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# A Review: The Mucoadhesive Microspheres as a Controlled Drug Delivery System

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**ABSTRACT**

Microspheres play with very important role of particulate drug delivery system because of their as a small size and other efficient properties. Microspheres have been proved to be a suitable bridge to scale the distance over to the formulate or effective dosage form, to simulate controlled drug release. Microspheres are the characteristically free flowing solid powders, which consist of Proteins or synthetic polymer, which are the biodegradable as a nature. Microspheres having particle dimension in range between 0.1-200 µm, can be delivered with the aid of countless routes like oral, parenteral, nasal, ophthalmic, transdermal, colonal etc. Various recent advancement in case of microspheres like mucoadhesive, hollow, floating microballoons, magnetic has been contributed to overcome the various problems that are associated with the use of microspheres. Mucoadhesive microspheres shows an extended residence time at the site of application or absorption and facilitate an intimate contact with the underlying absorption surface and for that reason make contributions to extended or higher therapeutic overall performance of drugs. At attempt has been made in this review article to introduce the readers to the mucoadhesive microspheres as a controlled drug delivery system which includes polymers used in mucoadhesive microspheres as a controlled drug delivery system, types of microspheres, methods of preparation, and evaluation parameters of mucoadhesive microspheres.

## INTRODUCTION:

Microspheres are the bearer connected medication drug delivery framework in which molecule size is ranges from 1-1000 µm extend in breadth having a center of medication and totally external layers of polymer as covering material. In any case, the Achievement of these microspheres is constrained because of their short habitation time at site of ingestion.[1]

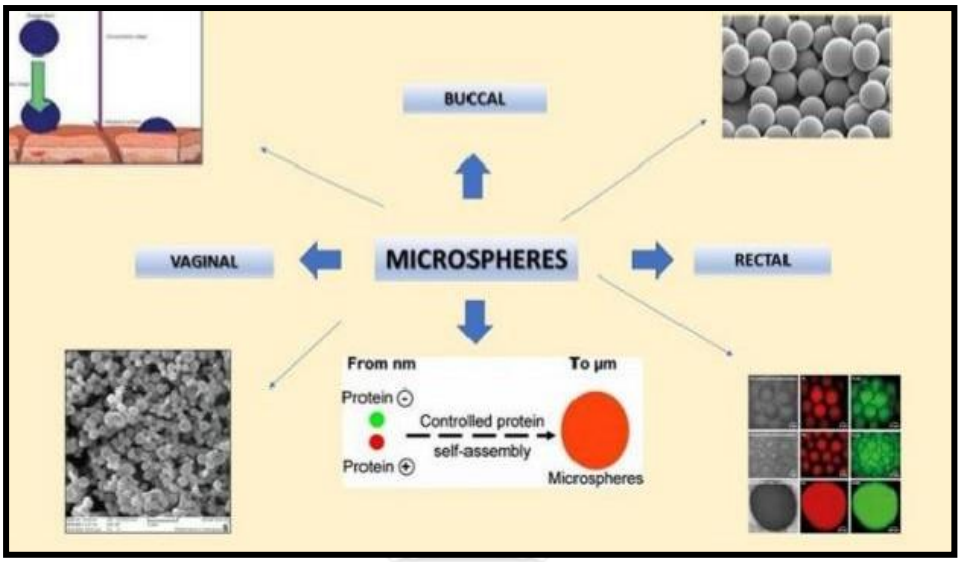


**Fig. 1: Graphical Abstract**

It would, in this way be favorable to have implies for giving a cozy contact of the medication drug delivery framework with the retaining layer [2]. This can be accomplished by coupling bioadhesion qualities to microspheres and creating "mucoadhesive microspheres" [3]. Mucoadhesive microspheres have points of interest like proficient retention and improved bioavailability of the medications because of a high surface To volume proportion, a substantially more cozy contact with the bodily fluid layer and explicit focusing of medicationsto the Retention site.[4]The oral course of medicate organization establishes the most advantageous what's more, favored methods for medication Drug delivery to fundamental dissemination of body.[5] microsphere dependent on different Polymers, strategy of readiness of mucoadhesive microspheres, strategy for assessment and their applications in drug delivery.[6] Mucoadhesive microspheres incorporate microparticles furthermore, microcapsules (having a Centre of medication) of 1-1000µm in breadth and comprising either completely of a Mucoadhesive polymer and having an external covering of it, separately.[7,8] Microspheres, by and large, have the potential to be utilized for focused

and controlled discharge medicate drug delivery; yet coupling of bioadhesive properties to microspheres has extra favorable circumstances for example effective ingestion and bioavailability of the Sedates because of high surface to volume proportion, a much increasingly private contact with the mucous layer.[9,10]

