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(54) Title: ABSORBABLE ADHESIVE COMPOSITIONS

(57) Abstract: A method of treating living tissue includes applying to living tissue a biocompatible adhesive composition, where the adhesive composition contains at least one alkyl ester cyanoacrylate monomer and a polymerization initiator or accelerator, wherein the polymerization initiator or accelerator is a quaternary amine, or where the adhesive composition contains a mixture of two monomer species having different absorption rates.

ABSORBABLE ADHESIVE COMPOSITIONS

BACKGROUND OF THE INVENTION1. Field of the Invention

The invention relates to monomer and polymer adhesive and sealant compositions, and to their production and use for industrial and medical applications.

2. State of the Art

Monomer and polymer adhesives are used in both industrial (including household) and medical applications. Included among these adhesives are the 1,1-disubstituted ethylene monomers and polymers, such as the α -cyanoacrylates. Since the discovery of the adhesive properties of such monomers and polymers, they have found wide use due to the speed with which they cure, the strength of the resulting bond formed, and their relative ease of use. These characteristics have made α -cyanoacrylate adhesives the primary choice for numerous applications such as bonding plastics, rubbers, glass, metals, wood, and, more recently, biological tissues.

Medical applications of 1,1-disubstituted ethylene adhesive compositions include use as an alternate or an adjunct to surgical sutures and staples in wound closure as well as for covering and protecting surface wounds such as lacerations, abrasions, burns, stomatitis, sores, and other surface wounds. When an adhesive of this type is applied, it is usually applied in its monomeric form, and the resultant polymerization gives rise to the desired adhesive bond.

For example, polymerizable 1,1-disubstituted ethylene monomers, and adhesive compositions comprising such monomers, are disclosed in U.S. Patent No. 5,328,687 to Leung et al. Suitable methods for applying such compositions to substrates, and particularly in medical applications, are described in, for example, U.S. Patents Nos. 5,928,611; 5,582,834; 5,575,997; and 5,624,669, all to Leung et al.

Some monomeric α -cyanoacrylates are extremely reactive, polymerizing rapidly in the presence of even minute amounts of an initiator, including moisture present in the air or on moist surfaces such as animal tissue. Monomers of α -cyanoacrylates are anionically polymerizable or free radical polymerizable, or polymerizable by zwitterions or ion pairs to form polymers. Once polymerization has been initiated, the cure rate can be very rapid to very slow, depending on the choice of monomer.

However, not all cyanoacrylates polymerize at the same rate; and therefore, various initiators have been added to cyanoacrylates to induce polymerization. For example, each of U.S. Patents Nos. 5,928,611 to Leung; 5,902,443 to Kanakubo et al.; 4,460,759 to Robins; 4,378,213 to Severy; 5,066,743 and 4,979,993 to Okamoto et al.; 5,262,200 to Puder et al.; 4,012,402 and 3,903,055 to Buck; and 3,940,362 to Overhults discloses cyanoacrylate monomers polymerized by the addition of various initiators. The compositions are however directed to catalyzing reactions which only require minor stimulation or initiation to occur. U.S. Patent No. 5,079,098 to Liu also addresses the addition of initiators to cyanoacrylates, but only for the purpose of promoting increased bonding.

U.S. Patent No. 5,928,611 to Leung broadly discloses 1,1-disubstituted ethylene monomers having a large number of possible substituent groups. The disclosure focuses on alpha cyanoacrylates, with alternative representation of ester cyanoacrylates having an organic radical substituent. However, the disclosure does not specify particular properties, such as absorbability, possessed by particular cyanoacrylates. The disclosure does not indicate which initiators work well with which cyanoacrylates. Not all cyanoacrylates work well with all initiators. The disclosure also does not disclose absorption rates, or the effect of the selection of initiators on the properties possessed by cyanoacrylates or polymerization products thereof.

U.S. Patent No. 3,995,641 to Kronenthal et al. discloses absorbable carbalkoxyalkyl 2-cyanoacrylates. The disclosure does not discuss the use of initiators, but rather indicates that blood and other body fluids polymerize the monomers. The disclosure also does not address the effect of the selection of initiators on the properties possessed by cyanoacrylates or polymerization products thereof.

Absorbable adhesives have additional benefits over non-absorbable adhesives under some circumstances, particularly for some medical applications. However, some absorbable cyanoacrylate adhesive compositions have particularly slow reaction kinetics which reduce their practical value as surgical adhesives. Therefore, there is still a need for an adhesive composition that combines absorbability and a rapid cure rate sufficient for medical applications.

In addition, of the various monomer compositions that can be used for medical and surgical purposes, degradation of the resultant formed polymer film is often a concern. Previously, it has been difficult to adjust the degradation rates and other chemical properties of the polymer film. Therefore, there is still a need for an adhesive

composition that allows for the tailoring of the degradation rate and other properties, to fit a particular desired use.

Some effort has been made in the field to produce absorbable cyanoacrylate polymer materials. For example, U.S. Patent No. 6,224,622 discloses bioabsorbable cyanoacrylate-based tissue adhesives containing bioabsorbable copolymers. The copolymers are preferably derived from ϵ -caprolactone, lactide and glycolide monomers or from butyl 2-cyanoacrylate, glycolide, lactide, ϵ -caprolactone monomers. The adhesives are described to have increased biodegradability, increased viscosity and increased flexibility. The adhesives are useful for wound and incision closure, and for medical devices, including implants. The adhesive can include a cyanoacrylate monomer or a blend of cyanoacrylate monomers, where the cyanoacrylate monomer or monomers are selected from the group consisting of alkyl 2-cyanoacrylate, alkenyl 2-cyanoacrylate, alkoxyalkyl 2-cyanoacrylate, and carbalkoxyalkyl 2-cyanoacrylate, and wherein the alkyl group of said cyanoacrylate monomers has 1 to 16 carbon atoms.

WO 00/72761 also discloses blends of absorbable materials including glycolide, lactide, caprolactone, dioxanone, trimethylene carbonate, alkylene glycols, and esteramides with cyanoacrylate. The blend of materials is described as being absorbable and providing flexibility and adhesive properties, while maintaining acceptable viscosity and curing time.

SUMMARY OF THE INVENTION

The present invention in embodiments thereof is based on a subclass of cyanoacrylates, alkyl ester cyanoacrylates, that possess exceptional adhesive characteristics and additionally are minimally toxic to non-toxic as well as absorbable by living organisms. Benefits of biocompatible adhesives of the invention include ease and rapidity of application, which may be accompanied by inhibition of microbial growth, and lower cost than sutures or staples. The present invention provides a method of treating living tissue, comprising applying to living tissue a biocompatible adhesive composition comprising at least one alkyl ester cyanoacrylate monomer and a polymerization initiator or accelerator, wherein the polymerization initiator or accelerator is a quaternary amine. The combination of an alkyl ester cyanoacrylate and a quaternary amine provides desirable reaction kinetics coupled with absorbability.

In another embodiment, the present invention provides a biocompatible adhesive composition, comprising a mixture of at least two different monomer species, where one monomer species produces a polymer that is more absorbable than a polymer produced by the other monomer species when used alone. The composition
5 can be used in a method of treating living tissue, comprising applying to living tissue the biocompatible adhesive composition, and allowing the composition to polymerize. The combination of a faster absorbing monomer species and non-absorbable (or less absorbable or slower absorbing) monomer species allows for adjustment and tailoring of the degradation rate of the resultant formed polymer.

10 For the purposes of this invention, the terms "absorbable" or "absorbable adhesive" or variations thereof mean the ability of a tissue-compatible material to degrade or biodegrade at some time after implantation into products that are eliminated from the body or metabolized therein. Thus, as used herein, absorbability means that the polymerized adhesive is capable of being absorbed, either fully or partially, by tissue
15 after application of the adhesive. Likewise, the terms "non-absorbable" or "non-absorbable adhesive" or variations thereof mean completely or substantially incapable of being absorbed, either fully or partially, by tissue after application of the adhesive. Furthermore, relative terms such as "faster absorbing" and "slower absorbing" are used relative to two monomer species to indicate that a polymer produced from one monomer
20 species is absorbed faster (or slower) than a polymer formed from the other monomer species.

