Review Article

Mucoadhesion Drug Delivery Sytem: A Propitious Approach

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ABSTRACT

Mucoadhesion drug delivery system engages much attention due to their benefits such as prolong retention time, fast uptake and increased bioavailability of active substance. The term mucoadhesion is the subgroup of bioadhesion and in the mucoadhesion formulation attaches with the mucus membrane. The mucoadhesion can be defined as the adhesion between the two materials in which one is biological material and other one is polymeric materials with the help of interfacial forces to increase the residence time. The mucoadhesion drug delivery system is better than the traditional drug delivery systems. The mucoadhesion bypasses the first pass metabolism and used for localized delivery of biomolecules such as peptides, proteins and oligonucleotides. In this review, we discussed about the structure of mucus layer, theories of mucoadhesion, factors affecting mucoadhesion, mucoadhesive drug delivery system, mucous mimetic materials, mucoadhesive polymers and recent drugs.

Keywords: Mucoadhesion; Drug delivery system; Mucous mimetic materials; Mucoadhesive polymers.

INTRODUCTION

With the advancement in the drug formulations and different routes of administration; the knowledge of drug transport across tissues have been increased, now a days. These advancements alter the patient attachment to the dosage regimen as well as pharmacological action. The bioadhesive drug delivery system means the attachment between a biological origin substance and a polymeric material. In the bioadhesive drug delivery systems, the attachment occurs between the additives of the formulations and the biological tissue. The term mucoadhesion is the branch of bioadhesion and in the mucoadhesive formulation attaches with the mucus membrane[1]. The mucoadhesion can be defined as the adhesion between the two substances in which one is biological material and other is polymeric materials in order to enhance the retention time of the drug. The binding between the two substances occurs through interfacial forces. The mucoadhesion drug delivery system is better than the traditional drug delivery systems. The mucoadhesive systerm bypasses the first pass metabolism and is used for localized delivery of biomolecules such as peptides, proteins and oligonucleotides. With the help of mucoadhesion drug delivery, different compounds can be given by different routes of administration like ocular, oral, vaginal, nasal and rectal[2]. The systemic and local delivery of drug is improved in mucoadhesion system as the contact time on the site of application is increased. The mucoadhesive polymers may also act as a therapeutic substance for tissue protection or lubrication.

Mucoadhesion drug delivery system has many advantages like[2]

- Prolonged retention time,
- Enhanced absorption of drug due to increased blood supply,
- Enhanced efficacy of the active substance,
- Enhanced bioavailability of drug due to avoidance of first pass metabolism.
- Prevention of drug degradation in the GIT due to the presence of acid.
- Better patient compliance due to the simple drug administration.
- Rapid onset of action.

The design of a mucoadhesives depend upon two important factors: has ability to prolong the release of the drug from matrix and strong attachment to the mucus. The adhesion with the mucus membrame is done by different types of polymers like thiomers, chitosan, lectins, acrylates, poloxamers, starch ,pectins, hydroxypropylmethylcellulose, gellan gum, xanthan gum, polyvinyl alcohol, methyl cellulose, carrageenan, polyvinyl pyrrolidone , guar gum, Hyaluronic acid, Gellan gum, Sulfated polysaccharide, PEG , cashew gum etc.

Structure of mucus layer

Mucous membranes are the wall lining of many body cavities for example: respiratory tracts and GIT etc. These are the moist surfaces containing goblet cell which releases mucus directly on to the epithelial surfaces. Mucus may exist as a suspended form or gel layer form or luminal soluble form. The major constituents of all mucus gels are mucin: inorganic salts, glycoproteins (0.5% – 5 %), water (95 %) and lipids (0.5 %- 5)[3,4]. Soluble mucins are high-molecular weight glycoproteins (0.5—40 MDa) composed of 500 kDa sub-units which are connected to

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each other by intramolecular cystein–cystein disulfide bridges and peptide linkages [3,5]. The mucin subunits contains: oligosaccharide-based grafted chains and protein-based backbones. The protein-based backbones are composed of 12–17% of the total mucin weight and the amino acids which includes 70% proline, serine and threonine. The oligosaccharides chains are composed of galactose, N-acetylglucosamine, fucose and N-acetylneuramic acid (sialic acid) [3,6]. According to the mucoadhesion perspective, the oligosaccharides give possibility for electrostatic interactions and hydrogen bonding with the carboxylic group of the sialic acid. Moreover, some sulfated sugars have been found at the terminal position of the oligosaccharides in the respiratory tract and colon which give one more site of electrostatic interactions [7]. Importantly, the pKa value of the acidic groups is between 1 and 2.6 which give negative charge in the mucin and the degree of ionisation of the mucin oligosaccharides will remarkably decrease when the pH in the stomach is 1 [8,9].

