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The chemistry of tissue adhesive materials

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ABSTRACT

Each year millions of people sustain traumatic or surgical wounds, which require proper closure. Conventional closure techniques, including suturing and stapling, have many disadvantages. They inflict additional damage on the tissue, elicit inflammatory responses and have a relatively long application time. Especially for the more demanding wounds, where fluids or gasses are to be sealed off, these techniques are often insufficient. Therefore, a large variety of tissue adhesives, sealants and hemostatic agents have been developed. This review provides an overview of such tissue adhesive materials from a polymer chemistry perspective. The materials are divided into synthetic polymer, polysaccharide and protein based adhesives. Their specific properties and behavior are discussed and related to their clinical application. Though each type has its specific advantages, yet few have become standard in clinical practice. Biomimetic based adhesives and other novel products have shown promising results but also face specific problems. For now, the search for better adhering, stronger, easier applicable and cheaper adhesives continues and this review is intended as starting point and inspiration for these future research efforts to develop the next generation tissue adhesives.

Contents

Abbreviations: AA, acrylic acid; CS, chondroitin sulfate; CSF, cerebrospinal fluid; DHMPA, 2,2-bis(hydroxymethyl)-propionic acid; DST, disuccinimidyl tartrate; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; FDA, U.S. Food and Drug Administration; GRF, gelatin-resorcinol-formaldehyde; GRFG, gelatin-resorcinol-formaldehyde–glutaraldehyde; HA, hyaluronic acid; HA-MA, methyacrylated hyaluronic acid; HDI, hexamethylene diisocyanate; IEMA, 2-isocyanatoethyl methacrylate; IPD, isophorone diisocyanate; LCST, lower critical solution temperature; MMA, methyl methacrylate; MDI, diphenylmethane diisocyanate; NHS, *N*-hydroxysuccinimide; PAA, poly(acrylic acid); PBS, phosphate buffered saline; PCL, poly(ε-caprolactone); PDMS, poly(dimethyl siloxane); PEG, poly(ethylene glycol); PGA, poly(glycolic acid); PGLSA, poly(glycerol succinic acid); PGSA, poly(glycerol sebacate acrylate); PLA, poly(lactic acid); PLGA, poly(lactic-*co*-glycolic acid); Plu, pluronic (PEG–PPO–PEG); Plu-SH, thiol functionalized pluronic; PPO, poly(propylene oxide); PS, polystyrene; PTMEG, poly(tetramethylene ether glycol); PTMC, poly(trimethylene carbonate); PVP, poly(N-vinylpyrrolidone).

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1. Introduction

Each year millions of people suffer from wounds that require closure. These wounds include skin wounds but also any surgical or traumatic disruption of solid and hollow organs, connective tissue, muscles, tendons and membranes. Suturing is the most common method to achieve tissue approximation and wound healing. For many purposes suturing has proven to be very suitable. Sutures can provide great tensile strength and show relatively low failure rate [1]. Suture materials can be grossly divided in biologic or synthetic and in absorbable or non-absorbable. Nylon was the first synthetic suture applied and is still the most widely used non-absorbable suture. Disadvantages are the need to remove the suture provoking high stress concentration at the suture point and the granuloma formation when it resides long in the body. Absorbable sutures are made of catgut, poly(lactic-*co*-glycolic acid) (PLGA), poly(glycolic acid), polydioxanone or poly(trimethylene carbonate) (PTMC), and degrade between 7 and 120 days depending on the material, which is long after they have lost tensile strength [2]. Absorbable sutures, however, frequently evoke inflammatory reactions and are relatively expensive. A common feature of suturing is the inevitable penetration of surrounding tissue, nerve damage and post-surgical adhesion which can occur and the ischemia and necrosis of entrapped tissue caused by damaged capillaries. Needle holes and necrotic spaces might provide a passage for fluids or air to leak out. Such compromised tissue anastomosis may result in severe complications depending on the leaking material (e.g. blood, bowel content, bile, cerebrospinal fluid or air). Gastro-intestinal anastomosis, for example, has a 3–15% risk of leakage which can cause intra-abdominal abscesses, fistula, peritonitis and mortality [3,4]. Other disadvantages of suturing are that it is time consuming, not always technically possible, anesthesia is needed and it induces undesirable scar formation [5].

Staples are a frequently used alternative to sutures. The application is faster compared to sutures and both absorbable and non-absorbable staples are available. Like sutures, however, staples tend to damage surrounding tissue, evoke an inflammatory response and cause scar tissue formation including intra-abdominal adhesions. Most importantly, the use of staples also harbors a significant failure rate [1,2].

In the past decades, a wide variety of chemical and mechanical closure materials has been developed with the intention of providing more reliable, more practical and faster methods of tissue closure or connection without compromising tissue vascularization. They can be categorized in hemostatic agents, sealants and adhesives. A hemostatic agent initiates the formation of a blood clot resulting in fibrin networks binding or covering tissues. Sealants are used to provide a watertight (e.g. for cerebrospinal fluid (CSF)) or airtight (e.g. after lung surgery) seal. Tissue adhesives are glues or patches that bind various tissues together in order to allow for the natural healing process to occur. Tissue adhesives are applied to a variety of tissues, such as skin, muscle and intestine [6,7].

Any material used as a hemostatic agent, sealant, adhesive or a combination of these should meet extensive requirements. Spotnitz and Burke in 2008 [6] listed five main requirements: safety, efficacy, usability, cost and approval from the US Food and Drug Administration (FDA) for use in the US and CE mark approval for use in the EU [7]. Some more specific requirements are biocompatibility, biodegradability, mechanical compliance with underlying tissue, an acceptable swelling index and shelf stability. Depending on the desired application additional requirements can be water tightness, tunable adhesion and even the ability to enhance the healing process by delivery of drugs or growth factors.

Biocompatibility means that the components and their degradation products should be non-toxic and non-hemolytic and cause minimal inflammatory or immune reactions. Also, the risk of microbial transmission or contamination and the risk of carcinogenic activity should be negligible. The material or its adhesive reaction must not have irritating effects and should not jeopardize normal

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