

METHODS FOR DRAPING SURGICAL INCISION SITES

BACKGROUND OF THE INVENTION

Field of the Invention

- 5 This invention is directed to methods for draping a surgical incision site prior to surgery. Specifically, the methods of this invention involve the *in situ* formation of a polymeric cyanoacrylate drape over a mammalian skin surface at the surgical incision site. An incision is made through the drape and surgery is then conducted through the incision.

10 References

The following publications, patent applications and patents are cited in this application as superscript numbers:

- 15 ¹ Masterson, M.D., "*Skin Preparation*", Chapter 9, in *Surgical Infections, Diagnosis and Treatment*, Meakins, Ed., Scientific American, Inc., New York, USA, Publisher, pp. 119-125 (1994)
- ² Osuna, et al., "*Comparison of an Antimicrobial Adhesive Drape and Povidone-Iodine Preoperative Skin Preparation in Dogs*", *Veterinary Surgery*, 21(6):458-462 (1992)
- 20 ³ Hagen, et al., "*A Comparison of Two Skin Preps Used in Cardiac Surgical Procedures*", *AORN Journal*, 62(3):393-402 (1995)
- ⁴ Alexander, et al., "*Development of a Safe and Effective One-Minute Preoperative Skin Preparation*", *Arch. Surg.*, 120:1357-1361 (1985)
- ⁵ Chiu, et al., "*Plastic Adhesive Drapes and Wound Infection After Hip Fracture Surgery*", *Aust. N.Z. J. Surg.*, 63:798-801 (1993)

- 6 Barley, "Methods for Retarding Blister Formation by Use of
Cyanoacrylate Adhesives", U.S. Patent No. 5,306,490, issued April 26,
1994.
- 7 Barley, et al., *Methods for Treating Suturable Wounds by Use of Sutures*
5 *and Cyanoacrylate Adhesives*, U.S. Patent No. 5,254,132, issued
October 19, 1993
- 8 McIntire, et al., *Process for the Preparation of Poly(α -Cyanoacrylates)*,
U.S. Patent No. 3,654,239, issued April 4, 1972
- 9 Barley, et al., International Patent Application Publication No. WO
10 93/25196, for *Methods for Treating Non-Suturable Wounds by Use of*
Cyanoacrylate Adhesives, published December 23, 1993
- 10 Barley, et al., *Methods for Reducing Skin Irritation From Artificial*
Devices by Use of Cyanoacrylate Adhesives, U.S. Patent No. 5,653,789,
issued August 5, 1997
- 15 11 Tighe, et al., *Methods for Inhibiting Skin Ulceration by Use of*
Cyanoacrylate Adhesives, U.S. Patent No. 5,403,591, issued April 4,
1995
- 12 Tighe, et al., for *Use of Cyanoacrylates for Providing a Protective*
Barrier, U.S. Patent No. 5,580,565, issued December 6, 1996.
- 20 13 Ritter, et al., "Retrospective Evaluation of an Iodophor-Incorporated
Antimicrobial Plastic Adhesive Wound Drape", *Clinical Orthopedics and*
Related Research, pp. 307-308 (1988)
- 14 Duhaime, et al., "Distribution of Bacteria in the Operating Room
25 *Environment and its Relation to Ventricular Shunt Infections: a*
Prospective Study", *Child's Nerv. Syst.*, 7:211-214 (1991)
- 15 O'Sullivan, et al., *High Viscosity Cyanoacrylate Adhesive Compositions,*
and Process for Their Preparation, U.S. Patent No. 4,038,345, issued
July 26, 1977

30 All of the above publications, patent applications and patents are herein
incorporated by reference in their entirety to the same extent as if each
individual publication, patent application or patent was specifically and
individually indicated to be incorporated by reference in its entirety.

State of the Art

Reduced morbidity and/or infection associated with surgical procedures necessitates the thorough preparation of the patient's skin prior to initiating any incision into the skin as part of the surgical procedure. The primary reason for patient skin preparation is to reduce the risk of wound infection by introduction of microbes into the incision site¹ from either endogenous sources or from air borne microbes.¹⁴ In turn, reduction in such risk correlates, obviously, with reductions in the population of microbes on the skin surface and especially at the skin surface adjacent to the incision site.

Suitable skin preparation involves, for example, application of an antimicrobial agent onto and around the skin surface adjacent to the incision site which reduces the population of microbes on these surfaces and, hence the relative risk of infection. However, the skin is never completely sterilized during these procedures and microbes from hair follicles and sweat/sebaceous glands will migrate to the surface of the skin thereby raising microbial populations and accordingly relative infection risks.² To counter possible microbial migration into the incision, it has become common practice to employ a surgical incise drape over the patient's incision site.

Conventional surgical incise drapes include those which comprise preformed, sized polymeric films coated with a pressure-sensitive adhesive. In some cases, an antimicrobial agent is incorporated directly into the adhesive in order to permit a continuous release of the antimicrobial agent onto the skin.^{3,13} After application of an antimicrobial agent onto the skin surface of the patient, the surgical incise drape is applied, adhesive side down, with pressure to effect adherence of the drape to the skin. A surgical incision is then made through the drape and the requisite surgery is conducted through this incision. After completion of the surgery, the drape is conventionally removed from the skin surface.

