Video Article

TAPE: A Biodegradable Hemostatic Glue Inspired by a Ubiquitous Compound in Plants for Surgical Application

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Abstract

This video describes the simplest protocol for preparing biodegradable surgical glue that has an effective hemostatic ability and greater water-resistant adhesion strength than commercial tissue adhesives. Medical adhesives have attracted great attention as potential alternative tools to sutures and staples due to their convenience in usage with minimal invasiveness. Although there are several protocols for developing tissue adhesives including those commercially available such as fibrin glues and cyanoacrylate-based materials, mostly they require a series of chemical syntheses of organic molecules, or complicated protein-purification methods, in the case of bio-driven materials (*i.e.*, fibrin glue). Also, the development of surgical glues exhibiting high adhesive properties while maintaining biodegradability is still a challenge due to difficulties in achieving good performance in the wet environment of the body. We illustrate a new method to prepare a medical glue, known as TAPE, by the weight-based separation of a water-immiscible supramolecular aggregate formed after a physical mixing of a plant-derived, wet-resistant adhesive molecule, Tannic Acid (TA), and a well-known biopolymer, Poly(Ethylene) glycol (PEG). With our approach, TAPE shows high adhesion strength, which is 2.5-fold more than commercial fibrin glue in the presence of water. Furthermore, TAPE is biodegradable in physiological conditions and can be used as a potent hemostatic glue against tissue bleeding. We expect the widespread use of TAPE in a variety of medical settings and drug delivery applications, such as polymers for muco-adhesion, drug depots, and others.

Video Link

The video component of this article can be found at <http://www.jove.com/video/53930/>

Introduction

In a past decade, efforts have been made to replace current surgical sutures and staples to close wounds with biodegradable/bioabsorbable adhesives due to their convenience in usage and low tissue invasiveness during surgical treatments. Commercially available tissue-adhesives are classified into four types: (1) cyanoacrylate derivatives¹, (2) fibrin glues formed by enzymatic conversion from fibrinogen to fibrin polymers by thrombin^{2,3}, (3) protein-based materials such as chemically or physically cross-linked albumin and/or gelatin^{4,5}, and (4) synthetic polymer-based ones⁶. Although they have been used in many clinical applications, all adhesives have their own intrinsic disadvantages and drawbacks that can be obstacles to their widespread usage. Cyanoacrylate-based glues show high adhesion strength to tissues, but their toxic by-products such as cyanoacetate and formaldehyde formed during degradation, often cause significant degrees of inflammatory responses⁷. Fibrin glues and albumin or gelatin-based materials have safety issues regarding the transmission of infectious components, such as viruses from animal sources: human blood plasma for fibrin glues and animals including cattle, chicken, pigs, and fish for gelatin-based glues⁸. Although a few synthetic polymer-based adhesives have been approved by the Federal Drug Administration (FDA), most adhesives made of synthetic polymers continue to have difficulties in minimizing the manufacturing process steps and achieving biocompatibility⁹. Most importantly, all glues suffer from poor mechanical and adhesion strength to wet tissues¹⁰. Recently, biomimetic tissue adhesives inspired by marine mussels¹¹⁻¹³, geckos¹⁴, gecko with mussel¹⁵, and endoparasitic worms¹⁶ have been emerging as promising alternatives to current medical glues due to their tunable mechanical and adhesive properties with biocompatibility. However, to this day, there are still issues to be addressed before they become commercial products¹⁷.

Here, we report an entirely new type of medical glue called TAPE that is prepared by the intermolecular hydrogen bonding between a plant-derived adhesive molecule, Tannic acid (TA), and a bio-inert polymer Poly(ethylene glycol) (PEG), as its name indicates. TA is a representative hydrolysable tannin ubiquitously found during the secondary metabolism of plants. It has attracted much attention due to its anti-oxidant, anti-mutagenic, and anti-carcinogenic properties and has been shown to participate in supramolecular interactions with many polymers, such as poly(*N*-isopropylacrylamide) (PNIPAM) and poly(*N*-vinylpyrrolidone) (PVPON), to form layer-by-layer (LbL) films¹⁸⁻²⁰ and drug-releasing microcapsules²¹⁻²³. In this study, we discover that TA can act as an efficient water-resistant adhesive functional moiety to form a medical adhesive, TAPE. By simple mixing with TA, a non-fouling polymer PEG becomes a supramolecular glue with 2.5-fold increased adhesion strength compared with commercial fibrin glue, and this adhesion was maintained throughout up to 20 cycles of attachment and detachment, even in the presence of water. Its hemostatic ability was tested on a liver bleeding model *in vivo* and showed good hemostatic ability to stop

