JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON MUCOADHESIVE MICROSPHERES AND ITS RECENT ADVANCES

ZEENATH BEGUM[1*], SK. SUSHMA TAJ[1], ZAHERA MUSKAN[1], K. JYOTHI[1], Dr. J.V.C Sharma[1]

[1] Department of Pharmaceutics, Joginpally B.R Pharmacy College, JNTUH, Bhaskar Nagar, Yenkapally, Moinabad, Telangana, India.

ABSTRACT:

Mucoadhesive microspheres are a type of carrier-linked novel drug delivery system with a drug core and a completely polymer-coated outside. Their diameter ranges from 1 to 1000 µm. The contact between mucin surface and synthetic or natural polymer is known as mucoadhesion. Mucoadhesive microspheres place a significant role in this particular drug delivery system because of their small size and other effective characteristics. Mucoadhesive microspheres have advantages such as effective absorption and enhanced bioavailability of the drugs due to a high surface to volume intimate contact with the mucus layer, controlled release, and increased residence time at the absorption site. These factors contribute to improved and better therapeutic performance of drugs. Mucoadhesive microspheres have been created for systemic or local effects in the oral, buccal, nasal, ophthalmic, rectal, and vaginal regions. It has a high safety profile and is the perfect targeting mechanism. This review article gives the information about mucoadhesive microsphere, theories of mucoadhesion, preparation methods, advantages, disadvantages and applications of mucoadhesive microspheres.

KEYWORDS: Microsphere, Mucoadhesive microsphere, Bioadhesion, Mucoadhesive polymer, Novel drug delivery system.

INTRODUCTION:

Action of drug can be increased by creating innovative drug delivery systems such as the Mucoadhesive microsphere. Mucoadhesive microspheres continue to be in close contact with the mucous membrane (the absorption tissue) and release the medication at the action site, increasing bioavailability and having both local and systemic effects.[1] The most practical and preferable method of drug administration to the body is by oral route. However, due to their failure to restrain and localize the drug to the gastro intestinal tract, oral administration of the majority of medications in conventional dosage forms have certain restrictions. Due to their small size and effective carrier capacity, microspheres play a significant role in these particulate drug delivery systems with a drug core and completely polymer outer layers as coating material.[2] Microspheres are the carrier-linked drug delivery technology with particle sizes in the 1-1000 µm range. The effectiveness of these microspheres is however constrained by their brief stay at the absorption site. Therefore, it would be useful to have methods for ensuring that the drug delivery system is in close contact with the absorbing membrane. This can be done by creating "mucoadhesive microspheres" by fusing bioadhesion properties to microspheres. Mucoadhesive microspheres have benefits such as effective absorption and increased bioavailability of the drug because of a high surface to volume ratio, much closer interaction with the mucus layer, and accurate drug targeting to the site of absorption.

MICROSPHERE:

Microspheres are small spherical particles, typically have dimensions between 1 and 1000 micrometres. The term "microparticle" can also be used to describe microspheres. Microsphere as drug carrier is one of the methods that can be used for controlled and prolonged release of drugs.[3] The development of innovative drug delivery systems has been greatly influenced by dosage forms that can accurately control the release rate of medications and target them to a specific body region. Two crucial components, namely Spatial placement and temporal delivery of drug are part of the goal of controlled release medication delivery.[4]

When a medicine is targeted spatially, it is administered to a specific organ or tissue, however when it is delivered temporally, the rate of drug delivery to the target tissue. Biodegradable polymer microspheres are one of the most often utilised types of controlled release medication delivery devices and have a number of benefits. Microspheres can simply be delivered with a syringe needle and can contain a variety of medications, including tiny chemicals, proteins, and nucleic acids. They are typically biocompatible, have a high bioavailability, and can release a substance continuously for a very long time.[5]

MUCOADHESIVE MICROSPHERE:

Recent developments in drug carrier technologies and polymer science have sparked the creation of innovative drug carriers including mucoadhesive microspheres, which have increased the use of bioadhesion in drug delivery.[6] Microparticles and microcapsules that are either totally made of mucoadhesive polymer or have an exterior covering with adhesive properties are

known as mucoadhesive microspheres.[7] The possibility for regulated and spatial drug delivery using microspheres exists. Mucoadhesivenes added to microspheres result in effective drug absorption and improved the bioavailability. The drug is precisely targeted to the absorption site.[8] The contact between a mucin surface and a synthetic or natural polymer is known as mucoadhesion.[9] The inclusion of mucoadhesive hydrophilic pharmaceutical polymers with formulations like "microspheres" along with the active pharmaceutical component has been widely promoted as a technique to achieve site-specific drug delivery (API). If modified, it is a dependable way to deliver the medication to the target site with precision and to keep the desired concentration at the site of interest without experiencing any negative side effects.[10] For both localised and systemic effects of medications, mucoadhesive microspheres can be used to adhere to the mucosal layer of the nasal cavity, gastrointestinal tract, and urinary tract. The kind of mucoadhesive polymers utilised to make the mucoadhesive microspheres has an impact on their features, including surface characteristics, mucoadhesion force, drug release pattern, and clearance. Microspheres got more interest for their sustained release and for their ability to direct anti-cancer drugs to the tumour. Microspheres by integrating different other techniques, will take centre stage in innovative medication delivery, diagnostics, gene & genetic research.[11]

USES OF MUCOADHESIVE DRUG DELIVERY SYSTEM.

