

Novel Bioadhesive Formulations in Drug Delivery

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Introduction

The term 'bioadhesive' describes materials that bind to biological substrates, such as mucosal membranes; this review will examine mucosal-adhesive drug delivery formulations targeted to sites including the eye, oral cavity, nasal cavity, GI tract and vagina. Adhesion of bioadhesive drug delivery devices to mucosal membranes leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drugs. In addition, bioadhesive dosage forms have been used to target local disorders at the mucosal surface (e.g. mouth ulcers) to reduce the overall dosage required and minimise side-effects that may be caused by systemic administration of drugs.

Bioadhesive drug delivery formulations were introduced in 1947 when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa; this was eventually to become Orabase[®] (Scrivener and Schantz, 1947). Recent reports have suggested that the market share of bioadhesive drug delivery systems is increasing (Jasti *et al.*, 2003). Table 1 lists some of the currently available bioadhesive drug formulations available within the UK.

This list of available bioadhesive drug delivery formulations highlights the fact that readily accessible sites are utilised, with the eye, oral cavity and vagina being targeted. The GI tract is a desirable site for bioadhesive drug delivery due to its propensity for drug

absorption, although as yet there are no commercially available products within the UK that are designed to adhere to the GI tract. The nasal cavity has also been extensively examined as a site for bioadhesive drug delivery formulations as this is a growing market that is yet to be fully exploited (Koch, 2003).

Formulation Strategies for Bioadhesive Drug Delivery Systems

Bioadhesive formulations use polymers as the adhesive component. These polymers are often water-soluble and when used in a dry form they attract water from the mucosal surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. Many theories have been proposed to explain the forces that underpin bioadhesion. However, there is yet to be a clear explanation. As bioadhesion occurs between inherently different mucosal surfaces and formulations that are solid, semi-solid and liquid, it is unlikely that a single, universal theory will account for all types of adhesion observed. However, bioadhesive polymers should possess certain physiochemical features including hydrophilicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with both mucus and epithelial tissue and visco-elastic properties upon hydration.

Product	Company	Bioadhesive agent	Pharmaceutical form
Buccastem [®]	Reckitt Benckiser	Polyvinylpyrrolidone (PVP), Xanthan gum and locust bean gum	Buccal tablet
Corlan pellets [®]	Celltech	Acacia gum	Oromucosal pellets
Suscard [®]	Forest	Hydroxypropyl methylcellulose (HPMC)	Buccal tablet
Gaviscon Liquid [®]	Reckitt Benckiser	Sodium alginate	Oral liquid
Orabase [®]	ConvaTech	Pectin, gelatin	Oral paste
Corsodyl gel [®]	GlaxoSmithKline	Hydroxypropyl methylcellulose (HPMC)	Oromucosal gel
Nyogel [®]	Novartis	Carbomer and polyvinylalcohol (PVA)	Eye gel
Pilogel [®]	Alcon	Carbomer	Eye gel
Timoptol-LA [®]	Merck, Sharpe and Dohme	Gellan gum	Eye gel-forming solution
Aci-Jel [®]	Janssen-Cilag	Tragacanth, acacia	Vaginal gel
Crinone [®]	Serono	Carbomer	Vaginal gel
Gynol-II [®]	Janssen-Cilag	Sodium carboxymethyl cellulose and PVP	Vaginal gel
Zidoval [®]	3M	Carbomer	Vaginal gel

Table 1 – Some of the currently available bioadhesive drug formulations available within the UK.

Solid Bioadhesive Formulations

Dry formulations achieve bioadhesion via dehydration of the local mucosal surface. Tablets that are placed directly onto the mucosal surface have been demonstrated to be excellent bioadhesive formulations, for example Buccastem® administered to the buccal mucosa. However, size is a limitation of tablets due to the requirement for the dosage form to have intimate contact with the mucosal surface.

