

Glubran2 Surgical Glue: *In Vitro* Evaluation of Adhesive and Mechanical Properties

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Background. In surgical and endoscopic procedures, tissue adhesives are commonly used as reinforcement of sutures or as bonding and hemostatic agents. Fibrin glues do not guarantee adequate properties for many clinical applications; on the contrary, cyanoacrylate glues guarantee high bonding strength between biologic tissues. The aim of this study was to provide evidence regarding adhesive and strength properties of a widely used cyanoacrylate glue, Glubran2, GEM s.r.l., Viareggio, Italy. Comparative tests were also carried out on a commercial fibrin glue.

Material and methods. Glubran2 is a modified n-butyl-2-cyanoacrylate glue approved for internal and external use, in Europe. The glue, on contact with living tissues polymerizes rapidly, generating a film that guarantees firm adherence of tissues. In this study, adhesive properties on biologic substrates, both of Glubran2 and of fibrin glue, were investigated according to American Society for Testing and Materials (ASTM) standards, while their strength, after polymerization on an inert substrate, was investigated according to Deutsches Institut Für Normung (DIN) standards.

Results. All tests evidenced a strong bonding capability of Glubran2 on biologic tissues and high tensile strength of polymerized film; high breaking strength of polymerized glue was highlighted by tensile tests.

Conclusion. The present study fills the gap concerning Glubran2 adhesive and tensile properties. All tests showed the intrinsic tensile strength of polymerized Glubran2 and its capability to realize a higher-resistance bonding among biologic tissues, in comparison with fibrin glue, giving strong indication of its usefulness in surgical and endoscopic practice, espe-

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Key Words: cyanoacrylate glue; fibrin glue; surgical glue; biologic tissues; adhesive properties; tensile strength.

INTRODUCTION

The use of tissue adhesives, to seal wound sites where sutures would be inappropriate or unable to control bleeding, is a widespread method in many open-surgical and endoscopic procedures, such as cardiovascular, thoracic, vascular and abdominal surgery [1]. Tissue adhesives can be classified into three major categories on the basis of their origin: biologic, synthetic, and genetically engineered polymeric proteins. All cyanoacrylate and noncyanoacrylate products, such as polymeric sealant, are considered of synthetic origin, whereas fibrin glues and animal derived hemostatic agents are considered to be of biologic origin.

In order for a glue to be used to secure a structure, together with sutures or by itself, it must possess adequate mechanical properties [2]: clinical performance of a sealant, in fact, is strongly influenced by its physical properties, such as elasticity and tensile and adhesive strength to biologic tissues.

In particular, bonding realized solely by glue has to effectively oppose itself to physiologic loads that tend to move tissues away from each other, and therefore must guarantee a uniform distribution of the loads throughout the affected areas, without compromising the elastic properties of the natural tissues.

Despite their elasticity, fibrin glues [3], the widely used biologic tissue adhesive in surgical practice do not provide significant tensile and adhesive strength,

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and require to be applied on dry substrates. On the contrary, cyanoacrylate glues guarantee adequate adhesive and mechanical properties for applications on living tissues.

Cyanoacrylates are a class of synthetic glues that rapidly solidify upon contact with weak bases, such as water or blood [4]; compared with other tissue adhesives are easier to use, have quicker polymerization [5] and guarantee higher bonding strength. Glubran2 (GEM s.r.l., Viareggio, Italy), a tissue adhesive with high adhesive and haemostatic properties, is a class III (for internal and external surgical use) medical-surgical product which fulfils the requirements of the European Directive on Medical Devices 93/42/EU, moreover, it has been approved for endoscopic use in Europe. Glubran2 is largely used in laparoscopic and traditional surgery, and in interventional radiology [6]; furthermore, it is diffusely applied on skin, eliminating the need for suture removal and providing good cosmetic results.

In vivo applications of Glubran2 evidenced its excellent hemostatic and adhesive properties; in particular in bonding biologic tissues to each other or with prosthetic implants; the adherence appeared tenacious instantly after application, and consolidated its strength during completion of polymerization process, guaranteeing rapid and efficacious results both in open and in laparoscopic surgery.

