(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 June 2016 (16.06.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/093788 A1

(51) International Patent Classification:
A61K 49/00 (2006.01) *A61B 5/01* (2006.01)

(21) International Application Number:
PCT/TR2015/050244

(22) International Filing Date:
10 December 2015 (10.12.2015)

(25) Filing Language: Turkish

(26) Publication Language: English

(30) Priority Data:
2014/14971 11 December 2014 (11.12.2014) TR

(72) Inventor; and
(71) Applicant : **IŞILDAK, Ibrahim** [TR/TR]; Yıldız Teknik Üniversitesi Davutpaşa Kampüsü Teknopark Kuluçka Merkezi No:126, Esenler/İstanbul (TR).

(72) Inventors: **ŞENEL, Ilkay**; Ali Rıza Gürcan Cad. Gürpınar Sk. No:5/26, Merter, İstanbul (TR). **ALTIKATOĞLU, Melda**; Yıldız Teknik Üniversitesi Fen-Edebiyat Fakültesi Kimya Bölümü, İstanbul (TR).

(74) Agent: **DESTEK PATENT, INC.**; Lefkoşe Cad., NM Ofis Park B Blok No:36/5, Beşevler, 16110 Bursa (TR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: AN EJECTABLE OR SPRAYABLE MIXTURE PROVIDING BLOOD VESSEL IMAGING

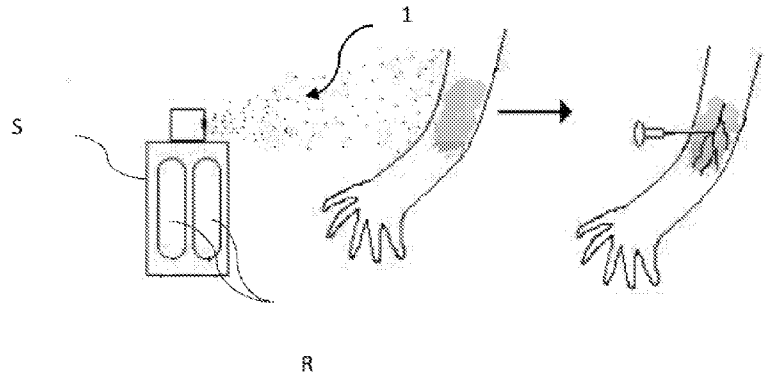

Figure 3

(57) Abstract: The present invention relates to an ejectable or sprayable mixture (1) for blood vessel imaging comprising at least two solutions, which comprise thermochromic components, monomer and/or polymers and/or biocompatible monomer and/or polymers, at least one redox couple which polymerizes via cross linking and rapid polymerizing reaction.

WO 2016/093788 A1

DESCRIPTION

AN EJECTABLE OR SPRAYABLE MIXTURE PROVIDING BLOOD VESSEL IMAGING

The Related Art

The invention relates to a mixture that can be used in certain therapeutic or healthcare-related applications to provide blood vessel imaging and a spray device by which this mixture is applied. The invention particularly relates to a spray device containing a sprayable hydrogel or polymer in order to ensure imaging of blood vessel on the basis of temperature difference due to a thermochromic substance it comprises.

The Prior Art

Medical applications and tests used in healthcare generally comprise taking a blood sample and analyzing this sample or injecting liquid into the blood vessel of the patient. In order to reach a blood vessel of a patient or a healthy person, of course, first of all, the location of the blood vessel should be determined. While locating the blood vessel is not difficult if the vessel is visible or apparent, usually an elastic band is tied down between the point of injection and the hearth of the patient in order to increase visibility or apparency. This method called as tourniquet does not provide good results in people with dark skin, children, and obese people, and also causes psychological and physiological problems in patents. Nowadays, not being able to find the blood vessels during injection and bloodletting operations becomes a significant problem for many people. Especially little children whose blood vessels are not completely developed yet, obese people, and patients who have received chemotherapy, it is harder to feel and see the blood vessels, bloodletting, and/or injecting liquids to the patient. The difficulty in finding the vascular access in babies and little children causes significant stress and psychological pressure on the child, relatives, and healthcare professionals.

