REVIEW ARTICLE

Journal of Pharmaceutical Advanced Research
(An International Multidisciplinary Peer Review Open Access monthly Journal)
Available online at: www.jparonline.com

Mucoadhesive Microspheres – A review

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Received: 27.03.2018 Revised: 14.04.2018 Accepted: 20.04.2018 Published: 30.04.2018

ABSTRACT: The mucoadhesive microparticulate drug delivery system is a popular novel drug delivery method because mucous membranes are relatively permeable, allowing for the rapid uptake of a drug into the systemic circulation and avoiding the first pass metabolism. Microspheres are the carrier linked drug delivery system which having the potential to be used for the targeted and controlled release drug delivery, when combining this properties with mucoadhesion leads to efficient absorption and enhanced bioavailability. In recent years such mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal and vaginal routes for either systemic or local effects. The current article focuses on review on mucoadhesive microspheres, including its principles underlying the formulation and evaluation of mucoadhesive microspheres.

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Key words: Microspheres, Mucoadhesion, Bioavailability, control release, polymers.

INTRODUCTIONS:

Drug delivery is the method of administering pharmaceutical compound to achieve a therapeutic effect in humans or animals. The drug delivery system can further be divided into two main types: a. Conventional drug delivery system. b. Novel drug delivery system [1].

Conventional drug delivery system is the classical methods for the delivery of drug into the body. The examples of these systems includes: Oral delivery, Buccal/ Sublingual delivery, rectal delivery, intravenous delivery, subcutaneous delivery, Intramuscular delivery etc. Limitations associated with such a conventional dosage forms: Poor patient compliance, difficult to attain steady state concentration, fluctuation in the concentration may lead to under medication or over medication and the fluctuating drug level may lead to

precipitation of adverse effect. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects [2].

There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are an important part of NDDSs and have the potential to deliver drug in a controlled manner.

Table 1. Classification of polymers used in mucoadhesive microspheres [24].

Anionic	Cationic	Non-ionic
Sod. alginate	Chitosan	Polyvinyl pyrrolidone
Xanthan gum	Polylysine	Hydroxy propyl cellulose
SCMC	Amino dextran	Poly vinyl alcohol
Pectin	DMAE dextran	Hydroxy propyl methyl cellulose
Polyacrylic acid	Trimethylated chitosan	Hydroxy ethyl starch
Dextran	Polybrene	Polyethylene glycol
Alginic acid		Hydroxy ethyl Cellulose
Chitosan-EDTA	--	Poly (ethylene oxide)
Carageenan	--	--

DMAE- Dimethyl amino ethyl and SCMC - Sodium Carboxy Methylcellulose.

Microspheres:

Microspheres are the carrier linked drug delivery system in which particle size is ranges from (1-1000 µm) range in diameter having a core of drug and entirely outer layers of polymers as coating material [3]. Properties of an ideal microsphere are the ability to incorporate reasonably high concentrations of the drug, stability of the preparation after synthesis with a clinically acceptable shelf life, controlled particle size and dispersibility in aqueous vehicles for injection, release of active reagent with a good control over a wide time scale and biocompatibility with a controllable biodegradability and susceptibility to chemical modification [4].

Types of Microspheres [5-11]:

Bioadhesive/ Mucoadhesive Microspheres: Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal, etc. can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.

Magnetic Microspheres: Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4 µm) but are sufficiently susceptible (ferromagnetic) to be captured in micro vessels and dragged into the adjacent tissues by magnetic field of 0.5- 0.8 tesla.

Floating Microspheres: Castro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period without affecting gastric emptying rate. The drug is released slowly at the desired rate.

Radioactive Microspheres: Radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. They are injected to the arteries that lead to tumor of interest. The different kinds of radioactive microspheres are α emitters, β emitters and γ emitters.

Polymeric Microspheres: Biodegradable polymeric microspheres are those which contain biodegradable polymers which prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium , results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. Synthetic polymeric microspheres are those which are made up of synthetic polymers and are used as used as bulking agent, fillers, embolic particles, drug delivery vehicles etc.

MUCOADHESIVE MICROSPHERES:

It include microparticles and microcapsules (having a core of the drug) of 1—1000 µm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it, respectively. It can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs [12]. The advantages of Mucoadhesive microspheres are prolonged and sustained release of drug, targeting at particular sites or tissues are high, excellent route, for

the systemic delivery of drugs, better patient compliance, increased safety margin of high potency drugs, reduction in fluctuation and reduced intensity of local or systemic side effects and drugs which are unstable in acidic and alkaline environment can be administered by this route [13].

Table 2. List of Research Work on Mucoadhesive Microspheres and Microcapsules [12].

