REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Bioadhesive Drug Delivery Systems: A Review

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Abstract

The mucus layer covering the mucosal epithelial surface and mucin molecules interact with the bioadhesive drug delivery method to increase the time the formulations remain at the absorption site. The mucus layer covering the mucosal epithelial surface and mucin molecules interact with the bioadhesive drug delivery method to increase the time the dosage form remains at the absorption site. Bioadhesive formulations may be developed to provide sustained retention at the place of application and to give a controlled rate of medication release for greater therapeutic efficacy. Various factors, including the polymeric formulation's physicochemical properties and the mucosal tissue's content, influence the dosage form's ability to adhere to mucosal surfaces. This review covers the subjects of bio-adhesion mechanisms and theories, bio-adhesion polymers and polymers, various dosage forms and microbead manufacturing techniques.

Keywords: Bio-adhesion; Drug delivery; Polymeric formulation; Microbeads.

1. Introduction

Pharmaceutical research is increasingly focusing on creating novel drug delivery systems (NDDS) for already-existing pharmacological molecules to increase their efficacy in terms of therapeutic action. The several compatible polymers that can change the drug's release strategy have made it possible to produce NDDS. Recent years have seen a rise in the pursuit of developing a drug delivery system that can adhere to related tissue or the surface coating of various absorptive mucosa, including those in the nasal, ophthalmic, buccal, pulmonary, and vaginal areas. This drug delivery system is known as the bio-adhesive drug delivery system (Xi 2021). This system has advantages like:

1. They prolong the contact time between the dosage form and the target organ
2. Extending the residence period that improves absorption and, consequently, the drug's therapeutic effectiveness.
3. Having excellent accessibility
4. Rapid absorption due to a large blood supply and high blood circulation rates.
5. Increasing the medication bioavailability due to the avoidance of first-pass metabolism.
6. Protecting drugs from destruction in the acidic environment of the gastrointestinal tract.
7. Being of greater patient cooperation and more straightforward medicine delivery.
8. Attaining a quicker onset of action due to the mucosal surface (Patil, Tiwari, and Repka 2016).

1.1. Bio-adhesion

The idea of mucosal adhesives, also known as mucoadhesive, was first brought to controlled medication administration in the early 1980s. Numerous researchers have been made aware of the mucoadhesive and the potential use of these polymers to overcome physiological barriers in long-term medication administration(Giuliano et al. 2018). The ability of a substance (mucoadhesive polymer) to stick to the mucosal layer is what is meant by the term "mucoadhesive." Interfacial pressures hold them together for a substantial period. The viscoelastic fluid known as mucus, which is generated by goblet cells (glandular columnar epithelial cells), makes up the mucosal layer (Rhushikesh and Suresh 2020).

1.2. Muco-adhesion Mechanisms

A bio-adhesion mechanism consists of two stages: the contact stage and the consolidation stage. The bio adhesive's initial contact with the mucous membrane, along with the formulation's subsequent swelling and spreading, represents the start of its deep engagement with the mucous layer. The presence of moisture during the consolidation stage activates the bio-adhesion materials. Moisture causes the system to become plastic, which allows the bio-adhesion molecules to separate and form weak van der Waals and hydrogen bonds (Asati, Jain, and Choubey 2019).

1.3. Theories of mucoadhesion

Mucoadhesion is a complicated process; several hypotheses have been formulated to explain how it works. Among these theories are the electronic theory, fracture theory, diffusion theory, adsorption theory and wetting theory (Mamatha and Venkatesh 2022).

1.3.1. Wetting theory

The wetting theory applies to liquid systems that tend to stick to surfaces. The contact angle is one measuring method that can be used to determine this affinity. According to the general rule, affinity increases as the contact angle decreases, Figure 1. To provide a sufficient spread ability, the contact angle must be equal to or near zero. According to the following equation, the spreadability coefficient, SAB, can be determined using the difference between the surface energies B and A and the interfacial energy AB. According to this theory, a good quantity of bio-adhesion depends on the contact angle, lowering surface, and interfacial energy.

$SAB = \gamma B - \gamma A - \gamma A$ (Ismail et al. 2021)

1.3.2. theory of diffusion

According to diffusion theory, both polymer and mucin chains must penetrate one another deeply enough to form an adhesive bond that is semi-permanent, Figure 2. It is thought that the degree of polymer chain penetration enhances the adhesive force. This penetration rate, however, is influenced by the mucoadhesive chains' contact time, mobility, nature, and flexibility and also depends on the diffusion coefficient. According to the research, the depth of interpenetration needed to create a reliable bio-adhesive bond is in the range of 0.20–5.25 m. The following equation can be used to measure the interfacial depth between mucin and polymer chains.

$l = (t_{Db})$ ½

Where t is the contact time, Db is the bio-adhesion material's mucus-specific diffusion coefficient. The strength of the mucoadhesive binding increases with structural similarity **(Mamatha and Venkatesh 2022).**

1.3.3. theory of fracture

In investigations on the mechanical assessment of mucoadhesion, this theory may be most frequently used, Figure 3. After establishing adhesion, the force necessary to separate two surfaces is analyzed. In tests of resistance to rupture, this force, Sm, is often determined by dividing the maximum detachment force, Fm, by the total surface area engaged in the adhesive interaction, Ao (Mamatha and Venkatesh 2022).