**MUCOADHESIVE MICROSPERES:**

Mucoadhesive microspheres incorporate microparticles furthermore, microcapsules (having a centre of medication) of 1-1000µm in breadth and comprising both definitely of mucoadhesive polymer and having an exterior covering of it, separately.[11]Microspheres, by means of and large, have the doable to be utilized for focused and managed discharge medicate drug delivery; but coupling of mucoadhesive microspheres as an extra advantages.[12]Application of mucoadhesive microspheres to the mucosal tissues of ocular cavity, gastric and colonic epithelium is used for administration of release of localized action. Prolonged launch of capsule and a reduction in frequency of drug.[13]

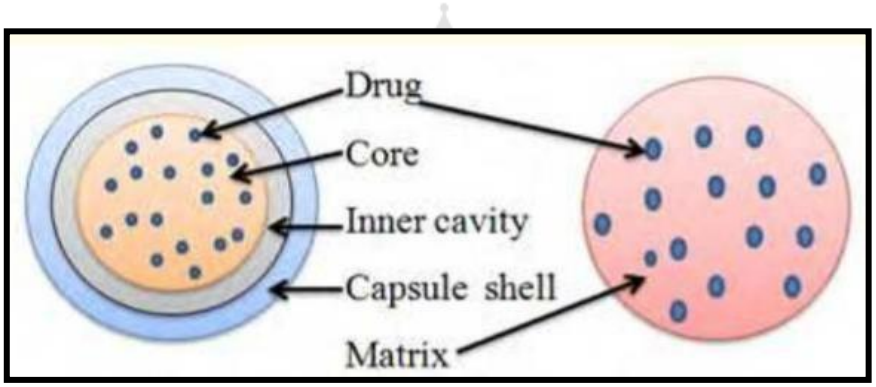


**Fig. 2: Microspheres drug in Matrix**

Administration to the ocular cavity can highly improve the affected person compliance. Thelatter can be additionally be got for drugs administered intra-nasally due to the reduction in mucociliary clearance of capsules adhering to nasal mucosa.[14] This uptake mechanism has been used for the transport of protein and peptide drugs, antigens for vaccination and plasmid DNA for gene therapy. The thought of a non-invasive single of vaccine, via skill of mucosal.

Immunization, affords controlled release of antigens and as a consequence type some other superutility of mucoadhesive microspheres.[15]

**ADVANTAGES OF MUCOADHESIVE MICROSPERES DRUG DELEVERY SYSTEM: [15,16, 17]**

1. Readily localized in the area utilized to enhance and enhance the bioavailability of drugs. E.g.,testosterone.

2. Facilitate intimate contact of the method with underlying absorption surface.

3. This allows amendment of tissue permeability for absorption of macromolecules. E.g., peptides and proteins.

4. Prolong residence time of the dosage form at the site of application and absorption to permitonce or twice a day dosing.

5. Offers a high-quality route, for the systemic delivery of drugs with high first-pass metabolism,there via presenting a greater bioavailability.

6. Additionally substantial price mark downs may be achieved and dose-related aspect effectsmay also be.

7. Microspheres provide steady and extended therapeutic effect.

8. Reduces the dosing frequency and there by improve the patient compliance.

9. They ought to be injected into the body due to the spherical shape and smaller size.

10. Better drug utilization will improve the bioavailability and limit the incidence or intensity ofunfavorable effects.

11. Microsphere morphology approves a controllable variability in a degradation and drug release.

**DISADVANTAGES OF MUCOADHESIVE MICROSPHERES DRUG DELIVERY SYSTEM: [16, 17]**

1. The release from the formulations may get modified.

2. The release rate may vary from a variety of factors Like food and the rate of transit thoughgut, mucin Turnover rate etc.

