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**Review Article**

# A Review: Mucoadhesive microspheres a promising tool in drug delivery system

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**ABSTRACT**
Mucoadhesive drug delivery systems promise numerous interests which occur from centralization at a specified objective site, extended dwelling time on the point of preparation absorption and an increased connection to the mucosa rising the drug absorption gradient. Mucoadhesive drug delivery system (MDDS) can be considered to manage drug release and to facilitate prolonged drug maintenance at the site of application. Conventionally typical adhesive materials used in mucoadhesive drug delivery systems generally are the family of hydrogels, such as natural gums, polyacrylates, and cellulose ethers. MDDS is a branch of a controlled delivery system that could be formed to regulate the drug release and to facilitate prolonged drug preservation by the site of application, which accordingly promotes therapeutic efficacy. The commonly essential adhesive materials used in the MDDS typically are the family of hydrogels, such as natural gums, polyacrylates, and polymers.

**Keywords:** Polymers, GRDDS, Bio/Mucoadhesive, bioavailability, Solubility.

## INTRODUCTION

The gastro retentive dosage formulae are retained in the stomach for a sustained time and discharge their active ingredients slowly. It is a broadly working outlook to maintain the dosage form in the stomach for an extended duration of time and liberate the drug steadily that can deal with numerous threats related with conventional oral delivery, along with poor bioavailability[1] and thus make possible sustained and extended participation of the drug to the overlying portion of the gastrointestinal tract[2]. One of the significant factors affecting the bioavailability of drug is gastric residence time[3]. Oral controlled drug delivery system is the mainly adaptable, suitable and generally utilized tract of drugs facing reduced residence time and plasma half-life inside GIT. A number of approaches have been projected in recent years to make available a dosage form including a prolonged penetration time and consequently increased absorption[4].

**Approaches for gastro retentive drug delivery systems[5]:-** shown in figure 1.

I. Bio/Mucoadhesive Drug Delivery System
II. Expandable Drug Delivery System
III. Floating Drug Delivery System
IV. High-density systems