Drug	Polymer	Route	Purpose / result
Acyclovir	Chitosan	Ocular	Slow release rates
Methyl pred-nisolone	Hyaluronic acid	Ocular	Slow & Sustained release rates.
Genta-micin	Hyaluronic acid	Nasal	Increase nasal absorption
Insulin	DSM_LPC	Nasal	Insulin delivery into The systemic circulation
Human growth hormone	DSM_LPC	Nasal	Rapid and increased absorption
Desmo-pressin	Starch	Nasal	Addition of LPC causes a 5 folds increase in C_{max} and 2 folds increase in bioavailability.
Beclo-methasone	HPC	Nasal	Increased bioavailability
Genta-micin	HA/ Chitosan	Nasal	Improved bioavailability
Genta-micin	HPMC	Nasal	Increased the absorption
Furose-mide	AD-MMS (PGEFs)	Nasal	Higher *AUC*, Effective absorption from the absorption window

(AD-MMS: adhesive micro matrix system, *AUC*: area under curve, DSM: degradable starch Microspheres, LPC: lysophosphatidylcholine, PEGs: Polyglycerol esters of fatty acids, HPC: hydroxy propyl cellulose, HPMC: hydroxy propyl methyl cellulose, HA: hyaluronic acid and Alginate: sodium alginate.

Mucoadhesion or bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are held together for a prolonged time period by means of interfacial forces. For a drug delivery purpose, the term Bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be either epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as Mucoadhesion [14].

Table 3. List of Research Work on Mucoadhesive Microspheres and Microcapsules [12].

Drug	Polymer	Route	Purpose
Ribo-flavin	AD-MMS (PGEFs)	GI	--
Amoxi-cillin	AD-MMS (PGEFs) Carbopol934	GI	Greater anti *H. pylori* activity
Cephra-dine	Chitosan/eth ylcellulose	GI	Prolonged the intestinal Absorption.
Vanco-mycin	PGEF coated with Eudragit S 100	Colonic	Well absorbed even without absorption enhancers.
Insulin	PGEF Eudragit S 100	Colonic	Absorbed only in the presence of absorption enhancers, *e.g.* EDTA Salts.
Insulin	HYAFF	Vaginal	Increased absorption from HYAAF microspheres compared to aqueous solution of the drugs.
Salmon calcitoni n	HYAFF	Vaginal	Increased absorption from HYAAF microspheres compared to aqueous solution of the drugs.
Acri-flavine	MC/Sodium CMC/Algina te/ Carbopol	Vaginal	Controlled release
Indome-thacin	Alginate + Sodium CMC/MC/C arbopol/ HPMC	Oral	Slow release rates
Glipi-zide	Alginate + Sodium CMC/MC/ Carbopol/ HPMC	Oral	Slow release rates

AD-MMS: adhesive micro matrix system, CMC: carboxy methyl Cellulose, HYAFF: hyaluronic acid esters,PEGs: Polyglycerol esters of fatty acids, MC: methyl cellulose, HPMC: hydroxy propyl methyl cellulose, and Alginate: sodium alginate.

Mechanism of mucoadhesion:

Mucoadhesion is the attachment of the drug along with a suitable carrier to the mucosal layer. Mucoadhesion is a complex phenomenon, which involves wetting, adsorption, and interpenetration of polymer chains [15]. Mucoadhesion has the following mechanism: intimate contact between a mucoadhesive delivery system and mucosal membrane (wetting or swelling phenomenon) and penetration of the mucoadhesive delivery system into the tissue or into the surface of the mucous membrane (interpenetration).

Table 5. Commercially available Oral Mucoadhesive Drug Delivery Systems [48]:

Drug	Dosage form	Product name	Manufacturer
Fentanyl citarte	Lozenge	Actiq	Cephalon
	Tablet	Fentora	Cephalon
	Film	Onsolis	Meda Pharm Inc
Buprenor-phine HCl	Tablet	Subutex	Reckitt Benckiser
Proclor-perazine	Tablet	Buccaste m	Reckitt Benckiser
Testo-sterone	Tablet	Striant SR	Columbia Pharm
Nitro-glycerine	Tablet	Nitrostate	W lambert-Davis
	Spray		Pfizer Pharm
Zolpidem	Spray	Zolpimist	Novadel
	Tablet	Suscard	Forest Lab
Glyceryl trinitrate	Spray	Nitromist	Novadel

Theories of Mucoadhesion [16,17]:

Electronic theory: It involves in the transfer of electron upon contact of adhesive polymer with a mucus glycoprotein network because of difference in their electronic structures. This results in the formation of electrical double layer at the interface.

Absorption theory: According to this theory, after an initial contact between two surfaces, the material adheres because of surface force acting between the atoms in two surfaces. Two types of chemical bonds resulting from these forces can be distinguished as primary chemical bonds of covalent nature and secondary chemical bonds having, many different forces of attraction, including electrostatic forces, Vander walls forces, hydrogen and hydrophobic bonds.

Diffusion theory*:* According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact.

Wetting theory*:* The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface.