Table 1: Functions of mucus layer [10, 11]

S No.	Functions	Comments
1	Protection	Selectively from the hydrophobicity.
2	Barrier	In tissue absorption of active substances and another substrates.
3	Adhesion	Binds enduringly to the epithelial cell surfaces and firmly cohesional properties.
4	Lubrication	Make mucosal surfaces moist.

Theories of Mucoadhesion

These theories illustrate the mechanisms in which mucoadhesive polymers bind to the mucosal membrane. These theories are depending upon the long-established theories of polymer and metallic adhesive[12]. These theories do not provide the whole explanation of the mechanism of mucoadhesion. The mucoadhesive process is a blend of these theories. The scientists favours to split the mucoadhesive process into consecutive steps, each individual theory is associated to a different mucoadhesive mechanism[13,14].

1. Wetting theory

- Applicable for liquids or low viscosity mucoadhesion systems.
- Compare the surface tension of the polymer (mucoadhesive) and mucus with mucoadhesive polymers potential to bulge and spread on the mucousal surface.
- It shows that interfacial energy plays a crucial role in mucoadhesive process.
- The contact angle (θ) is associated with the interfacial tension (γ) of the mucosa surface and mucoadhesive system as illutrate in eq. 1 and 2

$$\gamma SG = \gamma SL + \gamma LG \quad (1)$$

$$S = \gamma SG - (\gamma SL - \gamma LG) \quad (2)$$

Where,

γSG = surface tension at solid – gas interface

γLG = surface tension at liquid – gas interface

γSL = surface tension at solid – liquid interface

- The contact angle goniometry techniques are used to find out the affinity of a liquid for a surface to calculate the contact angle of the liquid on the surface. It is based on the principle that the affinity of the liquid to the solid surface will be greater when the contact angle is low.
- The spreading coefficient (S_{AB}) is determined from the surface energies of the solid and liquids using following equation:

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

Where,

γ_A = surface tension of the liquid A

γ_B = surface tension of the solid B

γ_{AB} = interfacial tension between the solid and liquid

- For the spontaneously spreading over the solid, the spreading coefficient must be positive for the liquid.
- The work of adhesion (W_A) constitute the energy needed to separate the two parts which are as follows:

$$W_A = \gamma_A + \gamma_B - \gamma_{AB}$$

- Higher the particular surface energy of the liquid and solid (related to the interfacial energy), higher will be the work of adhesion.

Adsorption theory

- Molecular bonding between the mucoadhesive polymers and the mucus.
- Primary and Secondary chemical bonds are the types of molecular bonding.
- Primary types of molecular bondings are covalent bonds which are nonessential in mucoadhesion due to their high strength which can cause perpetual bonds.

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- Secondary types of molecular bondings comprise variable force of attraction which are hydrogen, electrostatic forces, hydrophobic bonds and vander Waals forces.
- Presence of strong covalent bonding results in the interaction occurs in the interface (According to the chemisorption theory[15].

Electronic theory

- Due to presence of variation in their electronic structure; the mucus membrane is attached with the mucoadhesive polymers.
- Bonds are formed due to presence of electron transfer amongst the mucus membrane epithelium and polymeric system
- Therefore, the formation of a double layer of electrical charges takes place at the interface of the mucus and the mucoadhesive polymers[12].

Fracture theory

- The robustness of adhesive bond is the main force for polymer separation from the mucus
- The length of polymer network strands or the degree of cross-linking within system has a significant effect on the work facture. Work fracture is pronounced when the cross-linking is decreased[16].
- Physical attachment of a adhesive polymer with a mucus strand is not required.
- Applicable for the study of bioadhesive hard polymers that are deficient of flexible chains.
- The fracture strength is equivalent to adhesive strength which are as follows:

$$G = (E * \varepsilon/L)^{1/2}$$

Where,

L— Critical crack length when two surfaces are detached

ε— Fracture energy

G— Fracture strength

E— Young's modulus of elasticity[2]

Diffusion interlocking theory / Interpenetration theory:

- The strong semi–permanent mucoadhesive bond are formed when mucoadhesive polymer penetrate to the sufficient depth with mucus glycoproteins.
- Two-way diffusion process in which rate of penetration is based on the diffusion coefficients of both interactive polymers.
- Factors affecting the diffusion are: cross-linking density, chain flexibility, molecular weight,

  temperature and expansion capacity of both networks.
- For appropriate interpenetration and molecular entanglement; the critical chain length should be at least 100 kDa.
- Depth of interpenetration is based upon the contact time and the diffusion coefficient.
- Appropriate depth of penetration leads to the formation of a semi-permanent adhesive bond.
- Depth of penetration can be estimated by:

$$t = L^2/D_b$$

Where,

D_b = Diffusion coefficient

L = Depth of penetration

t = Time

- For the good diffusion, the bioadhesive and mucus should have similar chemical structure and have fine solubility of one compound in the other[17].

Mechanical theory

- Adhesive bonds are formed when non-uniformities on a rugged surface are filled by a mucoadhesive liquid.
- Irregularity increases the interfacial area which enhances the potency for interactions[18].