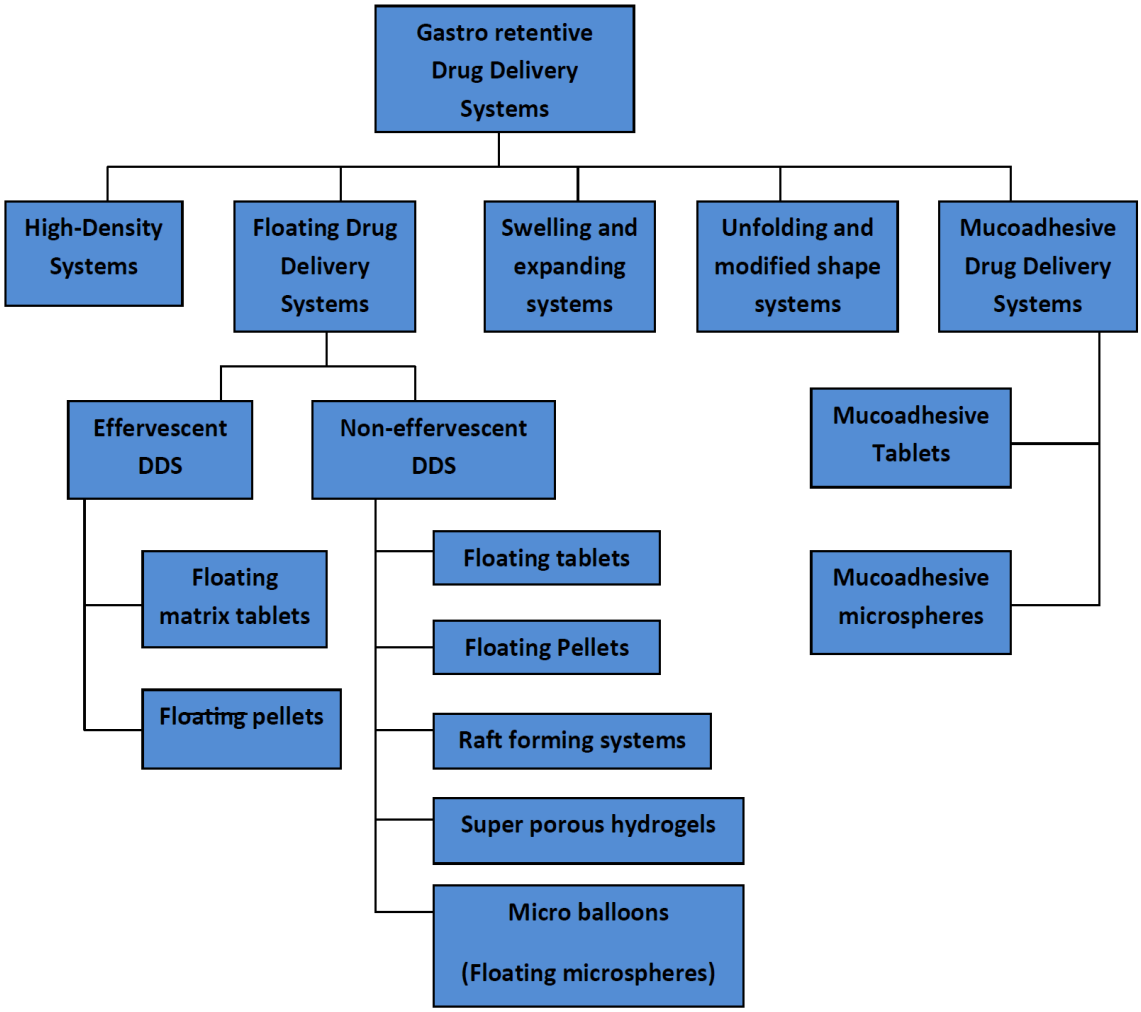


**Fig.1: Various approaches used in gastro retentive drug delivery systems.**

Limitations of the technique of gastro retention

1. It is not suitable for drugs which are not stable in the strong acidic environment and drugs that cause gastric lacerations.
2. Bio adhesion in the acidic ambiance and immense takings of mucus can raise queries regarding the efficacy of this system.
3. The floating systems in patients among Achlorhydria could take place doubtful in an instance of water-dispersible systems, quick swelling effects are mandatory and entire bumping of the system have to be completed effectively earlier than the gastric evacuating time.

Various types of GRDDS

1. Floating microspheres cefuroxime axitel, rosiglitazone, nateglinide, cefpodoxime.
2. Floating granules atorvastatin, ranitidine, lacidipine, metoprolol, simvastatin.
3. Films of cinnarizine.
4. Floating capsules diazepam, celecoxib, benserazide, pioglitazone, misoprostol, furosemide, pepstatin L-dopa and ursodeoxycholic acid.
5. Floating tablets ofloxacin, alfuzosin, loratadine, glipizide, losartan, propanolol.
6. Mucoadhesive system metformin, famotidine, venlafaxine, metoprolol[6].

Gastric retention of dosage formulae controlled by various factors[7] shown in figure 2.

