Cyano Acrylate Polymers in Medical Applications

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Abstract: Cyanoacrylates are solvent free adhesives that cure rapidly when pressed into a thin film between two surfaces. Their ease availability and use in various formulations made them attractive to manufacturers a wide variety of medical devices. Unfortunately, earlier generations of cyanoacrylates had several limitations, such as poor thermal resistance and peel strength. Subsequent developments in cyanoacrylate technology have greatly expanded the performance of these adhesives. This rubber-toughened, surface-insensitive, thermally resistant cyanoacrylate offers advantages over earlier toughened products which has been recently patented.

Keywords: Cyanoacrylates, polyglycerol sebacate acrylate (PGSA), folate-HNPEGCA-co-HDCA, control multifunctional nano device (CMND'S), fine particle fraction (FPF), actively targetable nanoparticles (ATN).

INTRODUCTION

The usage of cyanoacrylate medical adhesives as a replacement for the classical suture has been reported because of its good cosmetic effect, reduced pain and recovery period, and preference by patients. These techniques are more efficient, offers low surgery time and therefore, reduced cost. Still cyanoacrylates tecnology has some demerits. The low homologues of the cyanoacrylate family form brittle adhesive layers *in vivo* which may cause biodegradation of polymer by adverse tissue response. Biocompatible and more flexible bonds are formed using higher cyanoacrylate but these are more expensive. Therefore, there is a need to get high quality medical adhesives based on cyanoacrylates at an affordable price. For this, alkoxycarbonyl group of the molecule cyanoacrylate monomers are modified to obtain different ester residue chain length compounds. Short chain derivatives show a higher degree of tissue toxicity than the longer chain derivatives. Inflammation and histologic toxicity is related to the by-products of degradation of cyanoacrylates and alcohols. The concentrations of these breakdown products are proportional to the rate of degradation. Therefore, slow degradation rate results in decrease in toxicity to the tissues.

Currently, n-butyl-2-cyanoacrylate was the only commercially available cyanoacrylate tissue adhesive. As the n-butyl-2-cyanoacrylate is effective in closing superficial lacerations under low tension, it also has certain limitations. It produces brittle adhesive film on some specific medical applications and increases the cytotoxicity. The n-octyl-2-cyanoacrylate was formulated to correct these deficiencies. Slow degradation of cyanoacrylate polymer results in lowering the concentration of by-products in the surrounding tissues and produces less inflammation. Additionally, plasticizers are added for more pliablity and tissue compatiblity that flexes with the skin and remains inherent for longer time. This stronger, flexible bond may allow its use on longer incisions. This technology has a proposed the production of several cyanoacrylate adhesives of different ester radical lengths, by introducing a new degradation and stabilization system of cyanoacrylate oligomers depolymerisation. As compared to the known methods the cyanoacrylate technology is cleaner, faster and simple.

Various cyanoacrylate homologues with ester radical length in the C_1-C_8 range are obtained using this technology for direct application as medical adhesives with diverse setting times, bond strengths, degradation rates and biocompatibilities. Another advantage of this technology is used in the synthesis of nanostructured homo and copolymeric poly(cyanoacrylates). It's usefulness in drug delivery and targeting systems and in other various medicinal applications are discussed here.

The use of polyglycerol sebacate acrylate (PGSA) as a biodegradable and biocompatible tissue adhesive has been reported [1].

Clinical applications of 'Topical Tissue Adhesives' synthetic cyanoacrylate in various medical devices was approved by the US FDA. It includes cyanoacrylate liquid bandages, dental cements etc. [2].

A series of lipophilic derivatives of gemcitabine poly (H2NPEGCA-co-HDCA) nanospheres and nanocapsules has been synthesized. More lipophilic derivative such as, 4-(N)-stearoylgemcitabine are incorporated a high yield. Their cytotoxicity study was done on two human cancer cell lines and compared to gemcitabine and free 4-(N)-stearoyl-gemcitabine [3].

The few multifunctional nano device (MND) are discussed here. The folic acid MND is used as ligand, which conjugated to terminal amido of poly(aminopoly(ethylene glycol)cyanoacrylate-co-hexadecyl cyanoacrylate) (poly (H2NPEGCA-co-HDCA)) to synthesize poly(Folate-HNPEGCA-co-HDCA), protamine sulfate (PS) for nuclear

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transfer and DNA condenser. The experimental result shows optimum complexation of DNA i.e. about 97%. The MND loading pDNA/PS shows the luciferase activity over 0.5 ng luciferase/mg protein in KB cells. MND shows the highest transfection efficiency in KB cells as compared to A549 cells and other formulations such as LipofectAMINE, free pDNA/PS. Also, the transfection efficienecy of Controlled Multifunctional Nano Devices (CMNDs), is found higher than lipid film coated poly (HNPEGCA-co-HDCA) and DOPE. In addition, during encapsulation MND also shows good protection and low cytotoxicity. Overall, MND is a more potential non-viral vector used for DNA delivery [4].

A technique of latent fingerprints using controlled cyanoacrylate vapor exposure in fuming cabinets is used for artifacts recovered in investigations of forensic crime-scene. This technique involves the deposition of monomeric cyanoacrylate under warm, moist conditions onto the object to polymerize and produce a white film which renders the fingerprint visible. Raman spectroscopic study shows several bands in the spectra of poly(ethyl-cyanoacrylate) which indicates the presence of residual monomer and other species formed of the polymerizing material. The possible effect of unreacted monomer and other polycyanoacrylate film impurities on spectral analalysis is also highlighted [5].

An actively targetable nanoparticles (ATN), PEG-coated biodegradable polycyanoacrylate nanoparticles (PEG-nanoparticles), conjugated to transferrin for paclitaxel delivery, has been studied. PEGylated paclitaxel loaded nanoparticles were prepared using solvent evaporation technique. ATN were prepared by coupling of transferrin with PEG-nanoparticles. The result shows an average encapsulation efficiency of ATN. A low burst effect of paclitaxel loaded ATN exhibited only 16.2% drug release within the first phase. Subsequently, paclitaxel release profiles displayed a sustained release phase. The amtount of cumulated paclitaxel release over 30 days was 81.6%. ATN exhibited a markedly delayed blood clearance in mice, and the paclitaxel level from ATN remained much higher at 24 h as compared to free drug from paclitaxel injection. Distribution profiles of ATN in S-180 solid tumor bearing mice after i.v. administration shows the tumor accumulation of paclitaxel increase with time, and the paclitaxel concentration in tumor was about 4.8 and 2.1 times higher than those from paclitaxel injection and PEG-nanoparticles at 6 h after i.v. injection. The tumor burden with ATN-treated mice was much smaller compared with free paclitaxel or NTN-treated mice. In addition, the life span of tumor-bearing mice was significantly increased when they were treated with ATN. Thus, PEG-coated biodegradable polycyanoacrylate nanoparticles conjugated to transferrin could be an effective carrier for paclitaxel delivery [6].

Nanoparticles of poly(isobutylcyanoacrylate) with dispersed insulin in pluronic acid solution has been reported. The results show a decrease in particle diameter by increasing the pluronic acid concentration. Nanoparticles prepared in the presence of 2.5% pluronic acid results in particles of 85 nm diameters and 59% intra-particular insulin load without the use of the oily core. Streptozocin induced diabetic rats were used for *in vivo* study. Sub-cutaneous injection of insulin nanoparticles prolonged the duration of hypoglycemic effect from 6 to 72 h. As compared to non-encapsulated insulin, oral absorption of the entrapped insulin was found significantly better [7].

Spray drying is a common practice of powder preparation used to deliver particles to the lungs via a dry powder inhaler (DPI). In present study lactose was used as the excipient and spray-dried with gelatin and polybutylcyanoacrylate nanoparticles. In results, some carrier particles were found hollow while others had a continuous matrix. Gelatin nanoparticles incorporated the matrix and sometimes accumulated at one end of lactose. The polycyanoacrylate nanoparticles found clustered in different spots within the lactose carriers. Dispersion of the powder with an inhouse passive dry powder inhaler and subsequent cascade impaction measurements showed that incorporation of the nanoparticles did not affect the fine particle fraction (FPF) or mass median aerodynamic diam. The nanoparticles were delivered to the lungs via carrier particles that dissolve after contact with the aqueous environment of lung epithelium. This opens the way for new drug-targeting strategies using nanoparticles for pulmonary delivery of drugs and diagnostics [8].