• For preventing first-pass metabolism.

• Penetration enhancers can be added to improve peptide absorption.

• It prolongs residence time.

• Drug localization at a specific location is obtained.

• It should be in Close contact between the dosage form and the absorption site underneath.

• It Enhance the therapeutic effects of the medicine.

• For controlled drug release, ideally unidirectional, and high drug loading capacity.

MUCUS MEMBRANE:

Mucus is a translucent, viscid fluid that adheres to the mucosal epithelial surface as a thin, continuous gel. The moist surface lining walls of many body cavities, including the gastrointestinal and respiratory tracts, is known as a mucus membrane. The mucus is produced by goblet cells. Mucus can be found as a gel layer that is adhering to the mucosal surface, in suspension, or as a luminal solution. Mucin glycoprotein, water, lipids, and inorganic salts are the main ingredients of all mucus gels. The mucus provides lubrication as well as a barrier of protection.[12]

Mucus layer composition:[13]

• Water (95%)

• Free proteins (0.5-1%)

• Mineral salts (1%)

• Glycoprotein and lipids (0.5-5%)

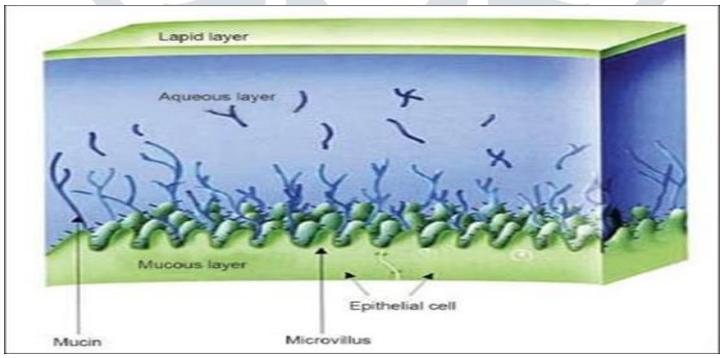

Figure 1: Structure of Mucus membrane.[14]

MUCOADHESIVE MECHANISM:

As previously stated, mucoadhesion is the bonding of the medicine to the mucosal layer coupled with an appropriate carrier. A complex phenomena that involves wetting, adsorption, and interpenetration is mucoadhesion.[15]

The following are characteristics of mucoadhesion Mechanism:

1. Polymer chains are involved in the intimate contact (wetting or swelling phenomenon) between a mucoadhesive delivery system and mucosal membrane.

2. The mucoadhesive delivery system entering the tissue or the mucous membrane's surface.[16]

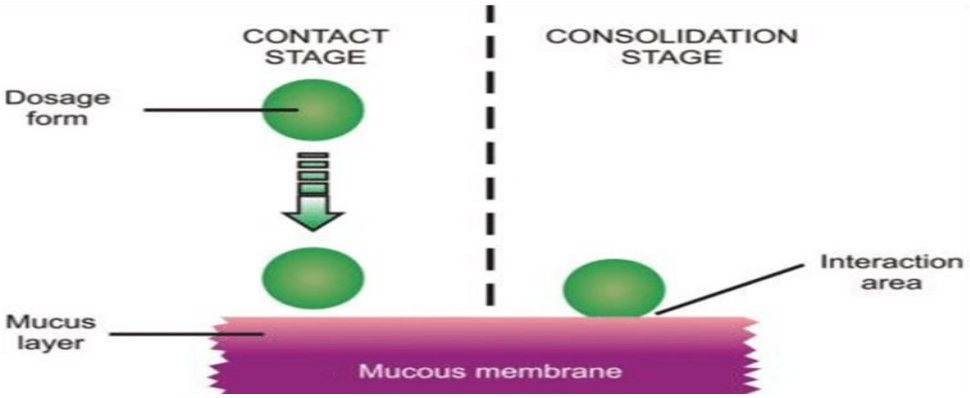

Figure 2: Mucoadhesive Mechanism [14]

MUCOADHESIVE POLYMER:

Water- soluble or water-insoluble polymers with expandable networks can be used as mucoadhesive polymers. The polymer should have the right balance of polarity and fluidity to allow for both mutual adsorption and interpenetration of the polymer and mucus. This will ensure that the polymer is adequately wetted by the mucus. The following desirable characteristics of controlled release systems are met by mucoadhesive polymers:[17]

a. Localization in specific areas to increase and improve drug bioavailability.

b. The best possible contact with the absorbing surface to allow for the modification of tissue permeability, which is crucial when dealing with peptides, proteins, and ionised species.

c. A prolonged residence time to allow for once-daily dosing, which increases patient compliance.[18]

Ideal mucoadhesive polymer characteristics: [19, 20]

1. The polymer and its degradation product should not be harmful and not absorbable from the GI system.

2. The mucous membrane should not be irritated by it.

3. It should ideally create a powerful non-covalent bond with the surface of the mucin-epithelial cell to form a connection.