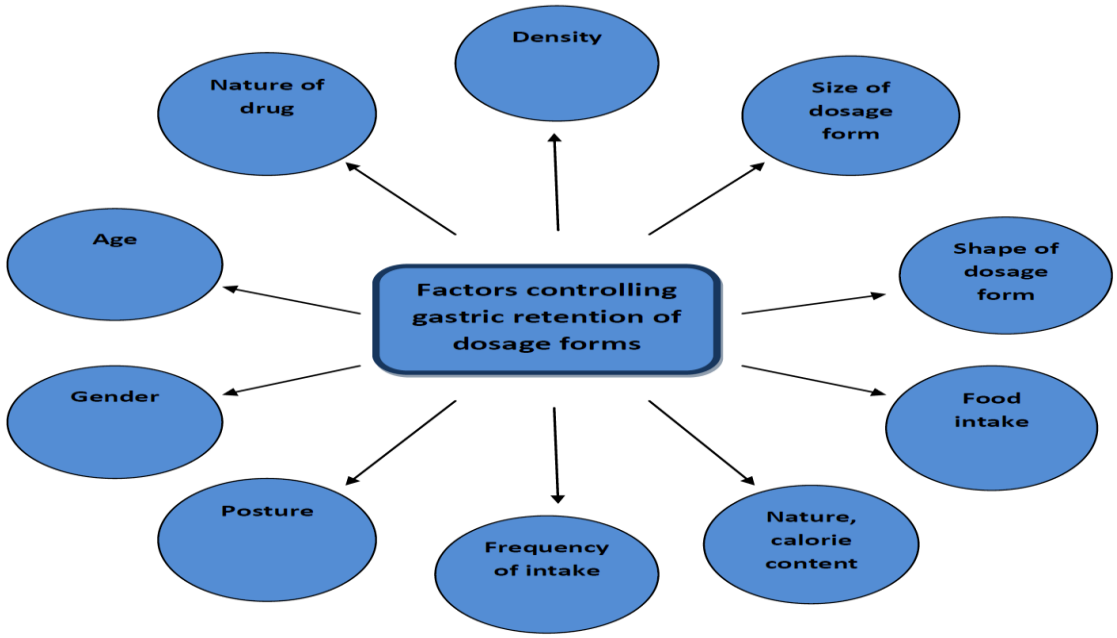


**Fig.2: Gastric retention of dosage formulae controlled by various factors.**

**Theory of Mucoadhesion**

The thought of bioadhesion or more apparently mucoadhesion is used to improve gastric preservation of drugs. Among a variety of approaches for mucoadhesion, microencapsulation method has obtained good acceptance as a method to attain controlled release and drug targeting[4].

Mucoadhesion is generally explained as the adherence involving two substances, out of which one is mucosal surface[8]. Mucoadhesive microspheres can be used by oral, nasal, buccal, vaginal, ocular and rectal for local or systemic effects. At the site of application, the mucoadhesive microspheres reveal an extended dwelling time and facilitate close connection with the fundamental absorption surface and hence provide enhanced beneficial execution of drug. Mucoadhesive drug delivery systems promise numerous interests which occur from centralization at a specified objective site, extended dwelling time on the point of preparation absorption and an increased connection to the mucosa rising the drug absorption gradient[2].

The title "bio-adhesion" can be prescribed simultaneously the "attachment of a synthetic or natural macromolecule to mucus and/or epithelial surface". Cohesion of a polymeric matter with natural or organic exteriors remained are admitted via the mucosal soft tissue have being established just as mucoadhesion. As a bioadhesive material, it should contact with mucus, which accommodates inorganic salts, lipids glycoproteins, and 95% water due to mass, forming this an extremely humidified system. The accumulation of non-covalent bonds like hydrogen bonds and ionic interchanges or only materialistic complexity among polymers and the mucus gel layer implements a superior mucoadhesion[9].

Mucoadhesive drug delivery system (MDDS) can be considered to manage drug release and to facilitate prolonged drug maintenance at the site of application. Conventionally typical adhesive materials used in mucoadhesive drug delivery systems generally are the family of hydrogels, such as natural gums, polyacrylates, and cellulose ethers. MDDS is a branch of a controlled delivery system that could be formed to regulate the drug release and to facilitate prolonged drug preservation by the site of application, which accordingly promotes therapeutic efficacy. The commonly essential adhesive materials used in the MDDS typically are the family of hydrogels, such as natural gums, polyacrylates, and polymers[10].

**Mucoadhesive drug delivery systems can be administered by different routes**:

- Oral
- Nasal
- Buccal
- Occular
- Vaginal
- Rectal
- Topical

**Mucoadhesive microspheres**

Microspheres may be described as solid, nearly globular particles size range from 1-1000 $\mu$m. Substances could be included inside microspheres

in the solid or liquid state throughout synthesize or consequently by absorption. Microspheres or microparticles are common terminologies that include both microcapsule & micro matrix. Micro-capsules, where the entrapped substance is entirely enclosed by an individual capsule hedge and micromatrices, where the entrapped substance is distributed all through the microsphere model. Microspheres comprise an essential section of an innovative drug delivery system because of their mini size and productive transporter measurements[11].