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

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

5. These kinds of dosage forms cannot be crushed or chewed.

**CLASSIFICATION OF MUCOADHESIVE POLYMERS:**

Mucoadhesion is described as interfacial pressure interactions between polymeric materials and mucosal tissues. In the remaining two many years mucoadhesive polymers have received considerable attention for graph of novel drug systems due to their capability to prolong the time of dosage varieties and to enhance drug bioavailability. Various Administration routes, such as ocular, nasal, gastrointestinal, vaginal and rectal, make Mucoadhesive drug transport structures appealing and bendy in dosage forms Development. Classified into Mucoadhesive polymer as, -

**A) Traditional Non-specific First-generation Mucoadhesive Polymers:**

First-generation mucoadhesive polymers may be divided into three main subsets, namely:

**a) Anionic polymers:** Anionic polymers are widely employed for its greatest.

Mucoadhesive strength or low toxicity. These polymers as a characterized by the presence of sulphate or carboxyl group that gives rise to net negative charge at a PH value exceeding the pka of polymers.[18]

**e.g.,** polyacrylic acid (PAA) & its weakly cross-linked derivatives, Sodium carboxymethyl cellulose (NACMC).

**b) Cationic polymers:** - The most conveniently and widely used cationic polymer is chitosan which is produced by deacetylation of chitin. Chitin is a natural polysaccharide

found predominantly in the shells of crustaceans such as crabs and shrimp, the cuticles of insects, and the cell walls of fungi. It is one of the most abundant biopolymers next to cellulose Most of the naturally occurring polysaccharides.

**e.g.,** cellulose, dextran, pectin, alginic acid, agar, agarose or carrageenan's are neutral and acidic in nature.

**c) on-ionic polymers**: These polymers are also used for its mucoadhesive property The example of Non-ionic polymer are, Hydroxyethylcelullose (HEC), Hydroxypropylcelullose (HPC, MM 300 kDa) Polyvinylpyrrolidone 44000 (PVP, MM 44 kDa) and Polyethylenglycole 6000 (PEG, MM 6 kDa).

**B) Novel second-generation mucoadhesive polymers:**

The main downside in using typical nonspecific mucoadhesive Systems (first generation) is that adhesion might also at sites different than those intended. Unlike First-generation non-specific platforms, positive second-generation polymer systems are Less to mucus turnover rates, with some species binding immediately to mucosal Surfaces; more precisely termed ''cytoadhesives". Furthermore, as floor carbohydrate and protein composition at conceivable target sites vary regionally, extra correct drug Delivery may additionally be achievable.[19]

**Examples:**

**a) Thiolated polymers:**

Thiolated polymers (thiomers) this type of 2nd generation mucoadhesive derived from hydrophilic polymers such as Polyacrylates, chitosan or deacetylated gellan gum.

**Examples of Chitosan–** Iminothiolane (250-fold improved mucoadhesive properties), Polyacrylic acid–Cysteine (100-fold improved mucoadhesive properties), Polyacrylic acid - Homocysteine (Approximately 20-fold improved mucoadhesive properties), and Chitosan–thioglycolic acid (Tenfold improved mucoadhesive properties), Chitosan–thioethyl amidine (Ninefold improved mucoadhesive properties) and alginate–cysteine.

**TYPES OF MICROSPHERES: [21,22]**

**1) Mucoadhesive Microspheres**:

Adhesion can be defined as the sticking of drug to the Membrane through the use of the sticking property of the water-soluble polymers. Adhesion of drug delivery to the mucosal membrane such as buccal, ocular, rectal, nasal etc. Can be termed as bio-adhesion. These types of microspheres off a prolonged Residence time at the site of application and causes intimatecontact with the absorption Site and produces higher therapeutic action.

**2) Magnetic Microspheres:**

This type of delivery system is very a great deal necessary which localizes the drug to the disorder site. In this larger amount of freely circulating drug can be changed by way of smaller amount of magnetically focused drug. Magnetic carriers receive magnetic responses to a magnetic subject from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc.

**3) Therapeutic magnetic microspheres:**

It is used as a deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted via this system. Diagnostic microspheres: Can be used for imaging liver metastases and additionally can be used to distinguish bowel loops from other belly constructions via forming nano dimension particles supramagnetic iron oxides.[20]

**4) Floating microspheres:**

In this kind of microspheres, the bulk density is much less than the Gastric fluid and so remains buoyant in stomach besides affecting gastric emptying rate. The release price of drug at the preferred rate, if the device is floating on gastric content and increases gastric house and will increase fluctuation in plasma concentration. Moreover, it also reduces possibilities dose dumping. Also, one most vital thing is to prolonged therapeutic impact and consequently reducesdosing frequencies.

**5) Radioactive microspheres:**

Radio emobilisation therapy microspheres sized 10-30 nm Are of large than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that

lead to tumour of interest.

**6) Polymeric microspheres:**

The one of a kind of polymeric microspheres can be classified as follows or this are biodegradable polymers microspheres and Synthetic Polymers.