Although Glubran2 has been used for several years in clinical applications, only a handful of works have been performed investigating its adhesive properties, applying it by itself on tissues or as suture reinforcing [7]. As a matter of fact an exhaustive investigation of Glubran2 adhesive and mechanical properties is lacking.

This work reports the results of adhesive and mechanical tests performed on Glubran2 in order to deeply characterize its behavior and to provide useful indications for its application. To make the results more clinically relevant and usable for the surgeon, the same tests were conducted, as comparison, on a commercial widely used fibrin glue (Tissucol/Tisseel; Baxter Healthcare, Deerfield, IL). To standardize the characterization of Glubran2, and to allow comparison with other available surgical glues, tests were conducted according to relative ASTM and DIN Standards [8–12].

MATERIALS AND METHODS

The Glues

Glubran2 is a tissue adhesive with high adhesive and haemostatic properties, which allows surgeons to reduce the use of surgical sutures. It is a synthetic surgical glue constituted of an N-butyl-2-cyanoacrylate (NBCA) modified by the addition of a monomer, synthesized by the manufacturer, which allows to obtain an exothermic polymeri-

zations reaction around 45°C [13] and a slightly higher polymerization time than other cyanoacrylate glues. Glubran2 is a pale-yellow transparent liquid, ready to use, supplied sterile in 1 mL mono-dose vials that have to be kept at temperature between 0° and +4°C. The glue must be aspirated from the vial using a sterile insulin syringe and applied to the treated area drop by drop. On contact with living tissues, in a moist environment, it polymerizes rapidly, generating a thin film with high tensile resistance, which guarantees firm adherence to tissues; the film is impermeable and may be easily perforated by a suture needle. Polymerization time depends on the type of tissue with which the glue comes into contact, on the amount and nature of fluids present on the substrate, and also on the quantity of product used. When applied properly, the glue starts to set after 1 to 2 s, completing its setting reaction after about 60 to 90 s. Glubran2 reaches its maximum mechanical strength on completion of this reaction; once set, it no longer possesses adhesive properties. The glue should be diluted only with additives used to make it radio opaque; any other substance generates a mixture that could cause polymerization times to be modified in proportion.

Tissucol (Baxter Healthcare, Deerfield, IL) is a two-component biologic tissue adhesive composed of a solution of Tissucol-aprotinin and a solution of thrombin-calcium chloride, both frozen. Tissucol is supplied in ready to use syringes that have to be defrosted up to 37°C before use. During the application, the solutions are mixed giving a viscous, whitish, elastic solution. The solidification process of Tissucol is similar to that of the former coagulation cascade phase.

Evaluation of Adhesive Properties

According to ASTM standards, the adhesive properties were assessed applying both the products on biological tissues, in conformity with the manufacturers' indications, and after complete polymerizations, subjecting the glued samples to different types of load, to mimic conditions occurring during *in vivo* applications. To standardize test results, with respect to the multiplicity of applications and of tissues treated, pig skin was used as unique substrate, as recommended by normative; for each test, sample dimensions, gluing and polymerization modalities, and test calculations were performed as indicated by the relative ASTM standard.

Polymerization Substrate—Pig skin

Fresh, shaved pig skin, obtained directly from a local slaughterhouse, was used for testing. Tissue was harvested bilaterally from the flanks of 1-y-old pigs and transported to the laboratory in saline solution; strips of skin were prepared as indicated in each standard. Briefly, skin was deprived of the fat layer by a microtome blade secured in needle holder. A dermatome (Zimmer; Fogal s.r.l., Viareggio, Italy), with a modifiable depth cutting blade, was used to remove epidermal layer of porcine skin. The samples of epidermis were cut into appropriate size strips for each test and immersed in saline solution until their use for no longer than 24 h from the explant. The thickness of each strip was determined by six measurements, acquired in different points, using a micrometer ($\pm 3 \mu$ at 20°C) (Mitutoyo, Milan, Italy).