Cohesive theory*:* The cohesive theory proposes that the phenomena of bioadhesion are mainly due to intermolecular interaction amongst like molecule.

Table 6. List of Patents on Mucoadhesive Microsphere Formulations [48]:

Patent No	Active Ingredients	Method (s)
United States Patent 6432449	Protein	Ionic gelation
United States Patent 7736669	Living cells	Ionic gelation
United States Patent Application 20040071780	Recombinant protein	Polymer dispersion technique
United States Patent 6733790	Dyes, perfumes etc.	Polymerization method
United States Patent 5489401	Microorganisms, pharmaceuticals, pesticides	Gelation method
United States Patent 7282220	-	Crosslinking method
United States Patent Application 20040247632	Retinoic acid	Precipitation method
United States Patent 6140089	Viable cells (neurosecretory cell lines, ß-cell, fibroblasts, myocytes and glial cells)	Non cross linked encapsulation method

Resease pattern was mucoadhesive sustained release.

Factors Affecting Mucoadhesion [18-23]:

Hydrophilicity: polymers containing hydroxyl and carboxyl groups allow hydrogen bonding with the substrate, swelling in aqueous media, thereby allowing maximal exposure of potential anchor sites. Leading to increased chain flexibility and efficient penetration.

Molecular weight: The low molecular weight polymers favor interpenetration of polymer molecules, whereas a high molecular weight polymer favors entanglements.

Cross linking and swelling: Cross link density of the polymer is inversely proportional to the degree of swelling. The lower the cross link density, the higher the flexibility and hydration rate; the larger the surface area of the polymer, the better is the mucoadhesion.

Concentration of active polymer: Optimum concentration of polymer is required to produce best mucoadhesion.

Spatial conformation: The helical conformation of the polymer primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation.

pH: The pH at the bioadhesive to the substrate interface can influence the adhesion of bioadhesives possessing ionizable groups. If the local pH is above the pKa of the polymer, it will be largely ionized; if the pH is below the pka of the polymer it will be largely unionized.

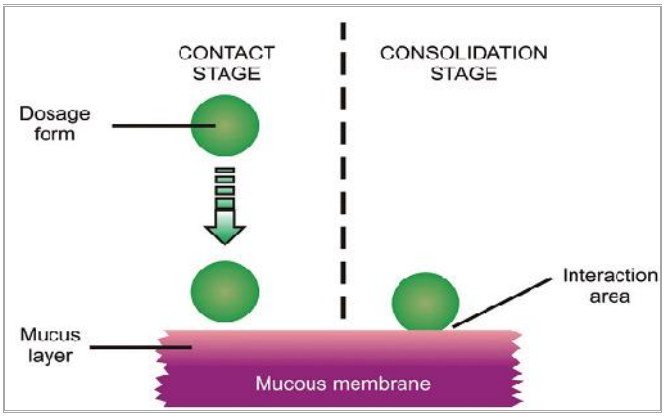

Fig 1. Mechanism of mucoadhesion.

Disease state: Changes in the physicochemical properties of the mucosal membrane will occur during Pathological condition like common colds, cystic fibrosis, ulcerative colitis, inflammatory conditions of the eye, bacterial and fungal infections of the female reproductive tract etc.

CHARACTERISTICS OF AN IDEAL MUCOADHESIVE POLYMER:

The ideal characteristics of mucoadhesive polymers are **t**he polymer and its degradation products should be non-toxic and non- absorbable from the GI tract, it should be non-irritant to the mucus membrane, it should adhere quickly to most tissue and should possess some site specificity, it should allow easy incorporation of the drug, the polymers must not decompose on storage or during the shelf life of the dosage form and the cost of the polymer should not be high so that the prepared dosage form remains competitive [21-25].

METHOD OF PREPARATION OF MUCOADHESIVE MICROSPHERES:

Solvent Evaporation:

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is heated to evaporate the solvent, then polymer shrinks around the core. Recovery of microspheres [26].

Hot Melt Microencapsulation:

In this method, the polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 mm.

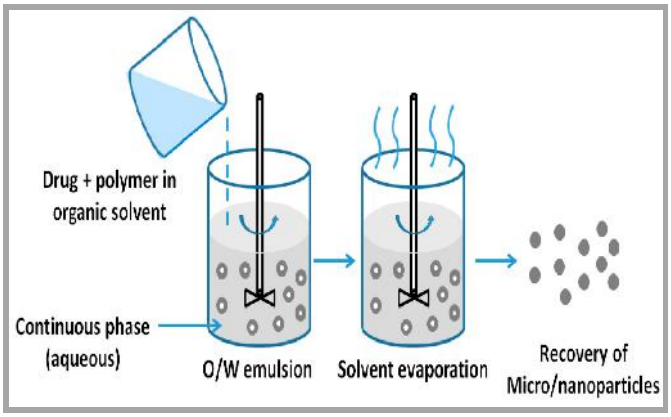

Fig 2. Solvent Evaporation.