4. It should adhere to most tissues quickly and should be somewhat site-specific.

5. It should make it simple to incorporate the drug and shouldn't prevent its release.

6. The polymers must not break down while being stored or during the dosage form's shelf-life.

7. The polymer and method of his should not be expensive.

FACTORS AFFECTING MUCOADHESIVE MICROSPHERE: [21,22]

1. POLYMER RELATED FACTORS:

- Molecular weight
- Concentration of active polymer
- Degree of hydration
- Spatial conformation
- Chain flexibility of polymer
- Functional group of polymer
- Swelling

2. ENIVIRONMENT RELATED FACTORS:

- p^H
- Applied strength
- Initial contact time
- Selection of the model substrate surface

3. PHYSICAL RELATED FACTORS:

- Mucin turn over
- Composition and characteristics of mucus
- Disease state
- Physiological consideration

THEORIES OF MUCOADHESION: [23,24,25]

A complex process underlies the phenomenon of bioadhesion. The theories mentioned below describe the bioadhesion mechanism,

1. Electronic theory:

According to electronic theory, an electric double layer is created at the mucoadhesive interface as a result of an electron transfer from the mucoadhesive polymer to the mucin glycoprotein network. As an illustration, consider the interaction of positively charged chitosan polymers with negatively charged mucosal surfaces, which upon hydration become sticky and allow for close contact between a dosage form and the absorbing tissue.

2. Wetting theory:

According to the wetting theory, liquids have a greater affinity for the substrate's surface if their contact angles are less. If the surfaces of two such substrates come into contact with the liquid, they may interact with each other and such liquid interconnect the substrate surfaces by acting as an adhesive.

3. Adsorption Theory:

In accordance with this theory, a substance sticks to two surfaces after making an initial contact with them due to the surface force between their atoms. These forces produce two different kinds of chemical bonds: primary chemical bonds of a covalent nature and secondary chemical links with a variety of attractive forces, including electrostatic forces, Vander Walls forces, hydrogen bonds, and hydrophobic bonds. According to electronic theory, an electric double layer is created at the mucoadhesive interface as a result of an electron transfer from the mucoadhesive polymer to the mucin glycoprotein network. As an illustration, consider the interaction of positively charged chitosan polymers with negatively charged mucosal surfaces, which upon hydration become sticky and allow for close contact between a dosage form and the absorbing tissue.

4. Diffusion Theory of Mucoadhesion:

According to diffusion theory, polymeric chains of the bioadhesive interpenetrate into glycoprotein mucin chains and enter the opposing matrix deeply enough to permit the creation of a semi-permanent connection. From the first point of touch, the process may be seen. As long as concentration gradients exist, the bioadhesive polymer chains will penetrate the mucus network and the glycoprotein mucin chains will penetrate the bioadhesive matrix. This process will continue until an equilibrium penetration depth is reached.

ADVANTAGE OF THE MUCOADHESIVE MICROSPHERE DRUG DELIVERY SYSTEM INCLUDES: [26,27]

1. The formulation stays longer at the delivery site due to adhesion and close contact, boosting API bioavailability at lower API doses for disease therapy.

2. Provides a excellent pathway for the systemic distribution of drugs.

3. A reduction in the frequency of administration may result from extended residence time paired with carefully timed API release.

4. Due to API localisation at the disease site, additional substantial cost savings may be made, and adverse effects linked to dosage may be minimised with high first-pass metabolism, increasing their bioavailability in the process

5. By utilising specialised bioadhesive molecules, it is possible to target particular areas or tissues, such as the gastrointestinal (GI) tract.

6. These produces higher safety margins for drugs with high potencies because plasma levels are better managed.

7. Greater processing efficiency (improving solubility, dispersibility, flowability).

8. Preservation of therapeutic drug concentrations in the plasma for longer duration.

9. Drug release that is prolonged and sustained.

10. Better patient compliance and convenience as a result of less frequent dosing.

11. A uniform and extensive diffusion of the drug throughout the gastrointestinal system, which enhances drug absorption.

12. Microsphere can be given in other routes for drug that are unstable in an acidic environment and are degraded by enzymatic processes or the alkaline environment of the intestine eg: buccal, sublingual, vaginal, etc.

13. Decreased fluctuations in steady state levels, which will improve disease control and lessen the severity of any local or systemic side effects.

14. The bioavailability of the medicine is improved by avoiding first-pass metabolism.

15. Rapid onset of action can be attained because of mucosal surface.

DISADVANTAGE OF MUCOADHESIVE MICROSPHERE DRUG DELIVERY SYSTEM:[5]

1. There may be changes in formulations release pattern.

2. A number of variables, such as food intake, gut transit times, mucin turnover rates, etc., may affect the release rate.

3. From one dose to the next, there can be variations in the release rate.

4. Potential toxicity may result from a dosage form's release pattern losing its integrity.

5. These dosage forms can't be chewed or crushed.

Table 1: List of Polymers.

NATURAL POLYMER	SYNTHETIC POLYMER
• Soluble starch • Sodium alginate • Pectin • Tragacanth • Gelatine • Xanthan Gum • Carrageenan • Karaya Gum • Lecithin • Chitosan • Guar Gum • Locust Bean Gum	• Poly Vinyl Alcohol • Poly Acrylic Acid • Poly ethylene oxide • Poly carbophil • Ester and Halides • Hydroxy ethyl cellulose (HEC) • Hydroxy propyl cellulose (HPC) • Sodium carboxy methylcellulose (NaCMC) • Methyl cellulose • Ethyl cellulose • Carbomers • Poly hydroxy ethyl methyl acrylate

PREPARATION METHOD OF MUCOADHESIVE MICROSPHERE:[28]

Mucoadhesive microspheres are prepared by general method of preparation of microsphere but using mucoadhesion/bioadhesion polymer. Different microspheres are prepared by using microencapsulation process, solid, liquid, or gas components can be included into one or more polymeric coverings. The diverse techniques used to manufacture different microspheres depend on the particle size, route of administration, duration of drug release, and these characteristics connected to rpm, method of cross-linking, drug of cross-linking, evaporation time, co-precipitation, etc. The different preparation strategies include.

