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REVIEW ON GASTRORETENTIVE MUCOADHESIVE MICROSPHERE

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ABSTRACT

The current article focuses on the principles of mucoadhesive drug delivery systems based on adhesion to biological surfaces that are covered by mucus. In recent years scientific and technological advancements have been made in the research and development of Mucoadhesive Microsphere by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. Gastroretentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Different approaches for Gastroretentive dosage forms include floating, expanding or swelling, bioadhesive or mucoadhesive and high/low-density systems. The Mucoadhesive Microsphere should be primarily aimed to achieving more predictable and increased bioavailability of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, useful for drugs acting locally in the GIT, drugs which are poorly soluble and unstable in intestinal fluids. These systems are advantageous in improving GIT absorption of drug with CR due to specific site absorption limitations. By using mucoadhesive hydrogels as drug carriers is given. Techniques that are frequently used to study the adhesion forces and physicochemical interactions between hydrogel, mucus, and the underlying mucosa are reviewed. Typical examples of applications of mucoadhesive hydrogels to mucosal routes of delivery are given. Various methods of preparation, evaluation test, application. Factors affecting, polymer used and mechanism of bioadhesion are discussed here. Mucoadhesive drug delivery systems is one of the most important novel drug delivery systems with its various advantages and it has a lot of potential in formulating dosage forms for various chronic diseases.

KEYWORDS: mucoadhesive, bioadhesive.

INTRODUCTION

The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. Although a lot of advancements have been seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). To modify the GI transit time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of pharmaceuticals is highly variable and dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes to 2 hours. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and the transit of dosage forms. It is characterized by four Phases.[7] Phase I– Period of no contraction (40-60 minutes) Phase II– Period of intermittent contractions (20-40 minutes) Phase III– Period of regular contractions at the maximal frequency also known as housekeeper Wave (10-20 minutes) Phase IV– Period of transition between Phase III and Phase I (0-5 minutes).

Drugs having a short half-life are eliminated quickly from the blood circulation and therefore bioavailability of the drug suffers. Gastro retentive dosage form improves bioavailability, therapeutic efficacy and may allow a reduction in the dose because of steady therapeutic levels of drug, for example furosemide and ofloxacin. The reduction of fluctuations in the therapeutic levels minimizes the risk of resistance especially in case of β-lactam antibiotics (penicillin and cephalosporin).[8] Gastric emptying of dosage forms is an extremely variable process. The ability of a dosage form to prolong and control the gastric emptying time is a valuable asset for drugs acting on GIT. Drug absorption from the GIT is a complex procedure and is subjected to many parameters to become bioavailable. It is widely

acknowledged that the contact time with the small intestinal mucosa is related with the degree of GIT drug absorption.[9] thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. Gastro retention provides better availability of new products with new therapeutic possibilities and substantial benefits for patients. Controlled release drug delivery systems that retain in the stomach for a long time have many advantages over sustained release formulations. Such retention systems (i.e. GRDDS) are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that act locally in the stomach. Gastric retention may increase solubility for the drugs which are poorly soluble in intestine due to alkaline pH before they get emptied from the stomach. These systems are also advantageous in improving GIT absorption of drug having narrow absorption windows and site-specific absorption limitations. These systems are useful in case of those drugs which are best absorbed in stomach for eg. Albuterol.[10] Hence, this review article focuses on the current technological developments and advancements in gastro retentive drug delivery system with special emphasis on the approaches and the advantages along with some marketed preparations of GRDDS.[11]

Approaches To Gastric Retention[12]

A number of approaches have been used to increase gastric retention time (GRT) of a dosage form in stomach by employing a variety of concepts. These includes in.

a) Floating Systems

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the 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 results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two distinct categories, noneffervescent and effervescent systems.[13] gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.[14]

f) Osmotic regulated systems

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric somotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.[13]

g) High density systems- They include coated pellets and have density greater than that of the Stomach content (1.004 gm/cm3). This formulation of high-density pellet is based on assumption that heavy pellet might remain longer in the stomach, since they are position in the lower part of the antrum.[15]

h) Low density approach

Floating systems come under low density approach. In this approach, the density of pellets should be less than 1 g/ml, so as to float the pellets or tablets in the gastric fluid and, release the drug slowly for a longer period of time. This type is also called as Hydrodynamically Balanced System (HBS). Polypropylene foam powder (Accurel MP 1000®).[16]