bleeding within a few seconds. TAPE has its significant meaning in a related field as the first plant-derived adhesive that can reveal new insight into solving the drawbacks of current problems with bio-inspired approaches. We also expect the widespread use of TAPE in a variety of medical and pharmaceutical applications such as muco-adhesives, drug-releasing patches, wound-care dressings, and others due to its simple preparation method, scalability, tunable biodegradation rate, as well as highly wet-resistant adhesion properties.

Protocol

All animal care and experiments are performed in accordance with the ethical protocol provided by the KAIST (Korea Advanced Institute of Science and Technology) IRB (Institutional Review Board).

1. TAPE Formation

- For preparing a TA solution, place a 4 ml-sized glass vial on a magnetic stirrer, and add 1 ml of distilled water with a stirring bar. Add 1 g of tannic acid to the vial, and dissolve it in the water by gentle stirring at 200 rpm for more than 1 hr. When the TA is completely dissolved, the mixture becomes transparent with a brown color.
- Prepare a PEG solution by adding 1 g of PEG powder (4-arms, 10 kDa, and linear, 4.6 kDa) to 1 ml of distilled water followed by mixing them by vortexing for few seconds to make a white slurry. Keep this slurry in the incubator at 60 °C for 10 min. until the white one becomes completely clear.
NOTE: The melting point of PEG with 10 kDa molecular weight is around 55 - 60 °C, and the 4 kDa one is 53 - 58 °C. Melted PEG becomes water-miscible so that a high concentration of PEG in water up to 1 g/ml can be achieved as a clear solution. Once a clear PEG solution is formed at a high temperature, the solution is still stable at room temperature after cooling.
- Add 329 μ l of the PEG (4-arms, 10 kDa) solution prepared in step 1.2 to 671 μ l of the TA solution prepared in step 1.1 (In the case of a linear PEG with 4.6 kDa, add 311 μ l of a PEG solution to 689 μ l of a TA solution) in a micro-centrifuge tube. Gently blend the two viscous and honey-like solutions with a narrow spatula to mix them homogeneously.
CAUTION: Both solutions are quite viscous, so the scientist must slowly but sufficiently pull up and transfer the solutions with a micropipette.
- Spin the mixture prepared in step 1.3 at 12,300 x g for 3 min in a centrifuge equipped with a fixed-angle rotor.
- Carefully remove as much of the supernatant as possible using a micropipette, and collect the product that has settled down: This is the fully formed TAPE. After TAPE formation, store it in the refrigerator (4 - 8 °C) for up to several weeks. **NOTE:** TAPE can be sterilized by gamma radiation or electron beam treatment prior to use in surgical applications.

