



Mucoadhesive Microsphere - Review

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Abstract:

Several approaches have been immersed to prolong the residence time of the dosage forms at the absorption site and one of them is the development of oral controlled release mucoadhesive system. Mucoadhesive drug delivery systems are used to enhance drug absorption in a site-specific manner. Bioadhesion has been defined as the attachment of synthetic or biological macromolecules to a biological tissue. The biological surface can be epithelial tissue or the mucous coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as mucoadhesion. Mucus is a thin blanket covering all epithelia that are in contact with the external environment in the gastrointestinal, respiratory, and urogenital tracts. This approach involves the use of mucoadhesive polymers, which can adhere to the epithelial surface in the stomach. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanospheres, liposomes, nanoparticles, etc., which modulates the release and absorption of the drug. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity.

Keywords: Mucoadhesive microspheres, mucoadhesive polymers, method of preparation.

INTRODUCTION:

Oral controlled release systems continue to be the most popular ones among all the drug delivery systems. It offers several advantages over the conventional systems like better plasma level profile, lower dosing and toxicity and many more. The problem frequently encountered with controlled release dosage form is its inability to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine. This may be due to the rapid gastrointestinal transit phenomenon of the stomach, which may consequently diminish the extent of absorption of many drugs since most of

drug entities are mostly absorbed from upper part of intestine. Therefore it would be beneficial to develop sustained release formulations which remain at the absorption site for an extended period of time. Several approaches have been immersed to prolong the gastric residence time of the dosage form at the absorption site and one of these is the development of oral controlled release mucoadhesive multiparticulate system. Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an

enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems. They have varied applications and are prepared using assorted polymers. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling mucoadhesion characteristics to microspheres and developing mucoadhesive microspheres. Mucoadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to the absorption site. Mucoadhesive and biodegradable polymers undergo selective uptake by the M cells of Peyer patches in gastrointestinal (GI) mucosa and this uptake mechanism has been used for the delivery of high molecular weight drugs (proteins and peptides), antigens. Carbopol-934P (acrylic acid homopolymer) is an anionic polymer that has been used in mucoadhesive systems by several researchers. Carbopol-934P was selected as a polymer in the preparation of mucoadhesive microspheres because of its good mucoadhesive and biodegradable properties and ethyl cellulose as carrier polymer for microspheres, sodium alginate as a matrix material to achieve controlled release drug delivery is due to its hydrogel forming properties.(1)

ADVANTAGES OF MUCOADHESIVE MICROSPHERES:

1) 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.

- 2) The use of specific bioadhesive molecules allows for possible targeting of particular sites or tissues, for example the gastrointestinal (GI) tract.
- 3) Increased residence time combined with controlled API release may lead to lower administration frequency.
- 4) Offers an excellent route, for the systemic delivery of drugs with high first-pass metabolism, there by offering a greater bioavailability.
- 5) Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.
- 6) Better patient compliance and convenience due to less frequent drug administration.
- 7) Uniform and wide distribution of drug throughout the gastrointestinal tract which improves the drug absorption.
- 8) Prolonged and sustained release of drug.
- 9) Maintenance of therapeutic plasma drug concentration.
- 10) Better processability (improving solubility, dispersibility, flowability).
- 11) Increased safety margin of high potency drugs due to better control of plasma levels.
- 12) Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- 13) 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.(2)

MUCOADHESIVE POLYMERS:

There are two broad classes of mucoadhesive polymers Hydrophilic polymers and hydrogels. In the large classes of hydrophilic polymers those containing carboxylic moiety exhibit the best mucoadhesive property, poly vinyl pyrrolidone (PVP), Methyl cellulose (MC), Sodium carboxy methyl cellulose (SCMC), Hydroxy propyl cellulose (HPC), Hydroxy propyl methyl cellulose (HPMC).

Hydrogels are the class of polymeric biomaterial that exhibit the basic characteristics of an hydrogels to swell by absorbing water interacting by means of adhesion with the mucus that covers epithelia i.e.