$$Sm = \frac{Fm}{Ao}$$

1.3.4. Theories of adsorption

The adhesive polymer and mucus substrate contact on different surfaces leads to adhesion in accordance with the adsorption principle. This surface interaction is referred to as primary and secondary bonding. After an initial connection between two surfaces, the materials remain adhered to one another due to surface forces working between the chemical structures at the two surfaces. At the contact, polar molecules or groups reorient when they are present. Because of their permanence, covalent, ionic and metallic bonds produced by primary bonds due to chemisorption are typically unwanted. When adhesion is exceptionally chemisorption, strong adsorption may take place. According to this notion, one or more secondary forces, including van der Waal's forces, hydrogen bonds, and hydrophobic bonds,

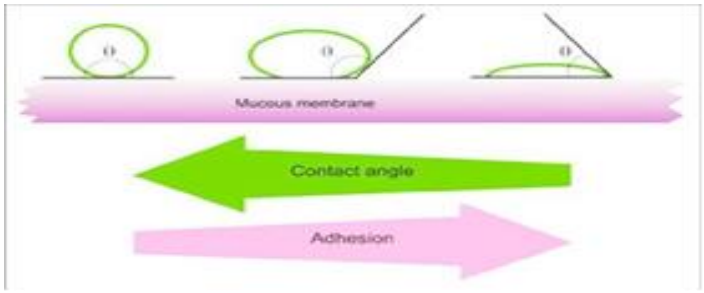

Figure 1. The effect of contact angle on bio-adhesion **(Mamatha and Venkatesh 2022).**

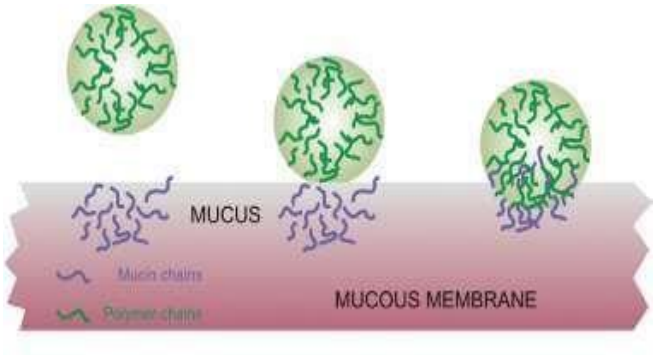

Figure 2. A secondary contact of the mucoadhesive device with mucus **(Mamatha and Venkatesh 2022)**

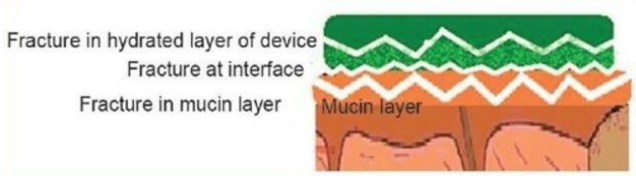

Figure 3. Fractures occur for mucoadhesion **(Mamatha and Venkatesh 2022).**

are ultimately responsible for the substance adhering to the tissue (Bal-Ozturk et al. 2021)**.**

1.3.5. Theory of electronic

This theory is founded on the idea that biological and mucoadhesive materials have polarized electrical charges. Thus, electrons are transferred as the two materials come into touch, creating a double electrical layer at the interface, ultimately developing attractive forces within this double layer (Sakshi et al. 2019).

1.4. The Muco-adhesive polymers

Mucoadhesive delivery techniques are being investigated to localize the active agents to a specific region or site. Polymers have been crucial in creating such systems to extend the active agent's residence period in the intended area. Mucoadhesive polymers can be made from either a water-soluble or water-insoluble polymer. It is practical to categorize mucoadhesive polymers that stick to the mucin-epithelial surface into three major groups:

1- Electrostatic interactions are the most common non-specific, non-covalent interactions that cause polymers to stick together (Although hydrophobic and hydrogen bonding may be crucial).
2- Tile surfaces that contain polymers that bind to a particular receptor location
3- When exposed to water, some polymers become sticky and are responsible for Bio-adhesion (Cazorla-Luna et al. 2021)**.**

Drug delivery can be done using any of the three

types of polymers.

1.4.1. Characteristics of perfect mucoadhesive polymer

1- They must be nontoxic and incapable of being absorbed through the digestive system.
2- It should not irritate the gastric mucosa.
3- It would need to ideally create a potent non-covalent connection with the mucin-epithelial cell surfaces.
4- It should bond to most tissues fast and have some site-specificity.
5- It should enable the drug to be incorporated daily and not obstruct its release.
6- Neither during storage nor the shelf life of the dosage form may the polymer begin to break down.
7- To maintain the competitiveness of the produced dosage form, the cost of the polymer should not be high (Ugoeze 2020).

1.4.2. Factors influencing mucoadhesive polymers

According to theories of adhesion, it can be said that a polymer's mucoadhesive property can be adjusted by modifying the parameters that can change how the polymer and the mucosal layer interact. Analyzing some variables that can modify a specific polymer's mucoadhesive characteristic will be attempted (Biondo 2020).

1.4.2.1. Factors related to polymers

It is possible to examine the contributions of the following parameters to the adhesive binding between a bio-adhesive system and mucin gel:

1- Chain length

The mucoadhesive characteristic of the polymers increases with the lengthening of their chains.