Samples Preparation

Each sample was obtained bonding two strips of similar thickness [2]. For all the tests, the gluing area was delimited by petroleum jelly and the glue was uniformly applied onto one of the strips of the couple; after overlapping the second strip, a load was applied for 10 min in order to allow complete polymerization. The quantity of glue for each test was decided experimentally. To condition the samples, glued skin was immersed in saline solution at $37 \pm 1^\circ\text{C}$ for $1 \text{ h} \pm 15 \text{ min}$, then retrieved and stabilized at test temperature for 15 min before testing. The samples were kept moist throughout the process to avoid shrinking due to the skin drying.

Test Methods

For all the test procedures, manual grips and a 50N load cell, mounted on a dual column bench top material testing machine (H10kT; Tinius Olsen, R an D Srl, Milan, Italy), were used. For each test, designation, type of solicitation, glue quantity, and load applied for preconditioning are described in Table 1; 10 replicates were performed for each procedure, according to ASTM indications.

Evaluation of Tensile Properties

Raw Material Samples Preparation

Samples were obtained dropping the glue in a S2 dumb-bell shaped silicone rubber mould (DIN 53504) mounted on a Teflon plate. For Glubran2 to trigger the polymerization process, an activator was sprayed on the Teflon substrate (Loxal Engineering Adhesives, Milan, Italy), then 2 mL of the product were dropped into the mould. After complete polymerization, which required 24 h at ambient temperature ($25 \pm 0.5^\circ\text{C}$), each sample was removed from the moulds and observed microscopically to evaluate the presence of internal or superficial defects.


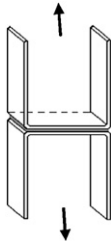
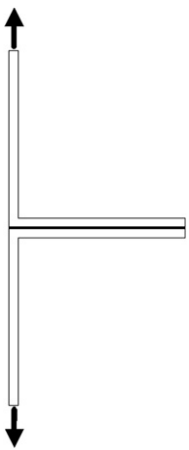

For Tissucol samples, components were heated at 37°C , then thrombin was diluted with distilled water up to 1:40 ratio to slow down coagulation time [14] giving sufficient time to allow a correct distribution of the fibrin glue into the mould. Having reached 37°C , components were mixed at a ratio of 1:1 to obtain 2 mL of solution, and deposited into the dumb-bell Teflon mould. Tissucol polymerization was completed placing the samples in a cell culture incubator (HeraCell; Heraeus, Hanau, Germany) for 2 h. Tests were performed within 3 h from the complete polymerization to avoid fibrin degradation. The thickness of each sample was measured by a micrometer in three points of the usable lengths.

Test Method

DIN 53504 "Determination of tensile stress/strain properties of rubber": Samples were mounted, using manual grips for Glubran2 and auto-locking grips for Tissucol, on a testing machine equipped with a 100 N load cell; contact-extensometers were adopted to take in consideration the deformation only of the usable tract of each dumb-bell sample. The specimens where breakage occurred out of the usable tract were discharged; tests were performed on three replicates. According to the normative (DIN 53504), break-strength, Young modulus, and elongation at break were evaluated during the test.

TABLE 1

List and Description of all the Adhesion Tests Performed on Glubran2 and Tissucol Surgical Glues

Normative designation	Glue amount (μL)	Load applied (N)	Type of solicitation
F2255-05: Standard test method for strength properties of tissue adhesives in lap-shear by tension loading	60	2	
F2258-05: Standard test method for strength properties of tissue adhesives in tension	60	2	
F 2256-05: Standard test method for strength properties of tissue adhesives in T-peel by tension loading	750	5	
F2458-05: Standard test method for wound closure strength of tissue adhesives and sealants	60	-	

Statistical Analysis

Student's *t* test and analysis of variance were used for statistical analysis. Data are presented as means ± standard deviation. Statistical significance was accepted to correspond to a *P* value less than *P* < 0.001.

RESULTS

Adhesive Properties

The Glues

Glubran2 was easy to spread on tissues and once polymerized appeared as a homogeneous, continuous, consistent, opalescent, and rough film, firmly attached to the substrate and resistant to traction. Glued samples were easy to handle due to cohesion guaranteed by the glue between treated tissues.

Samples treated with Tissucol appeared weakly glued by a gelatinous membrane, in most cases glued skin appeared difficult to handle due to the delicacy of bonding.

