REVIEW ARTICLE

Mucoadhesive films as perspective oral dosage form

Mukoadhezivní filmy jako perspektivní lékové formy pro orální podání

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Received 27 November 2012 / Accepted 3 December 2012

Summary

Mucoadhesion is a specific phenomenon of creating bonds during intimate contact between biological surfaces covered by a mucus layer and a mucoadhesive material. In recent years come to the forefront of interest in the pharmaceutical industry modern dosage forms based on this specific process. Films (discs, patches) composed of mucoadhesive polymers (cellulose derivatives, polyacrylates, polyoxyethylene, etc.) prepared by established methods (solvent casting, hot melt extrusion, etc.) could be perspective candidates for oral administration of many drugs due to their flexibility and comfortable use. In addition, they can circumvent the relatively short residence time of conventional oral dosage forms on the mucosa and provide a precisely measured drug dose to the application site. Moreover, they can also help to protect the wound surface, thus help to reduce pain and improve effectiveness of the therapy. The aim of this article is to give an overview about the principles of creation of mucoadhesive bonds and about novel dosage form – mucoadhesive films in terms of their composition, preparation and practical usage.

Keywords: oral mucosa • mucoadhesion principles • mucoadhesive dosage forms • films • patches • discs

Souhrn

Mukoadheze představuje specifický proces vytváření vazeb během těsného kontaktu mezi biologickými povrchy pokrytými slizovou vrstvou a mukoadhezivním materiálem. V posledních letech vstupují do popředí zájmu farmaceutického průmyslu moderní lékové formy založené na tomto procesu. Filmy složené z mukoadhezivních polymerů (deriváty celulosy, polyakryláty, polyoxyethylen atd.) připravené některou ze zavedených metod (odpařování rozpouštědla, extruze taveniny atd.) mohou být perspektivními kandidáty pro orální aplikaci mnoha léků, především pro jejich flexibilitu a pohodlné použití. K dalším výhodám této lékové formy patří zlepšení relativně krátké doby setrvání konvenčních orálních lékových forem na sliznici a dodání přesné dávky léčiva na místo aplikace. Kromě toho mohou také překrytím chránit povrch slizniční léze, což napomáhá ke snížení bolestivosti a zlepšení účinnosti léčby. Cílem tohoto článku je poskytnout přehled o principech vzniku mukoadhezivních vazeb a o inovativní lékové formě – mukoadhezivních filmech z hlediska jejich složení, přípravy a praktického využití.

Klíčová slova: sliznice dutiny ústní • principy mukoadheze • mukoadhezivní lékové formy • filmy • disky

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Mucoadhesion/bioadhesion

Mucus is composed of mucin glycoproteins (0.5–5%), lipids, inorganic salts, nucleic acids, enzymes and water (more than 95%). The mucin glycoproteins are the most important structure-forming components of the mucous, resulting in its gel-like characteristic, cohesive and adhesive properties[1, 2].

In 1986, Longer and Robinson defined bioadhesion as the phenomenon between two materials (a synthetic or natural macromolecule and mucus and/or epithelial surface), which are held together for extended period of time by interfacial forces[3]. In general, "bioadhesion" is a superior term used to describe adhesive interactions with any biological or biologically derived material, and "mucoadhesion" is used only when describing a bond involving mucus or mucosal surface[4].

The process involved in the mucoadhesion phenomenon has been described in three steps: an intimate contact with the tissue resulting from a good wetting of the mucosal surface and swelling of the mucoadhesive polymer; interpenetration of the polymer chains and entanglement with those of mucus; and finally the formation of weak chemical bonds between entangled chains[5].

To date, no single-valued theory has been accepted to explain mucoadhesion as a phenomenon occurring via

one plain mechanism. However, several theories have been developed and used to describe the complex phenomenon of mucoadhesion. Some of these theories are founded on physical interactions (diffusion theory) while others are based on chemical interactions, such as electrostatic, hydrophobic, hydrogen bonding and van der Waals interactions (adsorption and electronic theories)[6].

