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CURRENT TRENDS AND ADVANCES IN MUCOADHESIVE MICROSPHERES: A NOVEL APPROACH OF CONTROLLED RELEASE DRUG DELIVERY

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ABSTRACT

In the recent years, there has been a lot of interest in designing drug delivery systems that use mucoadhesive microspheres to build up unique controlled release drug delivery. Current drug delivery system having the novel approach is to concentrate the treatment to targeted site while lowering the drug concentration. Carrier technology provides an intelligent method of drug administration by mixing the medication with a carrier particle, such as microspheres, that controls the drug's release and absorption properties. Microspheres drug delivery, which is useful to improve the safety, efficacy, of the conventional dosage form and increase the patient compliance. This study designing it in form of mucoadhesive microspheres which prolong the residence time at the absorption site to facilitate intimate contact with absorption surface and thereby improve and enhance bioavailability. A well designed controlled drug delivery system can solve several issues with therapy. This mucoadhesion mechanism is based on various polymers, theories of mucoadhesion, suitable drug candidate. The mucoadhesive microspheres are prepared by various methods and its characterization which includes such as micromeritics properties, compatibility studies, particle size determination, percentage yield, drug entrapment efficiency, swelling index, mucoadhesive testing by in-vitro wash-off test, scanning electron microscopy, in-vitro drug release studies, and stability studies. The recent

advances & Future challenges in microspheres manufacturing technology are arises that are beneficial to develop the novel approaches in drug delivery.

KEYWORDS: Mucoadhesion, Entrapment efficiency, percentage yield, Swelling index, In-vitro drug release studies.

INTRODUCTION

Microspheres are a key innovative pharmaceutical drug delivery because of their small proportions size and excellent carrier capacity. In the early 1980s, the concept of Mucoadhesive is introduced into the controlled drug delivery area.[1,2] A well designed controlled drug delivery system can improve a medication's therapeutic efficacy and solve several issues with traditional therapy.[3] In recent years, many concepts have been proposed to create a dosage form with a longer transit time and, consequently, more effective absorption. This work of microspheres is to build up unique controlled release gastro-retentive medication delivery system.[4] Small spherical particles of microspheres having diameter in the micrometer range typically from 1µm-1000µm. Microspheres are also called as microparticles. Mucoadhesive microspheres are essential component of innovative medication delivery system. The short residence time of the microspheres at the absorption site can be overcome by coupling bioadhesion characteristics to the microspheres and developing bioadhesive microspheres called as mucoadhesive microspheres.[5] By intimate contact with the mucous layer and precisely directing the drug to the absorption site, mucoadhesive microspheres aid to improve localization of oral controlled or sustained release drug delivery systems and overcome the comparatively short GI residence duration.[6] The main goal of the innovative oral controlled drug delivery system design should be to improve and predict the bioavailability of medications.[7]

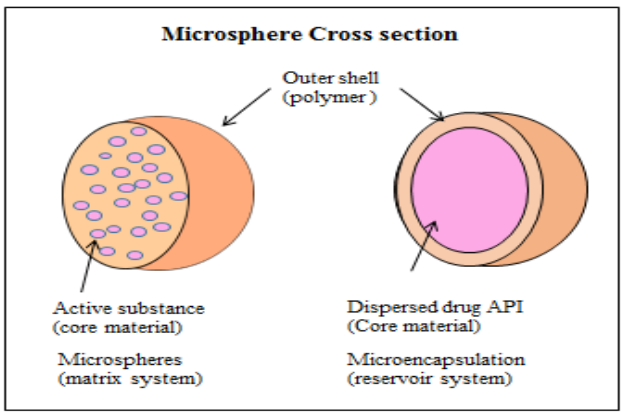

Fig. 1: Microsphere cross section.

Restraining a drug delivery system in a specific region of the gastro intestinal tract due to its mucoadhesive property increases the intimacy and duration of contact between a drug containing polymer and mucus surface. The mucoadhesion study will show improved microsphere retention in the intestinal duodenum and jejunum.[8] Additionally, the qualitative and quantitative GI distribution investigation will demonstrate the upper GI tract's noticeably greater retention of mucoadhesive microspheres.[9,10] A 3^2 full factorial design will employed to study the effect of independent variables, polymer-to-drug ratio, and stirring speed on dependent variables percentage mucoadhesion study.[11]

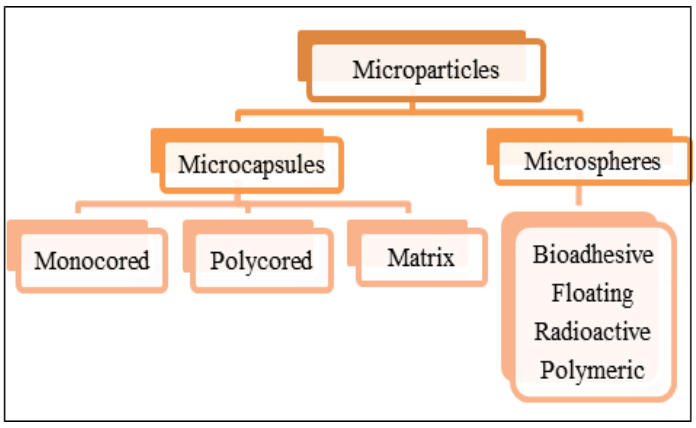

Fig. 2

Composition of mucus membrane[12, 13]

The layer of mucus membrane it protects the GI epithelium by trapping harmful micobes or any foreign particulate pathogens and subsequently clearing them before their penetration and absorption across the epithelium. Additionally, it safeguards the gut from the effects of chemicals or enzymes. Depending on the animal species, anatomical location, and the organism's normal or sick condition, mucus composition varies greatly. It is kept hidden either by unique exocrine glands with mucus cell acini or by the goblet cells lining the epithelia. Mucus secretions' lubricating qualities stem from their overall stickiness, viscosity, and gel-forming capabilities. Mucus's overall composed is as follows:

Table No. 1: Composition of mucous membrane.