Bio/Muco-adhesive Systems: Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending gastric residence time of drug delivery system in stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. Binding of polymers to mucin/epithelial surface can be divided into three broad categories.[17]

a) Hydration-mediated adhesion.
b) Bonding-mediated adhesion.
c) Receptor-mediated adhesion +

Types of drugs can benefit from using gastric retentive devices. These include

- Acting locally in the stomach.
- Primarily absorbed in the stomach.
- Poorly soluble at an alkaline pH.
- Narrow window of absorption.
- Absorbed rapidly from the GI tract.
- Degrade in the colon.

3. Suitable Drug Candidates For Gastroretention

In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

- Narrow absorption window in GItract, e.g., riboflavin and levodopa
- Primarily absorbed from stomach and upper part of GItract, e.g., calcium supplements, hlordiazepoxide and cinnarazine
- Drugs that act locally in the stomach, e.g., antacids and misoprostol
- Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole

- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

4. Muco-Adhesive Systems

The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bioadhesive drug delivery, the term oadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term ucoadhesion may be used synonymously with bioadhesion. Mucoadhesion can be defined as a state in which two components of which one is of biological origin are held together for extended periods of time by the help of interfacial forces. Generally speaking, bioadhesion is an term which broadly includes adhesive interactions with any biological or biologically derived substance, and mucoadhesion is used when the bond is formed with a mucosal surface.[18]

Microspheres are frequently used drug delivery system and may also possess mucoadhesive properties. Due to their micrometer size they may be applied to mucosa, where the other dosage forms, e.g. tablet, would represent a problem. Microencapsulation by various polymers and its applications are described in standard textbooks. Microencapsulation has been accepted as a process to achieve controlled release and drug targeting. Microspheres are free flowing powder and having diameter of 1-1000µm.Recently, dosage forms that can precisely control the release rates and targets drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery system**.** Mucoadhesion has been a topic of interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs. Several studies 2 reported mucoadhesive drug delivery systems in the form of tablets, films, patches, and gels for oral, buccal, nasal, ocular, and topical routes; however, very few reports on mucoadhesive microspheres are available. The objective of this study is to develop, characterize, and evaluate mucoadhesive microspheres of drug having less retention time employing mucoadhesive polymers for prolonged gastrointestinal absorption.

Need for Mucoadhesive Microsphere

a. A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs.
b. Are locally active in the stomach (misoprostol, antacids antibiotics against H.pylori). Have an absorption window in stomach or in the upper small intestine (L-dopa, aminobenzoic acid, furosemide).
c. Are unstable in the intestine or colonic environment (captopril).
d. Exhibit low solubility at high p^H values (diazepam, verapamil).
e. Alter normal flora of the colon (antibiotics).
f. Absorbed by transporter mechanism (paclitaxel).

Advantages[20]

1. Prolongs the residence time of the dosage form at the site of absorption.
2. Due to an increased residence time it enhances absorption and hence the therapeutic efficacy of the drug
3. Excellent accessibility
4. Rapid absorption because of enormous blood supply and good blood flow rates
5. increase in drug bioavailability due to first pass metabolism avoidance
6. Drug is protected from degradation in the acidic environment in the GIT
7. Improved patient compliance- ease of drug administration
8. faster onset of action is achieved due to mucosal surface

8. Mechanism of Mucoadhesion[2]

As stated, mucoadhesion is the attachement of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following mechanism,[3]

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon).[3,4]
2. enetration of the bioadhesive into the tissue or into the surface of the mucous Membrane (interpenetration).[3,4]

Residence time for most mucosal routes is less than an hour and typically in minutes, it can be increased by the addition of an adhesive agent in the delivery system which is useful to localize the delivery system and increases the contact time at the site of absorption.[6] The exact mechanism of mucoadhesion is not known but an accepted theory states that a close contact between the mucoadhesive polymer and mucin occurs which is followed by the interpenetration of polymer and mucin. The adhesion is prolonged due to the formation of vandervals forces, hydrogen bonds and electrostatic bonds.[3]

3. A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems. Several theories have been proposed to explain the fundamental mechanism of adhesion.
4. A General Mechanism of Mucoadhesion Drug Delivery system is show in Figure.