For the purposes of this invention, the term "substantially absorbed" means at least 90% absorbed within about three years. Likewise, the term "substantially non-absorbed" means at most 20% absorbed within about three years.

25 For the purposes of this invention, the term "biocompatible" refers to a material being suited for and meeting the requirements of a medical device, used for either long or short term implants or for non-implantable applications, such that when implanted or applied in an intended location, the material serves the intended function for the required amount of time without causing an unacceptable response. Long term implants are
30 defined as items implanted for more than 30 days.

The present invention also provides a kit, comprising a saleable package comprising a first container that contains at least one alkyl ester cyanoacrylate monomer; and a polymerization initiator or accelerator, wherein the polymerization initiator or accelerator can be, for example, a quaternary amine. In an alternative

embodiment, the kit can comprise a saleable package comprising a first container that contains a first monomer species, and a second container that contains a second monomer species having a polymer absorption rate different from a polymer absorption rate of the first monomer species. Alternatively, the first and second monomer species can be contained in the same container. The kit can also comprise, if desired, a third container containing a polymerization initiator or accelerator.

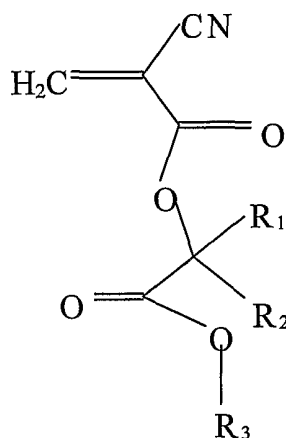
The present invention also provides a method of treating living tissue, comprising applying to living tissue a biocompatible adhesive composition. As described above, the biocompatible adhesive composition can be a composition comprising a polymerization initiator or accelerator and at least one alkyl ester cyanoacrylate such as butyl lactoyl cyanoacrylate monomer or butyl glycoloyl cyanoacrylate monomer. Alternatively, the biocompatible adhesive composition can be a composition comprising a mixture of at least two different monomer species, where one monomer species produces a polymer that is faster absorbing than a polymer produced by the other monomer species.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Absorbable cyanoacrylates have broad application for closure and hemostatic sealing of wounds and the like in various living tissue, including but not limited to internal organs and blood vessels. These absorbable formulations can be applied on the interior or exterior of various organs and tissues.

Adhesives of the present invention are biocompatible and may be applied internally or externally in or on living tissue.

In embodiments, the present invention provides at least one alkyl ester cyanoacrylate monomer having the formula



wherein R_1 and R_2 are independently H, a straight, branched or cyclic alkyl group, or are combined together in a cyclic alkyl group, and R_3 is a straight, branched or cyclic alkyl group.

The present invention also provides for the use with the monomers of quaternary amine polymerization initiators or accelerators such as quaternary amines having the formula



wherein R_4 , R_5 , R_6 and R_7 are each independently H or a substituted or unsubstituted straight, branched or cyclic alkyl group; a substituted or unsubstituted aromatic ring; a substituted or unsubstituted aralkyl group; or a substituted or unsubstituted alkyl or aromatic group which may include one or more hetero atom functionalities such as oxygen, sulfur, nitrogen, etc.; and X^- is an anion such as a halide, for example chloride, bromide, or fluoride, or hydroxyl; suitable quaternary amine initiators include but are not limited to domiphen bromide, butyrylcholine chloride, benzalkonium bromide and acetyl choline chloride.

The present invention provides a method of treating living tissue, comprising applying to living tissue a biocompatible adhesive composition comprising at least one alkyl ester cyanoacrylate monomer and a polymerization initiator or accelerator, wherein the polymerization initiator or accelerator is a quaternary amine. The present invention also provides a method of treating living tissue, comprising applying to living tissue a biocompatible adhesive composition comprising at least two different monomer species, where the different monomer species have different absorption or degradation rates, the composition optionally being applied with, or prior or subsequent to application of, a suitable polymerization initiator or accelerator. Preferably, in embodiments, one of the monomer species is an alkyl ester cyanoacrylate monomer, and the other monomer species is a cyanoacrylate monomer other than an alkyl ester cyanoacrylate or an alkyl ether cyanoacrylate, such as an alpha-cyanoacrylate monomer.

Preferred monomer compositions of the present invention, and polymers formed therefrom, are useful as tissue adhesives, sealants for preventing bleeding or for covering open wounds, and in other biomedical applications. They find uses in, for

example, preventing body fluid leakage, tissue approximation, apposing surgically incised or traumatically lacerated tissues; retarding blood flow from wounds; drug delivery; dressing burns; dressing skin or other superficial or deep tissue surface wounds (such as abrasions, chaffed or raw skin, and/or stomatitis); and aiding repair and
5 regrowth of living tissue. Monomer compositions of the present invention, and polymers formed therefrom, have broad application for sealing wounds in various living tissue and internal organs, and can be applied, for example, on the interior or exterior of various organs or tissues. Monomer compositions of the present invention, and polymers formed therefrom, are also useful in industrial and home applications, for
10 example in bonding rubbers, plastics, wood, composites, fabrics, and other natural and synthetic materials.

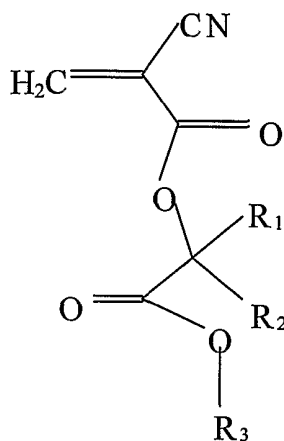
Monomers that may be used in this invention are readily polymerizable, e.g. anionically polymerizable or free radical polymerizable, or polymerizable by zwitterions or ion pairs to form polymers. Some such monomers are disclosed in, for example, U.S.
15 Patent No. 5,328,687 to Leung, et al., which is hereby incorporated in its entirety by reference herein.

Alkyl ester cyanoacrylates can be prepared according to the procedure described in U.S. Patent No. 3,995,641 to Kronenthal et al., which is hereby incorporated by
20 reference herein. In the Kronenthal et al. method, such cyanoacrylate monomers are prepared by reacting an alkyl ester of an alpha-cyanoacrylic acid with a cyclic 1,3-diene to form a Diels-Alder adduct which is then subjected to alkaline hydrolysis followed by acidification to form the corresponding alpha-cyanoacrylic acid adduct. The alpha-cyanoacrylic acid adduct is preferably esterified by an alkyl bromoacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct. Alternatively, the alpha-
25 cyanoacrylic acid adduct may be converted to the alpha-cyanoacrylyl halide adduct by reaction with thionyl chloride. The alpha-cyanoacrylyl halide adduct is then reacted with an alkyl hydroxyacetate or a methyl substituted alkyl hydroxyacetate to yield the corresponding carbalkoxymethyl alpha-cyanoacrylate adduct or carbalkoxy alkyl alpha-cyanoacrylate adduct, respectively. The cyclic 1,3-diene blocking group is finally
30 removed and the carbalkoxy methyl alpha-cyanoacrylate adduct or the carbalkoxy alkyl alpha-cyanoacrylate adduct is converted into the corresponding carbalkoxy alkyl alpha-cyanoacrylate by heating the adduct in the presence of a slight deficit of maleic anhydride.

Alkyl ester cyanoacrylates can also be prepared through the Knoevenagel reaction of an alkyl cyanoacetate, or an alkyl ester cyanoacetate, with paraformaldehyde. This leads to a cyanoacrylate oligomer. Subsequent thermal cracking of the oligomer results in the formation of a cyanoacrylate monomer. After further distillation, a
 5 cyanoacrylate monomer with high purity (greater than 95.0%, preferably greater than 99.0%, and more preferably greater than 99.8%), may be obtained.

Monomers prepared with low moisture content and essentially free of impurities (e.g., surgical grade) are preferred for biomedical use. Monomers utilized for industrial purposes need not be as pure.