2- Molecular weight

A polymer's ability to adhere to mucous membranes increases with the polymer chain's molecular weight (MW).

a) Spatial arrangement: Another essential component is the spatial configuration of a molecule.

b) Flexibility: Flexible polymer chains aid in improved mucosal layer penetration and tangling of the polymer chains, enhancing the bio-adhesive characteristic. The cross-linking processes and the hydration of the polymer network often impact the polymer chains' flexibility. The flexibility of polymer chains decreases with increasing cross-linking density.

c) Hydration of polymer: In addition to the polymer chains' decreased flexibility, cross-linking reduces water's ability to diffuse into the cross-linked polymer matrix. As a result, mucoadhesive strength is reduced by a heavily cross-linked polymeric matrix that prevents polymer and mucin chains from interacting with one another.

d) Hydrogen bonding: Generally, the greater the hydrogen bonding, the tighter the adhesion. The functional groups in charge of this form of interaction are the hydroxyl, carboxyl, and amino groups.

e) Polymer charge and ionization level: The strength of the bio-adhesion significantly depends on whether charged functional groups are present in the polymer chain. Comparing anionic polyelectrolytes to neutral polymers, it has been discovered that the former form stronger adhesion.

f) Concentration of polymers: Typically, mucoadhesive properties for biomedical applications can be achieved with polymer concentrations between 1 and 2.5 weight percent (Yermak, Davydova, and Volod'ko 2022).

1.4.2.2. Factors of the environment

In addition to the physicochemical characteristics of the polymeric network, several environmental factors are essential for bio-adhesion.

1- pH: According to some studies, the medium's pH affects how much the cross-links are hydrated.
2- Applied strength: The interpenetration depth may be influenced by the initial pressure applied to the Bio-adhesion tissue contact point. Even though polymers do not have a favourable interaction with mucins, they become mucoadhesive if intense pressure is applied for a sufficient amount of time.
3- Time of contact: The polymer matrix is hydrated more quickly, and the polymer chains subsequently interpenetrate with the initial lengthening of the contract duration. Depending on the pathophysiological composition of the human body, the mucosal layer's physiology can change.
4- Swelling: Polymer content and the presence of water are both factors that affect swelling. There is a reduced bio-adhesion when oedema is too severe (Yermak, Davydova, and Volod'ko 2022).

1.4.2.3. Physiological factors

The texture and thickness of the mucosa are two physiological factors essential for controlling a

polymer matrix's ability to adhere to mucous membranes.

1. **Mucin turnover**

The mucoadhesive residence period on the mucus layer is predicted to be limited by mucin turnover, regardless of the mucoadhesive strength.

2. **Disease steatite**

It is recognized that some illness states, such as the common cold, stomach ulcers, and UC, cause changes in the physicochemical characteristics of the mucus (Rhushikesh and Suresh 2020).

1.5. Mucoadhesive polymers classification

1.5.1. According to the origin

1- Synthetic polymers for mucoadhesion

Cellulose derivatives, polymers made of acrylic acid, polymers of hydroxyethyl methyl acrylate, polymers made of ethylene oxide, polymers made of vinyl pyrrolidone, and polymers (vinyl alcohol).

2- Mucoadhesive natural polymers

Tragacanth, sodium alginate, guar gum, xanthan gum, karaya gum, soluble starch, gelatin, pectin and chitosan.

1.5.2. According to nature

Hydrophilic polymers are types of polymers that can dissolve in water. When placed in an aqueous medium, matrices made with these polymers swell, leading to the matrix's eventual dissolution. The mucoadhesive properties of the polyelectrolytes are increased. It's not just poloxamer used for its mucoadhesive properties; poly (vinyl pyrrolidone), methylcellulose, poly (vinyl alcohol), and hydroxypropyl methylcellulose are all examples.

1.5.3. Derivatives of polysaccharides

Ocular mucoadhesive delivery systems utilize hyaluronic acid, methylcellulose, chitosan, hydroxy propyl methylcellulose, Xanthan gum, hydroxy propyl cellulose, carrageenan and guar gum. Film-forming and surface-active properties characterize cellulose and its derivatives. It is best to use cellulose derivatives that work on the eye's surface and cause minimal irritation when administered topically. The most efficient ocular mucoadhesive among the several cellulose derivatives is sodium carboxymethyl cellulose. This substance is made from cellulose. Combining cationic cellulose derivatives, such as cationic hydroxyethyl celluloses, with other anionic polymers has allowed researchers to develop effective delivery systems for an extended period. (Ugoeze 2020).

1.5.4. Sodium carboxymethyl cellulose

It is one of the several cellulose derivatives that has been shown to possess superior ocular mucoadhesive characteristics. Several anionic polymers have been mixed with cationic cellulose derivatives to generate sustained delivery systems (for example, cationic hydroxyethyl celluloses).

1.5.5. A Novel class of mucoadhesive polymers

In certain original mucoadhesive polymer situations, already-existing mucoadhesive polymers have been changed, while new materials have been developed in others (Brannigan and Khutoryanskiy 2019).

1.5.5.1. Lectins

Lectins are naturally occurring proteins that are essential to the biological processes of cell and protein recognition. Lectins are a class of structurally varied proteins and glycoproteins that can reversibly bind to particular carbohydrate residues. They can either stay on the cell surface after initially adhering to mucosal cells or, in the case of receptor-mediated adhesion, they may get internalized through endocytosis. In that, lectin-based platforms could regulate macromolecular pharmaceuticals' drug delivery through active cell-mediated drug absorption; such systems could provide a dual role. According to reports, this phenomenon is favourable since the mucus layer serves as an initial, fully reversible binding site before lectin-mediated drug delivery systems are distributed to the cell layer.

Three kinds of lectins can be identified based on molecular structure:

1- Mero lectins: lectins with a single domain that recognizes carbohydrates;

2- Holo lectins: lectins having two or more domains that recognize carbohydrates.