The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5° 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. polyanhydrides [18].

Solvent Removal:

It is a non-aqueous method of microencapsulation, particularly suitable for water labile polymers such as the polyanhydrides. In this method, drug is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. This mixture is then suspended in silicone oil containing span 85 and methylene chloride. After pouring the polymer solution into silicone oil, petroleum ether is added and stirred until solvent is extracted into the oil solution. The resulting microspheres can then be dried in vacuum [27].

Spray Drying:

In this process, the drug may be dissolved or dispersed in the polymer solution and spray dried. The quality of spray-dried microspheres can be improved by the addition of plasticizers, e.g. citric acid, which promote polymer coalescence on the drug particles and hence promote the formation of spherical and smooth surfaced microspheres. The size of can be controlled by the rate of spraying, the feed rate of polymer drug solution, nozzle size, and the drying temperature. This method of microencapsulation is particularly less dependent on the solubility characteristics of the drug and polymer and is simple, reproducible, and easy to scale up. One of the major advantages of process is feasibility of operation under aseptic conditions. This process is rapid and this leads to the formation of porous micro particles [28].

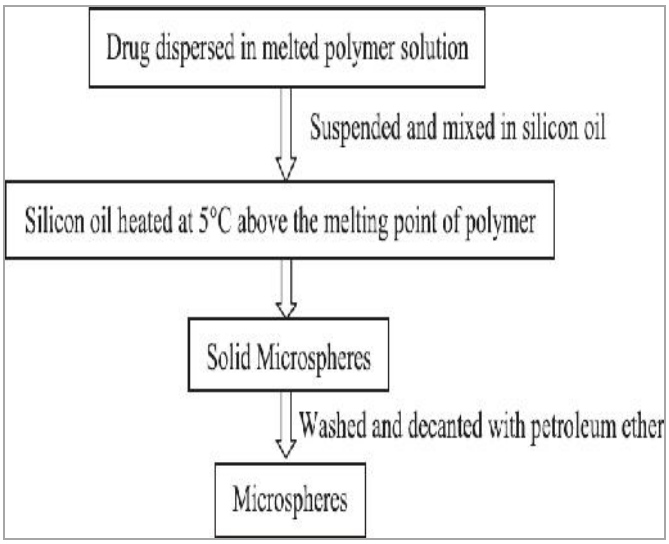

Fig 3. Hot Melt Microencapsulation.

Ionic gelation:

In this method, the polymer dissolved in an aqueous solution, then suspending the active ingredient in the polymer solution, producing micro droplets are allowed to fall into a hardening bath and slowly stirred. The hardening bath usually contains calcium chloride solution, whereby the divalent calcium ions crosslink the polymer, forming gelled microspheres. The particle size of microspheres can be controlled by using various size extruders or by varying the polymer solution flow rates [14,27].

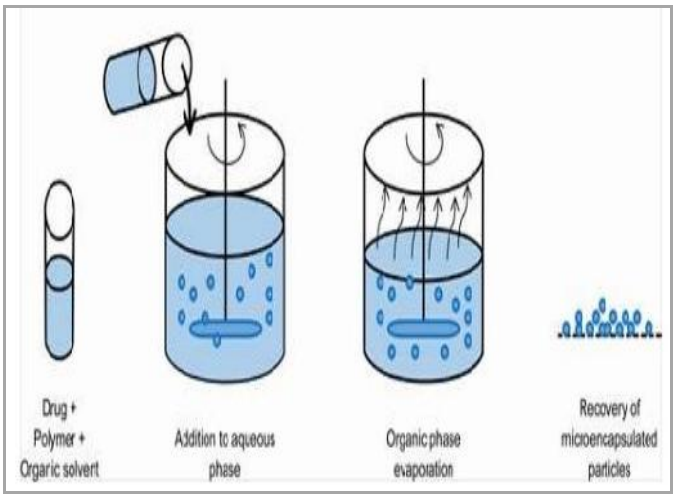

Fig 4. Solvent Removal.

Phase separation coacervation technique:

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and a mismatched polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size, and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates [14,29].

Emulsion cross-linking method:

In this method, the drug is dissolved in polymer solution. The solution is added drop wise to oil phase, results in w/o emulsion then further stirring is done for a specified time period. To which cross linking agent is added. The produced microspheres are washed respectively with suitable solvent. The resulting microspheres can then be dried in vacuum [144,29].

Emulsification method:

In this method, drug was dispersed in a polymer solution and this dispersion was emulsified in oil phase containing surfactant using a mechanical stirrer for specified time period. Then emulsion was stirred for 10 more minutes. The prepared microspheres were collected by filtration and washed with suitable solvent to remove oil phase. The resulting microspheres can then be dried in vacuum [30].