1. Solvent evaporation Technique:

Solvent evaporation is one of the earliest and most popular methods of making microspheres. This procedure creates an oil-in-water (o/w) emulsion by emulsifying a medicine, polymer, and solvent mixture (i.e., the oil phase) in water. A surfactant is often dissolved in the water phase prior to the formation of the o/w emulsion to aid in the emulsification process. A nice illustration is poly (vinyl alcohol) that has been partially hydrolyzed (88%) (PVA). The system is agitated at a steady pace. As the solvent evaporates, achieving the appropriate oil phase droplet size and emulsion stability. Add to an aqueous solution containing as the solvent largely evaporates. Solvent evaporation is the term for this process. Heating, vacuuming, or stirring are further methods for removing the organic solvent. When it appears that the solvent has evaporated completely, the microcapsules/microspheres are filtered away from the suspending medium, cleaned, and dried.

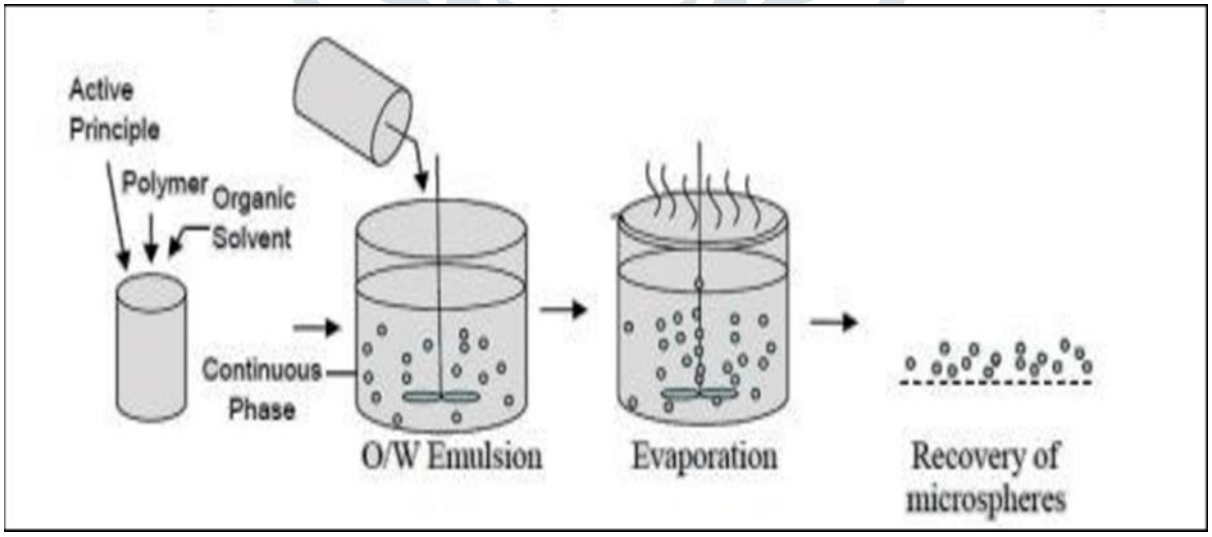

Figure 3: Solvent Evaporation Method.[29]

2. Hot Melt Technique:

A method called "hot melt" was created in the 1970s for use in photography. In this procedure, the medication is combined with the melted polymer. The combination is then heated to 5°C above the polymer's melting point while being agitated with a four-blade impeller in a mixture containing immiscible solvent. The emulsion is stabilised, then chilled to cause the core substance to solidify. Solvents such as silicon and olive oil may be utilised in this process.

3. Method of Solvent Removal:

This approach fabricates materials entirely in organic solvent at room temperature, which is crucial for hydrolytically labile polymers like poly-anhydrides. Aqueous solutions should be avoided at all costs. This process involves dissolving the polymer in methylene chloride, adding the necessary amount of medication, and then suspending the combination in silicon oil that contains Span 80 and methylene chloride. Petroleum ether is added after the polymer solution has been added to the silicon oil, and the combination is then agitated until the methylene chloride has been drawn out of the oil solution and the microspheres have sufficiently hardened. The resultant microspheres are filtered apart, cleaned with petroleum ether, and let to dry overnight under vacuum.

Microspheres are always smaller than 300 µm in size. Because the microencapsulation took place in an organic solvent and prevented drug loss by diffusion, the hydrophilic material produces the best correlation between expected and achieved loading.

4. Single and Double Emulsion Technique:

The double emulsion method, or water in-oil-in-water emulsion (w/o/w) emulsion, is the one that is most frequently used to make microspheres. To create a w/o emulsion, the aqueous protein solution is disseminated in an organic solvent made of polymer solution. A subsequent emulsification in an aqueous solution of a dispersing agent (w/o/w) stabilises this unstable emulsion. The polymer precipitates out to form tiny spheres containing the dispersed phase after the organic solvent is removed (protein). Finally, microspheres are gathered, cleaned, and dried. The synthesis of natural polymer and carbohydrate microspheres occurs via the single emulsion approach. After the polymer is initially dissolved or dispersed in an aqueous media, it is then distributed in a non-aqueous medium.