Bioadhesive microparticles

Bioadhesive microparticles offer the same advantages as tablets but their physical properties enable them to make intimate contact with a larger mucosal surface area, in addition, they can also be delivered to less accessible sites including the GI tract and upper nasal cavity. The small size of microparticles compared with tablets means that they are less likely to cause local irritation at the site of adhesion and the uncomfortable sensation of a foreign object within the oral or nasal cavity is reduced. Studies have been performed that examine the use of bioadhesive microparticles for a range of functions including intranasal delivery of insulin (e.g. Callens *et al.*, 2003). Bioadhesive microparticles have also been investigated for the ocular delivery of acyclovir using chitosan as the bioadhesive polymer where microspheres showed increased bioavailability of the drug (Genta *et al.*, 1997). Bioadhesive microparticulate drug delivery has also been the subject of several recent patents including one for the fast release of drugs from microspheres administered sublingually (Roversi and Cilurzo, 2002).

Bioadhesive inserts

Ocular inserts (solid devices, which are placed on the cornea or in the cul-de-sac of the eye) were introduced to the ophthalmic market 50 years ago. The earliest official record of a solid insert was described in the 1948 British Pharmacopoeia; it was an atropine-containing gelatin wafer. Ocular inserts offer many advantages over liquid formulations including longer retention times, accurate dosing, increased stability and shelf life. However, despite these advantages ocular inserts (e.g. Ocuser®) have not been widely used in ocular therapy. Combining an insert with a bioadhesive polymer offers additional advantages in that the device can no longer move freely over the surface of the eye, thus minimising irritation and preventing loss of the device. A recent study has indicated that ocular inserts incorporating a bioadhesive polymer, thiolated poly(acrylic acid) are promising new solid devices for ocular drug delivery (Hornof *et al.*, 2003).

Wafers

Bromberg *et al.* (2001) described a conceptually novel periodontal drug delivery system (DDS) that is intended for treatment of microbial infections associated with periodontitis. The DDS is a composite wafer with surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers

and matrix polymers. *In vitro* experiments demonstrated that the wafers are capable of zero-order release of antimicrobial agents such as silver nitrate, benzylpenicillin and tetracycline, for over 4 weeks (Bromberg *et al.*, 2001).

Lozenges

Bioadhesive lozenges may be used for the delivery of drugs that act topically within the mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. Conventional lozenges produce a high initial release of drug in the oral cavity, which rapidly declines to subtherapeutic levels, thus multiple daily dosing is required; a slow release bioadhesive lozenge offers the potential for prolonged drug release and once daily dosing with improved patient compliance. Codd and Deasy (1998) investigated bioadhesive lozenges as a means to deliver antifungal agents to the oral cavity.

Semi-Solid Bioadhesive Formulations

Gels

Gel-forming bioadhesive polymers include cross-linked polyacrylic acid that has been used to adhere to mucosal surfaces for extended periods of time and provide controlled release of drugs. Gels have been widely used in the delivery of drugs to the eye, oral cavity and vagina. Advantages of gel formulations include their ability to form intimate contact with the mucosal membrane and their rapid release of drug at the absorption site. Limitations of gel formulations centre on their inability to deliver a measured dose of drug to the site. They are therefore of limited use for drugs with a narrow therapeutic window or for sites that are not readily accessible. He *et al.* (2004) designed a novel, hydrogel-based, bioadhesive, intelligent responsive system for controlled drug release. This system combined several desirable facets into a single formulation; a poly(hydroxyethyl methacrylate) layer was used as a barrier to protect the drug; poly(methacrylic acid-g-ethylene glycol) was used as a biosensor that gels in response to pH and poly(ethyleneoxide) was used to promote mucoadhesion. This single unit has demonstrated effective drug release *in vitro*.

Films

Flexible films may be used to deliver drugs directly to a mucosal membrane as they have the flexibility to form intimate contact with the membrane. They also offer advantages over creams and ointments in that they provide a measured dose of drug to the site. Bioadhesive films may be designed for use within the buccal cavity or for administration to the eye. Zilactin® (Zila) is a bioadhesive film that is used in the therapy of canker sores, cold sores and lip sores.