Notwithstanding the benefits associated with a surgical incise drape, several problems exist which have both limited the general applicability of these drapes to surgical incisions and have actually increased the relative risk of infection. Specifically, the first most common and potentially serious problem associated with the use of conventional surgical incise drapes is the separation or lifting of the drape from the skin surface during surgery. In one study, it was reported that up to 44% of the drapes experienced at least partial separation during human surgery². In turn, Alexander, et al.⁴ report a sixfold increase in infection rates in operations in which the surgical incise drape separated from the skin during surgery as compared to infection rates in which the drape did not separate from the skin. Without being limited by any theory, it is generally believed that occlusion of the skin by the surgical incise drape provides a moist, warm skin surface which can encourage microbial growth. It is further believed that separation of the drape from the skin during surgery permits migration of microbes and/or microbial growth at these sites and, accordingly, in such cases, the use of a drape can actually promote rather than retard microbial populations at the incision site.

Non-adherence of the surgical incise drape to the patient's skin is, of course, related to adhesive failure as well as wrinkling of the preformed polymeric film during application. In the former case, this has lead to some attempts to increase the amount and/or strength of adhesive employed in the drape to secure the drape to the mammalian surface. However, this in turn may lead to more rather than fewer complications. In particular, since the drape is conventionally removed from the skin after surgery by, e.g., the peeling or pulling off of the drape, an increase in the relative strength of the adhesive leads to increased difficulty in so removing the drape from the skin. The effort required to effect such removal can lead to skin tearing, especially adjacent to the incision site, as well as removal of surface hair. Skin tearing is clearly disadvantageous and invariably raises additional infection risks because the mammalian skin surface is opened (compromised) and susceptible to

infection. Moreover, the removal of hair (shaving) has also been associated with increased infection rates² and hair removal due to adhesive/drape removal from the mammalian skin can also be expected to provide similar increased infection rates.

5 In the latter case, wrinkling of the polymeric drape is essentially irreversible because the wrinkles cannot be smoothed out absent complete removal of the drape and drapes, once removed, cannot typically be reapplied. Additionally, air pockets found in the wrinkles of such drapes are undesirable because they provide a source of microbes adjacent to the skin and, in some
10 cases, promote microbial growth. Wrinkling of the polymeric film is common to most applications of the surgical incise drapes but is particularly problematic with contoured surfaces such as elbows, knees, bony hips, etc. This, in turn, potentially limits the use of such conventional drapes.

 An additional problem associated with preformed polymeric films used
15 as surgical incise drapes arises because such drapes do not conform well to the three dimensional contours of the human or other mammalian body thereby increasing the possibility of separation during surgery. For example, while abdominal area through which the surgical incision is made is typically a good candidate for such conventional surgical incise drapes, other surfaces such as
20 elbow, knee, foot, and bony hip surfaces (as examples) have three dimensional contours which render consistent adherence of the drape over the incision site during surgery problematic at best. In this regard, Chiu, et al.³ report that the use of sterile adhesive drapes during hip fracture surgeries appeared to have actually encouraged microbial accumulation in the skin adjacent to the wound.

25 Still a further problem arises from the fact that many adhesives employed with the polymeric films do not adhere well to hair thereby limiting their utility². Additionally, as noted above, shaving to remove hair prior to surgery has been clinically associated with increased wound infection rates.¹

In an alternative embodiment, the art has proposed the use of emulsions/solutions containing a volatile organic solvent and a polymer. Upon application to the skin, the solvent dissipates leaving a polymeric film which acts as the incise drape. Significant problems exist with such a procedure and, 5 in particular, the polymeric film lacks strong adhesion to the skin and the volatile solvent can create irritation (e.g., skin, nose, etc.) as well as can be the source of a fire hazard in the operating room.

Lastly, while the most important purpose of using surgical incise drapes is to prevent postoperative wound infections, the simple fact of the matter is 10 that the drapes of prior art are removed after surgery and there is, accordingly, no postoperative antimicrobial effect available to the skin surface at the surgical incision site.

This invention is directed, in part, to the discovery that the *in situ* formation of a cyanoacrylate polymeric drape at the surgical incision site prior 15 to surgery overcomes many of the prior art problems associated with the use of conventional preformed surgical incise drapes and additionally provides incremental advantages heretofore not achieved by conventional drapes. For example, the cyanoacrylate polymer is known in the art to have bacteriostatic properties and the cyanoacrylate monomer permits the inclusion of compatible 20 antimicrobial agents if such is desired. Still another advantage is the formation of an appropriately configured drape without the need to modify the dimensions provided with commercial polymeric drapes. Still further, the methods of this invention result in incise drapes which mold directly to the multiple contours of the intended surgical site.

25 The use of cyanoacrylate polymers per this invention is in contrast to their known medical uses as an alternative or adjunct to sutures⁷ or as a hemostat⁸. Other described uses of cyanoacrylate prepolymers include their use to prevent friction blister formation⁶, treating small non-suturable wounds⁹, and

in inhibiting surface skin irritation arising from friction between the skin surface and artificial devices such as tapes, prosthetic devices, casts, and the like.¹⁰

SUMMARY OF THE INVENTION

5 This invention is directed to methods for draping a surgical incision site by application of a cyanoacrylate composition to the surface of the surgical incision site.

10 *In situ* polymerization of the cyanoacrylate composition provides for an adherent polymeric film over the surgical incision site which acts as a surgical incise drape during surgery. The adherence of the polymeric film to the skin surface is so strong that the possibility of separation of the drape during surgery is effectively removed. Additionally, the cyanoacrylate composition can be applied as a liquid/gel to the skin surface which permits formation of an
15 adherent film over any skin contour including elbows, knees, hips, and the like.

