**Fibrin Glue: A Modern Approach to Medical Solutions**

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**Abstract**

This chapter provides an update on the current market for hemostats, adhesives, and sealants, and compares them to other products. It also includes a review of a year's worth of articles on fibrin sealant, categorized by frequency of events. Scientists and clinicians have been working on creating a low-cost, widely usable substance for sealing and dressing wounds. A topical biological adhesive called fibrin glue which imitates the last stages of coagulation in its action. The substance is made up of concentrated human fibrinogen mixed with calcium chloride and bovine thrombin. It helps with tissue closure and hemostasis without causing inflammation. Fresh frozen plasma can be used to make the fibrinogen component, reducing the risk of transfusion-transmitted illnesses. A commercial product called vitagel is available for this purpose. Using a polyglycolic acid sheet coated with fibrin sealant and rubbing fibrinogen into the defect area has shown the best results in preventing postoperative air leakage. Chest tubes have also been used to drain air leaks patched with polyglycolic acid sheets and fibrin sealant in lower-risk patients.

1. **Introduction**

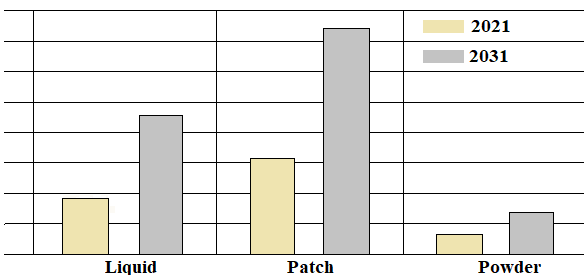
Scientist and clinicians have been working on creating a low-cost, widely usable substance that would not cause inflammatory reactions and could be used for sealing and dressing wounds as well as promoting wound healing for years now. Synthetic, semi-synthetic, or natural glues are an alternative to traditional surgical sutures or suture support because they cling to nearby tissues by adhesion processes like van der Waals forces, capillary forces, hydrogen bonds, static electric forces, and chemical interactions. Natural glues that are quickly absorbed enhance the body's natural processes of tissue mending and regeneration. A topical biological adhesive called fibrin glue which imitates the last stages of coagulation in its action. Fibrin glue (also called fibrin sealant) is a surgical formulation used to create a fibrin clot for hemostasis, cartilage repair surgeries or wound healing. The substance that makes up the glue is a solution of concentrated human fibrinogen that has been mixed with calcium chloride and bovine thrombin to activate it. The clot that forms help with tissue closure and hemostasis, and it is totally absorbed during wound healing without causing a foreign body reaction or significant fibrosis. Fresh frozen plasma acquired from single unit donations can be used to make the fibrinogen component of fibrin glue, lowering the risks of transfusion-transmitted illnesses associated with exposure to pools from several donors.

Fibrin glue contains separately packaged human fibrinogen (glycoprotein) and human thrombin (coagulation factor). It is actually available as two component system; first component contains highly concentrated fibrinogen, factor XIII, fibronectin and traces of other plasma proteins. The second component contains Thrombin, calcium chloride, and antifibrinolytic agents such as aprotinin. Mixing of two components promotes clotting with the formation and cross linking of fibrin. In this domain, clear definitions are essential. A hemostat induces blood clotting, primarily active when blood is present in the surgical field. In contrast, a sealant establishes a sealing barrier against gas or liquid leakage, self-polymerizing and functioning optimally in dry conditions. An adhesive binds structures, also self-polymerizing and typically most effective in dry settings. Both sealants and adhesives, when applied to potentially leaking blood vessels, can exhibit a hemostatic effect by sealing vessel holes and halting bleeding, but they don't necessarily trigger blood coagulation. It's imperative to differentiate these terms, as they serve distinct purposes in medical and surgical contexts, ensuring precision and safety in procedures. Fibrin sealant is the only commercially available FDA approved material for clinical use in all the three of these groupings: hemostats, sealants, and adhesives. Fibrin was first used as a hemostat by Bergel in 1909 [1], then by Young and Medawar as an adhesive in 1940 [2], by Matras as concentrated fibrinogen for nerve attachment in 1972 [3], and by the Food and Drug Administration (FDA) in 1998 [4, 5] and in 2010 [6, 7] for a fibrin sealant patch. In the United States, a human thrombin-containing formulation received medical approval in March 2003, and the European Union followed in October 2008 [8-10]. Additionally, wound dressings with adhesive integrated in them build impermeable barriers to microorganisms and potential contaminants. When the tissue is too delicate or thin for traditional suturation, for example, glues can be utilised as separate dressings or patches or in conjunction with surgical sutures. Materials like fibrinogen, gelatin, polyethylene glycol, polyacrylates (like cyanoacrylate), chondroitin sulphate, collagen, dextran, albumin, or chitosan are used to make tissue adhesives. Fibrin glue has been utilized in a range of surgical and urgent care procedures and is particularly successful in treating patients who have hemostatic system abnormalities or who are receiving heparin. However, fibrin glue is sold commercially in Europe under the trade names Beriplast, Tisseel, and Tissucol, where it is not available in the United States. Extemporaneous compositions of fibrin glue have often been used for therapeutic purposes in the United States [11, 12]. Depending on whether the plasma is taken from the same patient or someone else, many types of fibrin sealants have been created, such as autologous and homologous fibrin sealants. The fibrin glue does not result in tissue necrosis, fibrosis, or inflammation, is biocompatible, and is resorbable. Depending on the composition, fibrin glue degrades over a period of days to months. The risk of virus transmission still exists despite the fact that fibrin glue is used as a hemostatic agent in a variety of surgical procedures. The components of fibrin glue go through processes like pasteurisation, two-step vapour heat treatment, solvent-detergent cleaning, dry heat treatment, nanofiltration, precipitation, pH treatment, and some chromatographic procedures in order to screen for viruses and inactivate or reduce them. However, a combination of these treatments is generally required for medical application as because a particular treatment is not effective against all the viruses.In almost every surgical speciality, fibrin glue's hemostatic and adhesive qualities can be used. The benefits of the glue have been studied extensively in the disciplines of ENT, neurosurgery, and cardiovascular surgery.

