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Review on Mucoadhesive Microspheres

Lalugowda.V, Yogananda R, Maruthi N. Snehalatha, Nagaraja T S

Department of pharmaceutics SJM college of pharmacy, Chitradurga-577502, Karnataka, India

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ABSTRACT

To improve the duration of the dosage forms' residence at the absorption site, various methods have been developed, and one of them is to develop a controlled release adhesives system. Pharmaceutical researchers are now developing an interest in mucoadhesive polymers as a way to enhance medication delivery. Because they are fragile in size, microspheres have an effective carrier capacity. This review provides an overview of the potential uses of mucoadhesive microspheres as novel carriers for improving drug delivery through various modes of administration such as oral, nasal, ocular, topical, vaginal, and rectal administration, or for systemic effects. It also focuses on the types of mucoadhesive polymers, method of preparation of microspheres, and their evaluation in vitro and in vivo, respectively. In general, they have the potential to be used for targeting and controlled release of the drug. The binding of mucoadhesive properties to the microspheres has additional benefits like much more intimate contact with the mucus layer, effective absorption, and increased bioavailability of the drugs due to a large ratio of surface area to volume.

INTRODUCTION:

Recently the novel dosage forms which can control the release rate and target the active drug molecule to a particular site have attained a great formulation interest. Precisely designed controlled drug delivery system can overcome many problems of conventional therapy and enhance the therapeutic efficacy of a given drug. Drug action can be improved by developing new drug delivery system, such as the mucoadhesive microsphere drug delivery system. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site of leading to a Bioavailability increase and useful in both local and systemic effects.[1]

❖ Microspheres constitute an important part of particulate drug delivery system by virtue of their small size and efficient carrier capacity. Microsphere are the carrier linked delivery system in which particle size ranges from 1-1000 µm range in diameter having a core of drug and entirely outer layers of polymer as coating material. However, the success of these Microspheres is limited due to their short residence time at site of absorption. It would advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane. This can be achieved by coupling bioadhesion Characteristics to microspheres developing “mucoadhesive microspheres”.[2]

❖ Generally microspheres posess potentiality to be employed for targeted and controlled/extended release of drug, but incorporating mucoadhesive properties to microspheres will furthermore improve absorption and bioavailability of the drugs. Mucoadhesive microspheres enhance the intimate contact with the mucus layer and drug targeting to the absorption site by anchoring bacterial adhesions, plant lectins, antibodies etc. Mucoadhesive microspheres offers the possibilities of localized as well as controlled release of drugs by adherence to any mucosal tissue present in eye, nasal cavity, urinary and GI tract[4].

❖ **MUCOADHESIVE DRUG DELIVERY SYSTEM:**

- Mucoadhesive drug delivery methods make use of the bioadhesion of certain polymers, which become adhesive when hydrated and can be utilised to target a medicine to a specific area of the body for long periods of time. Bioadhesion is an interfacial phenomena in which two materials are held together by interfacial forces,at least one of which is biological. Adhesion between a polymer and a biological membrane is an example of an artificial material adhering to a biological substrate.

The word "mucoadhesion" is used to describe the attachment of a polymer to the mucin layer of a mucosal tissue. Various approaches can be used to deliver mucoadhesive drug delivery systems:-

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

Microparticles and microcapsules with a diameter of 1— 1000 μm and made wholly of a mucoadhesive polymer or with an exterior coating of it are called mucoadhesive microspheres. Microspheres, in general, have the potential to be used for targeted and controlled drug delivery; however, coupling bio-adhesive properties to microspheres has additional advantages, including efficient drug absorption and bioavailability due to a high surface to volume ratio, a much more intimate contact with the mucous layer, and specific drug targeting to the absorption site[3].

Mucoadhesion is topic of current interest in the design of drug delivery system. Mucoadhesive microsphere exhibit a prolonged residence time at the site of application and facilitate an intimate contact with the underlying absorption surface and thus contribute to improved or better therapeutic performance of drug. Mucoadhesive drug delivery systems promises several advantages that arise from localization at a given target site, prolonged residence time at the site of drug absorption and an intensified contact with the mucosa increasing the drug concentration gradient. Hence, uptake and consequently bioavailability of the drug is increased and frequency of dosing reduced with the result that patient compliance is improved[19].