Factors influencing the mucoadhesion

Many factors affecting the mucoadhesion like polymeric factors, environmental factors and mucus physiology etc. (Table 2 and table 3)

Table 2: Factors influencing mucoadhesion by polymer:

S No.	Factors	Effects on mucoadhesion	Comments	References
1	Hydrophilicity	• Maximum exposure. • Swelling polymers shows efficient penetration of substrate. • increased chain flexibility	Hydroxy and carboxy groups form hydrogen bonds with the substrate, swells in aqueous medium.	19,20,21

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2	Molecular weight	• LMWP penetrate the mucosal surface better than HMWP. • High molecular weight help to physical entangle.	Optimum molecular weight is between~$10^3 kDa$	21
3	Concentration of active polymer	• Low concentration polymer forms unstable interaction between mucus and the polymer	Number of penetrating polymer chains per unit volume of the mucus is small when the polymeric concentration is low and optimum concentration is between 0 –2.5%,	22
4	Flexibility of polymer chains	Cross-linked polymer • Decreases the penetration into the mucous layer. • Decreases the bioadhesive strength.	Cross-linked polymers decrease the ability to move the individual polymer chains and also reduce the length of the chain.	23
5	Hydrogen bonding capacity	Hydrogen bonding favors the mucoadhesive interaction	Polymers should have functional groups like COOH, OH, etc. which can positively formed hydrogen bonds.	24
6	Swelling	• Increase the penetration process between mucus and polymer. • Swollen polymers promote the mechanical entanglement.	Swelling provides exposure to the bioadhesive sites for electrostatic interaction or hydrogen bonding. The optium swelling is 58- 60.	25,26,27
7	Cross linked density	Increase in the density leads to decrease in interpretation rate between mucin and polymer.	Enhanced cross- linked density reduces the diffusion of water into the polymer network and causes the insufficient swelling of the polymer.	28
8	Charge	• Anionic charge increases the mucoadhesive strength • anion > cation > non-ionic	Strength of mucoadhesive polymers with carboxy groups are much stronger than the neutral groups.	29

(LMWP- Low molecular weight polymers, HMWP- High molecular weight polymers).

Table 3: Factors influencing mucoadhesion by environment and physiological factors

S No	Factors	Comments	References
1	PH	pH of the mucus and mucoadhesion polymers can affect the adhesive properties and ionization state of the polymer.	30
2	Applied strength	The depth of diffusion of chains alters.	31
3	Contact time	Contact time decides the area of swelling and interpenetration of the mucoadhesive polymer chains.	32
4	Mucin turnover rate	Determines the retention time of the mucoadhesives polymers on the mucosal surface. The mucus turnover in humans is between 12–24 hour	33
5	Disease state	Concomitant diseases affects the physicochemical factors of mucus	34

Mucosa – mimetic materials

These are the synthetic substitute of mucosal tissues. Though these materials do not secrete mucus but are required to mimic the cell surfaces of the columnar epithelial lining. These are used to test the mucoadhesive formulations. The applications of ex vivo mucosal tissues are employed for the flow-through or detachment type of testing depending on the nature of formulation whether in liquid or solid form.

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Table 4: Different mucosa – mimetic materials used in mucoadhesion

S No.	Sources	Material used	Special points	References
1	Animal and plant source	Lyophilized porcine dermis	Compare with rabbit peritoneal membrane.	35
2	Animal and plant source	Tanned leather as a model for sublingual mucosa.	Study on the adhesion carbopol tablets	36
3	Animal and plant source	Agar as a mimic which is a inhalable polymers	more similar with the behaviour of particles in the nasal cavity.	37
4	Animal and plant source	Cell culture	Tribological calculations of mucoadhesion nasal formulations.	38
5	Animal and plant source	Monolayer of goblet cells which secrete mucus by using the HT29-MTX-E12 cell line.	Compare to the polymers adhesion to rat intestinal sacs	39
6	Animal and plant source	Cells label with pyrene.	To calculate the polymer adsorption on to the monolayer	40
7	Synthetic type	PVC strips	Compare with rat intestinal mucosa	41
8	Synthetic type	Plexiglass (poly(methyl methac-rylate))	Compare with the bovine buccal mucosa.	42
9	Synthetic type	Rseconstituted porcine gastric mucin and plexiglass are used.	Measure the mucoadhesive polymers interaction of PAA hydrogels.	43
10	Synthetic type	Rehydrated porcine gastric mucin	These type of mucin have different rheology and composition than original mucin	44
11	Synthetic type	Artificial mucus containing porcine gastric mucin and porcine intestinal mucus	compared the diffusion of drugs through an artificial mucus containing porcine gastric mucin and porcine intestinal mucus	45
12	Synthetic type	Glutaraldehyde cross-linked porcine gastric mucin to form gels.	Can mimic the rheological properties of mucus from the trachea	46
13	Synthetic type	Wet glass	To find out glass property to mimic the mucus. The result came out was that the glass is a poor mimic of mucosa.	47
14	Synthetic type	Dialysis membrane	Assess the mucoadhesive property of some self-assembling peptides	48
15	Synthetic	Synthetic glycopolymer hydrogel	Compared porcine buccal mucosa by detaching the mucoadhesive tablets from these hydrogels	49
16	Semi synthetic	Hydrogen-bonded interpolymer complexes formed from poly(acrylic acid) and methylcellulose	To test on mucoadhesive tablets.	50