**METHODS OF PREPARATION OF MICROSPHERES:**

Microspheres are small spherical particles, with diameters in the micrometer vary (typically 1 μm to a thousand μm). Microspheres are every so often referred to as a microparticles. Various strategies of training of microspheres are the types;

**a) Emulsion solvent evaporation technique:**

In this approach the drug is dissolved in polymer which was once before dissolved in chloroform and the ensuing answer is introduced to aqueous section containing 0 .2 % Sodium of pvp as emulsifying agent. The above combination was once agitated at 500 rpm then the drug and polymer (eudragit) was once changed into fantastic droplet which solidified into inflexible microspheres by using solvent evaporation and then accrued by way of filtration and washed with demineralized water and desiccated at room temperature for 24hrs.Aceclofenac microspheres have been organized by way of this technique.[23]

**b) Emulsion-solvent diffusion technique:**

To improve the residence time in colon floating microparticles are prepared with the aid of this technique. The combination of ethanol and dichloromethane (1:1) and then drug polymer mixture dissolved in mixture of ethanol and dichloromethane and then the combination used to be Added dropwise to sodium lauryl sulphate (SLS) solution. The solution was stirred with Propeller type agitator at room temperature at 150 rpm for 1 hr. Thus, the shaped floating microspheres were washed and dried in a desiccator at room temperature. The following microparticles had been sieved and collected.

**c) Emulsion go linking method:**

In this technique drug was once dissolved in aqueous gelatin solution which used to be previously heated for 1 hr at 40 $^0$C. The answer was once added drop sensible to liquid paraffin whilst stirring the mixture at 1500 rpm for 10 min at 35°c, results in w/o emulsion

then further stirring is performed for 10 min at 15 0C. Thus, the produced microspheres had been washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for three hrs for cross linking and then was once handled with 100mL of 10mm glycine answer containing 0.1%w/v of tween eighty at 37 zero C for 10 min to block unreacted glutaraldehyde. Examples for this method is gelatin a microspheres.

**d) Multiple Emulsion Method:**

Oral controlled release drug delivery of indomethacin was prepared via this technique. In the beginning powder drug was once dispersed in answer (methyl cellulose) accompanied by means of emulsification in ethyl cellulose solution in ethyl acetate. The primary emulsion was once then re-emulsified in aqueous medium. Under optimized circumstance discrete microspheres were formed throughout this phase. [23,24}

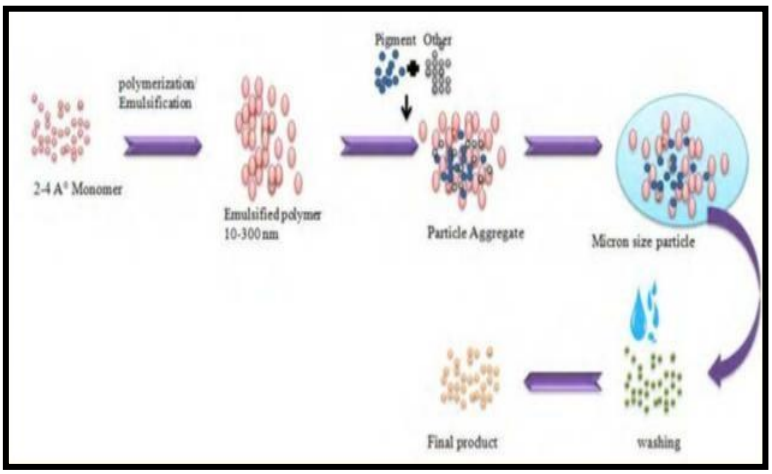


**Fig. 3: Multiple Emulsion Technique**

**e) Co-acervation method:** Co-acervation thermal change: Performed by weighed quantity of ethyl cellulose was once Dissolved in cyclohexane with full of life stirring at eighty 0C by wayof heating. Then the drug was finely pulverized and added with full of life stirring on the above answer and section Separation used to be performed via reducing temperature and the usage of ice bath. Then above product was once washed twice with cyclohexane and air dried then surpassed via sieve (sieve no. 40) to obtain character microcapsule-acervation non solventaddition: Developed via weighed quantity of ethyl cellulose was dissolved in toluene containing propyl Isobutylene in closed beaker with magnetic stirring for 6 hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then segment separation is

finished by using petroleum benzoin 5 times with non-stop stirring. After that the microcapsules were washed withn-hexane and air dried for two hr and then in oven at 50oc for four hr.

