Marine bioadhesives: opportunities and challenges

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“Mussel adhesive proteins, polysaccharides and exopolysaccharides are distinct categories of bioadhesives obtained from sea.”

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Marine invertebrates produce adhesives that retain adhesion even in harsh conditions of sea water. Mussel adhesive proteins, polysaccharides and exopolysaccharides are distinct categories of bioadhesives obtained from sea. Of these, the former two have been extensively explored for developing a variety of drug-delivery systems, including nanoformulations. Combination of adhesives and development of composite bioadhesives are newer approaches to overcome issues related to use of solitary adhesive in formulations.

The ability of marine invertebrates to produce adhesives that retain adhesion, in the presence of harsh sea water conditions, has garnered considerable attention of pharmaceutical researchers. Mussel adhesive proteins, polysaccharides and exopolysaccharides are distinct groups of bioadhesives obtained from the sea [1]. Many therapeutic agents can be delivered via the drug-delivery systems containing these bioadhesives, including anti-inflammatory agents, antihypertensive agents, peptides and low molecular weight proteins, etc. The bioadhesives can be utilized for local drug delivery (topical) and requirements for successful bioadhesive devices for sustained topical delivery of active ingredients include: establishing and maintaining intimate contact with the site of application; ensuring sustained/controlled delivery of the drug in pathological skin conditions; be sufficiently adhesive and cohesive; be nontoxic and nonirritating; and allowing easy termination of therapy [2].

Marine polysaccharides

Research efforts on algal bioadhesives have led to the isolation of polysaccharides that are promising biomaterials, especially as adhesives in ophthalmic therapies. For the purpose of drug delivery, many polysaccharides, including chitin, chitosan, agar, alginate and carrageenans, have been investigated. Chitosan, a biopolymer derived from chitin, has wide pharmaceutical applications, ranging from capability to form gels, films, micro/nanoparticles and beads, as wound dressing and as a carrier for drug/gene delivery [3]. It has been utilized for designing mucoadhesive dosage forms but suffers from its limited mucoadhesive strength and limited water solubility at neutral and basic pH. These issues have been tackled by designing chitosan derivatives such as carboxymethyl chitosan, chitosan-EDTA, glycol chitosan, chitosan-catechol and cyclodextrin-chitosan [4]. The derivatization of chitosan to improve its mucoadhesive properties has been explained in several publications. Few of them have demonstrated potential in transmucosal delivery, for example ChiSys[®] as a platform for nasal vaccination [5] and Lacimera[®] eye drops [6].

Alginates are linear polysaccharides obtained from seaweeds and marine algae, utilized in drug delivery, tissue engineering applications and immobilization of cells and enzymes owing to their ability to crosslink through bivalent cations. Alginates instantaneously form gel-spheres with divalent ions at pH >6 and are widely utilized for the microencapsulation of drugs. However, high viscosity gels are formed when the alginates are subjected to low pH values [7]. The ability of alginates to form pH-triggered gels has been widely used to develop ophthalmic drug-delivery systems. Furthermore, the ability of alginates to form microcapsules on cross-linking has been specifically explored for the oral delivery of low molecular weight proteins [8].

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Alginates can be combined with other bioadhesives to develop novel efficacious drug-delivery systems and the concept has garnered considerable interest among pharmaceutical formulation researchers. For example, the chitosan-alginate microbeads for sustained vaginal delivery of chlorhexidine digluconate, jackfruit seed starch-alginate microspheres of metformin HCl [9], tamarind seed polysaccharide-alginate beads for gliclazide oral delivery, etc. [10]. Alginates have also been utilized for drug-delivery systems based on composite technology. For example, montmorillonite-alginate nanocomposites have been developed for sustained delivery of vitamin B1 and B6 [11]. Modulated drug release was achievable by incorporating pH-independent hydrocolloids gelling agents or by addition of chitosan [12].

Large number of mucoadhesive systems based on alginates have been developed, such as a mucoadhesive vaginal tablet of acriflavine for veterinary purposes. The main drawbacks of alginate formulations are their rapid erosion at neutral pH and reduction in mucoadhesion on cross-linking with divalent cations. In order to strengthen the mucoadhesive property of alginates, these have been chemically derivatized; for example, alginate-polyethyleneglycol acrylate has gelation ability of alginate combined with mucoadhesive strength of acrylate functionality of polyethylene glycol [13]. Laurienzo *et al.* attempted modification of sodium alginate with amines and/or acid moieties that resulted in optimization of drug delivery properties, namely, the drug release rate, modulation of polysaccharide erosion pattern and adhesion to the biological substrates [14]. Bernkop *et al.* demonstrated an improvement of mucoadhesive properties and the release retardant properties of sodium alginate due to covalent linkage of cysteine [15]. The sustainment of drug release and improved mucoadhesion is exemplified by matrix tablets based on sodium alginate–cysteine conjugate containing tramadol hydrochloride as a model drug [16]. Furthermore, the low toxicity of these new excipients provides immense scope for utilization of thiolated polymers in mucoadhesive drug-delivery systems.

Adhesive proteins

Mussel adhesive proteins are recognized as powerful adhesives, which are stronger compared with the polymer-based adhesives. Most importantly, mussel adhesive proteins retain adhesive capacity in wet environments, which is not demonstrated by polymer-based adhesives. To date no polymer-based adhesives have been produced that can retain adhesion in an underwater environment. The strong adhesion of marine mussels under the sea inspired the development of several water-resistant adhesives. The catechol groups are present in large quantities in mussel adhesive proteins, which contribute to the outstanding adhesion of mussels on many different surfaces [17]. Catechols interact with biological surfaces, including mucus. These findings inspired researchers to examine catechol-chitosan mucoadhesive systems for drug delivery via oral, buccal and rectal routes. Catechol-modified chitosan hydrogel crosslinked by genipin is a promising mucoadhesive and biocompatible hydrogel system for buccal drug delivery [18]. Chitosan-catechol mucoadhesive gel allowed sulfasalazine delivery by rectal route more effectively and safely compared with oral administration [19].

It may become imperative for the researchers to amalgamate several adhesive proteins to develop improvised bioadhesive materials for novel applications including drug, protein and gene delivery. Novel drug delivery formulations consisting of polyphenolic proteins from mussels and marine origin polysaccharides are promising, especially as adhesive in ophthalmic therapies.

Marine exopolysaccharides

Exopolysaccharides are obtained from marine bacteria. However, most of these are poorly understood and only a few have been fully characterized. Of the various pharmaceutical roles of microbial exopolysaccharides, assistance in attachment to sea surfaces is of particular interest. Exopolymers of marine *Vibrio* MH3 are involved in reversible attachment. The cross-linking of adjacent polysaccharide chains aids in permanent adhesion [20]. Exopolysaccharides are yet to be explored for drug delivery. Interest is being directed toward extreme marine environments, which could represent a large source of unidentified bacteria.

Dedicated research by marine scientists has afforded discovery and production of many marine bioadhesives of pharmaceutical interest. The possibility of chemical modification, addition of biodegradable additives and production of hybrid bioadhesives permits modulation of properties of bioadhesives and new possibilities, particularly in the pharmaceutical area.

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