilic carbohydrate polymer of high molecular weight. They are generally insoluble in organic solvents, like hydrocarbon, ether. Gums either water soluble or absorb water and swell up or disperse in cold water to give a viscous solution or jelly.

S.no	Polymer	Source
1	Guar gum	Endosperm of seed of cynopsis tetragonolobus
2	Chitosan	Shell of marine invertibrates
3	Xanthum gum	Fermentation of glucose by Xanthomonas compestris
4	Gellan gum	Pseudomonas elodea
5	Sodium alginate	Laminaria hyperboria

Natural polymer has advantages over synthetic polymer. They are as follows:

- Biodegradable
- Biocompatible and non-toxic.
- Low cost.
- Environment friendly
- Local availability.

Natural polymer has some disadvantages. They are as follows:

- Microbial contamination
- Batch to batch variation
- Uncontrolled rate of hydration
- Reduced viscosity on storage[21]

Guar gum

Guar gum is naturally occurring galactomannan polysaccharide. Guar gum hydrates and swellsin cold water forming viscous colloidal dispersions or sols. This gelling property retard the drug release and make it a flexible carrier for extended release Dosage forms 26. In pharmaceutical guar gum is used as disintegrant and as a polymer in floating drug delivery system.

Properties of guar gum:

- It is soluble in water but insoluble in organic solvents.
- Strong hydrogen bond property.
- Excellent thickening, emulsion, film forming property.
- Ability to control rheology.

Advantages of guar gum in floating drug delivery system:

It has been reported that polymer swelling play an important role in the pattern and amount of drug release. It was found that guar gum formulations were relatively insensitive to stirring speed during in vitro drug dissolution testing and dissolution profile was not affected significantly[22].

Chitosan

Chitosan is natural polymer obtainer by deacetylation of chitin. It has favorable biological properties such as nontoxic, biodegrable, biocompatible. It is a bioadhesive polymer and has anti-bacterial properties thus make it suitable for site specific delivery. Chitosan is high molecular weight polycationic weak base with pka value of 6.2-7. On addition to acidic pH of 1.2 or neutral media it become buoyant in nature and provide control release 26. By increasing thickness of chitosan film release rate can be decreased[22].

Advantages of chitosan:

- It forms film that reduces effect of gastrointestinal transit time.
- Hallow microcapsule tend to float on gastric fluid for about 12hrs.
- Release rate of drug followed zero order kinetics[22].

Xanthan gum

Xanthan gum is a high molecular weight extracellular polysaccharide produced by pure culture aerobic fermentation of carbohydrate. Xanthan is a long chained polysaccharide with large number of trisaccharide side chains. Gum also has an excellent solubility and stability under acidic and alkaline conditions and in the presence of salts and resists common enzymes.

Advantages of Xanthan gum:

- It is used to increase or decrease rate of release of drug from formulation
- Soluble in water
- High viscosity at low concentration
- It has potential advantage of drug release at zero order kinetics.

Some tablet containing xanthan gum and citric acid show buoyancy for more than 24hrs.

Gellan gum

Gellan gum is an anionic, high molecular weight, deacetylated extracellular, linear polysaccharide. This gum has an outstanding flavor release, high gel strength, an excellent stability, process flexibility, high clarity, good film former and thermally reversible gel characteristics[20]. Gellan gum is produced as a fermentation product from spingomonas elodea.

Advantages of Gellan gum:

- It has excellent flavor release, high gel strength, and excellent stability.
- It forms gel when positively charged ions are added

Synthetic Polymers

Synthetic polymers are becoming increasingly important in pharmaceuticals. Uses of synthetic polymer are as binder, film coating agent, etc. Polymer are macromolecule having very large, contain a variety of functional group. Synthetic polymers are either purely synthetic or they are modified form of natural polymer know as semi-synthetic. List of synthetic polymer used is as follows:

1. Hydroxypropyl methyl cellulose
2. Eudragit
3. Ethyl cellulose

Disadvantages of synthetic polymer are as follows

- High cost toxicity environmental pollution
- Acute and chronic adverse effect
- Poor biocompatible
- Inflammatory response and local reaction[21].

1. Hydroxypropyl methyl cellulose

Hydroxypropyl methylcellulose ethers belong to an extensive family of white to off-white, odorless, water soluble polymers that bind, retain water, thicken, form films, lubricate. It is a semi synthetic, inert, viscoelastic polymer, used as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products.

Functional category:

Bioadhesive material, coating agent, controlled-release agent, dispersing agent, dissolution enhancer, emulsifying agent, emulsion stabilizer, extended-release agent, film-forming agent, foaming agent, granulation aid, modified-release agent, mucoadhesive, release-modifying agent, solubilizing agent, stabilizing agent, suspending agent, sustained release agent, tablet binder, thickening agent, viscosity-increasing agent[23].