2. Measurement of the Adhesion Strength of TAPE

- Prepare two pieces of porcine skin tissue with a diameter of 6 mm by cutting with a biopsy punch after removing all fat on the skin tissue.
NOTE: The porcine skin tissue was obtained from healthy porcine flank skin and was purchased from a local meat market located in Daejeon in South Korea.
- Apply commercial cyanoacrylate glue to the outer side of each tissue, and attach the tissue to the metallic rod.
NOTE: The metallic rod is used as a supplementary handle so tissues are not directly gripped by the machine. Accordingly, it can be replaced with other materials following the configuration of the tensile machine.
- Apply a drop of TAPE (a drop of TAPE is approximately 3 - 6 mg) to one side of the tissue. Then, spread the TAPE uniformly using another tissue between the two tissues on their inner sides so they are attached as shown in **Figure 2A**.
- Then, manually attach and detach the two sides of tissues several times to homogeneously mix and maximize the interface between each tissue and TAPE.
- With the UTM, carefully grip each side of the rod. The adhesion strength will be determined by the force needed to detach two tissues attached with TAPE. First, apply a force of 20 N for 1 min. Next, with the machine, pull each rod in an opposite direction at a rate of 1 mm/min. until the tissues are completely detached.
NOTE: Data will be given as a force-distance (F-D) curve detected by the motion of each rod.
- Calculate the adhesion strength of TAPE by dividing the maximum force (kN) shown at the F-D curve achieved in step 2.5 by the specimen surface area, that is, $3.14 \times (0.003 \text{ m})^2$.
- For monitoring the adhesion strength in the presence of water, add 20 μ l of water on the detached area between two tissues, and attach them immediately. With the machine, perform the detachment test again.

3. In Vitro Degradation Test

- Cut a cap (d = 8 mm) of micro-centrifuge tube, and weigh the cap to define it as W_c .
- Fill the cap with 150 mg of TAPE, and weigh all together again to set it as a total initial weight W_0 .
CAUTION: Do not overload TAPE in the cap. The height of TAPE should be lower than the top of the cap, as it can be a physical barrier to a stream of PBS buffer generated by the stirring process during the incubation in step 3.4.
- Put the cap containing TAPE into a cell culture flask (75 cm^2), and add 50 ml of PBS buffer (1x, pH 7.4) to the cell culture flask so the TAPE in the cap is completely immersed in the PBS buffer, as shown in **Figure 3A** (n = 5).
- Incubate the cell culture flask prepared in step 3.3 in an orbital shaking incubator at 37 °C, similar to physiological conditions, with gentle stirring (50 rpm).
CAUTION: Keep the stirring condition at 50 rpm. Higher rpm might cause a collapse of TAPE.
- At each time point, take the cap with TAPE from the cell culture flask, and then dry them by blowing nitrogen gas. Weigh the cap containing remaining TAPE. Set the weight at each time point to W_t . Replace the fresh PBS again, and shake it again after measuring W_t at each time point.
- Calculate the relative remaining weight (%) the following equation.

$$\text{Relative remaining weight (\%)} = (W_t - W_c) / (W_0 - W_c) \times 100\%$$

4. Hemostatic Ability of TAPE

NOTE: All animal experiments should be performed in accordance with the guidelines and ethical protocol provided by the Korean Ministry of Health and Welfare.

1. To evaluate the *in vivo* hemostatic ability, review the hemorrhaging mouse liver model as described in ref²⁴.
2. Anesthetize fifteen mice (normal ICR mouse, 6 weeks, 30 - 35 g, male) with an intraperitoneal injection of tiletamine-zolazepam (33.333 mg/kg) and xylazine (7.773 mg/kg) (n = 5 per group). To confirm proper anesthetization, pinch the animal's paw gently and observe movements such as withdrawing the paw, etc. No movement indicates that the animal is sufficiently anesthetized to do surgery.
3. To prevent dryness of animal's eyes, apply vet ointment to eyes sufficiently while under anesthesia. Expose the liver via a midline abdominal incision, and prick the liver with an 18 G needle to induce bleeding.
4. Remove the flowing blood with sterile gauze, and put 100 µl of TAPE or fibrin glue (positive control) immediately on the bleeding site.
NOTE: No further suturing is needed after applying TAPE due to its highly blood-resistant adhesive properties on wound tissues. For the negative control, no treatment occurs at the site of bleeding.
5. In each case, put a filter paper with known mass underneath the liver to collect the blood from the damage site. Replace the paper with a fresh one every 30 sec for 4 times (*i.e.*, 2 min).
6. Measure the mass of absorbed blood on each filter paper collected every 30 sec. After the animal experiment, sacrifice the mice through CO₂ asphyxiation euthanasia.