1. **Market overview:**

**By dosage Forms**

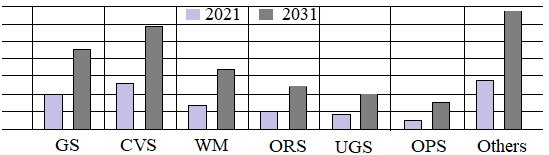
Since 1985, this Centre has utilized fibrin sealant's hemostatic and adhesive qualities in a wide range of operations with an average of over 90% success rate. The market for fibrin sealants was estimated to be worth $1.1 billion globally in 2021 and is anticipated to increase to $2.6 billion by 2031, with a predicted Compound annual growth rate (CAGR) of 9.5% from 2022 to 2031. Due to widespread use of patches for managing wounds and minimizing blood loss, as well as a rise in technological developments in fibrin sealant patches, the patch category earned the highest revenue in 2021 when analyzed by dosage form, figure 1 (Report Code: A31579, Source: https://www.alliedmarketresearch.com/fibrin-sealants-market). From the market survey report showed that the patch segment generated maximum revenue in 2021.



**Figure1: Fibrin Sealants Market by Dosage Forms**

**By Application**

Due to an increase in lung diseases, cosmetic surgeries, and dental surgeries, the others segment saw the highest revenue generation in 2021. The rise in lung cancer, which causes an increase in pulmonary surgery and fuels the growth of the others category, is also linked to the segment's expansion. Apart from the all segments, the others segment generated maximum revenue in 2021, owing to rise in number of dental surgeries, cosmetic surgery and pulmonary diseases, figure 2 (Report Code: A31579, Source: https://www.alliedmarketresearch.com/fibrin-sealants-market).



**Figure 2: Fibrin Sealants Market by Application**

[GS: General Surgery, CVS: Cardiovascular Surgery, WM: Wound Management, ORS: Orthopedic Surgery, UGS: Urological Surgeries, OPS: Ophthalmic Surgery]

### Composition:

Fibrin glue is composed of thrombin, fibrinogen and sometimes factor XIII and anti-fibrinolytic agents and it comes in two vials, respectively containing:

* Fibrinogen: Lyophilised pooled human concentrate.
* Thrombin: Originally from bovine, modern formulations now include human thrombin [13].

Both of the two components are mixed immediately before application [14]. Now a day formulation from different manufacturing company may also contain calcium salt [15], aprotinin, fibronectin, plasminogen, and factor XIII [16].

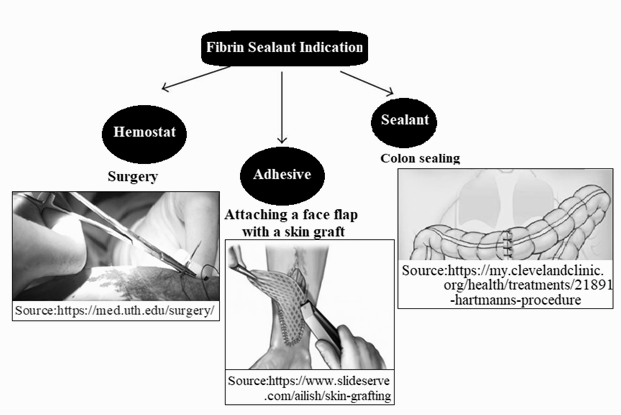
### Factors affecting structure:

Factors that influence dimensional structure of fibrin gel giving rise to fine or coarse gel:

* Changing concentration of fibrinogen
* Changing concentration of thrombin-increased concentration increases ultimate tensile strength and young modulus of gel
* Changing concentration of calcium
* pH
* Temperature

**Classification of Fibrin Glue:**

It has been possible to classify the FDA-approved hemostats, sealants, and adhesives using a framework that aids in understanding not only the range of commercially available products but also the incredibly varied capabilities of fibrin sealant [17-20]. FDA approved material for clinical use in all the three of these groupings: hemostats, sealants, and adhesives (Figure 3).



**Figure 3: The uses of fibrin sealant that the FDA has currently approved [21]**

The hemostats, sealants, and adhesives are the three main groupings that make up this system, as seen in Table 1. Each of these groups is divided into classes and then categories. It is instantly clear that fibrin sealant is the only commercially accessible substance present in all three groups, and that it is the only substance available in both liquid and patch forms, as highlighted (italics).

**Table 1: A system of classification for FDA approved local hemostats, sealants, and adhesives in 2013. The fibrin sealants are in bold font [20], adapted and reprinted with kind permission of the Southeastern Surgical Congress in [16, page 1306, Table 1].**

|  |  |  |
| --- | --- | --- |
| **Group** | **Category** | **Class** |
| Hemostats | Mechanical | Bovine collagen, Porcine gelatin, Oxidized regenerated cellulose, Polysaccharide spheres |
| Active | Human pooled plasma thrombin with or without porcine gelatin sponge or powder, Bovine thrombin, Recombinant human thrombin |
| Flowable | Porcine gelatin ± thrombin, Bovine gelatin and human pooled plasma thrombin |
| Fibrin sealant | Individual human plasma *liquid*,  bovine collagen, bovine thrombin and Human pooled plasma and oxidized regenerated cellulose *patch*,  Human pooled plasma and equine collagen *patch*, Human pooled plasma *liquid* |
| Sealants | Fibrin sealant | Human pooled plasma *liquid* |
| Polyethylene glycol polymer (PEG) | Two PEGs, trilysine amine, and FD&C Blue #1,  PEG and human serum albumin |
| Albumin & glutaraldehyde | Bovine serum albumin and 10% glutaraldehyde |
| Cyanoacrylate | Octyl and butyl lactoyl cyanoacrylate |
| Adhesives | Cyanoacrylate | Octyl cyanoacrylate with FD&C Violet #2 |
| Octyl cyanoacrylate with FD&C Violet #2 and polyester mesh,  Butyl cyanoacrylate with or without FD&C Violet #2 |
| Albumin & glutaraldehyde | Bovine serum albumin and 10% glutaraldehyde |
| Fibrin sealant | Human pooled plasma *liquid* |

Therefore, the only substance that has been thoroughly investigated and assessed in all three uses (as a hemostat, sealant, and adhesive) and in numerous forms (liquid and patch) is fibrin sealant. Table 2 provides an illustration of the commercial fibrin sealants that are now offered globally. The safety, effectiveness, usability, and price of these commercial goods are discussed in the sections that follow [17-20].