3- Chimero lectins: lectins having different unrelated domains.

Lectins can improve medication penetration and increase the adhesion of microparticles to the intestinal epithelium. It has been demonstrated that tomato lectin-coated polystyrene microparticles stick to enterocytes specifically. Since human cancer cell lines have a higher lectin binding capacity than normal human colonocytes, the use of lectins for medication delivery to tumour tissue is currently the subject of extensive research (Chettri et al. 2021).

1.5.5. 2. Thiolated polymers

Thiomers are a specific category of multifunctional polymers created by modifying existing polymers by including a thiol group. These hydrophilic macromolecules exhibit free thiol groups on the polymeric backbone.

Thiomers' ability to produce intra- and inter-chain disulfide bonds inside the polymeric network significantly improves the cohesive properties and durability of drug delivery systems like matrix tablets. By forming strong covalent bonds with mucus glycoproteins via a thiol-disulfide exchange reaction and an oxidation process, thiomers have the best mucoadhesive properties of any polymeric additives studied. Several thiolated polymers are like chitosan-iminothiolane, poly(acrylic acid) -cysteine, poly (acrylic acid) -homocysteine, chitosan-thioglycolic acid, chitosan-thioethylamidine, alginate-cysteine, and poly (methacrylic acid) -cysteine and sodium carboxymethylcellulose-cysteine (Grosso and de-Paz 2021).

1.5.5.3. Bio-adhesive nanopolymers as a drug delivery system

Nanomedicine uses nanometer-scale particles or systems to diagnose and treat diseases at the molecular level. Mucoadhesive nano polymers, particularly in ocular drug delivery systems, seem to be a successful approach to the problem of achieving bioavailability with topical medications. The development of particulate systems for the administration of ophthalmic medications is justified by the possibility of particle entrapment in the layer of mucus on the ocular surface and the interaction of bio-adhesive polymer chains with mucin, which lengthens the time the drug is present in the precorneal (Idrees et al. 2020).

1.5.5.4. Alginate-polyethylene glycol acrylate (alginate-PEGAc)

Alginate- polyethylene glycol acrylate (alginate-PEGAc), a new mucoadhesive polymer with an alginate backbone carrying acrylated polyethylene glycol, is created. Alginate's strength, simplicity, and gelation ability are combined with PEG's acrylate functionality and mucoadhesion capabilities to create this polymer. PEG's ability to interpenetrate the mucus surface and a Michael-type addition reaction between a polymer's acrylate end group and a mucin-type glycoprotein's sulfide end group cause strong attachment to mucus. It has developed many additional multifunctional biomaterials for biotechnological and biomedical applications (Yaqoob, Jalil, and Bernkop-Schnürch 2021).

1.6. Mucoadhesive polymers evaluation.

In-vitro and in vivo studies can be used to measure the adhesion strength of mucoadhesive polymers.

1.6.1. In-vitro and ex-vivo testing

The study of the precise mechanisms of bio-adhesion is essential. These include methods determining tensile strength, techniques for calculating shear stress, using either the adhesion weight or fluorescence probe techniques, the flow channel technique, method of mechanical spectroscopy, the technique of a liquid film that falls, colloidal-gold staining, the viscometer technique, the ability to conduct electricity, investigations of drug release in vitro swelling properties, and research on the tenability of Mucor.

1.6.2. In-vivo Techniques

The employment of radioactive elements, using gamma scintigraphy, the other options is to implement pharmacy scintigraphy, electron paramagnetic effect, O_2 Resonance (EPR) measurement, examination via X-ray and the Isolated Loop Method (Garg et al. 2018).

1.6.3. Recent tests for Muco-adhesion

Recently, investigations on mucoadhesion employing BIACORE® integrated chip (IC) systems have been published. The procedure entails immobilizing the polymer (powder) on the surface of the IC before wiping the mucin solution over it. The mucin interacts with the polymer surface as a result of this. Surface Plasmon Resonance (SPR), an optical phenomenon that quantifies the change in the refractive index when mucin adheres to the polymer surface, is used to quantify the interaction between the polymer and mucin(Hajikhani and Emam-Djomeh 2020).

1.7. Multiple-unit dosage forms utilized in drug delivery

Hydrogels were developed to prepare a mucoadhesive drug delivery system that can target a specific body location for an extended time or increase residence time. By improving the management of systemic drug delivery, undesirable effects and the first-pass effect can be reduced.

The most important objectives in the development of mucoadhesive vaginal delivery systems for

beneficial vaginal delivery of antimicrobial agents are that the drug delivery system should stay at the injection site for a long time through adhesion to the vaginal mucosa, extended-release, improved bioavailability, reduced side effects of the drug and ultimately improved patient compliance. This can be accomplished by including mucoadhesive polymers in the formulations for creating and perfecting mucoadhesive gel systems to deliver antifungal medications to the vagina.

Wichterle and Lim initially prepared hydrogels in 1960.(Kirtania, Kahali, and Maity 2020). Hydrophilic polymers that form three-dimensional networks when exposed to high water absorption rates make up hydrogels. One, two, or more monomers may be used to create the produced networks. Because most toxicity is associated with unreacted monomers, oligomers, and initiators, it is crucial to thoroughly wash off these gels(Sharma and Tiwari 2020).

Hydrogels can be utilized in various applications, including contact lenses, drug delivery systems, membranes for biosensors, and tissue engineering (for artificial hearts and skin) (Kesharwani et al. 2021).