Drug Delivery System

On the basis of different route of administration, mucoadhesive delivery system is categorized into oral, ocular, nasal, vaginal and rectal delivery systems, which are as follows:

Oral drug delivery system

It is a route of administration, in which the drug is taken orally through the mouth. They have a systemic effect therefore large quantities of drugs are given orally.

Oral drug delivery can be classified into 3 categories:

- Buccal
- Sublingual
- Local

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Buccal mucosa

Alike sublingual administration there is no quick absorption and adequate bioavailability in buccal mucosa as it is less permeable. It is the most appropriate site for oral controlled drug delivery system because it increases the residence time in the buccal mucus membrane which leads to pharmacological actions of drug in the controlled manner.

Sublingual mucosa

They are highly permeable which results in quick absorption, suitable bioavailability and are appropriate, approachable, and well received. Though sublingual mucosa has many advantages but still it is not convenient for oral transmucosal delivery system because it has unequal and moveable mucus which are washed by saliva and causes low residence time.

Local

Local delivery means the formulation is applied on the mucosa of oral cavity. Mucoadhesive local delivery system is used to treat the periodontitis (bacterial infection) [51].

Examples

- Mucoadhesive microparticles were prepared in form of capsule dosage form and were delivered into the GIT. These microparticles might be used for the local drug delivery [52].
- Mucoadhesive electrospun chitosan-based nanofibre mats were formulated for dental caries prevention[53].

When the drug is given orally, it has to pass through different barriers of oral drug delivery of proteins such as

- Drug deterioration is occur due to acid present in the stomach,
- hydrolytic deterioration due to the presence of proteolytic enzymes
- metabolism by luminal, brush border
- metabolism by cytosolic enzymes
- Decreased membrane permeability over the intestinal epithelium.

Therefore, Mucoadhesive drug delivery system is preferred over. Moreover in this drug delivery system, the non – covalent bonds are formed such as ionic interactions, hydrogen bonds and physical attachment occurs between the mucoadhesive polymers and mucosal surface.

Advantages:

- By this route macromolecules can be given easily.
- It avoids pain, discomfort and infections due to the use of needles.

The dosage forms of oral drug delivery system are as follows

Buccal tablets

These are most commonly used dosage form. These are oval, small and flat shaped tablets with a diameter of 5–8 mm. These are formulated by wet granulation techniques and direct compression method. Prepared tablets are coated by water impermeable materials (for example hydrogenated castor oil and ethyl-cellulose) to increase their sustained release and mucoadhesion property. Multilayered tablets formed by successively added and compressed the ingredients layer by layer [54].

Advantages[11,31,55]

- Convenient route of administration.
- Discontinuation of the therapy is easy.
- Provides increase retention time of the drug.
- Enhances bioavailability of the drug.
- Best route for the systemic delivery of drugs.
- Decreases immunogenic response, improves tissue permeability or inhibit protease activity
- Drugs not suitable in the acidic or alkaline media or demolished by the enzymatic conditions can be administered using this route.

Limitations

- Requires physical flexibility
- Poor patient compliance when the drug is used frequently and for long durations.

Examples

- Mucoadhesive buccal tablets of clonazepam were prepared to give improved local or systemic delivery. Mucoadhesive tablets were formed using direct compression method with the combinations of different polymers. Carbopol 971P/HPMC and Poloxamer/chitosan mixtures were selected for drug loading[56].
- Buccal absorption of diazepam was improved when bioadhesive tablets were delivered [57].

Buccal bioadhesive micro/nanoparticles

Due to their physical properties, these micro/nanoparticles are able form intimate contact with a larger mucus membrane area. These are delivered in various forms like pastes, aerosols, as aqueous suspension or in ointment forms. These micro/nanoparticles are small particle size and have better patient compliance. Due to the small particle size, they cause less local irritation at the adhering site and decrease the uncomfortability which occurs due to the presence of foreign particles in the oral cavity.

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Example

- Monti and co-workers developed microspheres which contain atenolol using Poloxamer 407 and evaluated the formulation in vivo in rabbits against a marketed tablet formulation [58].
- Alginate microspheres as nystatin carriers were prepared for oral drug delivery system [59].
- Film dosage form of chitosan coated mucoadhesive nanoparticles was formulated for buccal curcumin release[60].