- *Electronic theory* – the mucoadhesive polymer and mucin glycoproteins have typically different electronic characteristics, resulting in the formation of the electrical double layer at the interface. Attraction across the electrical double layer leads to adhesion of the two surfaces[7].
- *Adsorption theory* – the formation of mucoadhesive bonds could be a result of secondary surface forces such as van der Waals forces, hydrogen bonds and hydrophobic bonds. For bioadhesive polymers with carboxyl groups, hydrogen bonding is considered to be the dominant force at the interface[8, 9].
- *Diffusion theory* – is based on the diffusion and interpenetration of the adhesive polymeric chains and the substrate to a sufficient depth while creating a semipermanent adhesive bond. The penetration rate depends on concentration gradients and diffusion coefficients of interacting polymers (mucoadhesive polymer and glycoprotein chains of the mucus), which are affected by their molecular weight and cross-linking density[10].
- *Fracture theory* – relates the force required for the detachment of polymers from the mucus to the strength of their adhesive bonds. It has been found that the strength of adhesion decreases with increasing cross-linking density of the polymer[11].
- *Wetting theory* – is primarily applicable to liquid or semi-solid mucoadhesive systems and relates the ability of a mucoadhesive polymer to spread over a tissue. This theory uses surface tensions at the interfaces to calculate the spreading coefficient[12].

The mucoadhesion process probably involves all of the above-mentioned mechanisms and the decisive factor establishing the dominant one is the type of the particular mucoadhesive polymer.

Mucoadhesive films

Films or patches are the most recently developed dosage form for buccal administration. In the scientific literature it is possible to find equivalent terms “patches”, “films” and also “discs”. Some reviews include films (especially these forming *in situ*) into the semi-solid form[13]. Films are laminates usually consisting of two or three layers and, thanks to their flexibility and comfortable use, are preferred over adhesive tablets. Small thickness of the film with non-irritating properties and strong mucoadhesiveness of the polymer demand only minimal changes in the patients’ normal activities such as eating, drinking or speaking. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa and provide a measured dose of drug to the application site. Moreover, they can also help protect the wound surface or cover mucosal defects of the oral cavity, which leads to pain reduction[14]. Flexible patches of various sizes allow their adaptation to the morphology of the oral cavity and size of the defect. Structure of films, of used bioadhesive polymers and of other excipients and methods of preparation are described further.

Structure of mucoadhesive films

Till now, a relatively wide range of mucoadhesive films for oral use have been studied. Nafee et al. developed a single-layer buccal patch. The mucoadhesive layer contained polyvinyl alcohol, hydroxyethycelullose or chitosan, respectively. This type of patches with no supporting layer enables multidirectional controlled release of antiseptic and may be used to reach drug concentrations above the minimum inhibitory concentration in the oral cavity for a prolonged period of time[15].

Thin non-erodible mucoadhesive discs consisting of two layers were reported by McQuinn et al. A homogenous mixture of drug and mucoadhesive polymers (carbopol, polyisobutylene and polyisopropylene) was compressed to an appropriately thin mucoadhesive layer. A hydrophobic polymer, ethylcellulose, was then applied to one side of this film. This backing layer slows down the diffusion of saliva into the drug layer, thus enhancing the adhesion time and reducing drug loss caused by its administration into the oral cavity (unidirectional drug release). In addition to this, the backing layer prohibits adhesion to tissues from the opposite side[16].

Robinson et al. reported the use of buccal patches consisting of three layers: an impermeable backing layer; a release rate limiting middle membrane containing the drug; and a mucoadhesive basement layer containing the bioadhesive polymer polycarbophil for mucosal adhesion. This patch has been tested in human buccal mucosa and was shown to remain in place for up to 15 hours without any obvious discomfort, irrespective of food or drink consumption[17].

Mucoadhesive polymers used in formulation of mucoadhesive films

To date, a wide variety of mucoadhesive materials have been used for the development of new pharmaceutical preparations, including synthetic and natural polymers. In general, “polymer” is the term used to describe a long molecule – a chain consisting of structural units (monomers), which are repeated and connected by covalent bonds. The differences between monomers can affect properties such as solubility, flexibility and strength. Bioadhesive polymers should have certain physicochemical characteristics including hydrophilicity, visco-elastic properties, flexibility for interpenetration with mucus and epithelial tissue, and numerous hydrogen bond-forming groups such as hydroxylic -OH, carboxylic

-COOH, or amide -$CONH_2$. Some authors reviewed that mucoadhesive polymers should have the following characteristics[13, 18, 19]:

- Be non-toxic, non-irritant and free from leachable impurities (including the degradation products).
- Show bioadhesive properties in both dry and liquid state.
- Be able to incorporate both oil- and water-soluble drugs for the purpose of controlled drug delivery.
- Have a good spreadability, solubility, biodegradability, wetting and swelling properties.
- Quickly adhere to the buccal mucosa and possess sufficient mechanical strength.
- Exhibit strong interaction with the mucosal epithelial tissue.
- Be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- Have biocompatible pH and good visco-elastic properties.
- Possess peel, tensile and shear strengths at the bioadhesive range.
- Be unaffected by the hydrodynamic conditions, food and pH changes.
- Demonstrate local enzyme inhibition and penetration enhancement properties.
- Have required impact on drug release.
- Have optimum molecular weight.
- Possess adhesively active groups.
- Possess required spatial conformation.
- Be easily incorporated in various dosage forms.
- Demonstrate acceptable shelf life.
- Be easily available and economically acceptable.
- Not aid in development of secondary infections such as dental caries.