A molecular simulation of doxorubicin interacting with butyl-polycyanoacrylate has been studied. Emphasis is put on the tetrameric, hexameric and octameric oligomers (PACA's). Aggregation and desegregation mechanism of doxorubicin release can be summarized as follows: oligomeric PACA's are lipophilic entities facilitate scavenge amphiphilic doxorubicin already during the polymarization. The establishment of hydrogen bonds between the ammonium N-H function and the cyano groups is noteworthy. The cohesion in PACA nanoparticle comes, therefore, from a blend of dipole-charge interaction, H bonds, and hydrophobic forces [9].

Transferrin conjugated PEGylated polycyanoacrylate nanoparticles (TF-PEG-nanoparticles) microencapsulation of has been reported to determine the stability of pDNA against various conditions *in vitro* targeting cells association. The open circular forms of pDNA increased on emulsifing pDNA with organic solvent. Poly(aminopoly(ethylene glycol) cyanoacrylate-co-hexadecyl cyanoacrylate) (poly(H2NPEG-CA-co-HDCA)) shows a slight influence on pDNA in 0.1M $NaHCO_3$ at high concentration. K562 cell binding affinity of TF-PEG-nanoparticles was found greater than of non-targeted PEG-nanoparticles. The results indicate, TF-PEG-nanoparticles were useful in pDNA delivery to target cells [10].

Using poly(Bu-cyanoacrylate) (PBCA) nanoparticles coated with Polysorbate 80, drugs can be delivered to brain. These carriers can penetrate blood-brain barrier (BBB) and deliver drugs of various structures, i.e. peptides, hydrophilic and lipophilic compounds eliminated from brain with P-glycoprotein. The suspension of polysorbate-coated PBCA nanoparticles is introduced into blood; apolipoproteins of the blood plasma adsorb on the particle surface and interact with low concentrate receptors. Lipoproteins situated in endothelial cells of cerebral vessels, thus stimulating endocytosis [11].

Nanoparticles of poly(Bu-cyanoacrylate) (PBCA) and poly(octyl-cyanoacrylate) (POCA) have been reported to

study biodistribution in mice by loading radioiodine125I-labeled IUDdR. Nanoparticulate injection to brain increases the counts because of IUdR bioavailability in the brain when IUdR was loaded into NPs. The result shows nanoparticles crossed the blood brain barrier and reaches to brain tissues. [12].

Butylcyanoacrylate adhesive scaffold is used in a porcine model to enhance the tensile strength of tissue samples repaired in an *ex vivo*. The cyanoacrylate doped scaffold repairs approximately 30% organ tissues and approximately 20% vascular tissues. These scaffold-enhanced adhesive offers a quick application with less skilled professionals, paraprofessionals and bystanders in emergency [13].

Application of thermosensitive poly(cyanoacrylate) nanoparticles at high hydrostatic pressure (HHP) were also studied. Poly(cyanoacrylate) nanoparticles appeared to be extremely baroresistant. This process allowed the successful inactivation of vegetative bacteria, yeast, and fungi. HHP act as a new method for polymer drug carrier's sterilization [14].

The combination of polycyanoacrylate with bone morphogenetic protein-2 (rhBMP-2) nanoparticles injection is prepared by emulsion method. Their biological activities were tested *in vivo* as well as *in vitro*. It shows that the rhBMP-2 polycyanoacrylate nanoparticle was homogeneous and stable. *in vivo* Study showed 80% of rhBMP is released in 10 days. Addition of rhBMP nanoparticle to marrow stromal cell (MSC) system increases ALP level in MSC cultural significantly [15].

Recently, biodegradable poly(ethyl-cyanoacrylate) (PECA) nanospheres was used as carriers to deliver insulin orally. Screen absorption enhancers used to protect insulin-loaded PECA *in vivo* after oral administrations of streptozotocin-induced diabetic rats. Orally administered insulin absorption was evaluated using hypoglycemic effect. Blood glucose level is significantly reduced on oral administrations of protease inhibitor with insulin-loaded PECA nanospheres [16].

PEGylated polyalkylcyanoacrylate nanoparticles easily penetrate into central nervous system to a larger extent than other formulations because of their long-circulating properties in blood. Thus, PEGylated polycyanoacrylate nanoparticles are used as a new brain delivery reported system in neuroinflammatory diseases [17].

Pharmacokinetics study of poly(Bu-cyanoacrylate) nanoparticles loaded with sulfonated aluminum phthalocyanine (Photosense) as a delivery system has been reported [18].

Poly(Bu-cyanoacrylate) nanoparticles (PBCA nanoparticles) loaded with the hexapeptide dalargin has been studied. These nanoparticles were coated with apolipoproteins AII, B, CII, E, or J without or after precoating with polysorbate 80. The antinociceptive threshold was measured by the tail-flick test on i.v. injection to mice. The antinociceptive effect found to be reduced in apolipoprotein-E deficient mice. Transportation of drugs loaded to poly (Bu-cyanoacrylate) nanoparticles with apolipoproteins B and E across the blood-brain barrier has been done [19].

Polycyanoacrylate adhesives were also used in inguinal hernia repair. Since the evolution of laparoscopic inguinal hernia repair, the total extraperitoneal (TEP) repair is the most commonly employed technique by laparoscopic surgeons [20].

A biodegradable poly(iso-Bu-cyanoacrylate) (PIBCA) colloidal particulate system of pilocarpine, incorporate it into a Pluronic F127 (PF127)-based gel delivery system has been developed. Its ability to prolong the release of pilocarpine is elavuated. The PIBCA-NC of pilocarpine dispersed in the PF127MC gel delivery system has significant potential to prolong a delivery of pilocarpine and other hydrophobic drugs [21].

Allopurinol-loaded poly(Et-cyanoacrylate) nanoparticles were tested against *Trypanosoma cruzi* using *in vitro* cultures of epimastigotes. Increasing concentration of unloaded nanoparticles on vero-line cell cultures has done cytotoxicity study. The result subjected to, shows that the poly (Et-cyanoacrylate) nanoparticles comprises a good carrier of drugs against the trypanosoma cruzi. The allopurinol loaded-nanoparticles significantly increased the trypanocidal activity in comparison to the free drug [22].

PATENTS ON MEDICAL APPLICATIONS

Tissue Adhesives and Sealants and Method for their Use

US Patent 20070202075 reported the compositions containing both a biotin and avidin used as adhesives or sealants in medical or surgical applications. The biotin and avidin containing components are kept separate and mixed just prior to use to form a gel matrix for adhering tissue to tissue or adhering a medical device to tissue or sealing holes in tissue. Methods sealing a hole in tissue is done by applying a composition of biotin and avidin component to a defect tissue. It reports the use of specific apparatus in which first chamber containing a biotin and second chamber containing avidin component with one or more outlets for simultaneously dispensing the first and second compositions. It covers the use of bioabsorbable polymer to prepare the avidin containing component. The bioabsorbable polymer breaks down in the body and gradually absorbed or eliminated from the body by hydrolysis, metabolic processes, or bulk or surface erosion. These bioabsorbable materials suitable for making the avidin-containing component includes, polycaprolactone (PCL), poly-D, L-lactic acid (DL-PLA), poly-L-lactic acid (L-PLA), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(glycolic acid-cotrimethylene carbonate), polyphosphoester, polyphosphoester urethane, polyamino acids absorbable cyanoacrylates and other various biodegardeble polymers [23].

Surgical Adhesive Compostion and Process for Enhanced Tissue Closure and Healing

US Patent 20070092483 deals with the compositions and control *in vivo* degradation behavior, wound healing, and tissue regeneration. Furthermore, the brush likes pendant hydrophilic protects the molecule or polymer from immunological recognition and toxic degradation. The inclusion of minimal oligopeptide sequences can also impart specific bioactivity and cell mediated degradation to the materials. Polymerization of the macromers is initiated by

nucleophiles hydroxyl ions present in the moisture or on surfaces of biological surfaces or fluids, such as blood to form a solid polymer.

The present invention reported 1,1-disubstituted electron-deficient olefin macromers and their adhesive composition reacts with moisture on surfaces or in the presence of biological surfaces or fluids, such as blood to form a solid polymer. They are used to form an adhesive bond between two dissimilar or similar surfaces at the junction of living tissue. These inventive compositions possess an improved biocompatibility with controlled biodegradation and bioactivity. The compositions are used as surgical adhesives to provide mechanical fixation whereas promoting healing across the tissue junction. The co-monomer compositions are of at least one macromer with a pendant oligomeric/ linear/branched polymeric chain of ester linked to an acrylate group of the reactive olefin. The pendant polymer prevents non-specific protein adsorption, such as a polyethylene glycol (PEG). These polymeric grafts improved the biocompatibility of resulting adhesive and decrease the toxicity of polymer degradation products. The co-monomers of composition 1,1-disubstituted electron-deficient olefins and cross-linkers are different cyanoacrylate and PEG-dicyanoacrylate, respectively. The composition may have cyanoacrylate functionalized peptide co-macromers and cross-linkers. Cyanoacrylate pendant cell binding or signaling peptide domains and cleavable cyanoacrylate enzyme capped domains may also present in such compositions. Another important characteristic of these adhesive compositions is, the polymers formed are bioactive and degradable. Non-degradable cross-linking co-monomers or macromers are also incorporated in these compositions.