**Table 2: List of commercially available fibrin sealants**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Manufacturer** | **Function** | **Sources** | **Component** | **Brand Name** |
| Baxter International Inc. | Hemostat and sealant | Human pooled plasma | human thrombin-factor XIII-fibrinogen | Tisseel (USA, Europe), also appears as Tissusol |
| Ethicon | Hemostat | Human pooled plasma | human thrombin-fibrinogen | Evicel (USA) |
| Orthovita /Stryker, Malvern, PA | Hemostat | Individual plasma,bovine collagen and thrombin | Collagen with thrombin, fibrinogen, and platelets | *Vitagel*, |
| Baxter International Inc. | Hemostat | Human Thrombin, bovine collagen | Gelatin matrix thrombin | FloSeal (USA) |
| Omrix Biopharmaceuticals S.A. – Ethicon | Sealant | Human thrombin fibrinogen and fibronectin | Human thrombin-factor XIII-fibrinogen | Quixil (Europe) |
| Baxter, Westlake Village, CA | Adhesive | Human pooled plasma | Cyanoacrylate Albumin and glutaraldehyde | *Artiss* |
| King Pharmaceuticals | Hemostat | Human pooled plasma | Bovine thrombin | Thrombin-JMI (USA) |
| Nycomed Pharma | Hemostat | Human pooled plasma and equine collagen | Human thrombin-fibrinogen + collagen | *Tachosil*, Baxter,Westlake Village, CA |
| Ethicon/ J&J, Somerville, NJ | Hemostat | Human pooled plasma and oxidized regenerated cellulose | Matrix, coated with Human Fibrinogen and Human Thrombin | *Evarrest* |

**A. FDA Approved Hemostats:**

Fibrin sealants used in surgical procedures are categorized into four distinct classes. The first class is derived from human pooled plasma and primarily consists of fibrinogen and thrombin. The second class combines individual human plasma units with bovine elements to enhance clotting. In the third class, dry fibrin sealants are prepared from human plasma fibrinogen and thrombin and affixed to either equine collagen or oxidized regenerated cellulose patches for immediate use. These four categories offer surgeons diverse tools for managing bleeding and achieving tissue adherence in a variety of medical settings.

**1. Human Pooled Plasma Fibrinogen and Thrombin:**

The safety of these liquid agents relies significantly on their preparation using plasma pools from multiple donors (Tisseel, Baxter, Westlake Village, CA; Evicel, Ethicon/J&J, Somerville, NJ) [22, 23]. Both products contain highly concentrated fibrinogen and thrombin, with Tisseel at 85 mg/mL and 500 IU/mL and Evicel at 70 mg/mL and 1,000 IU/mL [22, 23]. However, there is a concern of potential transmission of viral diseases such as Parvovirus B19, hepatitis, and HIV, as well as prion diseases like Creutzfeldt-Jakob disease (CJD) [22, 23]. Reports of Parvovirus B19 transmission have been documented in Japanese literature [24, 25] because this virus is particularly resistant to removal from plasma. One study has suggested a risk of up to 20% for viral transmission in patients receiving pooled plasma fibrin sealant [26]. Nevertheless, it's crucial to note that no reports of hepatitis or HIV transmission associated with fibrin sealant have emerged in over two decades of worldwide literature. This is due to rigorous viral prevention measures, including viral screening through serology and polymerase chain reaction (PCR) testing, and viral reduction techniques like filtration, heat treatment (dry or vapor heating, pasteurization), solvent/detergent cleansing, precipitation, pH treatment, and chromatography [27]. Additional safety concerns encompass the prohibition of intravascular injection of any product containing thrombin, as it may lead to thrombosis, hypotension, and death. Moreover, it's critical to prevent fibrin sealant from entering cell saver or cardiopulmonary bypass circuits to avoid the risk of thrombosis [28]. Additional safety concerns include the danger of applying excessive fibrin sealant, which may contribute to infection and reduced healing, as well as air emboli associated with the use of gas-driven sprayers supplied by product manufacturers [28].

**2. Individually Obtained Units of Human Plasma (or Platelet-Enriched Plasma) Mixed with Bovine Thrombin and Collagen:**

In this particular class of fibrin sealants, we find a single commercial product known as Vitagel, manufactured by Stryker in Malvern, PA. Vitagel is provided as a kit containing bovine collagen (20 mg/mL) and thrombin (300 IU/mL in a 40 mM CaCl2 buffer), along with the necessary materials to collect plasma from the patient's own blood [29]. The manufacturer now advises the use of a platelet-enriched fraction of plasma to leverage the role of platelets in promoting blood clotting and healing [30].

The safety of this product primarily hinges on the use of bovine thrombin instead of human thrombin to convert plasma fibrinogen into fibrin. Although not associated with viral transmission in humans, bovine thrombin may lead to an immune-mediated coagulopathy. Bovine thrombin (Thrombin-JMI, King, Pfizer, UPM Pharmaceuticals, Bristol, TN) is accompanied by an FDA black box warning due to occasional laboratory clotting irregularities, coagulopathy, and, in rare instances, death [31]. These risks result from patients developing antibodies against bovine factor II (thrombin) and the presence of small amounts of bovine factor V as a contaminant. The risk of coagulopathy increases with repeated exposure. Some human antibodies produced in response to bovine clotting factor antigens can cross-react and neutralize human factor II and V, thereby obstructing the common pathway of the clotting process. Moreover, the bovine microfibrillar collagen in this specific formulation of fibrin sealant may lead to an increase in bovine serum antibodies [32]. The use of this form of fibrin sealant can also result in swelling due to the presence of bovine collagen, which can be particularly significant in enclosed spaces or in proximity to the central nervous system (CNS) [32]. The effectiveness of this product has been demonstrated in a comprehensive multicenter, prospective, randomized trial, encompassing patients from various medical specialties, including cardiology, hepatology, general surgery, and orthopedics [33-36]. This trial showed significant and clinically relevant improvements in the time required to achieve hemostasis across all specialty groups. As a result, this fibrin sealant has garnered broad regulatory approval for surgical hemostasis.

**3. Dry Human Pooled Plasma Fibrinogen and Thrombin Fixed on an Equine Collagen or Oxidized Regenerated Cellulose Patch:**

These two distinct categories of fibrin sealant hemostats will be discussed together because their primary difference lies in the material used to create the patch. Their safety profiles, represented by Tachosil (Baxter, Westlake Village, CA) and Evarrest (Ethicon/J&J, Somerville, NJ), closely resemble those of the liquid fibrin sealants prepared from pooled plasma. Therefore, we won't delve into the detailed risks associated with pooled plasma use in this section.

For both available patches, it's crucial to avoid packing them into tight spaces to prevent compression injuries, placing them in infected or contaminated areas to avoid exacerbating infections, and introducing them intravascularly to prevent life-threatening thromboembolic events [37, 38]. Both patches have the potential to trigger allergic or anaphylactic reactions due to the presence of human serum proteins in their preparations.

The patch employing equine collagen (Tachosil, Baxter, Westlake Village, CA) may incite allergic reactions in patients sensitive to horse proteins [37], while the patch with oxidized regenerated cellulose (Evarrest, Ethicon/J&J, Somerville, NJ) may be associated with adhesion formation. Notably, neither patch contains antifibrinolytic agents, thereby avoiding some potential complications linked to their use. Biodegradation occurs over a period of 8 weeks (Evarrest) to 13 weeks (Tachosil) [38].