Test Results

For all adhesion tests, solicitation curves can be divided into three distinct and successive phases: (1) initial assessment tract, (2) resistance to rupture, and (3) breaking of the sample. During the initial phase, the samples fixed to grips in relaxed configuration were extended and stretched up to a definite pre-load; very low resistance was opposed by the samples during distension phases. Increasing the distance between the grips, the resistance opposed by samples to tissues detachment produced a significant rise of stress and stiffness. Having reached maximum load, the progressive breakage of samples occurred. For each test, excepted for the T-peel, values related to first tracts of the solicitation curves were disregarded.

For each test, calculation procedures specified by standards and results, are reported in Table 2.

F2255-05 “Standard test method for strength properties of tissue adhesives in lap-shear by tension loading”: during lap-shear tests, rupture of samples occurred due

to detachment of Glubran2 films from the skin and not to mutual sliding of tissues; this should be the reason for the low extension at rupture and for the increasing of tension once the pre-load value is reached. Step-trend of tension curves during decreasing of loads (Fig. 1) was due to propagation of fractures in glue films; no ruptures of loaded skin portions was observed at the end of the tests. On the contrary, for Tissucol, a gradual and uniform mutual sliding of skin strips was observed. Once strips reached detachment, the load opposing deformation was attributable to fibrin membrane and not to bonding between tissues. Tension level was extremely low compared with Glubran2.

F2258-05 “Standard test method for strength properties of tissue adhesives in tension”: under tension solicitation, Glubran2 polymerized-films opposed strong resistance to the detachment of skin strips, remaining intact up to maximum load, as evidenced by regular trends of loads (Fig. 2). This behavior guaranteed a uniform distribution of stress throughout glued surfaces. Tissucol glued samples, on the contrary, showed weak bonding, the detachment of skin strips occurred from the initial phases of the test, fibrin clot already broke at low tension value, concentrating tension on anchoring points.

F2256-05 “Standard test method for strength properties of tissue adhesives in T-peel by tension loading”: to avoid making mistakes due to gripping and to sample weight, according to standards, in T-peel test average strength was calculated neglecting load data for the first 2.5 cm and for the last 2.5 cm of displacement. During loading, Glubran2 demonstrated its strength, strongly opposing itself to the peeling of skin strips. In usable tract, irregular trends of tension were evidenced due to jerks detachment of samples produced by fragmentation of Glubran2 films (Fig. 3). Tissucol glued samples showed a more regular trend of detachment curve due to elasticity of fibrin clot, but bonding strength was very low (near to load cell lecture limit) and in almost all samples, gluing was damaged by the weight of skin strips.

TABLE 2

Results and Statistical Significance of the Adhesion Tests Performed on Glubran2 and Tissucol Surgical Glue

Test	Glue	F2255-05	F2258-05	F2256-05	F2458-05
Test calculations		Apparent shear strength (MPa) as the maximum load divided by the bonding area	Tensile strength (MPa) as the maximum load divided by the bonding area	Average T-peel strength dividing the average load (N) by the width of the specimen (cm)	Median, mean, and standard deviation of the peak load at failure (N)
Mean strength	Glubran2	0.0326 MPa ± 0.089	0.021 MPa ± 0.06	0.269 N/cm ± 0.066	4.03 N ± 1.514
	Tissucol	0.0022MPa ± 0.0013	0.0007MPa ± 0.0006	0.045 ± 0.009	0.321 ± 0.151
Statistical significance <i>P</i>		<0.0001	<0.0001	<0.0001	<0.0001

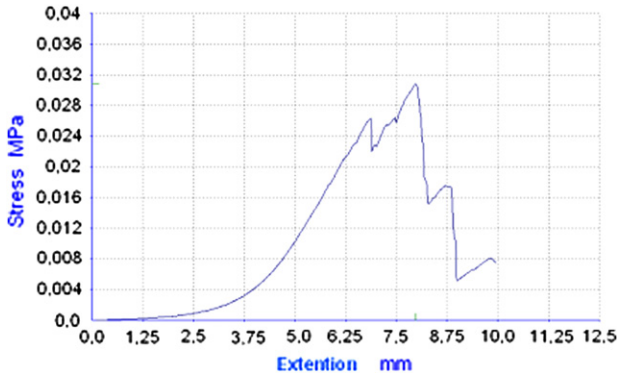


FIG. 1. Stress/extension graph of skin glued with Glubran2 under lap shear test (ASTM F2255-05): the step trend of the load curve was due to the propagation of fractures into glue film. Rupture occurred for the detachment of glue film from the skin and not for the mutual sliding of tissues.