Buccal liposomes

Liposomes are one of the alternatives forms of doasage form. Liposomes are used for that drugs which cannot be properly given by a solid dosage form and are less soluble. These are spherical vesicles having at least one lipid bilayer and are comprised of phospholipids.

Example

- Buccal liposomal mucoadhesive film for permeation of water-soluble vitamins and prolonged delivery were formed [61].
- For buccal and sublingual drug delivery; multi-layered nanofibrous mucoadhesive films were prepared [62].

Bioadhesive wafers

The bioadhesive wafers are the composite wafers which contain two layers. One is surface layers which possess adhesive properties and other one is bulk layer composed of matrix polymers, biodegradable polymers and antimicrobial agents.

Examples

- For buccal drug delivery; the econazole contained amidated pectin wafers were formed[63].
- Buccal formulations (films and wafers) containing sodium alginate and HPMC were prepared. These were used for nicotine replacement therapy and were found to be economical and effective alternative to currently used nicotine patch and chewing gum[64].

Bioadhesive Lozenges

Bioadhesive lozenge provides capacity for controlled drug release and better patient compliance. These are only used for those drugs which act in the mouth like antifungals, antimicrobials, antibiotics, corticosteroids, and local anaesthetics. The disadvantages of these are: low retention time at the absorption site and short residence time. Due to short residence time only limited amount of drug is delivered into the systemic circulation. The constant release of saliva also affects the performance of these type of dosage forms [65].

Examples

- Bioadhesive lozenges were formulated to administer as a antifungal agents, miconazole nitrate to the oral cavity [66].
- Bioadhesive Lozenge of Cetylpyridinium Chloride was developed for the better delivery [67].

Bioadhesive films/patches: These are laminates consisting of reservoir layer, backing layer and bioadhesive layer. The backing layer is an impermeable, a bioadhesive surface is for mucus membrane adhesion and reservoir layer releases the drug in a sustained manner. These patches are similar to the transdermal patches and are formed by direct milling and solvent casting. The backing layer can be used to stop the drug loss, reduce deformation, disintegration and sustain the drug release.

Examples

- The carvedilol contained chitosan–pectin complexes were formulated in the form of mucoadhesive buccal patches[68].
- The carbamazepine buccal patches of unidirectional release were formulated[69].
- The zolmitriptan bilayered mucoadhesive buccal patches using xanthan gum were prepared[70].

Buccal gels and ointments

Hydrogels containing mucoadhesive semi- solids are a fasicinating dosage form. In this drugs are given through intra-periodontal pocket or buccal mucosal which enhances the retention time and bioavailability. Gels have limited application in mucoadhesive system because of narrow therapeutic index. These are mostly used in oral medicines, gynecology and ophthalmology. Ointments are less selective for the buccal formulation.

Advantages

- Quick release of the drugs at the site of application by making intimate contact with the mucus layer.
- Hydrophobic drugs are delivered by using hydrogels from polymer mixtures.
- Gels gives long time release and better bioavailability[71].

Disadvantage

- When the hydrogel polymer has not adhering property than it causes the short residence time at the application site.

Examples

- Mucoadhesive formulation of buccal anesthesia by using iontophoresis and amino amide salts were prepared[72].

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- Bioadhesive gels of triamcinolone acetonide were formed to increase the bioavailability[73].

Medicated Chewing Gums

These gums provide large amount of drug in the oral cavity so as to get a local effect. When systemic absorption of drug occurs through the oral mucosa, these gums release the drug at the controlled rates which causes the prolonged retention time in the oral cavity. Though these gums possess difficulties to control the delivered dose but still are used to cure the oral cavity ailments and used in nicotine replacement therapy[74].

Examples

Bioadhesive nicotine microparticles medicated chewing gum was prepared[75].

Buccal liquid Dosage Forms

These are suspensions or solutions of active substances with the suitable aqueous vehicles. These formulations have the ability to exert local effect into the oral cavity. Many antibacterial mouthwashes and mouth-freshener are available in the market. Different polymers like Chitosan, polycarbophil, carbopol, gelatin and methylcellulose are used in the development of mucoadhesive liquids. The buccal surface is coated by the viscous liquids which behave as a vehicles or protectants to the mucus layer. The dry mouth condition is treated using artificial saliva solutions which also provide the lubrication on the mucosal surfaces. These solutions contain sodium carboxy methyl cellulose as mucoadhesive polymer.

Disadvantages

- They are not easily retained or act at the buccal mucosa
- In this the large amount of drug is given [76].

Examples

yaluronic acid thiolated derivatives were synthesized which contained mucoadhesive properties and produced enhanced staibility [77].

Opthalmic/ocular drug delivery system

Due to the presence of blood- ocular barrier, the topical route of administration is preferred for the treatment of ocular ailment. Drug bioavailability can be enhanced by producing a local action in the cul-de-sac and prolonging the retention time of the drug. To increase the bioavailability of ocular drugs; different approaches were established like by enhancing the contact time between the conjunctival or corneal epithelium and formulations.