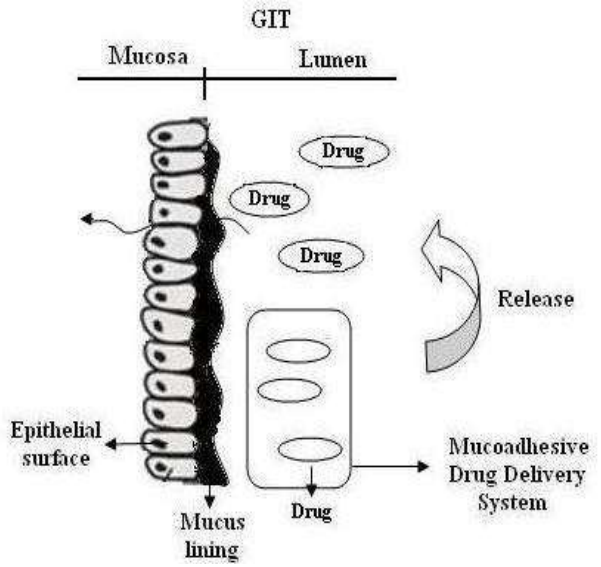

Figure 1: Mechanism of Mucoadhesion.

9. Theories of Mucoadhesion[21]

Bioadhesive drug delivery systems are used to localize a delivery device within the human to enhance the drug absorption in a site-specific manner. In this approach, various bioadhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they increase GRT of the dosage forms. The basis of micro adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are:-

a) Electronic theory.
b) Absorption theory.
c) Diffusion theory.
d) Wetting theory.
e) Cohesive theory.

a) Electronic theory

According to this theory, electron transfers occur upon contact of adhesive polymer with a mucus glycoprotein network because of difference in their electronic structures. This results in the formation of electrical double layer at the interface e.g. Interaction between positively charged polymers chitosan and negatively charged mucosal surface which becomes adhesive on hydration and provides an intimate contact between a dosage form and absorbing tissue.

b) Absorption theory

According to this theory, after an initial contact between two surfaces, the material adheres because of surface force acting between the atoms in two surfaces. Two types of chemical bonds resulting from these forces can be distinguished as primary chemical bonds of covalent nature and Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

c) Diffusion theory

According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact. The diffusion coefficient in terms depends on the value of molecular weight between cross linking and decreases significantly as the cross linking density increases.

d) Wetting theory

The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive among the substrate surface. This is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.

e) Cohesive theory

The cohesive theory proposes that the phenomena of bioadhesion are mainly due to intermolecular interaction amongst like molecule. Based upon the above theories, the process of bioadhesion can broadly be classified into two categories namely chemical (electron and absorption theory) and physical (wetting, diffusion and cohesive theory).

10. Polymersused In Mucoadhesive Microsphere[21,22]

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

Characteristics of an ideal mucoadhesive polymer[19]

1. The polymer and its degradation products should be nontoxic and should be no absorbable from the GI tract.
2. It should be nonirritant to the mucus membrane.
3. It should preferably form a strong no covalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to most tissue and should possess some site specificity.
5. It should allow easy incorporation of the drug and should offer no hindrance to its release.
6. The polymers must not decompose on storage or during the shelf life of the dosage form.
7. The cost of polymer should not be high so that the prepared dosage form remains competitive.
8. Long chain polymers-chain length must be long enough to promote the interpenetration and it should not be too long that diffusion becomes a problem High viscosity.
9. But as the cross linking increases, the chain mobility decreases which reduces the mucoadhesive strength.

10. Optimum Ph – mucoadhesion is optimum at low pH conditions but at higher pH values a change in the conformation occurs into a rod like structure making those more available for inter diffusion and interpenetration. At very elevated P^H values, positively charged polymers like chitosan form polyelectrolyte complexes with mucus and exhibit strong mucoadhesive forces.

Robinson and his group using the fluorescence technique concluded that

Cationic and anionic polymers bind more effectively than neutral polymers.