Drug release from hydrogels used as drug delivery systems can be managed chemically by swelling or diffusion. Drug release rates, duration, and dissolution profiles can be affected by the composition of hydrogels' polymers, water content, cross-linking density, crystallinity, amount of incorporated drug, and interactions between drugs and polymers(Khan et al. 2022)**.**

1.7.1. Spheroids / Micro granules

This drug's wet granulation, either on its own or combined with inert granules, is coated to regulate the release pattern(Dahmash 2020).

1.7.2. Pellets

Inert drug pellets are coated with film-forming polymers to create pellets. The number of coatings and the coating composition affect the release(Kállai-Szabó et al. 2022).

1.7.3. Microcapsules

The technique of placing a chemical into a smaller container known as a capsule is known as microencapsulation. Microcapsules are small spheres with a constant wall surrounding them. While the wall is occasionally referred to as the shell or covering, the material inside the microcapsule is known as the core or internal phase. Size of the microcapsules varies from 1 to 7 mm

1.7.4. Microspheres

Microspheres are small, spherical particles having dimensions between one and one thousand micrometres. They are biodegradable, free-flowing spherical particles made of proteins or synthetic polymers. Microcapsules and micrometric are two different forms of microspheres. Microspheres are tiny, spherical particles ranging from one to a million micrometres. They are spherical, biodegradable particles consisting of proteins or manufactured polymers. Micrometric are those in which the entrapped substance is spread throughout the matrix, whereas microcapsules are those in which a distinct capsule wall encircles the entrapped component. 'Microparticles' is another name for microspheres. Numerous organic and synthetic materials can be used to make microspheres. Microspheres are crucial for increasing the absorption of traditional medications and reducing adverse effects (Sonare, Jaiswal, and Mahanwar 2022).

1- Ideal microsphere properties

The following are listed as ideal microsphere properties:

a) The capability to incorporate a medicine at a reasonably high concentration.
b) Stability of the substance following synthesis with a shelf life that meets therapeutic requirements.
c) For injection, controlled particle size and dispersibility in aqueous vehicles.
d) Release of the active reagent over a significant period with adequate control.
e) Biodegradability with manageable biocompatibility.

2-Microspheres' advantages

The following is a list of the microsphere's advantages:

a) Reducing the size of the particles will help the poorly soluble medicine dissolve more easily.
b) Providing a consistent and long-lasting therapeutic effect.
c) Enabling the patient to take less of the drug and experience fewer side effects by keeping the drug's concentration in the blood constant.
d) The optimal method for medication distribution protects the drug against enzymatic and photolytic cleavage.(Sonare, Jaiswal, and Mahanwar 2022)

1.7.5. Microbeads

Microbeads have a small, spherical diameter of 0.5 to 1000 m. Solid or liquid particle carriers transport medication particles in solution or crystalline form and allow regulated release over a long period or many release profiles during therapy with different active agents. This has no repercussions. Localized, high-concentration drug administration using microbeads maximizes efficacy while reducing systemic adverse effects. They maintain physiological function.

Microbeads are manufactured from polymers such as chitosan, sodium alginate, gelatin, chondroitin sulfate, and avidin. The creation of controlled-release dosage forms now frequently uses microencapsulation. The medicine is coated or encapsulated in the centre of the beads, which are distinct spherical microcapsules that act as the solid substrate. Thanks to beads, drugs can be distributed more evenly throughout the gastrointestinal tract and with sustained-release qualities. Drugs that have been formulated in beads now have better bioavailability. Several investigations have used alginate beads as a controlled release carrier (Bhupathyraaj and Pole 2020).

1.7.5.1. Advantages of microbeads

The following are some advantages of microbeads:

1. Maintaining a therapeutic range of variation.
2. Decreasing adverse effects.
3. Lowering the dosage frequency.
4. An increase in bioavailability.
5. Increasing patient compliance (Ji et al. 2019).

1.7.5.2. Formulation criteria of sustained release microbead dosage form

Several formulation techniques have been devised to overcome the difficulty with immediate-release oral dosage forms. These procedures include embedding the medication in a plastic matrix, ion exchange resins, osmotic pumps, hydrophilic matrices, coatings, hydrophilic and hydrophobic polymer mixtures, and microencapsulation.

The criteria that must also be considered include the physiology of the digestive system, the drug's physicochemical characteristics, the pattern of drug release, and pharmacological effects. Aqueous solubility, stability, pKa, and permeability values are examples of the physicochemical properties of a medication(Murugesan et al. 2020).

In accordance with the Biopharmaceutical Classification System (BCS), a drug is divided into four categories:

1. High solubility and high permeability.
2. Low solubility and high permeability.
3. High solubility and low permeability.
4. Low solubility and low permeability.

Class 1 is the most appropriate grouping, while the poorest category is Class 4. Controlled oral dosage forms work well with highly soluble drugs in the intestinal tract. It is also essential to consider the drug permeability value, which should be higher than the target value. The optimal drug formulation would have a biological half-life between two and six hours, preventing the drug from building up in the body (Panwar 2021).

1.7.5. 3. Drug release kinetics criteria

A medication with high intestinal solubility is an excellent option for an oral dosage form with regulation. The drug permeability value should be higher than the specified value and must also be considered. For a formulation of an essential prescription, a biological half-life of between two and six hours is excellent since it prevents drug accumulation in the body.