Sr. No.	Components	Amount of %
1	Water	95 %
2	Glycoproteins and lipids	0.5-5 %
3	Mineral salts	1 %
4	Free proteins	0.5-1 %

The stomach wall's glandular and epithelial cells secrete gastric mucus, a gel-mucous barrier. It is a component of the barrier that protects the stomach wall from the stomach lumen's acid and digestive enzymes. Together with the closely packed epithelial cells, this barrier is also composed of a bicarbonate secretion. When combined, these elements affect the stomach's ability to properly digest food. Only mucus is secreted by these gastric glands in the cardia and pyloric area in the stomach's outermost regions. In the other regions however, there is greater cellular diversity in the constituents of the gastric glands:[14]

1) Parietal cells secrete hydrochloric acid and Intrinsic factor
2) Chief cells secrete pepsinogens
3) ECL cells secrete histamine

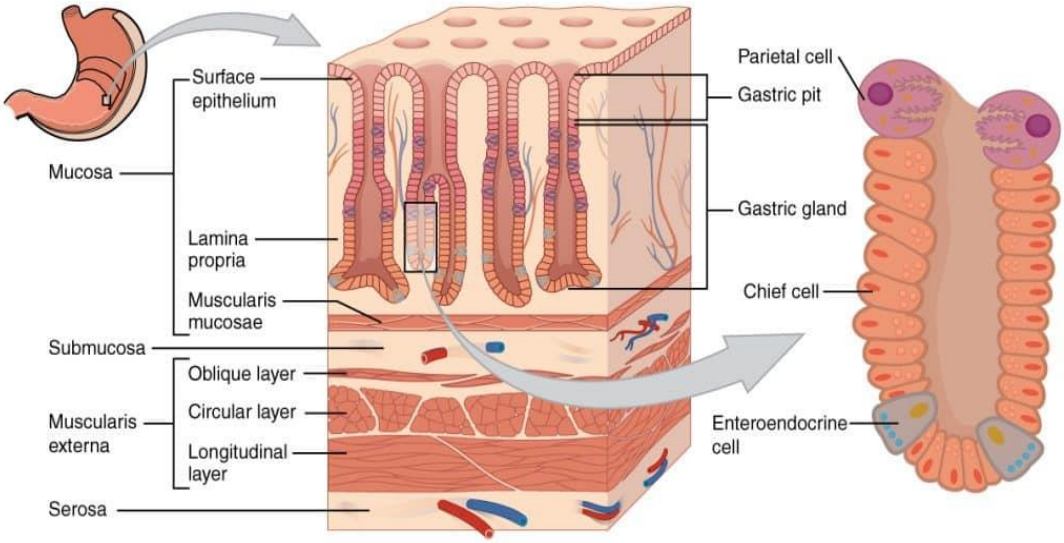

Fig. 3: Composition of mucous membrane.

Mucoadhesion significance[4]

Mucoadhesion is an issue of contemporary interest and concern in desigining drug delivery system. By enabling close interaction with the underlying absorption surface and demonstrating a prolonged residence duration at the site of absorption, mucoadhesive microspheres increase the therapeutic efficacy of pharmaceuticals. This increases the drug's absorption and bioavailability.

Mucoadhesion mechanism[4,5]

- Intimate close contact between a mucoadhesive delivery method and the mucosal membrane (Wetting or swelling event.)
- Penetration of the mucoadhesive delivery system into the tissue or into the surface of the mucous membrane (Interpenetration, shows the mechanism of mucoadhesion).

Mucoadhesion is a complex phenomenon. There are six theories that might explain the mechanism of mucoadhesion occurred between bioadhesive polymers and biological mucosal surface, including electronic, wetting, adsorption, diffusion, mechanical and fracture theories. The occurrence of mucoadhesion has been said to experience two stages, the contact (Wetting) stage followed by the consolidation stage (The establishment of adhesive interactions).

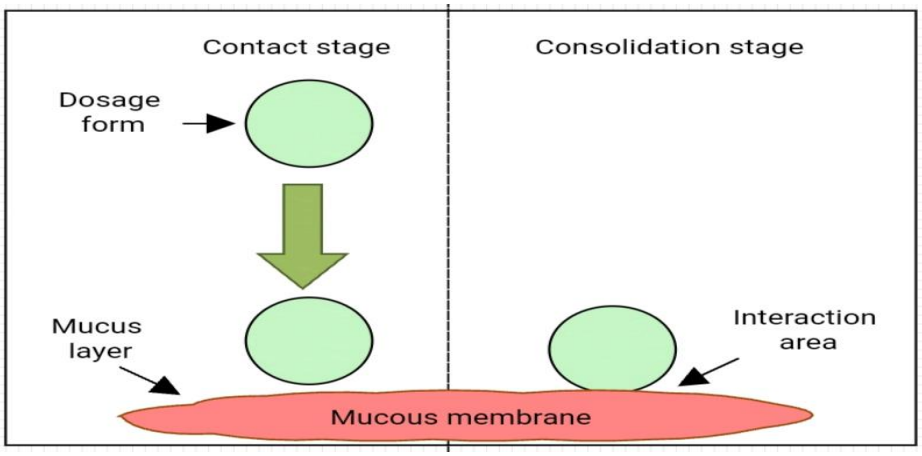

Fig. 4

Theories of mucoadhesion[4,15,16]

