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A REVIEW ON BIOADHESIVES FOR TISSUE REPAIR AND REGENERATION

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ABSTRACT :

A potential technique for tissue regeneration and repair, bio adhesives provide better tissue integration, decreased scarring, and increased wound closure. Recent developments in the design, composition, and uses of bio adhesives are highlighted in this study. The creation of hydrogel-based adhesives, adhesives reinforced with nano fibers, and biomimetic adhesives that replicate the characteristics of natural tissue are all covered. It is investigated how bio adhesives might be used in a range of medical fields, such as tissue engineering, wound healing, and regenerative medicine. With an emphasis on integrating these cutting-edge materials into clinical practice, issues and potential paths in bio adhesive research are also covered. Bio adhesives can be used to close wounds, which lowers the risk of infection and speeds up the healing process. Regeneration of Musculoskeletal Tissue: Bio adhesives have the potential to improve the healing of connective tissues, including tendons.

In order to promote tissue regeneration and repair, bio adhesives are specialized adhesives made to adhere to tissues. Natural or synthetic materials designed to adhere to biological components, bioadhesives, have received significant attention in clinics and surgeries. As a result, there are several commercially available, FDA-approved bio adhesives used for skin wound closure, hemostasis, and sealing tissue gaps or cracks in soft tissues. Recently, the application of bio adhesives has been expanded to various areas including musculoskeletal tissue engineering and regenerative medicine. The instant establishment of a strong adhesion force on tissue surfaces has shown potential to augment repair of connective tissues. Bioadhesives have also been applied to secure tissue grafts to host bodies and to fill or seal gaps in musculoskeletal tissues caused by injuries or degenerative diseases. In addition, the injectability equipped with the instant adhesion formation may provide the great potential of bio adhesives as vehicles for localized delivery of cells, growth factors, and small molecules to facilitate tissue healing and regeneration. This review covers recent research progress in bioadhesives as focused on their applications in musculoskeletal tissue repair and regeneration. We also discuss the advantages and outstanding challenges of bio adhesives, as well as the future perspective toward regeneration of connective tissues with high mechanical demand.

Key terms- Tissue engineering, wound healing, tissue regeneration, bio adhesives, and Tissue repair.

INTRODUCTION

Bio adhesion: Bio adhesion can be define as the ability of a drug carrier system {synthetic or biological} to adhere to a biological substrate for extended period of time. Bioadhesion is an phenomena of interfacial molecular attractive force amongst the biological substrate and the natural or synthetic polymers, which allow the polymer to adhere to the biological surface for an extended period of time.[1]

Meachanism of bioadhesion: The meachanism responsible in the formation of bioadhesive bonds are not fully known. Most research has focused on analyzing the bioadhesive interaction between polymer hydrogel and soft tissue.

- Wetting and swelling of poly mer.
- Interpenetration between the polymer chains and the mucusol membrane.
- Formation of chemical bonds between the entangled chains

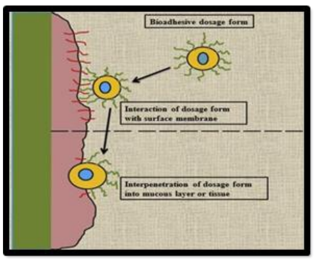

Fig.1: Mechanism of Bio adhesion

Mechanism of mucoadhesion: The major constituents of mucus is mucin are the higher molecular weight glycoproteins, mucin also has different charge density depending on the PH.

- For good bioadhesion hydrogel, such as polycarbophil the penetration into the mucous layer is depending on the intial applied pressure.
- A moderately bioadhesion hydrogel, like {polyacrylate} shows a capability to entangle with the mucus layer.
- A poor bioadhesion hydrogel, like polyhyhroxy ethylmethacrylate PHEMA, shows little penetration into the mucous layer.

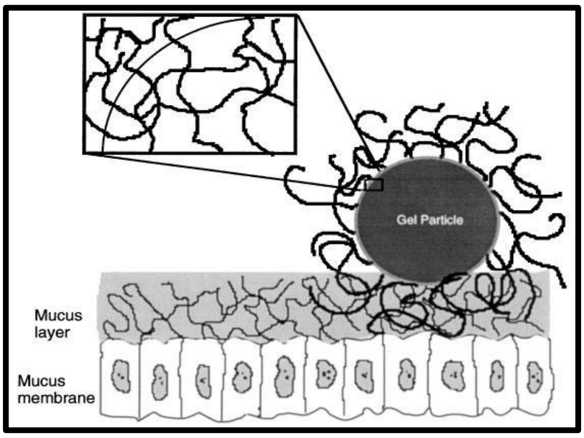

Fig.2: Mechanism of mucoadhesion

Designing regenerative bioadhesives for tissue repair and regeneration

Tissue through injury, surgery and disease motivates the development of new biomaterials to enable tissue repair and regeneration. A new generation of regenerative bioadhesives is created to posses dual functions of seamless tissue adhesion and effective tissue repair. Case studies of regenerative bioadhesives for loadbearing organ such as-skin, tendon and invertebral discs are presented.