Liquid Bioadhesive Formulations

Viscous liquids may be used to coat mucosal surfaces either as protectants or as drug vehicles for delivery to the mucosal surface. Traditionally, pharmaceutically acceptable polymers were used to enhance the viscosity of products to aid their retention in both the eye and within the oral cavity. Indeed, artificial tears for the treatment of dry eye (e.g. Viscotears®, **Novartis**) are carbomer solutions that adhere on the surface of the eye providing a lubricated surface. Dry mouth is treated with artificial saliva solutions that are retained on mucosal surfaces to provide lubrication. These solutions contain bioadhesive polymers including sodium carboxymethyl cellulose (e.g. Luborant®, **Antigen**; Saliveze®, **Wyvern**).

Gastric reflux of acidic material from the stomach into the oesophagus leads to damage of the oesophageal epithelium; bioadhesive liquids that coat the oesophagus after oral administration may be used to protect this mucosal surface from the damage caused by gastric reflux. Solutions of sodium alginate, a component of Gaviscon Liquid® (**Reckitt Benckiser Healthcare**), have been shown to adhere to oesophageal tissue for periods of up to 1 hour as well as offer protection from components of gastric reflux (Batchelor *et al.*, 2002; Tang *et al.*, 2004). In addition, adhesive liquids that coat the oesophagus may be used to deliver drugs for the treatment of local disorders including motility dysfunction, fungal infections and oesophageal cancer (Batchelor *et al.*, 2004).

Suspensions

Sucralfate suspensions adhere directly to mucosal surfaces within the GI tract. This adhesion is not due to the presence of bioadhesive polymers but to acidification of the insoluble powder leading to the formation of an adhesive paste. Incorporation of a bioadhesive agent, however, has demonstrated enhanced *in vitro* adhesion of sucralfate formulation within the oesophagus (Dobrozi *et al.*, 1999).

Gel-forming liquids

This type of formulation is liquid upon instillation and undergoes a phase transition to form a viscoelastic gel in response to a stimulus such as temperature, ionic strength or pH. Carbomers become more viscous upon increased pH. Poloxamers and Smart Hydrogel® (**Advanced Medical Solutions**) gel at approximately body temperature. Gellan gum and alginate both form gels in response to increased ionic strength (particularly with Ca²⁺ ions). Gel-forming formulations are currently used for sustained ocular delivery, including Timpotal-LA® (**Merck, Sharpe and Dohme**). Recent work has examined the oesophageal retention of Smart Hydrogel®, a liquid that gels in response to both high force and temperature, with its gelling temperature at about 32°C (Russell *et al.*, 2004). The force involved in a swallow and the concomitant increase in temperature upon oral administration indicate that Smart Hydrogel® is well retained within the oesophagus. **West Pharmaceuticals** have developed a pectin-based system

that is applied as a spray into the nasal cavity where pectin droplets convert to a bioadhesive gel upon contact with the nasal mucosa.

Specific Bioadhesives

Although much research utilises pharmaceutically acceptable polymers as bioadhesive agents, these systems lack specificity, which is especially important for orally delivered formulations that are targeted to sites within the GI tract. This lack of specific targeting results in polymers adhering to the first mucosal surface that is encountered, which in turn may lead to problems such as those seen with tablets and capsules that adhere to the oesophageal mucosa causing localised tissue damage. Another issue with lack of specificity is that the formulation may interact with 'loose' mucus within the GI tract and be coated with this material and pass through the GI tract without coming into close contact with absorbing mucosal membranes. Specific adhesion is demonstrated by a range of biological molecules that recognise and bind to specific target chemical structures on the surface of cells or within mucus. Specific targeting of bioadhesive particles to M cells has implications in oral vaccination strategies and has been reviewed by Jepson *et al.* (2004). Examples of molecules that exhibit specific adhesion include lectins, bacterial fimbriins and invasins. Incorporation of these molecules into bioadhesive formulations, including liquids, semi-solids and solids, provides additional specificity of targeting and may enhance the overall efficacy of the formulation.

Conclusions

Due to the large number of target sites for bioadhesive drug delivery there are many formulations that may be explored for drug delivery purposes. Currently solid dosage forms, oral liquids and gels applied to readily accessible sites including the eye, oral cavity and vagina are commercially successful. The future direction of bioadhesive drug delivery lies in vaccine formulations that adhere to the mucosal surface and result in mucosal immunity. This is especially relevant in nasal and oral vaccination programmes. Microparticulate bioadhesive systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that results from increased contact time provided by the bioadhesive component.

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