Various techniques have been developed in order to determine the positions of blood vessels and improve their visibility. One of these methods comprises the technique of using infrared light to make the blood vessels visible during injection and bloodletting operations. Another one comprises viewing blood vessels via ultrasound. Both of these methods are expensive and also

they are not easy to use in blood vessel imaging over the skin, and therefore, they are not preferred.

Medical personnel and clinical researchers have focused on thermal techniques that are simple and effective in determining the positions of blood vessels below the skin surface. The thermal technique is based on the fact that the temperature of skin around areas adjacent to a blood vessel is higher than the temperature of the skin at the remaining parts. For determining this region that has higher temperature, liquid crystal and thermochromic substances that change colour at the desired temperatures are used.

The document No. US3998210 encountered in the known status of the art describes the use of liquid crystal capsules for finding blood vessels within the body.

On the other hand, hydrogel structures with thermochromic characteristics have been developed for providing solution to said problem. One of these applications is disclosed in Document No. CA2772555 A1. However, these hydrogel structures do not provide functionality in practical use, since they are pre-formed structures.

Therefore, need has occurred for simple, useful, and economical methods providing imaging and determination of blood vessels in a quick and effective manner.

Brief Description of the Invention

The purpose of the invention is to form an ejectable blood vessel imaging mixture for imaging and determining vascular accesses, comprising a hydrogel and/or polymeric formulation with thermochromic substance(s).

With the present invention, blood vessels can easily be observed and made apparent in relation to invasive applications.

Moreover, for instance, by means of imaging the temperature difference obtained due to higher veining in cancerous tissues than normal tissues, preliminary diagnosis of skin cancer, breast cancer etc. peripheral cancerous tissues can be easily made.

The ejectable or sprayable mixture for blood vessel imaging according to the invention it comprises at least two solutions comprising thermochromic components, monomer and/or polymers and/or biocompatible monomers and/or polymers.

The ejectable or sprayable mixture according to the invention may comprise an anti-microbial and painkiller agent or a combination thereof in low levels in dispersed form.

The ejectable or sprayable mixture for blood vessel imaging according to the invention comprises at least one redox couple, which is polymerized by cross-linking and rapid polymerization reaction, and in which each oxidizing agent is found in a solution, while each reducing agent is found in another solution.

The ejectable or sprayable mixture for blood vessel imaging according to the invention comprises at least two solutions, each of which comprising monomer and/or polymer structures and/or biocompatible monomers and/or polymers, thermochromic components, and a redox couple. The thermochromic components found in the ejectable thermochromic substance have colour-switching characteristics with regard to temperature difference.

The ejectable or sprayable mixture according to the invention is used for blood vessel imaging and determination purposes in the main application of the invention.

The ejectable or sprayable mixture for blood vessel imaging according to the invention comprises the redox couple as two individual agents, one being an oxidizing agent in a solution, while the other being a reducing agent in another solution. The mixture preserved in two separate media, is combined at the moment of application on the skin.

The ejectable or sprayable mixture for blood vessel imaging according to the invention comprises a reaction initiating agent in the first solution and a reduction agent in the second solution as the redox couple.

The redox couples, oxidizing, or reducing agents used in the ejectable or sprayable mixture for blood vessel imaging according to the invention are selected from peroxydiphosphate systems, organic-inorganic redox couples (For instance oxidation via Ce^{+4}), and besides the redox type, thermal free radical initiators that cause initiation at low temperatures.

The oxidizing or reducing agents used in the ejectable or sprayable mixture according to the invention are selected from Ferric/Ferrous, Cupric/Cuprous, Seric/Serous, Cobalt (II)/Cobalt (III), Vanadate (V)/Vanadate (VI), permanganate, Manganic/Manganese, and peroxygen-containing compounds, for instance, peroxides and hydrogen peroxides, benzyl peroxide, t-butyl hydroperoxide, t-butyl peroxide, benzoyl peroxide, and cumyl peroxide.

The biocompatible polymer and/or monomer and/or polymers and/or monomers found in the solutions used in the ejectable or sprayable mixture according to the invention are selected from polymers and/or monomers suitable for physical and/or chemical cross linking.