Antibiotic and anti-inflammatory drugs are hormones or gene-therapy vectors also incorporated in the adhesive polymer compositions. Polymerization and/or polymer modifying additives such as free-radical stabilizers, anionic stabilizers, initiators, accelerators, inhibitors, plasticizers, and rheology modifiers may also be incorporated in the composition. Formaldehyde scavenging compounds may also be included in the composition. Furthermore, fiber or particular filler material may be added in composition to provide a reinforced polymer composite. The filler material may be composed of degradable synthetic or natural polymer, protein, mineral, or bio-glass. Easily releasing drug or biologic may also be added in the degradable filler material. It also includes polymer/mineral cement composites, which cure by polymerization and precipitation of mineral to form an interpenetrating composite micro-structure. Micro-structural with the cell-mediated degra-dation and bioactive properties of the polymer promotes cell and tissue growth and provide mechanical stability during healing and replacement of the material by native tissue. It also covers the preparation methods of monomers and adhesive compositions and their use as surgical adhesives [24].

Cyanoacrylates and their derivatives are commonly employed as adhesives because of their fast curing rate, high bonding strength, wide range of substrates, and ease of use. Cyanoacrylate adhesives are extensively used in industrial and commercial applications but their use in medicine is limited. Short chain alkyl cyanoacrylate adhesives were showed severe inflammatory effects on tissues. Butyl cyanoacrylate was the first cyanoacrylate adhesive show low tissue toxicity and good bonding strength. The toxicity of cyanoacrylate decreases with increasing alkyl chain length. 2-Octyl cyanocrylate Dermabond®, shows improved mechanical and biological properties and used in dermal wound closure and protection. It is also served as haemostatic agent and orthopedic adhesives. Advantages of cyanoacrylate adhesives over sutures or staples include lower infection rates, better cosmesis, and faster wound closure. Cyanoacrylate used to join living tissues result in obstruction of the healing path and intense foreign body response. When used for direct bonding, cyanoacrylate adhesives bridge and block the living tissue junction being adhered. This prevents cell migration and infiltration and replacement of the material by native tissue [24].

Microcapsules and Nanocapsules Made from Polymers for Drug Delivery

CN Patent 101053810 is related with the method that comprises dissolving aliphatic polyester, polycyanoacry-late, polyorthoester polymers of mol. wt. of 5000-500,000 in oil-solution to give polymer solution. Mixing water or drug solution with the polymer solution at volume ratio of 1:(2-40) forms water-oil emulsion. Resultant emulsion on mixing with precipitating agents like methanol, ethanol, etc. at 1:1 volume ratio results in suspension of microcapsules. The microcapsules are separated by washing, freeze drying and stored in a sealed container. The sealed container on vaccumization and pressure forms polymer micro-nano capsule. The polymer capsule realizes compatibility of water-solution, drug and oil-solution, provides sustained release function. Thus, these compositions are used for ultrasonic contract and molcular imaging [25].

Body Fluid Biodegradable Medical Implant and its Preparation

CN Patent 101015711 deals with the implant made up of compact or porous Mg-Ca alloy and biodegradable polymer or biodegradable ceramic coating on the alloy. The Mg-Ca alloy contains Mg 7-10, Ca 0-3, and Zn, Zr, Ag, or rare earth elements 0-1 part. The biodeg-radable polymer is polycyanoacrylate, polyhydroxy acetic acid, polylactic acid, L-polylactic acid, polycaprolactone, polydioxanone, polyanhydride, polyphosphazene, poly-hydroxybutyrate, hydroxyvalerate, and one or more copolymer of polyhydroxy acetic acid, polylactic acid, L-polylactic acid, polycaprolactone, polycyanoacrylate and polydioxanone. The biodegradable ceramic is hydroxyapatite, -tricalcium phosphate, -tricalcium phosphate or tetracalcium oxygen phosphate.

The implant is prepared by the mixing of magnesium and calcium powder with one of Zn, Zr, Ag, Sn, and rare earth elements. This mixture on smelting at 700-850ºC under vaccum results in a compact Mg-Ca alloy. The alloy further on sintering or self-propagating at higher temperature gave porous Mg-Ca alloy. In coating of biodegradable polymer, the obtained implant was washed with acid. Biodegradable polymer is dissolved in trichloroethane solution and is subjected centrifuging for 10-30 minutes. Electrophoresis deposition or hydrothermal anodization methods are used in biodegradable ceramic coating. The implant shows good

histocompatibility and blood compatibility. Thus they can be used as implanting stenting, bone prosthetic devices, and dental prosthetic devices [26].

CT-Detectable Biodegradable Nanocapsule for Controlled Drug Delivery and its Preparation Method

CN Patent 1973832 deals with biodegradable nanocapsule manufactured from biodegradable polymer, CT contrast core and hydrophilic or water-drug solution. The biodegradable polymer used, are polycyanoacrylate poly (lactic acid), polyglycolide, lactic acid-glycolic acid copolymer, polycyanoacrylate, poly (alkyl cyanoacrylate), polyanhydride, poly(caprolactone) and its copolymer, poly (hydroxyvaleric acid), polyethylene terephthalate, poly(malic acid), poly(tartronic acid), etc. The CT contrast agent used is meglumine adipiodone, meglumine diatrizoate, amipaque, ultravist or iodized oil. The preperation method comprises dispersion of CT contrast agent, hydrophilic or water-drug solution and surfactant or emulsifier in water to obtain solution A. Mixing of biodegradable polymer with organic solvent has been done to obtain solution B. Surfactant or emulsifier on dispersion in water results in solution C. Solution A on addition to the solution B gave a homogenous W/O emulsion. Addition of this emulsion into the solution C results in a W/O/W multiple emulsion system. The emulsion is stirred to evaporate the organic solvent and cured to obtain nanocapsule. The nanocapsule realizes *in vitro* controlled delivery of drug because of the advantages of high drug loading capacity, targeted and controllable drug delivery and detectability due to CT [27].

Novel Compositions of Fat-Soluble Substances

US Patent 20070248683, is related to novel composition of fat-soluble substances. It includes the novel powder form of fat-soluble composition of substances and their emulsion form. These novel compositions are used as additives in food, beverages, animal feeds, cosmetics or drugs to incorporate fat-soluble ingredients into such items. A important feature of these novel composition is the encapsulation of the fat-soluble substance(s) to form an inner phase within an outer continuous phase of a matrix substance.

In the synthesis of these novel compositions, synthetic polymers are used from acrylic polymers (methacrylic acid copolymers and ammonio methacrylate copolymers), polyethylene, coumarene-indene resins, polylactic acid (PLA) and poly(lactic/glycolic) acid (PLGA), polyorthoesters, polyphosphazenes, polyanhydrides, polyglycolide (PGA), poly(epsilon-caprolactone), polydioxanone, trimethylene carbonate, poly(β-hydroxybutyrate), poly(γ-ethyl glutamate), poly(DTH iminocarbonate), poly(bisphenol A imino [28].

Immunogenic Compositions Containing Antrhrax Antigen, Biodegradable Polymer Microparticles, and Polynucleotide-Containing Immunological Adjuvant

CA Patent 2588089 describes several immuno-genic compositions. The composition comprises: 1. An antigen derived from bacillus anthracis, 2. Polymer micro-particles comprising a biodegradable polymer and 3. Polynucleotide containing immunological adjuvant.

The biodegradable polymer used in these immunogenic composition is selected from a polycyanoacrylate, poly (alpha-hydroxy acid), polyhydroxy butyric acid, polycrolactone, apolyrthoester and polyanhydride [29].

Slow-Released Nanoparticles Containing Neurotrophic Factors Encapsulated in Biocompatible Polymers for Nerve Repairs

CN Patent 1876175 deals with neurotrophic factors (NTFs) comprises nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, neurotrophin-4/5, neurotrophin-6, ciliary neurotrophic factor, glia cell line-derived neurotrophic factor. In this method encapsulation polymers of polylactic acid, polyglycolide, poly (lactide-co-glycolide), polycyanoacrylate, poly-Bu cyanoacrylate are dissolved in dichloromethane and envelop with solution of NTFs in water. The emulsifying mixture was obtained above in ice water bath for first latex. Drip addition of first latex into dispersant solution has been done fastly at high stirring speed (10000-15000 rpm) for 1-5 minutes to obtain an emulsion. The emulsion is diluted with distilled water and further stirred at 300-600 rpm for 2-6h. High speed centrifuging results in nanosized sphere which are washed with distilled water for 3 times and lyophilized for 24 h. Slow release nanosized NTFs formulation is used to cure nerve damage disease, cauyda equina syndrome [30].