General properties common to the Hypremellose are listed below. Individual type exhibits these properties to varying degrees and may have additional properties that are desirable for specific applications.

- Apparent density: 0.25~0.70g/cm3
- The refractive index=1.336
- Surface tension: 42 to 56mn/m

Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of HPMC are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. Some grades are swellable in ethanol[24].

Applications:

- In oral products, HPMC is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules[23].
- Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.
- Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Examples of film coating materials that are commercially available include Any Coat C, Spectracel, Pharmacoat, and the Methocel E Premium LV series.
- Hypromellose is also used as a suspending and thickening agent in topical formulations.
- Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%.
- Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

Advantages

 Water soluble and most abundant polymer in nature

 Used as a thickener, film former and water retention agent

 Hydrophilic matrix is the simplest sustained release technology for oral dosage form[25].

2. Eudragit

Nonproprietary names: BP: Acidum methacrylicum et methylis methacrylas polymerisatum 1:2 USPNF: Methacrylic acid copolymer

Synonyms: Polymeric methacrylates.

Functional category: Film former; tablet binder; tablet diluent

Description:

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60: 40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent. Eudragit S 100 is available as powder and solvents used for this is 95 % Acetone and alcohols which is soluble in intestinal fluid from pH 7 and used as an enteric coating material.

Eudragit L and S also referred to as methacrylic acid copolymers in the USPNF 23 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1:1 in Eudragit L (Type A) and approximately 1: 2 in Eudragit S (Type B). Both polymers

are readily soluble in neutral to weakly alkaline conditions (pH 6– 7) and form salts with alkalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. Eudragit L-100 and Eudragit S-100 are white free-flowing powders with at least 95 % of dry polymers.

Incompatibilities:

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

Applications:

- Polymethacrylates (Eudragit) are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced. Eudragit S 100 is soluble in acetone and alcohols and 1N NaOH. In contrast, Eudragit L, S and FS types are used as enteric coating agents because they are resistant to gastric fluid. Different types of enteric coatings are soluble at different pH values: e.g. Eudragit L is soluble at pH >6 whereas, Eudragit S and FS are soluble at pH >7. The S grade is generally used for coating tablets, while the flexible FS 30 D dispersion is preferred for coating particles.
- Eudragit RL, RS, NE 30D, NE 40D and NM30D are used to form water-insoluble film coats for sustained release products. Eudragit RL films are more permeable than those of Eudragit RS, and films of varying permeability can be obtained by mixing the two types together.
- Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct compression processes in quantities of 10–50%. Polymethacrylates polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration[26].

3. Ethyl cellulose

Ethocel (Ethylcellulose polymers) has been widely used in the pharmaceutical industry for over 50 years. Ethylcellulose has been used for choice in pharmaceutical formulations for various purposes, such as taste-masking of bitter actives, moisture protection, stabilizer, extended release multiparticulate coating, micro-encapsulation of actives, extended release binder in inert matrix systems, solvent and extrusion granulation.

Solubility: Ethyl cellulose is a water insoluble cellulose ether, which is prepared from cellulose, it is a partly O-ethylated cellulose, its ethoxy content (- OC2H5) is between 44-51 %. . It is insoluble at any pH that occurs in organism, but in the presence of the gastric Juice it undergoes swelling. It is then permeable for water and permits extended modified drug release. This makes it suitable for improved patient compliance.

Applications:

- The application of EC in wet extrusion processes is limited, since the polymer has considerable elastic properties, but can be successfully used as matrix former in combination with some plasticizing agents. The potential of coarse Ethyl cellulose (CPEC) and fine particle Ethyl cellulose (FPEC) as diluent with high molecular weight polyethylene oxide (PEO), which was used as an extrusion aid and a binder have shown that water is sufficient to prepare a wet granulation product when using FPEC. MCC was included in formulations to contribute its plasticity to the wetted mass during extrusion and to the extrudate during spheronization.

- Ethyl cellulose is an ideal polymer for the formation of products allowing modified drug release. A small number of Ethyl cellulose polymers have been approved for general pharmaceutical application and are used in extended release solid dosage formulations. Several types of such Ethyl cellulose exist, e.g. Ethocel 4, Ethocel 10 and Ethocel 45, which differ in the length of the polymer chains, the rate of dissolution, and the viscosity of their solution. Ethyl cellulose is suitable to prepare MR coatings[27].

Limitations/Disadvantages Of Fdds:

1. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat.
2. Not suitable for drugs that have solubility or stability problem in GIT.
3. Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable
4. Drugs which are irritant to gastric mucosa are also not desirable or suitable.
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
6. The dosage form should be administered with a full glass of water (200-250 ml).
7. These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract[28,29,30].