A "microcapsule" may be defined as a spherical particle with size varying from 1 to 1000μm containing a core substance. Microcapsules are mono or multinuclear materials embedded in a spherical coating matrix are called microcapsules. This is an operation through which solids, liquids or only gases may be surrounding microscopic elements by the development of fine layers of the fence materials nearby the substance. Also, some related terms are used as well, for example, "microbeads" and "beads" alternatively[12]. Mucoadhesive microspheres reveal an extended residency at the application site and promote a close interaction by the primary absorption surface and hence impart enhanced or improved therapeutic effect of drug[9].

Microspheres with mucoadhesive properties can be developed for both targeted and controlled release drug delivery systems[11]. Microspheres are commonly used for drug delivery to the systemic circulation and constitute a significant part of such novel drug delivery systems[13]. The mucosal membranes of organs such as GIT, ocular, buccal, vaginal, rectal and nasal are the various sits of drug absorption[14].

### Factors affecting mucoadhesion

1. Physiological related factor:- Mucin turnover, disease state
2. Environmental related factor:- Applied strength, pH, selection of the model substrate surface, initial contact time.
3. Polymer related factor:- Spatial conformation, degree of hydration, molecular weight, gathering of active polymer, chain elasticity of polymer swelling, charge and degree of ionization of polymer[1,15].

### Mucoadhesive or bioadhesive polymeric arrangement

Mucoadhesive polymers are of both types of water-insoluble and water-soluble, which are water-swelling systems, attached by cross-linking means. The aforesaid polymers obtain optimized separation to prove that these allow adequate moistening by the mucous and optimum fluidness this grants the combined adsorption and permeation of polymer and mucus directed toward. A mucoadhesive polymer is formed of a natural or synthetic polymer that attaches to mucosal membranes performing as a biological substrate. These kinds of mucoadhesive polymers are called as biological 'glues' get included with drugs to permit these drug moieties to attach to their target tissues. Several mucoadhesive polymers that have been used for the growth of oral delivery systems incorporate chitosan, sodium carboxymethyl cellulose and poly(methacrylic acid)[16].

Mucoadhesive polymers particularly cling to the mucosal-epithelial surface have been broadly categorized into three well-known known classes are[17,18].

1. Polymers that turn out to be adherent when put in liquid and owe their mucoadhesion as a result of dampness.
2. Polymers which stick across indefinite, noncovalent intercommunications which are fundamentally electrostatic.
3. Polymers owing their mucoadhesion attach to specified receptor sites on tile character of the exterior.

### Attributes of a model mucoadhesive polymer

1. The used polymer should be harmless and non-absorbable by the GIT.
2. It must be soothing to the membrane of mucous.
3. It shall ideally configure a well built noncovalent connection by the mucin-epithelial cell Surface.
4. It shall stick rapidly into tissue mostly and shall have a few site-specificity.
5. It shall let regular inclusion to the drug and provide no obstacle to its relief.
6. The polymer should not decay on warehousing or throughout the dosage form shelf life
7. The price of polymer ought not to be high so that the formulated dose lasts ruthless[2,19].

**Table 1. List of polymers**

| Polymers from natural origin | Polymers form synthetic origin |
|---|---|
| Sodium alginate | Derivatives of cellulose(Ethylcellulose, Methylcellulose, Hydroxypropyl cellulose, Sodium carboxymethyl cellulose, HPMC) |
| Pectin | Esters and halides, polymethacrylic acid |
| Tragacanth | Polyacrylic acid |
| Gelatin | Polyvinyl pyrrolidine |
| Soluble starch | Polyvinyl alcohol |
| Xanthan gum | Poly hydroxymethyl methyl acrylate |
| Carrageenan | Hydroxypropyl cellulose |
| Chitosan | Polyethylene oxide |
| Karaya gum | Carbomers, Polycarbophil |