Antifungal Nano-Preparation of Amphotericin b (AmB) and its Preparation

CN Patent 1850032 deals with the process developed by dissolving 6 mg/ml stabilizing agent dextran-70 or poloxamer 188 in distilled water. Cosolvent sodium deoxycholate 0-0.4 mg/ml. may be added or not as per requirement. Bu- cyanoacrylate is added at pH 3 with stirring for 4 h. pH of the solution is adjusted to 7.5-8.5 to obtain Poly(Bu-cyanoacrylate) nanoparticle gel solutions. AmB powder is added to gel solution and the mixture was further stirred for 4 h to obtain AmB-Bu polycyanoacrylate nanoparticle gel solutions. This nano preparation shows good antifungal activity [31].

Magnetic Nanoparticles Containing Mitomycin C and its Application

CN Patent 1803133 deals with the nanoparticle prepared from mitomycin C1 of high molecular weight polymers. High molecular weight compounds are poly-lactide, poly(lactide-glycolide), polycyanoacrylate, or amino acids. The diameter of prepared nanoparticles is maintaining 50-300 nm. These magnetic nanoparticles are used to treat gastric, intestinal and liver cancer [32].

Porous Scaffold Material Composed of Recombinant Spider Silk Protein and Polymer Used in Tissue Engineering

CN Patent 1751748 deals with the material prepared by cross-blending a recombinant spider silk protein 55-95 wt.% with a biodegradable polymer 45-5 wt.%. The biodegradable polymer used may be a polylactic acid (PLA), polyglycolic acid (PGA), copolymer of polylactic acid and polyglycolic acid (PLGA), polycyanoacrylate, polycapro-lactone, etc.

This porous scaffold material has good biocompatibility, biodegradability and mechanical property [33].

Composite Polymeric Nanoparticles

FR Patent 2872703 deals with the preparation and use of biodegradable composite polymeric nanoparticles aqueous suspensions with active ingredient. Preperation of composite nanoparticles of poly(iso-Bu-cyanoacrylate) /poly(caprolactone)/poly(ethylene glycol) with 1.7% busulfan has been described. The average diameter of composite nanoparticles was 40 nm and the surface potential of nanoparticles was 41 mV [34].

Imageable Elements Containing Cyanoacrylate Polymer Particles

US Patent 20067070902 is related to the lithographic printing. In this invention binder cynoacrylates polymer are imaged to form lithographic printing plates.

In the preparation cynoacrylate polymer is dissolved in a coating solvent and the resulting coating solution coated over the donor support to form the layer of the cynoacrylate polymer. The solvents used in this coating are acetonitrile, dichloromethane, chloroform and methyl chloroform which are toxic. Thus, there is a need to develop such process which does not require the use of any toxic organic solvents [35].

Stabilized Polyester/Cyanoacrylate Tissue Adhesive Formulation

US patent 7,083,634 is deals with the adhesive formulations of 2-alkoxyalkyl cyanoacrylate. These adhesive formulations are useful as tissue adhesives/sealants, hemostatic agents, or as a means of patching and anastomotic coupling of damaged organs.

The basic aspect of this invention is bound to a bioabsorbable adhesive formulation, which is an admixture of an alkoxyalkyl cynoacrylates, an absorbable liquid or solid polymeric modifier, and a stabilizer against premature anionic polymerization of the cynoacrylate components. In this formulation the said stabilizers are one or more miscible acidic compounds, includes pyrophosphoric acid, polyphosphoric acid and phosphoric acid or monobasic organic sulfonic acids such as p-toluenesulfonic acid, trifluoroacetic acid, and methanesulfonic at a concentration exceeding 1 ppm [36].

Chemically Based Vascular Occlusion Device Deployment with Gripping Feature

CA patent 2551328 deals with a vascular occlusion device deployment system of polycyanoacrylate foam for the vasculature of a patient.

The deployment system includes the mixing and dispensing of the reactant into the cavity of interior chamber. It also covers the deployment system wherein the first dispensing unit comprises a first lumen and the second dispensing unit comprises a second lumen [37].

Nano Granules Adhesive to Mucous Membrane, Preparation Method and Application

CN patent 1760223 is concerned with a synthesis of mucosa adhesive nanoparticle used in medicine, food and cosmetics. These are prepared from (alkyl polyacrylate, alkyl methylacrylate, or polycynoacrylate foam [38].

Wound Dressing Comprising a Cyanoacrylate Adhesive

US Patent 2005244366 deals with wound dressing material of butyl-cyanoacrylate adhesive. The adhesive is applied directly to the wound site and extend at a distance beyond the wound site to form a peripheral edge. The method especially used in pediatric patient or a patient having poor skin turgor. The dressing also includes a second layer of a butyl-cyanoacrylate adhesive applied directly to the first layer and overlapping the peripheral edge of the first layer. In a moderate tension wound the second layer extends the entire area of the first layer, but also extends a distance beyond the peripheral edge [39].

Medical Device with Mechanically Attached Fibrous Coatings

WO Patent 05079335 is related to nanofibrous polymeric coatings on medical devices. The medical devices are surgical mesh or stent, wherein the mechanical coating to the device is done using thermal methods. The mechanism of such coating is achieved by causing the fibers to permeate and entangle with the substrate. The fibrous coating consist of at least one polymeric component from the group of polycyanoacrylate polycaprolactone, polylactic acid, polyglycolic acid, polydioxanone, polyanhydride, poly(hydroxybutyrate), poly(Et-glutamate), poly(DTH iminocarbonate), poly(bisphenol A iminocarbonate), poly(ortho ester), polyphosphazene, nylons, polyesters, polyethylene terephthalate, silicon-contg polymers, elastomeric silicone polymers, polyolefins, etc [40].

Microparticles with Adsorbent Surfaces, Methods of Making Same, and Uses Thereof

US Patent 20056884435 reported the microparticles formation and their applications. The microparticles used for a vaccine, for raising an immune response, for treatment and diagnosis of a disease. The microparticles are prepared from a biodegradable polymer polycyanoacrylate, poly(hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride. The detergent used is one from a cationic detergent and an anionic detergent. Further the microparticles comprise an antigen adsorbed on the surface of the microparticle [41].

Microparticle-Based Delivery of Adsorbed Toxoid and Polysaccharide-Containing Antigen

WO Patent 05020964 is related to immunogenic compounds microparticles with adsorbed toxoid antigen or polysaccharide containing antigen. This microparticle comprises (a) a biodegradable polymer; (b) an antigen adsorbed on microparticles can be a toxoid antigen such as a tetanus toxoid, a diphtheria toxoid, or a combination thereof,

or a polysaccharide antigen such as a Hib polysaccharide antigen. A Hib conjugate antigen comprising polysaccharide and polypeptide regions, a meningococcal polysaccharide antigen, a meningococcal conjugate antigen comprising polysaccharide and polypeptide regions, a pneumococcal polysaccharide antigen, and a pneumococcal conjugate antigen comprising polysaccharide and polypeptide regions or a combination thereof; and (c) a pharmaceutically acceptable excipient. The biodegradable polymer may be a polycyanoacrylate, poly(hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride. The microparticle also used in immunization against infection by pathogenic organisms and stimulating immune responses. It also covered the methods of microparticle synthesis using a water-in-oil-in-water emulsion process [42].

Microparticle Compositions and Methods for the Manufacture Thereof

RU Patent 2257198 is related to the biologically active microparticles composition. These microparticle composition comprises: a) polymer such as polycyanoacrylate, poly-(alpha hydroxyacid), polyhydroxybutyric acid, polycaprolactam, poly-ortho-ester, polyanhydride and b) the detergent that is bound with polymer and also complex adsorbed on microparticles complex that comprises: a) biologically active macromolecules and b) the detergent part wherein biologically active macromolecule is taken consisting of polypeptide, polynucleotide, polynucleoside, antigen, pharmaceutical agent, hormone, enzyme, transcription or translation mediating agent, metabolite, an immunomodulating agent and adjuvant [43].

Immunogenic Compositions Containing Microparticles Comprising Adsorbed Toxoid And Polysaccharide-Containing Antigens

US Patent 2005118275 is related to immunogenic vaccine compositions comprising biodegradable polymer microparticles possessing toxoid and polysaccharide containing antigens.

