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Review Article

Mucoadhesive vs. mucopenetrating particulate drug delivery

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ABSTRACT

Mucus layer is a hydrophilic absorption barrier found in various regions of the body. The use of particulate delivery systems showed potential in drug delivery to mucosal membranes by either prolonging drug residence time at the absorption or target membrane or promoting permeation of particles across mucus gel layer to directly reach underlying epithelium. Mucoadhesive particles (MAP) are advantageous for delivering drug molecules to various mucosal membranes including eyes, oral cavity, bladder and vagina by prolonging drug residence time on those membranes. In contrast, a broader particle distribution and deeper penetration of the mucus gel layer are accomplished by mucopenetrating particles (MPP) especially in the gastrointestinal tract. Based on the available literature in particular dealing with *in vivo* results none of both systems (MAP and MPP) seems to be advantageous over the other. The choice of system primarily depends on the therapeutic target and peculiar properties of the target mucosa including thickness of the mucus gel layer, mucus turnover rate and water movement within the mucus. Future trends are heading in the direction of combining both systems to one i.e. mucoadhesive and mucopenetrating properties on the same particles.

1. Introduction

Mucosal drug delivery offers various advantages including the ability to target local disorders in order to reduce systemic dose thereby minimizing side effects and to promote systemic drug delivery through various routes of administration. Mucosal membranes are found in many regions of the body including eyes, respiratory tract, gastrointestinal tract and reproductive organs. The presence of a mucus gel layer on these membranes, however, is in many cases a huge hurdle for delivering drug molecules to the underlying epithelium.

For a more efficient mucosal drug delivery with micro- and nanocarriers two opposing strategies namely mucoadhesive and mucopenetration are utilized. Mucoadhesive delivery systems are able to adhere to the mucus gel layer leading in particular on mucosal membranes with a comparatively slow mucus turnover to a prolonged residence time of incorporated drugs. In contrast, mucopenetrating micro- and nanocarriers exhibit an improved spreading over the mucosa and can penetrate in deeper mucus regions to some extent reaching even the epithelium of the absorption membrane. Although displaying exactly opposite properties both mucoadhesive and mucopenetrating particulate delivery systems have shown great potential in numerous *in vitro* and *in vivo* experiments leading to a strongly improved local and systemic therapeutic efficacy. How can this be the case? Within this review article we address this key question describing the ratio behind both strategies, their pros and cons as well as their future potential. Moreover, we discuss first developments combining both strategies in the same delivery system.

2. Mucus gel layer and its impact on particle movement

Mucus is a viscous gel layer produced from goblet cells, mucus secretory cells or submucosal glands found on various mucous membranes including eyes [1], gastrointestinal tract [2] and respiratory tract [3]. In case of stomach, mucus is produced by epithelial cells [4] while vaginal fluid results from the mixture of different fluids including cervical mucus [5]. The presence of mucus on the membrane provides protective films for underlying epithelium.

Main composition of mucus is water (up to 95% by weight) [6]. Mucus is composed of, regardless the origin, cross-linked and entangled mucin fibers, sloughed cells, bacteria, lipids, salts, proteins, macromolecules and cellular debris [7–9]. Mucus thickness and pH can vary depending on the location of mucus membrane and numerous additional parameters. In the intestine, for instance, thickness of mucus varies depending on digestive activity and dietary condition [10–12]. An overview about different types of mucosal membranes is provided in Table 1.

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Table 1
Physiological properties of human mucus at different locations.

Mucus membrane	Temperature (°C)	Total mucus thickness (μm)	Firm mucus layer thickness (μm)	Loose mucus layer thickness (μm)	pH of mucus layer	Water movement	Mucus turnover/flow rate
Buccal	36.2–36.7 [102]	70–100 [103,104]	70–100 [104–106]	28 [104]	6.5–7.5 [107]	±[a]	12–24 h [107]
Nasal	30.2–34.4 [108]	10–15 [109]	6 [109]	4–9 [109]	5.5–6.5 [109]	±	Mucociliary clearance: 6 mm/min [110] Transit time: 15–20 min [111]
Pulmonary	32.5–35.5 [112]	5–55 [22]	5–10 [22]	5–10 [22]	7.0 [22]	±	10–20 min [113]
Ocular	34.0 [114,115]				7.8 [22]	±	5.5–7.7 min [22]
Mucus only		0.02–0.05 [22]	n/a	n/a			
Tear film		3 , 6–7 [22]	n/a	n/a			
Gastric (antrum)	37.0	30–300 [116]	110.5 ± 37 [117]	n/a	6.40 ± 0.24 [118]	±	24–48 h [119]
Small intestinal	37.0	150–400 [120]	15.5 ± 4.5 [117]	n/a	5.5–7.5 [121]	+++[b]	
Colonic	37.0	30–280 [122], 700 [123]	5–13 [122]	n/a	7.0 [123]	+++	
Intravesical	37.0	10–20 [124]	n/a	n/a	n/a	±	Depend on urine voiding time
Vaginal	37.0	50 [125]	n/a	n/a	3.5–4.0 [125]	±	1.5 ml/day[c], 6.0 ml/day [46][d]