Presently, the fibrin sealant equine collagen patch (Tachosil) is FDA-approved exclusively for use in cardiac surgery. This patch has undergone evaluation in multicenter, prospective, randomized clinical trials in cardiac, hepatic, and renal operations, with clinically and statistically significant benefits in achieving hemostasis in all investigations [39, 40, 41, 42].

Conversely, the fibrin sealant oxidized regenerated cellulose patch (Evarrest) is FDA-approved only for soft tissue surgery. A multicenter, prospective, randomized trial involving its application in retroperitoneal, intra-abdominal, pelvic, and noncardiac thoracic procedures has demonstrated clinically and statistically significant benefits in achieving hemostasis across all arms of the study.

A notable advantage of both patches [37, 38] is their straightforward storage requirements; they do not need complex conditions like freezing or refrigeration and are readily available for use once the packaging is opened.

**B. FDA Approved Sealant:**

The fibrin sealant category of sealants [20] consists of one class containing one FDA approved commercial product.

**Human Pooled Plasma Fibrinogen and Thrombin:**

Regarding its effectiveness as a sealant, this specific type of fibrin sealant has received FDA approval for use in preventing the leakage of bowel contents during colostomy closure [22]. Its application in sealing the colon was demonstrated in a single-center, prospective, randomized trial, showing statistically significant reductions in complications related to bowel anastomoses, including issues like leakage, abscess formation, the need for reoperation, shock, and even mortality [22]. It's important to note that there haven't been any multicenter, prospective, randomized trials published in this particular indication [20]. Based on my experience, when used for intestinal sealing, fibrin sealant exhibits only moderate strength and is most effective when applied to a dry surface [22].

**C. FDA Approved Tissue Adhesive:**

The fibrin sealant category of adhesives [20] consists of one class containing one FDA approved commercial product.

**Human Pooled Plasma Fibrinogen and Thrombin:**

The sole product in this category, Artiss by Baxter in Westlake Village, CA, is composed of concentrated fibrinogen (85 mg/mL), thrombin (5 IU/mL), and synthetic aprotinin (3,000 KIU/mL). It shares a similar safety profile with pooled plasma fibrin sealant hemostats and sealants, such as Tisseel by Baxter [43]. One significant safety concern with this adhesive application is the risk of applying an excessively thick layer before placing the skin graft or flap, which could impede nutrient diffusion to the graft or the healing of the flap [43].

The FDA has granted approval for this adhesive to be used in placing skin grafts during burn debridement procedures as an alternative to sutures or staples, and for attaching skin flaps during rhytidectomy (face-lift) procedures. The rate of fibrin formation is influenced by the thrombin concentration when thrombin is combined with fibrinogen. This specific formulation contains a lower thrombin concentration (5 IU/mL) compared to other forms of fibrin sealant used for hemostasis or adhesion. As a result, it polymerizes more slowly, allowing approximately one minute for the proper placement of grafts or flaps. Two multicenter, prospective, randomized trials support the use of this fibrin sealant for attaching skin grafts and flaps [43, 44, 45].

In the skin graft study [44], patients were their own controls, comparing graft attachment at burn sites using fibrin sealant versus skin staples in two similar size and location burns. The quality of graft attachment, as measured by wound closure on day 28, was found to be noninferior with the fibrin sealant. Moreover, there were statistically significant reductions in hematoma and seroma formation in the fibrin sealant group, and participating investigators noted statistically significant benefits in terms of graft adherence quality, fixation method preference, satisfaction with fixation, and overall healing. Patient-determined outcomes also favored fibrin sealant, with less anxiety and a preference for using the sealant over staples.

**D. Plasma Fractionation Derived Fibrinogen with Calcium and Commercial Thrombin:**

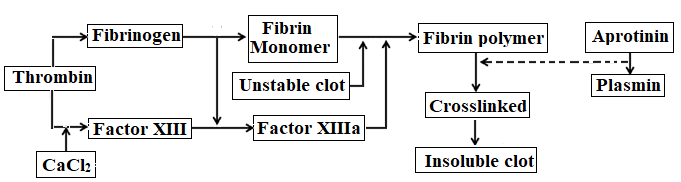
There is now a diverse range of devices designed to aid in obtaining platelet-poor or platelet-rich plasma, which can serve as a source of nonconcentrated fibrinogen (typically within the range of 20-40 mg/mL). This fibrinogen can be combined with one of the commercially available standalone thrombins, such as Thrombin-JMI (King, Pfizer, UPM Pharmaceuticals, Bristol, TN), Evithrom (Ethicon/J&J, Somerville, NJ), or Recothrom (The Medicines Company, Parsippany, NJ) to produce fibrin sealant. These devices, including Amicus (Baxter, Round Lake, IL), Cell Saver (Haemonetics, Braintree, MA), Harvest (Smith and Nephew, Memphis, TN), Magellan (Medtronic, Minneapolis, MN), Recover (Biomet Biologics, Warsaw, IN), and Symphony (Depuy, Raynham, MA), are capable of producing fibrinogen. When combined with calcium and thrombin, these devices generate fibrin sealant. Calcium chloride is necessary to counteract the anticoagulant effects of sodium citrate, which is often used to prevent clotting of the harvested plasma.

While this form of fibrin sealant employs lower-concentration fibrinogen compared to commercially available concentrated pooled fibrin sealants, resulting in reduced strength, it has the potential to produce a platelet-enhanced fibrin sealant that may have beneficial implications for wound healing [46, 47].

1. **Mechanisms of Fibrin glue:**

When human tissue is injured, it naturally goes through a process of bleeding followed by the formation of a blood clot. This clotting mechanism is an essential part of the body's natural wound closure process. The formation of a clot occurs as a result of the final common pathway in the coagulation of blood. Fibrin glue works by imitating this coagulation cascade, which gives it its adhesive properties.

The coagulation cascade is initiated when the tissue is injured. Activated factor X plays a crucial role in this process by selectively breaking down prothrombin into thrombin. In the presence of thrombin, fibrinogen is transformed into fibrin. Additionally, thrombin activates factor XIII, which is present in the fibrinogen component of the glue. Factor XIII helps stabilize the clot by promoting the polymerization and cross-linking of the fibrin chains, leading to the formation of long fibrin strands in the presence of calcium ions (Figure 4). This final common pathway for both the extrinsic and intrinsic coagulation pathways in the body is replicated by fibrin glue to induce tissue adhesion.