CHARACTERIZATION OF MUCOADHESIVE MICROSPHERES [24-33]:

Percent yield:

The prepared microspheres are evaluated for percentage yield. The percentage yield is calculated as per equation below,

$$\text{Yield}\,(\%) = \frac{\text{Amount of microspheres}\,(g)}{\text{The theoretical amount}\,(g)} \times 100 \quad \ldots\ldots\ldots (1)$$

Micromeritic properties:

The microspheres are characterized for micromeritic properties such as true density, tapped density, compressibility index and flow properties. The tapped density is measured using Bulk density apparatus and compressibility index is determined by using tapped and bulk densities.

Angle of repose:

Flow ability of the prepared microspheres is determined by calculating angle of repose by fixed funnel method. A funnel with 10 mm inner diameter of stem is fixed at a height of 2 cm. over the platform.

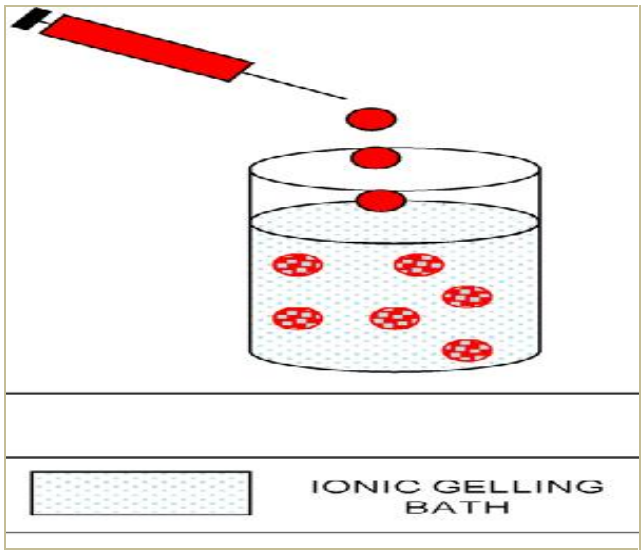

Fig 5. Ionic gelation method.

About 10 gm of sample is slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle is drawn around the pile base and the radius of the powder cone is measured. Angle of repose is calculated by using the following formula,

$\theta = \tan^{-1}(h/r)$ ……. (2)

Where, θ = Angle of repose, h = Height of the pile and r = Average radius of the powder cone.

Carr's Index (CI):

It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. A useful empirical guide is given by the Carr's compressibility.

$$CI\ (\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \text{..... (3)}$$

Particle size analysis:

The Mucoadhesive microspheres are examined by optical microscope. The freshly prepared suspension of microspheres is examined on an optical microscope and size of the microspheres is measured by using a pre-calibrated ocular micrometer and stage micrometer.

Drug entrapment efficiency (EE):

Drug loaded microspheres (100 mg) are powdered and transferred into 100 ml volumetric flask dissolved in 10 ml of solvent and the volume is made up with suitable dissolution medium. The resultant dispersion was kept for 24 hrs for complete dissolution and filtered through a 0.45 µm membrane filter. The drug entrapment efficiency is determined spectrophotometrically after appropriate dilutions at respective λ_{max}. The drug entrapment efficiency is calculated by the following equation,

EE (%) = (PC/ TC)×100 ……(4)

Where, PC and TC are practical and theoretical content.

Determination of drug content (DC) in microspheres:

Drug loaded microspheres (100 mg) are powdered and transferred into 100 ml volumetric flask dissolved in 10 ml of solvent and the volume is made up with suitable dissolution medium. The drug content is determined spectrophotometrically after appropriate dilutions at respective λ_{max}. The drug content is calculated by the following equation,

DC (%) = (Qd in microspheres/Qm) × 100 ……..(5)

Where, Qd is amount of drug in microspheres and Qm is amount of microspheres.

Determination of drug loading in microspheres:

The drug loading in the microspheres is estimated by using the formula;

L = (Qm/Wm) × 100 ……(6)

Where, L is percentage of drug loading in the microspheres, Wm is weight of microspheres in g and Qm is quantity of drug present in Wm g of microspheres.

Swelling index:

The swelling index is a property measured to know the behavior of polymer in physiological solution. It is determined by keeping the microspheres in buffer solution for 24 h and washed. The swelling index is calculated using formula,

α = (W2-W1)/W1 ……..(7)

Where, α is swelling index, W1 is weight of microspheres before swelling and W2 is weight of microspheres after swelling.

***In-vitro* bioadhesion:**

Animal mucous membrane is collected and is reverted and filled with buffer solution, both ends are tied. Further these sacs are inserted into tubes containing a suspension of accurately weighed microspheres (A1). These tubes are shaken for 30 min. The not attached microspheres are dried and weighed (A2). The bioadhesion (%) can be calculated as [(A1-A2) × 100].