1. Polyanionsarebetterthan polycations in terms of binding/potential toxicity, and
2. further, that water-insoluble polymers give greater flexibility in dosage form design compared with rapidly or slowly dissolving water-soluble polymers.
3. Anionic polymers with sulfate groups bind more effectively than those with carboxylic groups.Degree of binding is proportional to the charge density on the polymer. Highly binding polymers include carboxy methyl cellulose, gelatine, hyaluronic acid, carbopol, and polycarbophyl.

Molecular characteristics

Investigations into polymers with various molecular characteristics have led to a number of conclusions regarding the molecular characteristics required for mucoadhesion. The properties exhibited by a good mucoadhesive may be summarized as follows:

1. Strong hydrogen-bonding groups [-OH, -COOH]
2. Strong anionic charges
3. Sufficient flexibility to penetrate the mucus network or tissue crevices
4. Surface tension characteristics suitable for wetting mucus/mucosal tissue surface
5. Polymer must have a high molecular weight upto 100.00 or more this is necessary to promote the adhesiveness between the polymer and mucus.

The rheology of the mucoadhesion is a typical topic and it deals with a number of forces, factors of the components, state of the material, its derived properties. Based on the rheological aspects, we can categorise the mucoadhesive polymers into two broad categories, materials which undergo matrix formation or hydrogel formation by either a water swellable material or a water soluble material. These carriers generally polymers are classified as,

a) Hydrophilic polymers

The polymers within this category are soluble in water. Matrices developed with these polymers swell when put into an aqueous media with subsequent dissolution of the matrix. The polyelectrolytes extend greater mucoadhesive property when compared with neutral polymers. (A. Ludwig, et.al. 2005).

Hydrophillic polymers Contains carboxylic group and possess excellent mucoadhesive properties. These are

1. Pvp(poly vinyl pyrrolidine)
2. Mc(methyl cellulose)
3. Scmc(sodium carboxy metyhyl cellulose)
4. Hpc(hydroxyl propyl cellulose)

b) Hydrogels

These swell when in contact with water and adhere to tne mucus membrane. These are further classified according to their charge.

a) Anionic polymers- carbopol, polyacrylates
b) Cationic polymers- chitosan
c) Neural/ non ionic polymers- eudragit analogues

They can also be classified as,

a) Synthetic polymers - cellulose derivatives, carbopols, etc
b) Natural polymers - tragacanth, pecyin, gelatin sodium alginate, acacia.

c) Chitosan

It is a cationic polymer (polysaccharide), it is produced by the deacetylation of chitin. Chitosan is gaining importance in the development of mucoadhesive drug delivery system because of its good biocompatibility, biodegradability and non toxic nature. It binds to the mucosa via ionic bonds between the amino group and sialic acid residues. Chitosan being linear provides greater polymer chain flexibility. Onishi and Machida showed that chitosan and its metaboloized derivatives are quickly eliminated by the kidney.[2]

d) Newer second generation polymers They have the following advantages,

a) More site specific hence called cytoadhesives.
b) Are least effected by mucus turnover rates.
c) Site specific drug delivery is possible.

a) **Lectins**

Lectins are naturally occurring proteins that are useful in biological recognition involving cells and proteins. Lectins are a class of structurally diverse proteins and glycoprotein that bind reversibly to specific carbohydrate residues. After binding to the cell the lectins may either remain on the cell surface or may be taken inside the cell via endocytosis., they hence allow a method for site specific and controlled drug delivery. The lectins have many advantages but they also have the disadvantage of being immunogenic.

b) Thiolated polymers

These are thiomers which are derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gallan gum. The presence of the thiol group increases the residence time by promoting covalent bonds with the cystiene residues in mucus. The disulphide bonds may also alter the mechanism of drug release from the delivery system due to increased rigidity and cross linking.[2]

e.x. Chitosan iminothiolane.
PAA homocystiene.
Paa cystiene.
Alginate cystiene.

c) Polyox WSRA
Class of high molecular weight polyethylene molecular weright polyethylene oxide homopolymers having the following properties,