Anionic group – Carbopol, Polyacrylates and their cross-linked modifications

Cationic group - Chitosan and its derivatives

Neutral group - Eudragit- NE30D etc..(3)

Characteristics of an Ideal Mucoadhesive Polymer:

1. The polymer and its degradation products should be nontoxic and should be non absorbable from the GI tract.
2. It should be nonirritant to the mucus membrane.
3. It should preferably form a strong non 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. It should be inert and compatible with the environment
9. The polymer should be easily available in the market and economical.
10. It should allow easy incorporation of drug into the formulation.(3)

Sr. No.	POLYMER	Relative mucoadhesive force	Quality of mucoadhesion
1	CMC	193	Excellent
2	Carbapol	185	Excellent
3	Tragacanth	154	Excellent
4	Sod.alginate	126	Excellent
5	HPMC	125	Excellent
6	Gelatin	116	Fair
7	Pectin	100	Poor
8	Acacia	98	Poor
9	Providone	98	Poor

FACTORS AFFECTING MUCOADHESION:

In the following table various factors are enlisted that affects mucoadhesion attachment.(4)

Polymer Related Factors	Environmental Related Factors	Physiological related factors
Molecular weight	pH	Mucin turnover
Concentration of active polymer	Applied strength	
Spatial Conformation	Initial contact time	
Degree of Hydration	Selection of the model substrate surface	
Chain flexibility of polymer		
Functional Group Contribution		
Swelling		

METHOD OF PREPARATION:

1) Solvent Evaporation:

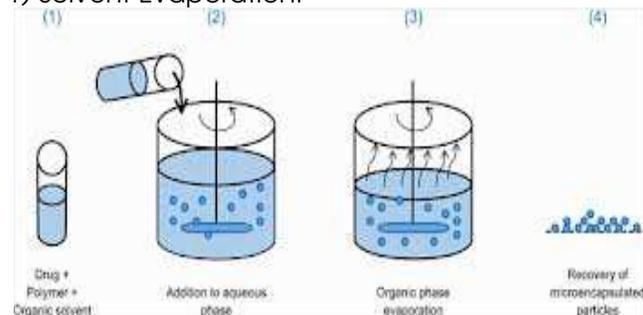


Fig. Solvent evaporation technique

Solvent evaporation technique involves four major steps, like incorporation of pharmaceuticals, droplet formation, solvent removal, and drying.

1) Incorporation of pharmaceuticals: The polymer is dissolved in a suitable water immiscible solvent, and the pharmaceutical agent is directly added into the solution of polymeric-matrix materials by dissolution/dispersion in suitable solvents, or emulsification of aqueous solution of the pharmaceutical agents immiscible with the matrix-material solution. For the preparation of solution or dispersion of pharmaceutical agents, impeller or static mixing, high speed-stator mixing or microfluidization techniques are generally used.

a) Droplet formation: This step determines the size of resulting microcapsules. The size of microcapsules affects the drug encapsulation efficiency and the rate of drug release. The following procedures used in droplet formation, namely:

b) Stirring: The external phase is filled into a vessel and agitated by an impeller. The drug/matrix dispersion is then added, drop wise or all at once, under agitation at a speed sufficient to reach the desired droplet size.

c) Static mixing: Static mixer consists of baffles or other flow obstacles installed in a tube. The baffle arrangement repeatedly splits and recombines the stream of fluid passing through the tube.

d) Extrusion: It involves feeding of drug/matrix dispersion through single or multichannel pathways directly into the continuous phase. When drug/ matrix dispersion leaves the pathways, discrete droplets are formed within the slow flowing continuous phase. In extrusion, flow is laminar, the droplets are formed at the site of introduction of drug/matrix dispersion into continuous phase, due to which there is no effect on size of droplets formed thereafter. Where as in

static mixing, turbulent flow occur which constantly act on the disperse phase and thus, there is a continuous change in the size of droplets.

e) Dripping: Microcapsules have been prepared by dripping 10 % and 15 % (w/w) solution of poly (ethylene-co-acetate) in dichloromethane, containing dispersed protein particles from a needle into an electric field. The droplet formed was detached from the needle by electrostatic forces.