The appearance of vaccines subunit includes polypeptide, polysaccharide, conjugate, and DNA vaccines. All these vaccines have been intensified the need for safe and effective adjuvants containing compositions. Microparticles are prepared by various techniques, after which the antigen is adsorbtion to the microparticle. Polymer microparticles formed from sterilizerable, substantantially non-toxic and biodegradable materials. Such materials include polycyanoacrylates poly(α-hydroxy acid), polyhdroxy butyric acid, polycaorolactones, polyorthoesters, polyanhydrides.

In this invention an immunogenic composition comprises: a) biodegradable polymer microparticles of a polycyanoacryalate, poly (α-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoeste, a polyanhydride; b) an antigen adsorbed to the microparticles selected from i) a toxoid antigen such as a tetanus toxoid, a dipheria toxoid, or a combination thereof, an/or ii) a polysaccharide containing antigen such as a Hib polysaccharide antigen, a Hib conjugate antigen comprising polysaccharide and polypeptide regions, a meningococcal polysaccharide antigen, a meningococcal conjugate antigen compmprising polysaccharide and polypeptide regions, a pneumococcal polysaccharide antigen, a pneumococcal conjugate antigen comprising polysaccharide and polypeptide regions, or a combination threrof; and c) a pharmaceutically acceptable excipient [44-45].

Continuous Processes and Apparatus for Forming Cyanoacetate and Cyanoacrylate

US patent 182271 deals with the cyanoacrylate formation include stripping a solvent from a reaction mass; cracking a polymer in the reaction mass to form a cracked cyanoacrylate monomer and residue substances; and distilling the cracked cyanoacrylate monomer to produce a cyanoacrylate monomer product. These steps can be performed in short-path, wiped-film evaporators. Polycyano-acrylate used in the processes is obtained using cyanoacetate produced by processes for continuously producing cynoacetate by forming a higher homologue cyanoacetae from a lower homologue cyanoacetae. The cyanoacetate can be formed in short-path, wiped-film evaporators [46].

Scretory Vacuole Structured Particles of Poly Cyan Acrylic Estyers and Method of Duplex Inducing Bionic Preparation Process

CN Patent 1687151 invention provides a biodegradable high-molecular polycyanoacryalate (PACA) scretory vacuole structure particle by utilizing ACA monomer polymerization. Invention also provides the concrete characteristics of said high-molecular secretory vacuole structure particle [47].

Synthetic Resin for Identification

JP patent 164341 is related to obtain a novel and useful synthetic resin easily applied to an identifing object comprising a material of each kind, enhanced in environmental resistance and having various characteristics, such as a property being hardly noticed of the applications to the synthetics resin or the like.

The synthetics resin for identification is selected from among nylon 6,6, an aromatic polyamide, a formal resin, an acetal resin and polycyanoacryalate. This synthetic resin for identification is preliminarily applied to an article, and the vibration spectrum is read in a non-destructive manner to decide the genuineness of the article or to certificate the origin of the article [48].

Solid Cyanoacrylate Adhesive Composition and Method for its Use

US Patent 20046797107 reported solid cyanoacrylate adhesives at room temperature are liquefy at higher than room temperature and further polymerize to form adhesive bonds or adhesive coatings. The adhesive compositions are easy to be applied in industrial applications as well to skin or living tissue. They are useful in medical applications, includes wound and surgical incision closure, sealants and void fillers, medical device fixation, embolic agents etc. In method of the solid cyanoacrylate formation in various composition is reported. If the substrates are not at above room temperature, the adhesive polymerizes to form a strong adhesive bond at higher temperature. The invention also reports the solid cyanoacrylate adhesive delivering method, using a suitable dispenser to a substrate. At higher

temperature, the solid adhesive converts into a viscous liquid and further polymerizes to form a coating. The invention provides a cyanoacrylate adhesive composition in a new form. The adhesives are preferably in a solid form at room temperature and below room temperature. Room temperature is considered from 15°C to 37°C and more preferably from 15°C to 25°C. This makes the application of the adhesive easy and controlled. The adhesive is activated when the temperature of substrate reaches a temperature above room temperature, to renders the adhesive in liquid form. The liquefied adhesive spreads and wets the underlying substrate surface and polymerize as a typical cyanoacrylate adhesive. The liquidification and polymerization of the adhesive is achieved by bringing the temperature higher than 25°C to 30°C. In industry the essential heating is achieved by heating thermally, IR, UV or by microwave radiation.

The solid cyanoacrylate compositions may contain a biodegradable or bioabsorbable component. The bioabsorbable cyanoacrylate compositions described in US Patent 6224622 is suitable for inclusion into the solid cyanoacrylate adhesives of the present invention. One embodiment of this work is directed for making a cyano-acrylate adhesive composition in a solid form at room temperature by dissolving a cyanoacrylate monomer or a mixture of cyanoacrylate monomers one or more solidifying polymers or copolymers at elevated temperature. Then the solution is allowed to stand for a sufficient time at room temperature or below room temperature to form a solid at room temperature. The cyanoacrylate monomers are prefer-ably selected from the group consisting of alkyl 2-cyanoacrylates, alkenyl 2-cyanoacrylates, alkoxyalkyl 2-cyanacrylates, and carbo-alkoxyalkyl 2-cyanoacrylates. The alkyl group of the one or more cyanoacrylates preferably has 1 to 16 carbon atoms. The solidifying polymer or copoly-mers is preferably a poly (ε-caprolactone) [49].

Embolic Compositions with Non-Cyanoacrylate Rheology Modifying Agents

EU Patent 1425319 describes a composition comprising a matrix forming component, a solid aggregate material and a polymeric rheology modifier. The matrix-forming component comprises liquid alkyl cyanoacrylate monomers at least with a stabilizer and a plasticizer. A solid aggregate material is incorporated in the composition with matrix-forming component, comprises at least a radiopaque powder radiopacifier. A rheology-modifying agent is also incorporated into the composition, in combination either with the matrix-forming component or with the solid-aggregate material. The rheology-modifying agent used is a non-cyanoacrylate polymer. A fine inorganic particulate compound is used as a second rheology modifier present in the solid aggregate material. This composition is useful in a therapeutic regimen in the treatment of vascular abnormalities. Administrating the composition includes, AVMs, aneurysms, fistulas, and tumors treat vascular abnormalities. In presence of ionic environment, the viscosity of liquid composition is rapidly increases, forming a solidified composition of a rubbery polymeric matrix.

The method also described administration of the composition for tissue bulking, filling, or occluding, either partially or entirely, a volume or cavity in a mass. The volume or cavity filled by the method is a lumen or passageway in the body, for example, a blood vessel, a duct, an aneurysm, or a fistula. The solid composition formed is useful for abating disease of the vascular tissues or by cutting the blood supply to undesired tissue. A tumor or abnormality is occluded by cutting off the blood supply to the diseased area, resulting in diminished growth or death of the tumor or abnormality. The method also includes administration of composition to embolize a vascular space. The composition is administered to a patient who needs a treatment for vascular abnormalities, to form an embolic block at the site of diseased, damaged, or otherwise compromised vasculature. The above aspects, advantages, and novel features of the invention will become apparent from the following detailed description.

All the materials used are either incorporated into a single injectable embolic composition along with the matrix-forming components or included in one of the separately packaged mixtures use to form the embolic composition. The stabilizing component is comprised of an acidic stabilizer, a free radical inhibitor, an antioxidant, or their mixture. The plasticizer used are non-polymeric compounds impart the flexibility, prevent the brittleness, reduce adhesiveness to catheter delivery devices, and are compatible with alkyl cyanoacrylate monomers. The solid-aggregate material comprises a radiopacifier, includes a rheology-modifying agent. The rheology-modifying agent has capacity to increase the Newtonian viscosity of the composition imparting non-Newtonian behavior upon the liquid composition. The fluids show such behaviors are generally known as "shear thinning." The rheology-modifying agent also improves the surface tension of composition as it solidifies.

Different composition is used for embolizing a vascular space, or cavity. The matrix forming components are combined with one or more solid aggregate materials. In particular, the matrix forming components includes liquid cyanoacrylate monomers, a stabilizer, and a plasticizer, comprises at least a radiopacifier. The composition is typically a liquid injectable composition that solidifies in ionic environment like blood. The matrix forming component or the solid aggregate material contains a non-cyanoacrylate compound, which imparts improved rheology, cohesiveness, suspension stability, and radiopacity properties of injectable composition liquid. In addition, the inclusion of a non-cyanoacrylate polymer compound improved a hydrolytic stability of the solidified composition rendered in the body. The composition is useful for stabilizing or mitigating rupture of an aneurysm. The composition also is used to occlude the interior space of an unruptured or previously ruptured aneurysm.