F2458-05 “Standard test method for wound closure strength of tissue adhesives and sealant”: in this test, the resistance opposed by the samples to the detachment of skin strips was due to adhesion of polymerized film to tissues; no overlapping between skin strips was carried out in this case.

During stress, Glubran2 films hindered the separation of materials taking them in traction. Rupture of samples was due to the detachment of Glubran2 films from tissues and not to fragmentation of the films themselves; intrinsic bonds of glue were therefore stronger than that established with skin. Wound closure remained intact up to the maximum load, as evidenced from the regular increase of a representative stress/strain curve plotted in Fig. 4. Tissucol glued samples appeared poorly glued; fibrin clot did not oppose significance resistance to skin detachment, in each phase of the test.

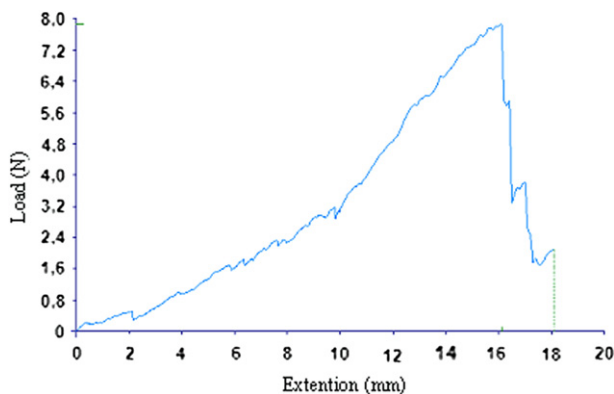


FIG. 2. Load/extension graph of skin glued with Glubran2 under tension test (ASTM F2258-0): the tensional state was uniformly distributed on the entire glued surface, the rupture was sudden, film opposed itself strongly to separation of tissues.

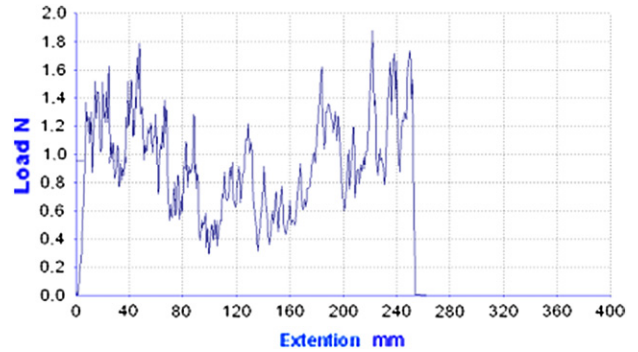


FIG. 3. Load/extension graph of skin glued with Glubran2 under T-peel test (ASTM F2256-05): the irregular trend of solicitation curve was due to the fragmentation of glue film at the interface with skin.

Tensile Properties

Polymerized Glue

Some problems were encountered in obtaining Glubran2 dumb-bell specimens, due to the amount of glue and to the particular shape of the mould. Many specimens were discharged due to the presence of air bubbles included into thickness. After complete polymerization, the dumb-bell test specimens were transparent, rigid, with smooth surfaces and resistant to traction. Dumb-bell test specimens obtained with Tissucol, on the contrary, once polymerized appeared whitish, gelatinous, and delicate to handle. Many samples were discharged due to poor uniformity in aspect and thickness.

