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Review Article

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Mucoadhesive Polymer-Based Formulations for Drug Delivery

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ABSTRACT

Over the years, muco-adhesive systems, have been explored in order to obtain a controlled and efficient drug delivery. These systems also provide therapeutic benefits and increased retention time. Muco-adhesive polymers are biopolymers that adhere to the mucosal surface layer for an extended period of time. There are certain muco-adhesive systems that have the tendency to be easily eroded, tasteless and possess low cost. With these properties, they can reduce dosing frequency and also enhance patient safety. Although there are limitations that hinder the performance of muco-adhesive systems such as permeation and enzymatic barriers of the mucosa, these challenges could be overcome by research and development (R and D). The aim of this review was to elaborate on the different aspects of muco-adhesive polymers which include majorly the mechanisms, theories, principles and properties.

Keywords: Controlled Delivery, Drug Delivery, Muco-Adhesion, Retention Time.

INTRODUCTION

The term muco-adhesion refers to the ability of a material to adhere to a surface over a certain period of time [1]. Some of the routes that have deployed this muco-adhesive technique include: buccal, nasal, vaginal and rectal routes in drug delivery system [2-6]. Scientists have documented the ability/tendency of muco-adhesive drug delivery system to increase retention time at the site of action. This is achieved by two major processes such as gastric enzyme modification and first-pass hepatic metabolism by-pass [7]. For drugs that are easily degraded in the acidic and alkaline environments, low enzymatic activity plays a major role in improving the

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bioavailability of such drugs [8]. There are certain muco-adhesive systems that have the tendency to be easily eroded, tasteless and possess low cost. With these properties, they can reduce dosing frequency and also enhance patient safety [9]. Although, there are limitations that hinder the performance of muco-adhesive systems, these challenges could be overcome by research and development (R and D) [10]. There are many factors that affect the formulation of a muco-adhesive system which include: the type of polymer, biocompatibility and release rate mechanisms.

THEORIES OF MUCO-ADHESION

Some major properties that are useful in muco-adhesive drug delivery system include: swelling, wetting, surface area, contact angle and water absorption rate.

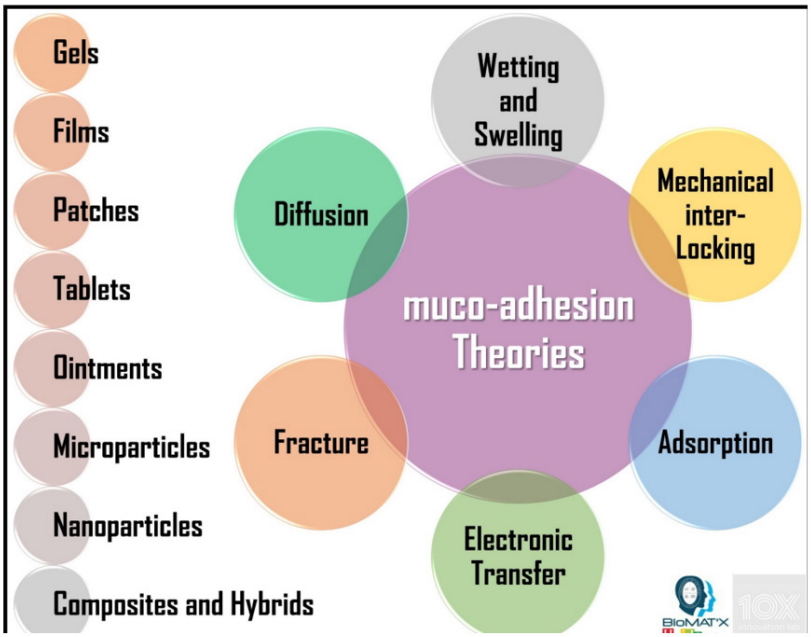

Figure 1. Summary of muco-adhesion theories [11].

Types of muco-adhesion theories.

Wetting Theory

This theory explains the molecular content that occurs between two materials [12]. The theory also demonstrates the relationship that exist between the formulation and the mucosal surface. The concept of spreadability exists between the adhesive and cohesive forces that act on a particular system [12-15]. The adhesive force that exists between the liquid and the surface of the substrate enables the liquid to spread. This ensures that the shape of the droplet is maintained. Contact angle less than 90o favors wetting more when compared to a contact angle greater than 90o, thus is an inverse relationship that exists between the spreadability of a single drop of liquid and the contact angle [16].