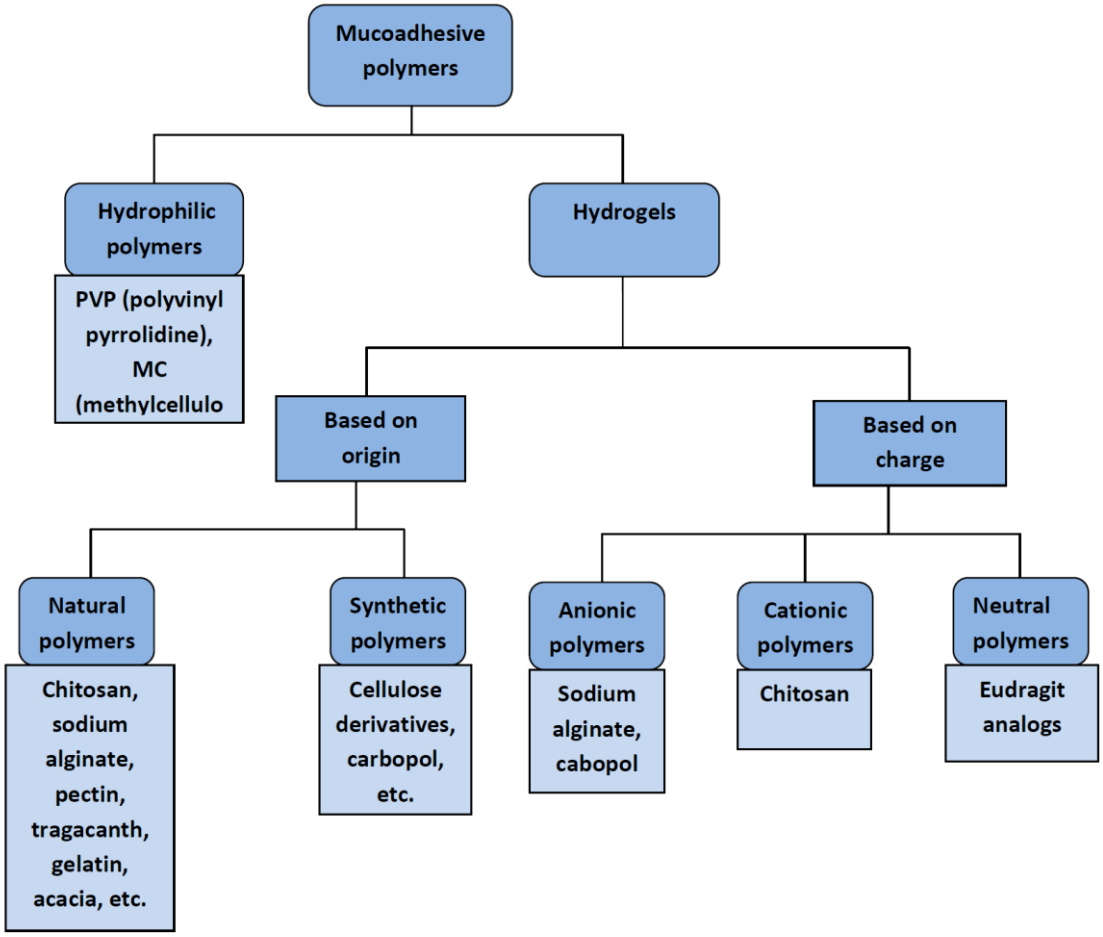


**Fig.3: Classification and examples of mucoadhesive polymers.**

**Method of preparation of mucoadhesive microspheres**[1,2,11,17]

Embodiment of solid, liquid or gases centered in one or added polymeric layers could be finished by microencapsulation procedure. The various approaches utilized for different microspheres composition lean on administration route, particle size, drug release duration and these up beyond characters associated to revolution per minute, evaporation time, process of cross-linking, co-precipitation, drug of cross-linking, etc. Several preparatory methods are:-

**Ionotropic gelation technique**

By using this technique, alginate/chitosan particulate system for ibuprofen release was developed. In this process, the drug is put on in sodium alginate (aqueous solution). Continuous stirring is done to obtain the thoroughly mixed solution and the following solution is added into $CaCl_2$ solution dropwise. The formulated

microspheres were left in the primary solution for 2 hours of stirring at 700 rpm for interior gelification followed by separation by filtration process. The total relief is achieved at pH 6.5-7.4 but at the acidic pH, the drug will not discharge.