Bioadhesives for mucoskeletal tissue regeneration: Natural or synthetic materials designed to adhere to biological components, bioadhesives received significant attention in clinics and surgeries. FDA-approved bioadhesives used for skin wounds, closure, hemostasis and sealing tissue gaps or cracks in soft tissues. Bioadhesive have also been applied to secure tissue grafts to host bodies and to fill a seal gaps in mucoskeletal tissues caused by injuries or degenerative disease. In addition, the injectibility equipped with the instant adhesion formation of provide the great potential of bioadhesives as vehicle for localized delivery of cells, growth factor and small molecules to facilitate tissue healing and regeneration.

Bioactive and bioadhesive catechol conjugated polymers for tissue regeneration

The effective treatment of chronic wounds constitutes one of most common worldwide healthcare problem due to presence of high level proteases, free radical, and exadutes in the wounds, which constantly activate the inflammatory system avoiding tissue regeneration. The natural polyphenol {catechol} is the key molecule responsible for the meachanism of adhesion of muscle providing also the functionalized polymer with bioadhesion in the moist environment of the human body. Multifunctional bioactive and reabsorable membrane with in-built antioxidant agent catechol for the continuous quenching pf free radicals as well as to control inflammatory response helping to promote the wound- healing process.

Mucoskeletal Tissue Repair

Regenerative bioadhesives are in high demand for repairing various musculoskeletal tissues, including tendon, intervertebral disc, cartilage, and ligaments. These tissues are associated with diseases such as low back pain and arthritis, which are leading causes of disability affecting millions of people and resulting in enormous burdens. The injury and degeneration of musculoskeletal tissues often result in tissue fracture or defects, which traditionally are repaired with suturing that has been linked with micro trauma, inflammation, and other complications. In addition, some musculoskeletal tissues such as intervertebral disc tendon have low cellularity, limited vasculature, and low nutrient supply, resulting in a limited self-regenerative capacity that necessitates the intervention of regenerative approaches. To address these issues, ideal a cellular bioadhesives biomaterials should not only repair and support the mechanical properties, but also provide regenerative properties to restore biological functions in the long term. Leveraging bioadhesives for cell and drug delivery can meet the demand for tissue engineering and regeneration of musculoskeletal tissues. As such, the regenerative bioadhesive could fill the injury/degenerated defects, accommodate physiological loading and deformation of the Tendons are important components of the musculoskeletal system, responsible for connecting muscles to bones and transmitting forces generated during movement. Tendinopathies, such as tendinitis and tendinosis, are common conditions that can cause pain, inflammation, and impaired mobility.

To treat tendon injuries, bioadhesives have emerged as a promising approach. Unlike cartilage and intervertebral disc, tendons are primarily subjected to tensile stress and exhibit very large elastic modulus (≈tissue, and replenish and/or recruit cells to the degenerated sites so boosting the regeneration progress.

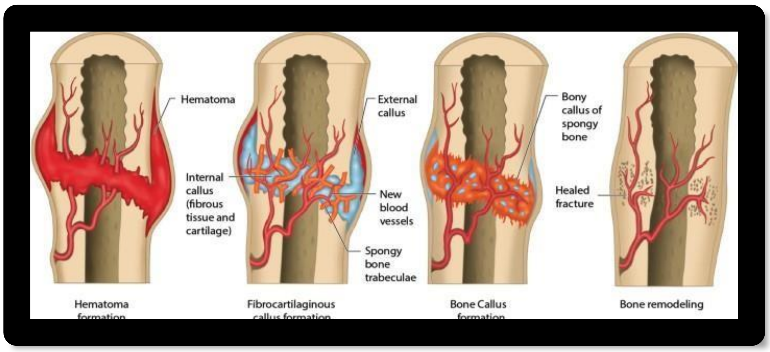

Fig.3 Mucoskeletal tissue repair

Theories Of Mucoadhesion

Adsorption Theory: According to this theory, after an intial contact between two surfaces, the materials adhere because of surface forces acting between the atoms into the two surfaces. Two types of chemical bonds such as primary covalent (permanent) and secondary covalent bonds (including electrostatic forces, vander waal forces and hydrogen and hydrophobic bonds) are involved in the absorption process.

Electronic Theory: According to this theory, electronic transfer occur upon contact of an adhesive polymer and the mucus glycoprotein network because of difference in their electronic structure. This result in the formulation of an electronic double layer at the interface, adhesion occur due to attractive forces across the double layer.

Diffusion Theory: Interpenetration of the chains of polymer and mucus may lead to formation of sufficiently deep layer of chains. The diffusion meachanism is the intimate contact of two polymers of two pieces of same polymer. During chain interpenetration, the molecules of the polymer and the dangling chains of the glycoprotein network are brought in the intimate contact. Due to the concentration gradient, the bioadhesive polymer chains penetrates at rates that are dependent on the diffusion coeficent of macromolecule through a cross-linked network and the chemical potential gradient. In addition, good solubility of bioadhesive medium in the mucus is required in order achieve bioadhesion. Thus, the difference of the solubility parameters of the bioadhesive medium and the glycoprotein should be as close to zero as possible. Thus the glycoprotein bioadhesive medium must be of similar chemical structure to.