2) Solvent removal: Solvent removal can be achieved either by evaporation or by extraction. In both processes, the drug/matrix dispersion should be slightly soluble in the continuous phase, so that, partitioning into continuous phase can occur that leads to precipitation of the matrix material. The two ways of solvent removal can be performed, namely:

a) Solvent evaporation: In this method, the capacity of the continuous phase is insufficient to dissolve the entire volume of disperse phase solvent. Thus, solvent evaporates from the surface of the dispersion to obtain hardened microcapsules.

b) Solvent extraction: This is a two-step process. Firstly, the drug/matrix dispersion is mixed with a small quantity of continuous phase to yield desired size of droplets. Then secondly, further more continuous phase and/or additional extraction agents are added at an amount sufficient to absorb the entire solvent leaching from droplets of drug/matrix. This results into formation of solid microcapsules.

3) Drying: Solidified microparticles from the continuous phase are by either filtration or centrifugation. Then the particles are rinsed with

suitable liquids to remove adhering substance such as dispersion stabilizers or non-encapsulated drug. Finally, these microparticles are dried at elevated temperature or under reduced pressure to yield free flowing powder.(5)

There are several factors that influence the formation of microspheres when solvent evaporation technique is employed.

1. Type of emulsion used
2. Type and concentration of emulgent used.
3. Solubility of the drug and polymer in dispersed phase and the continuous phase
4. Characteristics of the drug and the polymer and the drug/polymer ratio
5. Stirring rate or agitator characteristics
6. Inner water/oil ratio
7. Other factors.

Selection of phases for the preparation of microspheres

(A)The dispersed phase:

While making the selection ,the factors considered are

- Successful entrapment of the drug
- Ability to dissolve the polymers and the drug excipients

(B)The continuous phase;

While making the selection ,the factors considered are

- Immiscibility with the dispersed phase solvent
- Inability to dissolve the polymer as well as the drug.

When the drug is hydrophilic the non aqueous medium selected as a continuous phase. Most commonly liquid paraffin is used as it is inert to the drug as well as the polymers .when the drug is hydrophobic then the aqueous medium is used.(6)

2) Ionic gelation technique:

Procedure:

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.(7)

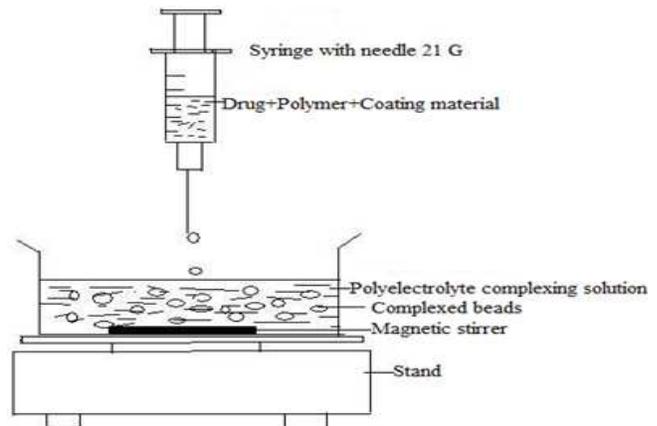


Fig. Ionotropic gelation method

Mechanism:

Microspheres prepared by ionotropic gelatin technique mechanism involves electrostatic interaction between amine groups of polymer and negatively charged group of polyanion such as tripolyphosphate.chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for microsphere formation. As calcium ions are being released by ion exchange with sodium ion in the medium,electrostatic repulsion between the carboxylate anions further accelerates the swelling and erosion of alginate gels .on account

of short time release in alkaline media, alginate was not found to be an ideal sustained release wall material for microencapsulation.(1)