**Figure 4. Mechanism of fibrin glue clot formation similar to physiological coagulation**

In a nutshell, thrombin with Ca2+ and fibrinogen with factor XIII make up fibrin sealants. To create fibrin monomer, thrombin separates fibrinopeptides A and B from α and β chains of fibrinogen, respectively. An unstable clot is created when the monomer physically cross-links through hydrogen bonding. Factor XIII is a fibrin stabilizing factor that is activated by thrombin and forms factor XIIIa with Ca2+ as a cofactor. The unstable clot or fibrin monomer is subsequently affected by factor XIIIa, creating amide connections between glutamine and lysine residues that create cross-links and create an insoluble clot that is resistant to proteolytic digestion (Figure 4). Along with strengthening the clot and preventing fibrinolysis, the cross-linking reaction involves the attachment of plasmin inhibitors to the fibrin chain, such as the α 2-plasmin inhibitor (α2-PI), α2-macroglobulin, and PAI-2. Other adhesive glycoproteins like fibronectin, thrombospondin, vitronectin, and von Willebrand factor are also affected by factor XIII. The process of forming a clot involves several cross-linking processes; for instance, at the site of the wound, fibrin principally forms cross-links with both collagen and adhesive glycoproteins. Cross-linking also takes place simultaneously between collagen and other tissue proteins and the adhesive glycoproteins. The creation of a strong, adhesive, insoluble clot resistant to fibrinolysis is the combined effect of all the cross-links at the wound site and the presence of plasmin inhibitors [48].

There is subsequent proliferation of fibroblasts and formation of granulation tissue within hours of clot polymerization. Clot organization is complete two weeks after application. The resultant fibrin clot degrades physiologically.

**Role of calcium ions**:

Fibrin (ogen) has calcium ion (Ca2+) binding sites that are crucial for its stability and that encourage polymerization. Each of the γ-nodules (γ1 and γ2) and β-nodules (β1 and β2) contains two calcium-binding sites. The side chains of residues γAsp318 and γAsp320 and the backbone carbonyls of residues γPhe322 and γGly324 make up the high-affinity γ1 site, which is situated close to hole 'a'. The backbone carbonyls of the residues γGly296 and γAsp298 make up the lower affinity site γ2, together with γAsp294 and γAsp301. The sites β1 and β2 both have a modest affinity for Ca2+, but site β2 forms a Ca2+ bridge that joins the b-nodule to the coiled coil. Sialic acid offers more Ca2+ binding sites with modest affinity. Ca2+ has a small impact on the thrombin-catalyzed release of fibrinopeptide, but it has a significant impact on the succeeding stages of polymerization. While alterations of the low-affinity calcium-binding site do not significantly alter fibrin polymerization, key high-affinity calcium-binding residues in the γ nodule appear to be required for protofibril production and fibrin characteristics. Higher Ca2+ concentrations result in the formation of thicker fibres because Ca2+ accelerates the rate and extent of lateral aggregation.

**Pharmacokinetics**

In rabbit studies, only 1 to 2% of the applied thrombin dose reached the bloodstream. It reached highest blood plasma concentrations after 6 to 8 hours.

1. **Methods of Preparation**

Numerous methods have been employed to create fibrin glue, and these methods can utilize either homologous or autologous plasma sources. Autologous sources are preferred because they eliminate the potential risk of viral transmission. In the case of homologous fibrin glue, it is prepared from plasma donors who undergo screening, much like other blood product donors. This is followed by a virus inactivation step through solvent and detergent treatment [49].

The preparation process involves centrifuging the plasma, resulting in a precipitate that contains fibrinogen and a supernatant that contains thrombin. The precipitate is then re-suspended in a small volume of the supernatant, and this mixture is used as the fibrinogen component of the glue. The supernatant is further treated by inducing clotting to convert any remaining fibrinogen into fibrin, which is then isolated through filtration. The resulting serum is used as the thrombin component of the glue.

**The various methods of preparation are:**

1. Fibrinogen: Modified Hartman’s Procedure [50]

2. Thrombin: Armand J Quick method [51]

3. Fibrinogen rich concentrate

4. Preparation during emergency need [52, 53]

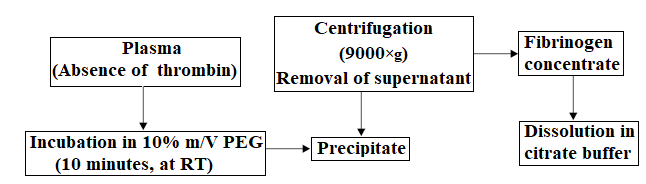
**Large-scale preparation of thrombin from human plasma:**

Recently, Aizawa and colleagues discussed a method for preparing thrombin on a large scale for extensive use [54]. Additionally, Alston and others described another cost-effective approach for creating autologous fibrin sealant using protamine-precipitated fibrinogen concentrate [55]. De Somer and coauthors have demonstrated the mechanical and chemical characteristics of autologous surgical glue, which is created by mixing ultra-filtered plasma with glutaraldehyde [56]. These methods represent advancements in the development and preparation of fibrin sealants and thrombin, potentially offering more accessible and cost-effective solutions for medical applications.

**Chemical methods: Fibrinogen rich concentrate**

Chemical precipitation was the foundation of the initial laboratory techniques for generating fibrinogen concentrate. In the presence of chemicals like ammonium sulphate, ether, ethanol, polyethylene glycol (PEG), or glycine, fibrinogen precipitates from plasma (‘Cold’ precipitation). One of them is mixed with plasma in the proper amount before being incubated under carefully planned conditions. The fibrinogen precipitates as a result, and the supernatant is centrifuged to get fibrinogen concentrate, which is subsequently dissolved to the necessary volume, for example, in citrate buffer (Figure 5). The preparation can be kept at -200C for up to 3 weeks.

The concentration of polyethylene glycol (PEG) was increased (by 10-15%), or freezing-thawing of the precipitate was added, to boost fibrinogen concentration. There is no denying that chemical precipitation results in better yields of fibrinogen concentrate, but it must be remembered that the chemicals cannot be entirely removed from the finished product.