Mechanical inter-locking theory

Surface irregularities that some polymers exhibit could be caused by low surface tension and high spreadability coefficient [17]. This theory explained that the adhesion on the surface of a liquid and a rough surface could be caused by increased surface rigidity [18]. This theory explains what happen to the adhesion that exists between a liquid and a rough surface. One of the limitations of this theory is its inability to explain the adhesion substrates with smooth surfaces. A strength that is intermediate, exits between the adhesive and the oxide. This will increase the toughness on the interface.

Adsorption theory

This theory explains the adhesion that occurs on the surface contact of a material. Due to the nature of the substrate surfaces, weaker secondary bonds such as hydrogen bonds, Van der Waals forces and electrostatic attraction are more desirable than stronger primary bonds which include both the ionic and covalent bonds 20-22 Chemisorption is the term that explains the chemical bond that form across the interface.

Electronic transfer theory

This theory talks about the relationship that involves both substrate and mucus membrane [20]. The difference in electronic properties leads to a double layer of electrical charges at the interface of the mucosal layer [20]. The muco-adhesive layer strength depends on the forces within the electronic double layer.

Fracture theory

Fracture theory also known as adhesive strength is a force that exists in two separate adhered surfaces [21,22]. The performance of the system is affected by three key factors: environmental factor, physiological factor and the bio-polymeric factor. The usefulness of this theory is applicable only on single component rigid muco-adhesive materials that possess a defined structure at the interface.

Diffusion Theory

This theory explains the relationship that exists in the penetration between mucoadhesive and glycoprotein chains. There are different factors that influence the penetration rate such as diffusion coefficient and flexibility [23,24].

Table 1. Different categories of muco-adhesion theories

Type of theory	Concept
Wetting	This is suitable for liquid bio-adhesives. These adhesive agents have high tendency to spread on the surface.
Mechanical inter-locking	This theory explains that mechanical inter-locking is responsible for the adhesion in a liquid and a rough surface.
Adsorption	Adhesion that occurs between the mucus adhesive device and the membrane.
Electronic	Electronic transfer between the mucus adhesive surface and the membrane.
Fracture	Established the force required to detach two surfaces
Diffusion	It explains the formation of a bond and also the relationship that exists between the adhesive force and the degree of penetration.

MUCO-ADHESION MECHANISM OF ACTION

Due to the ability of muco-adhesive system to be held by inter-facial forces, the tendency to promote local drug concentration is high. Modulation of the dosage form is affected by two principal stages such as the contact and the consolidation stage [7].