### Spray Drying (An anhydrous technique)

This method includes the utilization of volatile organic solvents like dichloromethane, acetone, etc in which polymer is primarily diffused, afterward the solid drug is steadily distributed in this polymer solution accompanied by constant stirring at fast-moving homogenization. At that point, the dispersion is disintegrated in a streamlet of very warm air. After a homogenous mixture is obtained, and the procedure is known as atomization. Minute droplets or the fine mist of drug-polymer solutions formulated succeeding the atomization cause the construction of the mini drops or the adequate spray causing the establishment of the microspheres having a size range 1-1000 $\mu$m following vaporization of volatile solvent instantaneously. These microparticles are separated through the cyclone separator from hot air throughout the time the strain of any liquid is replaced using vacuum drying. One of the considerable profits of this procedure is being rapid and suitability of functioning below sterile state and causes the development of spongy microparticles. The spray-dried gained microspheres could be made better in superiority via the accumulation of plasticizers like citric acid, which promotes polymer affiliation in contact with the drug particles and thus help out in the construction of round and even-surfaced microspheres. Additionally, the rate of spraying, nozzle size, the feed rate of polymer-drug solution, and the drying temperature influences the dimensions of microspheres. This technique of microencapsulation is still uncomplicated, reliable, simple to range up and free from the solubility properties, originality of the drug and polymer.

### Solvent evaporation

In the liquid manufacturing vehicle, solvent evaporation method is used. During the process, the drug is disintegrated in polymer, that was formerly fused in chloroform and the following arrangement is mixed with the fluid stage containing 0.2 % emulsifying agent (PVP), the drug and polymer mixture was agitated at 500 rpm. A core material can be water-soluble or insoluble, to be microencapsulated is distributed in the solution of polymer used for coating. With agitation, the material placed in the core of the microcapsule mixture is diffused in the fluid producing vehicle stage to attain the suitable sized microcapsule through evaporation of solvent and afterward by filtration collected the microsphere and carry away by distilled water and dried at for 24 hours at temperature of room.

### Hot Melt Microencapsulation

Firstly the polymer is molten and afterward transfused with drug particles that have been sieved to fewer than 50 $\mu$m. Then the mixture is put up in a non-miscible solvent like silicone oil, ceaselessly stirred and warmed up to 5°C more than the melting point of the polymer. Thereafter the emulsion is balanced, allowed to cool until the solidification of the polymers is done. The resultant microspheres are washed via transfusion with petroleum ether. The main aim of rising this process is to expand a microencapsulation technique appropriate for the water labile polymers, e.g. polyanhydrides. Microspheres obtained range in diameter of 1-1000 $\mu$m and the size distribution may be controlled without difficulty by reorganizing the stirring rate. The solely drawback of the technique is the average temperature at which the drug is left open.

### Complex Coacervation

This method is simply broadly applicable. The arrangements of two hydrophilic colloids are blended, resulting in a partition of liquid precipitate and the coating material stage, arranged by solvating non-miscible polymer in a practical vehicle and the key ingredient is sprinkled in a solution of the coating polymer after fixed mixing. The formulated capsules were toughened in the counterion solution before washing and drying to form a self-sustaining microsphere.

### Phase Inversion Method

The technique included the incorporation of drugs within dilute polymeric arrangement in methylene chloride and the resulting combination is decanted within an unmixed tough non-dissolvable oil ether solvent, a ratio of 1: 100. Microspheres delivered are later elucidated, washed by petroleum ether and air-dried. It is the simplest and fast procedure of microencapsulation involving negligible damage of drug and polymer.

### Single emulsion technique

During this procedure, a dispersion of polymer and drug is scattered in a watery means. The mixture is then dissolved in the dry medium (like oil) results out to the development of globules, and after that, the scattered globule are cross-linked by both heat or chemical cross-linkers. The

material crosslinkers utilized are formaldehyde, glutaraldehyde, diacid chloride, etc.

