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Mini Review

Mucoadhesion of Polymeric Drug Delivery Systems: Polymeric Nanoparticles and its Interactions with the Intestinal Barrier

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Abstract

The oral route is the most common and physiological way to administer drugs. Nevertheless, this drug delivery route is always associated to intrinsic difficulties. For instance, some drugs are poorly or non-absorbable in the intestine and cannot access the systemic circulation. On the other side, when the desired effect is topical into the intestinal mucosa, the major disadvantage is the clearance of the drug through absorption to systemic circulation or the excretion due to intestinal motility. Several drug delivery systems have been developed to modify drug absorption, according to the desired activity.

Intestinal mucus is a complex, viscous and elastic layer that can importantly affect drug delivery. The attachment of molecules to the mucus and/or the epithelial surface is therefore worth to investigate. Thereby the resident time of the drug can be increased at the absorption or targeting site. Future strategies are heading into the combination of mucoadhesive and mucopenetrating particles to modify the absorption, and facilitate targeting to the intestinal mucosa.

Thanks to these drug delivery systems, and through several strategies, first pass effect can be avoided, the drug bioavailability can be increased, or targeting to the mucosa can be achieved. In this sense, drugs can be delivered in a very slow release rate, increasing its permanence onto the tissue, producing local effects while reducing the systemic side effects. The nature of the polymer is a key factor to achieve an effective mucoadhesion. Their molecular weight, viscosity, degree of cross-linking, flexibility, concentration and pH have been described as properties affecting this behavior, being the degree of ionization the most important ones. Anionic polymers have showed higher mucoadhesive strength than cationic and non-ionic ones.

In summary, mucoadhesive drug delivery systems are being developed with the aim to provide more effective dosage forms for oral administration. Encapsulation of drugs in different polymers can help retaining the drug on the absorption membrane, which is in this case, also the target tissue, increasing the compliance of the patient.

INTRODUCTION

To lead to the appropriate plasma peaks, which are directly related to the therapeutic effect and the ability of the drug to reach the target organs, drugs need to be absorbed through several biological barriers. The most used administration way nowadays, due to its comfort for the patient is the oral one, as it is pain-free and a physiological administration route for nutrients [1]. The intestine is the tissue of the GI-tract that mainly regulates the extent of absorption of orally administered drugs. Furthermore, the intestine and the liver are also involved in the first-pass effect, which would clear part of the absorbed drug [2,3]. The highest drug absorption rate is most frequently observed at the small intestine, due to its large surface area and the presence of villi and microvilli, structures, which greatly increase the absorption area [4].

However, this absorption route is not free of drawbacks and not all drugs can be easily absorbed via this route. Factors such as chemical instability within the stomach, gastric emptying time, intestinal transit time, and inability to diffuse through the intestinal wall can all reduce drug absorption after oral administration, leading to lower bioavailability [5]. Poorly absorbable drugs via the intestinal route have traditionally needed to be administered via intravenously, which is much less comfortable for the patient or by inhalation, whose inaccurate dosing may lead to failure of the therapy [6].

In the last decades, drug absorption of poorly absorbed drugs has been regarded as a challenge and has been extensively investigated from different points of view. Today, several drug delivery systems have been developed to modify drug absorption. Several attempts have been done to locate drugs on a specific target site, to obtain prolonged drug release rates and thus reduce dosing. Also, to achieve a delayed release while bypassing, for example, the acidic environment of the gastric content, to increase drug solubility or to promote the absorption

of low absorbable drugs, this last strategy leading to higher bioavailability ratios [7].

One of these very promising attempts to increase drug bioavailability is the formulation of these drugs in micro- and nanoscaled drug delivery systems, which have become more and more popular among researchers in the last years [8]. These drug delivery systems can be effective independently on the physicochemical properties of the drug rather than the chemical structure and reactivity. Among all these devices, liposomes [9,10], solid lipid nanoparticles [11], polymeric micelles [12,13], polymeric particles [14], microemulsions [15,16], and others, can be cited. The intended strategies of these drug delivery systems are also varied but all are focused on targeted (local, direct application onto colon, etc.) and/or controlled drug delivery (absorption enhancement, prolonged drug delivery, spaced drug delivery, etc.).