1. Water soluble.
2. Hydrophillic nature.
3. High molecular weight.
4. Functional group for hydrogen bondimg.
5. Biocompatible and non toxic.
6. Can be formulated into tablets, films, gels, microcapsules, syrups.

d) Novel Polymers

a. Tomato lectin showed that it has binding selectivity to the small intestine epithelium.
b. Shajaei and Li have designed and characterized a co polymer of PAA and PEGMono ethylether mono methacrylate (PAA-co-PEG) for exhibiting optimal buccal adhesion.
c. Lele et al, investigated novel polymers of PAA complexed with PEGylated drug onjugate.
d. New classes of hydrophilic pressure sensitive adhesives (PSA) have been developed by corium technologies. Complex have been prepared by non covalent hydrogen bonding cross linking of a film forming hydrophilic polymer with a short chain plasticizer having reactive OH groups at chain ends.
e. Bogataj et. Al prepared and studied Mucoadhesive microspheres for application in urinary Bladder.
f. Langath N et.al. Investigated the benefit of thiolated polymers for the development of buccal drug delivery systems.
g. Alur H.H. et.al., studied the transmucosal sustained delivery of chlorphenazine maleate in rabbits using a novel natural mucoadhesive gum from hakea as an excipient in buccal tablets. The gum provided sustained releawse and sufficient mucoadhesion.

11. Factors Affecting Mucoadhesion[27]

a) Physiological Factors.
b) Environment-related factors.
c) Polymer-related factors.

a) Polymer-related factors

i. Molecular weight

The optimum molecular weight for maximum bioadhesion depends upon type of mucoadhesive polymer at issue. It is generally understood that the threshold required for successful bioadhesion is at least 100 000 molecular weight. For example, polyethylene glycol (PEG), with a molecular weight of 20 000, has little adhesive character, whereas PEG with 200 000 molecular weight has improved, and PEG with 400 000 has superior adhesive properties. The fact that mucoadhesiveness improves with increasing molecular weight for linear polymers implies two things: (1) interpenetration is more critical for a low-molecular-weight polymer to be a good mucoadhesive, and (2) entanglement is developed by corium technologies. Complex have been prepared by non covalent hydrogen bonding cross linking of a film forming hydrophilic polymer with a short chain plasticizer having reactive OH groups at chain ends. e. Bogataj et. Al prepared and studied Mucoadhesive microspheres for application in urinary Bladder.

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ii. Concentration of active polymer There is an optimum concentration for a mucoadhesive polymer to produce maximum bioadhesion. In highly concentrated system, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chain available for interpenetration becomes limited.

iii. Flexibility of polymer chains

Chain flexibility is critical for interpenetration and entanglement. As water soluble polymers become cross-

linked, the mobility of an individual polymer chain decreases and thus the effective length of the chain that can penetrate into the mucus layer decreases, which reduces mucoadhesive strength.

iv. Spatial conformation

Besides molecular weight or chain length, spatial conformation of a molecule is also important. Despite a high molecular weight of 19 500 000 for dextrans, they have adhesive strength similar to that of PEG, with a molecular weight of 200 000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation.

v. Swelling

Swelling characteristics are related to the mucoadhesive itself and its environment. Swelling depends on the polymer concentration, the ionic strength, and the presence of water. During the dynamic process of bioadhesion, maximum bioadhesion *in vitro* occurs with optimum water content. Overhydration results in the formation of a wet slippery mucilage without adhesion.

b) Environment-related factors

i. P^H of polymer-substrate interface

P^H can influence the formal charge on the surface of the mucus as well as certain ionizable mucoadhesive polymers. Mucus will have a different charge density depending on pH due to the difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. Some studies had shown that the pH of the medium is important for the degree of hydration of cross-linked polycyclic acid, showing consistently increased hydration from pH 4 through pH 7, and then a decrease as alkalinity or ionic strength increases, for example polycarbophil does not show a strong mucoadhesive property above pH 5 because uncharged, rather than ionized, carboxyl group reacts with mucin molecule, presumably through numerous hydrogen bonds. However, at higher P^H, the chain is fully extended due to electrostatic repulsion of the carboxyl ate anions.

ii. Applied strength

To place a solid mucoadhesive system, it is necessary to apply a defined strength. Whatever the polymer, poly (acrylic acid/divinyl benzene) or carbopol 934, the adhesion strength increases with the applied strength or with the duration of its application, up to an optimum. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interactions with mucin. bacterial, and fungal infections of female reproductive tract, and inflammatory conditions of the eye. The exact structural changes taking place in mucus under these conditions are not clearly understood. If mucoadhesives are to be used in the disease states, the mucoadhesive property needs to be evaluated under the same conditions.