 Since the polymeric film is naturally shed from the skin surface 1-4 days after application, there is no need to effect removal of the drape after surgery or to cause the skin trauma potentially associated with drape removal. This polymeric film forms a bacteriostatic or bactericidal barrier to external sources
20 of wound contamination. Moreover, in a preferred embodiment, the cyanoacrylate composition is formulated to contain an antimicrobial agent which, over time, will be released from the resulting film thereby providing for peri- and post-surgical infection protection not now available from conventional drapes.

25 Accordingly, in one of its method aspects, this invention is directed to a method for forming an adherent, surface conforming drape at a surgical incision site of a patient which method comprises:

- (a) defining a surgical incision site on the patient;

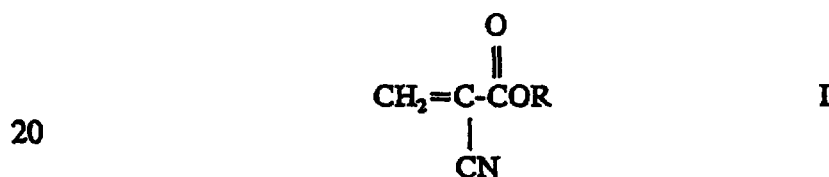
(b) applying a sufficient amount of a composition comprising a polymerizable cyanoacrylate ester to the skin surface at the surgical incision site defined in (a) above so as to cover this site with the composition;

(c) polymerizing the cyanoacrylate ester so as to form a flexible, waterproof, adhesive polymer layer which adheres to the area(s) where the adhesive was applied; and

(d) creating an incision through the polymer layer formed in (c) above.

Application of the layer of composition comprising the cyanoacrylate ester is preferably made onto the surface of intact or injured skin and the incision is made subsequent to formation of the cyanoacrylate polymer layer. More preferably, the skin is intact skin further characterized as lacking any infection, open wounds, etc. which would permit the polymer to penetrate from the surface of the epidermis to or beyond the dermal layer.

Preferably, the polymerizable cyanoacrylate ester comprises an ester which, in monomeric form, is represented by formula I:



where R is selected from the group consisting of:

alkyl of 1 to 10 carbon atoms,

alkenyl of 2 to 10 carbon atoms,

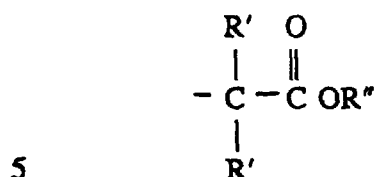
cycloalkyl groups of from 5 to 8 carbon atoms,

phenyl,

2-ethoxyethyl,

3-methoxybutyl,

and a substituent of the formula:



wherein each R' is independently selected from the group consisting of:

hydrogen and methyl, and

R'' is selected from the group consisting of:

- 10 alkyl of from 1 to 6 carbon atoms,
 alkenyl of from 2 to 6 carbon atoms,
 alkynyl of from 2 to 6 carbon atoms,
 cycloalkyl of from 3 to 8 carbon atoms,
 aralkyl selected from the group consisting of benzyl,
 15 methylbenzyl and phenylethyl,
 phenyl, and
 phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

- 20 More preferably, in the cyanoacrylate esters of formula I, R is alkyl of from 2 to 10 carbon atoms and more preferably alkyl of from 2 to 8 carbon atoms. Even more preferably, R is butyl, pentyl or octyl and most preferably, R is *n*-butyl.

- 25 In another preferred embodiment, the polymerized cyanoacrylate composition has a thickness of no more than about 1 millimeter and, more preferably, the polymer layer has a thickness of from about 2 to about 500 microns and still more preferably from about 20 to about 100 microns.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention is directed to methods for draping a surgical incision site prior to surgery. However, prior to discussing this invention in further detail, the following terms will first be defined.

5 Definitions

As used herein, the following terms have the following meanings:

The term "surgical incision site" refers to the skin surface to which the surgical incision is to be made as well as the immediate area adjacent to the incision. This immediate area typically extends at least 0.1 to 2 inches (0.254
10 to 5.08 cm) in all directions beyond the incision and preferably extends by about 0.25 to 12 inches (0.635 cm to 30.48 cm) beyond the incision.

The term "incision" or "surgical incision" refers to any surgical penetration which extends beyond the dermal or epidermal layer of the patient's skin and includes, by way of example, incisions or punctures made by needles,
15 knives (including surgical knives, surgical cautery knives, and the like), lasers (medical surgical laser), trocars, IV punctures, blood transfusion/donation punctures, vaccine inoculation punctures, medicament punctures (e.g., insulin injections), punctures associated with hemodialysis, etc.

20 The term "polymerizable cyanoacrylate esters" refers to polymerizable formulations comprising cyanoacrylate monomers or polymerizable oligomers which, in their monomeric form, are preferably compounds represented by formula I as described above.

More preferably, in formula I, R is an alkyl group of from 2 to 10
25 carbon atoms including ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *n*-pentyl, *iso*-pentyl, *n*-hexyl, *iso*-hexyl, 2-ethylhexyl, *n*-heptyl, octyl, nonyl,

and decyl. More preferably, R is butyl, pentyl or octyl and most preferably, R is *n*-butyl. Mixtures of such compounds can also be employed.

A preferred cyanoacrylate ester for use in the invention is *n*-butyl-2-cyanoacrylate.

5 The polymerizable cyanoacrylate esters described herein rapidly polymerize in the presence of water vapor or tissue protein, and the *n*-butyl-cyanoacrylate bonds to mammalian skin tissue without causing histotoxicity or cytotoxicity.

Such polymerizable cyanoacrylate esters are sometimes referred to
10 herein as prepolymers and compositions comprising such esters are sometimes referred to herein as prepolymer compositions.