[a] Low or no water movement.
[b] Pronounced water movement toward the absorption membrane.
[c] Cervical mucus production rate [46].
[d] Vaginal fluid production rate (considerably increased with sexual stimulation) [46].

According to the method used for determination, mucus turnover rate is counted from the time which mucus is secreted by goblet cells and mucus secreting cells until removed from the mucosal membrane and completely replaced by the newly produced mucus [13,14]. As the mucus turnover has great impact on the performance of micro- and nanocarriers in the mucus gel layer, it is described in detail in the following. Generally mucus turnover rate correlates with mucus thickness. The thinner mucus layer exhibits faster turnover rate [15]. The thickness of mucus layer is controlled by the equilibrium between rates of secretion and shedding [15]. In addition, toxic and irritating substances can stimulate mucus secretion resulting in the increasing of mucus thickness. However, stimulated mucus is also rapidly removed from mucous membrane [12]. Table 1 summarizes thicknesses and mucus turnover rates of various mucosal membranes. Regarding the thickness and mucus turnover rate, mucus can be divided into two types: loose and firm mucus [15–17] (Fig. 1).

Loose mucus or sloppy mucus is a type of mucus being found on mucosal membranes including the surface of stomach, small intestine, colon and respiratory tract [16,18]. This type of mucus is easy to be removed by suction and shear [19]. Regarding the composition, loose mucus is composed of high fibrous contents resulting in the water absorption of the fibrous and thus high thickness of the layer [18].

The other type of mucus is firm mucus or membrane-bound mucus. Mucin of firm mucus is typically high molecular mass protein of 0.5–40 MDa and mucin monomers molecular mass of 0.3–0.5 MDa [15]. This type of mucus adheres firmly or anchors to the epithelium surface by a transmembrane domain and forms a layer to protect surfaces. Firm mucus is resistant to the removal by suction and shear [19]. Regarding the firmness of adherence, firm mucus layer is an effective barrier to bacteria, enzymes and toxins. However, the presence of firm mucus on mucosal membranes results in the formation of unstirred-water layer, the barrier for poorly soluble drugs, especially class II and IV of the Biopharmaceutical Classification System.

On certain mucosal membranes and especially in the gastrointestinal tract a constant water movement toward the epithelium has a great impact on the movement of particles in the mucus gel layer. In the small intestine the absorption process of water generates the force to drag the particles and move them closer to the underlying epithelium. The quantity of water absorption from the human intestine was determined to be 0.1–0.2 ml/h cm^2 [20]. This leads to a comparatively much faster movement of particles in mucus than that can be achieved via diffusion due to a steep particle concentration gradient.

Takeuchi et al. pioneered the penetration ability of chitosan-coated liposomes into the mucus layer after oral administration of liposomes to rat by confocal microscopy technique [21]. It was also found that liposomes, both non- and chitosan-coated, exhibiting a diameter of 100 nm can penetrate the mucus layer to the higher extent than larger ones. Therefore, particle size plays an important role in the movement of particles in the mucus. Entanglement of mucin results in formation of dense fiber mesh in mucus gel layer structure. Average mesh size of ~100 nm was estimated from the movement of various size of viruses [22]. Although this mesh size could be confirmed by various electronic microscopic analyses, it should nevertheless be used for orientating calculations with caution, as the mucus is a very dynamic and not a static system. Moreover, this mesh size can be found just in certain microstructure regions of the mucus but not uniformly throughout the entire mucus gel layer. The dense fiber mesh exhibits significant steric inhibition of particle movement and immobilizes particles within the mucus gel layer. The dense fiber mesh blocks the movement of large size particles. Lai et al., for instance, reported that the movement of MPPs as large as 530 nm is in human mucus