1) **The wetting theory:** This theory applies to liquids and states that a higher affinity for adhesion will result from a lower contact angle between the liquid and the substrate surface.
2) **The electronic theory:** The theory states that as electrons move between the mucoadhesive and mucosal membranes, an electrical double layer is created.
3) **The adsorption theory:** This hypothesis states that intermolecular interactions, such as hydrogen bonds and Vander Waal's forces, cause the mucoadhesive to be adsorbed on the mucosal surface.
4) **The diffusion theory:** According to this idea, the dispersion of the polymer chains on the mucoadhesive surface results in the formation of a network structure between the mucoadhesive and the mucosal surface.
5) **The mechanical theory:** This theory explains that how liquid adhesives diffuse into the microcracks and imperfections on the mucoadhesive substrate to generate an interlocking structure that leads to mucoadhesion.
6) **Fracture theory:** The forces needed to separate the two adhering surfaces after contact are related to the strength of the adhesive bonds by the fracture theory.

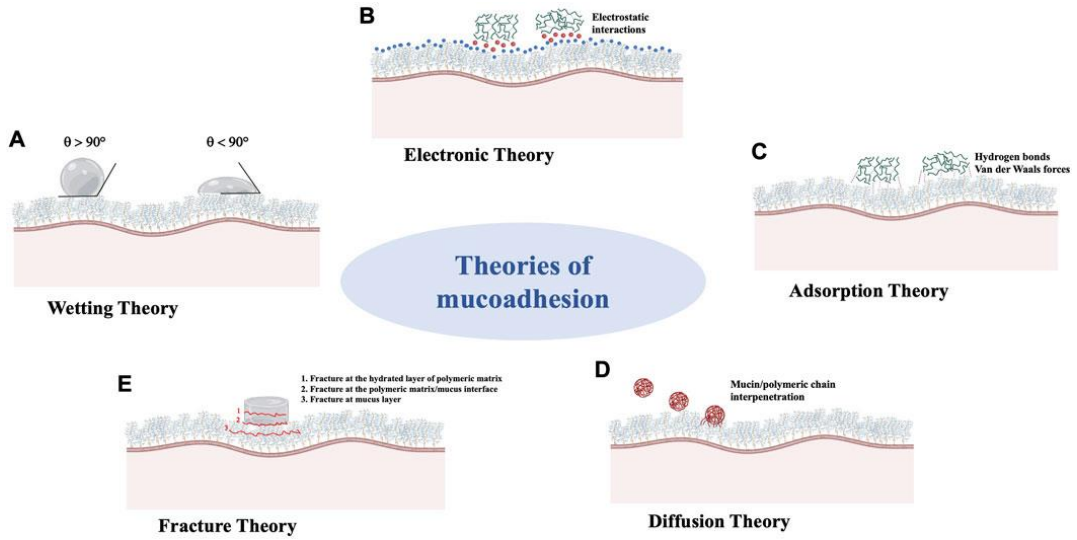

Fig. 5: Theories of mucoadhesion.

Drug & Polymers selection criteria for mucoadhesive drug delivery

1) Effect of local action of drugs e.g. in ulcerative conditions such as treatment of helicobacter pylori.
2) To enhance the Residence time of drug at specific site of GIT.
3) Those drugs comes under moderately weak acids and shows greater ionization at basic P^H.
4) The polymer and its degradation products should be nontoxic and should be non-absorbable from the gastrointestinal tract.
5) It should make the drug's inclusion simple and provide no obstacles to its release.
6) To maintain the produced dosage form's competitiveness, the polymer's cost should not be excessive.
7) It should be nonirritant to the mucus membrane.
8) It should adhere quickly to most tissue and should possess some site specificity.[17]

Advantages of mucoadhesive microspheres[2, 3,5,17]

1) Enhanced first-pass biotransformation
2) Targeted treatment for upper GIT local conditions
3) Reduced fluctuations of drug concentration
4) Site specific drug delivery
5) Constant and longer therapeutic effect.
6) Masking of odor or taste (Bitter)
7) Improves patient compliance by lowering the frequency of daily administration.
8) Increase the drug's absorption to increase its bioavailability and lower the chances of side effects.

Limitation of mucoadhesive microspheres[5, 17]

1) It's possible that the formulas' release will undergo modifications.
2) A number of variables, such as the diet, the rate of transit through the stomach, the mucin turnover rate, etc., might affect the release rate.
3) Variations in the rate of release can be observed between doses.
4) These kinds of dosage forms cannot be crushed or chewed.