A sustained-release system aims to distribute a drug at the rate required to maintain a consistent drug blood level. It indicates that during a set period, the rate of medication administration should be constant and independent of the amount of drug present in the dosage form. It indicates that zero-order kinetics should control the rate. Theoretically, the zero-order release might be preferred. In many situations, non-zero-order release rates may be therapeutically similar to constant release. The dose form should typically have two components to quickly reach a therapeutic level and keep it there for a predetermined time. The complete medicine in the controlled oral dosage forms should be divided into two portions, a loading dose and a maintenance dose. Upon injection, the initial loading dose is quickly released. A first-order kinetic process is what gives the medication its characteristic release. As a result, the amount of drug still in the body does not affect how quickly it is released. In the controlled oral dose form, the maintenance dosage is released at a rate equal to the drug's elimination rate (Laracuente, Marina, and McHugh 2020).

1.7.5.4. Mechanism of drug release

Dissolution, diffusion, polymer degradation, hydrolysis/erosion, and other common mechanisms for drug release from the microbead formulation are included.

1.7.5.5. Systems of controlling dissolution

Dissolution is the rate-regulating process in this

system. The medication is coated with a slow-dissolving material incorporated in a matrix that erodes, dissolves slowly, or both. There are two types of it. Matrix and encapsulation(Huynh and Lee 2014)

1- Encapsulation

Using microencapsulation procedures, slow-dissolving substances, including waxes, polyethylene glycol, cellulose, and polymethacrylates, coat or encapsulate the drug particle. The solubility and coating thickness affects how quickly something dissolves (Khandbahale 2020).

2- Matrix

Monoliths is another name for it. They use waxes like beeswax, hydrogenated castor oil, and carnauba wax, which regulate drug absorption by changing the matrix's porosity and the fluid absorption rate. Typically, the wax-embedded drug is made by spreading it in molten wax, allowing it to congeal, and then granulating it, Figure 4(Choudhary, Waghmare, and Kamble 2021).

1.7.5.6. Systems of controlling diffusion

Drug diffusion via an inert, water-insoluble membrane barrier is the rate-limiting stage. In the case of a polymer matrix, the active ingredient may diffuse through the water-filled pores or the complete polymer network. Drugs that dissolve in water may also do so in aqueous pore networks. Polymer chains swell when they absorb water, signalling the development of new holes or the presence of osmotic pressure.

More drug molecules reach the watery component, swelling increases volume, and the drug's effective diffusion coefficient increases. The location of the homogeneous or heterogeneous polymer breakdown also affects the release rate. The drug dissolution rate in the dissolution fluid, the rate at which the dissolution fluid enters the microbeads, and the rate at which the dissolved drug exits from the microbead determine the drug release, Figure 5. (Huynh and Lee 2014; Bhupathyraaj 2021)

Some coatings can be made to wear away progressively over time, releasing the medication that is encapsulated inside the particle. The monomer accumulation in the release media occurs concurrently with the polymer erosion or loss of polymer. The degradation of the polymer starts with changes in the microstructure of the carrier when water seeps through and plasticizes the matrix (Bhupathyraaj et al. 2022; Bhupathyraaj 2021).

1.7.5.7. Formulation methods for microbeads

1- Ionotropic gelation method

One technique places the cross-linker ion outside, whereas the second incorporates the cross-linker ion in an inactive state into the polymer solution. Internal and external ionotropic gelation methods are the two types under which they belong.

2- External gelation method

The metal ion solution provides the cross-linking ion for external gelation. A needle injects the drug-containing polymer solution while stirring. When a polymeric drop meets a metal ion solution, self-sustaining beads form instantly, Figure 6 (Shivhare et al. 2013; Bhupathyraaj 2021).

3- Internal gelation method

The internal gelation process produces the cross-linker ion " in situ. This technique obtains the cross-linking cation from insoluble metal salts, such as barium and calcium carbonate. Lowering the pH of the solution causes the metal salt to dissolve, releasing the metal ion and releasing the cation in situ., Figure 7(K.M, Shivakumar, and Kumar 2010; Bhupathyraaj 2021).

4- Emulsion gelation method

Emulsion gelation procedures are another way to prepare microbeads. The weighed amount of sodium alginate is dissolved in deionized water to create the sodium alginate solution. A precisely weighed amount of drug is added to the sodium alginate polymeric solution and swirled magnetically with low heat to create a homogenous drug polymeric mixture.

A cross-linking agent is injected to create a viscous dispersion, Using a syringe with a size 1500 flat-tipped needle and magnetic fields, which is then extruded into oil containing span 80 and 0.2% glacial acetic acid. Microbeads in oil for 30 min. Generate hard particles. Decanted items are rinsed with chloroform to eliminate any remaining oil. Microbeads are dried at 400°C for 12 h, Figure 8 (Bhupathyraaj 2021; Bhupathyraaj et al. 2022).

5- Polyelectrolyte complexation method

The complicated coacervation of materials with opposite charges, such as poly-electrolytes, polycations, and polyanion compounds, is another technique for making microbeads. Under easy conditions, biocompatible and biodegradable alginate chitosan microcapsules can be made even under some physiological circumstances, making them appropriate for use in biological fields.

Alginate-chitosan microcapsules have recently attracted attention as potential drug-delivery vehicles for proteins and polypeptides. The mixture will be separated into two distinct phases with this method, depending on the polyion concentration of pH and ionic strength: a dense concretive phase in which the microbeads are suspended and a more dilute equilibrium phase.

For the best yield with coacervation bead preparation, conditions should be set to a pH of 3.9, an ionic strength of 1 mm, and an 0.15% weight-averaged total polyion concentration. For instance, spraying the sodium alginate solution into the chitosan solution led to the complicated coacervation of alginic acid and chitosan, Figure 9 (Chen et al. 2020).