13. Techniques of Formulation of Mucoadhesive Microspheres[23]

Mucoadhesive microspheres can be prepared using any of the following techniques.

a) Solvent Evaporation

It is the most extensively used method of microencapsulation first described by *Ogawa et al.*4 Buffered or plain aqueous solution of the drug (may contain a viscosity building or stabilizing agent) is added to an organic phase consisting of the polymer solution in solvents like dichloromethane (or ethyl acetate or chloroform) with vigorous stirring to form the primary water in oil emulsion. This emulsion is then added to a large volume of water containing an emulsifier like PVA or PVP to form the multiple emulsions (w/o/w). The double emulsion, so formed, is then subjected to stirring until most of the organic solvent evaporates, leaving solidmicrospheres. The microspheres can then be washed, centrifuged and lyophilize to obtain the free flowing and dried microspheres.[24]

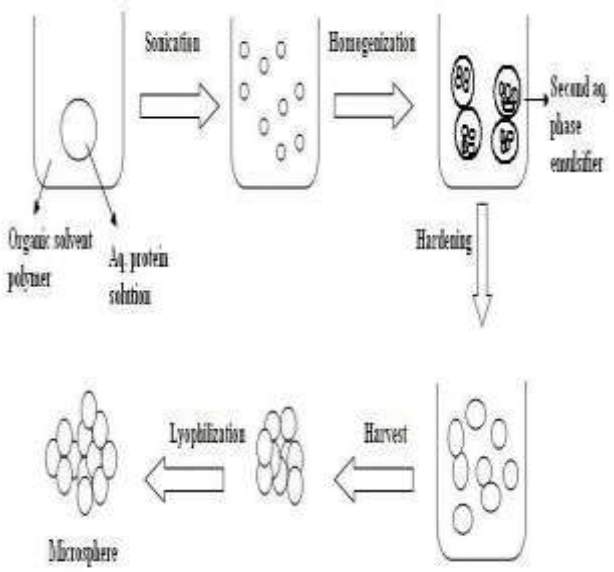

Figure 2: Solvent evaporation method for preparation of microsphere.

b) Hot Melt Microencapsulation[25]

In this method was first used by Mathiowitz and langer**5** to prepare microsphere of polyanhydride copolymer of poly[bis(*p*-carboxy phenoxy)propane anhydride]with sebacic acid , the polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 ,m. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method

is to develop a microencapsulation process suitable for the water labile polymers, *e.g.* polyanhydrides. Microspheres with diameter of 1-1000, m can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is moderate temperature to which the drug is exposed.

c) Solvent Removal

It is a non-aqueous method of microencapsulation, particularly suitable for water labile polymers such as the ploy anhydrides. In this method, drug is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride.6 this mixture is then suspended in silicone oil containing span 80 and methylene chloride. After pouring the polymer solution into silicone oil, petroleum ether is added and stirred until solvent is extracted into the oil solution. The resulting microspheres can then be dried in vaccum.[1]

d) Hydrogel Microspheres

Microspheres made of gel-type polymers, such as alginate, are produced by dissolving the polymer in an aqueous solution, suspending the active ingredient in the mixture and extruding through a precision device, producing micro droplets which fall into a hardening bath that is slowly stirred. The hardening bath usually contains calcium chloride solution, whereby the divalent calcium ions crosslink the polymer forming gelled microspheres. The method involves an "all-aqueous" system and avoids residual solvents in microspheres. Lim and Moss**100** develop this method. This method can be used for encapsulation of live cells, as it does not involve harsh conditions, which could kill the cells. The surface of these microspheres can be further modified by coating them with polycationic polymers, like polylysine after fabrication. The particle size of microspheres can be controlled by using various size extruders or by varying the polymer solution flow rates.

e) Spray Drying

In this process, the drug may be dissolved or dispersed in the polymer solution and spray dried. The quality of spray-dried microspheres can be improved by the addition of plasticizers, *eg* citric acid, which promote polymer coalescence on the drug particles and hence promote the formation of spherical and smooth surfaced microspheres. The size of microspheres can be controlled by the rate of spraying, the feed rate of polymer drug solution, nozzle size, and the drying temperature. This method of microencapsulation is particularly less dependent on the solubility characteristics of the drug and polymer and is simple, reproducible, and easy to scale up.