Alkyl cyanoacrylate monomers are prepared by forming the desired ester from the corresponding alcohol and cyanoacetic acid. The reaction of the alkyl alcohol with the cyanoacetic acid forms an alkyl cyanoacetate, which can be converted into the desired alkyl cyanoacrylate compound. The preparation of the alkyl cyanoacrylate compounds has been described in US Patents 20006015541, 20006037366, and PCT International Publication WO000044287. Starting materials for preparing the alkyl cyano-acrylate monomer are commercially available from, Aldrich Chemical Company,

Sigma Chemical Company, or Fluka Chemical Company [50].

Cyanoacrylate-Capped Heterochain Polymers and Tissue Adhesives and Sealants Therefrom

US Patent 20046699940 deals with a cyanoacrylate-based tissue adhesive or sealant composition comprising a cyanoacrylate capped heterochain polymer with two or more cyanoacrylate ester groups. The heterochain polymer used for capping is made up of one or more absorbable polymer such as, polyester, polyester-carbonate, polyether-carbonate, and polyether-ester. The capped polymer may be synthesized from polyethylene glycol or polypropylene glycol. Hetero-chain polymer capping is done using alkyl cyanoacrylate or an alkoxyalkyl cyanoacrylate such as ethyl cyanoacrylate or methoxypropyl cyanoacrylate respectively in the presence of phosphorus acids. Radiochemically sterilized formulations are used as sterile adhesives, sealants, or blocking agents in repairing mechanically or pathologically compromised internal organs or tissues or in blocking body conduits, such as blood vessels [51].

Cyanoacrylate capped heterochain polymers and their use as absorbable or non-absorbable tissue adhesives, sealants, blocking agents, and/or hemostatic adhesives in medical or non-medical applications has been covered. One aspect of this invention is covalent binding of cyanoacrylate func-tionality to a heterochain polymer molecule. The process of transesterification between a hydroxyl group and a simple cyanoacrylate ester to yield a cyanoacrylate capped heterochain polymer in the presence pyrophosphoric acid catalyst has been done. Another aspect of this invention is the preparation of cyanoacrylate-capped (CC) polyalkylene oxide or copolymers to produce a range of anionically fast polymerizing CC polyethers with a broad range of hydrophilic/hydrophobic content. The cyanoacrylate used is in the form of an alkyl or alkoxyalkyl ester. It also deals with prepartion of sterile adhesive or sealant formulations using radiochemical sterilization as per US Pat. 5,422,068.

Illustrations of this invention are provided in the two examples. 1) Preparation and curing of a tissue adhesive formulation comprising cyanoacrylate-capped polyethylene glycol-600 (PEG-600) and 2) Preparation and curing of tissue adhesive comprising cyanoacrylate-capped Triaxial Poly (ε-caprolactone-co-trimethylene carbonate) (TCT) and Ethyl Cyanoacetate (EC) [52].

Manufacture of Freeze-Dried Colchicine Microparticles as Anticancer Agent

CN Patent 1533765 deals with the manufacturing of freeze-dried colchicine microparticles. The preparation of these microparticles takes place in three steps, Step 1. To the solution of poly (vinyl alcohol) in distilled water sodium chloride is added to obtain isotonic solution as like blood plasma, Step 2. Colchicine and polycyanoacrylate are dissolved in organic solvent. The colchicine solution is fastly added to a solution of step 1 with constant heating and stirring, Step 3. Surfactants and freeze-drying agents are added and the mixture is subjected to vacuum freeze-drying to obtain the final products. The surfactants used may be tween-80, tween-20, span-80, span-20 or poloxamer. The organic solvent used can be chloroform, dichloromethane, and ethanol. The freeze-drying protecting agents may be one from glycine, sorbose, sorbitol, glucose, and lactose. As colchicin inhibits karyokinesis of cells, suppress proli-feration of cancer cells. These microparticles used in the treatment of mammary cancer, primary gout, hepatic injury and hepatic fibrosis [53].

Biodegradable Polymer Microparticles with Absorbed Polynucleotides Encoding Antigen and Adjuvant as Vaccine Against Tumor and Infection

WO Patent 04065578 deals with the synthesis and applications of microparticles with adsorbed polynucleotide. The microparticles comprised (a) one of the biodegradable polymer from a polyhydroxy butyric acid, a polyca-prolactone, a polyorthoester, a polyanhydride, or a poly-cyanoacrylate, (b) a cationic surfactant cetyltrimethyl-ammonium bromide and (c) a polynucleotide species adsorbed on the surface of the microparticles with at least 5 percent of polynucleotide species of total weight of said microparticles. Polynucleotide species includes immuno-logical adjuvants, such as CpG oligonucleotides, and polynucleotide species that encode polypeptide antigens such as RNA and DNA vector. These microparticles are used for delivering a therapeutic amount of a polynucleotide species to the host animal to stimulate an immunogenic response. They are also used for treating a host animal having a pathogenic organism infection and used as vaccines [54].

Vaccine Compositions Containing Phospholpid Adjuvant Against Infection and Cancer

WO Patent 04060396 deals with the immunogenic compounds containing phospholipid adjuvants, includes microparticle and emulsion compounds. According to the aspect of invention, an immunogenic microparticle compounds is provided that comprises: water; a polymer microparticle comprising a biodegradable polymer, e.g., a polymer selected from a poly (hydroxy acid), a polyhydroxy butyric acid, a polycapro-lactone, a polyorthoester, a polyanhydride, and a polycyano-acrylate; an antigen adsorbed to the microparticle; and a phospholipid compd., e.g., a synthetic phospholipid compd. comprising: (i) one or more phosphoryl groups indepen-dently selected from a phosphato group and a phosphodiester group; (ii) a plurality of linear alkane groups. According to another aspect of the invention an immunogenic emulsion compounds is provided that comprises: water; a meta-bolizable oil; an emulsifying agent; an antigen; and a phospholipid compounds, e.g., a synthetic phospholipid compounds. The emulsion compound is an oil-in-water emulsion having oil and aqoues phases, in which the oil phase is in the form of oil droplets. The antigen is viral, bacterial, fungal, parasitic or neoplastic antigen [55].

New Copolymer-Based Compounds and their Applications as Blood Substitutes and Cleansing Agents

FR Patent 2844512 deals with the new compounds useful as blood substitutes and cleansing agents comprise a hemo-protein associated with a copolymer sequence block conting an oligo or polysaccharide hydrophilic segment connecting to at least a hydrophobic segment. The nanoparticles of the title compounds was prepared by polymerisation of dextran

and iso-Bu cyanoacrylate and used to prepare an associated product with Hbs [56].

Polyester/Cyanoacrylate Tissue Adhesive Formulations

US Patent 20046723114 invention is directed to bioadsorbable adhesive/hemostatic formulations of a 2-alkoxyalkylcyanoacryalate and liquid or solid polymeric modifiers and adjuvant. The present adhesive formulations are useful as tissue adhesive/sealants, hemostatic agents, and as a means for patching or anastomic coupling of damaged organs.

In one aspect, the present invention is directed to a bioadsorbable adhesive formulation, which is an admixture of 2-alkoxyalkylcyanoacrylate and an oxalate polymer of polyethylene glycol, wherein the polyethylene glycol has an average degree of polymerization of more than 4 [57].

Polyoxyethylene Grafted Polycyanoacrylate for Drug Delivery and its Preparation

CN Patent 1417242 is related to the polyethylene glycol grafted polycyanoacrylate, used to prepare the nanocapsules of taxol, ibuprofen hydrophobic drug via self-assembly. The graft is prepared by reacting one side-terminated polyethylene glycol with maleic anhydride at 65-120°C under vacuum for 2-8 h. The obtained monoacrylate polyoxyethylene alkyl ether further refluxed with diiso-cyanate at 70-90°C for 2-5 h and 2-hydroxyalkyl metha-crylate at <50°C. The product is mixed with alkyl cyano-acrylate and polymerizes in the presence of an initiator [58].

Method for High-Pressure Sterilization of Pharmaceu-tical Compositions in Micro- or Nanodispersed Form

FR Patent 2838969 granted to sterilization process without degrdation of a pharmaceutical compound in a micro-dispersed or nanodispersed form comprises an active ingredient, characterized in it uses high pressures of 200-1000 MPa, preferably 300-800 MPa. Thus, nanospheres were prepared containg poly(hexadecyl 2-cyanoacrylate)and PEG acrylate. The nanospheres were subjected to high-pressure sterilization [59].