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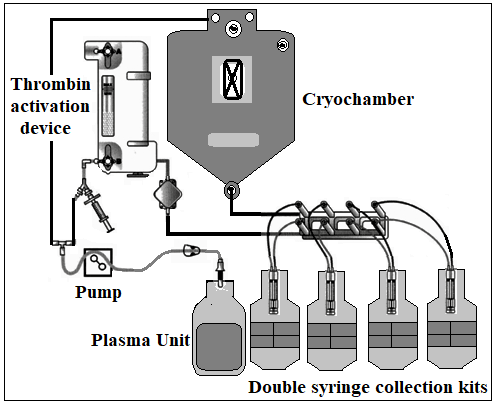
**Figure 5. Fibrinogen concentration is prepared chemically using polyethylene glycol (PEG)**

**RT: Room temperature, %m/V: Mass-volume concentration, g: spin force**

Additionally, when PEG concentration rises, contaminants in the finished product increase and residual chemical compounds may have an impact on the chemical and physical characteristics of fibrin glue. For example, residual ethanol may promote clotting and activate factor XIII, making the clot less elastic. Even the use of sterile disposable equipment cannot lessen the substantial danger of bacterial contamination when the treatment is carried out in an open system, as is the situation with chemical precipitation. More focus is now being placed on cryoprecipitation as a result of the constraints of the chemical approach outlined above (sterile chemicals and sterile disposable equipment, preparation in an open system in class A clean rooms). The risk of pathogen transmission is significantly decreased by the cryoprecipitate method's ability to isolate fibrinogen concentrate in a closed system [57].

**Automated Cryo Seal system method**

Thermogenesis, a company in the United States, created an automated CryoSeal system that reduced preparation time and allowed for the closed-loop extraction of 4 pieces of thrombin solution and fibrinogen concentrate from a single unit of plasma. The Thrombin Processing Device (TPD) kit, a set of four pairs of 3 ml barcoded syringes, and a cryochamber make up the CryoSeal system. The cryoprecipitate method is used to create fibrinogen concentrate, and negatively charged ceramic beads are used to activate plasma prothrombin to produce thrombin. The syringes are filled with equal amounts of thrombin solution and fibrinogen concentrate when the procedure is finished (Figure 6). The two liquids combine during application to produce fibrin glue. The entire process takes about 60 minutes.



**Figure 6. Automated Cryo Seal (Thermogenesis) system [57]**

Another accessible system is the Vivostat (Vivostat A/S, Denmark), which is based on whole blood rather than plasma. Chemical precipitation is used to separate the patient's whole blood after collection.

In this technique, fibrinogen concentrate and thrombin are produced using a biotin-batroxobin mixture and a buffer with a pH that has been carefully chosen. The full process in the Vivostat system takes around 30 minutes [57, 58].

1. **Clinical application**

Fibrin glue is widely used in a variety of medical sectors as a sealant, adhesive, healing aid, or to facilitate the site-delivery of active ingredients. The nature of the clot may be greatly impacted, as was previously stressed, by variations in the concentrations of the two fundamental components of fibrin glue [59, 60].

**Orthopedic Joint Repair:**

The fundamental question in orthopaedic surgery regarding joint replacement is whether or not fibrin sealant is capable of lowering blood loss and total knee arthroplasty (TKA) cost. The use of fibrin sealant to lessen bleeding is supported by two studies detailing prospective, randomised trials. There were notable decreases in the amount of drainage output, haemoglobin loss, need for transfusions, time required for functional recovery, and hospital stay. Another prospective, randomised series found that employing fibrin sealant significantly reduced drainage volume but did not affect cost. A thorough retrospective analysis indicated that employing fibrin sealant significantly reduced drain output but had no positive effects on haemoglobin levels, transfusion rates, or cost.In terms of drain output or indicators of recovery, a double-blind, placebo-controlled, prospective, randomised research demonstrated no benefit to employing fibrin sealant in TKA. The use of fibrin sealant did not reduce blood loss, costs, or duration of stay, according to a sequential nonrandomized experiment. In-vitro and in-vivo testing of this method employing bone fragments and a bone scaffold made of hyaluronic acid, fibrin sealant, and PRP to promote one-step osteochondral repair was reported. The method was described as a new way to measure adhesive strength in joint repair.

**Ophthalmology:**

Over the past ten years, the number of submissions to the ophthalmic literature on fibrin sealant has increased, with 21 publications published in the most recent year. The majority of the references focused on the use of fibrin sealant as a tool for intraocular lens fixation. With the caveat that use in ectopia lentis in people with Marfan's Syndrome may have a high incidence of associated retinal detachment, new contributions to the field of ophthalmology suggest reduced complications in a series of cases [61] compared to suture fixation (7/25, 28% versus 14/25, 56%); successful use [62] in children; and in order to fix a previously implanted posterior chamber intraocular lens that has become subluxated or decentered, haptics are used in conjunction with corneal transplantation (penetrating keratoplasty or Descemet-stripping automated endothelial keratoplasty) for aphakic or pseudophakic bullous keratopathy [60].

According to an in-vitro study, treatment of the human Descemet's membrane with fibrin sealant (Tisseel VH Fibrin Sealant, Baxter Healthcare (Asia) Pte Ltd., Singapore) by creating a network of fibres improved the membrane's mechanical properties in terms of stabilising and stiffening as well as bending rigidity, which may allow for easier manipulation and less "rolling up" during selective corneal transplant. In practise, Descemet's membrane microperforations that occur during deep anterior lamellar keratoplasty have been sealed with fibrin sealant (Tisseel, Baxter, Westlake Village, CA), preventing the need for penetrating keratoplasty.

In ophthalmology, fibrin sealant is utilised in a range of therapeutic settings with a focus on tissue sealing and avoiding sutures. These include conjunctival-limbal autograft implantation for the treatment of pterygium in children or for limbal stem cell shortage, sealing scleral patch grafts or fistulas during trabeculectomy or repairing fat prolapse, and conjunctival closure. One of these investigations used fibrin sealant to measure pain at the first and second weeks of recovery and found a considerable reduction in operating time. In the sealant group, there were two dehiscences, but there were none in the sutured group.

Fibrin sealant was successfully used in four other studies in a range of circumstances. The first was a prospective, randomised trial that demonstrated how the use of fibrin sealant considerably decreased operating time as well as postoperative pain and suffering in amniotic membrane grafting for the treatment of pterygium. Another used a fibrin sealant patch surrounded by an inner and outer layer of amniotic membrane to cure a significant corneal perforation while preparing for a subsequent keratoplasty. Using fibrin sealant to stop recurring epithelial ingrowth, a third documented treatment of a central buttonhole defect of a LASIK flap with accompanying epithelial ingrowth. In the most recent study, a series of patient eyes underwent conjunctival redundancy removal utilising a ‘paste-pinch-cut’ technique, wherein fibrin sealant was applied to secure the conjunctiva that remained after the procedure. One dehiscence reportedly occurred as a result of a failed polymerization of the sealant.

**Noncardiac Thoracic Surgery:**

The treatment of pneumothorax, chylothorax, or hydothorax as well as tracheobronchial injury using mesh with fibrin sealant is the focus of the recently published publications.