In oral drug delivery, mucoadhesion is provided by the formation of non-covalent bonds such as hydrogen bonds and ionic interactions or physical adhesion between the mucus layer and mucoadhesive polymers. In early days antimicrobial agents are orally administered to produce a systemic effect, but this application induces some side effects like hypersensitivity, gastrointestinal intolerance, and development of bacterial resistance. Mcquinn et al. prepared a terminating drug delivery system to obtain sustained serum levels of buprenorphine for up to 24h upon single application of the patch and it was found to remain intact for about 12–24 h period and can be easily removed at any time after application.[4]

MUCOADHESION:

Mucoadhesive drug delivery systems are used to enhance drug absorption in a site-specific manner mucoadhesion is defined as the interaction between a mucin surface and a syntheticor natural polymer. Mucoadhesion is defined as the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesion has been widely promoted as a way of achieving site-specific drug delivery through the incorporation of mucoadhesive hydrophilic polymers with in pharmaceutical formulations such as "Microspheres" along with the active pharmaceutical ingredient(API)[4].

Mechanism of Mucoadhesion:

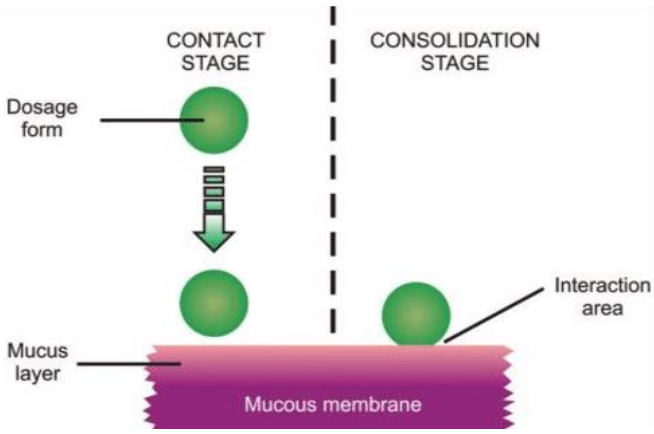

Fig No:1: Mechanism of Mucoadhesion:

1.Adsorption theory : According to this theory the mucoadhesive get adsorbed on the mucosal surface by intermolecular forces, viz. Vander Waal's forces, hydrogen bonding.[4]

2.The fracture theory: This is by-far the most accepted theory on bioadhesion. It explains the forces required to separate the two surfaces after adhesion has taken place. It measures the maximum Tensile stress(sm) produced during detachment as follows ((Mathiowetz E et al., 2010), s m = Fm/Ao.[5]

3.The Electronic Theory: Involves the formation of an electric double layer at the mucoadhesive interface by the transfer of electrons between the mucoadhesive polymer and the mucin glycoprotein network. For example: 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.[6]

4.Wetting theory : States that If the contact angle of liquids on the surface of the substrate is less, then there is a larger affinity for the liquid to the surface of the substrate, as stated by the statement. When two substrate surfaces of this kind are brought into touch with each other in the presence of liquid, the liquid itself may function as an adhesive between the substrate surfaces.[7]

5.mechanical theory : Adhesion arises from an interlocking of liquid adhesive into irregularities on the rough surface which provide an increased surface area available for interaction.[8]

6. Cohesive Theory: According to this theory the phenomena of mucoadhesion is mainly due to the intermolecular interactions amongst like-molecules.[9]

Characteristics of an ideal mucoadhesive polymers:

- It should be non-irritant to the mucous membrane.
- It should preferably form a strong no covalent bond with the mucin-epithelial cell surfaces.
- It should adhere rapidly to tissue and should have some site specificity.
- It should allow easily integrated into the drug and should offer no hindrance to its release.
- The polymers must not decompose on storage of the dosage form and its shelf life.
- The cost of the polymer should not be high so that the prepared dosage form remains competitive.
- It should be nonabsorbable from GI tract.
- Robinson and his group using the fluorescence technique concluded that:
- Cationic and anionic polymers bind more effectively than neutral polymers.
- Polyanions are better than polycations in terms of binding/potential toxicity, and further, that water-insoluble polymers give greater flexibility in dosage form design compared with rapidly or slowly dissolving water-soluble polymers.
- Anionic polymers with sulfate groups bind more effectively than those with carboxylic groups. iv. A degree of binding is proportional to the charge density on the polymer.
- Highly binding polymers include carboxymethylcellulose, gelatin, hyaluronic acid, 173arbopol, and polycarbophil[16].

Advantages of mucoadhesive microspheres drug delivery system:

➢ As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower API concentrations for disease treatment.

➢ The use of specific bioadhesive molecules allows for possible targeting of particular sites or tissues, for example the gastrointestinal (GI) tract.

- Increased residence time combined with controlled API release may lead to lower administration frequency.