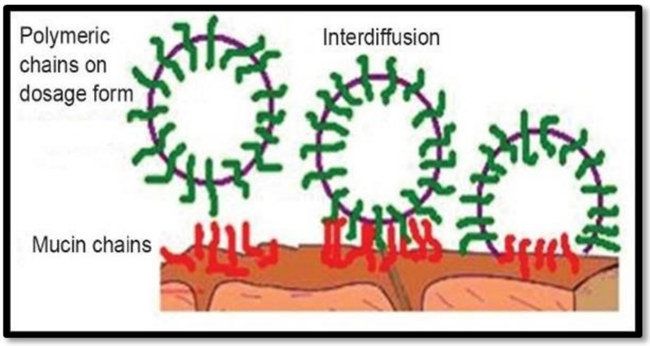

Fig.4 Diffusion of polymeric chain

Wetting Theory: The wetting theory implies to liquid system which related to the current affinity to the surface in order to broadcast over it. Contact angle which is considered as one of the prime measurement tools for the creation of such kind of affinities. The universal rule indicates that the greater affinity correlates to lower contact angle. The contact angle is supposed to be the identical or close up to zero in order to afford sufficient spreadability.

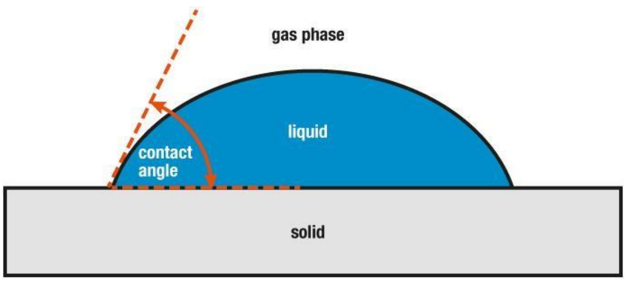

Fig.5 Wetting theory

Fracture theory : Fracture theory of adhesion is related to the separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength. this is most accepted theory in case of mucoadhesion. This theory analysis the force required to detach two surfaces after adhesion. It measures the maximum tensile strength during detachment and it can be expressed by formula given below:

G=(E£\L)

Where,

E= Young's modulus of elasticity.

£= Fracture energy.

L= Critical crack length when two surfaces are separated,

G= Fracture strength.

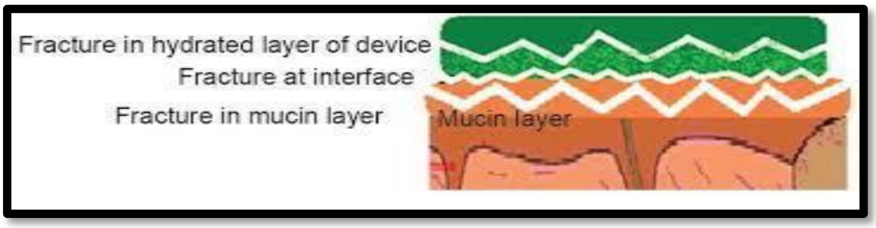

Fig:6 Fracture theory

Factors affecting Muco/Bioadhesion:

- Polymer related factors
- Environment related factors
- Physiological variables

Polymer related factors:

1 **Molecular Weight:** The bioadhesive force increases with molecular weight of polymer , upto 10000 and beyond this level there is no much effect. To allow chain imterpenetration, the molecule have an adequate length. [13-16]

2 **Concentration of active polymers:** there is an optimum concentration of polymer corresponding to the best bioadhesion effect, in concentration solutions, the coiled molecules become solvent poor and the chains available for interpenetration are not numerous, for solid dosage forms such as tablet showed that the higher the polymer concentration the stronger the bioadhesion. [13-16]

3 **Flexibility of polymer chain:** flexibility is an important factor for interpenetration and enlargement. As water soluble polymer becomes cross linked, the mobility of individual polymer chain decreases. As the cross linking density increases, the effective length of the chain which can penetrate into the mucous layer decreases further and mucoadhesive strength is reduced.[17]

Environment Related Factors:

PH: PH influences the charge on the surface of both mucus and the polymers. Mucus will have different charges density depending on PH because of difference in dissociation of functional groups on the carbohydrate moiety and amino acids of the polypeptide back bone.

Applied Strength: To place a solid bioadhesive system, it is necessary to apply a defined strength.

Initial Contact time: The mucoadhesive strength increases as initial contact time increases.

Selection of Model substrate surface: The variable of biological substrate should be confirmed by examining properties such as permeability, electrophysiology of histology.

Swelling: Swelling depends on both polymers concentration and on presence of water. swelling is too great a decrease in bioadhesion occurs.

Physiological Variables

Mucin turnover: The natural turnover from the mucus layer is important for at least two reasons. The mucin turnover is expected to limit the residence time of mucoadhesive on the mucous layers. Mucin turnover results in substabtial amounts of soluble mucin molecules.

Disease states: Physiochemical properties of mucous are known to change during disease states, such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of female reproductive tract and inflammatory conditions of the eye.