Table No. 2: A shortlist of mucoadhesive polymers.[5,17]

Sr. No.	Synthetic polymers	Natural polymers
1	Hydroxypropyl methylcellulose (HPMC)	Chitosan
2	Poly (Acrylic acid) polymers (Carbomers, polycarbophil)	Sodium alginate
3	Polyvinyl pyrrolidone (PVP)	Pectin
4	Polyvinyl alcohol (PVA)	Locust Bean gum
5	Polyhydroxyethyl methylacrylate	Guar gum
6	Polyethylene oxide	Xanthan gum
7	Sodium carboxy methyl cellulose (Na CMC)	Karaya gum
8	Hydroxyl ethyl cellulose (HEC)	Gelatin
9	Hydroxy propyl cellulose (HPC)	Tragacanth
10	Ethyl cellulose (EC)	Soluble starch
11	Methylcellulose (MC)	Lecithin

Table No. 3: Polymers and their bioadhesive properties.[3]

Sr. No.	Polymer	Bioadhesive property
1	Carboxy methylcellulose (CMC)	Excellent
2	Carbopol 934	Excellent
3	Polycarbophil	Excellent
4	Tragacanth	Excellent
5	Poly (acrylic acid / divinyl benzene)	Excellent
6	Sodium alginate	Excellent
7	Hydroxy ethylcellulose (HEC)	Excellent
8	Gum karaya	Fair
9	Gelatin	Fair
10	Guar gum	Fair
11	Polyvinyl pyrrolidone (PVP)	Poor
12	Polyethylene glycol (PEG)	Poor

Types of microspheres[18,19]

1) Bioadhesive microspheres
2) Magnetic microspheres
3) Floating microspheres
4) Radioactive microspheres
5) Polymeric microspheres

a. Biodegradable polymeric microspheres
b. Synthetic polymeric microspheres

Methods of preparation of mucoadhesive microspheres[5,19]

1) Solvent Evaporation Method
2) Single emulsion technique
3) Double emulsion method
4) Ionotropic gelation Method
5) Spray drying method
6) Phase inversion method
7) Complex Coacervation
8) Hot melt microencapsulation

Solvent evaporation method[20]

Solvent evaporation method is most widely used for microencapsulation. First described by Ogawa and co-workers. Formulation of microspheres by solvent evaporation will be carried out in a manufacturing vehicle phase. The coating of microcapsule is first dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. In this process coating polymer solution, a core material to be microencapsulated is dissolved or dispersed. Agitation is used to evenly distribute the core material mixture in the liquid manufacturing vehicle phase, resulting in an adequate microcapsule size. If required, provide heat to the mixture to evaporate the solvent. If the core material dissolves in the covering polymer, Matrix-type microcapsules are generated. The suitable drug candidate for formulated through solvent evaporation method such as the core material may be either water soluble or water insoluble material. Solvent evaporation method creates an emulsion between a polymer solution and an immiscible continuous phase, either aqueous or non-aqueous.

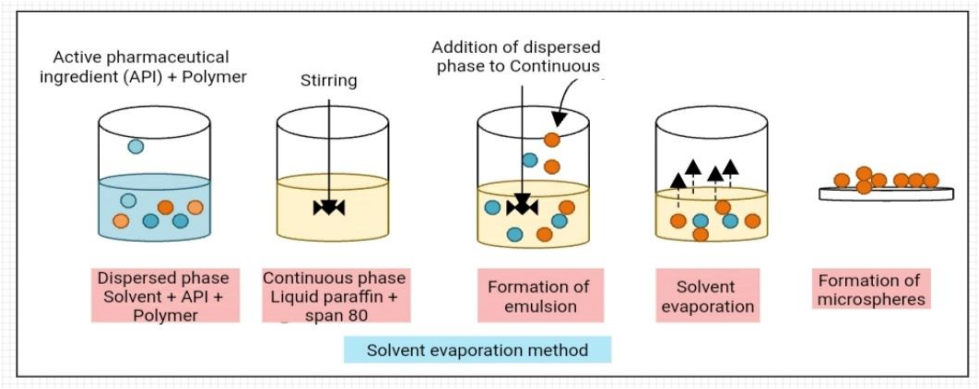

Fig. 6: Solvent evaporation method.

Single emulsion technique[20,21]

Proteins and carbohydrates, microparticulate carriers of natural polymers can be prepared by single emulsion technique. Natural polymers are first dissolved in aqueous medium, then distributed/ dispersed in non-aqueous media like oil. Then, crosslinking can be done using heat or chemical crosslinkers. In this cross linking process the various cross linking agents such as glutaraldehyde, formaldehyde, acid chloride etc. can be used. In the process of chemical cross linking overexposure of the active components it is disadvantage of this method. The final multiparticulate product's size, size distribution, surface morphology, drug loading, drug release, and bioperformance will all be significantly impacted by the different types of surfactants that are helpful in stabilising the emulsion phases after centrifugation, washing, and separation.

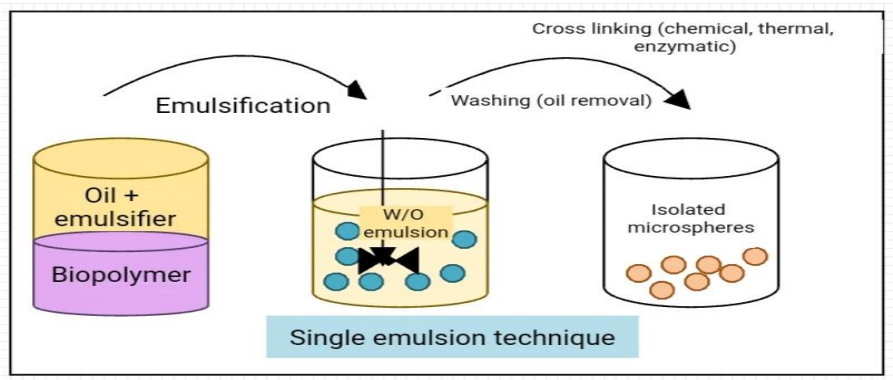

Fig. 7: Single emulsion technique.

