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Polymers and Permeation Enhancers: Specialized Components of Mucoadhesives

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Review Article

ABSTRACT

Mucoadhesive polymers have recently gained interest among pharmaceutical scientists as a means of improving drug delivery by promoting dosage form residence time and contact time with the mucous membranes. Mucoadhesion occurs between two surfaces, one of which is a mucous membrane and another is drug delivery system. Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because mucoadhesion could be a solution for bioavailability problems that result from a too short length of stay of the pharmaceutical dosage form at the absorption site within the gastro-intestinal tract. It has been a great challenge to the pharmaceutical sciences in order to enhance localised drug delivery or to deliver 'difficult' molecules (proteins and oligonucleotides) into the systemic circulation. Mucoadhesive systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the site of action leading to increase in bioavailability (both local and systemic effects). Extending the residence time of a dosage form at a particular site and controlling the release of drug from the dosage form are useful especially for achieving controlled plasma level of the drug as well as improving bioavailability. The present review describes mucoadhesion, mucoadhesive polymers and use of these polymers in designing different types of mucoadhesive drug delivery systems.

***Key words*:** Mucoadhesion, Mucoadhesive polymers, Mucoadhesive force, Bioadhesive property.

INTRODUCTION

Mucoadhesives are synthetic or natural polymers that interact with the mucous layer covering mucosal epithelial surface, main molecules constituting a major part of mucus (Patil *et al.*, 2006). Mucoadhesion is a topic of current interest in the design of drug delivery systems (Asane, 2007). Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion keeps the delivery system adhering to the mucous membrane (Semalty, 2006). Mucoadhesion can be defined as the ability of synthetic or biological macromolecules to adhere to mucosal tissues. It is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time to improve and enhance the bioavailability of drugs (Bhatt, 1998). In case of mucoadhesion, the biological tissue is the mucous membrane (Patil *et al.*, 2006). The first stage involves an intimate contact between a mucoadhesive polymer and a membrane, either from good wetting of the mucoadhesive surface or from the swelling of the mucoadhesive. In the second stage, after contact is established, penetration of the mucoadhesive into the crevice of the tissue surface or interpenetration of the chains of the mucoadhesive with those of the mucous takes place. The third stage involves formation of chemical bonds between the entangled chains (Bhatt, 2009; Aidoo, 2008; Smart, 2005; Hagerstrom, 2006, Sharma *et al.*, 2009).

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Table 1. Classification of polymers based on source.

Natural Polymers	Synthetic Polymers
Agarose	**Polymers based on poly(meth)acrylic acid.**
Chitosan	Carbopol
Gelatin	Polycarbophil
Hyaluronic acid	Polyacrylic acid
Carrageenan	Polyacrylates
Pectin	Copolymer of acrylic acid
Sodium alginate.	Polyethylene glycol
	Copolymer of methylvinyl ether and
Cellulose derivatives	Methacrylic acid
Carboxy methyl cellulose.	Poly-2-hydroxyethylmethacrylate
Thiolated Carboxy methyl cellulose	Copolymer of acrylic acid and
Sodium Carboxy methyl cellulose	Ethylhexylacrylate
Hydroxyethylcellulose,	Polymethacrylate
Hydroxypropylcellulose,	Polyalkylcyanoacrylates
Hydroxypropylmethylcellulose	Polyisobutylcyanoacrylate
Methylcellulose	Polyisohexylcyanoacrylate.
Methylhydroxyethylcellulose.	
	Others
	Poly-N-2-hydroxypropylmethacrylamide
	Polyhydroxyethylene
	Poly vinyl alcohol
	Poly vinyl pyrrolidine
	Thiolated polymers

Table 2. Classification of polymers based on aqueous solubility.

Water Soluble Polymers	Water Insoluble Polymers
Cellulose derivatives	**Polymers based on poly(meth)acrylic acid**
Carboxy methyl cellulose	Carbopol
Thiolated Carboxy methyl cellulose	Polycarbophil
Sodium Carboxy methyl cellulose	Polyacrylic acid
Hydroxyethylcellulose	Polyacrylates
Hydroxypropylcellulose	Copolymer of acrylic acid
Hydroxy propyl methyl cellulose	PEG
Methylcellulose	Copolymer of methylvinyl ether
Methylhydroxyethylcellulose.	Methacrylic acid
	Poly-2-hydroxyethylmethacrylate
Others	Copolymer of acrylic acid and
Poly-N-2-hydroxypropylmethacrylamide	Ethylhexylacrylate
Polyhydroxyethylene	Polymethacrylate
Poly vinyl alcohol	Polyalkylcyanoacrylates
Poly vinyl pyrrolidine	Polyisobutylcyanoacrylate
Thiolated polymers.	Polyisohexylcyanoacrylate
Ethylcellulose	

Table 3. Classification of polymers based on charge.

Cationic Polymers	Anionic Polymers	Non ionic Polymers
Aminodextran	Carboxy methyl cellulose	Hydroxy ethyl starch
Chitosan	Pectin	Hydroxy propyl cellulose
	Cabopols	Polyethyleneglycol,
	Polyacrylates	Polyvinylalcohol,
		Polyvinylpyrrolidine
		Eudragit- NE30D

MUCOADHESIVE POLYMERS

Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: *polys* meaning 'many' and *meros* meaning 'parts' (Punitha and Girish, 2010). A polymer is a substance formed by the linkage of a large number of small molecules known as monomers. Mucoadhesive polymers are water-soluble and water insoluble polymers, which have swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucous and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucous takes place (Roy *et al.,* 2006).