Biodegradable Polymer based Tissue Adhesives:

Many patients undergo surgical closure or tissue repair every year. Tissue adhesives are increasingly being used for wound closure. Compared with conventional sutures, clips and staples, tissue adhesives provide significant advantages, including easy sticking, less trauma, less pain, ease of preparation and application. Tissue adhesives have become common in surgical procedures, mainly as a haemostatic agent to control or prevent bleeding or as a sealant to close tissue openings or defects. Tissue adhesives are also used in dentistry and orthopaedics and for treating cardiovascular and ophthalmic trauma. for example in the treatment of joint fracture.

Tissue adhesive acts as a sub chondral spacer to compensate for the displacement of the joint surface. In recent years, researchers have become interested in the application of tissue adhesives in other fields, such as artificial soft tissues, controlled drug release, and biological agent delivery systems. Tissue adhesives have been used to release antibiotics and antibacterial drugs in the buccal or nasal cavity for intestinal or rectal delivery and even in the urinary system. Tissue adhesives can be divided into three categories: (1) tissue adhesives based on synthetic polymers,

(2) tissue adhesives based on synthetic polymers and natural polymer composites, and (3) natural polymer tissue adhesive for the base. There are already some tissue adhesives existing in the market, such as cyano acrylate and fibrin glue. However, cyano acrylate produces formaldehyde upon degradation in the body, which is toxic to the human body.

Chitosan-Based Tissue Adhesive: Chitosan (CS) is a linear polysaccharide composed of randomly distributed β-(1,4) cross-linked good biocompatibility still needs to be developed. In recent years, hydrogels have received widespread attention to be used as tissue adhesives in biomedical applications, including wound closure and injectable drug delivery systems. Owing to the presence of hydrophilic moieties in the polymer backbone, the hydrogel retains a large amount of water inside the polymer network and exhibits a 3-D network structure was implanted under the skin of rats, and the hydrogel was basically degraded after 4 weeks. Most importantly, the adhesive CS-HA/hmCS hydrogel can close wounds in a seamless manner and promote wound healing. Since the catechol groups can interact with the amine or thiol group in the tissue to form a covalent bond, the catechol-modified chitosan has strong wet tissue adhesion ability. The hydrogel immediately cured on the tissue surface after injection and exhibited excellent wound haemostasis. These catechol functionalized chitosan and Pluronic composite hydrogels are expected to be applied for novel tissue adhesives for drug delivery and tissue regeneration. synthesised a photo crosslinkable chitosan-based adhesive hydrogel by grafting methacrylic anhydride and catechol groups onto chitosan. The adhesive hydrogel exhibited excellent wet adhesion ability on biological tissues, and the adhesive strength was strong to resist different deformations. Due to the presence of various enzymes (including lipase, collagenase, protease and lysozyme) in mice, the volume of the chitosan-based hydrogel gradually decreased in mice. In addition, the hydrogel exhibited good blood compatibility and an excellent haemostatic effect when treating bleeding from wounds.

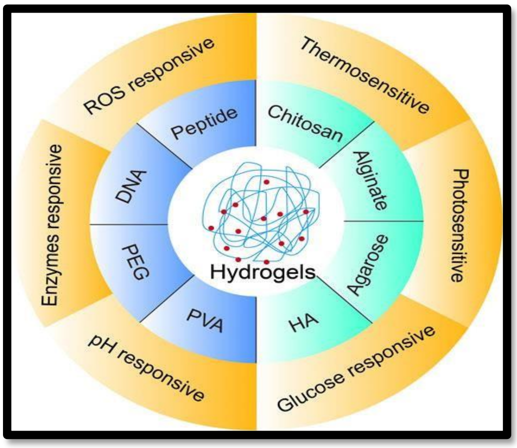

Fig:7 Chitosan bases tissue adhesive

Hyaluronic Acid-Based Tissue Adhesive: Hyaluronic acid is a non-sulphated glycosaminoglycan widely distributed in epithelial tissues and nerve tissues (such as the skin, cartilage and the vitreous humour). It has been demonstrated that HA plays a key role in cell proliferation, angiogenesis, and the wound healing process. In addition, HA has a high water absorption capacity, which can promote the diffusion of nutrients to the wound site and maintain humidity of wound beds. Thus, HA is a natural polymer that is generally used to develop biocompatible and biodegradable hydrogels as tissue adhesives for wound healing and tissue regeneration. Since HA itself presents three main functional groups (carboxylic acids, hydroxyls, and -NHCOCH3 groups) that do not have tissue adhesion, it is necessary to modify HA with tissue reactive groups to produce HA conjugates (catechol, dopamine, pyrogallol, aldehyde, or amine) with tissue adhesion. The adhesion tests demonstrated that the HA-CA hydrogel has strong tissue adhesion and can adhere to wet tissues (such as those of the Liver and the heart). The HA-CA hydrogel can be completely degraded after 16 h in hyaluronidase solution. The same research group further prepared a freeze-dried HA-CA hydrogel to develop a HA-based adhesive hydrogel patch, which can be used as a tissue tape for immediate wound treatment a tissue adhesive and an anti-inflammatory hydrogel based on epigallocatechin gallate modified HA. In the presence of hyaluronidase, the hydrogel can degrade within 15 days to 1 month. Therefore, the functional hydrogel can be used for promoting wound healing or treating inflammatory wounds. Although the developed adhesive based on catechol modified HA has good tissue adhesion, there are still limitations due to the low substitution of catechol groups, resulting in insufficient adhesion and a fast degradation rate. Consequently, the resulting DAHA hydrogel had stronger tissue adhesive strength to different wet tissues. In addition, the hydrogel has good biodegradability, which is suitable for tissue adhesion and tissue regeneration. [30-35]