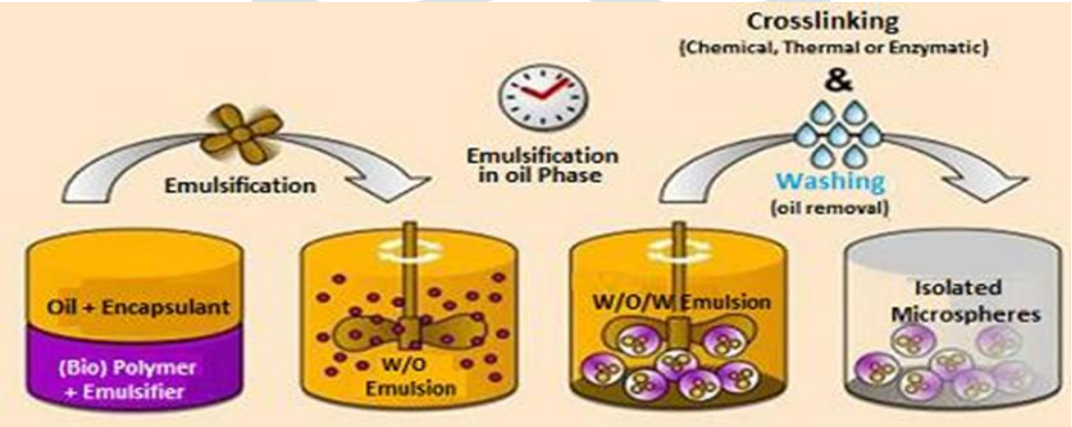

Figure 4: Double Emulsion Method [30]

5. Spray Techniques:

Microspheres can also be produced using a spray-based technique called spray congealing or spray drying. These techniques work on the basic idea of drying the medicine and polymer in the air. The polymer is first dissolved in an appropriate volatile organic solvent, such as acetone. Following the homogenization of the drug in the solution, the mixture is subsequently atomized in the hot air stream. The mist or particles that result from this are between 1 and 100 m in size. The cyclone separator is used to separate the microspheres and vacuum drying is used to remove any remaining solvent. While drying depends on the solvent being removed, congealing depends on the cooling of the polymer solution. It works well for both batch and large-scale manufacturing. While spray congealing is utilised for sulpha ethyl amine mono nitrate, microsphere spray drying is used to prepare penicillin microspheres.

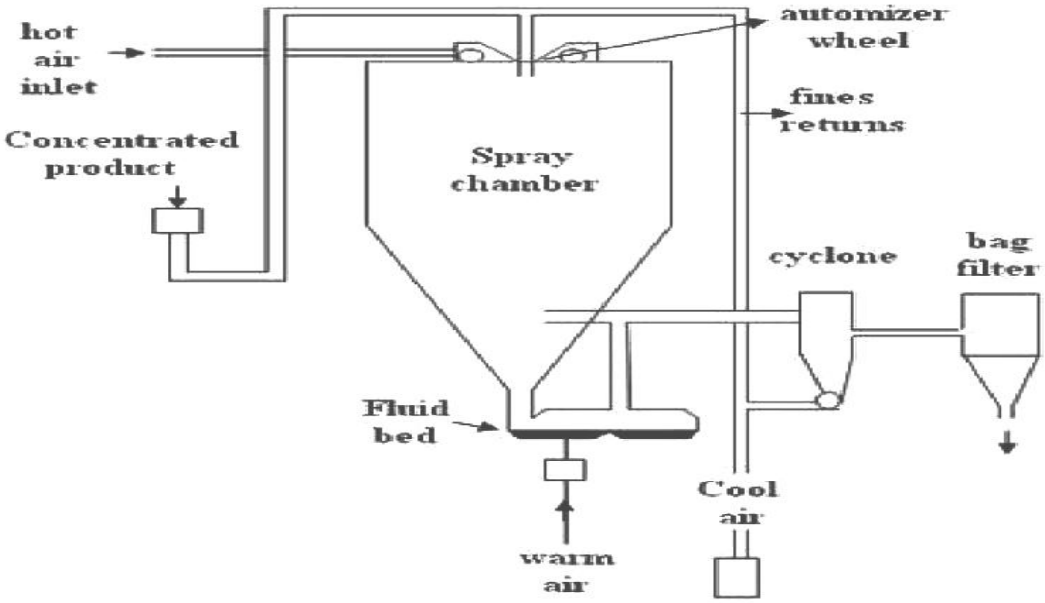

Figure 5: Spray Drying Method [31]

6. Freeze Drying Method:

The freezing of an emulsion is a step in the freeze drying process, and it is crucial to consider the relative freezing temperatures of the continuous and scattered phases. Typically organic, the continuous phase solvent is eliminated by sublimation at low temperatures and pressure. Finally, sublimation is used to remove the droplet's dispersion phase solvent, leaving the polymer drug particles as microspheres.

7. Wax Coating Technique:

In this technique, the core particles are coated with wax. When the medicine or other substance to be encapsulated is dissolved or disseminated in the molten wax, a simple emulsion is most frequently formed. High-speed mixing is used to distribute the waxy solution into a cold solution, such as liquid paraffin. After stirring the mixture, the exterior phase is excreted and the microcapsules are subsequently cleaned and dried. This is a cost-effective procedure. Beeswax and carnauba wax are both suitable coating materials.