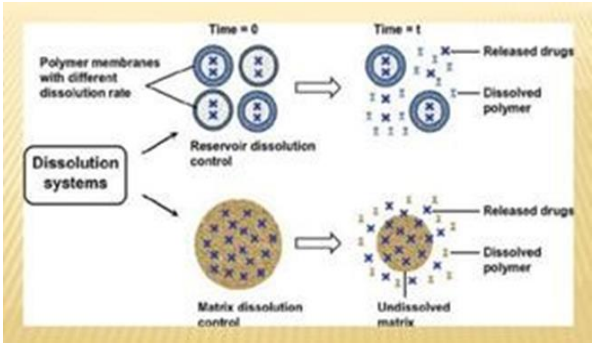

Figure 4. Controlled release mechanism dissolution system (Huynh and Lee 2014).

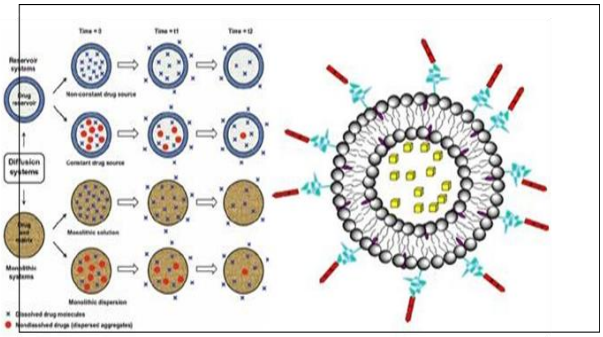

Figure 5. A System for controlling the release mechanism by diffusion **(Huynh and Lee 2014).**

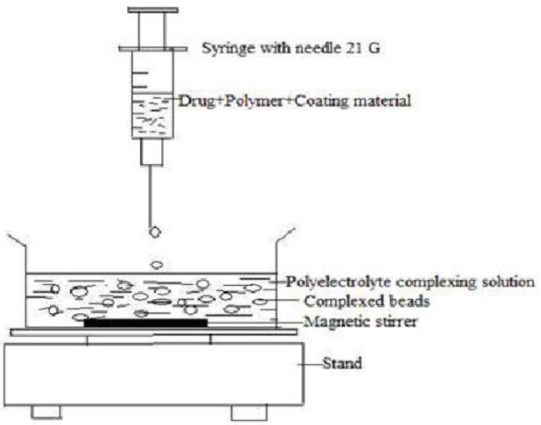

Figure 6. External gelation method **(K.M, Shivakumar, and Kumar 2010)**

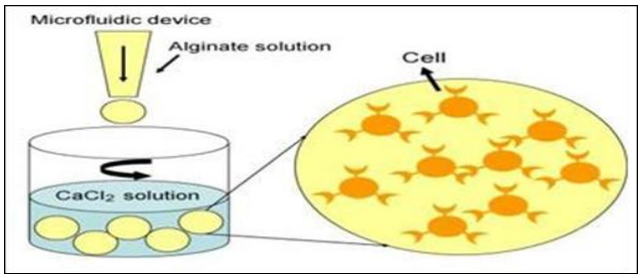

Figure 7. Internal gelation method **(Bhupathyraaj 2021)**

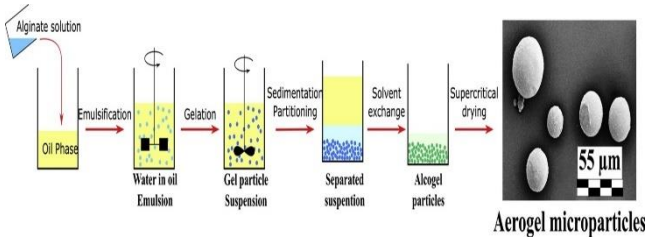

Figure 8. Emulsion gelation method **(Baudron, Gurikov, and Smirnova 2019)**

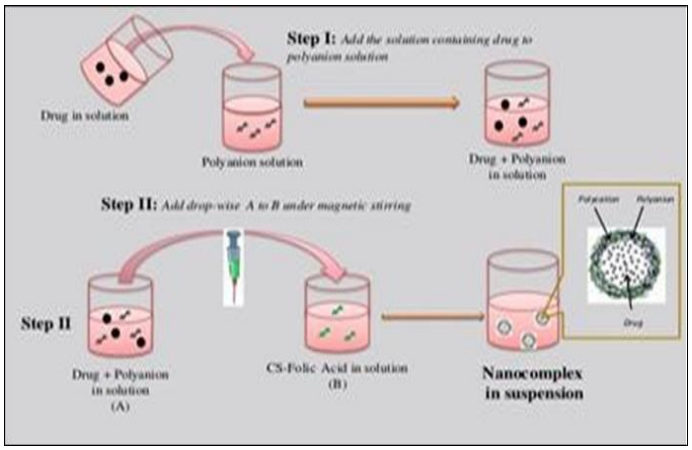

Figure 9. Polyelectrolyte complexation method **(Bhupathyraaj 2021)**

1.7.5.8. Polymers used to prepare micro-beads

Various materials, both biodegradable and non-biodegradable, have been studied for microbead production. These materials consist of modified natural components and polymers with synthetic and natural origins.

Some examples are albumin, Sodium Alginate, Gelatin, Starch, Chitosan, Dextran, olyglycolide, Polyanhydride, Polyphosphazene, etc. polymers. Sodium alginate microbeads are a multiparticulate drug delivery system used to boost bioavailability and stability, achieve sustained and regulated drug delivery, and selectively deliver drugs to specific sites. Oral drug delivery systems like microspheres and beads, which are made up of multiple unit dosage forms, are becoming more and more common because they allow for more uniform drug distribution throughout the gastrointestinal tract, uniform drug absorption, decreased local irritation, and the elimination of unwanted intestinal retention of polymeric material (Mythri et al. 2011).