Intraoperative air leaks caused by patients undergoing excision for primary or metastatic tumours were fixed using fibrin sealant alone or in combination with a polyglycolic acid (PGA) sheet. The rubbing of fibrinogen, the rubbing of thrombin, the application of the patch, the rubbing of thrombin into the patch, and the rubbing of fibrinogen once more on top of the patch were all done sequentially when applying the fibrin sealant.

The second method showed statistically significant decreases in the frequency of protracted (>1 week) air leaks as well as the duration of pleural drainage. A similar trial using three distinct approaches for placing PGA sheets and fibrin sealant was conducted by a team of researchers on 126 consecutive patients undergoing video assisted thoracic surgery (VATS). They found that placing a PGA sheet coated with fibrin sealant and rubbing fibrinogen into the defect area had the best results at preventing postoperative air leakage when compared to the other two approaches. This conclusion was further supported by a laboratory model that displayed considerably higher seal breaking pressure for the third application procedure.

Another human study examined the use of chest tubes to drain air leaks that had been patched with PGA sheets and fibrin sealant in lower-risk patients. The procedure involved applying fibrinogen-soaked PGA sheets to the area of the leak before applying drops of thrombin to seal the sheet. Only 2.9% of patients required reinsertion of their chest tubes due to recurrent air leaks, according to this study, and segmentectomy patients were more likely to require reinsertion of their chest tubes than lobectomy patients. Chest tubes could be taken out of the vast majority of patients (91%) on the first postoperative day because there were no air leaks in their bodies.

When a low calcium (0.59%) concentration fibrin sealant was given through the chest tubes to a preterm newborn with bilateral pneumothorax, the air leaks were stopped and complications including hypercalcemia and bradycardia were allegedly avoided. The patient underwent fibrin sealant pleurodesis while being monitored by a fluoroscope after attempts to cure a rare incidence of pneumothorax associated with chronic graft versus host disease (cGVHD) with autologous blood via chest tubes failed. The approach employed in 2000 at the University of Virginia can be compared to this one. The body of research supporting the use of fibrin sealant now includes the example of a newborn with trachea-esophageal fistula and esophageal atresia who required a repeat thoracotomy for treatment after the initial repair resulted in a chylothorax.

A second instance of peritoneal dialysis-related hydrothorax was effectively treated by VATS mattress suturing, PGA felt application, and fibrin sealant application. Two reports of membrane tracheobronchial ruptures that responded well to treatment were also found. Bovine pericardial patch was used to repair the trachea, and the suture lines were then sealed with fibrin sealant without the requirement for autologous tissue reinforcement in one operation.

The other treatment involved tracheal repair utilising a catheter and fibrin sealant administered by a bronchoscope, along with small amounts of adipose tissue. A third case report describes the effective treatment of a bronchopleural fistula in a 3-week-old baby who had undergone a right lower lobectomy for a congenital cystic adenomatoid malformation. The procedure involved the bronchoscopically implanted pig skin collagen and fibrin sealant. The use of local bronchoscopic fibrin sealant application to treat severe hemoptysis brought on by invasive pulmonary aspergillosis was described in a final case report that was published.

In a case report, it was claimed that the use of fibrin sealant to seal a pulmonary bullectomy excision line resulted in an eosinophilic postoperative pleural effusion (14% eosinophils), which was confirmed by a positive drug lymphocyte stimulation test. This case report raised concerns about the potential side effects of using fibrin sealant in thoracic surgery. However, a multicenter, prospective, randomised examination of fibrin sealant in patients undergoing significant thoracic surgery revealed a mortality of 1.1% in the fibrin sealant group and 5.3% in the control group, indicating the safety of fibrin sealant. Between the two groups, there were no appreciable differences in the frequency of hyperpyrexia or thromboembolic events (none in either group).

There were no negative side effects; however 37% of patients who got fibrin sealants did generate antibodies against the bovine aprotinin that was present. Although postoperative air leakage significantly decreased in the fibrin sealant group, the period until chest tube removal did not change in a significant way.

**Hernia Repair**

Laparoscopic or endoscopic inguinal hernia repair employing either a transabdominal preperitoneal (TAPP), totally extraperitoneal (TEP), or ventral hernia repair techniques is the subject of the majority of clinical research on hernia repair with fibrin sealant. Comparing traditional and fibrin sealant in a prospective, randomised, multicenter trial. Fibrin sealant was statistically superior to conventional suturing in the Lichtenstein repair for open inguinal hernia repair in terms of procedure time, numbness at week one and month one, the need for analgesia at week one and month one, and postoperative pain at week one and month one. One dehiscence occurred in the group that underwent fibrin sealant therapy. Another multicenter, prospective, randomised clinical trial of fibrin sealant versus traditional suture of small to medium sized hernia repair was carried out by a different group of investigators in response to the excellent results and low levels of follow-up pain (0% severe, 2.7% moderate) noted in a large (> 600) single centre retrospective nonrandomized series. In the fibrin sealant group, issues overall significantly decreased at year one, according to the results of the multicenter trial. When the one-year complication data was split into the active and retired subpopulations, the findings favouring less problems in the retired fibrin sealant treatment group disappeared. Furthermore, there were no appreciable differences between the fibrin sealant and sutured groups in terms of pain, hernia recurrences, problems from wound healing, length of surgery, hospital stay, time to return to work, or quality of life assessments. A nonrandomized trial comparing fibrin sealant and sutures for mesh fixation in inguinal hernia repair revealed a significant improvement in the fibrin sealant group for days to full wound healing and pain score 12 months following surgery. On 87 high-risk elderly patients (median age 81, range 70-92) with diabetes mellitus (44%), coagulation pathology (38%), grade B or C child's cirrhosis (18%), or cardiovascular disease under dicumarol treatment, an open hernia repair experiment using mesh fixation and fibrin sealant was carried out. Several research teams have also studied strategies to lessen seromas and adhesions following ventral hernia surgery. In a prospective, non-randomized, single-center experiment, patients undergoing laparoscopic surgery were compared with compression bandage wrapping alone and percutaneous fibrin sealant injection into the ventral hernia sac. In terms of seroma occurrence at weeks one and two, seroma volume at weeks one and two, and abdominal wall normalisation as judged by patients at weeks one and two, the fibrin sealant group considerably outperformed the control group.