Test Results

Tensile test solicitation curves of Glubran2 dumb-bell shape specimens can be divided in two successive phases: (1) an initial tract relative to the sample settlement and (2) a tract relative to the resistance at

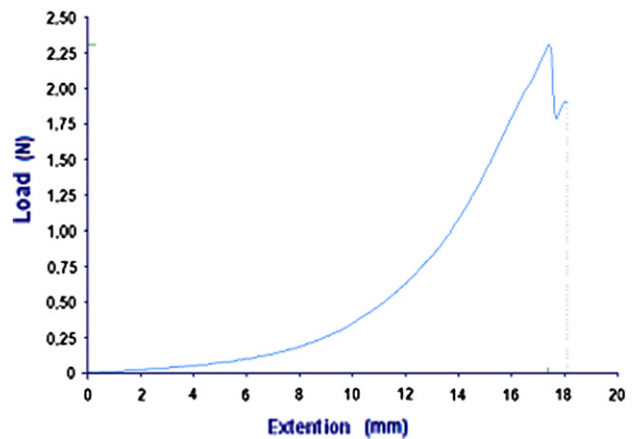


FIG. 4. Load/extension graph of skin glued with Glubran2 under wound closure strength test (ASTM F2458-05): integrity of gluing was preserved up to rupture, as evidenced by regular trend of the curve.

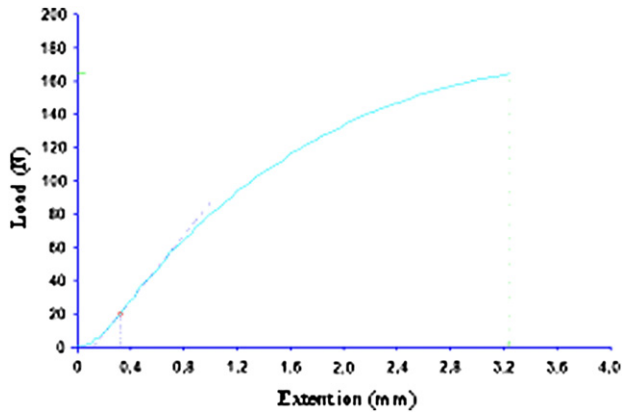


FIG. 5. Load/elongation graph of Glubran2 dumb-bell test specimen under tensile test (DIN 53504): the high slope of solicitation curve is due to glue strength. The breaking behavior evidenced the fragile nature of polymerized glue.

rupture. Mean values measured in the tests were $20.44 \text{ MPa} \pm 2.83$ for the breaking strength, $283.9 \text{ MPa} \pm 30.5$ for the Young modulus and $13.21\% \pm 4.32\%$ for the elongation at break respectively. Glubran2 samples demonstrated to strongly oppose to ruptures, reaching high loading values; the stiff nature of synthetic glue polymerized on inert substrate was responsible for a very low extension and a fast growth of load in tension (Fig. 5). The rupture, sudden and with production of a lot of fragments, was typical of a fragile material. Fibrin glue dumb-bell clot, on the contrary, showed viscoelastic behavior with low stress level and high rupture elongation; rupture was gradual, with a rubber-like trend (Fig. 6). Mean values measured in the tests were $0.1408 \text{ MPa} \pm 0.0187$ for breaking strength, $0.0368 \text{ MPa} \pm 0.0061$ for the Young modulus, and $363.1\% \pm 30.58$ for the elongation at break respectively ($P < 0.0001$ for all values compared with Glubran2).

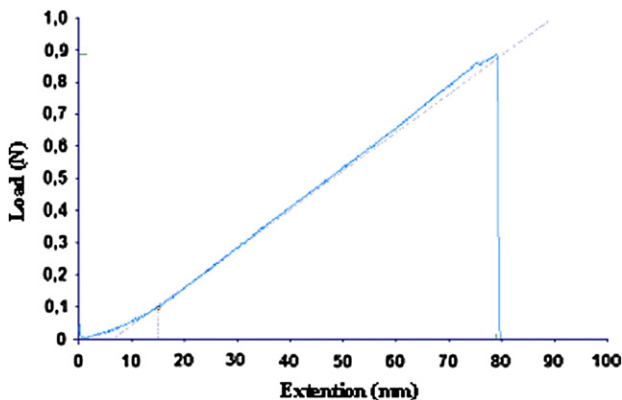


FIG. 6. Load/elongation graph of Tissucol dumb-bell test specimen under tensile test (DIN 53504): material showed a viscoelastic behavior with Young modulus and rupture strength lower than that of Glubran of various orders of magnitude.