Alliginated Based- tissue Adhesives: Alginate is a natural linear polysaccharide with good biocompatibility and excellent biodegradability [36]. Alginate-based tissue adhesives can be achieved through the following three pathways: The first one is the physical barrier by directly using an alginate film. Forexample used sodium alginate solution as a surgical sealant. an uncrosslinked alginate membrane with good tissue adhesion. However, the non-crosslinked sodium alginate binder has problems such as poor mechanical properties and instability. [36]

Gelatin-Based Tissue Adhesive: Gelatin is a derivative of collagen, which is obtained by breaking down the natural triple helix structure of collagen into single stranded chains. Gelatin is biodegradable, biocompatible and easy to obtain; therefore**,** it has been widely used in the medical field in the form of capsules, forexample, as capsules, sponges, stents and hydrogels. However, gelatin-based hydrogels show poor mechanical properties and sensitivity to degradation in water which limits its clinical applications. To improve their mechanical and biochemical properties, many researchers prepared gelatin hydrogels by crosslinking gelatin with other biodegrade polymers with functional groups that can react with amino groups on gelatin. For example**,** an adhesive hydrogel composed of aldehyde-based dextran (Dex-U-AD) and gelatin. The amino groups on gelatin chains could react with the aldehyde groups in Dex-U-AD to form a hydrogel network. The Dex-U-AD/gelatin hybrid hydrogel not only showed better adhesive strength than commercially available fibrin-based adhesives but also had no cytotoxicity to the growth of L929 cells and had good in vitro biocompatibility. These adhesives have the potential to be used as bioadhesive materials. In recent years, photo crosslinkable gelatin has been developed, which can be crosslinked to form a 3-D hydrogel with high elasticity and excellen tissue adhesiveness. In addition, the photo-induced cross-linking process is relatively simple, fast, and gentle, which is suitable for in situ curing adhesives [37-40]

Dextran-Based Tissue Adhesive: Dextran is a natural polysaccharide mainly composed of linear α-1,6-glycosidic bonds. Due to its good biocompatibility and biodegradability, dextran is another widely used substance to fabricate tissue adhesive materials. However, dextran does not contain tissue reactive groups in its backbone. For preparation of a dextran-based tissue adhesive hydrogel, dextran is first oxidised by $NaIO_4$ to obtain an oxidised form with aldehyde groups similar to alginate. The oxidised dextran with aldehyde groups can react with amine groups- containing polymers or crosslinkers to in situ form hydrogels for application as haemostatic agents and tissue adhesive. chitosan as a polymer crosslinker to react with oxidised dextran to form an in situ curing adhesive hydrogel, which can be used as a haemostatic material. The efficacy of the adhesive as a haemostate was demonstrated in a rabbit liver injury model. The adhesive also demonstrated its efficacy as a drug delivery vehicle. developed an adhesive hydrogel dressing composed of oxidised dextran and hydrophobically modified chitosan. In a haemorrhagic rat liver model, the viscous hydrogel was proved to have haemostatic ability in vivo. The wound healing function of the hydrogel was verified by an infected rat skin wound model. The above findings indicate that the hydrogel has the potential to heal bleeding and infected wounds. The freeze-dried sponge achieved rapid haemostasis through rapid blood absorption and excellent tissue adhesion. The important thing is that this haemostatic sponge has excellent biodegradability and almost no skin irritation and will be a promising haemostatic dressing. [41-42]

Cellulose-Based Tissue Adhesive: Cellulose has been widely used as a tissue engineering material due to its low cost and biodegradability. Cellulose based hydrogels have been extensively studied due to their excellent biocompatibility. Cellulose is a naturally abundant biological macromolecule with good biodegradability and biocompatibility**.** Cellulose does not present reactive functional group, and requires chemical modifications The CMC-DA hydrogel had high wet tissue adhesion strength (28.5 kPa) that was approximately six times higher than that of commercially available fibrin glue. In addition, 85% of the CMC-DA hydrogel was degraded in 30 days in the cellulase solution. dopamine hydrochloride to cellulose through an amidation reaction and prepared a catechol containing cellulose-based adhesive hydrogel with strong adhesion and good biocompatibility. The adhesion strength increased with the increase of catechol contents, and the maximum adhesive strength on porcine skin was 88.0kPa. The viscous hydrogel can be used as a biocompatible adhesive for wound suture and tissue engineering.