- Offers an excellent route, for the systemic delivery of drugs with high first-pass metabolism, there by offering a greater bioavailability.

- Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.

- Better patient compliance and convenience due to less frequent drug administration.

- Uniform and wide distribution of drug throughout the gastrointestinal tract which improves the drug absorption.

- Prolonged and sustained release of drug.

- Maintenance of therapeutic plasma drug concentration.

- Better processability (improving solubility, dispersibility, flowability).

- Increased safety margin of high potency drugs due to better control of plasma levels.

- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.

- Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestine can be administered by this route e.g. buccal, sublingual, vagina.[10]

Disadvantages of Mucoadhesive Microspheres Drug Delivery System:

- The release from the formulations may get modified.

- The release rate may vary from a variety of factors like food and the rate of transit though gut, mucin turnover rate etc.

- Differences in the release rate can be found from one dose to another.

- Any loss of integrity in release pattern of the dosage form may lead to potential toxicity.

- These kinds of dosage forms cannot be crushed or chewed[9].

CLASSIFICATION OF MUCOADHESIVE POLYMERS:

There are various mucoadhesive polymers of synthetic and natural origin, which are classified in the Table below:

Table 1: A shortlist of Mucoadhesive Polymers:

SL.NO	Synthetic Polymers	Natural Polymers
1.	Hydroxypropyl methylcellulose (HPMC)	Chitosan
2.	Poly (acrylic acid) Polymers (carbomers, Polycarbophil)	Sodium alginate
3.	Polyvinyl pyrrolidine (PVP)	Pectin
4.	Polyvinyl Alcohol (PVA)	Locust Bean Gum
5.	Polyhydroxy ethyl methyl acrylate	Guar gum
6.	Polyethylene Oxide	Xanthan gum
7.	Sodium carboxy methyl cellulose (Na CMC)	Karaya gum
8.	Hydroxy ethyl cellulose (HEC)	gelatin
9.	Hydroxy propyl cellulose (HPC)	Tragacanth
10.	Ethyl cellulose (EC)	Soluble starch
11.	Methylcellulose	Lecithin[11]

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Strategies For Preparation Of Mucoadhesive Microspheres:

Mucoadhesive microspheres can be set up by utilizing extraordinary systems like:

METHODS OF PREPARATION:

1.Emulsion cross linking method: Natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in the non-aqueous medium i.e., oil. In the second step, cross-linking of the dispersed globule is carried out either by means of heat or by using the chemical cross- linking agents like glutaraldehyde, formaldehyde. Heat denaturation is not suitable for the thermolabile drugs while the chemical cross-linking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation. The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent from the polymer of the core material, then polymer shrinks around the core.[10]

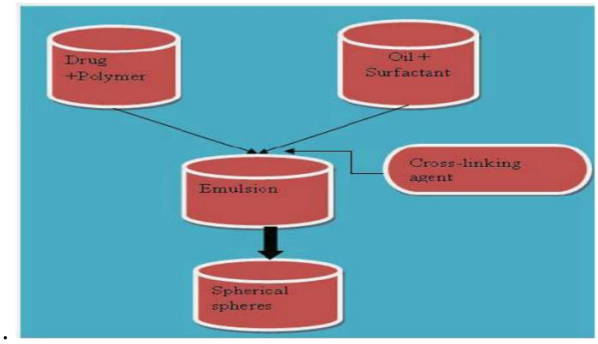

Fig No2: Emulsion cross linking method

2.Solvent Evaporation: This is carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size of microcapsule. The mixture is then heated if necessary to evaporate the solvent from the polymer of the core material, then polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The core materials may be either water soluble or water insoluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous[8].

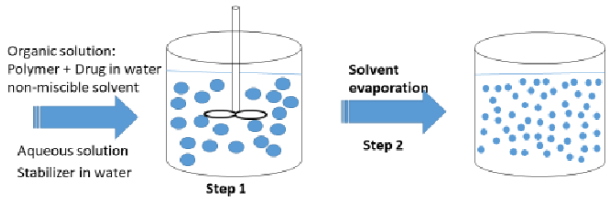

Fig No: 3.Solvent Evaporation:

3.Hot melt microencapsulation: This method is reported by Mathiowetz, E. and Langer, R., in 1987 for the preparation of polybis (p carboxyphenoxy) propane anhydride polyanhydride copolymer microcapsules with sebacic acid. In this method, the solid drug particles are dispersed in melted polymer and obtained mass was sieved at less than 50 µ. The mixture is suspended in an immiscible solvent (such as silicone oil), continuously stirred and heated to 5°C above the melting point of the polymer. Once the emulsion was

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stabilized, cooled until the polymer particles are solidified. The resulting microcapsules are washed by decantation with petroleum ether.