Representative Results

TAPE is a supramolecular aggregate that settles down after centrifuging the mixture of two aqueous solutions containing TA (1 g/ml in distilled water) and PEG (1 g/ml in distilled water) with 2:1 volume ratio (**Figure 1A**). The mixing ratio is the key factor in achieving high adhesion strength; when TAPE is formed by a 2:1 mixing ratio, 20 units of the hydroxyl group (-OH) in 25 units of TA interact with each ether group (-O-) in PEG, resulting in the highest intermolecular hydrogen bond formation with maximum adhesion properties. The remaining five units of -OH seem to be consumed by the intramolecular hydrogen bonding with adjacent carbonyl groups (C=O) in TA (**Figure 1B**). When either one of the components was in excess of the 2:1 volume ratio, the adhesion strength was notably decreased²⁵. Hydrogen bonding will also be the critical molecular level interaction with tissues. Controlling the inter- and intra-molecular hydrogen bonding between TA and PEG for the cohesion, and between TA and the tissues for the adhesion might be a plausible mechanism of TAPE as an effective surgical glue.

For measuring the adhesion strength, TAPE was first applied between each epidermic side of two porcine skins with a diameter of 6 mm. Subsequently, it was gripped on a tensile machine via rods attached outside each porcine skin, as depicted in **Figure 2A**. The force needed to detach two porcine skins was measured by the machine in the absence (**Figure 2B**) and presence of water (**Figure 2C**) after each 5 cycles of repeated attachment and detachment, up to 20 cycles. The adhesion strength in a dry state was about 200 kPa at the initial measurement, and even increased to about 250 kPa after 20 cycles. In the presence of water added to each cycle, adhesion was about 90 kPa, which then decreased to 50 kPa after 20 cycles. The adhesion strength in a wet state was lower than that in a dry state, but it was still comparable with the commercial adhesive, fibrin glue, which was about 70 kPa measured by a setting identical to ours in the absence of water²⁵.

The degradability of TAPE was investigated by gravimetric analysis *in vitro* (**Figure 3**). TAPE was immersed in 1x PBS (pH 7.4) at 37 °C with gentle stirring, then the mass remaining each time was measured up to 21 days. Photos of the remaining TAPE each time are also shown in **Figure 3B**. The TAPE made by mixing TA and PEG with a 1:1 ratio was completely degraded after 13 days, and 42% of TAPE made by two components with a 2:1 ratio was degraded after 21 days (**Figure 3C**). The degradation rate is in inverse correlation with the adhesion strength, because faster degradation is mainly due to lower intermolecular interaction, and this condition creates lower adhesion strength in the case of TAPE, as previously mentioned. So the result was as expected; TAPE mixed by a 2:1 ratio showed slower degradation than by a 1:1 ratio because all reactive -OH in TA and all -O- in PEG formed the highest number of intermolecular hydrogen bonds. At a 1:1 ratio, the excess amount of -O- in PEG might weaken the cohesiveness, resulting in faster degradation.

Finally, the hemostatic ability of TAPE was investigated *in vivo*. TAPE was first applied on the mouse liver immediately after damage from an 18 G needle, as shown in **Figure 4A**. The amount of bleeding during an initial 30 sec after the treatment was collected by adsorbing blood onto a filter paper and comparing the negative (no treatment) and positive control (fibrin glue) (**Figures 4B and 4C**). The total amount of bleeding was also calculated by collecting the amount of bleeding every 30 sec. until it stopped. As shown in **Figure 4D**, bleeding was significantly suppressed by the hemostatic ability of TAPE (The total bleeding amount was only 15.4% of the untreated case) rather than a commercial product, fibrin glue (The total bleeding amount was 60.7% of the untreated case).