Tissue adhesive for wound closure

Wounds are usually triggered by external forces, which will subsequently damage the structure of cells, blood vessels, and extracellular matrix (ECM). To Avoid, any tissue damage needs to be closed and repaired in a timely manner. Surgical sutures are widely used to seal and repair tissues since they have high tensile strength and low dehiscence rate, facilitating wound closure. However, the surgical suturing process is in herently damaging to the tissues, May require anesthesia, and has a high probability of post operative infection, inflammation, nerve damage, and scar tissue formation. In addition, the surgical suturing process is time-consuming and requires ahigh level of suturing skills for certain specific tissues, which affects the success rate of the procedure. In recent years, tissue adhesives have become a promising alternative to sutures, with the advantages of being simple, time-saving, and avoiding the problems and complications associated with surgical sutures, and have therefore received much attention and research. [45]

Tissue adhesives have been extensively employed as wound dressing for rapid tissue wound treatment and inductive regeneration. Due to the complexity of the wound, tissue adhesives should be biocompatible and biodegradable to allow proper tissue repair and have strong adhesive strength to the tissues, mechanical stability forbearing the dynamic force from tissues, and low cost of production. Never the less, preparing a tissue adhesive that can fulfill all requirements is still tricky. Suitable tissue adhesives should be developed according to the properties required for a particular application and the nature of the wounds.

Preparation of adhesives involves an inter-disciplinary effort, such as the chemical, mechanical and biological intersections, since the physiochemical abilities of the adhesives mainly dictate the properties of the adhesives, the interactions between the tissue and adhesives, the immunological responses of the host, and the topical environmental features. To date, although researchers have produced and commercialized a variety of tissue adhesives, many challenges still restrict their use in numerous clinical applications. [46-48]

Table 1 Common commercially available tissue adhesives for medical devices.

Categories	Commerical product	Manufacturer	Constituents
Natural biological adhesives	Crosseal	Omrix	Human fibrinogen, human thrombin.
	TachoSil	Pharmaceuticals International GmbH	Equine collagen patch, human fibrinogen
	GRF	Microval	Gelatin, resorcinol, formaldehyde

	Evicel	**Ethicon**	**Human factor XII, calcium chloride.**
Synthetic polymer- based tissue ahesives	**Omnex**	**Ethicon**	**n-Octyl-2-cyanoacrylate**
	Indermil	**Henkel**	**n-Butyl-2-cyanoacrylate**
	IFABond	**IFA medical**	**N-Hexyl-2-cyanoacrylate**
	TissGlue	**Coheramedical**	**Lysinedi/tri isocynate-PEG prepolymer.**

APPLICATIONS FOR AHESIVES WOUNDS AND CLOSURES

SKIN: Skin, as the most prominent tissue in the human body, serves roles, primarily providing a defensive barrier to external physical forces or chemical products and infectious pathogens and microorganisms. Trauma or surgical procedures may cause skin injury by impairing its architectural integrity and functions, leading to increased contagious risk. Traditional therapy for treating skin are mainly wound dressing and surgical sutures or staples injury. Wound dressing can supply a physiologically humid surrounding to the injured area and regulate the exudate. Nonetheless, most dressings lack adhesive abilities, which need to be used with the assistance of bandages. Suture or staple is widely used for the repair of injured skin. Although they have high tensile strength and low desihance rate, which facilitate wound closure the drawback such as the high probability of postoperative infection, inflammation, nerve damage, and scar tissue formation, still limit their applications. Therefore, tissue adhesives have been widely developed for wound closure. A strategy based on polyphenol-protein complexation was proposed by Jiang et al. to prepare hydrogels with body temperature-triggered fast adhesion and damage free on demanding peeling The polyphenol prepolymer (PGA) rich in phenolic and quinone groups, was formed by alkaline oxidative pre-polymerization. The multiple interactions of polyphenol groups were used in the gelatinization process of GelMA. The PGA-GelMA hydrogel exhibited mechanical flexibility and high ductility matching the skin tissue and avoiding the damage caused by pulling the hydrogel when peeled on the skin surface. In addition, the PGA-GelMA hydrogel showed excellent anti inflammatory, antioxidant, and anti-allergic bioactivities, which can effectively avoid skin irritation or allergy caused by conventional skin adhesive in long-term skin contact. [50]