Evaluation parameters of floating tablet-

Fourier Transform-Infra Red (FT-IR) Studies[6,7]

Samples are prepared using KBr disc method and spectra are recorded over the range 600-4500 per cm. Spectra are analyzed for drug-carrier interaction and functional groups involved in the compellation process. Formulation and evaluation of ciprofloxacin floating tablet the floating tablet of ciprofloxacin was prepared by wet granulation method using different grade of polymers and excipients like HPMC K-4 M, HPMC K-100, Sodium bicarbonate and microcrystalline cellulose. Three formulations were prepared as per formula designed.

Preformulation study for Ciprofloxacin floating tablets -:

Angle of Repose[7,8]

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

Tan (θ) = tan-1 (h / r)

Where,

θ =is the angle of repose

h= is the height in centimeters

r= is the radius in centimeters.

Bulk Density[10]

It is the ratio of total mass of powder to the bulk volume of powder. Bulk density is calculated by pre weighted powder was poured in to measuring cylinder and then the initial volume was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

Db = M/ Vb

Where,

M= is the mass (weight) of powder

Vb= is the bulk volume of the powder.

Tapped Density[5,9]

Tapped volume was measured by, pre weighted powder was poured in measuring cylinder and noted the volume, start tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is greater than 2%, tapping is continued for 1250 times and tapped volume was noted.

Dt =M / Vt

Where,

M= is the mass of powder,

Vt =is the tapped volume of the powder.

Percentage of compressibility (or) Carr's index[7,10]

It indicates powder flow properties. It is expressed in percentage and is give

$$I = \frac{Dt}{Db} \times 100$$

Where,

Dt= is the tapped density,

Db= is the bulk density

Hausner's ratio[11]

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post compression evaluation of floating tablet

Thickness and Diameter[12]

Tablet thickness and diameter measured by varnier calipers. 5 tablets were taken and their thickness and diameter were measured.

Hardness[9]

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of floating tablets because excessive crushing strength

significantly reduces the disintegration time.

Weight variation test[7,13]

20 tablets were selected randomly from the all formulation and weighted individually to check for weight variation. Weight variation specification asper I.P. is shown in the table.

Friability test[10,14]

Friability of the tablet determined using friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre weighted tablets samples was placed in to the friabilator and allowed rotate 100 times. Tablets were dusted by using a soft muslin cloth and reweighed. The friability (F) is calculated by the formula.

$$\text{Friability} = \frac{\text{W intial} - \text{W final}}{\text{W initial}}$$

Uniformity of Drug Content[15]

Twenty tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 10mg of Ciprofloxacin was weighed and dissolved in acid buffer pH 1.2, the volume was made up to 100ml with pH 1.2 acid buffer. From the stock solution 1ml sample was withdrawn and diluted to 10ml with acid buffer pH 1.2, the absorbance was measured at wavelength 277nm using UV-Visible spectrophotometer. Content uniformity was calculated using formula.

$$\%\text{DC} = \frac{\text{Absorbance of unknown (Au)}}{\text{Absorbance of standard (As)}}$$

Swelling index[8,9,16]

The floating tablets were weighed individually (W0) and placed separately in glass beaker containing 200 ml of 0.1N hydrochloric acid buffer at 370 ± 10C at regular 2-hour intervals tablets were removed from beaker and weighed (Wt) and the percentage of swelling index was calculating

$$\text{Swlling index} = \frac{(\text{Wt}-\text{Wo}}{\text{Wo}} \times 100$$

Where,

Wt = weight of the tablet at time t,

W0 = weight of the tablet before immense.

In vitro drug release studies[16,17]

Dissolution studies of all tablets were performed using dissolution tester. Tablets were added to the 900 ml of 0.1N hydrochloric acid buffer pH 1.2 at 37°C ± 0.5°C, which was stirred with a rotating paddle at 50 rpm. 5ml samples were withdrawn from the dissolution apparatus at the specified time intervals, equal volume of fresh medium was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test.

Floating / buoyancy test[18,19]

The tablets were placed in 100ml beaker containing 0.1N hydrochloric acid buffer. The time taken for the dosage from to reach (float) on upper surface of the medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time the dosage form remains buoyant is called Total Floating Time.

Conclusion:

The FDDS become an additional advantage for drugs that are absorbed primarily in the upper segments of GI tract, i.e., the stomach, duodenum and jejunum. Polymers are used for the purpose of the controlled release of drug from dosage form. Polymers are the substances which are being used in the formulations for many reasons like gelling agents, emulsifying agents, viscosity increasing agents, rate retarding agents etc. Therefore knowledge of the polymer in field of the drug delivery plays an important role. However a lot of work is still needed to be done to overcome the different physiological and pharmaceutical barriers to develop the more effective dosage forms. It is suggested that future research work in the FDDSs should be aimed at discovering means to accurately control the drug input rate into the GI tract for the optimization of the pharmacokinetic and toxicological profiles of medicinal agents.

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