The fixation strength was stronger when using uncoated mesh with sutures rather than fibrin sealant in an in-vivo Wistar rat study that entailed attaching pieces of mesh to the abdominal wall. Neither coated nor untreated polypropylene mesh formed adhesions. However, the procedure recommended applying a single drop of fibrin sealant to the centre of the patches rather than four sutures to each of their four corners. Another in-vivo pig study using laparoscopic implantation of PTFE and PP meshes showed that PTFE produced fewer visceral and omental adhesions than PP and that fibrin sealant coating of the PP and PTFE meshes reduced adhesion formation.

Although all three glues were significantly better than no fixing at all (N), the fibrin sealant (N) offered less strength than butyl-cyanoacrylate (N) or bovine serum albumin cross-linked with glutaraldehyde. In-vitro research on the mechanical glue strength (stamp penetration) of polypropylene mesh attached to muscle led to the discovery of this. A prospective randomise single centre experiment found that using fibrin sealant rather of staples did not significantly reduce chronic pain or lower quality of life after laparoscopic TAPP hernioplasty. Each of the two groups only experienced one occurrence of recurrence.

Self-gripping mesh was statistically proven to be 4.5 minutes shorter than fibrin sealant inserted mesh in a comparable trial, but there was no discernible difference in postoperative pain at one or three months.

Last but not least, an in-vivo randomised prospective pig model was used to evaluate laparoscopic hiatal hernia repair using fixation of the acellular dermal matrix with sutures or fibrin sealant. It was concluded that the decrease in operating time for the fibrin sealant group was statistically significant. At necropsy (30 days later), all meshes were intact, and there was no observable difference in mean peel force between the groups.

**Fistula Closure**

In 2012, there was just one multicenter, prospective, randomised, clinical trial that used fibrin sealant to close fistulas. It involved treating fistula-in-ano with suture closure of the internal fistula opening in addition to employing autologous adiposederived stem cells alone, fibrin sealant alone, or both. At 24-26 weeks in this phase III trial, the healing rates for the three groups-39.1%, 43.3%, and 37.3%-were not statistically different from one another. The rates were 57.1%, 52.4%, and 37.3% after one year, indicating a potential trend in favour of a fibrin sealant advantage. With healing rates of 54.55%, 83.33%, and 18.18%, a selective study of the beginning center's data indicated a significant benefit to therapy with cells and fibrin sealant at 24-26 weeks. Treatment centre and fistula severity were independent predictors of fistula healing, according to a multivariate study. Additionally, a comparison of patients who received cells with or without fibrin sealant against patients who received fibrin sealant alone showed that patients who received at least some cells saw a doubling of the healing rate. Additionally, a tendency towards significant antibiotic use was seen. There were no noteworthy negative incidents. A retrospective follow-up examination of patients who had previously participated in a phase II study from the originating site itself, however, unfavourably found a low percentage of patients who had not experienced a recurrence after three or more years of surveillance.

In the first study, over the course of 5 years, only 26% of patients who were treated with application via an endoanal ultrasonographic-assisted percutaneous transperineal approach (initial 90.5% success at 4 weeks) had their fistula tracts completely sealed off with fibrin sealant or cyanoacrylate (cyanoacrylate in only the first two patients as vulvar ulceration was noted following use in the second patient). In the second research, transsphincteric cryptoglandular fistulas were treated in two stages over the course of six years with the same patients. The major tract was fistulized using a seton in the first stage, and the remaining secondary tract segments were sealed with fibrin sealant in the second stage. None of these patients had incontinence, and at a mean of 20.6 months, 67.8% of them had no recurrence (range: 3-60 months). Although results with fibrin sealant produced some lower long-term success rates and have been used less in the last five years, a third large retrospective series of patients over 34 years found a continuing trend towards more conservative non-cutting procedures and away from fistulotomy. According to a meta-analysis, using fibrin sealant as a fistula plug is less efficient than using regular surgery. Fibrin sealant was nevertheless described in a final evaluation study of the treatment for fistula-in-ano as having strong early results but not long-term success. It was indicated that fibrin sealant would still be helpful as a component of a conservative treatment plan that also included seton assisted fistulotomy.

Recent case reports of intestinal tract fistulas that were successfully closed with fibrin sealant include endoscopic instillation for the treatment of an esophageal perforation brought on by a fish bone, platelet-poor concentrated plasma placement via a tract catheter for the closure of a colocutaneous fistula, platelet-rich concentrated plasma placement via a tract catheter for the closure of an intestinal fistula, and endoscopic treatment of a gastro-jejunal fistula.

1. **Advantages**

Due to the reduced amount of time needed to insert stitches, fibrin glue speeds up surgery [63,64]. Contrary to traditional suturing, the use of adhesive has been demonstrated to reduce the likelihood of post-operative wound infection. This is caused by the buildup of mucus and debris in the sutures, which may serve as an infection nidus [64]. However, there is little evidence to support the low frequency of infection and postoperative response[65]. Antibiotics are mixed with fibrin glue to deliver antibacterial action locally. It has moderate antibacterial activity, is well tolerated, and is not hazardous to the tissue wherever it is applied.The bond has a stronger tensile strength as a result of the smooth seal running the full length of the wound edge, and it is also more resistant to shearing force. In some surgical patients, fibrin glue is a helpful adjuvant to stop bleeding. The likelihood of allergic responses is low. However, there have been reports of anaphylactic responses after its use [66, 67]. The aprotinin found in fibrin glue has been blamed for this reaction. When used on diseased tissues, fibrin glue promotes the development of adhesions. Vedung and Hedlung [68] have documented its usage in infected wounds. The inclusion of aprotinin, which has some antibacterial activity, may make this conceivable[69]. By measuring the extent of the bacterial growth inhibition, Chen et al. found that fibrin glue failed to display any bacteriostatic effects to either Gram-ve or Gram+ve microorganisms [70].They also found a small amount of cytotoxic activity, but clinically, this was not significant.

1. **Disadvantages**

The potential of disease transmission between pooled and single blood donors is the main disadvantage of its use [71-73]. By using blood from healthy donors who have undergone screening, the risk of this can be greatly reduced [71, 74]. The most secure preparation is to make fibrin glue from the patient's own blood. The processing time for an autologous donation is at least 24 hours, and it is pricey. The end product frequently has varying concentrations, making its performance unpredictable. Furthermore, because it depends on a number of unrelated parameters, the tensile strength of fibrin glue has not been sufficiently characterized and prevents quantification.

1. **Conclusion**

This spotlight chapter's goals are to update the reader on the hemostats, adhesives, and sealants that are currently on the market, as well as to give a framework for comparing these hemostats, adhesives, and sealants with other goods. A review of a year's worth of articles on fibrin sealant, based on both laboratory and clinical research, has also been presented. These reports have been broken down into categories and are organised by frequency, with the most frequent events being reported first.

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