**f) Ionic gelation technique:** Alginate/chitosan particulate system for diclofenac sodium release was prepared diclofenac sodium this technique. 25 % (w/v) of diclofenac sodium was added to 1.2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Ca2+ /Al3+ and chitosansolution in acetic acid. Microspheres which were formed were kept in original solution for 24 hr for internal gellification followed by filtration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.

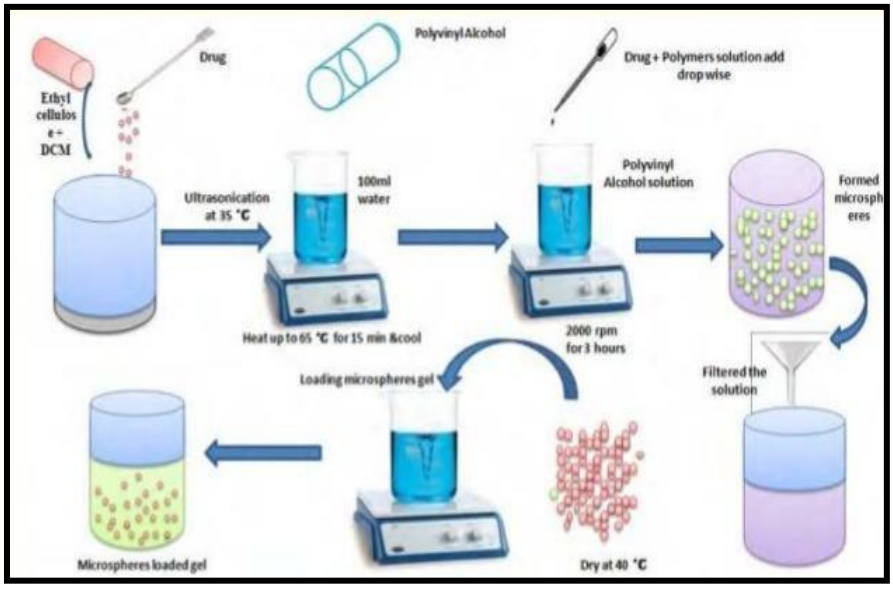


**Fig. 4: Ionic Gelation Technique**

**g) Spray Drying Technique:** This used to be used to put mutually polymeric blended microsphere loaded with ketoprofen drug. It includes dispersing the core material into liquefied coating material and then spraying the mixture in the surroundings for solidification of coating discovered with the aid of rapid evaporation of solvent.[26] Organic of poly (epsilon- caprolactone) (PCL) and cellulose acetate butyrate (CAB), in one of a weight ratio and ketoprofen had been geared up and sprayed in different experimental circumstance accomplishing drug loaded microspheres. This is rapid on the other may lose crystallinity due to fast drying process.[26]

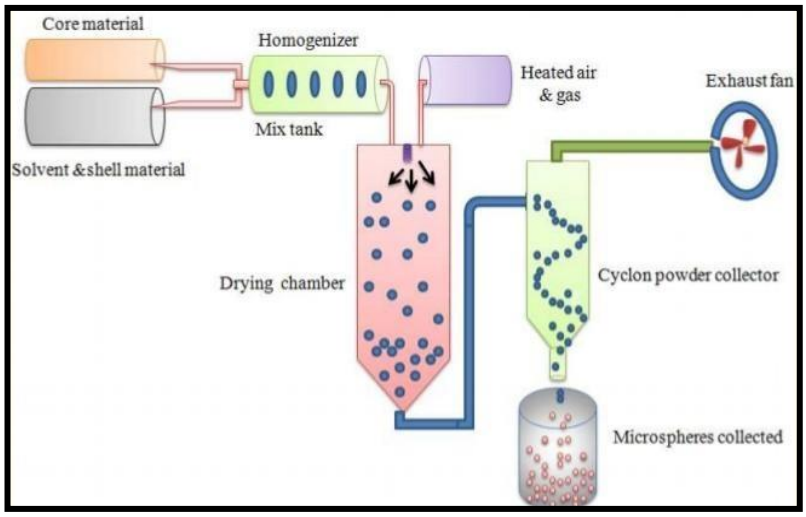


**Fig.5: Spray Drying Technique**

**Principle:**

1. **Atomization:** Liquid feed changed into fine droplets.

2. **Mixing:** It involves passing of hot gas stream through spray droplets which results in evaporation of liquid leaving dry particles.

3. **Drying:** Dry powder is separated from the gas stream and collected.

**h) Single emulsion technique:** Mucoadhesion is a topic of design of drug delivery systems. Thismethod is used to make a variety of carbohydrate and protein products. Natural polymers are firstdissolved in aqueous media, then spread in non-aqueous media (oil phase), and finally Cross- linked globules that have been dispersed are formed accomplished in two ways.