Study of effect of various factors:

a) Effect of orifice diameter of needle:

Effect of orifice diameter (needle no 18, 20 and 23) on formation of microspheres is summarized below. Small particle size with rigid nature of microspheres was possible with needle no 20 and 23. However, as viscosity plays important role in passage of solution from needle, a difficulty was observed for needle no 23. Therefore, needle no. 20 was suggested for this process.

b) Effect of dropping height on formation of microspheres:

While doing practically, apart from distance of 15 cm and 6 cm, the observation was also noted for distance more than 15 cm. At this distance, no proper shape of microspheres was observed immediately after formation in beaker and even after drying. Elongated microspheres and sometimes elongation with flat surface of microspheres was observed. Wide particle size distribution was experienced. At distance of 15 cm, shape was slightly spherical but no integrity in surface was observed immediately after formation and subsequent drying. But as the distance was reduced, significant change in shape, size and surface integrity was observed.

c) Stirring speed:

Stirring speed affect on drug entrapment efficiency. It was found that drug entrapment efficiency decreases with increase in stirring speed.(8)

3) Spray drying:

In spray drying, volatile organic solvent such as dichloromethane, acetone, etc are used. Dispersion of drug and the polymer solution made by using high-speed homogenizer. This dispersion is then atomized in a stream of hot air. Mechanism of formation of microsphere involves mainly atomization leads to the formation of the small droplets or the fine mist, the solvent evaporation. Formation of the microspheres in a size ranges 1-100 μm . Microparticles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying.(9) Process control variables include feed materials properties such as viscosity, uniformity and concentration of core and coating material, feed rate, method of atomization and the drying rate and the air stream solvent concentration.(6)

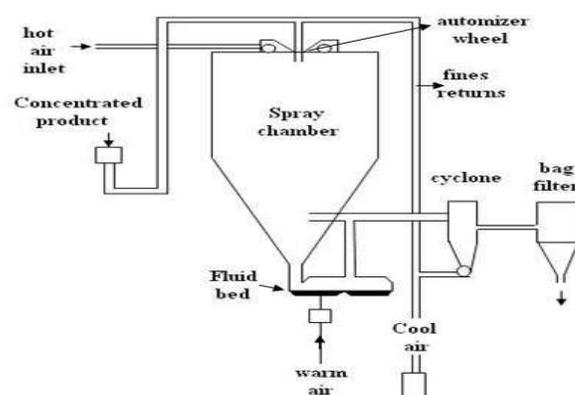


Fig: spray drying method

4) Wet inversion technique:

Chitosan solution in acetic acid was dropped in to an aqueous solution of counter ion sodium tripolyphosphate through a nozzle. Microspheres formed were allowed to stand for 1 hr and cross linked with 5% ethylene glycol diglycidyl ether. Microspheres were then washed and freeze dried. Changing the pH of the coagulation medium could modify the pore structure of CS microspheres.(9)

5) Hot melt microencapsulation:

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 μm . 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. poly anhydrides. Microspheres with diameter of 1-1000 μm 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.(9)

6) Preparation of microspheres by glutaraldehyde cross linking:

In this method, generally chitosan is used which act as a mucoadhesive polymer for the microsphere. chitosan is dissolved in aqueous acetic acid solution, drug was dispersed in the polymer solution. Above drug and polymer solution was added to light liquid paraffin and heavy liquid paraffin in the ratio of 1:1 , 0.5% (w/v) Span 85,tween 40,tween20 used as an emulgent to form a water in oil (w / o) emulsion. Stirring was continued at 2000 rpm using a 3- blade propeller stirrer. A drop-by-drop solution of a measured quantity cross linking agent glutaraldehyde (25% v/v) was added at 15, 30, 45, and 60 minutes. Stirring was continued for 2.5 hours and separated by filtration under vacuum and washed, first with petroleum ether (60 °C- 80 °C) and then with distilled water to remove the adhered liquid paraffin and glutaraldehyde, respectively. The

microspheres were then finally dried in vacuum desiccators. According to literature survey
Dispersed phase: Chitosan and drug in acetic acid solution