In general, several criteria such as the origin, aqueous solubility, or charge can be used for classification of adhesive polymers. The most commonly used *synthetic* polymers are poly(acrylic acid)-based derivatives (carbomer, polycarbofil, etc.). Cellulose derivatives (carboxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, etc.) or chitosan are typical representatives of *semi-synthetic* mucoadhesive polymers. *Natural* mucoadhesive polymers are agarose, gelatin, hyaluronic acid, pectin, and various gums such as guar, xanthan, gellan carrageenan, or sodium alginate[14, 18].

Polymer charge also affects its bioadhesive properties. Cationic and anionic polymers adhere to the mucous membrane more effectively than neutral polymers[13]. Examples of *cationic* mucoadhesive polymers are chitosan or dextran; *anionic* polymers are for example polyacrylates, carboxymethylcellulose, polyacrylic acid, or sodium alginate. Poly(vinylalcohol), poly(vinylpyrrolidone), poly(ethylene oxide), hydroxypropylmethylcellulose, or methylcellulose belong to *neutral* polymers with mucoadhesive properties[14].

In recent literature, newer "second generation" of mucoadhesives (for example thiolated polymers), specific for its capability of forming stronger chemical interactions – even covalent bonds – with the mucus or/and the cell surface, eventually targeting specific receptors, is widely discussed. Thiolated polymers are enhanced derivatives of a polymer such as chitosan, poly (acrylic acid), etc. containing characteristic free thiol groups on the polymeric backbone. These groups form covalent disulphide bonds with cysteine-rich subdomains of mucus glycoproteins[20]. Another class of compounds with the ability of strong and quick direct binding onto the mucosal cell surface rather than the mucus itself is called lectins. These proteins or glycoproteins have been isolated from animals, plants or are of microbial origin. They bind to sugar-moieties of the cell membrane with significant specificity. An example of non-toxic lectin is tomato lectin isolated from *Lycopersicum esculetum*. Lectin-mediated bioadhesive polymers can improve drug delivery via specific binding and can increase the residence time of the dosage form[21].

Other excipients used in formulation of mucoadhesive films

Plasticizers are other crucial excipients in film formulation. They significantly improve properties such as flexibility and reduce fragility of the film. Glycerol, propylene glycol, low molecular weight polyethylene glycols, phthalates and citrate derivatives, or castor oil are some of the commonly used plasticizers[22].

Problems with lower drug absorption through the epithelial barrier (if systemic absorption of the drug is required) can be overcome using *enhancers*[23]. Although absorption enhancers belong to various chemical classes, they should be in general safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic. They can be divided into several groups: surfactants (sodium lauryl sulphate, polyoxyethylene, lecithine), bile salts (sodium glycocholate, sodium taurocholate, sodium deoxycholate), chelators (EDTA, citric acid, sodium salicylate), fatty acids (oleic acid, capric acid, lauric acid), alcohols (ethanol, propylene glycol), and others (azone, dextran sulfate, sulfoxides)[24].

Protein and polypeptide drugs are prone to enzymatic degradation. *Enzyme inhibitors* can reduce this problem. In particular, competitive inhibitors of proteolytic enzymes are used. Examples of protease inhibitors investigated in buccal mucosal delivery are aprotinin, betastin, or puromycin[24]. Some mucoadhesive polymers such as poly(acrylic acid) derivatives or chitosans show these properties, too[25].

Sweetening agents, natural as well as artificial sweeteners, are used to improve the palatability of the formulations used in the oral cavity. Common natural sweeteners are sucrose, dextrose, fructose, glucose, maltose, and polyhydric alcohols (polyols) such as sorbitol, mannitol, or maltitol. The artificial sweeteners such as saccharin, cyclamate, aspartame, acesulfame-K, or sucralose are several hundred to several thousand times

sweeter than sucrose, but they usually have an unpleasant aftertaste effect[22].

Technology of mucoadhesive film manufacturing

The most widely used technology for formulation of mucoadhesive films is the *solvent casting method*. This method is quite simple and no special equipment is needed. A prepared casting solution or suspension is transferred to a casting mould and the solvent evaporated. The final steps are cutting the dosage form and packaging. Problems that may occur when employing this technology include bad rheological properties of the solution or suspension, entrapped air bubbles, insufficient content uniformity, or residual solvents in the final dosage form[26].