Polymerizable cyanoacrylate esters are known in the art and are described in, for example, U.S. Patent Nos. 3,527,224; 3,591,676; 3,667,472; 3,995,641; 4,035,334; and 4,650,826 the disclosures of each are incorporated
15 herein by reference in their entirety.

The term "biocompatible plasticizer" refers to any material which is soluble or dispersible in the cyanoacrylate composition, which increases the flexibility of the resulting polymeric film coating on the skin surface, and which, in the amounts employed, is compatible with the skin as measured by
20 the lack of moderate to severe skin irritation. Suitable plasticizers are well known in the art and include those disclosed in U.S. Patent Nos. 2,784,127 and 4,444,933 the disclosures of both of which are incorporated herein by reference in their entirety. Specific plasticizers include, by way of example only, acetyl tri-*n*-butyl citrate (preferably ~20 weight percent or less), acetyl trihexyl
25 citrate (preferably ~20 weight percent or less) butyl benzyl phthalate, dibutyl phthalate, dioctylphthalate, *n*-butyryl tri-*n*-hexyl citrate, diethylene glycol

dibenzoate (preferably ~20 weight percent or less) and the like. The particular biocompatible plasticizer employed is not critical and preferred plasticizers include dioctylphthalate and C2-C4-acyl tri-*n*-hexyl citrates.

5 The term "surgical incision drape" refers to the drape formed over the surgical incision site and through which the surgical incision is made. The term surgical incision drape is synonymous with the term "incise drape" as used by Osuna, et al.²

10 The term "antimicrobial agent" refers to agents which destroy microbes (i.e., bacteria, fungi, yeasts and viruses) thereby preventing their development and their pathogenic action.

Methods

The methods of this invention comprise the *in situ* formation of a cyanoacrylate polymer film on the skin surface at the surgical incision site of a patient which polymeric film acts as a surgical incision drape.

15 The surgical protocol preferably involves skin preparation prior to *in situ* formation of the cyanoacrylate polymer drape over the surgical incision site. Specifically, an antimicrobial agent is applied to the cleaned surgical incision site. The antimicrobial agent can be any suitable agent including iodine based solutions, alcohols, etc. In one embodiment, an iodine prep
20 solution is first applied to the surgical incision site. The patient's skin is then cleansed and scrubbed with this solution and subsequently washed off. Afterwards, an alcohol solution or a povidone iodine solution is applied to the surgical incision site to complete the skin preparation.

25 The surgical incision site is preferably dried and then an adherent polymeric drape is formed over this site by applying a cyanoacrylate adhesive composition to the skin surface at the surgical incision site. As noted above,

this composition comprises polymerizable cyanoacrylate monomers and/or reactive oligomers which, upon contact with the surface skin moisture, tissue protein, etc. polymerizes *in situ* to form a polymeric film.

Polymerization occurs at ambient skin temperature while maintaining the skin surface under suitable conditions to allow polymerization to proceed. In general, the particular length of time required for polymerization will vary depending on factors such as the amount of adhesive composition applied, the temperature of the skin, the moisture content of the skin, the surface area of skin to which the adhesive was applied, and the like. However, in a preferred embodiment, polymerization is generally complete within about 10 to about 60 seconds while the skin is maintained at ambient conditions; however, in some cases, polymerization can occur up to about 5 minutes. During this period, the patient is maintained in a position which permits the cyanoacrylate to polymerize and form a polymeric drape while minimizing any patient movement which might dislodge the cyanoacrylate from that surgical incision site or create undesirable bonding.

Sufficient amounts of the composition are employed to cover (i.e., coat) the entire surgical incision site with a layer of the cyanoacrylate polymer. If necessary, excess cyanoacrylate monomer and/or oligomer can be removed from the skin with a wipe or tissue paper before polymerization or, after polymerization, any polymer formed at unintended sites can be removed with materials such as acetone (nail polish remover).

After polymerization, the resulting polymeric film forms a surgical incise drape which strongly adheres to the skin, is flexible and waterproof. Such strong adherence effectively eliminates the possibility that the drape will separate from the patient's skin during surgery. However, notwithstanding such strong adherence, the polymeric film defining the drape will only adhere to the skin for a period of about 1-4 days after which time it sloughs off. This occurs

because the cyanoacrylate polymer adheres only to the uppermost portion of the epidermal layer which is continuously in the process of being sloughed off and replaced by the underlying cells. Accordingly, the cyanoacrylate drape need not be removed in the manner of conventional preformed drapes attached
5 through an adhesive layer whose removal can result in skin trauma.

The polymeric drape should be maintained in an unbroken manner over the entire surgical incision site. This can be assured by careful application of the cyanoacrylate adhesive onto the skin. Additionally, the use of a plasticizer will facilitate the maintenance of the polymeric drape in an unbroken manner
10 and will inhibit cracking of the drape.

In one embodiment, after application of the initial polymeric layer, a second, preferably thinner, layer is applied thereto. Additional amounts of cyanoacrylate adhesive composition can be applied as needed to maintain an unbroken coating covering over surface skin areas.

15 Application is conducted under conditions wherein the polymeric drape preferably has a thickness of no more than about 1 millimeter and, more preferably, the polymer layer has a thickness of from about 2 to about 500 microns and still more preferably from about 20 to about 100 microns. If thinner polymeric drapes are desired, then the polymeric drape should have a
20 thickness of from about 2 to about 50 microns and preferably from 10 to 40 microns. The amount of cyanoacrylate composition applied to a unit area of skin to obtain such thicknesses is well within the skill of the art.