Advantages

- Better shelf life.
- Rapid absorption and effect.
- Less systemic adverse effects.
- Better patient compliance.

Need of mucoadhesive opthalmic drug delivery system

- To instil a drug into the eye is the biggest challenge due to the presence various protective mechanisms like tear production, tear turnover and blinking.
- The semi-solid preparations such as ointments and gels causes discomfort, reflex blinking, irritation and blurred vision[78].

Ocular liposomes

Many factors influence the effectiveness of ocular liposomes like liposomal surface charge which affects the pre corneal vesicle residence time [79,80]. It was found that positive charged liposomes increases the corneal penetration of active substances as compared to negative or neutral charged liposomes. Carbopol 934P, polyalkylcyanoacrylate (PACA), poly-ε-caprolactone (PECL) and carbopol 1342 are the mucoadhesive polymers which are used to increase pre corneal residence time in the liposomes [81,82].

Examples

- The new chitosan-coated deformable liposomes were formed for an opthalmic drug delivery system[83].
- Silk fibroin-coated liposomes were fabricated and characterised for ophthalmic drug delivery system[84].

Ocular nanoparticles

These nanoparticles are designed to cross the barriers and enhance the drug levels by few intervals of drug administrations. The drug penetration at the site of action in fewer doses without causing any toxicity as compare to the traditional eye drops**.** By surficial applications and intravitreal injection, nanoparticles could target at cornea, retina and choroid.

Examples

- Topical mucoadhesive ocular nanoemulsions of an immunosuppressant agent were formulated[85].
- Dexamethasone; hyaluronic acid coated chitosan nanoparticles were developed for topical ophthalmic drug delivery[86].
- Nanosized linear sodium, zinc hyaluronate and cross-linked sodium were compared to evaluate the action as an ophthalmic mucoadhesion drug delivery system[87].

Ocular microspheres

These are monolithic particles composed of a solid or porous polymer matrix and the microcapsules are composed of membrane of polymers which is enclosed

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with a liquid or solid drug reservoir. These are spherical, solid particles and their size is from 1 to 1000μm. These are composed of waxy, polymeric and some other protective materials which are gums, waxes, fats, starches, and proteins. These materials are used as carrier matrix of drug in the drug delivery.

Examples

- Acyclovir chitosan-*N*-acetyl cysteine microspheres were synthesized for the ophthalmic drug delivery[88].
- Rokitamycin loaded novel chitosan derivatives microspheres were prepared for the ophthalmic or nasal delivery[89].

Ocular inserts

Ocular inserts are the dosage forms which are composed of polymers and are used due to their ability to control the release of drug and long residence time property. These can be used in the upper and frequently in the lower conjunctival sac of the eye.

Examples

- New nano type lipid carrier inserts were formed for mucoadhesive opthalmic drug delivery[90].
- Piroxicam bioadhesive ocular inserts were synthesized for evaluating the ocular anti-inflammatory activity in rabbits[91].

Vaginal drug delivery system

In ancient times, this route of administration was used for local treatment and delivery of contraceptives but now days this is used for systemic delivery of drugs. The length of the vagina varies between 6 and 10 cm in adults.

Advantages

- Bypass first-pass metabolism in liver and reduces the hepatic and gastrointestinal side-effects.
- Improve permeability for peptides and proteins[92].
- It is an alternate path of the parenteral route of administration for some drugs like oxytocin, human growth hormone, calcitonin, steroids and bromocriptine used for contraception or replacement therapy.

Disadvantages

- Systemic drug delivery through this route is depend upon the epithelial thickness, the cervical mucus, the vaginal fluid (volume, viscosity, pH), gender, the menstrual cycle , hormones and age[93].
- Slow retention time and leakage causes poor patient compliance.

Examples

- Acyclovir Thiolated Cyclodextrin were formed for Mucoadhesion Vaginal Delivery System[94].
- Mucoadhesive sponges of cellulose derivative were formed for vaginal drug delivery system[95].
- Mucoadhesive starch was developed in form of vaginal preparation which is used as a veterinary medicine[96].

Pessaries

Pessaries are medical products which are given through the vagina. These are used to provide structural supportand also used to deliver a medication.

Examples

- Controlled released butoconazole pessary were formed which are used to treat the vulvo-vaginal candidiasis[97].

Vaginal topical administration

It is a locally applied on or in the body. These are applied on the body surfaces like mucus layers or skin to treat diseases. Different type of dosage forms is available like foams, creams, lotions, ointments and gels.

Examples

- Formulation and evaluation of anise-based bioadhesive vaginal gels [98].
- Curcumin loaded vaginal in-situ hydrogel were optimized by box-behnken statistical design for contraception [99].