Another technology, *hot melt extrusion,* has been widely used in the pharmaceutical industry to manufacture tablets, granules, and pellets over the last 20 years. Recently, Repka et al. investigated the use of hot-melt extrusion for manufacturing mucoadhesive buccal films[27]. Extrusion is the process of converting a blend of pharmaceutical ingredients into a product of uniform shape and density. Molten raw material is forced through an orifice (the die) under controlled conditions to yield a more homogeneous material in different shapes. Extrusion can be operated as a continuous process with a consistent product flow[28]. This procedure has many advantages in comparison with the solvent casting method, such as shorter processing time and greater time-effectiveness, no need of solvents (and therefore no solvent residues in the final dosage form), high stability, and improved solubility and bioavailability of poorly soluble drugs. The relevant disadvantages are a requirement of thermal stability of all components at the processing temperature, the fact that components must be almost moisture free, and investment into specialized equipment[29].

Use of the buccal mucoadhesive films

Permanent exposure of the oral mucosa to external factors leads to various disorders including RAS, which affect, in the course of life, the majority of population and are manifesting by painful lesions on the mucous membrane. They can be treated locally by a wide range of topical oral drug systems. Drugs investigated for use in buccal mucoadhesive films for *local treatment* are listed in Table 1. For example, mentioned can be: anaesthetics (lidocaine, tetracaine), antibiotics (ciprofloxacin, ofloxacin, tetracycline), antifungal drugs (miconazole, nystatin, cotrimazole), antiseptics (chlorhexidine, cetylpyridinium chloride), or non-steroidal anti-inflammatory drugs (ibuprofen, flufenamic acid, benzydamine).

The region of the oral cavity and its mucosa is attractive not only for application of locally acting drugs, but also as a route for systemic administration of drugs. Direct access from the buccal mucosa to the systemic circulation

Table 1. List of investigated buccal mucoadhesive films/patches for local action

Drug	Bioadhesive polymers	Investigators
benzydamine, lidocaine	PC, CP, xanthan gum, tamarind gum	Burgalassi et al.[32]
cetylpiridinium chloride	PVA, HEC, chitosan	Nafee et al.[15]
chitosan	chitosans	Skinci et al.[33]
chlorhexidine diacetate	EC	Jones and Medlicott[34]
chlorhexidine digluconate	chitosan	Senel et al.[35]
ciprofloxacin HCl	HPMC, PVA	Choudhury et al.[36]
clotrimazole	HPC, poly(ethylene oxide), PC	Repka et al.[37]
flufenamic acid	chitosan	Mura et al.[38]
ibuprofen	PVP, NaCMC, Eudragit, HPMC, CP	Perioli et al.[39]
ipriflavone	PLGA, chitosan	Perugini et al.[40]
lidocaine	HPC, EC	Kohda et al.[41]
lidocaine	HPC	Okamoto et al.[42, 43]
lidocaine	chitosan	Varshosaz and Karimzadeh[44]
lidocaine	HPC, CP	Ishida et al.[45]
lidocaine	HPC, HPMC, PC, poly(ethylene oxide)	Repka et al.[46]
lycopene	CP, PVP, HPMC	Shah et al.[47]
miconazole nitrate	NaCMC, chitosan, HEC, PVA, HPMC	Nafee et al.[48]
nystatin	chitosan	Aksungur et al.[49]
nystatin	carbomer, NaCMC	Llabot et al.[50, 51]
paracetamol	NaCMC	Boateng et al.[52]
tetracaine, ofloxacin, miconazole, guaiazulene	HPC	Oguchi et al.[53]
tetracycline HCl	PLGA	Agarwal et al.[54]
toluidine blue O	PMVE/MA	Donnelly et al.[55]
triamcinolone acetonide	chitosan/PAA complex	Ahn et al.[56]
triamcinolone acetonide	CP, poloxamer, HPMC	Chun et al.[57]
triamcinolone acetonide	CP, poloxamer, HPMC	Kim et al.[58]

Table 2. List of investigated buccal mucoadhesive films/patches for systemic action