Phase Inversion Microencapsulation[26] The process involves addition of drug to a dilute solution of the polymer (usually 1-5% w/v in methylene chloride). The mixture is poured into an unstirred bath of strong non-solvent (petroleum ether) in a solvent to non-solvent ratio of 1:100, resulting in the spontaneous production of microspheres in the size range of 0.5-5.0, m can then be filtered, washed with petroleum ether and dried with air. This simple and fast process of microencapsulation involves relatively little loss of polymer and drug.

Evalution Method of Mukoadhesive Micrsphere[28]

The best approach to evaluate mucoadhesive microspheres is to evaluate the effectiveness of the mucoadhesive polymer to prolong the residence time of drug at the site of absorption, there by increasing absorption and bioavailability of the drug. The methods used to evaluate mucoadhesive microspheres include the following.

a) In-vitro drug release

The release rate of drug from mucoadhesive microspheres was determined using dissolution testing apparatus 2 (paddle type). The dissolution test was performed using 900 mL of suitable dissolution medium at 37± 0.50 C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 24 hrs, and the sample were replaced with fresh dissolution medium to maintain the sick condition. The samples were filtered through a membrane filter and diluted to a suitable concentration with same dissolution medium. Absorbance of these solutions was measured at suitable λmax using a double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve and same studies were performed in 6.8 pH phosphate buffer solutions. The drug release experiments were conducted in triplicate (n = 3).

b) In vivo drug release

In vivo evaluation studies for drug mucoadhesive microspheres were performed in diabetics' albino rats of either sex, weighing between 230-270g. After 16 h overnight fast, the experimental animals were made diabetic by single intravenous administration of cold, freshly prepared solution of alloxan (CDH New Delhi) at dose of 65-70 mg/kg dissolved in normal saline solution. After 1 week, animal with fasting blood glucose of 300 mg/dl or more were considered diabetic and were used in the study. No food or liquid other than water was given during the experimental period. The product in the study was administered orally. After the confirmation of diabetes; the rats were divided randomly into three groups of four rats each and treated as follow: group1 was administered with 4 mg/kg body weight of drug solution; group 2 was administered mucoadhesive microspheres and group 3 was administered marketed conventional drug tablet. Blood samples were withdrawn by the retro orbital puncture at predetermined time at 1 hour intervals up to 24 hours; Blood samples collected were allowed to clot without any anticoagulant and were centrifuged immediately at 5000 rpm for 20 minutes to separate the serum. The absorbance of the pink-colored solutions was measured in a spectrophotometer at 505 nm using a reagent blank. Serum glucose levels (mg/100

ml) and percentage reduction in serum glucose levels were calculated.

c) In-vitro Mucoadhesivity

The mucoadhesive property of microspheres was evaluated by in-vitro wash off test for mucoadhesion. Pieces of intestinal mucosa (3cm×2cm) were mounted onto glass slides using cyanoacrylate glue. About 200 mg of microspheres were spread onto each wet rinsed tissue specimen and immediately thereafter the support was hung onto the arm of USP disintegration apparatus. By operating the disintegration test machine, the tissue specimen was given a regular up and down movement in dissolution medium at suitable P^H at 37°C taken in a 1 liter vessel of the machine. At the end of 30 minutes, 1 hour and then at hourly intervals, the machine was stopped and the microspheres adhering to the tissue, dissolution medium was centrifuged, dried and weight. The mucoadhesiveness of these microspheres was calculated.