In general, after oral administration, nano- and microparticles can follow three different pathways: direct transit and elimination, bio- or mucoadhesion, and/or oral absorption (Ponchel and Irache, 1998) [17]. The identification of these three pathways is of major importance to forecast the drug delivery of the designed particles and are the main focus of this review.

The mucus layer and its interactions with oral drug delivery systems

Mucus is a complex aqueous mixture of water, glycol proteins, lipids and salts covering several epithelial surfaces in the body, as it is the case of the gastrointestinal tract. Mucosal membranes cover several body cavities, and mucus layers, which act as adhesive barriers, protect mucosal tissues [18]. Mucoadhesion is defined as the attachment of a synthetic or natural macromolecule to the mucus and/or an epithelial surface, phenomenon that can improve controlled drug delivery by attachment of the carrier in close contact with the mucosa [19].

When studying the interaction of micro- and nanoparticles with the oral mucosa after administration, it has been observed that they often interact with this layer, whose rheological behavior is the one of an elastic hydrogel and can extensively modify the absorption of drugs. The viscous, elastic and sticky mucus layer is able to rapidly trap and remove xenobiotics, such as drugs or excipients [20]. This mucus layer can difficult the passage of the drug, but mucoadhesion, in combination with a smart drug delivery system, can be taken as an advantage. Through this strategy in the residence-time of the drug in the lumen can be highly increased, thus enhancing the local therapeutic effect of the drug. This strategy can also lead to a prolonged drug delivery to systemic circulation of a drug with good oral biovailability, if the dose and the release rate of the drug delivery system are conveniently adjusted [7]. There can also be a prevention of intestinal first pass metabolism, or drug instability due to the acidic environment of the stomach, because the carrier can be designed to protect the drug from these issues. Finally, some carriers can enhance or allow drug permeability of drugs, which are unable to be absorbed by the GI-tract. All these advantages allow an easier and safer drug administration that will lead to a higher compliance by the patient [21].

Drug delivery systems interact with the different mucosal membranes and are useful either to prolong the residence time of the drug at the absorption/targeting site, or to enhance the permeation of the particles across the mucus layer to directly reach the underlying epithelium [17]. Mucoadhesive particles have several advantages in delivering drug molecules to the mucosal membranes. Besides, to achieve a broader particle distribution and a deeper penetration, mucopenetrating particles can also be designed, especially to target the gastrointestinal tract. The choice of the nanoparticle type depends mostly on the therapeutic target, and on the properties of the mucosa, as well as on the thickness of the mucus layer, mucus turnover rate and water movement within the mucus. The future strategies are heading towards the combination of both systems into one [22].

Mechanisms of mucoadhesion

The mechanisms of interactions between polymers and mucus have also been extensively studied. Various theories of adhesion have been suggested, but none has still been categorically accepted. Nevertheless, two basic steps are generally accepted. Step I, the contact stage, in which an intimate contact between the mucoadhesive particle and the mucus gel layer is formed. In step II, the consolidation stage, the adhesive joint is strengthened and consolidated, providing a prolonged adhesion [23].

The most accepted theories about how adhesion takes place are summarized below [24]:

- The adsorption theory suggests that the attachment of adhesive particles is due to the establishment of covalent bonds, hydrogen bonds and/or van der Waals forces, depending on the nature of the materials used for particle design.

- The electronic theory proposes the formation of an electrical double layer at the interface particle-mucus, due to the transfer of electrons upon contact by differences in the electronic structure of the mucus and the adhesive system.

- The *wetting theory* has primarily postulated in the case of liquid systems that present affinity to the surface and can therefore spread over it. It is defined by the contact angle and the energy needed to separate the two phases.

- The diffusion or interpenetration theory describes how mucoadhesive agents interpenetrate to sufficient depth into the mucus glycoproteic network. This interaction would lead to a strong semi-permanent adhesive bond. The depth to which the polymer chains penetrate depends on their own diffusion coefficient and the duration of the contact. The polymeric chain flexibility is here a crucial parameter favoring an effective interpenetration.