Figure 1: Formation of TAPE. (A) Serial steps of making TAPE (scale bar: 0.5 cm). (B) A chemical reaction of TAPE formation via intra- and inter-molecular hydrogen bonding. [Please click here to view a larger version of this figure.](#)

Figure 2: Adhesion Strength of TAPE on Porcine Skin. (A) A scheme of measurement setting. (B - C) Adhesion strength changes during repeated attach- and detachment on porcine skin (B) in the absence and (C) in the presence of water. Error bars represent the mean $\pm$ standard deviation (SD) of 3 repeated measurements (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ and **** $p < 0.0001$, with one-way ANOVA test). (Re-print with permission from ref²⁵.) [Please click here to view a larger version of this figure.](#)

Figure 3: Degradation Rate of TAPE in Physiological Conditions. (A) A photo of the measurement setting. (B) Representative photos of remaining TAPE at each degradation test. (C) The remaining % mass changes after a period of time incubating in a 1x PBS buffer (pH 7.4) at 37 °C was monitored up to 21 days (TA:PEG = 2:1 and 1:1) ($n = 5$, error bars $\pm$ SD). [Please click here to view a larger version of this figure.](#)

Figure 4: Hemostatic Ability of TAPE *In Vivo*. (A) A photo indicating the application of TAPE on the surface of a liver damaged by an 18 G needle. (B) Representative photos showing the amount of bleeding an initial 30 sec. after the treatment of TAPE, as well as the negative (no hemostatic agent) and positive control (fibrin glue). Each quantitative amount of bleeding was shown in (C). (D) The total amount of bleeding, collected every 30 sec until it stopped. Error bars represent the mean $\pm$ standard deviation (SD) of 5 repeated measurements (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ and **** $p < 0.0001$, with one-way or two-way ANOVA test). (Re-print with permission from ref ²⁵.) [Please click here to view a larger version of this figure.](#)

Discussion

We developed an entirely new class of hemostatic adhesive named TAPE inspired by the water-resistant molecular interaction of a plant-derived polyphenolic compound, TA. TA is a representative hydrolysable tannin that has significantly attracted attention due to its anti-oxidant, anti-bacterial, anti-mutagenic, and anti-carcinogenic properties.

The process of making TAPE is extremely simple, scalable, and environmentally friendly, as it is just the one-step mixing of two aqueous solutions followed by centrifuging without any further chemical synthetic procedures.

The two component mixing protocol is the most typical and simplest method to form tissue adhesives used in conventional products, such as fibrin glue. It is formed by mixing fibrinogen and thrombin right before applying to the tissues³. However, multi-step chemical synthesis is needed to prepare the components of an adhesive in the case of cyanoacrylate glue and synthetic polymer-based adhesives. In addition, highly toxic chemicals are sometimes involved as one component to chemically crosslink the other component comprised of polymeric precursors in protein-based materials, cured by glutaraldehyde and glue containing formalin and resorcinol.

Materials cured by glutaraldehyde showed high *in vivo* inflammatory response on lung and liver tissues in animal studies using rabbits, although it has been approved by the FDA for aortic tissues. Materials glue containing formalin and resorcinol also suffers from toxicity concerns arising from formalin reacting with surrounding tissues²⁶.

The centrifuge step is the only drawback of TAPE developing as an *in situ*-forming, injectable adhesive in the body, but TAPE's plenteous advantages promise its open, widespread use. A critical step of TAPE formation is that the mixing of two components might be slightly tricky because of their high viscosity, but overall, anyone can consistently make huge amounts of TAPE in a laboratory without any batch-to-batch variations.

The adhesion strength of TAPE was 2.5 times higher than that of widely used commercial adhesive, fibrin glue, and mass bleeding was successfully suppressed by the blood-resistant attachment of TAPE on the wound site in our mouse liver-bleeding model *in vivo*. The degradation rate and mechanical properties of TAPE can be further tunable by using branched/multi-armed PEG as well as one having end-functional groups such as amine, carboxylate, and epoxide. The maximum adhesion strength in our data was optimized by the ratio of one kind of PEG (4-arms, 10 kDa and 2-arms, 6.4 kDa) to TA, but it should also be affected by end-functional groups, number of arms and molecular weight of PEG.

We expect that TAPE can also have widespread use as a drug depot and adhesive patch for wound healing purposes, not just as a hemostatic agent due to its ability to encapsulate chemicals via the well-known affinity of TA to a variety of macromolecules, including bovine serum albumin²⁷, DNA²⁸, poly(*N*-isopropylacrylamide) (PNIPAM)²⁹, and metal ions³⁰.

Disclosures

The authors have nothing to disclose.

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