***In vitro* drug release study:**

The drug release is studied by using USP type II apparatus at 37±0.5 ^{0}C and at 100 rpm in dissolution medium. Five ml of the sample solution is withdrawn at predetermined time intervals, filtered, diluted suitably

and analyzed spectrophotometrically. Equal amount of the fresh dissolution medium is replaced immediately after withdrawal of the test sample. Percentage drug dissolved at different time intervals is calculated using the Lambert-Beer's equation. The result is obtained in triplicate and the average value reported.

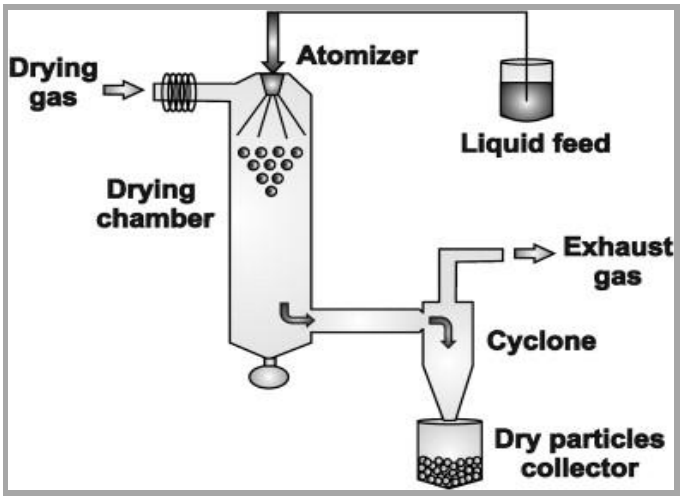

Fig 6. Spray Drying.

Surface topography by Scanning Electron Microscope:

The surface morphology and structure are visualized by scanning electron microscopy (SEM).

Drug release pattern from microspheres:

In order to understand the mechanism and kinetics of drug release, the results of the in vitro drug release study are fitted with various kinetic equations like zero order, first order and Higuchi model. In order to define a model this will represent a better fit for the formulation.

APPLICATIONS OF MUCOADHESIVE MICROSPHERES IN DRUG DELIVERY SYSTEM [2,34,35]:

Ophthalmic Drug Delivery:

Polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic properties, polymer hydro gels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments. Ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow. In addition, its penetration enhancement has more targeted effect and allows lower doses of the drugs. In contrast, polymer based colloidal system were found to work as transmucosal drug carriers, either facilitating the transport of drugs to the inner eye (chitosan-coated colloidal system containing indomethacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nanoparticulate containing cyclosporine). The micro particulate drug carrier (microspheres) seems a promising means of topical administration of acyclovir to the eye.

Oral drug delivery:

Drug delivery through the oral mucosa has gained significant attention due to its convenient accessibility. The buccal and sublingual routes are considered as the most commonly used rotes. The nonkeratinized epithelium in the oral cavity, such as the soft palate, the mouth floor, the ventral side of the tongue, and the buccal mucosa, offers a relatively permeable barrier for drug transport. Drug delivery through the oral mucosa has proven particularly useful and offers several advantages over other drug delivery systems including bypassing hepatic first-pass metabolism, increasing the bioavailability of drugs, improved patient compliance, excellent accessibility, unidirectional drug flux, and improved barrier permeability compared, for example, to intact skin. The oral cavity has been used as a site for local and systemic drug delivery.

Local drug therapy is used to treat disease states like aphthous ulceration gingivitis, periodontal disease, and xerostoma. Different dosage designs include adhesive gels, tablets, films, patches, ointments, mouth washes, and pastes. The potential of polymer films containing diazepam as an oral drug delivery was investigated in rabbits. The results indicated that a film composed of a 1:0.5 drug-polymer mixture might be an effective dosage form that is equivalent to the commercial tablet dosage forms. The ability of polymer to form films may permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make polymer a unique polymer for oral drug delivery applications.

Nasal drug delivery:

The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. Polymer based drug delivery systems, such as microspheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the

nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Various polymer salts such as chitosan lactate, chitosan aspartate, chitosan glutamate and chitosan hydrochloride are good candidates for nasal sustained release of vancomycin hydrochloride. Nasal absorption of insulin after administration in to polymer powder were found to be the most effective formulation for nasal drug delivery of insulin in sheep compared to chitosan nanoparticles and chitosan solution.