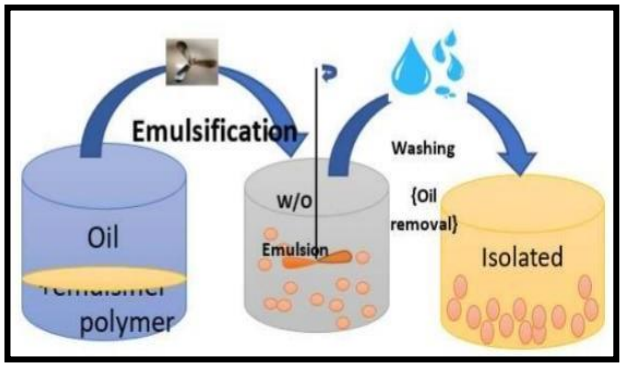


**Fig. 6: Single emulsion technique**

**i) emulsion technique:** This approach is better ideal for water soluble medicines, peptides, proteins, or vaccines and can be utilized with the both natural and manufactured polymers. In this method of making microspheres necessitates as a creation of several emulsions. Aqueous protein solutions are disseminated in lyophilic organic continuous phase, which contains the active ingredients, in this approach. Polymer solution encapsulates protein distributed in aqueous phase in this continuous phase. The initial emulsion is then homogenized before being added to a PVA aqueous solution. After Forming Double emulsions, emulsions are processed to remove the solvent by either solvent extraction or solvent.

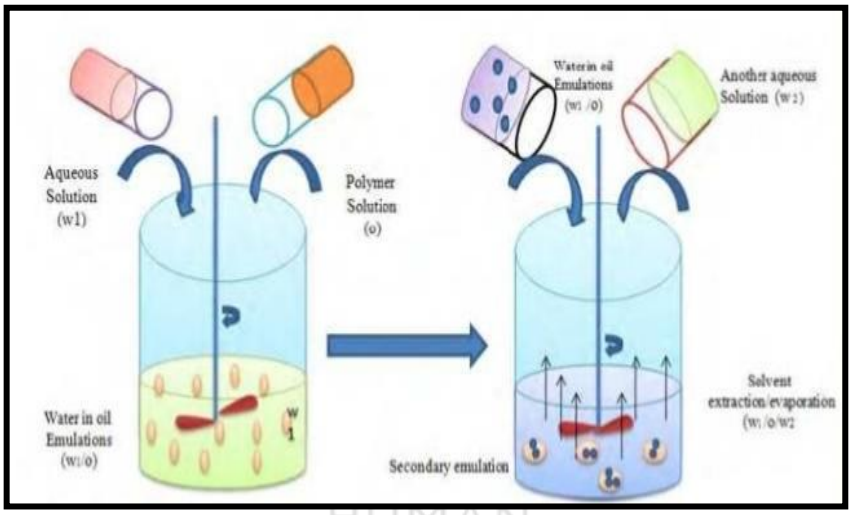


**Fig. 7: Double Emulsion Technique Evaluation Parameters of Mucoadhesive Microspheres:**

**1) Particle Size and Shape:** Particle measurement can be determined with the aid of optical microscopy with the help of calibrated eyepiece micrometer. The size of around 100 microspheres is measured and their average particle size is calculated by,

$$D \text{ mean} = \sum n\, d / \sum n$$

Where, n = number of microspheres checked; d = Mean size.

**2) Density Determination:** The density of microspheres can be measured by using a multi quantity pycnometer. Accurately weighed sample in the cup is placed into the multi-Volume pycnometer. Helium is introduced at the constant pressure in the chamber and allowed to expand. This expansion results in the decrease in Pressure within the chamber. Two consecutive readings of reduction in pressure at a different initial pressure are noted.

From two pressure readings the volume and hence the density of microsphere carriers is determined.[27]

**3) Isoelectric Point:** The isoelectric point can be measured by the using of micro electrophoresis apparatus with the aid of measuring electrophoretic mobility of microspheres. The mean velocityas a different pH value from 3-10 is calculated by measuring the time of particle movement over the distance of 1nm.[28]

**4) Angle of Contact:** It is angle of repose Ø of microspheres, which measures the resistance to particle flow is calculated by the,

$$\tan \Theta = 2h/d$$

Where, 2h /d is the surface area of free-standing height of microspheres heap that is formed after making microspheres flow from the glass funnel.