Double emulsion technique[21]

This technique involves the formation of multiple emulsion or double emulsion of type w/o/w emulsion. The suitable Drug candidates for double emulsion are water soluble drugs, peptides, proteins and vaccines. The polymer solution that ultimately encapsulates the protein present in dispersed aqueous phase often makes up the continuous phase. Then, primary emulsion is sonicated before being added to the polyvinyl alcohol (PVA) aqueous solution. As a result, a double emulsion is produced. Then remove the solvent by solvent evaporation or solvent extraction. Using the technique of double emulsion solvent evaporation, water soluble drugs like luteinizing hormone (LH-RH) agonist, vaccines, proteins/peptides are successfully integrated into the microspheres.

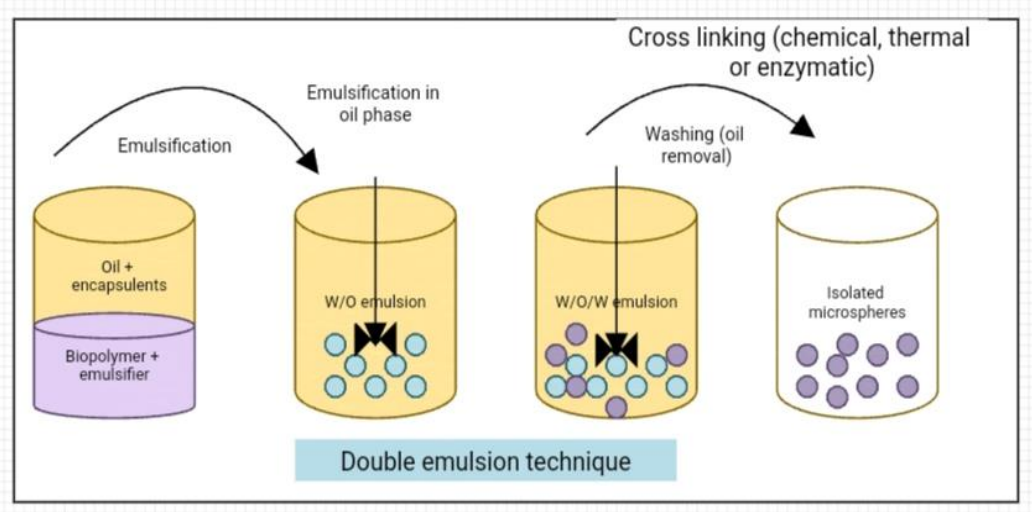

Fig. 8: Double emulsion technique.

Complex Coacervation method[21]

Complex coacervation method includes suitable conditions when solutions of two hydrophilic colloids mixed, result into a separation of liquid precipitate. This technique involves dispersing the core material in a coating polymer solution and creating the coating material phase by dissolving an immiscible polymer in an appropriate vehicle under continuous stirring. Changing the temperature of the polymer solution, altering the medium's pH, introducing a salt, an incompatible polymer, or a nonsolvent to the polymer solution, or causing a polymer-to-polymer contact are all ways to achieve microencapsulation. Coatings are frequently hardened via thermal cross linking or desolvation techniques to produce a self-sustaining microsphere.

Ionotropic gelation technique[1,20-22,25]

The ionotropic gelation approach makes use of polyelectrolytes, such as polysaccharides, which can undergo the sol–gel transition when they combine with oppositely charged molecules, such as cations. Lim and Moss created this technique. Recently interest in polysaccharide-based hydrogels for API encapsulation has steadily grown. This process develops microspheres by dissolving gel-type polymers, like alginate, in an aqueous solution, then suspending the active ingredient in the mixture and extruding the mixture through a needle to create microdroplets that drop into a calcium chloride-containing hardening solution while being stirred slowly. Gelled microspheres are generated when the polymer is cross-linked by divalent calcium ions found in the hardening solution.

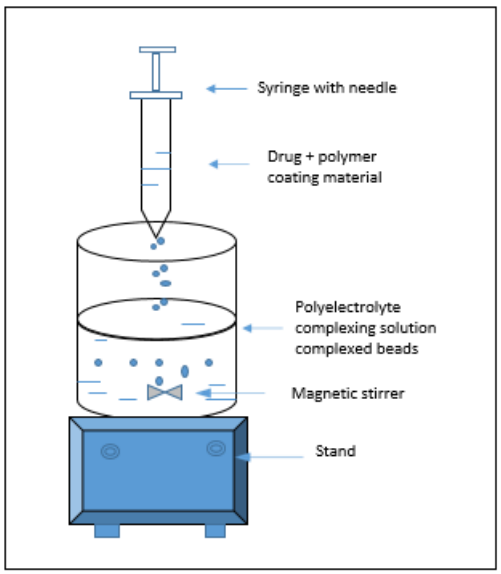

Fig. 9: Ionotropic gelation technique.

Spray drying technique[20, 21, 23]

Using this method, the polymer is first dissolved in an appropriate volatile organic solvent, like acetone or dichloromethane. The solid drug is then dispersed throughout the polymer solution after high-speed homogenization. After then, a stream of heated air atomises this dispersion. The atomization process creates tiny droplets or a fine mist, from which the solvent instantly evaporates to generate microspheres that range in size from 1 to 100 µm. The cyclone separator is used to separate the microparticles from the hot air, and vacuum drying is used to eliminate any remaining solvent. The process's ability to function under aseptic circumstances is one of its main benefits. The creation of permeable microparticles is the result of this quick process.