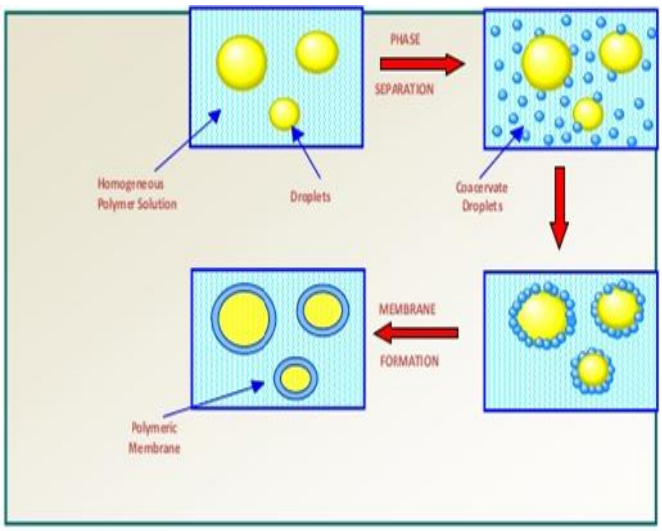

Fig 7. Phase separation coacervation technique.

Buccal drug delivery:

In the oral cavity, buccal region deals with an acceptable route of administration for systemic drug delivery from the various transmucosal available sites, buccal cavity mucosa was the most convenient and also easily approachable site for the purpose of delivering the therapeutic agents for both local as well as systemic delivery used as retentive dosage forms. Mucosa has a rich blood supply so it is highly permeable. Buccal tablets based on chitosan microspheres containing chlorhexidine diacetate gives prolonged release of the drug in the buccal cavity improving the antimicrobial activity of the drug. Polymer microparticles with no drug incorporated have antimicrobial activity due to the polymer. The buccal bilayered devices (bilaminated films, palavered tablets) using a mixture of drugs (nifedipine and propranolol hydrochloride) and chitosan, with or without anionic cross linking polymers (polycarbophil, sodium alginate, gellan gum) has promising potential for use in controlled delivery in the oral cavity.

Gastrointestinal drug delivery:

Polymer granules having internal cavities prepared by de-acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug prednisolone. Floating hollow microcapsules of melatonin showed gastro retentive controlled-release delivery system. Release of the drug from these microcapsules is greatly retarded with release lasting for 1.75 to 6.7 h in simulated gastric fluid. Most of the mucoadhesive microcapsules are retained in the stomach for more than 10 h e.g., Metoclopramide and glipizide loaded chitosan microspheres.

Peroral drug delivery:

As polymer and most of its derivatives has a mucoadhesive property, a presystemic metabolism of peptides can lead to a strongly improved bioavailability of many per-orally given peptide drugs, such as insulin, calcitonin, and buserelin. Unmodified chitosan has a permeation enhancing effect for peptide drugs. A protective effect for polymer-embedded peptides towards degradation by intestinal peptidases can be achieved by the immobilization of enzyme inhibitors on the polymer. The mucoadhesive property of polymer gel can be enhanced by threefold to sevenfold by admixing chitosan glyceryl monooleate. Drug release from the gel followed a matrix diffusion controlled mechanism. Nifedipine embedded in a chitosan matrix in the form of beads have prolonged release of drug compared to granules.

Rectal drug delivery:

Permeability characteristics of the colorectal area to drugs are quite different from both oral cavity and small intestine, rectal absorption is primarily a simple diffusion process through the lipid membrane. The absorption via the rectal mucous membrane is most consistent with pH partition. Therefore, the absorption rate of the most drugs increase with increasing solubility and release rate by vehicles. Due to relatively easy access to the absorptive membrane of the rectum, and the possibility of using permeability enhancers, drug delivery by this route seems more promising than in the intestine.

Vaginal drug delivery:

Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer, embeds clotrimazole, animidazole derivative, is widely used for the treatment of mycotic infections of the genitourinary tract. By introducing thiol groups, the mucoadhesive properties of the polymer are strongly

improved and this is found to increase the residence time of the vaginal mucosa tissue and 26 times longer than the corresponding unmodified polymer guaranteeing a controller drug release in the treatment of mycotic infections. Vaginal tablets of polymer containing metronidazole and Acriflavine have showed adequate release and good adhesion properties.

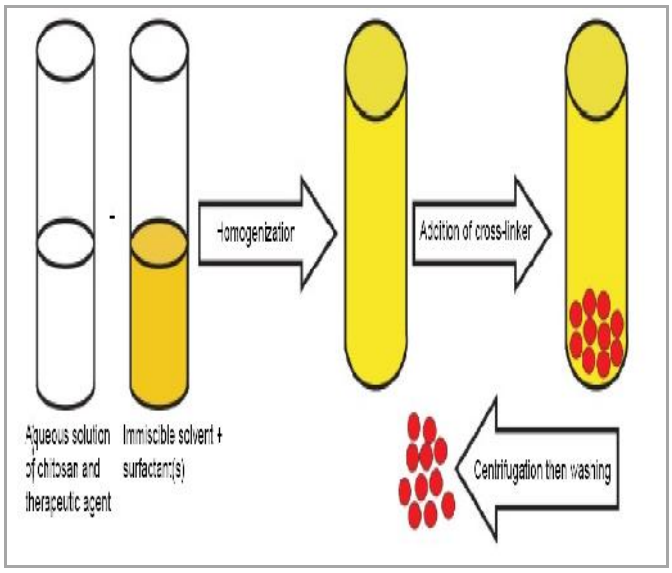

Fig 8. Emulsion cross-linking method.