**5) Electron Spectroscopy for Chemical Analysis:** It is surface chemistry of microspheres can be determined by using electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of atomic composition of the surface. The spectra obtained using ESCA can be used to determine the surface degradation of biodegradable microspheres. [27,28]

**6) Fourier Transform Infrared Spectroscopy:** Drug polymer interaction and degradation of themicrospheres can be assessed by the FTIR.

**7) Drug Entrapment Efficiency:** Weighed amount of the microsphere are taken and crushed. After then dissolved in the buffer solution with the help of stirrer and filtered. The filtrate is assayed by UV spectrophotometer at a particular wavelength by using calibration curve.

[Drug Entrapment efficiency = Actual weight of Microspheres/Theoretical weight of drug and Polymer × 100]

**8) Percentage Yield:** Calculated by the weight of microspheres obtained from each batch dividedby total weight of drug and polymer used to the prepare that batch multiplied by 100.

**9) Swelling Index**: It is determined by measuring the extent of swelling of microspheres in the particular Solvent. The equilibrium swelling degree of Microspheres is to determined by

swelling of 5mg of Dried microspheres poured in 5ml of buffer solution Overnight in a measuring cylinder. As a calculated by given formula. Swelling index = Mass of swollen microsphere – Mass of dried microspheres ×100 / Mass of dried Microspheres.

**10) In-vitro methods:** This method allows to the determination of release characteristics and permeability of as a drug through the membrane. In-vitro method is employed to the quality control procedure in the pharmaceutical production and in product development etc. Sensible and reproducible release data derived from the physically, chemically and the hydro dynamically defined as conditions are necessary.[29]

**11) Dissolution Apparatus Method:** it is Standard USP and BP dissolution apparatus have been used to study in-vitro released to the profiles using both rotating elements Paddle and basket. Dissolution medium used for the study various from 100-500ml and speed of the rotation from 50-100rpm.

**12) In-vivo method:** In this method studying the permeability of intact mucosa comprises of technique that gives the biological response of the organism locally or systemically and those that involve direct local measurement of uptake and accumulation of the penetrate at their surface. [29,30]

**13) In-vitro/in-vivo correlation:** Correlations between in-vitro dissolution rates and the rate and extent of availability as a determined by blood concentration and or urinary excretion of drug and metabolites are referred to as “in-vitro-in-vivo correlation”. Such correlations allow one to the development of product specifications with availability.

**CONCLUSION**:

From overall Literature study in connection to area of interest, Mucoadhesive microsphere drug delivery system provides opportunities for designing new controlled and delayed released oral formulations. Microspheres are the good choice of drug delivery system than many other types of drug delivery system. Micro-spheres can be used to the deliver drug to specific parts of the body. The molecular structure of the polymeric material, the polymer’s susceptibility to Degradation, and the surface area as well as the porosity of microspheres all impact the rate of drug released. In particular, defective cell sorting, diagnosis, gene and biologically active, safe, controlled, Specific, and effective in-vitro administration, and supplementation of the diseased tissues and tissues within the body.

## REFERENCES:


1) Lin C.Y., Lin S.J., Yang Y.C., Wang D.Y., Cheng H.F., and Yeh M.K., degradable polymeric microsphere-based vaccines and their applications in infectious diseases. Human Vaccines & Immunotherapeutics 2015; 11:650-656. DOI: 10.1080/21645515.2015.1009345.

2) Dhadde G.S., Mali H.S., Raut I.D., Nitalikar M.M., Bhutkar M.A., A Review on Microspheres: Types, method of preparation, characterization and Application. Asian J of Pharm and Tech. 2021;11(2):1-7.

3) Sipai A.B., "Mucoadhesive Microsphere An overview". American Journal of Pharmtech Research 2.1 (2012): 237-258.

4) Syed T.R., Mukherjee J., A Review on Mucoadhesive Microsphere as an Efficient Drug Delivery System. Indo American J of Pharm Res, 2020; 10(1): 573-579.

5) Jagtap Y.M.,"Effect of various polymers concentrations on physicochemical properties of floating microspheres". Indian Journal of Pharmaceutical Sciences 74 (2012): 512-520.

6) Ghalop S.B., "Hollow microsphere a Review". International Journal of Pharmaceutical Science Review and Research 1 (2010): 10-15.

7) Akiyama, Y., Yoshioka, M., Horibe, H., Inada, Y., Hirai, S., Kitamori, N., Toguchi, H., Anti-hypertensive effect of oral controlled release microspheres Containing an ACE inhibitor (Delapril hydrochloride) in rats. J. Pharm. Pharmacol. 46, 661–665.