d) Determination of drug entrapment efficiency

10mg of dried microspheres were weighted accurately and drug was extracted from microspheres by digesting for 24 hours in 10 ml of 6.8 pH phosphate buffer solution. During this period the suspension was agitated. After 24 hrs the suspension was centrifuged at 2000 rpm for about 3 minutes. The supernatant obtained was assayed spectrophotometrically for drug contents. The drug entrapment efficiency (DEE) was determined as:

DEE = (Practical Drug Content / Therotical Drug Content) x100

15. Advantages of Gastroretentive Mucoadhesive Drug Delivery Systems

1) Enhanced bioavailability: The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by gastroretentive drug delivery approaches in comparison to the administration of non-gastroretentive drug delivery. There are several different factors related to absorption and transit of the drug in the GIT that act concomitantly toinfluence the magnitude of drug absorption.

2) Sustained drug delivery: As mentioned earlier, drug absorption from oral controlled release dosage forms often limited by the short GRT available for absorption. Gastroretentive dosages forms can produce prolong and sustained release of drugs from dosage forms. However, HBS or bioadhesive or expandable systems type dosage forms can remain in the stomach for several hours and therefore, significantly prolong the GRT of numerous drugs. For drugs with relatively short half life, sustained release may result flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.

3) Site specific drug delivery: The controlled, slow delivery of drug form gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects. Hence they are useful in the treatment of disorders related to stomach and small intestine (e.g. eradication of Helicobacter pylori).

4) Reduced fluctuation of drug concentrations: Continuous input of the drug following controlled release gastroretentive delivery produces systemic drug concentrations within a narrower range compared to the immediate release oral dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent side effects that are associated with peak concentrations can be prevented.

5) Improved selectivity in receptor activation

The controlled release modes of drug administration of gastroretentive systems have the important feature that have an impact on the magnitude of the pharmacologic response, which minimizes fluctuation in blood drug concentrations (i.e. between peak and trough). However, due to the pronounced non-linear relationship between drug concentration and pharmacologic effect (i.e. pharmacodynamic) the impact of this property differs considerably as a function of the shape of the pharmacodynamic profile and the position of the specific range of concentrations on the curve of this profile. The minimizations of fluctuations in drug concentrations also make it possible to achieve certain selectivity in the elicited pharmacological effects of drugs that can activate different receptors at different concentrations.

16) Future Potential

The control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. It is anticipated that various novel products using gastroretentive drug delivery technologies may enhance this possibility. Further investigations may concentrate on the following concepts:

- Design of an array of gastroretentive drug delivery systems, each having narrow GRT for use according to the clinical need, e.g., dosage and state of diseases.
- The quantitative efficiency of gastroretentive drug delivery systems in the fasted and fed states.
- Determination of minimal cut-off size above that dosage forms retained in the GIT for Prolonged period of time.
- Design and development of gastroretentive drug delivery systems as a beneficial strategy for Treatment of gastric and duodenal cancers.
- Development of various anti-reflux formulation utilizing gastroretentive technologies.

- Exploring the eradication of *Helicobacter pylori* by using various antibiotics.
- Design and development of gastroretentive drug delivery systems for drugs, which are potential to treat Parkinson's disease.
- Study of the effect of various geometric shapes in a more excessive manner than previous studies.
- Design and synthesis of novel polymers according to their clinical and pharmaceutical need. Design and synthesis of novel mucoadhesive agents to develop bioadhesive drug delivery systems for improved gastro retention Design of novel mucoadhesive delivery using various natural mucoadhesive agents according to their clinical and pharmaceutical need.

17. Limitation of Gastroretentive Mucoadhesive System

- Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique. Similarly retention of high density system in the antrum part under the migrating waves of the stomach is questionable.
- Not suitable for drug that may cause gastric lesions eg. Non- steroidal anti-inflammatory drug. Drug that are unsuitable in the strong acidic environment, these system do not offer significant advantages over the conventional dosage forms for drugs, that are absorbed throughout the gastrointestinal tract.
- The mucus on the walls of the stomach is in a state of constant, resulting in unpredictable adherence.
- In all the above systems the physical integrity of the system is very important and primary requirement for the success of these systems.
- The bioadhesion system in patients with achlorhydria can be questionable in case of swellable system, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.
- Drugs that are irritant to gastric mucosa are not suitable for GRDDS.

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