Continuous phase: Light liquid paraffin and heavy liquid paraffin

Emulgent: Span 85,tween 40,tween20

Crosslinking agent: Glutaraldehyde(dilution with water)(9)

7) Preparation of microspheres by thermal cross-linking:

This is same as above described; only two major points Citric acid as a cross-linking agent,

And use of temperature conditions. The chitosan cross-linker solution was cooled to 0 °C and then added to 25 mL of corn oil previously maintained at 0 °C, with stirring for 2 minutes. This emulsion was then added to 175 mL of corn oil maintained at 120 °C, and cross-linking was performed in a glass beaker under vigorous stirring (1000 rpm) for 40 minutes. The microspheres obtained were filtered and then washed with diethyl ether, dried, and sieved. Only difference is use of citric acid as a cross linker instead of glutraldehyde. (9)

CHARACTERIZATION OF DRUG LOADED BIOADHESIVE MICROSPHERES:

1) Size of microspheres:

Microsphere size was determined by using an optical microscope. The mean microsphere size was calculated by measuring 300 microspheres with the help of a calibrated ocular micrometer. (10)

2) Morphological Study:

Morphological study was carried out by using Scanning electron microscope (SEM). A scanning electron micrograph of drug loaded microspheres was obtained. A small amount of microspheres

was spread on glass stub. Afterwards, the stub containing the sample were placed in scanning electron microscope (JEOL JSM-6360A) chamber. The photomicrograph was taken at 5.0 KV.(10)

3) Micromeritics Study:

a) Angle of repose: Angle of repose of each batch was carried out by glass funnel method. Angle of repose was calculated by the formula, $\theta = \tan^{-1}(h/r)$.

b) Bulk density: Bulk density of known mass of microspheres in graduated measuring cylinder. The bulk density was calculated by taking ratio of weight of microspheres in gram to bulk volume of microspheres in cm^3

c) Tapped density: Tapped density is the volume of powder determined by tapping using measuring cylinder containing pre-weighed amount of sample. Tapped density of microspheres was calculated by the ratio of weight of microspheres in gram to volume of microspheres after tapping in cm^3 .

d) Carr's compressibility index :

Carr's compressibility index = $(\text{Tapped density} - \text{Bulk density}) / \text{Tapped density} \times 100$ (10)

4) Percentage yield:

Prepared microspheres of all batches were accurately weighed. Percent yield was calculated by using following formula.

Percentage yield = $(\text{Actual weight of product} / \text{Total weight of excipients and drug}) \times 100$

5) Drug entrapment efficiency:

Microspheres equivalent to 50 mg of drug were taken for evaluation. Drug entrapment efficiency was estimated by crushing the microspheres and extracting with aliquots of hydrochloric acid buffer of pH 2.2 repeatedly. The extract was diluted to 100 ml in a volumetric flask using hydrochloric acid

buffer of pH 2.2. The solution was filtered and amount of metformin hydrochloride was estimated against appropriate blank. (10)

6) In vitro wash off test:

In-vitro bioadhesive properties of microspheres were evaluated by in -vitro wash off test. A 1cm x 2 cm piece of stomach mucosa of goat was tied on glass slide using thread. A fixed number of microspheres were spread on this mucosa and allowed to wet by mucus for 5 min. This glass slide was hanged in grove of USP disintegration test apparatus containing hydrochloric acid buffer of pH 2.2 and operated for regular up and down movements as shown in figure . After 15 minutes number of microspheres remain adhered on the mucus membrane were counted and further percentage was calculated. (10)