Occlusive Composition Comprising Poly (2-Cyanoacrylate)

US Patent 2003194389 this invention provides an occlusive compound comprising: (a) a poly(2-cyano-acrylate) monomer, and (b) a visualization agent. The present invention also provides a method for creating a solid mass in an ionic fluid-contining bodily cavity within a living organism, comprising delivering into the bodily cavity a clinical sufficient amount of an occlusive compound preperation of poly(2-cyanoacrylate) deriv. of iopamidol was exemplified [60].

Composite Bone Material Implant and Method

US Patent 2003036800 relates to a method of forming a bone composite of the desired shape. The binder is a biological adhesive, bioactive glass ceramic, dental resin sealant, glass ionomer cement, gelatin-resorcinol-form-aldehyde glue, collagen-based glue, cellulosic, bioabsorbable polymer, non-bioabsorbable polymer, starch/ethylene-vinyl alc. copolymer, polycyanoacrylate, or polyphosphazene. The composites may be, used, a bone pin, screw, or prosthesis [61].

Adherable Biomaterial Patches and Methods for Producing and for Using Same

US Patent 20036632450, invention relates to a method for producing an adherable biomaterial patch. The patch is capable to join onto a tissue substrate. The invention is also directed to the patch and producing the biomaterial patch, which is joined onto a substrate. These preferred patch are exess in a highly acidic environment. The invention comprises providing a biomaterial patch consisting essentially of elastin or an elastin base biomaterial having at least one outer surface. Other at least one outer surface of the biomaterial patch is treated with a selected cyanoacrylate adhesive to produce an adherable biomaterial patch.

A biomaterial patch include of selected cyanoacrylate adhesive effectively seal an injury of the gastrointestinal system, the pulmonary system, or vascular system, thereby preventing leakage from that organ. The biomaterial patch, of elasin, or an elastin biomaterial, served as an effective physical and chemical barrier for repair of injuries, which occur in human body, particularly in portion of body, which can exhibit highly acidic environments. Typically, the biomaterial patch tissue seal formed is water tight in nature. The biomaterial patches of the present invention are non-toxic, non-inflammatory, sterilizable, biodegradable, flexible and exhibit excellent strength properties. The patch-tissue seal can be formed within minutes so that repair procedure can be per formed quickly and maintained in place during the healing process.

The biomaterial patch material is relatively chemically inert. Therefore, it provides sufficient resistance to degradation by, if need be, highly acidic contents, to allow healing. Using a tissue adhesive as opposed to traditional suture, a modified cyanoacrylate-based adhesive, biomaterial patch can be quickly applied. Then, the patch typically achieved a fluid-tight or air-tide seal and they're by decreases the rate of infection, air or fluid leaks that may be deleterious to haling and tissue health.

Other considerable properties of these patchs are it is sterilizable, immunogenic, and resistance to digestive enzymes and acids. This combination of biomaterial patch, and tissue adhesive joined the patch onto the tissue for a period of time sufficient to facilitate healing of the damaged tissue, and provide an innovative approach to repair of these injuries by decreasing post-operative complications, by increasing chances of full functional recovery [62].

Method of Treatment of a Wound or Incision

US Patent 20026479725 deals with an incision or wound dressing comprises polymerized multilayers of 2-octyl cyanoacrylate adhesive applied to a wound or incision site. Each layer covers the site and extending to at least about 5 mm from each side of the site [63].

Flavored Cyanoacrylate Compositions

US Patent 20026352704 reported a sterile or non-sterile flavored monomeric adhesive composition applied to skin or inside of the mouth. The flavored adhesive composition is

prepared from α-cyanoacrylate monomers. The adhesive properties of α-cyanoacrylate monomers and polymers are discovered for their wide use in numerous applications such as bonding plastics, rubbers, glass, metals, wood and biological tissues. α-cyanoacrylate adhesive composition applications include its use as an alternate and adjunct to surgical sutures and staples in wound closure, for covering and protecting open surface wounds. α-cyano-acrylate compositions used in mouth or on surface skin, to be sterilized before application [64].

Various flavored 2-octyl cyanoacrylate monomer compositions are prepared by adding a selected amount of a flavorant to 2 mL of 2-octyl cyanoacrylate monomer. Specific flavorants and the respective amounts added are identified in Table **1**.

Vascular Embolization with an Expansible Implant

US Patent 20026500190 describes a vascular implant of a compressible foam material expands to the shape and size of a vascular site to be embodied. The implant is formed of a hydrophobic, macro porous foam material having a configuration of vascular site model. The implant is compressed and passed through a micro catheter to embody a vascular site. The implant expands in situ substantially to fill the vascular site when enters the vascular site. A flexible tubular element is used to pass the implant and the retention element through the micro catheter to separate the implant from the retention element when the implant has been passed out of the micro catheter and into the vascular site.

The present invention used as a device for occluding a vascular site, such as an aneurysm, comprising a conformal vascular implant made up of an expansible material. The implant is a water-swelling foam matrix formed as a macro porous solid comprising a foam stabilizing agent and a polymer or copolymer of a free radical polymerizable hydrophobic olefin monomer cyanoacrylate cross-linked with up to about 10% by weight of a multiolefin-functional cross-linking agent. The invention provides an effective vascular embolization implant that can be deployed within a vascular site with excellent locational control with a lower risk of vascular rupture, tissue damage, or migration than with prior art implant devices. Furthermore, the implant device, modelled on the actual vascular site in which it is to be implanted, affects a conformal fit within the site that promotes effective embolization. It is delivered to the site in a highly compressed configuration facilitates precise and controllable deployment with a micro catheter. In addition, the method of fabricating the implant device, by modeling it on each individual site, allows implant devices to be made that can effectively embolism vascular sites of different sizes, configurations, and neck widths [65].

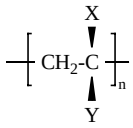
Block-Structure Copolymer Consisting of a Saccharide Segment Bound to at Least a Biodegradable Hydrophobic Segment, and Corresponding Particles

WO Patent 02039979 concerns a block-structure copolymer consisting of a hydrophilic saccharide segment and at least a biodegradable hydrophobic segment of general formula I, wherein: X represents a CN or CONHR radical; Y

Table 1.

Example	Flavorant	Amount Added	Notes @ -1 min	Notes @ 24+ Hours
1	5-Fold Orange Oil	100 uL	Dark Yellow Solution	Dark Yellow Solution
2	Anethole	100 uL	Clear Solution	Clear Solution
3	Banana Distillate	100 uL	2 phase solution	Cloudy Solution
4	Benzaldehyde	100 uL	Clear Solution	Clear Solution
5	Clove Oil	400 uL	Clear Solution	Clear Solution
6	Cold Pressed Valencia Orange Oil	100 uL	Yellow Solution	Yellow Solution
7	Cold Pressed Grapefruit Oil	100 uL	Light Yellow Solution	Light Yellow Solution
8	Cold Pressed Lemon Oil	100 uL	Light Yellow Solution	Clear Solution
9	Cold Pressed Lime Oil	100 uL	Dark Yellow Solution	Yellow Solution
10	Cucumber Distillate	100 uL	2 phase solution	Cloudy Solution
11	Honey Distillate	100 uL	2 phase solution	Cloudy Solution
12	Menthol	100 mg	Clear Solution	Clear Solution
13	Methyl Salicylate (Oil of Wintergreen)	400 uL	Clear Solution	Clear Solution
14	Peppermint Oil	400 uL	Clear Solution	Clear Solution
15	Thymol	20 mg	Clear Solution	Clear Solution
16	Vanillin	20 mg	Clear Solution	Clear Solution

represents a COOR', CONHR" radical with R, R' and R" representing, independently of each other, a hydrogen atom, a linear or branched C1-C20 alkyl group, a linear or branched C1-C20 alkoxy group, an amino acid radical, a monohydroxylated or polyhydroxylated radical or a C5-C12 aryl or heteroaryl radical, said saccharide segment being bound either by one of its ends to a single segment of general formula I, or by each of its two ends, to a segment of general formula I, the two hydrophobic segments being identical or different. The invention also concerns particles based on said copolymer and a corresponding prepn. method. Iso-Bu cyanoacrylate was copolymd. with heparin. The anti-coagulation factor Xa of heparin-iso-Bu cyanoacrylate copolymer was 408 IU/mL [66].



US Patent 20056881722 deals with the use of the polypeptide Saratin in the manufacturing of medicaments having capability to decrease significantly platelet adhesion and platelet accumulation after vascular injuries or endar-terectomy. It also relates to the use of saratin as a thrombosis inhibitor and intimal hyperplasia, wherein the saratin polypeptide used locally as a topical agent or as a coating on, or associated with medical devices. The invention reports the inhibition of vWF-dependent binding of platelets to vascular wall collagens under elevated conditions to a use of saratin in various medicinal applications.