8) Deshmukh R., Wagh P., Naik J., Solvent Evaporation and Spray Drying Technique for Micro and Nanosphere/ particles preparation: A Review. Drying technology an Int J, 2016; 1-59.

9) Kaurav H., Harikumar S.L., Kaur A., Mucoadhesive Microspheres as Carriers in Drug Delivery: A Review. Int Jof Drug Dev and Res, 2012; 4(2) 21-34.

10) Thummar A.V., Kyada C.R, Kalyanvat R., Shreevastva B.A., Review on Mucoadhesive Microspheres as a NovelDrug Delivery System. Int J for Pharma Res Sch, 2013; 2(2): 188-200.

11) Chauhan K., Mahor S., Chodha H., A Review article on Novel Floating Mucoadhesive Microspheres and their Development. WJPPS, 2020; 9(11): 844-854.

12) Madhav N.S., "Review on microparticulate drug delivery system". International Journal of Pharm Tech Research3 (2011): 1242-1254.

13) Ahuja, A., Khar, R.K., Ali. A Review article on Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm. 23,489–515.

14) Milena L., Nikolett K.S, Vince A., Andras J.L, Istvan A., Micro particles, Microspheres, and Microcapsules for Advanced Drug Delivery. Scientia Pharmaceutics, 2019;1-31.

15) Ratnaparkhi M.P., Wattamwar M.M., Kutmalge M.D., Jadhav A.N., Chaudhari S.P., Mucoadhesive MicrosphereReview. Int J drug Dev and Res, 2014; 6(2): 10-19.

16) Kumari N., Aggarwal G., Harikumar S.L., Mucoadhesive Microsphere: A Review. J Drug Deli Thera, 2014;4(5): 48-54.

17) Gaba P., "Galactomannan gum coated mucoadhesive microspheres of glipizide for treatment of type 2 diabetes mellitus: In vitro and in vivo evaluation". The Saudi Pharmaceutical Journal 19.3(2011):143-152.

18) Carvalho F.C., Bruschi M.L., Evangelista R.C., Gremio M.P.D., Mucoadhesive drug Delivery system. Brazilian Journal of Pharmaceutical Sciences 2010; 46(1): 1-17.

19) Azmat A.k., "Antifungal efficacy of amphotericin B encapsulatedfibrin microsphere for treating Cryptococcusneoformans infection in Swiss albino mice". 593(2016):1-7.

20) Paolo Yammine., "Study of different processing Parameters for polylactic acid microspheres formulations". International Journal of Pharmaceutical Sciences and Research 5.10 (2014): 4176-4181.

21) P. Dutta J., "Floating Microsphere: Recent Trends in The Development of Gastroretentive Floating Drug Delivery System". International Journal of Pharmaceutical Science and Nanotechnology 4.1 (2011): 1293-1306.

22) Chien Y.W., "Concepts and System Design for Ratecontrolled Drug Delivery" Chapter 1". Novel Drug Delivery System 2 (19920): 1-42.

23) Kataria S., "Microsphere A Review". International Journal of Research in Pharmacy and Chemistry 1(2011): 1184-1198.

24) Carvalho F.C., Bruschi M.L., Evangelista R.C., Gremio M.P.D., Mucoadhesive drug Delivery system. Brazilian Journal of Pharmaceutical Sciences 2010; 46(1): 1-17.

25) Dixit M., "Spray Drying: A crystallization Technique: A review". International Journal of Drug Formulation and Research 1 (2010): 1-29.
26) Bansal H., Kaur S.P., Gupta A.K., Microsphere: Method of Preparation and Application; A comparative study. Int J of Pharm Sci Rev and Res, 2011; 10(1): 69-78.
27) Kunchu K., "Albumin microspheres: An Unique System as drug Delivery Carriers for non-steroidal anti-inflammatory drugs (NSAIDS)". International Journal of Pharmaceutical Sciences Review and Research 5(2010): 10-17.
28) Srivastava P., "Application and advancement of microspheres as controlled drug delivery system". International Journal of Pharmacy and Life Sciences 4 (2013): 2583-2594.
29) Tarun V., "In vitro Evaluation and Characterization Methods of Antifungal Agent as Microspheres". International Journal of Pharmacy and Pharmaceutical Sciences 17 (2018): 90-96.
30) Patil S.S., and Gupta V.R.M., Design and in vitro evaluation of Multiparticulate system for the chronomodulated delivery of Lornoxicam. Journal of Drug delivery and therapeutics 2015; 5:62-71.