Once the polymeric surgical incise drape is formed over the surgical incision site (which as defined above includes the areas adjacent to the incision
25 site), the polymeric surgical incise drape can then optionally be overdraped with sterile towels and sheets. In this optional embodiment, such towels and sheets are laid over (i.e., overdrape) the surgical incision drape to define a limited

field of the surgical incise drape in which the actual incision is to be made and the subsequent operation is to be conducted.

In either case, the surgical incision is made through the polymeric surgical incise drape. Any conventional incision can be made including those
5 created by needles, knives (including surgical knives and surgical cautery knives), lasers, trocar, and the like. The particular incision made is not critical and is, of course, made relative to why the incision is created (e.g., surgery).

Once the incision is made, the surgery or other procedure is conducted using conventional methods. When surgery is conducted, upon completion of
10 the surgery, the surgical wound is closed by conventional methods. In one embodiment, however, closure of the epidermal or dermal layer of the surgical wound can be accomplished by application of cyanoacrylate adhesive composition over the joined opposed skin sections and maintaining skin closure until the cyanoacrylate has polymerized.

15 The size and thickness of the polymeric drape formed onto the skin surface area can be readily controlled by the amount and viscosity of cyanoacrylate adhesive composition packaged in a single dose product or by use of a multiple use dispenser which governs the amount of material applied onto a unit area of surface skin. In this regard, the dispenser described by Otake,
20 U.S. Patent No. 4,958,748, which is incorporated by reference in its entirety, is one example of a dispenser which dispenses the cyanoacrylate adhesive composition in a controlled dropwise manner. Other methods for the controlled dispersement of the cyanoacrylate adhesive include, by way of example, a spray applicator, brush, wipe, swab or solid paddle applicator, applicators for
25 repeated and intermittent use of the cyanoacrylate composition and the like.

In applicators, the cyanoacrylate composition is stored at ambient conditions and can be provided in sterile form.

Because the cyanoacrylate polymer layer is waterproof, the patient is not prevented from bathing or being bathed and other activities involving exposure to water during the period the polymer layer protects the surgical incision site provided a further application of the cyanoacrylate composition is made over
5 the incision site.

Compositions

The cyanoacrylate compositions comprising the polymerizable cyanoacrylate esters are prepared by conventional methods of mixing the appropriate components until homogenous.

10 The specific viscosity of these compositions depends, in part, on the intended application of the composition. For example, relatively low viscosities are often preferred where application is to be made to a large surface area (e.g., abdominal surfaces). This preference results from the fact that those
15 forms are less viscous and, accordingly, will permit more facile large surface area application of a thin application. Contrarily, where application is to be made to a specific position on the skin (e.g., elbow surfaces, knee surfaces and the like), higher viscosity compositions, including those containing thixotropic materials, are preferred to prevent "running" of the compositions to unintended locations.

20 Accordingly, these compositions have a viscosity of from about 2 to 50,000 centipoise at 20°C. Preferably the less viscous compositions have a viscosity of from about 2 to 1,500 centipoise at 20°C. More preferably, the cyanoacrylate ester employed in these compositions is almost entirely in monomeric form and the composition has a viscosity of from about 5 to about
25 500 centipoise at 20°C.

A thickening agent is optionally employed to increase the viscosity of the composition, which thickening agent is any biocompatible material which

increases the viscosity of the composition. Suitable thickening agents include, by way of example, polymethyl methacrylate (PMMA) or other preformed polymers soluble or dispersible in the composition, a suspending agent such as fumed silica and the like with PMMA being preferred. Fumed silica is particularly useful in producing a gel for topical application having a viscosity of from about 1500 to 50,000 centipoise at 20°C. Suitable thickening agents for the compositions described herein also include a partial polymer of the alkyl cyanoacrylate as disclosed in U.S. Patent Nos. 3,654,239⁸ and 4,038,345¹⁵ both of which are incorporated herein by reference in their entirety.

Thickening agents are deemed to be biocompatible if they are soluble or dispersible in the composition and are compatible with the skin as measured by the lack of moderate to severe skin irritation.

The cyanoacrylate adhesive compositions preferably include a biocompatible plasticizer and such plasticizers are preferably included in the composition from about 10 to 30 weight percent and more preferably from about 18 to 25 weight percent based on the total weight of the composition absent any antimicrobial agent.

Additionally, the cyanoacrylate compositions described herein preferably include a polymerization inhibitor in an effective amount to inhibit premature polymerization of the composition during storage. In a particularly preferred embodiment, this inhibitor is sulfur dioxide which is employed at from about 50 to 500 ppm, preferably 200 to 500 ppm, based on the total weight of the composition absent any antimicrobial agent. Other preferred polymerization inhibitors include glacial acetic acid, free radical inhibitors (e.g., hydroquinones) and the like which can be used alone or in combination with SO₂.

The polymerizable cyanoacrylate ester compositions may additionally contain one or more optional additives such as colorants, perfumes, anti-diffusion agents, rubber modifiers, modifying agents, etc. In practice, each of these optional additives should be both miscible and compatible with the cyanoacrylate composition and the resulting polymer. Compatible additives are those that do not prevent the use of the cyanoacrylates in the manner described herein.

In general, colorants are added so that the polymer layer formed on the skin will contain a discrete and discernable color. Perfumes are added to provide a pleasant smell to the formulation. Rubber modifiers are added to further enhance the flexibility of the resulting polymer layer. The amount of each of these optional additives employed in the composition is an amount necessary to achieve the desired effect.

Preferred cyanoacrylate compositions useful in the practice of this invention are also disclosed by Greff, et al., U.S. Patent No. 5,480,935, which application is incorporated herein by reference in its entirety.