Vaginal microspheres

Nanoparticles are nano sized; colloidal structures which are made up of synthetic or semi synthetic polymers and microspheres are spherical microparticles. Their size are between between 0.1 and 100 μm

Examples

- Spray dried tenofovir loaded mucoadhesive microspheres were formed which are used for HIV prevention[100].
- Econazole nitrate lipid polymer based mucoadhesive microspheres were prepared for the vaginal drug delivery [101].

Vaginal tablets

These tablets which are inserted into the vagina to treat vaginal infection. These types of formulations are characterized by friability, in vitro release, DSC, hydration, hardness and mucoadhesion.

Examples

- Benzydamine novel solid mucoadhesive systems were formed for vaginal drug delivery[102].

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- Itraconazole contained cyclodextrin complex bioadhesive tablets were formed which is used to cure vaginal candidiasis[103].

Nasal drug delivery system

The nasal mucosal is used for both systemic drug delivery and for local drug delivery. Nasal drug delivery system is used for the delivery of peptides and small proteins as compared to oral and parenteral route as this route influence their absorption. The enhanced absorption is due to high porosity and epithelial permeability. By the nasal administration, the drug released can be controlled.

Advantages

- Self-medication and painless.
- Nasal administration can be given in some conditions like severe nausea and vomiting.

Disadvantages

- It is mostly used for potent drugs as only limited volume can be sprayed in the nasal cavity.
- Continuous administration of drug can affect the nasal epithelium[34].

Examples

- Zolpidem Mucoadhesive Formulations for Intranasal Delivery were formulated[104].
- Effect of mucoadhesive additives on the nasal residence time and effect of antibody on the intranasal influenza vaccine were evaluated[105].
- Rizatriptan benzoate contained new *Hibiscus rosasinensis* polysaccharide mucoadhesive nasal gel were developed[106].
- Naratriptan hydrochloride thermoreversible mucoadhesive in-situ gel were formulated and evaluated for nasal drug delivery[107].

Nasal microspheres

Water-insoluble microspheres are used for the nasal drug delivery systems. These microspheres absorb water into their sphere's matrix which causes the swelling of the spheres and the formation of a gel. The additives used in the preparation of microspheres are dextran, hyaluronic acid, starch and albumin. The low-molecular weight drugs can be delivered in microspheric preparations. The cavity of microspheres enhances the retention time of drug.

Examples

- ApxIIA contained mannan-decorated mucoadhesive HPMCP microspheres were formed for nasal drug delivery system[108, 109].
- Diltiazem hydrochloride chitosan-based spray-dried nasal mucoadhesive microspheres were evaluated[110].
- Mannan-decorated thiolated Eudragit microspheres were formed for used as nasal vaccination[111].
- Nasal Microspheres were formed which contained Hydroxypropyl-β-cyclodextrin on β-Amyloid[112].

Nasal liposomes

Liposomes are one of the alternatives forms of doasage form. Liposomes are used for that drugs which cannot be properly given by a solid dosage form and are less soluble. These are spherical vesicles having at least one lipid bilayer and are comprised of phospholipids.

Examples

- Effect of BSA spray-dried liposomes were evaluated for nasal drug delivery[113].
- Mucoadhesive liposomes for nasal drug delivery were formed which are used to treat influenza virus vaccine in chickens[114].

Rectal route

In the rectal drug delivery system, the medication and other fluids is given in the rectum. The drug is absorbed by the blood vessels which are present in the rectum and flow into the body circulatory system. This route is used for both local and systemic treatment. Absorption of the drug in lower part of the rectum results in bypassing the first-pass metabolism thus preventing the degrading of the drug.

Examples

- Mucoadhesive and sustained release mesalamine loaded formulations were formed which is used to treat ulcerative colitis[115].

Rectal nasal gels

Gels are transparent or translucent dispersion of liquid molecule within a solid continuous phase and are considered as cross -linked diluted systems.

Examples

- Nimesulide contained poloxamer as novel carrier mucoadhesive gel for rectal drug delivery[116].
- Quinine based poloxamer hydrogels were formed for the rectal drug delivery[116].

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Table 5: Showing recent drugs along with various polymers used