- The fracture theory describes the forces required for the detachment of the two involved surfaces after adhesion. However, the detachment does not occur at the exact contact point between the adhesive and the mucus layer, but typically, at the weakest point of the system, which is the cohesiveness of one of the compounds.

- The mechanical theory suggests an interlocking of a liquid/semisolid adhesive into irregularities on a rough surface or cavities of the mucosa.

- The mucus dehydration theory assumes that dehydration of a mucus gel layer can increase its cohesive properties and promote the retention of an adhesive system.

However, because of the regular renewal of the mucus layer on the surface, mucoadhesion duration will be limited [25]. Therefore, if this is the aim of the formulation, drug release and adsorption should be completed before clearance of the mucus with the attached particles. In this case, direct attachment to the surface of the cells of the mucosa would be preferred, although specific interactions between a receptor present at the cell surface and a ligand should be established. Furthermore, particles are often unable to diffuse or be absorbed through the mucus layer or into the epithelial cells [17].

Factors affecting mucoadhesion

Several substances with bioadhesive and mucoadhesive properties have been studied to improve oral drug delivery. There are properties that should be taken into account when selecting a polymer, because its chemical and physical properties will determinate the level of adhesion, but also the drug release properties and its interactions with the drug and the mucosa.

Two of the most important properties are the charge and degree of ionization of the polymer. The mucoadhesive strength can be ordered as anion > cation > non-ionic, so the anionic polymers will be the more mucoadhesive and the non-ionic will be the less ones [21]. However, it should be taken into account that the mucus layer is negatively charged [26] and the intestinal mucosa is positively charged [27]. Therefore, the ionic interactions are of high importance to achieve successful delivery and should not be disregarded in the search of effective mucoadhesion. Anionic polymers as polyacrylic acid and carboxymethyl cellulose exhibit strong hydrogen bonding with the mucin in the mucosal membrane. They are the most widely used mucoadhesive polymers in the pharmaceutical industry because of their high mucoadhesion strength and their low toxicity. In the group of cationic polymers, one of the most used is Chitosan, formed by the deacetylation of chitin, which is also popular due to its good biocompatibility and easy degradation [28].

Poloxamer, methylcellulose or polyvinyl alcohol are examples of extensively selected among the uncharged polymers [29]. The last group of mucoadhesive particles that are in use are lectins, which have gained increased attention in the last decade, as they can naturally bind specifically to free sugar residues of polysaccharides, glycoproteins or glycolipids, free or bounded [30]. Lectins are especially good candidates for oral drug delivery as they can resist the acidic pH and enzymatic degradation of the GI-tract environment [31]. The main problem is that the binding is only possible if the corresponding sugar moieties are available in the mucosal epithelium, so these carriers are still in development.

The molecular weight of the drug-carrier constituent is also a key factor. To enhance mucus adherence, it is recommended to use high molecular weight polymers, although there is usually an optimal length, to assure the contact and drug diffusion of the drug, without allowing the carrier to diffuse through the mucosa [17].

The degree of cross-linking should be moderate. Highly cross-linked polymers swell in the presence of water losing their compact structure and therefore favoring release of drug in an uncontrolled manner. As the cross-linking increases, the mobility of the polymeric chains decreases, allowing a better control in drug release, thus improving mucoadhesion.

The polymer chain needs to be flexible and the concentration of the polymer will be very important as well, but will depend on the desired dosage form. In addition, it has also been observed that mucoadhesion is optimum at low pH conditions [21].