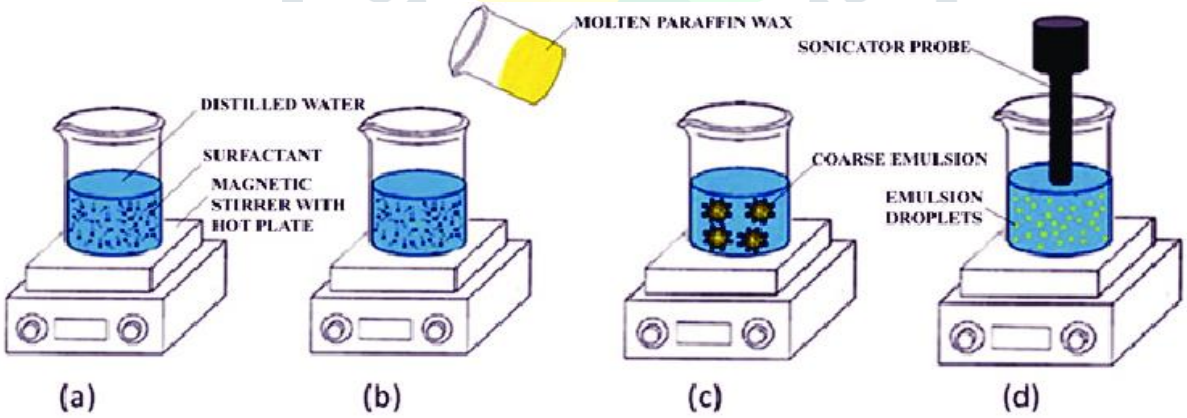

Figure 6: Wax Coating Technique [32]

8. Thermal and Chemical Cross-linking Technique:

A cross-linking procedure is used to create microspheres manufactured from natural polymers. A solution of the polymer containing the medicine to be integrated is dissolved in water to create a w/o emulsion. The oil phase is an appropriate oil-organic solvent mixture, such as an oil-soluble emulsifier, or organic vegetable oil. The water soluble polymer is solidified by a cross-linking agent, which causes thermal treatment or the addition of a chemical cross-linking agent such as gluteraldehyde to generate a stable chemical cross link once the desired w/o emulsion has been created.

9. Coacervation Phase Separation Technique:

A dense coacervate phase and a dilute equilibrium phase are formed upon coacervation, which is the division of a macromolecular solution into two immiscible liquid phases. This process is known as simple coacervation when there is only one macromolecule present. Complex coacervation is the term used to describe the process when two or more macromolecules with the opposing charge are present. The inclusion of a temperature shift, together with the preference of polymer-polymer interactions over polymer-solvent interactions, can produce simple coacervation. Complex coacervation between two or more macromolecules is driven by

electrostatic interaction forces. This approach has the potential to be helpful for the distribution of medications made of proteins and polypeptides as well as other substances that cannot withstand the cross-linking process.

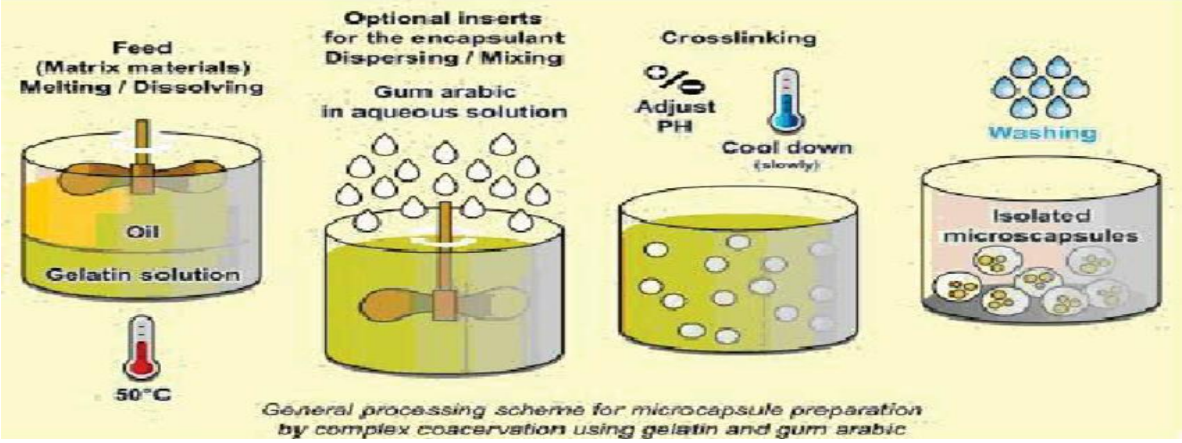

FIGURE 7: COACERVATION METHOD [30]

APPLICATINONS OF MUCOADHESIVE MICROSPHERES AS DRUG DELIVERY SYSTEM:[33]

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

1. Microsphere as novel dosage form used to get obtained sustained and controlled release of drugs.

2. Microspheres might be used to create enteric-coated dose forms so that the medication would specifically be absorbed in the intestine rather than the stomach.

3. Encapsulation is used to separate inappropriate elements, such as medicinal eutectic combinations because these liquefy when they get in contact with each other.

4. Microspheres can be used to reduce the volatility. An explosive material that has been sealed up can be kept in reserve for a long time without experiencing significant evaporation.