Microcapsules a diameter of 1 to 1000 µ can be obtained and the particle size distribution can be easily controlled by changing the stirring speed. The main problem for the development of this process is to provide a suitable method for the microencapsulation of water labile polymers, such as field anhydride. Disadvantage of this method was the moderate temperature at which the formulation is exposed[9].

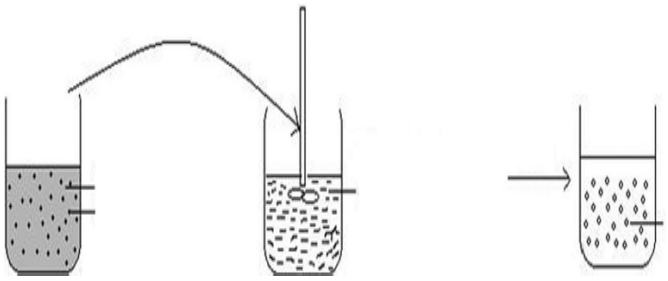
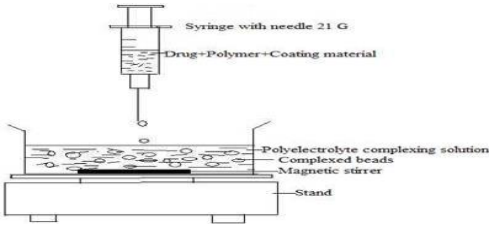


Figure 4. Hot melt microencapsulation

4.Ionic gelation technique: Sodium alginate and the mucoadhesive polymer are dispersed in purified water (50 ml) to form a homogeneous polymer mixture. Drug is added to the polymer matrix and mixed thoroughly to form smooth viscous dispersion. Resulting dispersion is then sprayed into calcium chloride (10% w/v) solution by continuous stirring. Produced droplets are retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce rigid spherical microspheres. The resulting microspheres are collected by decantation, and the thus separated is washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then dried at 45°C for 12 hrs.[9]



FigNo5: Ionic gelation technique:

5.Solvent removal: It is a non-aqueous microencapsulation method, particularly suitable for water-resistant polymers such as polyanhydrides. In this method, the drug is dispersed or dissolved in a solution of the selected polymer solution (volatile organic solvent such as methylene chloride). This mixture was then suspended in a silicone oil containing methylene chloride. After suspending petroleum ether was added and stirred for complete solvent extraction. The resulting microcapsules can then be dried under vacuum[12].

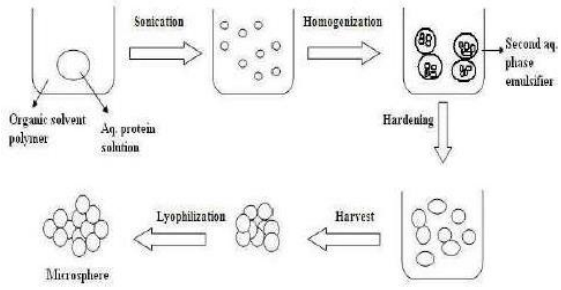
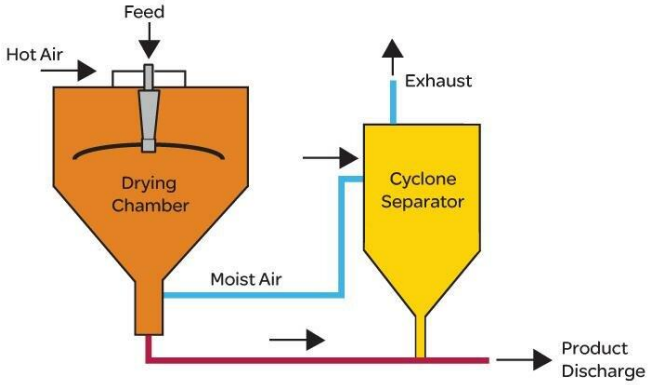


Figure 6. Solvent removal/ Evaporation method Microspheres preparation

6.Spray Drying: In Spray Drying, the polymer is first dissolved in a suitable volatile organic solvent. The drug is dispersed in the polymer solution under high-speed homogenization (Figure 3). This dispersion is then atomized in a stream of hot air, leads to the

formation of the small droplets from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 µm[13].



FigNo7.Spray Drying

7.Phase separation coacervation technique: In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non solvent results in the solidification of polymer. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer.[13]

8.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 developed this method 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[14].