1- Alginates

Brown seaweed contains natural polysaccharide polymers called alginates (Phaeophyceae). Alginate can be transformed into salts, of which sodium alginate is the most widely utilized type.

Alginates have several uses in drug delivery, including the delivery of biomolecules in tissue

engineering applications, matrix-type alginate gel beads, liposomes, and modifying gastrointestinal transit time. Alginates are helpful in the pharmaceutical sector because of their bio-adhesive properties.

Sodium alginate-based drug delivery systems have a wide range of applications and can be made into matrices, gels, nanospheres, membranes, microbeads and microspheres, among other forms.

Alginate beads can be taken orally by either compressing them into a tablet or adding them to capsules. Creating systems that can alter drug release in response to physiological demands is a novel use of alginate polymer in the pharmaceutical industry (e.g., pH-responsive systems based on polymer swelling and magnetically triggered delivery systems). Alginate also has the physicochemical characteristics necessary to contribute significantly to this field of future study (Pereira and Cotas 2020).

2- Chitosan

Crab and shrimp shell wastes are the primary sources of chitosan, a natural cationic polysaccharide generated from crustaceans' chitin.

As a relatively recent invention, the properties of chitosan make it a novel excipient in a pharmaceutical formulation. They include the degree of deacetylation, the average molecular weight of the polymer, low toxicity, and good bioavailability. To create various polyelectrolyte complex products, a chitosan biopolymer can be combined with natural polyanions, including xanthan, alginate, and carrageenan. Recently, numerous formulations based on chitosan and its derivatives were produced and studied in various dosage forms, including ocular, nasal, sublingual, buccal, periodontal, gastrointestinal, colon-specific, vaginal, transdermal, and gene carrier. Chitosan is a good choice for biomedical applications since it is biocompatible and exhibits antimicrobial and antifungal properties. Numerous studies have demonstrated the value of chitosan in promoting the growth and repair of tissues as well as in therapies that speed up bone regeneration and wound healing (Bakshi et al. 2020).

Pectin is employed as a gelling and thickening agent. It is essentially an a-D- galacturonic acid polymer with 1-4 links. Pectin is a naturally occurring biopolymer that can form gels, making it suitable for pharmaceutical use.

It may also be utilized in drug formulation and production as a carrier for a wide range of physiologically active compounds, including those with sustained release potential and those with local or systemic action in the colon (Amara 2022).

4- Gum

Extracellular polysaccharides and natural biosynthetic xanthan gum are edible gums. Glucuronic acid, mannose, and glucose make up xanthan gum. Due to the polyelectrolyte structure of the xanthan molecule, it is extremely soluble in cold and hot water.

A Xanthan gum is primarily used to increase viscosity and is thought to be a nongelling agent. It quickly hydrates in cold water without lumping to produce a consistent viscosity. Xanthan gum is a thickening stabilizer, emulsifier, and foaming agent. Xanthan may offer the benefit of zero-order release kinetics for medication release. But its main flaw is that the pH and ion content of the medium affects how much medication is released(Elella et al. 2021).

Conclusion

This overview of mucoadhesive dosage forms may be helpful for the effective design of new mucoadhesive drug delivery systems.

Applications for mucoadhesive drug delivery systems include creating new mucoadhesive, device design, mechanisms of mucoadhesion, and permeation improvement. Novel mucoadhesive formulations need much more development before they can be used clinically to treat systemic and localized illnesses. Microbeads are made using the ionotropic gelation technique to increase bioavailability, decrease dose frequency, and achieve an oral controlled release of the medication. Microbeads will eventually take centre stage in novel drug delivery by fusing a variety of other techniques, especially in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, precise, and effective in-vivo delivery, and supplements as miniature replicas of diseased organs and tissues in the body.

Thus, it was determined that mucoadhesive systems might become more important in forming new pharmacists.

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Table 1. Formulation of microbeads of various drugs and various polymers **(Hakam et al. 2022; Jana et al. 2022; Okunlola and Adewusi 2019; Deshmukh et al. ; Bharathi 2018; Kumar et al. 2018)**

No.	Type	Drug	Polymer	Method	Significance
1	Microbeads	Ibuprofen	Alginate	Ionotropic gelation method.	Prepared Rioprostil micro beads showing a higher drug entrapment and prolonged release characteristics
2	Microbeads	Diclofenac	Alginate and PVP K_{30}	Ionotropic gelation method	Oral alginate-PVP K_{30} microbeads for a controlled delivery system of DS were successfully developed by alginate-PVP K_{30} blending using ionotropic gelation
3	Microbeads	Theophylline	Chitosan and alginate	Ionotropic gelation method	As the conc., of polymer increased, the size of beads increased. Lower cross-linking time, lower the size diameter of gel beads.
4	Microbeads	Venlafaxine HCl	Alginate and $CaCl_2$	Ionotropic gelation method	Good encapsulation efficiency and micron-sized alginate spheres.
5	Microbeads	Nifedipine	Alginate and pectin	Ionotropic gelation method	The mean particle size of microbeads increased significantly with the increasing pectin concentration
6	Microbeads	Norfloxacin	Alginate and pectin	Ionotropic gelation method	The sustained release was observed with the increased percentage of sodium alginate.

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