Fig.8 Adhesives for skin

CORNEA: The cornea is a vital tissue in the visual system. Trauma, infection, autoimmune diseases, and burns are the primary triggers of corneal scarring and damage, resulting in it being one of the leading blindness causing diseases worldwide. Currently, there are two types of standard corneal patches according to the grafting method: suture- patches that need to be fixed to the injured area using surgical sutures and noninvasive adhesive-type patches that can be used as adhesives themselves and adhered directly can be used as adhesives themselves and adhered directly to the injured area. However, the surgical suturing process damages the cornea, and the residual sutures may cause inflammation and vascularization. Therefore, adhesive material have emerged as a progressive therapy for healing corneal injury. Generally, materials utilized to engineer corneal replacement should have a structure and physiochemical properties similar to those of the natural cornea. The desired material to promote corneal restoration should be biocompatible and biodegradable, mechanically stable, highly transparent, highly adhesive to the cornea, and capable of supporting the growth of cells and regeneration of tissues. a light-cured corneal matrix (LC-COMatrix), which was synthesized from the decellularized porcine cornea containing undernatured collagen. The LO-CO Matrix was multifunctional and had an appropriate swelling ratio, biodegradability, and viscosity to apparently improve the mechanical property, stability, and adhesion of the hydrogel. The LC-CO Matrix can adhere firmly to the human cornea and effectively occlude the corneal perforation. The in vivo studies also demonstrated that the LC- CO Matrix could seal corneal perforation and replace cornea stromal defects in a rabbit. GelMA- based hydrogels (GelCORE) for the sutureless repair of corneal injuries. The physiochemical abilities of Gel CORE can be well regulated by changing the polymer concentrations and photo- crosslinking time. Gel CORE demonstrated superior tissue adhesive strength compared to commercially available adhesives. In vivo experiments indicated that Gel CORE can effectively adhere to the defected cornea and stromal regeneration and reepithelization [52]

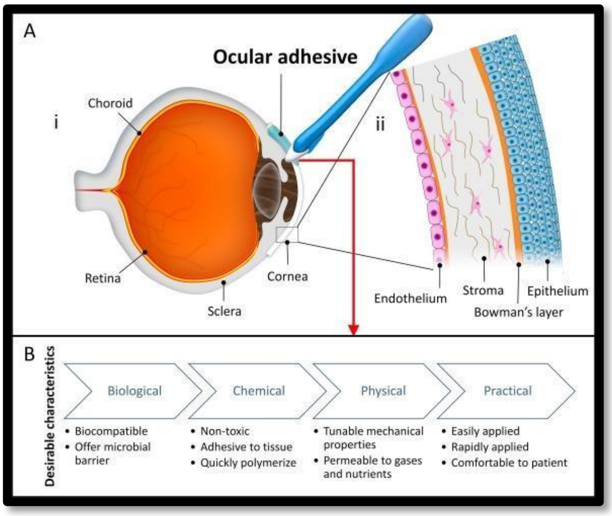

Fig.9 Ocular adhesive

GASTROINTESTINAL TISSUE: Apart from skin and cornea, tissue adhesives have also been widely used in gastrointestinal (GI) tissues. The primary function of GI tissue is to transport, digest, and absorb food for the body. GI tissue surgery usually needs the stomosis between two discrete tissues for the restoration of GI continence.96 GI surgeries may induce severe complications, such as an astomotic dehiscence, which is primarily destructive and can lead to leaky luminal components and hemorrhage. A variety of technics, such as-Sutures and staples, are widely employed to sustain an astomotic conservation. However, an a stomotic leakage can still happen in as high as 23% of cases, and low colorectal and coloanal an astomoses can lead to increased mortality. In recent years, tissue adhesives have been developed to enhance the lines of sutures and staples for the prevention of leakage. Various materials are employed as GI tissue adhesives, such as fibrin, albumin-based, PEG-based, and gelatin-based adhesives. Fibrin is a potent sealing agent with excellent biocompatibility in GI procedures. Still, the ability to improve wound healing is limited, and it may inhibit bacterial phagocytosis by immune cells. Although albumin-based adhesives can offer a strong sealing for an a stomosis, the high stiffness and poisonous by-product can be risky. Researchers presented a polyethyleneimine and polyacrylic acid (PEI/PAA) powder with self-gel and adhesion properties that could upscale interfacial water in situ to construct a physically crosslinked hydrogel within a few seconds because of the strong physical interactions between the materials. In addition, the physically crosslinked materials could penetrate the substrate polymer networks to improve wet adhesion. The PEI/PAA powder surface deposition can seal the injured pig stomach and intestine despite their irregular and highly mechanically challenging surfaces. The researchers further demonstrated that PEI/PAA powder was an effective sealer for improving the healing of gastric perforationinrats. PEI/PAA powder has robust wet adhesion, good compatibility, adaptability to complicated sites. LAP was composed of a peptide hydrogel with high water absorption, an adhesive layer decorated with a butyramide (NB) group, and a basal membrane constructed by poly(l-lactic acid) (PLLA) to improve mechanical stability. Light activated LAP has been shown to rapidly and firmly close multi- visceral open wounds with only 15s pressure on the defect. In vivo studies have demonstrated that LAP had good biodegradability provided an immunological microenvironment favorable for angiogenesis and tissue regeneration. In a rabbit gastric perforation model, LAP can be used for suture less wound closure and total gastric repair. The progress made in this study will demonstrate next-generation adhesive patches with mechanical abilities and macrophage modulation capabilities.[54]