Transdermal drug delivery:

Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Chitosan-alginate polyelectrolyte complex has been prepared in-situ in beads and microspheres for potential applications in packaging, controlled release systems and wound dressings. Polymer gel beads are a promising biocompatible and biodegradable vehicle for treatment of local inflammation for drugs like prednisolone which showed sustained release action improving therapeutic efficacy. The rate of drug release was found to be dependent on the type of membrane used. A combination of chitosan membrane and chitosan hydrogel containing lidocaine hydrochloride, a local anesthetic, is a good transparent system for controlled drug delivery and release kinetics.

Colonic drug delivery:

Polymer has been used for the specific delivery of insulin to the colon. The chitosan capsules were coated with enteric coating (Hydroxy propyl methyl cellulose phthalate) and contained, apart from insulin, various additional absorption enhancer and enzyme inhibitor. It was found that capsules specifically in the colonic region. It was suggested that this disintegration was due to either the lower pH in the ascending colon as compared to the terminal ileum or to the presence bacterial enzyme, which can degrade the polymer.

CONCLUSION:

Novel drug delivery systems achieved a great interest in recent years in the field of modern pharmaceutical formulations. To derive maximum therapeutic benefits from certain drug substances, it is desirable to prolong their residence time. Mucoadhesive microspheres will ensure the maintenance of effective plasma concentration over prolonged period of time by extending the release of drug release with enhanced bioavailability over longer periods of time, and for drug targeting to various sites in the body.

ACKNOWLEDGEMENT:

Authors wish to thanks College of Pharmacy, Mother Theresa Post Graduate and Research Institute of Health Sciences, for providing library facility to carry out this review article.

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Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Ilaveni S, *et al*. Mucoadhesive Microspheres – A review. J Pharm Adv Res, 2018; 1(3): 135-147.

Table 4. List of Techniques used for the preparation of some Mucoadhesive Microspheres [36-48]:

Drug	Technology	Coating Polymers	Result
Aceclofenac	Cross linking	Gelatin	Entrapment efficiency, particle size and drug release were increased.
Chlorpromazine hydrochloride	Coacervation and phase separation	Gelatin	Microcapsules of Chlorpromazine hydrochloride may reduce the occurrence of extrapyramidal side effects.
Centchroman	Ionic Gelation method.	Alginate, Chitosan, Albumin, PLGA.	PLGA appears to be superior micro carrier for preparing Centchroman microspheres, then Alginate, Albumin, &Chitosan.
Amlodipine Besylate	Simple emulsification cross linking	Chitosan	Chitosan microspheres have potential to deliver the drug following intranasal administration.
Atenelol	Orifice ionic gelation	HPMC 50cps, HPMC K4M	MC8 formulation with Alginate: HPMC (K4M) ratio 5:1 containing 4% w/w Magnesium Stearate has shown promising results. Released 72.16% in 8hours.
Budesonide	Spray drying	Chitosan, Gelatin.	Spray drying technology can be used to generate microspheres and porous particles with improved pulmonary deposition.
Captopril	Emulsification ionic gelation	Alginate, HPMC, Carbopol 934, Chitosan, CAP	Microspheres exhibited good mucoadhesive property. The release is slow and extended over a long period of time.
Clonazepam	Emulsion cross linking method	Gelatin, Chitosan	A formulation was developed for better drug distribution, increasing therapeutic index & reducing side effects.
Diltiazem	Emulsification internal gelation technique.	Sodium alginate, HPMC, Carbopol 934P.	Microspheres exhibited good mucoadhesive properties compared to non mucoadhesive, Ethyl cellulose polymers
Insulin	Emulsification method.	Chitosan	DG1E(1ml crosslinking agent) and DC1E(1ml crosslinking agent) formulations were found to be better and selected as optimized formulations for further study. It was further observed Glutaraldehyde cross linked microspheres are better than citric acid cross linked microspheres.
Ketoprofen	Emulsion solvent evaporation.	Polystyrene, PVP.	Polystyrene was found to be highly impermeable to drug release. Incorporation of PVP easily modulated drug release.
Ketorolac tromethamine	Phase separation coacervation, non-solvent addition	Poly (lactic acid).	Drug release decreased with increase in polymer ratio. This may due to the low permeability of polymer to the drug. Drug release was found to be in a controlled manner releasing up to 80% of drug within 36hours.
Lansaprazole	Emulsion solvent diffusion technique.	HPMC, Methyl cellulose, Chitosan.	Drug to Chitosan ratio 1:1 showed good incorporation efficiency and high percentage release. Prepared micropellets floated more than 12hrs.