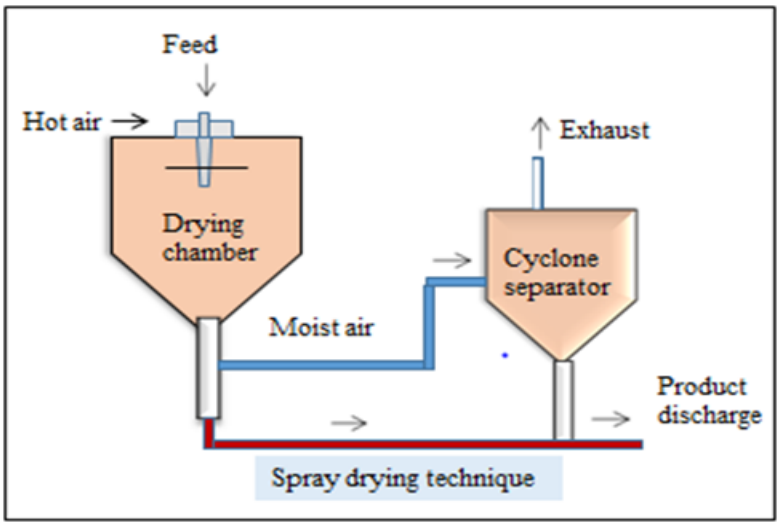

Fig. 10: Spray drying technique.

Phase inversion method[21,23]

The procedure is adding the medication to a diluted polymeric solution in methylene chloride, and then pouring the liquid into an unagitated bath of petroleum ether, a potent non-solvent, in a 1:100 ratio. The resulting microspheres are further washed with petroleum ether, clarified, and air dried.

Hot melt microencapsulation[21,23]

Formulation of microspheres by polyanhydride copolymer of poly bis(p-carboxy phenoxy) propane anhydride with sebacic acid. This method involves melting the polymer first, then adding the solid drug particles while continuously mixing. A non-miscible solvent is then used to suspend the produced combination. such as silicone oil while churning, and heated to a temperature higher than the polymer's melting point while swirling constantly to create a stabilised emulsion. After cooling the resulting emulsion to solidify the polymer particles, the microspheres are filtered and cleaned using petroleum ether.

Drug loading in microsphere[5]

There are two main ways to load the pharmaceuticals into the microspheres: either while the microsphere is being prepared or after it has been prepared by incubating it with the drug solution. Physical entrapment, chemical bonding, and surface absorption are several methods of loading the active ingredients. It was found that adding the drug during the preparation phase could maximize drug loading in microspheres; however, this could be impacted by a number of other process variables, such as the presence of additives, the preparation technique, the heat of polymerization, the degree of agitation, etc. After the microspheres are prepared, they can be loaded with a high concentration of the drug by incubating them in an appropriate solvent. In this case, the medicine may be loaded into the microspheres by either absorbing the drug on the microsphere's surface or by diffusing or penetrating via the microsphere's pores. The drug-loaded microsphere is then left behind once the solvent is eliminated.

Table No. 4: Factors affecting mucoadhesion.[12,24-26]

Polymer related factors	Environmental factors	Physiological factors
Molecular weight	pH of polymer - substrate interface	Composition and characteristics of mucous
Concentration of active polymer	Applied strength	Mucin turnover
Flexibility of polymer chain	Initial contact time	Disease state

Spatial conformation	Selection of model substrate surface	
	Swelling	

Preformulation studies

Compatibility studies[22,27, 28]

1) IR-Spectroscopy[17,22]

The drug polymer and polymer-polymer interaction are studied by the FTIR spectrometer. By pelleting the samples with KBr, the FTIR spectrophotometer will record the microsphere's infrared spectra between the ranges. After that, the resulting spectra will be compared with standard reference and observe for any kind of variation from it. The characteristic peaks were recorded.

2) Differential scanning calorimetry (DSC)[27,28]

It is a thermoanalytical technique in which the amount of heat required to increase the temperature of sample and reference is measured as a function of temperature. DSC thermograms of the microspheres will be recorded with DSC. Accurately weigh samples of the drug are taken in the pans. An empty aluminum pan can be used as a reference pan. The system will be purged with nitrogen gas. Heating will be done at a fix rate.

Flow properties[1,22,41,45]

1) **Bulk density:** It is measured by pouring a sample of microspheres of known weight into a measuring cylinder without tapping and measuring its length, and then dividing the weight by the volume.

Bulk density = Total wt. of microspheres/bulk volume.

2) **Tapped density:** It is determined by pouring a sample of microspheres of known weight into a measuring cylinder & thoroughly tapping it & measuring its volume, then dividing the weight by the volume.

Tapped density = wt. of the microspheres/volume after tapping

3) **Hausner's ratio:** A Low Hausner's ratio of < 1.2 indicates a free-flowing microsphere.

Hausner's ratio = Tapped density / Bulk density

4) **Carr's Index:** Carr's Index It is also one of the simple methods to evaluate flow property of powder.

Carr's index = Tapped density – Bulk density/ Tapped density x 100

5) **Angle of repose:** It is defined as the maximum angle to the horizontal plane that is attainable by a heap of microspheres.

Angle of Repose = (tan−1) h/r

r = the radius of the base of the heap of microsphere

h = height of the heap of microsphere

Evaluation and Characterization of microspheres[20,23,28,45,46]

1) **Particle size determination:** Average particle size of mucoadhesive microspheres determined by optical microscopy.

2) **Percentage yield:** Percentage Yield: The entire quantity of microspheres will be weighed and assessed in order to determine the yield.