DISCUSSION

The ever-increasing role assumed by synthetic biocompatible glues in surgical and endoscopic applications led to the necessity to extensively investigate their characteristics. In particular, adhesive and mechanical properties of surgical glues are of a primary importance in guaranteeing the solidity of gluing between biologic tissues and with artificial implants, and in preserving their haemostatic as well as their aerostatic function without inducing alterations of treated tissue properties.

In this work, results of adhesive and tensile tests performed on a cyanoacrylate surgical glue, named Glubran2, are reported. Glubran2 is the only glue based on cyanoacrylate approved in Europe for surgical and endoscopic applications on different internal organs and for skin wound closure applications. Interest in this product derives from the excellent performance observed during *in vivo* applications, especially in terms of adhesive capability on biologic tissues in wet environments. Despite the major use of Glubran2 in clinical practice, to date a complete characterization of its properties in comparison with other commercial tissue adhesives is still lacking. In the present study, Glubran2 characterization in terms of adhesion and strength, in comparison with a widely used commercial fibrin glue, Tissucol, were carried out. All tests were performed according to ASTM and DIN standards and were related to internal glue applications.

The study evidenced that unlike Tissucol clot, which appeared like a gelatinous viscoelastic material and difficult to distribute uniformly on skin and to handle, polymerized Glubran2 appeared like a consistent, uniform opalescent film, slightly granular, as occurs during *in vivo* applications, demonstrating *in vitro* reproducibility of polymerization process. Moreover, the polymerization time of this particular formulation of cyanoacrylate tissue adhesive, slower than all other commercial cyanoacrylate glues, allowed to obtain a uniform distribution of Glubran2 with complete coverage of the surfaces to be bonded. No problem was encountered during gluing and preconditioning phases of the samples preparation with cyanoacrylate glue.

Unlike Tissucol, which demonstrated weak adhesive and tensile properties when subjected to tension loading, tests carried out on Glubran2 evidenced its capability in realizing strong bonding between natural tissues. Adhesive capacity of Glubran2 on biologic surfaces was very high, attributable to an excellent penetration of the bonding agent into tissue; even so, in some cases, it appeared that intrinsic bonding of Glubran2 was more tenacious than the link established with biologic tissues. For all the various loads, both those applied in parallel and orthogonal to the resistance area,

Glubran2 strongly resisted to the detachment of tissues. Almost in all cases the integrity of samples was maintained up to the rupture and the elasticity of the sample was preserved, according to the research carried out by Paez *et al.* [7]. Tension test performed on Glubran2 polymerized on an inert substrate, evidenced the consistency and the resistance to stretching and rupture of the raw polymerized glue, showing a rupture modality typical of fragile materials. Moreover, the maintenance of tissue elasticity after Glubran2 bonding allowed to reduce the internal stress commonly generated by sutures that often cause limited durability of some implants and operations.

Finally, Glubran2 properties, evidenced by *in vivo* applications and confirmed by the positive results of *in vitro* test, recommend its utility in surgical and endoscopic practice, guaranteeing the integrity of bonding up to high loads, avoiding risks of bleeding, aerial loss, or partial detachment of the involved tissues.

CONCLUSIONS

To date, much is still unknown regarding the adhesive and mechanical properties of the cyanoacrylate surgical glue Glubran2 and its failure manner. This study is an initial effort to investigate the behavior and the characteristics of this product with test methods and analyses recommended by American Standards concerning tissue adhesives in medicine. From the investigations undertaken, and from the comparison with Tissucol, the most common commercial fibrin glue, it was apparent the very interesting properties of Glubran2, in particular its capability to make strong bonding between wet tissues, was fully demonstrated in the various tests performed. Glubran2 realized resistant gluing of tissues without inducing significant alteration of elasticity in samples, and preserving its integrity even in very high tensile levels. The modality of polymerization, strongly dependent upon substrates of application, encourages to thoroughly analyze the

behavior of Glubran2 on different typologies of tissue. Despite the excellent results obtained by the glue, further elastic formulation is desirable in order to reduce the fragile behavior evidenced especially in tensile tests performed on raw material.

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