S No.	Drugs	Polymer	Dosage form	Uses	Delivery System	References
1	Zolpidem	HPMC, sodium carboxy methyl cellulose and sodium alginate.	Oral	Insomnia	Intranasal	105
2	Cyclosporine A	Chitosan	Nanoemulsion	Cornea transplant rejection. Kerato conjunctivis sicca (dry-eye disease).	Ocular	85
3	Cefuroime axetil immediate release	Poloxamer 188 and Sylysia 350	Minitablets	Treat bacterial infections	Oral	117
4	Cefuroime axetil sustained release	Chitosan, HPMC K 100M and sodium carboxy methyl cellulose	Minitablets	Treat bacterial infections	Oral	117
5	Brazilian green propolis extract	poloxamer 407 and carbopol 934P	Nanocculsive	Treatment of Lesions Caused by Herpes	Topical	118
6	Cellulose triacetate	Gellan gum	Films	NSAIDS	Oral	119
7	Bidens pilosa L. (Asteraceae)	Poloxamer	Liquid	Reduce intestinal injury	Intraperit oneal (mice)	120
8	Naratriptan hydrochloride	carbopol 934 , poloxamer 407	Gel	Migraine headaches	Intranasal	121
9	5-aminosalicylic acid and curcumin	Thiolated chitosan, alginate	microparticulate	Treatment of colitis	Multi drug delivery system	122
10	ApxIIA toxin	Thiolated hydroxyl propyl-methyl cellulose phthalate(HPMCP)	Microspheres	Used against *Actinobacillus pleuropneumoniae*	Nasal route	109
11	Antigen BLSOmp31	Poloxamer 407 (P407) and chitosan	in situ gel	for prevention of ovine brucellosis	vaccine delivery system	123
12	Combined form of doxorubicin and peptide-modified cisplatin	chitosan–polymethacrylic acid	Nanocapsules	Used for chemotherapy of bladder cancer	Oral	124
13	Metoprolol Tartrate	Alginate	Floating beads	Treat hypertension	Oral	125
14	propranolol hydrochloride	chitosan–gelatin	Tablets	treat tremors, angina , hypertension	Buccal	126
15	Ibuprofen	Chitosan	colloidal nanocarriers	To reduce fever and pain	Ophthalmi c	127
16	Albendazole	Chitosan	Matrix tablet	Anthelmintic	Oral	128
17	Tramadol hydrochloride	different grades of PVP K-90 and PVP K-70 and chitosan	Films	effective against pain	Buccal	129
18	Combined form of pioglitazone and felodipine	PEON80, amount of HPMCK4M	Pellets	Treat diabetes and hypertension	Buccal	130

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19	Ziprasidone	crosslinked of low-methoxyl pectinate–sterculia gum	Beads	Antipsychotic drug	intragastric	131
20	Garcinia mangostana	chitosan and thiolated chitosan	Nanofibre mats	Antibacterial activity	Oral	53
21	Simvastatin	Tamarind seed xyloglucan	Matrix tablets	Reduce the cholesterol level	gastric retentive drug delivery	132
22	propranolol hydrochloride	Chitosan	gel	treat tremors, angina, hypertension	Transdermal delivery	133
23	Metronidazole	Chitosan	Capsule	*Used Clostridium difficile* infections	gastrointestinal tract	134
24	Nystatin	sodium carmellose	Films	antifungal	Oral	52
25	amoxicillin trihydrate	sodium alginate, hydroxypropyl methylcellulose and chitosan	Floating beads	Used against *Helicobacter pylori*	Oral	135
26	diclofenac sodium	Combination of natural gum isolated from Prunus cerasoides and sodium alginate	beads	Reduce pain and inflammation	Oral	136
27	Curcumin	Chitosan	Nanoparticles	Reduce inflammation	Oral	137
28	sOfloxacin	Carbopol 934 and Carbopol 940 and Hydroxypropyl methylcellulose	suspensions	Antibacterial	Oral	138
29	Indomethacin	Pluronic®F127	Micelles	Used in arthritis, gout, bursitis, and tendonitis	micellar drug delivery	139
30	clotrimazole	Chitosan	Microparticulate	Treat yeast infections	Vaginal	140

Mucoadhesive polymers		
Natural polymers	**Semi-synthetic polymers**	**Synthetic polymers**
• Gellan gum[119] • Sodium alginate[135] • Gum isolated from *Prunus cerasoides*[136] • Tamarind seed xyloglucan[132] • Alginate125 • Sterculia gum131 • Lectins141 • Gelatin126 • Cedrela gum142 • Cashew gum52 • Locustbean gum143	• .HPMC138 • Sodium carmellose52 • Thiolated hydroxyl • propyl methyl cellulose phthalate109 • Sodium Carboxymethyl cellulose117	• Chitosan[52] • Carbopol 934130 • Carbopol 940130 • Thiolated chitosan50 • Poloxamer 407123 • Carbopol 934P118 • crosslinked low-methoxyl pectinate131 • PVP K-90129 • PVP K-70129 • Poloxamer120

CONCLUSION

The study on mucoadhesive system contains the variety of aspects. It is a marvellous examination which focuses on the development of novel products and polymers. It also developed the novel methods that would enhance of the mucoadhesion process phenomenon. Mucoadhesive polymers may play a vital role to enhance the bioavailability of the drug by prolonging the retention time at the application site and bypass the first pass metabolism in the GIT and hepatic first-pass elimination. This review focused on the study of different aspects of mucoadhesion. The structure of mucus membrane gives

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the better understanding of mucus membrane, mucoadhesive theories and the study of mucous mimetic materials which are beneficial for the evaluation of mucoadhesion formulations. Also the remarkable advancement has been made in the field of mucoadhesion but still there are many difficulties ahead. However, the novel mucoadhesive formulations were developed for the treatment of both systemic and topical diseases.

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