### Double emulsion method

This process consists of the configuration of numerous emulsions or double emulsion of water in oil in water (w/o/w) type and is appropriate for drugs soluble in water. In this formulation, both natural and synthetic polymers are included. Firstly, a water-soluble drug and polymer solution is isolated in a fat-soluble organic continuous phase beneath strong stirring to generate a homogeneous mixture. The continuous phase comprises a polymer solution that ultimately encloses the drug therein dissipated in the aqueous phase. This major emulsion is next put to sonication before accumulation to the liquified solution of polyvinyl alcohol (PVA) which results out to the foundation of double emulsion. The later double emulsion produced is opened to the solvent extraction process along with preserving emulsion at decreased pressure or stirring to volatile organic phase flees out. The emulsion is mixed with a huge amount of water (with or without surfactant) to the organic phase separated and the solid microspheres are filtered out after washing.

### Advantages of mucoadhesive drug delivery system

- Easily generalized in the area applied to promote and better the bioavailability of drugs.
- Due to first-pass metabolism avoidance, the bioavailability of the drug is increased.
- Rapid onset of action is attained because of the mucosal surface.
- Ease close contact of the formulation with the primary absorption surface.
- At the action site, prolong the dwelling time of the dosage form.
- Because of enhanced dwelling time, it increases absorption and therefore the remedial ability of the drug.
- Drug is sheltered from deprivation in the acidic medium in the gastrointestinal tract.
- Absolute contact by intestinal cells, which is the step earlier to absorption of particles.
- Improved patient acceptance- ease of drug administration.
- Pronged and sustained delivery of drug.
- Reduced frequency of dosing.
- The fluctuations in the concentration of drug is reduced.
- Localization of the medication delivery system at the particular target site.
- Superior flexibility, accessibility, and adaptability of dosage forms[11,15,16].

### Applications of microspheres in drug delivery systems

Microsphere based drug delivery systems are established for oral, sublingual, mucosal, nasal, ocular, buccal, vaginal, rectal, GI tract, topical and vascular routes for both local and systemic effects.

1. Dosage form of sustained and controlled release.
2. Microspheres could be utilized to formulate enteric-coated dosage form in such a way that the medication would be particularly soaked up in the intestine instead of the stomach.
3. The drug preserve in the microspheres from environmental conjectures such as heat, oxygen, moisture, or sunlight; eg. vitamin A and K have been revealed to be secured from humidity and air through the microsphere.
4. The separation of unsuitable materials, for example, pharmaceutical eutectic mixtures are being accomplished by encapsulation. In this situation, absolute contact of materials outcomes in production of liquid.
5. The volatility can be decreased by using microspheres. An encapsulated explosive material could be held in reserve for a prolonged time without considerable evaporation.
6. Microspheres are also used to reduce the possible danger of the practice of poisonous or destructive constituents. The toxicity occurs due to the usage of fumigants, pesticides, insecticides, and herbicides has been constructively decreased thereafter microencapsulation.
7. The hygroscopic properties of different midst materials can be decreased with microspheres.
8. Microencapsulation of several preparations is used for reducing irritation of gastric mucosa.
9. The microspheres have been investigated for the preparation of intrauterine contraceptive devices (IUCD).
10. Radioactive microspheres are utilized for taking pictures of lungs, bone marrow, liver, spleen, etc and also for picturing of thrombus in extensive vein thrombosis[11].

## RESULTS AND DISCUSSION

Microsphere based drug delivery systems are established for oral, sublingual, mucosal, nasal, ocular, buccal, vaginal, rectal, GI tract, topical and vascular routes for both local and systemic effects. Mucoadhesive polymers are of both types of water-insoluble and water-soluble, which are

water-swelling systems, attached by cross-linking means. The aforesaid polymers obtain optimized separation to prove that these allow adequate moistening by the mucous and optimum fluidness this grants the combined adsorption and permeation of polymer and mucus directed toward. A mucoadhesive polymer is formed of a natural or synthetic polymer that attaches to mucosal membranes performing as a biological substrate.

### Declaration of interest

The authors report no conflicts of interest.

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