10 Preferred alkyl ester cyanoacrylate monomers have the formula

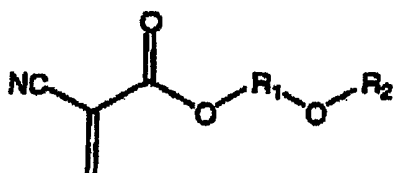


wherein R_1 and R_2 are, independently H, a straight, branched or cyclic alkyl, or are combined together in a cyclic alkyl group, and R_3 is a straight, branched or cyclic alkyl group. Preferably, R_1 is H or a C_1 , C_2 or C_3 alkyl group, such as methyl or ethyl; R_2 is H
 15 or a C_1 , C_2 or C_3 alkyl group, such as methyl or ethyl; and R_3 is a C_1 - C_{16} alkyl group, more preferably a C_1 - C_{10} alkyl group, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl, octyl, nonyl or decyl, and even more preferably a C_2 , C_3 or C_4 alkyl group.

Examples of preferred alkyl ester cyanoacrylates include, but are not limited to,
 20 butyl lactoyl cyanoacrylate (BLCA), butyl glycoloyl cyanoacrylate (BGCA), isopropyl glycoloyl cyanoacrylate (IPGCA), ethyl lactoyl cyanoacrylate (ELCA), and ethyl glycoloyl cyanoacrylate (EGCA). BLCA may be represented by formula (I) above, wherein R_1 is H, R_2 is methyl and R_3 is butyl. BGCA may be represented by formula (I) above, wherein R_1 is H, R_2 is H and R_3 is butyl. IPGCA may be represented by formula
 25 (I) above, wherein R_1 is H, R_2 is H and R_3 is isopropyl. ELCA may be represented by formula (I) above, wherein R_1 is H, R_2 is methyl and R_3 is ethyl. EGCA may be

represented by formula (I) above, wherein R₁ is H, R₂ is H and R₃ is ethyl. Other cyanoacrylates useful in the present invention are disclosed in U.S. Patent No. 3,995,641 to Kronenthal et al., the entire disclosure of which is hereby incorporated by reference.

Alternatively, or in addition, the present invention provides for the use of alkyl ether cyanoacrylate monomers. Alkyl ether cyanoacrylates have the general formula:



(II)

where R₁ is a straight, branched or cyclic alkyl, and R₂ is a straight, branched or cyclic alkyl group. Preferably, R₁ is a C₁, C₂ or C₃ alkyl group, such as methyl or ethyl; and R₂ is a C₁-C₁₆ alkyl group, more preferably a C₁-C₁₀ alkyl group, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl, octyl, nonyl or decyl, and even more preferably a C₂, C₃ or C₄ alkyl group.

Examples of preferred alkyl ether cyanoacrylates include, but are not limited to, isopropoxy ethyl cyanoacrylate (IPECA) and methoxy butyl cyanoacrylate (MBCA). IPECA may be represented by formula (II) above, wherein R₁ is ethylene and R₂ is isopropyl. MBCA may be represented by formula (II) above, wherein R₁ is n-butylene and R₂ is methyl.

Alkyl ester and alkyl ether cyanoacrylates are particularly useful for medical applications because of their absorbability by living tissue and associated fluids. According to the present invention, 100% of the polymerized and applied cyanoacrylate may be absorbed in a period of less than 2 years, such as approximately 2-24 months after application of the adhesive to living tissue. Alternatively, the absorption rate can be tailored to provide absorption rates of, for example, 3-18 months, including 3-6 months, 6-12 months, or 12-18 months. Of course, the present invention is not particularly limited to any absorption time, as the desired absorption time can vary depending on the particular uses and tissues involved. Thus, for example, longer absorption time may be desired where the adhesive composition is applied to hard tissues, such as bone, but a faster absorption time may be desired where the adhesive composition is applied to softer tissues.

The selection of monomer will affect the absorption rate of the resultant polymer, as well as the polymerization rate of the monomer. Two or more different

monomers that have varied absorption and/or polymerization rates may be used in combination to give a greater degree of control over the absorption rate of the resultant polymer, as well as the polymerization rate of the monomer. Thus, an important aspect of embodiments of the invention lies in the selection of the monomer and initiator to control within relatively narrow and predictable ranges both the polymerization and absorption rates.

According to embodiments of the present invention, the adhesive composition comprises a mixture of monomer species, where one monomer species is absorbable and the other monomer species is non-absorbable, or where both monomers are absorbable but one monomer species has a faster absorption or degradation rate than the other monomer species. Where two monomer species having different absorption rates are used, it is preferred that the absorption rates be sufficiently different that a mixture of the two monomers can yield a third absorption rate that is effectively different from the absorption rates of the two monomers individually. Thus, for example, it is preferred that the absorption rate of the faster absorbing monomer species be at least 10% faster than the absorption rate of the slower absorbing monomer species. More preferably, the absorption rate of the faster absorbing monomer species be at least 25% or 50% faster, or even 75% or 100% faster, than the absorption rate of the slower absorbing monomer species. Preferably, according to embodiments, the absorbable or faster absorbing/degrading monomer species is an alkyl ester cyanoacrylate or alkyl ether cyanoacrylate, while the non-absorbable or slower absorbing/degrading monomer species is not an alkyl ester cyanoacrylate or alkyl ether cyanoacrylate. The non-absorbable or slower absorbing/degrading monomer species can be, for example, any suitable and biocompatible monomer species, such as a 1,1-disubstituted ethylene monomer including but not limited to cyanoacrylates such as alkyl alpha-cyanoacrylates.

More particularly, the non-absorbable or slower absorbing/degrading monomer species is a polymerizable monomer that is readily polymerizable, e.g. anionically polymerizable or free radical polymerizable, or polymerizable by zwitterions or ion pairs to form a polymer. Such monomers are disclosed in, for example, U.S. Patents Nos. 5,328,687 and 5,928,611 to Leung et al., U.S. Patent Application Serial No. 09/430,177, filed on October 29, 1999, and U.S. Patent Application Serial No. 09/471,392 filed December 23, 1999, which are hereby incorporated in their entirety by reference herein. Preferred monomers include 1,1-disubstituted ethylene monomers,

such as α -cyanoacrylates including, but not limited to, alkyl α -cyanoacrylates having an alkyl chain length of from about 1 to about 20 carbon atoms or more, preferably from about 2 to about 12 or more, and more preferably from about 3 to 8 carbon atoms. Examples of such suitable monomers thus include, but are not limited to, alkyl
5 α -cyanoacrylates such as octyl (such as 2-octyl), hexyl, and butyl α -cyanoacrylates.

In embodiments, the respective monomer species can be mixed in any suitable ratio to provide the desired degradation rate of the final polymer material. Thus, for example, suitable mixing ratios can range anywhere from about 1:99 or from about 10:90 to about 90:10 or about 99:1 in terms of parts by weight faster absorbing
10 monomer to parts by weight non-absorbable or slower absorbing monomer. Preferred ratios are from about 15:85 to about 85:15 or from about 25:75 to about 75:25. For example, a desired degradation rate can be obtained by mixing faster absorbing monomer species and non-absorbable or slower absorbing monomer species in a weight ratio of about 50:50. In embodiments, a suitable composition can be obtained by mixing
15 faster absorbing monomer species and non-absorbable or slower absorbing monomer species in a weight ratio of from about 40:60 to about 60:40. These ratios are particularly beneficial for achieving a desired balance between the relatively fast degradation rates of alkyl ester cyanoacrylates and the relatively slow degradation rates of other monomer species such as alkyl alpha-cyanoacrylates. However, these ratios and
20 the present invention are in no way limited to such combinations.

For example, suitable compositions according to the present invention can be prepared by mixing suitable quantities of 2-octyl alpha-cyanoacrylate with one of butyl lactoyl cyanoacrylate (BLCA), butyl glycoloyl cyanoacrylate (BGCA), isopropyl glycoloyl cyanoacrylate (IPGCA), ethyl lactoyl cyanoacrylate (ELCA), and ethyl
25 glycoloyl cyanoacrylate (EGCA). Preferably, such mixtures range from ratios of about 75:25 to about 25:75 by weight such as from about 60:40 to about 40:60 by weight.