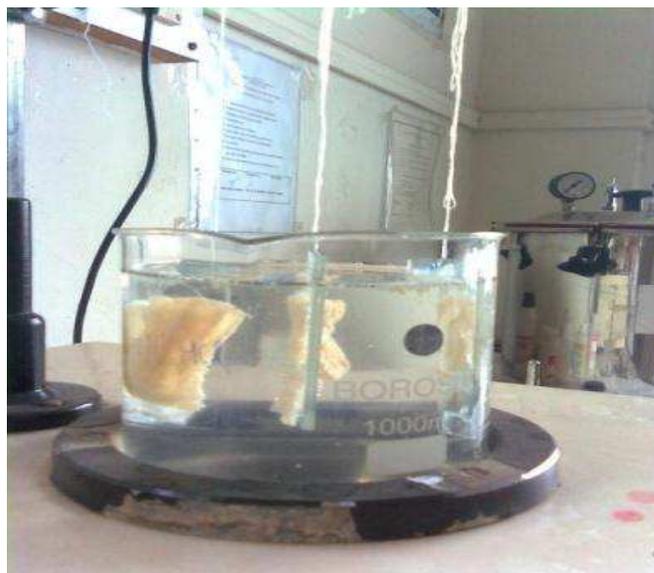


Figure: Bioadhesion testing by in vitro wash off test

8) In Vitro drug release:

In vitro dissolution studies can be studied by using were carried out by using USP paddle type dissolution apparatus Weighed amount of drug loaded microspheres were introduced into 900ml Five ml of aliquots were withdrawn at

predetermined time intervals and equal volume of fresh dissolution medium was replaced to maintain sink condition. The samples were analyzed spectroscopically at λ_{\max} to determine the concentration of drug present dissolution medium of hydrochloric acid buffer maintained at 37°C at certain RPM.(10)

APPLICATIONS OF MUCOADHESIVE MICROSPHERES:

Some of the applications of microspheres are described in detail as following: -

1. Controlled and sustained release dosage forms.
2. Microsphere can be used to prepare enteric-coated dosage forms, so that the medicament will be selectively absorbed in the intestine rather than the stomach.
3. It has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat. Microsphere does not yet provide a perfect barrier for materials, which degrade in the presence of oxygen, moisture or heat, however a great degree of protection against these elements can be provided. For example, vitamin A and K have been shown to be protected from moisture and oxygen through microsphere.
4. The separations of incompatible substances, for example, pharmaceutical eutectics have been achieved by encapsulation. This is a case where direct contact of materials brings about liquid formation. The stability enhancement of incompatible aspirin chlorpheniramine maleate mixture is accomplished by microencapsulating both of them before mixing.
5. Microsphere can be used to decrease the volatility. An encapsulated volatile substance

can be stored for longer times without substantial evaporation.

6. Microsphere has also been used to decrease potential danger of handling of toxic or noxious substances. The toxicity occurred due to handling of fumigants, herbicides, insecticides and pesticides have been advantageously decreased after microencapsulation.
7. The hygroscopic properties of many core materials may be reduced by microsphere.
8. Many drugs have been microencapsulated to reduce gastric irritation.
9. Microsphere method has also been proposed to prepare intrauterine contraceptive device.
10. Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system. Mucoadhesive microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.
11. Radioactive microspheres are used for imaging of liver, spleen, bone marrow, lung etc and even imaging of thrombus in deep vein thrombosis can be done .(2)

CONCLUSION:

Mucoadhesive microspheres drug delivery system have been gaining a lot of interest of various researchers and scholars, because of their advantages of controlled and sustained release action, and versatility as a drug carrier. Mucoadhesive microspheres will ensure the maintenance of effective plasma concentration over prolonged period of time by extending the

release of drug. These carrier systems will also increase the residence time of the drug in the gastrointestinal tract. Mucoadhesive drug delivery is a promising area for systemic delivery of orally inefficient drugs as well as an attractive alternative for noninvasive delivery of potent peptide and perhaps protein drug molecules.

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