The polymer and/or monomer and/or biocompatible polymers and/or monomers found in the solutions used in the ejectable or sprayable mixture according to the invention are selected from among polymers with ionic structure suitable for physical cross linking, metal ions with divalent cationic structure, poly(styrene), poly(caprolactone), poly(oxyethylene), poly(butadiene), poly(n-alkylacrylamide) etc. other block and graft copolymers of water soluble and insoluble polymers, some natural polymers such as gelatine and glucosaminoglycans, and pH-sensitive polymers and/or monomers.

The polymers with ionic structure used in the ejectable or sprayable mixture according to the invention are selected from alginates, xanthan gums, gum acacia, natural gum, agar, agarose, seaweed, fucoidane, furcellarane, laminarane, hypnea, eucheuma, karaya gum, arabinogalactan, pectin, and amylopectin.

The biocompatible polymers and/or monomers used in the ejectable or sprayable mixture according to the invention are selected from large monomers and polymers comprising all small or polymerizing groups such as acrylic acid and vinylprolactam that can form a biocompatible surface coating via chemical and/or physical cross linking.

The biocompatible monomers and/or polymers used in the ejectable or sprayable mixture according to the invention are selected from acrylic acid, vinylcaprolactam, polyethylene glycol diacrylate, polymers comprising ethylene unsaturated groups, PVA (Polyvinyl alcohol) and derivatives, PVP (Polyvinylpyrrolidone) and derivatives, polyacrylic acid and derivatives, polyacrylamides and derivatives, hydroxypropyl methacrylamide and derivatives, divinyl ether

anhydride and derivatives, polyoxazoline and derivatives, polyphosphates and derivatives, polyphosphazenes and derivatives, polyethylene glycol and derivatives.

The thermochromic components used in the ejectable or sprayable mixture according to the invention are selected from thermochromic dye and ink, liquid crystals (e.g. cholesteryl pelargonate, cholesteryl benzoate, cholesteryl oleyl carbonate etc.), other thermochromic materials or polymers that change colour with the impact of heat such as NIPAAM.

The thermochromic substance used in the ejectable or sprayable formulation according to the invention comprises thermochromic components that change colour at different temperatures (28-40℃) for use at different blood vessel temperature s.

The thermochromic components, monomers and/or polymers and/or biocompatible monomers and/or polymers, and redox couples found in both of the solutions used in the ejectable or sprayable mixture according to the invention have suitable characteristics for chemical, mechanical, or electronic ejection and transformation into sprayable forms.

The ejectable or sprayable mixture for blood vessel imaging according to the invention forms a hydrogel layer on the skin in 1 to 120 seconds, after it is applied on the skin. Following application, the thickness of the gel to be formed on the skin can be between 0.001 to 10 mm. Said gel thickness can preferably be between 0.1 mm to 4 mm.

When the ejectable or sprayable mixture according to the invention is applied on the skin, the gel formed on the skin surface comprises pores, into which injectors or catheters used in invasive applications can enter.

The ejectable or sprayable mixture according to the invention may also comprise antibiotic, antiseptic, and analgesic substances, besides the monomers and/or polymers and/or biocompatible monomers, thermochromic components, and redox couple.

The ejectable or sprayable mixture according to the invention is also used in early diagnosis of cancers such as skin and breast cancer by making use of the thermal difference that occur between the cancerous tissue and normal tissue, since cancerous tissues have more blood vessels than normal tissues.

The ejectable or sprayable mixture according to the invention is placed in a bottle or container comprising at least two sections and ensuring ejection or spraying.

Brief Description of the Figures

Figure 1 is a schematic view of the spray and the bottle of the spray according to the invention that comprises thermochromic substance and ensures imaging blood vessels.

Figure 2 is a view of the spray and the bottle of the spray according to the invention that comprises thermochromic substance and ensures imaging blood vessels, during application on forearm surface.

Figure 3 is a view of the spray and the bottle of the spray according to the invention that comprises thermochromic substance and ensures imaging blood vessels, showing the thermal appearance of blood vessels following the application made on the forearm surface as in Figure 2.

Description of References

The parts found in the attached figures according to the purpose of the invention are enumerated respectively and the corresponding reference numbers for these parts are given below.

1. Mixture comprising a thermochromic substance, redox couples, and hydrogel and/or polymer molecules, and having ejectable or sprayable characteristics.

S. Container or bottle

R. Sections

Detailed Description of the Invention

The mixture (1) for blood vessel imaging according to the invention comprises one or more thermochromic substances that change colour at different temperatures and it is formed of two separate solutions found in two separate sections.