In addition, although the above discussion is with respect to a composition containing only two different monomer species, the present invention is not limited to such an embodiment. Rather, as desired, the monomer composition can have two or
30 more different monomer species, to provide further control over the absorption/degradation rate and other characteristics of the resultant polymer. Thus, for example, the composition can include two, three, four, five or even more different monomer species. Furthermore, where more than two monomer species are used, the

various monomer species need not all have different absorption/degradation rates, although it is preferred that the monomer species individually provide at least two different absorption/degradation rates.

Some alkyl ester cyanoacrylate monomers may react slowly due to bulky alkyl groups, apparently limiting their applicability as surgical adhesives. By themselves, alkyl ester cyanoacrylates cure in several hours, or in some cases do not fully cure at all. To overcome problems associated with slow polymerization of the monomers, a compatible agent which initiates or accelerates polymerization of the alkyl ester cyanoacrylate monomer, may be used with the monomer composition. Initiators and accelerators particularly suitable for use with alkyl ester cyanoacrylates provide a fast cure rate while retaining the absorbable properties of the adhesive. Alkyl ester cyanoacrylates stimulated to cure by a suitable initiator or accelerator may be made to cure in as short as a few seconds to a few minutes. The cure rate may be closely controlled by selection of an amount or concentration of initiator or accelerator added to the cyanoacrylate and may thus be readily controlled by one skilled in the art in light of the present disclosure. A suitable initiator provides a consistent controllable complete polymerization of the monomer so that the polymerization of the monomer can be made to occur in the time desired for the particular application. Quaternary amine initiators or accelerators are particularly desirable with alkyl ester cyanoacrylate monomers for such reasons.

The initiator or accelerator may be in the form of a solid, such as a powder or a solid film, or in the form of a liquid, such as a viscous or paste-like material. The initiator or accelerator may also include a variety of additives, such as surfactants or emulsifiers. Preferably, the initiator or accelerator is soluble in the monomer composition, and/or comprises or is accompanied by at least one surfactant which, in embodiments, helps the initiator or accelerator co-elute with the monomer composition. In embodiments, the surfactant may help disperse the initiator or accelerator in the monomer composition.

The initiator or accelerator may be applied to tissue before the monomer composition, or may be applied directly to the monomer composition once the monomer composition is applied to tissue. In embodiments, the initiator or accelerator may be combined with the monomer composition just prior to applying the composition to tissue.

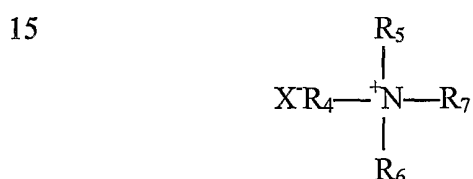
The selection of an initiator or accelerator may additionally affect the rate at which the polymerized monomer is absorbed by living tissue. Therefore, the most suitable initiators or accelerators are those that polymerize the monomer at a rate suitable for medical applications while providing a polymer that is substantially
5 absorbed in less than two years. For the purposes of this invention, the phrase "suitable for medical application(s)" means that the initiator or accelerator polymerizes the monomer in less than 5 minutes or less than 3 minutes, preferably in less than 2.5 minutes, more preferably in less than 1 minute, and often in less than 45 seconds. Of course, the desired polymerization time can vary for different compositions and/or uses.
10 Preferably, a suitable initiator or accelerator and a suitable monomer are selected to provide a polymer that is substantially absorbed by a living organism in 2-24 months, such as 3-18 months or 6-12 months after application of the adhesive to living tissue.

The present invention provides a method of treating living tissue, where a selected absorption rate of the polymer can be provided by selecting an alkyl ester
15 cyanoacrylate monomer for treatment of the tissue; selecting a suitable polymerization initiator or accelerator for the monomer on the basis of the desired absorption rate; and applying to living tissue the polymerization initiator or accelerator and said monomer to form an absorbable adhesive polymer. A suitable initiator or accelerator in a suitable quantity can be selected in light of the present disclosure, in combination with the
20 selection of monomer, to produce a polymer with a desired absorption rate. A screening process utilizing routine experimentation may be used to identify combinations of monomers and initiators or accelerators that possess the desired reaction kinetics and produce a polymer that is absorbed *in vivo* in the desired period of time. Particularly beneficial initiators or accelerators, as well as monomers, are identified by the present
25 disclosure. Therefore, for example, a butyl lactoyl cyanoacrylate monomer may be polymerized with, for example, domiphen bromide to test the polymerization rate. The quantity, or type, of initiator or accelerator or monomer may be adjusted if the desired polymerization rate is not achieved. Further, the polymer may be tested by *in vivo* application on animal (including human) tissue to determine absorption rates.

30 Depending, for example, on the necessary healing time for a wound, a corresponding absorption rate may be desired. Since healing times vary in different organisms and different tissues, the ability to control the absorption rate of the adhesive is beneficial to ensure that the adhesive polymer lasts long enough to provide time for the wound to heal, but absorbs within a reasonable time, preferably within 2 years from

application of the adhesive to living tissue. Thus, according to the present invention, the absorption rate of the adhesive material can be selected in one of several ways. First, the absorption rate can be selected by determining desired specific monomer and initiator species. Thus, for example, where an alkyl ester cyanoacrylate is used as the monomer, 5 the absorption rate can be selected by proper selection of a desired initiator or accelerator, such as a quaternary amine polymerization initiator or accelerator. In other embodiments, for example where a mixture of monomer species is used, such as where a faster absorbing alkyl ester cyanoacrylate and a non-absorbable or slower absorbing cyanoacrylate are used, the absorption rate can be selected by proper selection of the 10 desired monomer materials, and their relative mixing proportions, and optionally further by proper selection of a desired initiator or accelerator.

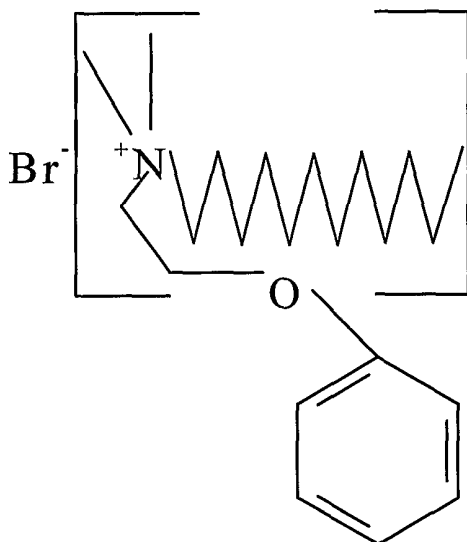
In preferred embodiments, the present invention provides for the use of quaternary amine polymerization initiators or accelerators such as quaternary amines having the formula



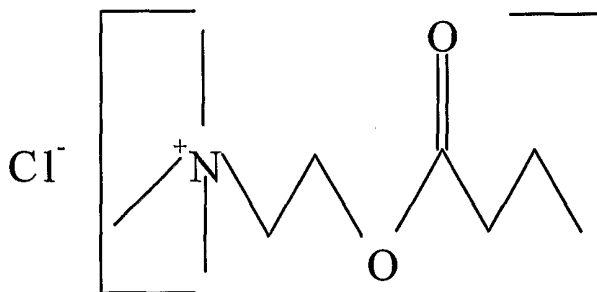
20 wherein R₄, R₅, R₆ and R₇ are each independently H or a substituted or unsubstituted straight, branched or cyclic alkyl group; a substituted or unsubstituted aromatic ring; a substituted or unsubstituted aralkyl group; or a substituted or unsubstituted alkyl or aromatic group which may include one or more hetero atom functionalities such as oxygen, sulfur, nitrogen, etc.; and X⁻ is an anion such as a halide, for example chloride, 25 bromide, or fluoride, or hydroxyl. In preferred embodiments, at least one of R₄, R₅, R₆ and R₇ includes an aromatic group and/or a hetero atom functionality such as an ether or ester linkage or corresponding linkages where the hetero atom is sulfur or nitrogen. Preferred quaternary amine initiators are selected from the group consisting of domiphen bromide, butyrylcholine chloride, benzalkonium bromide and acetyl choline chloride.