Percentage. Percentage yield = Actual practical yield/ Theoretical yield x 100

3) **Drug entrapment efficiency:**[29] The microspheres will triturate and make powdered using mortar and pestle. The drug equivalent of accurately weighted microspheres will be sonicated after suspending in suitable solvent. The resulting solution will filter, and make upto 100ml with suitable solvent. The solution will filtered after suitable dilution, drug content in filtrate will analyzed at specific wavelength of drug in nm using UV-Visible spectrophotometer. The obtained absorbance will plot on standard curve to get exact concentration of entrapped drug. Determine the volume, dilution factor, and concentration to determine the proportion of the medicine that is really encapsulated in microspheres. The following relationship will be used to calculate the drug entrapment efficiency.

% entrapment efficiency of drug = Practical drug content/ Theoretical drug content × 100

4) **Swelling index:** The dynamic swelling behaviour of mucoadhesive microspheres will study by mass measurement. The microspheres are incubated with suitable solvent in petridishes at 37^0 C. The swollen microspheres are weighed using the electronic balance. The studies will perfomed by using following formula.

Swelling Index = Weight of wet microspheres – Weight of dry microspheres/ Weight of dry microspheres × 100

5) **Mucoadhesive Testing by *in-vitro* wash-off test:**[29,31] The wash-off method, an in-vitro adhesion testing technique, will be used to assess the microspheres' mucoadhesive

properties. Freshly excised pieces of stomach mucosa (4×5 cm) from sheep were mounted onto glass slides (3×1 inch). The support was instantly attached to the arm of a USP tablet dissolving test apparatus after two glass slides were joined with an appropriate wet-rinsed tissue sample. When using the disintegrating test machine, the tissue sample is slowly and steadily moved up and down in the test fluid, which is kept in a 1000 ml vessel at 37^0 C. The machine stopped after an hour and then every hour for a total of 12 hours. The number of microspheres that were remained attached to the tissue was then counted. The test was performed in stomach. Mucoadhesion was calculated using formula:

% Mucoadhesion = Number of microspheres adhered/Number of microspheres applied × 100

6) **Scanning Electron Microscopy (SEM):** The microspheres are observed under a Scanning Electron Microscopy. SEM creates three-dimensional pictures with a better resolution than can be achieved with a light microscope.

7) ***In-vitro* drug release studies:**[31] In vitro drug release studies are conducted using USP dissolving test equipment. A specific quantity of microspheres are kept in basket type apparatus and immersed in 900ml of Hcl buffer in 900ml dissolution flask and temperature was maintained at 37 ± 0.5^0C throughout the study. 5 ml, of the samples were taken out and replaced into the buffer-containing dissolving flask at predetermined intervals. The absorbance of sample are measured at specific wavelength of drug after required dilution with the fresh medium.

8) **Kinetics of *In-vitro* drug release:** Kinetic model study will show the drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. The exact mechanism of release from the microsphere will further studied by kinetic models. The drug release data analyze by zero order, first order, Higuchi, Korsmeyer Peppa's and Hixson Crowell models.

9) **Stability studies:**[29,43] Stability studies includes the evidence about the quality of a drug substance or drug product that changes over time due to a range of environmental conditions, including temperature, humidity, and light. Formulations are selected for stability on the basis of the In-vitro drug release profile. The optimized formulations will be subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) Q1A guidelines. The microspheres were kept under the following circumstances after being put in a screw-capped glass container**.**

- Ambient humid condition
- Room temperature (27+/-20^{o}C) s
- Oven temperature (40+/-20^{o}C)
- Refrigerator (5^{o}C -8^{o}C).

It is carried out of a 60 days/3 months and the drug content of the microsphere is analyzed.

Recent advances in microspheres manufacturing technology[25,33]

1) Microsphere preparation of PLA for cancer therapy
2) Magnetic microspheres as a magnetically targeted drug delivery system
3) Tumour targeting via magnetic microspheres
4) microspheres as a nasal drug delivery system
5) Thermo-responsive Systems
6) Nanoparticles Integration
7) Combination therapy.
8) Multi-drug Delivery
9) Preparation of Biodegradable Microspheres

Applications of mucoadhesive drug delivery[18,19,24,30]

Mucoadhesive microspheres as a novel carrier system to improve drug delivery by various routes of administration like buccal, oral, nasal, ocular, vaginal and rectal, either for systemic or for local effects.[31] Mucoadhesive microspheres are used in a number of pharmacological and therapeutic applications.

1) **Oral mucoadhesive drug delivery systems:** Oral mucosal drug delivery has gained significant attention due to its convenient accessibility, and patient compliance.[32] Oral mucosal drug delivery has been shown to be especially effective and has a number of benefits over other drug delivery methods, such as avoiding hepatic first-pass metabolism, boosting drug bioavailability, improving patient compliance, having excellent accessibility. Drugs have been delivered both locally and systemically through the mouth cavity. Oral mucosal ulceration, gingivitis, periodontal disease, and xerostoma are among the conditions that are treated with local medication therapy. The medication is released by these drug delivery systems in a regulated, predictable, and predefined manner.[35]

2) **Nasal Mucoadhesive drug delivery system:**[33] The short residence period at this mucosal surface may impede the nasal administration of protein and peptide therapies.

Benefits include avoiding first-pass hepatic metabolism and quick absorption. Furthermore, retention period can be further extended by applying liquids, semisolids, and solids bioadhesively. Intranasal vaccinations against tetanus, influenza, and diphtheria are a few examples of these nasal drug delivery.