5. Using the microspheres to create intrauterine contraceptive devices (IUCD) has been researched

6. Radioactive microspheres are used to image the lungs, bone marrow, liver, spleen, and other organs. They are also used to image thrombi in extensive vein thrombosis

7. Microspheres can be used to lessen the hygroscopic characteristics of various materials.

8. To lessen irritation of the gastric mucosa, various preparations are microencapsulated.

9. Additionally, the usage of microspheres helps to lessen any potential risks associated with the use of toxic or harmful substances. Following the introduction of microencapsulation, the toxicity caused by the use of fumigants, pesticides, insecticides, and herbicides has been decreased.

10. Drugs have been shielded from environmental dangers including humidity, light, oxygen, or heat using this technique. Although the microspheres do not yet offer a perfect barrier for substances that deteriorate in the presence of oxygen, moisture, or heat, it is nevertheless capable of offering a high level of defence. Vitamins A and K, for instance, have been demonstrated to be shielded from oxygen and moisture by microspheres.

11. Oral drug delivery: Microspheres containing polymer can be used to create film dosage forms as an alternative to pharmaceutical tablets since they can form films.

12. Gene delivery: Microspheres, like chitosan and gelatin, have adhesion and transport capabilities in the GI tract that make them effective as oral gene carriers.

13. Nasal medication delivery: Microspheres have been shown to have high bioadhesive properties and to swell readily when in contact with the nasal mucosa, improving the drug's bioavailability and residence time.

14. Buccal drug delivery: Because polymer has muco or bioadhesive properties and can boost absorption, it is a great material to use for buccal drug delivery.

15. Mucoadhesive microspheres are used to deliver drugs to specific disease sites. Eg: AIDS, peptic ulcer, diabetes mellitus, and hypertension.

Table 2: List of Drug which are given as Microspheres

SNO	DRUG	INDICATION	POLYMER USED	RESULT
1.	Amoxicillin	Anti-pylori for gastric and duodenal ulcer	Carbopol 940P, Sodium CMC, HPMC, Guargum	Amoxicillin administration in the form of Amoxicillin mucoadhesive microsphere more effectively cleared H.pylori than in the form of suspension.
2.	Glipizide	Anti-diabetic	Sodium alginate	By using sodium alginate mucoadhesive microsphere of Glipizide should increase the length of stay of Glipizide for the treatment of diabetes.
3.	Nifidipine	Anti- hypertensive	HPMC, Carbapol	Mucoadhesive microsphere of Nifedipine showed good controlled release properties and polymer used showed good entrapment efficiency.
4.	Furosemide	Diuretics	Sodium alginate, Carbopol	Mucoadhesive microsphere of Furosemide Showed increase bioavailablity.
5.	Ranitidine	Gastroretentive	Chitosan, Sodium carboxy methyl cellulose	Mucoadhesive microspheres of Ranitidine hydrochloride were prepared.
6.	Cephalexin	Treatment of respiratory infection	Sodium alginate, Guargum	Improved bioavailability of Cephalexin and decrease the frequency of dosage form administration.
7.	Propranolol	Hypertension	Sodium carboxy methyl cellulose, carbapol934P, HPMC	Mucoadhesive microsphere can successfully design for sustain delivery of Propranolol hydrochloride and improve patient compliance
8.	Simvastatin	Hypolipidemic	Carbapol 940P, sodium CMC, HPMC, Sodium aliginate	Mucoadhesive microsphere of Simvastatin were prepared and drug release was diffusion controlled

CONCLUSION:

Mucoadhesive microspheres may eventually take the lead role by combining with a number of other techniques to form brand new drug delivery. Microsphere drug delivery system offers possibilities for creating new, controlled formulations for oral use with delayed release. Microspheres provide a range of opportunities including spatial targeting, dissolution rate reduction, and protection and masking of the substance that is active. As a result of this strategy, there is decreased drug concentration at sites other than the target organ or tissue, delivery of modest amounts of potent medications, and protection of labile compounds both before and after administration. When delivering drugs with a high safety profile, microspheres are the perfect delivery system.

REFERENCES:

1. Carvalho FC, Bruschi ML, Evangelista RC, Gremio MPD. 2010. Mucoadhesive drug delivery system. Brazilian Journal of Pharmaceutical Sciences, 46(1):1-17.
2. Parmar H, Bakliwal S, Gujarathi N, Rane B, Pawar S. 2010. Different method of formulation and evaluation of mucoadhesive microsphere. International Journal of Applied Biology and Pharmaceutical Technology,1(3):1157-1167.
3. Jain N K. 2001. Controlled and Novel drug delivery. 4th ed. Cbs Publishers & Distributors, p. 236-237.
4. Kataria sahil, middha Akanksha, Sandhu premjeet, AjayBilandi, Bhawna kapoor. 2011. A Review: Microsphere: International Journal of Research in pharmacy and chemistry, 1(4)-2231-2781.
5. Kumari Navita, Aggarwal Geeta, Harikumar SL. Mucoadhesive microspheres:A Review Journal of Drug Delivery and Therapeutics 2014; 4(5):48-54.
6. Sinha V R, Bansal K, Kaushik R, Kumria R, Trehan A. 2004. Polycaprolactone microspheres and nanospheres: International Journal of Pharmaceutics, 278(1):1–23.
7. Shaikh R, Singh TRR, Garland MJ, Donnelly RF. 2011. Mucoadhesive Drug Delivery Systems: Journal of Pharmacy and Bioallied Sciences, 3(1):89-100.
8. Mathiowitz E, Langer R. 1987. Polyanhydride microspheres as drug carriers I: Hot-melt microencapsulation, Journal of controlled Release, 5(1):13-22.
9. Gabor F, Wirth M, Jurkovich B, Haberl I, Theyer G, Walcher G, Hamilton G. 1997. Lectin mediated bioadhesion, Proteolytic stability and binding characteristics of wheat germ agglutinin and Solanum tuberosum lectin on Caco-2, HT-29 and humancolonocytes: Journal of Controlled Release, 49:27-37.