30 Benzalkonium halides, such as benzalkonium chloride, are particularly preferred in embodiments. When used, the benzalkonium halide can be benzalkonium halide in its unpurified state, which comprises a mixture of varying chain-length compounds, or it can be any suitable purified compound including those having a chain length of from about 12 to about 18 carbon atoms, including but not limited to C₁₂, C₁₃, C₁₄, C₁₅, C₁₆, 35 C₁₇, and C₁₈ compounds.

Domiphen bromide is preferred in other embodiments. Domiphen bromide may be represented by the following formula:



Butrylcholine chloride may be represented by the following formula:



5

Initiators or accelerators, such as quaternary amines mentioned above, are preferably used in the present invention, but other initiators or accelerators may also be selected by one of ordinary skill in the art without undue experimentation. Such suitable initiators or accelerators may include, but are not limited to, detergent compositions; surfactants: e.g., nonionic surfactants such as polysorbate 20 (e.g., Tween 20TM from ICI
 10 Americas), polysorbate 80 (e.g., Tween 80TM from ICI Americas) and poloxamers, cationic surfactants such as tetrabutylammonium bromide, anionic surfactants such as sodium tetradecyl sulfate, and amphoteric or zwitterionic surfactants such as

dodecyldimethyl(3-sulfopropyl)ammonium hydroxide, inner salt; amines, imines and amides, such as imidazole, tryptamine, urea, arginine and povidine; phosphines, phosphites and phosphonium salts, such as triphenylphosphine and triethyl phosphite; alcohols such as ethylene glycol, methyl gallate, ascorbic acid, tannins and tannic acid; 5 inorganic bases and salts, such as sodium bisulfite, magnesium hydroxide, calcium sulfate and sodium silicate; sulfur compounds such as thiourea and polysulfides; polymeric cyclic ethers such as monensin, nonactin, crown ethers, calixarenes and polymeric epoxides; cyclic and acyclic carbonates, such as diethyl carbonate; phase transfer catalysts such as Aliquat 336; organometallics such as cobalt naphthenate and 10 manganese acetylacetonate; and radical initiators or accelerators and radicals, such as di-t-butyl peroxide and azobisisobutyronitrile.

In embodiments, mixtures of two or more, such as three, four, or more, initiators or accelerators can be used. A combination of multiple initiators or accelerators may be beneficial, for example, to tailor the initiator of the polymerizable monomer species. 15 For example, where a blend of monomers is used, a blend of initiators may provide superior results to a single initiator. For example, the blend of initiators or accelerators can provide one initiator that preferentially initiates one monomer, and a second initiator that preferentially initiates the other monomer, or can provide initiation rates to help ensure that both monomer species are initiated at equivalent, or desired non-equivalent, 20 rates. In this manner, a blend of initiators can help minimize the amount of initiator necessary. Furthermore, a blend of initiators may enhance the polymerization reaction kinetics.

Specific compositions of the invention may have various combinations of alkyl ester cyanoacrylates and thickeners, plasticizers, colorants, preservatives, heat 25 dissipating agents, stabilizing agents and the like, which will be described in more detail below. Preferably, according to one embodiment of the present invention, a composition of this invention has from 65 to 99.9 weight % of monomer such as an alkyl ester cyanoacrylate or blend of cyanoacrylates and is promoted to polymerize by 0.005 to 10 weight % of an initiator or accelerator. More preferably, a composition of 30 this invention has from 80 to 99.9 weight % of an alkyl ester cyanoacrylate and is promoted to polymerize by 0.02 to 5 weight % of an initiator or accelerator. Even more preferably, a composition of this invention has 85 to 99.9 weight % of monomer such as an alkyl ester cyanoacrylate, such as butyl lactoyl cyanoacrylate or a blend of

cyanoacrylates, and is promoted to polymerize by 0.05 to 3 weight % of an initiator or accelerator, such as domiphen bromide.

5 Compositions of this invention may also include 0 to 25, more preferably 0 to 10, for example 0 to 5 weight % based on a total weight of the composition of at least one of the following: thickeners, plasticizers, colorants, preservatives, heat dissipating agents, stabilizing agents and the like. Of course, other compositions based on other proportions and/or components can readily be prepared according to embodiments of the present invention in light of the present disclosure.

10 Compositions of the present invention may be utilized in conjunction with other sealing means. For example, an adhesive may be applied to a wound that has been closed using surgical suture, tape, or staples. Adhesives of the present invention may also be used in conjunction with other sealing means, such as means identified in U.S. Patent No. 6,014,714, the entire disclosure of which is incorporated herein by reference.

15 Compositions of the present invention may be applied in single or multiple applications. The adhesives may be applied in a first layer, and after the first layer is allowed to fully or partially polymerize, a subsequent layer may be added. Such a process may be conducted numerous times, depending on the size of the wound and the amount of adhesive applied in each application.

20 The monomeric composition may be packaged in any type of suitable container fabricated from materials including, but not limited to, glass, plastic, metal packages, and film-formed packages. Suitable containers preferably include those into which the compositions may be dispensed and sterilized without unacceptable damage to, or degradation of, the container or the components of the monomer composition. Post-halogenated, such as fluorinated, polymeric barrier layers on at least the monomer-
25 contacting surfaces of the container provide a superior shelf-life for monomer compositions, as disclosed in U.S. Patent Application No. 09/430,280, filed October

comprises a saleable package comprising a first container that contains at least one alkyl ester cyanoacrylate monomer; and a polymerization initiator or accelerator, wherein the polymerization initiator or accelerator is a quaternary amine. The kit may comprise a second container containing the quaternary amine as described herein. Or, 5 the first container could have the initiator or accelerator in or on it as long as the initiator or accelerator is not in contact with the monomer prior to the desired use.

In other embodiments, the present invention also provides a saleable kit for delivering a combination cyanoacrylate adhesive having two different monomers each having different absorption rates, to tissue. The kit comprises a saleable package 10 comprising a first container that contains a monomer composition comprising a mixture of a non-absorbable monomer species and an absorbable monomer species, or a mixture of a monomer species with a slow absorption/degradation rate and a monomer species with a fast absorption/degradation rate. If desired or necessary, the kit can also include a polymerization initiator or accelerator, wherein the 15 polymerization initiator or accelerator is an initiator or accelerator for at least one of the monomer species and can be, for example, a quaternary amine. The kit can also include one or more other additives, including such additives as are described in detail below. When present, each of the additives can independently be either packaged separately from or in combination with the other additives or the monomer 20 composition. As desired, the different monomer species can be packaged separately or together in suitable containers. If packaged separately, the kit provides the user the option of tailoring the absorption or degradation rate by suitably selecting a mixing ratio for the monomer species. The kit may comprise a second container containing a suitable initiator or cross-linking agent, such as a quaternary amine as described herein. 25 Or, the first container could have the optional initiator or accelerator in or on it as long as the initiator or accelerator is not in contact with the monomer prior to the desired use.

The initiator or accelerator is selected so that it functions in conjunction with the co-packaged polymerizable monomer composition to initiate polymerization of at least one of, and preferably at least all of, the monomer species or to modify (e.g., accelerate) 30 the rate of polymerization for the monomers to form a polymeric adhesive. The proper combination of initiator or accelerator and polymerizable monomer can be determined by one of ordinary skill in the art without undue experimentation in light of the present disclosure.

In each of the above embodiments, the kit may also include a suitable applicator, such as a brush, swab, sponge or the like, to assist in applying the composition to living tissue. If desired, the quaternary amine or other initiator and/or other additives can be located in or on the applicator.