In a particularly preferred embodiment, the cyanoacrylate adhesive composition further comprises an antimicrobially effective amount of a compatible antimicrobial agent. Such compositions preferably comprise from about 1 to about 40 and preferably 5 to 30 weight percent of the compatible antimicrobial agent either as a solution or as a suspension based on the total weight of the composition. Compatible antimicrobial agents are those which are either soluble or suspendable in the cyanoacrylate composition, which do not cause premature polymerization of the cyanoacrylate composition, which do not prevent polymerization of the cyanoacrylate composition when applied to mammalian skin, and which are compatible with the intended use including biocompatibility with the patient's skin.

In a particularly preferred embodiment, the compatible antimicrobial agent comprises a complex of iodine molecules with a biocompatible polymer. Such complexes are well known in the art and the resulting complex typically comprises both available iodine and iodide anions. These complexes, on
5 contact with mammalian skin, provide for a source of antimicrobial iodine. In any event, such complexes are employed only as starting materials herein and, by themselves, do not form a part of this invention. Suitable biocompatible polymers include, by way of example only, polyvinylpyrrolidone polymer which, when complexed with iodine, is also referred to under the common
10 name of povidone-iodine available from BASF, Mt. Olive, New Jersey, USA. When povidone-iodine is employed in the cyanoacrylate composition, it is preferably from about 5 to about 40 weight percent and more preferably from about 10 to 25 weight percent is added to the cyanoacrylate composition based on the total weight of the composition.

15 Cyanoacrylate compositions comprising, for example, povidone-iodine are described by Greff, et al., U.S. Patent Application Serial No. 08/781,409 filed as Attorney Docket No. 026446-066 and entitled "Cyanoacrylate Compositions Comprising an Antimicrobial Agent" which application is incorporated herein by reference in its entirety.

20 Other suitable antimicrobial agents include complexes of iodine molecules with copolymers of vinylpyrrolidone and vinyl acetate, copolymers of vinylpyrrolidone and vinyl acetate cross-linked with polyisocyanates, copolymers of vinylpyrrolidone and vinyl functionalities, polymers of pyrrolidone and the like. Preferably, however, the iodine containing polymer is
25 Povidone Iodine which is commercially available from a number of sources.

The use of a compatible antimicrobial agent in the composition permits the agent to be released from the polymeric drape thereby reducing microbial growth under the drape during surgery. Additionally, since the drape is

maintained over the surgical incision site for 2-4 days after surgery, the release of antimicrobial agent further provides post-surgical anti-infection benefits.

Utility

The methods described herein are useful in forming a polymeric surgical
5 incise drape over the surgical incision site of a mammalian patient. The
polymeric drape finds particular utility in inhibiting microbial contamination of
the incision during surgeries conducted on such patients. Such mammalian
patients preferably include humans as well as domestic animals such as horses,
cows, dogs, sheep, cats, etc. The maintenance of the polymeric film over the
10 surgical incision after completion of the surgery is expected to reduce the
incidence of infection by inhibiting microbial contamination of the incision.

The following examples illustrate certain embodiments of the invention
but is not meant to limit the scope of the claims in any way.

EXAMPLE 1

15 This example illustrates how a surgical incise drape formed in the
manner of this invention could be used during surgery. In this example, an
abdominal surgical incision is to be made through a surgical incise drape of an
adult human male and subsequent bladder surgery conducted through the
incision site.

20 Specifically, an adult human male (age 58) diagnosed with bladder
cancer is scheduled for surgery. The patient, after thorough cleaning, is placed
and secured on an operating table and anesthetized. Shaving of the surgical
incision area can be performed if such is deemed necessary by the attending
surgeon. The patient then undergoes a five minute abdominal scrub using
25 cleansing pads and an iodine based cleansing solution such as ethanolic
povidone-iodine. After the surgical scrub, the abdomen is thoroughly rinsed

with sterile distilled water. An antimicrobial solution of iodine is then applied to the same area and allowed to dry.

At this time, an antimicrobial cyanoacrylate composition comprising 73% by weight butyl cyanoacrylate, 17% by weight dioctylphthalate, 10% povidone iodine and 200 parts per million sulfur dioxide (each based on the total weight of the composition) is applied to an area of approximately 20 centimeters by 30 centimeters with the proposed incision site to be located in the center of this area. The composition is allowed to thoroughly cure (~ 60 seconds) whereupon a coherent, durable and flexible surgical incise drape is formed over the applied area. This area is then draped with standard sterile surgical drapes made of a waterproof paper material to create a surgical field. The surgical field defines an area of approximately 10 centimeters by 20 centimeters at approximately the center of the surgical incise drape. An incision is then made through the surgical incise drape in this surgical field by a surgical knife and the bladder is removed uneventfully. Afterwards, the peritoneum, fascia and subcutaneous layers are closed with standard absorbable surgical sutures. The skin is then closed with a standard running skin suture or staples.

At this time, the sterile surgical drapes made of a waterproof paper material are removed from the patient leaving only the surgical incise drape which is strongly adherent to the skin. A surgical dressing is applied over the incision site and the patient is awakened from the anesthetic agent. The surgical dressing is checked every 4 hours for signs of seepage and changed daily until patient is discharged (typically 2-3 days after surgery).

The surgical incise drape formed by the film of cyanoacrylate polymer sloughs off naturally over 1-4 days after surgery as the patient's outer layer of skin naturally sloughs off without any complications. The povidone-iodine in

the film is antimicrobial thereby providing an antimicrobial effect during this period.