10. Alexander A, Tripathi DK, Verma T, Patel S. 2011. Mechanism responsible for mucoadhesion of mucoadhesive drug delivery system: International Journal of Applied Biology and Pharmaceutical Technology, 2(1): 434-445.
11. Mathew ST, Devi GS, Prasanth VV, Vinod B. 2008. NSAIDs as microsphere: The International Journal of pharmacology, 6:1-9.
12. Mohsin Khan, Vaseem A Ansari, Poonam khuswaha, Arun kumar, Juber Akhtar. 2015. Mucoadhesive Microsphere For Controlled Delivery of Drugs: Asian Journal of Pharmaceutical and Clinical Research, 8(4).
13. Boddupalli BM, Zulkar MNK, Nath RA, Banji D. 2010. Mucoadhesive Drug Delivery System: An Overview. Journal of Advance Pharma Tech Research, 1(4):381-387.
14. Dr Prashant Upadhyay. 2012. Mucoadhesive Microspheres: A Short Review. Asian Journal of Pharmaceutical and Clinical Research, 5(3): 24-27.
15. Ankita Garg, Prashant Upadhyay. 2012. Mucoadhesive Microsphere: A Review. Asian journal of pharmaceutical and Clinical Research, 5(3):24-27.
16. Carvalho FC, Bruschi ML, Evangelista RC, Gremiao MPD. 2010. Mucoadhesive drug delivery systems. Brazil Journal Pharm Science, 46:1-17.
17. GU JM, Robinson JR , Leung S.H.S. 1988. CRC, Crit. Review on Therapy Drug Carrier system, 5:21.
18. Sanjay B.Patil and krutika K.Sawant. 2008. Mucoadhesive Microsphere: A Promising Tool in Drug Delivery. Current Drug Delivery, 5.
19. Jimenez-Castellanos MR, Zia H, Rhodes CJ. 1981. Mucoadhesive drug delivery. Indian Pharm 1993; 19 (1 and 2): 143.
20. Longer RS, Peppas NA. Biomaterials, 2: 201.
21. Hans Raj, Ankita Sharma, Shagun Sharma, kapil kumar verma, Amit Choudhary. 2021. Mucoadhesive Microsphere: A Targeted Drug Delivery System. Journal of Drug Delivery and Therapeutics, 11(2):150-155.
22. Moy A, Mathew S, Mathapan R, Prasanth V. 2011. Microsphere:An Overview. International Journal of Pharmaceutical and Biomedical Sciences, 2(2):322-338.
23. Park JB. 1983. Acrylic bone cement: in vitro and in vivo property structural relationship: a selective review. Annals of Biomedical Engineering, 11:297–312.
24. Smart JD. 2005. The basics and underlying mechanisms of Mucoadhesion: Advanced drug delivery reviews, 57:1556–1568.
25. Gu JM, Robinson JR, Leung S. 1998. Binding of acrylic polymers to mucin/epithelial surfaces: Structure-property relationship. Critical Reviews in Therapeutic Drug Carrier System, 5:21-67.
26. Hemlata kaurav, Harikumar SL and Amanpreet Kaur. 2012. Mucoadhesive Microsphere as carriers in Drug Delivery: A Review. International Journal of Drug Development and Research, 4(2):21-34.
27. Sunita Devi, Kanika Sharma. 2022. Mucoadhesive Microsphere a Promising Tool in Drug Delivery System, 12(2):46-53.
28. Jain NK. 2017. Introduction to novel drug delivery systems. 2nd ed, chapter10, p.175-178.
29. Nisha Sharma, Neha Purwar and Prakash Chandra Gupta. 2015. Microsphere as drug carriers for controlled drug delivery: A review. International journal of pharmaceutical science and research, 6(11):4579-4587.
30. Manjanna KM, Shivakumar B, Pramod TM Kumar. 2010. Microencapsulation: An Acclaimed Novel Drug Delivery System for NSAIDs in arthritis. Critical Review: in Therapeutics Drug Carrier System, 27(6): 501-532.
31. Hemlata Kaurav, Harikumar SI, Amanpreet Kaur. 2012. Mucoadhesive Microspheres as carriers in Drug Delivery: a Review. International Journal of Drug Development and Research, 4(2): 21-34.
32. Kh. Gopal Krishna Singh, Sudipta Haider, Sukumar Patr and Jialai Wang. 2018. Microencapsulation of paraffin wax microsphere with silver. Defence science journal, 68(2):218-224.
33. Ratnaparkhi MP, Wattamear MM, Kutmalge MD, Jadhav AN, Chaudhari SP. 2014. Mucoadhesive Microsphere. International Journal Drug Delivery and Research, 6(2):10-19.