Drug	Bioadhesive polymers	Investigators
acyclovir	copolymer AA, PEGMM, EGDMA	Shojaei et al.[59, 60]
acyclovir	chitosan, PAA sodium salt	Rossi et al.[61]
buprenorphine	CP, PIB, PIP	McQuinn et al.[16]
buprenorphine	CP, PIB, PIP	Guo[62], Guo and Cooklock[63]
carvedilol	HPMC, Eudragit, CP, EC	Thimmasetty et al.[64]
carvedilol	HPMC, CP	Choudhary et al.[65]
chlorpheniramine maleate	polyoxyethylene	Tiwari et al.[66]
diltiazem HCl	NaCMC, PVP, PVA	Semalty et al.[67]
famotidine	HPMC, NaCMC, PVA	Manish et al.[68]
fentanyl	PVP	Diaz del Consuelo et al.[69]
fexofenadine HCl	HPMC, Eudragit, CP, EC	Thimmasetty et al.[70]
glibenclamide	chitosan	Ilango et al.[71]
glipizide	HPMC, sodium CMC, CP, Eudragit	Semalty et al.[72]
insulin	gelatin, CP	Ritschel et al.[73]
isosorbide dinitrate	CP, PVP, Eudragit	Doijad et al.[74]
losartan potassium	HPMC, EC or Eudragit	Koland et al.[75]
metoprolol tartrate	Eudragit, HPMC, NaCMC, CP	Wong et al.[76]
nifedipine	sodium alginate, MC, PVP	Save et al.[77]
nifedipine or propranolol HCl	chitosan with/without PC, sodium alginate, gellan gum	Remuñán-Lopez et al.[78]
nitrendipine	HPMC, HPC, NaCMC, sodium alginate, PVA, PVP, CP	Nappinnai et al.[79]
oxytocin	CP	Li et al.[80, 81]
pimozide	HPMC, CP, PVA, PVP	Basu et al.[82]
plasmid DNA (CMV-ß-gal)	PC, Eudragit	Cui and Mumper[83]
propranolol HCl	CP, PVP, Eudragit	Patel et al.[84]
protirelin	HEC, HPC, PVP, PVA	Anders et al.[85]
salbutamol sulphate	PVA, chitosan, PVP	Patel and Poddar[86]
salbutamol sulphate	HPMC, EC, Eudragit	Pavan Kumar et al.[87]
salmon calcitonine	PC, Eudragit	Cui and Mumper[88]
terbutaline sulphate	HPMC, HPMCP, chitosan	Pramodkumar et al.[89]
testosterone	PC, Eudragit	Jay et al.[90]
thyrotropin-releasing hormone	organic polymers	Li et al.[91]
ß-galactosidase protein	PC, Eudragit	Cui and Mumper [83]

through the internal jugular vein bypasses the hepatic first pass metabolism, which leads to increased bioavailability of the drug. Other advantages such as low enzymatic activity, good accessibility, painless administration and easy drug withdrawal in the case of adverse side effects predetermine buccal mucoadhesive films as a promising object for further research[30]. Development of new mucoadhesive films should deal with a low permeability of the buccal mucous membrane and other disadvantages such as the continuous saliva secretion (500–2000 mL/day), fast turnover of the mucus, or need of food and liquid intake during administration[31]. The benefits are however potentially significant and for this reason numerous drugs were investigated as possible active ingredients of buccal mucoadhesive films for systemic action (Table 2.). These included peptidic hormones (insulin, oxytocin, protirelin, calcitonine), analgesics (especially opioid drugs like fentanyl or buprenorphine), antihypertensive drugs (metoprolol, propranolol, carvedilol, nifedipine, losartan), bronchodilators (salbutamol, terbutaline), anti-diabetic drugs (glibenclamide, glipizide), histamine antagonists (H_1 – fexofenadine, chlorpheniramine; H_2 – famotidine), and others.

Abbreviations

CMC	carboxymethylcellulose
CP	carbopol
EC	ethylcellulose
EGDMA	ethylenglycol dimethacrylate
HEC	hydroxyethylcellulose
HCl	hydrochloride
HPC	hydroxypropylcellulose
HPMC	hydroxypropylmethylcellulose
HPMCP	hydroxypropylmethylcellulose phthalate
MC	methylcellulose
NaCMC	sodium carboxymethylcellulose
PAA	poly(acrylic acid)
PC	polycarbophil
PEGMM	polyethyleneglycol monomethylether monomethacrylate
PIB	polyisobutylene

PIP	polyisoprene
PLGA	poly(D, L-lactide-co-glycolide)
PMVE/MA	poly(methylvinylether-co-maleic anhydrid)
PVA	polyvinyl alcohol
PVP	poly(vinylpyrrolidone)

Conflicts of interest: none.

This article was completed with support of a Ministry of Health of Czech Republic research project NT11396 and IGA VFU Brno, Czech Republic, research project No. 78/2012/FaF.

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