EXAMPLE 2

This example illustrates how a surgical incise drape formed in the manner of this invention could be used during arthroscopic surgery correcting a partial medial collateral ligament tear to a patient's knee. Because of the conformation of the knee, a higher viscosity cyanoacrylate composition is desirable in order to prevent "running" of the composition prior to formation of the polymeric drape. In this example, three separate surgical incisions are made creating portals through which cannulas are placed through a polymeric surgical incise drape formed in the manner of this invention over the knee and subsequent repair of the torn ligaments is conducted through these cannulas.

Specifically, an adult female (age 36) diagnosed with a torn medial collateral ligament of the right knee is scheduled for outpatient surgery to arthroscopically repair the torn ligament. The patient, after thorough cleansing, is placed and secured on an operating table, and is anesthetized. The patient then undergoes a five minute scrub using cleansing pads and an iodine based cleansing solution such as ethanolic povidone-iodine. After the surgical scrub, the knee is thoroughly rinsed with sterile distilled water. An antimicrobial solution of iodine is then applied to the same area and allowed to dry.

At this time, a viscous antimicrobial cyanoacrylate composition comprising 68% by weight butyl cyanoacrylate, 5 weight percent polymethyl methacrylate, 17% by weight dioctylphthalate, 10% povidone iodine and 200 parts per million sulfur dioxide (each based on the total weight of the composition) is applied to the entire knee area extending approximately 5 centimeters above and below the knee joint with the proposed trocar incision sites to be located within the boundaries of this area. The composition is allowed to thoroughly cure (~ 60 seconds) whereupon a coherent, durable and

flexible surgical incise drape is formed over the applied area. This area is then draped with standard sterile surgical drapes made of a waterproof paper material to create a surgical field within the surgical incise drape. Three separate incisions are made into the knee joint through the surgical incise drape in this surgical field and three separate cannulas are placed in a position such that the medial collateral ligament tear is repaired uneventfully. Afterwards, the skin is closed with a separate cyanoacrylate composition comprising *n*-butyl cyanoacrylate and 100 ppm sulfur dioxide that bonds the skin together. The cyanoacrylate polymeric film naturally sloughs off within 1-4 days after formation. The povidone-iodine in the film renders the film antimicrobial thereby providing an antimicrobial effect during this period.

EXAMPLE 3

The following example was conducted to ascertain the antimicrobial effect of a cyanoacrylate polymer film comprising PVP-iodine.

15 A. Preparation of the Inoculum

Specifically, the surfaces of two TSA plates, 100 x 15 mm, were inoculated with stock cultures (maintained on TSA slants) with the following microorganisms using a sterile inoculating loop: *Staphylococcus aureus* (ATCC No. 6538) and *Staphylococcus epidermidis* (ATCC No. 12228). The plates were incubated at 30° to 35°C for 24 hours. The surfaces of two SAB-DEX agar plates were streaked with *Candida albicans* and incubated at 20-25°C for 48 hours.

The cultures were harvested with sterile saline. Each culture suspension was collected in a sterile container and sufficient sterile saline was added to reduce the microbial count to obtain a working suspension of approximately 1 x 10⁸ CFU's per mL.

The specific microorganisms recited above were selected for inclusion herein because they are common human skin pathogens (bacteria and fungus).

B. Inoculation of Plates

Each of the three test microorganisms was used to inoculate individual
5 TSA plates by streaking them with sterile cotton tip applicators saturated with the appropriate suspension. The plates were allowed to dry.

C. Inhibition Study

Films of polymerized *n*-butyl cyanoacrylate comprising 0%, 10%, 15%,
20% or 30% iodine polyvinylpyrrolidone complex were formed on filter disks
10 (25 mm in diameter) by addition of the corresponding prepolymerized cyanoacrylate composition to the disks and subsequent polymerization *in situ*. The films were then cut into approximately 11 to 13 mm pieces. The pieces were placed in the center of the appropriate inoculated TSA plates. An
15 untreated filter disk was cut into half, and one-half was placed in the center of the appropriate inoculated TSA plate and the other one-half was placed in the center of non-inoculated TSA plates, to serve as a negative control. Two inoculated plates of each microorganism were also used as positive controls without the test article. These plates were then incubated for 3 days at 30° to
20 35°C. After incubation, the plates were removed and examined for any signs of microbial growth inhibition. The results of this analysis are set forth in Tables I-III below. The sample sizes reported are the portion of the sample actually in contact with the agar. The sizes of the zone of inhibition include the diameters of the entire zone including the test article size.

TABLE I

Results for *Staphylococcus aureus*

5	SAMPLE: <i>n</i> -butyl cyanoacrylate comprising	SAMPLE SIZE ¹ (in mm)	ZONE OF INHIBITION ¹ (in mm)
	0% PVP-I ₂	12	12
	10% PVP-I ₂	12	15
	15% PVP-I ₂	12.5	14
	20% PVP-I ₂	11.5	15.5
10	30% PVP-I ₂	12.5	20
	Untreated Filter Disk	13 ²	13 ²
	Negative Control	13 ²	13 ²
	Positive Control	n/a	0

TABLE II

15 Results for *Staphylococcus epidermis*

20	SAMPLE: <i>n</i> -butyl cyanoacrylate comprising	SAMPLE SIZE ¹ (in mm)	ZONE OF INHIBITION ¹ (in mm)
	0% PVP-I ₂	12	12
	10% PVP-I ₂	12.5	15
	15% PVP-I ₂	12	15.5
	20% PVP-I ₂	12.5	20.5
	30% PVP-I ₂	13	27.5
	Untreated Filter Disk	13 ²	13 ²
25	Negative Control	13 ²	13 ²
	Positive Control	n/a	0