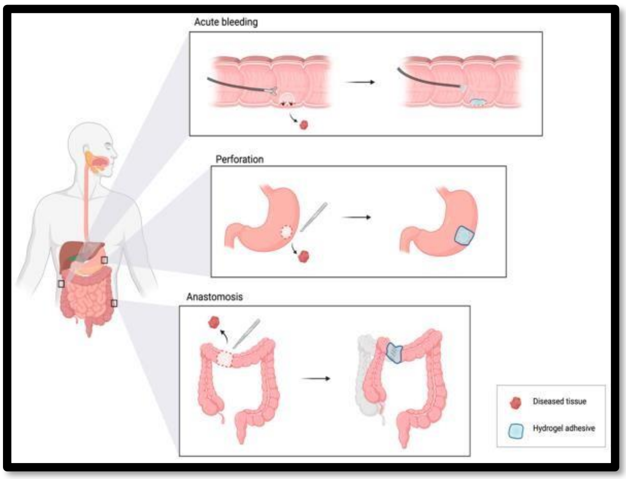

Fig.10 Gastrointestinal adhesive Table 2 Taditional tissue adhesive available in clinical application

S.NO.	Tissue adhesive	Components	Advantages	Clinical application	Reference
1)	Cyanoacrylate glues	2-MCA, 2-ECA, ICA, and2-OCA.	Strong adhesion. Easy to use.	Plastic surgery, including wound closures of face, head, neck.	[56]
2)	Fibrin sealent	Concentrated fibrinogen cryoprecipitate, thrombin.	Fast curing. Biocompatible	Orthopedic surgery, breast cancer surgery, nervous system prevention.	[57]
3)	Gelatin-based sealant	Gelatin-based sealant	Biodegradibility.	Acute type A dissection treatment	[58]
4)	BioGlue sealants	45% bovine albumin, 10% gliutaraldehyde.	Fast curing. Biodegradibilty	Seal pulmonary air leak. Reducing blood loss.	[59]

DISCUSSION

In the fields of biomedical engineering and regenerative medicine, bioadhesives are essential for tissue regeneration and repair. These substances, which include both synthetic and natural variants like cyanoacrylates and fibrin, attach themselves to biological tissues by means of chemical bonding and physical interactions. Their uses are numerous and include everything from helping with tissue grafting to closing wounds. Bioadhesives aid in the formation of scaffolds for cell proliferation and differentiation in regenerative medicine, which promotes tissue regeneration in organs such as the liver and heart. Despite their promising potential, challenges such as biocompatibility and degradation rates persist, driving ongoing research for enhanced properties and expanded applications. Ethical considerations and safety aspects, including allergic reactions and long-term effects, also warrant attention in the development and use of bioadhesives for medical purposes. Overall, bioadhesives represent a significant advancement in improving patient outcomes and advancing the field of regenerative medicine

Because they form a strong link with biological tissues and facilitate tissue regeneration and repair, bioadhesives are indispensable instruments in contemporary medicine. Collagen and fibrin are examples of natural bioadhesives that are biocompatible and aid healing without causing negative side effects. Strong adherence and quick wound closure are provided by synthetic bioadhesives such cyanoacrylates. Due to their adhesive qualities, which serve to reduce bleeding and hasten healing, these materials are frequently employed in surgical operations such as wound closure, tissue grafting, and organ repair. Bioadhesives are essential for tissue engineering in regenerative medicine. They facilitate the creation of new tissues and organs by acting as scaffolds for cell adhesion and proliferation. This application shows great promise in treating tissue damage brought on by illnesses or injuries, potentially curing ailments that were previously difficult to treat successfully. The creation of customized, high-tech bioadhesives with features like regulated rates of degradation and improved adhesion strength keeps pushing the boundaries of tissue regeneration and repair techniques.

Bioadhesives have many benefits, however there are drawbacks and things to think about. To guarantee compatibility with the body's natural functions and reduce negative reactions, biocompatibility is still essential. Furthermore, careful assessment and monitoring are necessary to determine the long-term effects of bioadhesives on tissues and overall patient health. The development and usage of bioadhesives must take into account safety precautions to mitigate potential dangers, such as allergic reactions, as well as ethical issues pertaining to their use in medical procedures.Forward-looking, current research endeavors to surmount current constraints and open up novel avenues for bioadhesives in tissue regeneration and repair. Advances in biotechnology, medical engineering, and biomaterials research could potentially improve the safety and effectiveness of medicines based on bioadhesives. In the end, bioadhesives are essential elements in the rapidly changing field of medical technologies, providing flexible ways to enhance patient care and results in tissue healing and regenerative medicine.

CONCLUSION

In conclusion, bio adhesives represent a transformative approach in the field of tissue repair and regeneration, offering versatile solutions with significant potential for improving patient outcomes. These materials, whether derived from natural sources or synthetically engineered, exhibit strong adhesive properties that enable secure bonding to biological tissues. In applications ranging from wound closure and surgical procedures to tissue engineering and organ regeneration, bio adhesives play a pivotal role in promoting healing, minimizing bleeding, and supporting the growth of new tissues. While bio adhesives hold tremendous promise, ongoing research and development efforts are essential to address challenges such as biocompatibility, long-term effects, and ethical considerations. Advancements in biomaterials science, coupled with innovations in biotechnology and medical engineering, are driving the evolution of bio adhesive technologies towards safer, more effective solutions.

Ultimately, the continued exploration and refinement of bio adhesives for tissue repair and regeneration herald a future where these materials contribute significantly to advancing regenerative medicine, offering hope for better treatments and outcomes for patients facing tissue injuries or degenerative conditions.

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