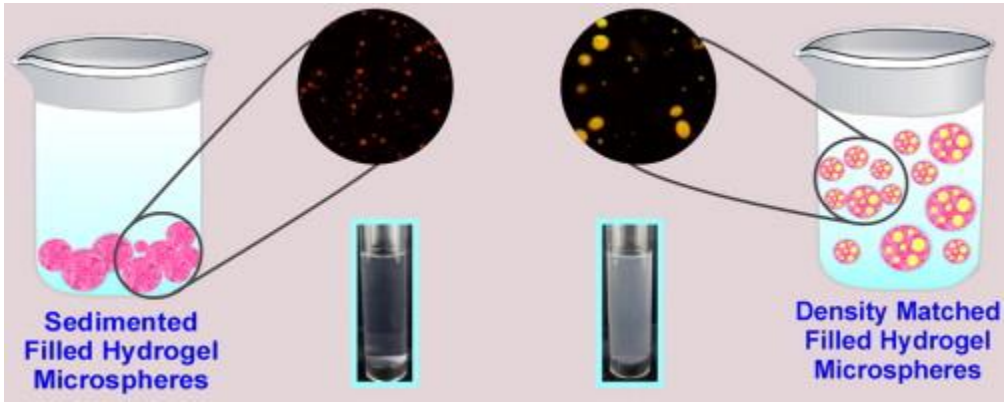


Fig No 8:Microsphere preparation technique

Evaluation:

1. Yield of Microspheres: The prepared microspheres were collected and weighed. 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 excipients and drug) x 100

2. Particle size determination: The particle size can be determined by using an optical microscope under regular polarized light, and mean particle size was calculated by measuring 100 particles with the help of a calibrated colourimeter.

3. Bulk density: Bulk density can be determined by three tap method, after filling the weighed quantity of microspheres in a graduated cylinder, the volume occupied by microspheres should be determined.

4. Optical Microscopy: This method was used to determine particle size by using optical microscope (Meizer OPTIK) The measurement was done under 450x (10x eye piece and 45x objective) and100 particles were calculated.

5. Entrapment Efficiency: Microspheres containing of drug should be crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr, and was filtered then assayed by UV-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content[8].

6. Swelling Index: Swelling list represent the capacity of the mucoadhesive microspheres to get expand at the engrossing surface by retaining liquids accessible at the site of ingestion, which is an essential necessity for inception of mucoadhesion. The percent growing worth can be resolved utilizing following condition.

Percent swelling = DT - D0/D0 × 100

Where, D0 = weight of dried microspheres DT = weight of expand microspheres.[18]

7. *In-vitro* drug release: The in vitro dissolution studies for all the formulations were carried out in two steps, using USP apparatus type-I (basket) at 100 rpm. The dissolution medium consisted of 0.1 N HCl for first 2 h followed by phosphate buffer pH 6.8, maintained at 37 °C±0.5 °C. The drug release at different time intervals (Acid stage: 120 min; Buffer stage: 10, 20, 30, 45 and 60 min) was measured by UV-spectrophotometer (Shimadzu 1700, Japan) at 302 nm[17].

8. *In-vitro* diffusion studies: *In-Vitro* diffusion studies were performed using in vitro nasal diffusion cell. The receptor chamber was filled with buffer maintained at 37 ± 2 °C. Accurately weighed microspheres equivalent to 10 mg were spread on sheep nasal mucosa. At selected time intervals 0.5 mL of diffusion samples were withdrawn through a hypodermic syringe and replaced with the same volume of pre warmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples were analysed spectrophotometrically[8].

Applications of Mucoadhesive Microspheres:

- Controlled and sustained release dosage forms
- Enteric coating dosage forms can be prepared
- Protects drug from environmental hazards
- Can be used for separation of incompatible substances
- The hygroscopic properties of many core materials may be reduced by microspheres.
- Microencapsulated drugs reduce gastric irritation
- Therapeutic magnetic microspheres can be used to deliver the drug to liver tumour 8. Radioactive microspheres are used for imaging of liver, spleen, lung, bone marrow etc.[15],

CONCLUSION:

The capability of microparticles to adhere to mucosal membranes in the mouth, nose, and gastrointestinal system is known as membrane adhesion. One approach that shows promise is the delivery of the medication to the desired area using a mucoadhesive microsphere. It increases the plasma drug concentration, extends the drug's residence time, enhances its bioavailability, and protects the medication. A mucoadhesive microsphere's primary objective is to deliver controlled drug release. As a result, it was determined that mucoadhesive microspheres enhance drug bioavailability and offer controlled medicine release.

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