In general, this invention involves the introduction of platelet adhesion inhibitor saratin into or onto a specific location within or on a lumen in a tissue. Saratin is used locally as a topical agent or a adherent coating on the surface and prevents an undesirable thrombotic and/or restenotic response to vessel wall injury. These includes, injury in angioplasty, stents, dialysis graftsand other vascular grafts, and the treatment of benign hypertrophic scar formation, as well as the treatment and passivation of unstable athero-sclerotic plaques [67].

WO Patent 0056885 on saratin is described recombinant protein originally isolated from a leech. The protein inhibits vWF-dependent binding of platelets to arterial wall collagens under conditions of elevated conditions to makes saratin suitable to inhibit arterial thrombosis. It can be also used as a topical agent at the site of injury and decreases the thrombosis and or intimal hyperplasia without any systemic effects. This represents a modal with specific and localized effects for application by both surgeons and interventional radiologists alike. Saratin combines with different therapeutic agents for on-site delivery. Examples for use in coronary-artery applications are anti-thrombotic agents, e.g., prostacyclin and salicylates, thrombolytic agents, e.g., streptokinase, urokinase, tissue plasminogen activator (TPA) and anisoylated plasminogen-streptokinase activator com-plex (APSAC), vasodilating agents, i.e., nitrates, calcium channel blocking drugs, anti-proliferative agents, colchicine and alkylating agents, intercalating agents, growth modu-lating factors such as interleukins, transformation growth factor-beta and congeners of platelet derived growth factor, monoclonal antibodies directed against growth factors, anti-inflammatory agents, both steroidal and non-steroidal, and other agents that can modulate vessel tone, function, arteriosclerosis, and the healing response to vessel or organ injury post intervention. Antibiotics may be included in combinations or coatings comprised by the invention. Moreover, a coating is used to for pharmaceutical delivery focally within the vessel wall. Incorporation of the active agent in a swellable polymer the active agent released on swelling of the polymer. The coating is made of a hydro-gel, such as polyethylene oxide, albumin, hydrophilic poly-methacrylates and hydrophilic polyurethanes. This invention comprised to use for catheter-based devices to deliver saratin locally. The catheter is capable to maintain a high concentration of drug in the selected vessel space to give an improved vessel coating with saratin alone or with additional treatment agents [67].

Methods for Embolizing a Target Vascular Site

US Patent 20016299619 reported an embolization device along a filamentous carrier. The carrier used is of a suitable length, thin, highly flexible filament made up from nickel or titanium alloy. The embolizing elements are separated on the carrier by radiopaque spacers of highly flexible microcoils made of platinum or tungsten alloy. Embolizing elements are hydrophilic, macroporous, cyano-acrylate, hydrogen foam material. The device is particularly suited for embolizing a vascular site such as an aneurysm. The embolization bodies have an initial configuration in the form of small, cylindrical "micropellets" of small sufficient diameter to fit within a microcatheter. The bodies are hydrophilically expansible into an expanded configuration in which they conform to and fill the vascular site on con-necting to the carrier. A method for embolizing a vascular site using this device includes the steps of: (a) passing a microcatheter intravascularly; (b) providing a vascular embolization device of highly expansible embolizing elements carried on a filamentous carrier and separated from each other on the carrier by microcoil spacers; (c) passing the embolization device through the microcatheter into the vascular site; and (d) expanding the embolizing elements in situ substantially to fill the vascular site while retaining the embolizing elements on the carrier. Preferably, the method also includes the step of deploying a vaso-occlusive device in the vascular site, or an intravascular device in a blood vessel adjacent the vascular site, before embolization device is passed through the microcatheter [68].

Cyanoacrylate Compositions with Vinyl Terminated Ester Groups

US Patent 20016174919 is directed to useful monomer compositions in industrial, consumer or medical adhesives, sealants and methods of applying such compositions. The present investigation is reported the monomeric cyano-acrylate compositions with vinyl terminated ester groups that cross-link via vinyl group and its uses in biomedical applications. In embodiments, the chemical durability, flexibility and elasticity of the resulting polymers or copoly-mers may be increased with reduction in degradability. In addition, high temperatures or ultraviolet initiators may not be needed for cross-linking. Wherein the substitutes R_1 is alkyl, alkoxy, anhydride, ether, ester, or amide, and R_2 and

R_3 are independently alkyl, alkoxy, hydrogen, hydroxy, alkenyl, ester, carboxylic acid, ether, or electron withdrawing groups such as halogens, amides, cyanos, esters, acids and ethers. The R_1 group extends the distance of R_2 and R_3 groups away from the carbonyl group making them more chemically accessible and improving chemical durability, flexibility and elasticity of a polymer comprising the monomer. In embodiments the adhesive may also contain heat and/or light initiators and to initiate cross-linking of the cyanoacrylate compounds. Specific initiators are readily selected for particular systems without undue experimentation. Suitable initiators used in polymerization of cyanoacrylate composition includes nonionic surfactants polysorbate 20 (Tween 20™), polysorbate 80 (Tween 80™) and poloxamers. Aminopyridine and dimethylaminopyridine used as an initiator for cyanoacrylate as well as for the radical polymerization of the vinyl moiety [69]. US Patent 3940362 reports, a catalytic amount of amine may be added to initiate polymerization of the cyanoacrylate monomer/ crosslinking agent blend. The composition contains one or more adjuvant substances such as thickening agents, medicaments to improve the medical utility of the monomer in medical applications.

The monomer compositions and their polymers are used as tissue adhesives, sealants, for preventing bleeding or for covering open wounds and in other biomedical applications. They also used in apposing surgically incised or traumatically lacerated internal and/or external tissues; setting fractured bone structures; retarding blood flow from wounds; drug delivery; dressing burns; and aiding repair and regrowth of living tissue. This composition may include at least one plasticizing agent that imparts flexibility to the polymerized monomer formed on the wound or incision. The plasticizing agent preferably contains little or no moisture and should not significantly affect the polymerization of the monomer.

US Patent 5624669 reported the hemostatic procedures for sealing punctures and incisions in blood vessels and internal organs using a cyanoacrylate monomer. Although the cyanoacrylate may polymerize and cross-link *in vivo*, it is achieved without any external sources of physical initiation such as irradiation.

US Patent 4134929 investigates a polymerizable allyl 2-cyanoacrylate monomer containing organic peroxide free radical to provides crosslinking of a difunctional monomer diester with the allyl 2-cyanoacrylate.

US Patent 4136138 investigates a polymerizable allyl 2-cyanoacrylate monomer containing organic peroxide free radical to provides crosslinking of a difunctional monomer diester with the allyl 2-cyanoacrylate. The allyl 2-cyanoacrylate-based adhesive compositions are especially useful as dental adhesives.

US Patent 3975422 reporeted difunctional monomers derived from diol or dihalide. These difunctional monomers are worked as crosslinking agents for 2-cyanoacrylates esters. Copolymerized compositions of these mono and difunctional monomer blends are usedl in dental applications as adhesives.

New Process of Obtaining Cyanoacrylate Monomers as Medical Adhesives and Cyanoacrylate Nanoparticles for Drug Delivery Systems (Not Yet Granted)

Portugal Patent application 2007-07-11 describes the new and simple process in reactor designing which does not involve the formation of liquid wastes and excludes the use of hazardous inhibition gases.

As compared to the other methods, this method is cleaner, faster and simple. Thus, the finished monomer product obtained at a low cost. This process allows the production of other types of adhesive after further validation and the development of a significant product pipeline. Another advantage of this technology is prepared cyanoacrylate monomers are used in the synthesis of nanostructured homo and copolymeric poly(cyanoacrylates). Various cyanoacrylate nanoparticlulate medical products are already in clinical development for cancer therapy. The cyanoacrylate nanoparticles allow lowering the dose of the anti-tumor drug and target drug directly to the tumor location. Recent investigations resulted in developing a process transforming the cyanoacrylate monomers of various sizes in the middle and upper nanometer range.

CURRENT & FUTURE DEVELOPMENTS

Cyanoacrylate adhesives provide unique benefits for use them in medical device manufacturing processes. Advances in cyanoacrylate technology have led to the development of a wide variety of adhesives offering performance and process improvements for device manufacturers. Some of their products include surface-insensitine cynoacrylates which are well on acidic surfaces. Low-bloom cynoacrylates after low-irritating order; rubber toughened cynoacrylates have improved peel strength and impact resistance. Whereas, thermally resistant cynoacrylates provide long-term performance up to maximum temperature of 250°F. The latest generation of thermally resistant cynoacrylates combines the benefits of rubber toughening and surface insensitivity with thermal resistance. Thermal resistant cynoacrylates products are used as perform of structural adhesive. The use of different poly cynoacrylates improves the biological performance significantly.

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