Mucoadhesive nanoparticles

Several kinds of Mucoadhesive nanoparticles have been designed aiming prolongued residence time on mucosal tissues. In this context, thiolation of the polymers has been extensively studied to improve mucoadhesive properties of polymeric particles by forming disulphide bonds with cysteine-rich domains of mucus glycoproteins. In addition, mucosal permeation properties are enhanced by a gluthation regeneration mechanism. Finally, they have potential antiprotease activity due to their ability of binding divalent cations such as Zn^{2+} or Mg^{2+}, which are cofactors of many proteases [32-34]. All these characteristics make thiolated chitosan very promising materials for the mucosal administration of peptides and proteins. A good example is the cysteine-ethyl-esther/polyacrylic acid nanoparticle type, designed by [35] and synthesized by attachment of cysteine ethyl ester to polyacrylic acid. For this nanoparticles, it has been observed that the higher the degree of thiolation of the polymer, the higher the viscosity and the residence time [35]. Another example of these new nanoparticles is the thiopyrazole-preactivated chitosan polymer. Müller et al developed 3-methyl-1-phenylpyrazole-5-thiol (MPPT) microparticles for this purpose, to which they added chitosan. For these particles, an increased stability of the polymeric matrix was observed, as well as an improved ability to absorb water and release fluorescein isothiocyanate dextran (FD4), in comparison with non-thiolated chitosan. In addition, the mucoadhesive qualities on porcine intestinal mucosa could be improved 38-fold, due to a thiol/sulfide exchange reaction between the chitosan-S-S-MPPT and the mucus. Furthermore, this biomaterial can be used to design formulated disulfide conjugation-based delivery systems, able to release the antibacterial thiopyrazole when they contact the intestinal mucosa. All these properties, added to the safe toxicological profile of the new chitosan-based material, make it a really interesting and valuable carrier for this purpose [36].

Soliman et al. studied the effects of incorporating hydrocaffeic acid (HCA) to chitosan nanoparticles, which resulted in an enhancement of the chitosan mucoadhesion, which was 6 times higher than unmodified chitosan in rabbit small intestine. Furthermore, these conjugates also facilitated the permeability to hydrophilic molecules, in particular to fluoresce in isothiocyanate-labeled dextran [37].

Mucus penetrating thiomer nanoparticles have also been developed by Köllner et al. with thiolated poly-(acrylic acid). These particles have mucolytic properties to promote particle diffusion into deeper mucus regions before the adhesion takes place. This is mediated by the addition of carbodiimide, cysteine,

and the enzyme papain, which has mucolytic properties, as it disintegrates the mucus decreasing the viscoelastic properties of the mucus layer. The conjugates were co-precipitated with calcium chloride to obtain papain modified (PAA-pap) thiolated nanoparticles (PAA-cys) and (PAA-cys-pap). Due to the presence of papain, these last PAA-cys-pap nanoparticles were able to cleave mucoglyco protein substructures and exhibit a 2-fold higher penetration into the mucus layer compared to PAA-cys. PAP-pap exhibited a 1.9-fold increase. The combination of mucus-permeating and mucoadhesion properties is therefore a promising strategy for the development of new oral drug delivery systems [38].

Albrecht et al. compared different delivery systems based on a thiolated polymer: polycarbophil-cysteine (PCP-Cys) and Eutex®-capsules, which are developed using Eudragit® L100-55 and latex. Magnetic resonance *in vitro* tests were performed, showing that PCP-Cys formulated in Eutex®-capsules had a 1.9-fold higher mucoadhesive properties compared to a conventional enteric-coated capsule [39].

Therefore, based on all these specific-interactions, different types of smart drug carriers are being constantly developed, to enhance drug-carrier mucus interactions [40] and selectively promote drug absorption or increase drug permanence on the absorption site.

CONCLUSIONS

In summary, several mucoadhesive drug delivery systems have been developed and tested with the aim to obtain safer and more effective dosage forms for oral administration. Encapsulation in drug delivery systems such as liposomes and polymeric micelles, micro and nanoparticles or micro- or nanocapsules can help the drug to have the desired distribution in the body, allowing it to reach its pharmacological target at the appropriate concentration. Furthermore, it can reduce or avoid its distribution to other tissues where it can be toxic or simply not desirable, leading to systemic side effects. Encapsulation may also allow the drug to overcome the biological barriers allowing the drug to reach the target site. Finally, these systems can also deliver the drug at a time-controlled manner, being prolonged over time or differed after adhesion to mucus layers that cover several body sites. Especially, this strategy can be used in the case of the oral administration as an advantage, to prolong the contact of the drug with the mucosa, though polymer thiolation to increase specific interactions polymer-mucus [40].

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