5 The kit is also preferably sterilized; however, the containers and components may be sterilized separately or together. Preferably, kits and the kit components (including compositions) of the present invention have a sterility level in the range of 10^3 to 10^{-6} Sterility Assurance Level (SAL) and are sterile for surgical purposes. Various designs of such kits are disclosed, for example, in U.S. Patent Application No.
10 09/385,030, filed August 30, 1999, the entire disclosure of which is herein incorporated by reference. The sterilization may be accomplished by techniques known to the skilled artisan, and is preferably accomplished by methods including, but not limited to, chemical, physical, and irradiation methods. Examples of physical methods include, but are not limited to, sterile fill, filtration, sterilization by heat (dry or moist) and retort
15 canning. Examples of irradiation methods include, but are not limited to, gamma irradiation, electron beam irradiation, and microwave irradiation. Preferred methods are dry and moist heat sterilization and electron beam irradiation. In embodiments where a composition is to be used for medical applications, the sterilized composition should show low levels of toxicity to living tissue during its useable life.

20 In embodiments of the present invention, any suitable applicator may be used to apply the adhesive composition to a substrate. For example, the applicator may include an applicator body, which is formed generally in the shape of a tube having a closed end, an open end, and a hollow interior lumen, which holds a crushable or frangible ampoule. The applicator and its related packaging may be designed as a
25 single-use applicator or as a multi-use applicator. Suitable multi-use applicators are disclosed, for example, in U.S. Patent Application No. 09/385,030, filed August 30, 1999, the entire disclosure of which is incorporated herein by reference.

 In embodiments of the invention, the applicator may comprise elements other than an applicator body and an ampoule. For example, an applicator tip may be
30 provided on the open end of the applicator. The applicator tip material may be porous, absorbent, or adsorbent in nature to enhance and facilitate application of the composition within the ampoule. Suitable designs for applicators and applicator tips that may be used according to the present invention are disclosed in, for example, U.S. Patent No. 5,928,611 to Leung and U.S. Patent Applications Nos. 09/069,979, filed

April 30, 1998, 09/069,875, filed April 30, 1998, 09/479,059, filed January 7, 2000, and 09/479,060, filed January 7, 2000, the entire disclosures of which are incorporated herein by reference.

In embodiments of the present invention, an applicator may contain the initiator
5 or accelerator on a surface portion of the applicator or applicator tip, or on the entire surface of the applicator tip, including the interior and the exterior of the tip. When the initiator or accelerator is contained in or on an applicator tip, the initiator or accelerator may be applied to the surface of the applicator tip or may be impregnated or incorporated into the matrix or internal portions of the applicator tip. Additionally, the
10 initiator or accelerator may be incorporated into the applicator tip, for example, during the fabrication of the tip.

In other embodiments, the initiator or accelerator may be coated on an interior surface of the applicator body and/or on an exterior surface of an ampoule or other container disposed within the applicator body, may be placed in the applicator body in
15 the form of a second frangible vial or ampoule and/or may be otherwise contained within the applicator body, so long as a non-contacting relationship between the polymerizable monomer composition and the initiator or accelerator is maintained until use of the adhesive.

Various designs of applicators and methods for incorporating the initiator or
20 accelerator into the applicator are disclosed in U.S. Patent No. 5,928,611 to Leung and U.S. Patent Applications Nos. 09/069,979, filed April 30, 1998, 09/069,875, filed April 30, 1998, 09/145,200, filed September 1, 1998, and 09/479,059 and 09/479,060, both filed January 7, 2000, the entire disclosures of which are incorporated herein by reference.

In embodiments, the polymerizable compositions according to the present
25 invention can further comprise one or more suitable or desirable additives. When incorporated into the composition or used with the composition, it is preferred although not required that the additive or additives also be absorbable. Preferably, the additives have an absorption rate that is about comparable to the absorption rate of the
30 resultant polymer material, although slower or faster absorption rates can be used, as desired.

The polymerizable compositions useful in the present invention may also further contain one or more preservatives, for prolonging the storage life of the composition. Suitable preservatives, and methods for selecting them and incorporating

them into adhesive compositions, are disclosed in U.S. Patent Application No. 09/430,180, the entire disclosure of which is incorporated herein by reference.

Monomer compositions of the invention may also include a heat dissipating agent. Heat dissipating agents include liquids or solids that may be soluble or
5 insoluble in the monomer. The liquids may be volatile and may evaporate during polymerization, thereby releasing heat from the composition. Suitable heat dissipating agents may be found in U.S. Patent No. 6,010,714 to Leung et al., the entire disclosure of which is incorporated herein.

The composition or solution of the present invention may optionally include at
10 least one plasticizing agent that assists in imparting flexibility to the polymer formed from the monomer. The plasticizing agent preferably contains little or no moisture and should not significantly affect the stability or polymerization of the monomer. Examples of suitable plasticizers include but are not limited to tributyl citrate, acetyl tri-
n-butyl citrate (ATBC), polydimethylsiloxane, hexadimethylsilazane and others as listed
15 in U.S. Patent Application Serial No. 09/471,392 filed December 23, 1999, the disclosure of which is incorporated in its entirety by reference herein.

The composition or solution of the present invention may optionally also include thickeners. Suitable thickeners include those listed in U.S. Patent Application
Serial No. 09/472,392 filed December 23, 1999, the disclosure of which is incorporated
20 by reference herein in its entirety.

The composition or solution of the present invention may also optionally include at least one thixotropic agent. Examples of suitable thixotropic agents and thickeners are disclosed in, for example, U.S. Patent No. 4,720,513, and U.S. Patent Application Serial
No. 09/374,207 filed August 12, 1999, the disclosures of which are hereby
25 incorporated in their entireties by reference herein.

The composition or solution of the present invention may optionally also include one or more stabilizers, preferably both at least one anionic vapor phase stabilizer and at least one anionic liquid phase stabilizer. These stabilizing agents may inhibit premature polymerization. Suitable stabilizers may include those listed in U.S.
30 Patent Application Serial No. 09/471,392 filed on December 23, 1999, the disclosure of which is incorporated by reference herein in its entirety. Other stabilizing agents, such as free radical stabilizing agents, can also be included as desired.

Compositions or solutions of the present invention may also include at least one biocompatible agent effective to reduce active formaldehyde concentration levels

produced during *in vivo* biodegradation of the polymer (also referred to herein as "formaldehyde concentration reducing agents"). Preferably, this component is a formaldehyde scavenger compound. Examples of formaldehyde scavenger compounds useful in this invention include sulfites; bisulfites; mixtures of sulfites and bisulfites, etc.

5 Additional examples of formaldehyde scavenger compounds useful in this invention and methods for their implementation can be found in U.S. Patents Nos. 5,328,687, 5,514,371, 5,514,372, 5,575,997, 5,582,834 and 5,624,669, all to Leung et al., which are hereby incorporated herein by reference in their entireties.

The compositions of the present invention may also include pH modifiers to control the rate of degradation of the resulting polymer, as disclosed in U.S. Patent

10 Application No. 08/714,288, filed September 18, 1996, the entire disclosure of which is hereby incorporated by reference herein in its entirety.

To improve the cohesive strength of the compositions or solutions of this invention, difunctional monomeric cross-linking agents may be added to monomer

15 compositions of this invention. Such crosslinking agents are known. U.S. Patent No. 3,940,362 to Overhults, which is hereby incorporated herein in its entirety by reference, discloses exemplary cross-linking agents.

The compositions or solutions of this invention may further contain fibrous reinforcement and colorants such as dyes, pigments, and pigment dyes. Examples of

20 suitable fibrous reinforcement include PGA microfibrils, collagen microfibrils, and others as described in U.S. Patent Application Serial No. 09/471,392 filed on December 23, 1999, the disclosure of which is incorporated by reference herein in its entirety.

Other modifications to compositions of the present invention are exemplified by U.S. Patents Nos. 5,624,669; 5,582,834; 5,575,997; 5,514,371; 5,514,372; and

25 5,259,835; and U.S. Patent Application No. 08/714,288, the disclosures of all of which are hereby incorporated in their entirety by reference.