TABLE III

Results for *Candida albicans*

5	SAMPLE: <i>n</i> -butyl cyanoacrylate comprising	SAMPLE SIZE ¹ (in mm)	ZONE OF INHIBITION ¹ (in mm)
	0% PVP-I ₂	12	12
	10% PVP-I ₂	12.5	18.5
	15% PVP-I ₂	12.5	23
	20% PVP-I ₂	12.5	20.5
10	30% PVP-I ₂	13	29.5
	Untreated Filter Disk	13 ²	13 ²
	Negative Control	13 ²	13 ²
	Positive Control	n/a	0

¹ average of two runs

15 ² single run only

20 The above data demonstrates that the compositions of this invention produce a polymeric cyanoacrylate film which have broad spectrum of antimicrobial activity. Based on these results, it is expected that these compositions would be antimicrobial when formed *in situ* on mammalian skin surfaces.

From the foregoing description, various modifications and changes in the composition and method will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.



WHAT IS CLAIMED IS:

1. A method for forming an adherent, surface conforming drape at a surgical incision site of a patient which method comprises:
 - (a) defining a surgical incision site on the patient;
 - (b) applying a sufficient amount of a composition comprising a polymerizable cyanoacrylate ester monomer or oligomer onto the skin surface at the surgical incision site defined in (a) above so as to cover this site with the cyanoacrylate composition;
 - (c) polymerizing the cyanoacrylate ester so as to form a flexible, waterproof, adhesive polymer layer which adheres to the area(s) where the composition was applied and which layer has a thickness of from about 2 to about 500 microns; and
 - (d) creating an incision through the polymer layer formed in (c) above.
2. The method according to Claim 1 wherein the polymerizable cyanoacrylate ester, in monomeric form, is represented by formula I:

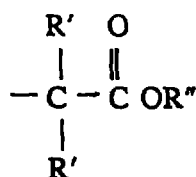


where R is selected from the group consisting of:

- alkyl of 1 to 10 carbon atoms,
- alkenyl of 2 to 10 carbon atoms,
- cycloalkyl groups of from 5 to 8 carbon atoms,
- phenyl,
- 2-ethoxyethyl,
- 3-methoxybutyl,
- and a substituent of the formula:

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wherein each R' is independently selected from the group consisting of:

hydrogen and methyl, and

R'' is selected from the group consisting of:

alkyl of from 1 to 6 carbon atoms,

alkenyl of from 2 to 6 carbon atoms,

alkynyl of from 2 to 6 carbon atoms,

cycloalkyl of from 3 to 8 carbon atoms,

aralkyl selected from the group consisting of benzyl,

methylbenzyl and phenylethyl,

phenyl, and

phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

3. The method according to Claim 2 wherein R is alkyl of from 2 to 10 carbon atoms.

4. The method according to Claim 3 wherein R is alkyl of from 2 to 8 carbon atoms.

5. The method according to Claim 4 wherein R is selected from the group consisting of butyl, pentyl or octyl.

6. The method according to Claim 5 wherein R is *n*-butyl.

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7. The method according to Claim 1 wherein said cyanoacrylate adhesive composition further comprises an antimicrobially effective amount of a compatible antimicrobial agent.

8. The method according to Claim 7 wherein the compatible antimicrobial agent is polyvinylpyrrolidone iodine.

9. The method according to Claim 1 wherein said cyanoacrylate adhesive composition further comprises a biocompatible plasticizer.

10. The method according to Claim 9 wherein said biocompatible plasticizer is dioctyl phthalate.

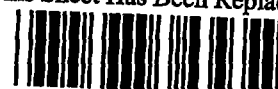
11. The method according to Claim 1 wherein said cyanoacrylate adhesive composition further comprises a polymerization inhibitor.

12. The method according to Claim 11 wherein said polymerization inhibitor is SO_2 .

13. The method according to Claim 1 which further comprises closing the dermal layer of the surgical incision with a polymerizable cyanoacrylate ester composition comprising cyanoacrylate and an polymerization inhibitor.

14. A method for forming an adherent, surface conforming surgical incise drape at a surgical incision site of a patient which method comprises:

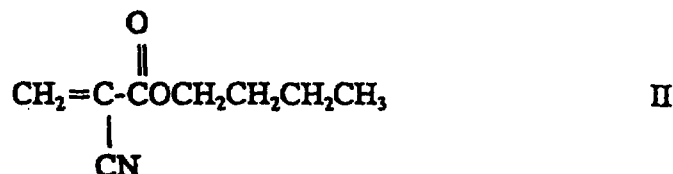
- (a) defining a surgical incision site on the patient;
- (b) applying a sufficient amount of a polymerizable cyanoacrylate ester composition onto the skin surface at the surgical incision site defined in (a) above so as to cover this site with the composition wherein the polymerizable cyanoacrylate ester composition comprises:





-30-

(i) polymerizable *n*-butyl cyanoacrylate which, in monomeric form, is represented by formula II:



(ii) from 18 to 25 weight percent of dioctylphthalate based on the total weight of the composition absent polyvinylpyrrolidone iodine;

(iii) from about 50 to 500 ppm sulfur dioxide based on the total weight of the composition absent polyvinylpyrrolidone iodine; and

(iv) from 5 to 40 weight percent of polyvinylpyrrolidone iodine based on the total weight of the composition;

(c) polymerizing the cyanoacrylate composition thereby forming a flexible, waterproof, adhesive polymer layer which adheres to the area(s) where the composition was applied and which layer has a thickness of from about 2 to about 500 microns; and

(d) creating an incision through the polymer layer formed in (c) above.

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