CLASSIFICATION OF POLYMERS

The polymers can be classified based on source (Table 1), solubility (Table 2), charge (Table 3) and bioadhesive forces (Table 4).

Depending upon source (Chickering *et al.,* 1996; Punitha and Girish, 2010)

A. Natural Polymers
B. Synthetic Polymers

Depending upon aqueous solubility (Semalty, 2006; Roy *et al.,* 2006)

A. Water Soluble
B. Water insoluble

Table 4. Classification of polymers based on bioadhesive forces.

Covalent Bonds	Electrostatic Interactions	Hydrogen Bonds
Cyanoacrylate	Chitosan	Acrylates Carbopol Polycarbophil Polyvinylalcohol

Depending upon charge (Abnawe, 2009; Majumdar *et al.,* 2010):

A. Cationic polymers
B. Anionic polymers
C. Nonionic polymers

Depending upon potential bioadhesive forces (Punitha & Girish, 2010):

A. Covalent Bonds.
B. Electrostatic Interactions.
C. Hydrogen Bonds.

Table 5. Order of mucoadhesive force for various polymers (Roy *et al.,* 2010; Hunt *et al.,* 1987; Abnawe, 2009).

Mucoadhesive Polymers	Mean Adhesive Force (%) with Standard Deviation
Poly(acrylic acid)	185.0 ±10.3
Tragacanth	154.4 ±7.5
Poly(methylvinylether comaleic anhydride)	147.7 ±9.7
Poly(ethylene oxide)	128.6 ±4.0
Methylcellulose	128.0 ±2.4
Sodium alginate	126.2 ±12.0
Hydroxypropylmethyl cellulose	125.2 ±16.7
Karaya gum	125.2 ±4.8
Methylethyl cellulose	117.4 ±4.2
Soluble starch	117.2 ±3.1
Gelatin	115.8 ±5.6
Pectin	100.0 ±2.4
Poly (vinyl pyrrolidone)	97.6 ±3.9
Poly (ethylene glycol)	96.0 ± 7.6
Poly (vinyl alcohol)	94.8 ±4.4
Poly(hydroxyethyl-methacrylate)	88.4 ±2.3
Hydroxypropylcellulose	87.1 ±13.3

Table 6. Relative mucoadhesive performance of some potential bio (muco) adhesive pharmaceutical polymers (Ganga, 2007; Rathore ***et al.,*** 2009; Yadav ***et al.,*** 2010).

Polymer	Bioadhesive Property
Carboxy methyl cellulose	+++
Hydroxy propyl methyl cellulose	+++
Carbopol 934	+++
Tragacanth	+++
Sodium alginate	+++
Polycarbophil	+++
Hydroxy ethyl cellulose	+++
Gelatin	++
Guar gum	++
Gum karaya	++
Pectin	+
Acacia	+
Polyvinyl pyrrolidone	+

PERMEATION ENHANCERS

Substances that facilitate the permeation through mucosa are referred to as permeation enhancers. Membrane permeation is the limiting factor for many drugs in the development of mucoadhesive delivery system. The epithelium that lines the mucosa is a very effective barrier to the absorption of drugs especially buccal mucosa (Chattarajee and Walker, 1995). The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties (Shojaei, 1998).

Properties

According to Aungst (1994) permeation enhancers should be-

- Safe
- Non- toxic
- Non -irritant
- Non-allergeic
- Pharmacologically and chemically inert

Surfactants such as anionic, cationic, nonionic and bile salts increase permeability of drugs by perturbation of intercellular lipids. Chelators act by interfering with the calcium ions. Fatty acids act by increasing fluidity of phospholipids. Positively charged polymers act by ionic interaction with negative charge on the mucosal surface (Schipper *et al.,* 2004).

Table 7. List of permeation enhancers (Lee *et al.,* 2000)

Chelators	EDTA, Citric acid, Sodium salicylates, Methoxy salicylates
Surfactants	Sodium lauryl sulphate, Polyoxyethylene, Polyoxyethylene-9-laurylether , Polyoxythylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, Cetylpyridinium chloride, Cetyltrimethyl ammonium bromide
Bile Salts	Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxycholate, Sodium taurodeoxycholate
Fatty Acids	Oleic acid, Capric acid, Lauric acid, Lauric acid/ propylene glycol, Methyloleate, Lysophosphatidylcholine, Phosphatidylcholine
Non Surfactants	Unsaturated cyclic ureas.
Inclusion Complexes	Cyclodextrins
Thiolated Polymers	Chitosan-4-thiobutylamide, Chitosan-cysteine, Poly (acrylic acid)-homocysteine, Polycarbophil-cysteine, Polycarbophil-cysteine/gsh, Chitosan-4-thioethylamide/gsh, Chitosan- 4-thioglycholic acid
Others	Aprotinin, Azone, Cyclodextrin, Dextran sulfate, Menthol, Polysorbate 80 , Sulfoxides and various alkyl glycosides.

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