Although not limited to any particular formulation, a particular composition suitable for use in the present invention comprises a blend of butyl lactoyl cyanoacrylate (BLCA) and octyl cyanoacrylate (OCA). Suitable blends preferably range from about

30 25:75 to about 40:60 (weight ratio BLCA:OCA). The composition also preferably includes a suitable stabilizer system, such as one comprising specified amounts of sulfuric acid (such as about 25 to about 100 ppm of sulfuric acid, preferably about 20 ppm), sulfur dioxide (such as about 1 to about 50 ppm, preferably about 10 to about 12 ppm), hydroquinone (such as about 100 to about 2000 ppm, preferably about 960 to

about 1200 ppm), p-methoxyphenol (such as about 10 to about 200 ppm, preferably about 96 to about 120 ppm), and butylated hydroxyanisole (such as about 100 to about 10,000 ppm, preferably about 500 to about 800 ppm). The composition can include additional materials, such as a colorant such as D & C violet #2 (such as 20 to about 5 2000 ppm, preferably about 35 to 100 ppm) and the like. Suitable initiators can include, for example, domiphen bromide or benzalkonium chloride, in amounts ranging from about 100 to about 15,000 ppm.

EXAMPLES

The present invention will be further understood by reference to the following 10 non-limiting examples.

Example 1:

70 μ l of butyl lactoyl cyanoacrylate are mixed with 2.5 μ moles of domiphen bromide as the monomer is passed through a porous applicator tip. The resulting mixture sets in approximately 40 seconds. In these Examples, "setting time" is 15 measured as the time when the material reaches its maximum exotherm.

Example 2:

36 μ l of butyl lactoyl cyanoacrylate are mixed with 0.625 μ moles of butyrylcholine chloride as the monomer is passed through a porous applicator tip. The resulting mixture sets in approximately 60 seconds.

20 Example 3:

A polymer is formed from the initiation of butyl lactoyl cyanoacrylate monomer with domiphen bromide in situ on a polypropylene mesh and placed in a phosphate buffer at 39°C. Samples are rinsed, dried and weighed, and the degradation results of the polymer are shown in the table below, wherein Mn is the number 25 average molecular weight of the sample.

Time (days)	0	28	56	84	112	140
Mass loss (%)	0	8	18	31	45	60
Mn x 1,000	84	12	6.2	3.1	1.9	1.3

A polymer is formed from the initiation of butyl lactoyl cyanoacrylate monomer with azobisisobutyronitrile in situ on a polypropylene mesh and placed in a 30 phosphate buffer at 39°C. Samples are rinsed, dried and weighed, and the degradation

results of the polymer are shown in the table below, wherein Mn is the number average molecular weight of the sample.

Time (days)	0	28	56	98	112	140
Mass loss (%)	0	3	6	9	10	12
Mn x 1,000	28	23	23	21	—	20

Example 4:

- 5 An absorbable adhesive polymer is formulated by the combination of:
- | | |
|-------------------------------------|--------------------------|
| Butyl lactoyl cyanoacrylate monomer | 98.2600% (by weight); |
| Domiphen bromide | 1.7300% (by weight); |
| H ₂ SO ₄ | 0.0025% (by weight); and |
| Butylated hydroxyanisole | 0.0075% (by weight). |

10 Example 5:

- Various monomeric adhesive compositions are formulated using varying amounts of butyl lactoyl cyanoacrylate (BLCA) and 2-octyl alpha-cyanoacrylate (2OCA). The compositions as formulated also include about 20 ppm sulfuric acid, 0 to 20 ppm sulfur dioxide, 0 to 2000 ppm hydroquinone, 0 to 180 ppm p-methoxyphenol, and 0 to 2000 ppm butylated hydroxyanisole. The mixing ratios of the monomers are set forth in the following Table. The compositions are initiated with domiphen bromide and applied to a surface, and the setting time of the compositions are measured. The setting time results are also set forth in the following Table.

Sample	wt% BLCA	wt% 2OCA	Setting Time (s)
A	0	100	92
B	25	75	60
C	50	50	49
D	75	25	45
E	100	0	42

20

Example 6:

- The same compositions as used in Example 5 are tested *in vitro* for their absorption/degradation rates. As in Example 5, the compositions are formulated using varying amounts of butyl lactoyl cyanoacrylate (BLCA) and 2-octyl alpha-cyanoacrylate (2OCA). The mixing ratios of the monomers are set forth in the following Table.

25

Samples for *in vitro* degradation testing are prepared by initiating a quantity of the respective monomer composition and expressing it onto a pre-weighed polypropylene mesh having a thickness of approximately 0.19 mm and cut to dimensions of approximately 10 mm x 35 mm. The mesh is sandwiched between two surfaces of ultra high molecular weight polyethylene, which are separated by 0.203 mm thick stainless steel shims. After curing, the samples are removed from the mold and excess polymerized material is trimmed away. A portion of the trimmed away material is used for determining the starting molecular weight of each sample.

The samples are placed into sterilized extraction thimbles to minimize contact with the polymer material. The samples are then placed in sterile glass vials and filled with 21 ml of Dulbecco's phosphate buffered saline (PBS) with antibiotic/antimycotin added. The vials are placed in a water bath at 39°C. The PBS solution is exchanged weekly.

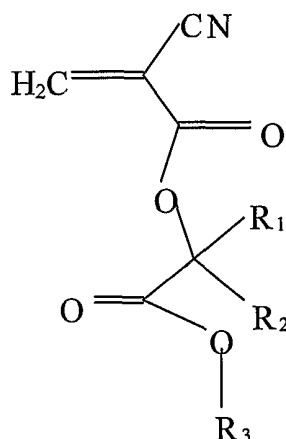
At intervals of 7 and 13 days post-polymerization, the formed polymer is tested to determine the absorption/degradation of the polymer. The absorption/degradation is measured by determining the change in mass% of the formed polymer. The testing is conducted by removing the sample from the buffer solution and rinsing them three times with sterile water. The samples are dried for 24 hours in vacuo before re-weighing. The measurements are also set forth in the following Table.

Sample	wt% BLCA	wt% 2OCA	Mass% Change	
			7 days	13 days
A	0	100	-0.4	-0.9
B	25	75	-1.4	-2.1
C	50	50	-2.5	-3.4
D	75	25	-3.6	-5.4
E	100	0	-4.8	-7.8

While the invention has been described with reference to preferred embodiments, the invention is not limited to the specific examples given, and other embodiments and modifications can be made by those skilled in the art without departing from the spirit and scope of the invention.

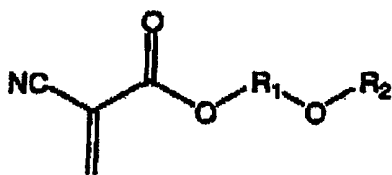
WHAT IS CLAIMED IS:

1. A biocompatible adhesive composition, comprising:
 a first monomer species; and
 a second monomer species different from said first monomer species,
 wherein at least said first monomer species is absorbable, and
 an absorption rate of said first monomer species is different from an
 absorption rate of said second monomer species.
2. The biocompatible adhesive composition of claim 1, wherein said first
 monomer species comprises an alkyl ester cyanoacrylate.
3. The biocompatible adhesive composition of claim 2, wherein said alkyl
 ester cyanoacrylate has the formula



- wherein R_1 and R_2 are independently H, a straight, branched or cyclic alkyl
 group, or are combined together in a cyclic alkyl group, and R_3 is a straight, branched or
 cyclic alkyl group.

4. The biocompatible adhesive composition of claim 2, wherein said alkyl
 ester cyanoacrylate is selected from the group consisting of butyl lactoyl cyanoacrylate,
 butyl glycoloyl cyanoacrylate, isopropyl glycoloyl cyanoacrylate, ethyl lactoyl
 cyanoacrylate, and ethyl glycoloyl cyanoacrylate.
5. The biocompatible adhesive composition of claim 1, wherein said first
 monomer species comprises an alkyl ether cyanoacrylate.
6. The biocompatible adhesive composition of claim 5, wherein said alkyl
 ether cyanoacrylate has the formula



where R₁ is a straight, branched or cyclic alkyl, and R₂ is a straight, branched or cyclic alkyl group.