The ejectable or sprayable mixture (1) for blood vessel imaging according to the invention comprises a monomer and/or polymer structure and/or a biocompatible polymer and/or monomer

structure with hydrogelling and polymerizing characteristics and it is formed of two separate solutions found in two separate sections.

The mixture (1) for blood vessel imaging according to the invention is also formed of two separate solutions each comprising a different redox couple in the two separate sections.

The mixture (1) for blood vessel imaging according to the invention may also comprise antibiotic, antiseptic, and analgesic substances, besides the monomers and/or polymers and/or biocompatible monomers, thermochromic components, and redox couple.

The solution comprising the thermochromic substance, redox couples, and monomer and/or polymer molecules is found in two separate sections found within the spray bottle, and it has ejectable characteristic and fluidity.

The redox couples found in the ejectable or sprayable mixture (1) for blood vessel imaging according to the invention may be preserved in two separate media and combined at the moment of application on the skin.

The monomers and/or polymers found in the mixture (1) for blood vessel imaging according to the invention have suitable structure for cross linking via physical and/or chemical method.

Physical cross linking is performed by intermolecular or intramolecular bonding. Intermolecular linking, for instance, can be performed between the ionic-structure polymers and the divalent cationic-structure metal ions. Therefore, the monomers and/or polymers found in the mixture (1) comprising the thermochromic substance, redox couples, and monomer and/or polymers for blood vessel imaging can be ionic-structure polymers presenting physical cross linking.

Said ionic-structure polymers are selected from among alginates, xanthan gums, gum acacia, natural gum, agar, agarose, seaweed, fucoidane, furcellarane, laminarane, hypnea, eucheuma, karaya gum, arabinogalactan, pectin, and amylopectin.

Moreover, the polymer and/or monomer and/or biocompatible polymers and/or monomers found in the solution (1) for blood vessel imaging can be selected from other block and graft copolymers of

water soluble and insoluble polymers, e.g. poly(styrene), poly(caprolactone), poly(oxyethylene), poly(butadiene), since the hydrophobic interactions cause physical cross linking.

The polymers and/or monomers found in the mixture (1) for blood vessel imaging according to the invention can also be selected from poly(n-alkylacrylamide), gelatine and glycosaminoglycans etc. other natural polymers and pH-sensitive polymer and/or monomers, which can perform bonding via physiological temperature which is another factor that may cause physical cross linking.

The biocompatible polymers and/or monomers found in the mixture (1) for blood vessel imaging according to the invention may be selected from among large monomers and polymers comprising all small or polymerizing groups that can form a biocompatible surface coating and generate chemical cross linking. For instance, they are selected from acrylic acid, vinylcaprolactam, polyethylene glycol diacrylate, ethylene, polymers comprising unsaturated groups, PVA (Polyvinyl alcohol) and derivatives, PVP (Polyvinylpyrrolidone) and derivatives, polyacrylic acid and derivatives, polyacrylamides and derivatives, hydroxypropyl methacrylamide and derivatives, divinyl ether anhydride and derivatives, polyoxazoline and derivatives, polyphosphates and derivatives, polyphosphazenes and derivatives, polyethylene glycol and derivatives.
The mixture (1) for blood vessel imaging according to the invention comprises biocompatible polymers and/or monomers and provides application opportunity without harming the body of patients.

The thermochromic components found in the structure of the mixture (1) for blood vessel imaging according to the invention are selected from thermochromic dyes and inks, liquid crystals (e.g. cholesteryl pelargonate, cholesteryl benzoate, cholesteryl oleyl carbonate etc.), other thermochromic materials or polymers that change colour after gelling without addition of any thermochromic substance, such as NIPAAM.

The mixture (1) for blood vessel imaging according to the invention is either kept separately in at least two different sections (R) within a closed container (S) to be combined later on via spraying or kept in two separate spray containers. Both of the solutions forming the thermochromic substance comprise a thermochromic component and a biocompatible monomer and/or polymer. The first solution further comprises reaction initiating components and the second solution further comprises reduction agents. The solutions (1) comprising the thermochromic substance; after being sprayed through two separate routes from the sections where they are stored, the reaction initiating

components found in the first solution and the reduction agents found in the second solution are combined on a spraying surface and electron transfer occurs. The electron transfer occurring causes the reaction initiators to be decomposed into a free radical and an anion. The free radical formed initiates polymerization by reacting with the monomer chain.