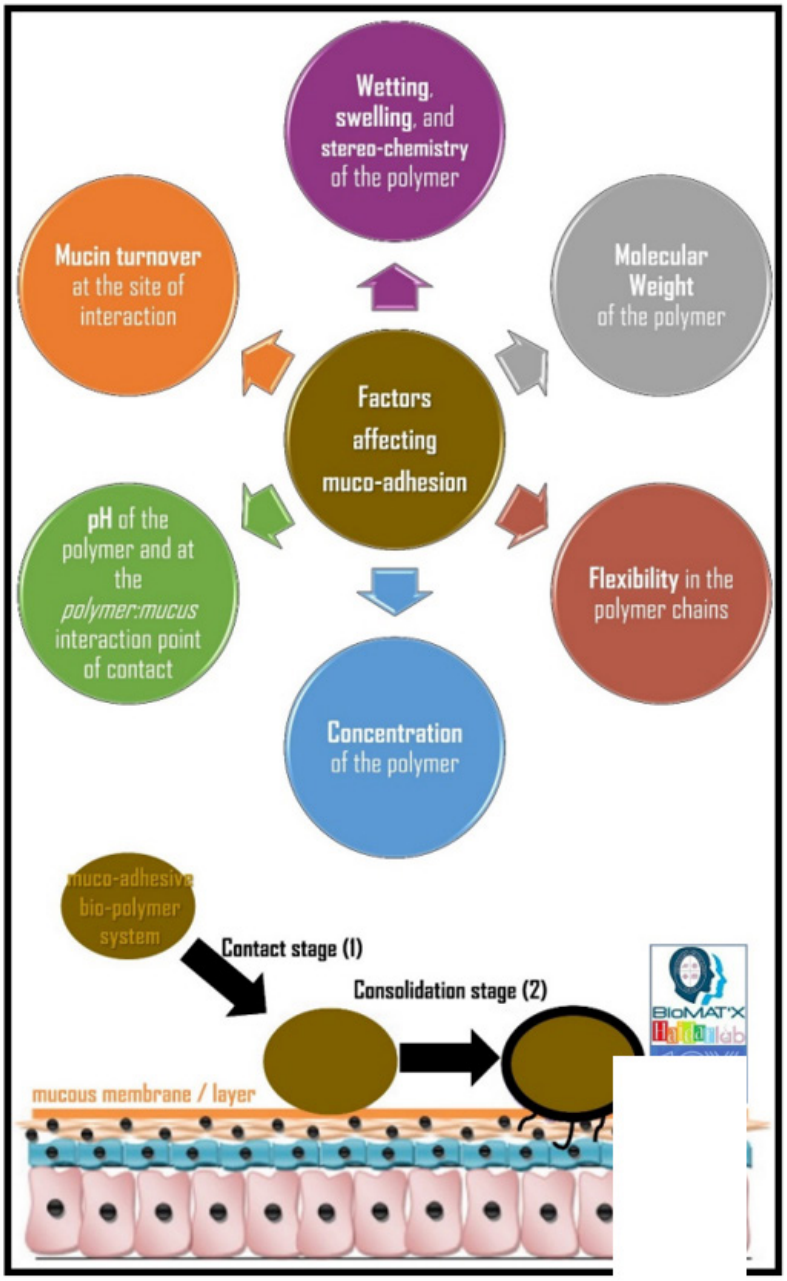

Figure 2. Mechanism in muco-adhesion drug delivery [11].

The contact stage involves the connection that exist between the muco-adhesive polymer film and the mucosal membrane. The formation of the muco-adhesion is the first initial step, which enhances the intimate contact with the mucosal membrane [25,25].

The second stage known as consolidation stage, involves activation of the muco-adhesive materials by moisture in order to plasticize the system and allow free bonding with hydrogen bond and van der Waals [27,28]. The muco-adhesive strength is affected by the contact of the mucus gel layer and the hydration of the dosage form. Dehydration theory, explains that the contact these polymers have with the aqueous environment is what causes the water to move until equilibrium is established [28]. For solid or extremely hydrated formulations, the dehydration theory cannot apply.

THE MUCO-ADHESIVE DRUG DELIVERY SYSTEMS AND THEIR DEVELOPMENT

Evaluation of muco-adhesion system

Several reports have been documented on both the process and development of much-adhesion. Three main tests exist in the development of muco-adhesion. They include tensile, shear and peel strength. Among the three texts, the most commonly used one is the tensile strength [29,30].

Delivery sites for muco-adhesive drug delivery systems

Increase in residence time, requires that the muco-adhesive dosage forms must be in contact with the absorbing surface. There are certain areas of the body that have higher advantage of mucus-adhesive drug delivery due to the high concentration of the mucosa lines in such regions. They include the conjunctiva, vagina, nasal cavity and the oral cavity [30,31].

Buccal cavity

This is the preferred location for drug delivery due to its ease of access. This is achieved by by-passing hepatic first-pass metabolism and local oral lesion treatments [2,32]. The mucoadhesive formulation is more controlled in the buccal mucosa, thus making it suitable for such drug delivery. The drug delivery system of buccal and sub-lingual, could be in form of tablets, film or spray formats.

Ocular cavity

There are different regions in the eye that have been explored in topical treatment such as the iris, cornea, conjunctiva and anterior chamber. The region that gets the desired response to treatment is the eye conjunctiva due to the mucin secreted by the goblet cells [31].

Reproductive lumen

The hepatic first-pass metabolism could be by-passed by the systemic vaginal delivery and this ensures that the dosing frequencies are lowered and that it remains in the vagina for prolonged period [30,31]. This route has a major challenge associated with it, which is the issue of migration of the drug within the vagina. But with the use of muco-adhesive polymers, the migration is minimized and this helps to improve the therapeutic efficacy of the drug [31].

Nasal cavity

The presence of glycoprotein and mucin has been recorded in the nasal cavity. This nasal cavity increases both the extent and rate of drug absorption. The surface area of the nasal mucosal layer ranges from 150-200 cm.

MUCO-ADHESIVE BIOPOLYMERS

Characteristics of bio-polymers

In terms of adherence to surfaces of biological origin, polymers are classified into three major classes. They include: non-covalent polymers, hydrophilic functional groups polymers and receptor site polymers [2]. Another classification of polymer is based on hydrophilic, hydrogels or thermoplastic [36]. Biopolymers should possess some distinct characteristics such as: non-irritant, non-toxic, biodegradability, longer shelf-life and cost-efficient [2].

Factors that affect muco-adhesion

Hydrophilicity

The hydrophilic functional groups enhance the bonding between hydrogen and substrate. This ensures their exposure to anchor sites [2].

Molecular weight

Bio-polymers allow for inter-penetration and entanglements respectively, thus improving muco-adhesion.