7. The biocompatible adhesive composition of claim 6, wherein said alkyl ether cyanoacrylate is selected from the group consisting of isopropoxy ethyl cyanoacrylate and methoxy butyl cyanoacrylate.

8. The biocompatible adhesive composition of claim 1, wherein said second monomer species comprises a cyanoacrylate other than an alkyl ester cyanoacrylate and an alkyl ether cyanoacrylate.

9. The biocompatible adhesive composition of claim 8, wherein said second monomer species is an alkyl α -cyanoacrylate, having an alkyl group of from about 2 to about 12 carbon atoms.

10. The biocompatible adhesive composition of claim 1, wherein a weight ratio of said first monomer species to said second monomer species is from about 25:75 to about 75:25.

11. The biocompatible adhesive composition of claim 1, wherein said composition further comprises at least one additive selected from the group consisting of anionic stabilizing agents, free radical stabilizing agents, colorants, and plasticizers.

12. The biocompatible adhesive composition of claim 1, wherein said composition comprises:

a monomer blend comprising from about 25 to about 40 parts by weight butyl lactoyl cyanoacrylate and from about 60 to about 75 parts by weight octyl cyanoacrylate (OCA);

at least one anionic stabilizer; and

at least one radical stabilizer.

13. The biocompatible adhesive composition of claim 12, wherein said at least one anionic stabilizer comprises about 25 to about 100 ppm of sulfuric acid and from about 1 to about 50 ppm sulfur dioxide, and said at least one radical stabilizer comprises from about 100 to about 2000 ppm hydroquinone, from about 10 to about 200

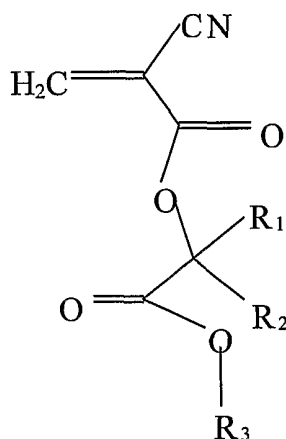
ppm p-methoxyphenol, and from about 100 to about 10,000 ppm butylated hydroxyanisole.

14. A method of treating living tissue, comprising:
 applying to living tissue of a living organism a biocompatible adhesive
 5 composition comprising at least one alkyl ester cyanoacrylate monomer and a polymerization initiator or accelerator, wherein said polymerization initiator or accelerator is a quaternary amine.

15. The method of claim 14, wherein the living tissue is internal tissue.

16. The method of claim 14, wherein two or more polymerization initiators
 10 or accelerators are applied to said living tissue.

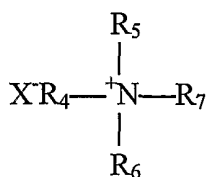
17. The method of claim 14, wherein said at least one alkyl ester cyanoacrylate monomer has the formula



wherein R₁ and R₂ are independently H, a straight, branched or cyclic alkyl
 15 group, or are combined together in a cyclic alkyl group, and R₃ is a straight, branched or cyclic alkyl group.

18. The method of claim 14, wherein the polymerization initiator or accelerator is combined with the at least one monomer prior to applying the composition
 to living tissue.

19. The method of claim 17, wherein said polymerization initiator or
 20 accelerator has the following formula



25

wherein R_4 , R_5 , R_6 and R_7 are each independently H or a substituted or unsubstituted straight, branched or cyclic alkyl group; a substituted or unsubstituted aromatic group; a substituted or unsubstituted aralkyl group; or a substituted or unsubstituted alkyl or aromatic group containing one or more hetero atoms; and X^- is an anion.

5 20. The method of claim 19, wherein at least one of R_4 , R_5 , R_6 and R_7 comprises at least one member selected from the group consisting of an aromatic ring and a hetero atom-containing linkage.

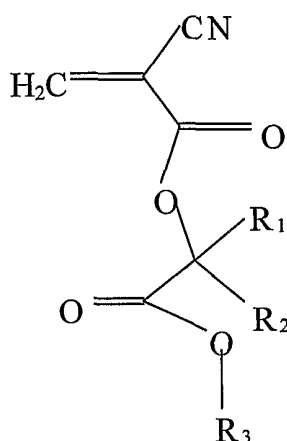
 21. The method of claim 19, wherein X^- is a halogen radical.

 22. The method of claim 14, wherein said polymerization initiator or
10 accelerator is at least one member selected from the group consisting of domiphen bromide, butyrylcholine chloride, benzalkonium bromide, benzalkonium chloride, and acetyl choline chloride.

 23. The method of claim 14, wherein the method is used to close or seal a wound.

15 24. A kit comprising a saleable package comprising:
 a first container that contains a biocompatible adhesive composition comprising at least one alkyl ester cyanoacrylate monomer; and
 a polymerization initiator or accelerator, wherein said polymerization initiator or accelerator is a quaternary amine.

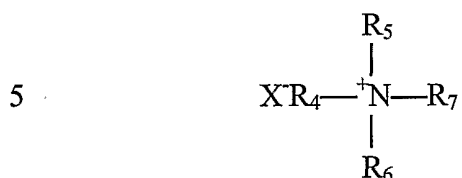
20 25. The kit of claim 24, wherein said at least one monomer has the formula



wherein R_1 and R_2 are independently H, a straight, branched or cyclic alkyl group, or are combined together in a cyclic alkyl group, and R_3 is a straight, branched or cyclic alkyl group.

25 26. The kit of claim 24, wherein said polymerization initiator or accelerator is contained in a separate container not in contact with said monomer.

27. The kit of claim 25, wherein said polymerization initiator or accelerator has the following formula



10 wherein R_4 , R_5 , R_6 and R_7 are each independently H or a substituted or unsubstituted straight, branched or cyclic alkyl group; a substituted or unsubstituted aromatic group; a substituted or unsubstituted aralkyl group; or a substituted or unsubstituted alkyl or aromatic group containing one or more hetero atoms; and X^- is an anion.

15 28. The kit of claim 27, wherein at least one of R_4 , R_5 , R_6 and R_7 comprises at least one member selected from the group consisting of an aromatic ring and a hetero atom-containing linkage.

29. The kit of claim 27, wherein X^- is a halogen radical.

30. The kit of claim 24, wherein said polymerization initiator or accelerator is at least one member selected from the group consisting of domiphen bromide, butyrylcholine chloride, benzalkonium bromide, and acetyl choline chloride.

20 31. A polymerized film formed from the polymerization of a first monomer species and a second monomer species different from said first monomer species, wherein at least said first monomer species is absorbable and an absorption rate of said first monomer species is different from an absorption rate of said second monomer species.

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INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 01/24128

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L24/04 C09J4/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L C09J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, COMPENDEX, CHEM ABS Data, INSPEC, IBM-TDB

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 965 623 A (CLOSURE MEDICAL CORP) 22 December 1999 (1999-12-22) paragraph '0065! - paragraph '0074! paragraph '0036! - paragraph '0038! claims ---	1-31
X	EP 0 374 252 A (VNII ISPYTATEL MED TECH) 27 June 1990 (1990-06-27) examples claim ---	1, 2, 5, 6, 8-11, 31
X	WO 97 31598 A (CLOSURE MEDICAL CORP) 4 September 1997 (1997-09-04) page 6, line 19 -page 8, line 2 page 10, last paragraph claims 1,9,10 ---	1-13,31
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
E earlier document but published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
O document referring to an oral disclosure, use, exhibition or other means	*Z* document member of the same patent family
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 16 January 2002	Date of mailing of the international search report 23/01/2002
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Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Thornton, S
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/24128

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JAFFE H ET AL: "Synthesis and bioevaluation of alkyl 2-cyanoacryloyl glycolates as potential soft tissue adhesives" JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, vol. 20, no. 2, 1986, pages 205-212, XP001058226 introduction abstract page 210 -page 211 -----	1-31
P,X	WO 01 32319 A (CLOSURE MEDICAL CORP) 10 May 2001 (2001-05-10) cited in the application page 13, line 1 - line 29 page 15, last line -page 16, line 2 page 26, line 19 -page 30, line 22 claims -----	1-31

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