3) **Ocular mucoadhesive drug delivery system:**[33] This drug delivery intended to create bioadhesive sodium sulfacetamide microspheres that would stay on the surface of the eye longer and improve the effectiveness of treatment for ocular keratitis. By employing a spray-drying technique, microspheres were created by combining various ratios of polymers, including pectin, polycarbophil, and HPMC. The effectiveness and mode of action of a hyaluronan (HA) and chitosan (CS) bioadhesive DNA nanocarrier intended especially for topical ocular gene therapy.

4) **Vaginal mucoadhesive drug delivery system:**[36] This drug delivery bioadhesives can control the rate of drug release from, and extend the residence time of, vaginal formulations. These formulations may contain drug or, quite simply, act in conjunction with moisturizing agents as a control for vaginal dryness. created an acid-buffering bioadhesive vaginal tablet for the treatment of genitourinary tract infections that contains the antifungal clotrimazole and the antiprotozoal and antibacterial metronidazole by this drug delivery system.

5) **Cervical and Vulval drug delivery systems:**[36] A novel bioadhesive cervical patch containing 5-fluorouracil for the treatment of cervical intraepithelial neoplasia described by this drug delivery system. Clinically, this drug delivery extensively used in successful vulval intraepithelial neoplasia, lichen sclerosus, squamous hyperplasia, Paget's disease, and vulvodynia.

6) **Buccal mucoadhesive drug delivery system:**[39] The buccal cavity's surface size is just about 50 cm2, there are are some benefits to treating oral lesions i.e. local and for systemic drug absorption. First pass metabolism is avoided by this drug delivery. Because of the flow of saliva and swallowing, materials in the buccal cavity have a brief residence duration, making them an excellent choice for the creation of mucoadhesive devices.

7) **Gastrointestinal mucoadhesive drug delivery systems:** One of the most crucial routes of administration in recent years has been the gastrointestinal tract (GIT). Bioadhesive

polymers are used in bioadhesive retentive systems because they may stick to the GIT's epithelial surface. It would be possible to enhance GI transit time and bioavailability by using bioadhesive drug delivery system.[39]

8) **Intratumoral and Local drug delivery:** Polymer films are created to deliver paclitaxel to the tumour location at a therapeutically appropriate dose. Drug mixtures including gelatin, PLGA, and chitosan show promise for application in controlled oral administration.[40]

9) **Gene delivery:** Microspheres could be a useful oral gene carrier be-cause of its adhesive and transport properties in the GI tract. e.g. Chitosan, Gelatin, viral vectors, cationic liposome, polycation complexes and Gene therapy with DNA plasmids and also delivery of insulin.[40,46]

10) **Monoclonal antibodies:** Monoclonal antibodies or targeting microspheres are biologically immune microspheres. This type of targeting is used to achieve selective targeting to specific sites of the body organ.[40,47]

11) **Vaccine drug delivery:** Delivery of vaccines to treat illnesses such as birth control, ricin toxoid, hepatitis, influenza, pertussis, and diphtheria. Microsphere in vaccine delivery have a specific advantage like improved antigenicity by adjuvant action, modulation of antigen release, stabilization of antigen.[41,47]

12) **Rectal mucoadhesive drug delivery systems:**[36,44] Delivering medications to the rectal area, particularly to regions around the anus, can be quite beneficial for those that are susceptible to substantial first-pass metabolism. Additionally, the migration distance in the rectum decreased with the addition of the bioadhesive polymer. To increase the rectal bioavailability of flurbiprofen by creating a thermoreversible liquid suppository base made of sodium alginate and poloxamer in this drug delivery system.[44]

Mucoadhesive microspheres are used as targeted drug delivery system for various diseases such as Hypertension, Diabetes mellitus, Peptic ulcer, AIDS etc.[4]

Summary of mucoadhesive microspheres research work

Irbesartan (Ionic gelation method),[1] Acyclovir (Spray drying technique),[6] Acyclovir (Solvent evaporation method),[8] Aceclofenac (O/W/O emulsification cross linking method),[9]

Glipizide (Simple emulsification phase separation technique),[11] Pioglitazone HCL (Ionotropic gelation method),[27] Amoxicillin (Single emulsification phase separation technique),[28] Valsartan (Emulsion solvent evaporation method),[34] Diclofenac sodium (Ionic gelation method),[37] Metronidazole (Ionotropic gelation method), Simvastatin (Oil in oil Emulsion coacervation method),[42] Sumatriptan (Emulsification cross linking method).

Future challenges in microspheres manufacturing technology

Future challenges are arises in microspheres technology because of their many uses in molecular biology, microspheres appear to have a bright future, especially in the medical field. For instance, a microsphere-based genotyping technology may identify six single nucleotide polymorphisms, yittrium-90 microspheres can prevent tumors following liver transplantation, and they are an innovative method of delivering proteins and vaccinations.

CONCLUSION

The benefits and lot of interest of mucoadhesive microspheres as a medication delivery mechanism have drawn the attention of numerous researchers and academic scholars. Now more than ever, drug delivery systems designed to improve patient comfort and compliance are essential. Therefore, there is a lot of work being done to create innovative dosage forms to meet the growing patient demand for more practical dosage forms. Its adaptability as a drug carrier, as well as regulated and prolonged release activity. By prolonging the drug's release, mucoadhesive microspheres will guarantee the maintenance of an effective plasma concentration for an extended amount of time. Additionally, the drug's residence period in the gastrointestinal tract will be prolonged by these carrier systems.

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