Cross-linking and swelling factor

It could be affected by biopolymer concentration, ionic strength and water concentration. The degree of swelling is inversely proportional to the cross-link density.

pH

This applies to the role of ionizable groups and polyanions [31]. Large ionization is associated with local pH level, higher than the polymer pK.

Active bio-polymer concentration

Increase in polymer concentration, leads to a decrease in access to the polymer chain. This leads to a decrease in adhesion due to the limited available chain length or mucoadhesion strength and polymer concentration are related for solid dosage forms [32].

POLYMERS AND THEIR APPLICATIONS IN DRUG DELIVERY

Chitosan

Chitosan is a natural, biocompatible, and biodegradable polysaccharide, derived from shell-fish, that has been extensively used for wound closure, hemostatic, and other applications and that is soluble in aqueous solutions with pH less than 6.5 [32,33]. Lehr *et al.* evaluated the muco-adhesive properties of chitosan in vitro by measuring detachment forces for swollen pig intestinal mucosa polymer films in saline media [34]. Whereas natural polymers hydroxypropyl- and carboxymethylcellulose exhibited almost no muco-adhesion, the cationic polymer chitosan was muco-adhesive relative to Polycarbophil. Further, He *et al.,* evaluated the muco-adhesive properties of chitosan microspheres *in vitro* by measuring the mucin absorbed on microspheres and using turbidimetric measurements [35]. Adsorption studies between mucin and chitosan microspheres with varying crosslinking studies indicated strong interactions [35]. Chitosan microspheres were also retained in biological tissue. In another study, Sogias et al., investigated the interactions between chitosan and gastric mucin to understand why this polymer is muco-adhesive [33]. Decreasing the number of amino groups enhanced the pH solubility window of chitosan yet decreased its ability to aggregate mucin. Although the electrostatic attraction interactions between chitosan and gastric mucin can be inhibited with 0.2 M sodium chloride, these forces do not suppress aggregation of mucin particles when chitosan is present [33].

Mussel Adhesive Protein (MAP) MAP, or mussel adhesive protein

This is a 130-kDa protein that adheres to underwater surfaces [36]. MAP is likely muco-adhesive and it contains DOPA, which has a hydrogen bond capability that has been attributed to its ability to interact with mucosal surfaces [37].

Carbopol 934P

Carbopol gels in water have also been evaluated for their muco-adhesive properties [38]. Tamburic et al., evaluated Carbopol 934, rheologically, with continuous shear, creep, and oscillatory measurements [39]. When compared to other gel systems, Carbopol 934 had the highest degree of gel network elasticity and viscosity, with low thixotropy. Tamburic et al. also investigated the muco-adhesive properties of different polyacrylic acid gel systems [40]. When compared to EX-214 and Noveon AA-1, Carbopols 934P and 974P had the greatest muco-adhesive strength and had small differences between these two systems due to the neutralizing agents. In addition, there was a correlation between muco-adhesive strength and rheological tan δ (phase lag) values. Furthermore, Carbopol has been combined with other polymers to develop a drug delivery system with a mucoadhesive-controlled release [38].

Spider Silk

This is a strong polymer that is biocompatible, biodegradable, non-toxic, and lightweight. Spider silk has great potential to be used as an adhesive material [41]. They have inspired several polymer blends, including 4RepCT variants, aggregate silk, and pyriform silk, yet require further research to explore the potential of each polymer as a mucoadhesive [41].

CONCLUSION

The residence time and contact time between bioactive drug and polymer can be increased with muco-adhesion delivery system. Some of the limitations associated with these sites such as permeability, stability, drug-loading enhancement and muco-adhesion strength are being investigated by most of the recent advances. Also, the use of nanoparticles and hydrogels in formulations are been considered in muco-adhesive drug delivery systems [33,34]. There are some potential muco-adhesive systems that are being explored with different synthetic rate controlling agents such as poly (acrylic acid)-based polymers. Polymer manipulation is essential for controlling the absorption rate and bio-availability of drugs, which may lead to promote advanced treatment approaches and superior therapeutic outcomes.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

AUTHORS CONTRIBUTION

Ezegbe CA: investigation, visualization, writing editing, Ezegbe AG: writing, editing, Anikwe CC: writing, editing, Okafor NP: writing, editing, Onyia OO: writing, editing, Agu AA: writing, editing, Ugorji AC: writing, editing, Uchenna CP: writing, editing, Onoduagu Simeon Chinedu: writing, editing, Dingwoke Juliet Obianuju: writing, editing, Onyekwere Favour Ezinne: Writing, editing.

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