The redox couples found in two different solutions in two different sections that form the mixture (1) for blood vessel imaging according to the invention are selected from metal ions that one of them used as oxidizing and the other one used as reducing, peroxydiphosphate systems, organic-inorganic redox couples (For instance oxidation via Ce^{+4}), and besides the redox type, thermal free radical initiators that cause initiation at low temperatures.

The metal ions that can be used as oxidizing agents or reducing agents are selected from Ferric/Ferrous, Cupric/Cuprous, Seric/Serous, Cobalt (II)/Cobalt (III), Vanadate (V)/Vanadate (VI), permanganate, Manganic/Manganese, and peroxygen-containing compounds, for instance, peroxides and hydrogen peroxides, benzyl peroxide, t-butyl hydroperoxide, t-butyl peroxide, benzoyl peroxide, and cumyl peroxide.

In an embodiment of the invention, the biocompatible monomer and/or polymer found in both solutions comprising thermochromic components, for instance, specifically comprise PEDGA monomer. In this embodiment, hydrogen peroxide is found in the first solution as reaction initiator component, and iron-II gluconate is found in the second solution as reduction agent.

In this embodiment, hydrogen peroxide is combined with the iron-II gluconate found in the second solution as reduction agent, and electron transfer occurs from the iron ion to the peroxide ion. The electron transfer occurring causes the peroxide to be decomposed into a free radical and an anion. The free radical formed initiates and sustains polymerization by reacting with the monomer chain.

In this embodiment, the 1st solution comprises: 580 ppm hydrogen peroxide, 3000 ppm ascorbic acid, 10ml 10% PEGDA polymer, and 0.3 g thermochromic ink; The 2nd solution comprises: 1000 ppm iron gluconate, 3000 ppm ascorbic acid, 10ml 10% PEGDA polymer, and 0.3 g thermochromic ink.

When the monomer and/or polymer structures found in the solutions and the redox couples found in separate sections are combined via spraying, cross linking occurs with a sudden polymerization

and the hydrogel or polymer is formed, in which the thermochromic component would be kept. Said cross linking may be physical and/or chemical cross linking.

Following application via physical and/or chemical cross linking; the thermochromic components are kept in the ejectable or sprayable mixture (1) that turns into a polymeric gel form, and thus it is prevented from flowing off the skin surface on which it is applied.

The components of the first solution and the second solution found in the ejectable or sprayable mixture (1) for blood vessel imaging according to the invention have suitable characteristics for chemical, mechanical, or electronic ejection methods, by which the solutions are turned into spray form.

The thermochromic components and the ejectable solutions are found in two separate sections (R) at certain volumes such as 50 cc or 100 cc. Both of the solutions are sprayed through individual carrier channels allocated for them and applied on the skin surface. The solutions are preserved in this two-section container, which comprises aerosol, and which is suitable for spraying.

Since the redox couples found in the solutions (such as hydrogen peroxide and iron-II gluconate) would form a free radical and then form hydrogel by cross linking the biocompatible monomer and/or polymer (such as PEGDA monomer) at the moment they come together, the two-section redox system is kept separate from each other until the moment of use.

The aerosol propellants required for transforming the solutions found in the container and comprising monomer, polymer, thermochromic component, and redox couples into ejectable form can be placed into the container via cold filling or pressurized filling method. When the triggering button found on the container is pressed, the first solution and the second solution found in the sections (R) are ejected through the carrier channel found in the container (S). Just a little before getting out, or in other words, at a small distance from the exit, the two-section redox system is combined and mixed.

The mixture (1) for blood vessel imaging according to the invention turns into a hydrogel layer on the skin in 1 to 120 seconds, after it is applied on the skin. The thickness of the gel to be formed on the skin is between 0.001 to 10 mm, preferably between 0.1 mm to 4 mm.

In the ejectable mixture (1) comprising the thermochromic substance that gels after being applied on the skin, the thermochromic component(s) change colour by being affected from the blood vessel temperature and thus ensure seeing the blood vessel. When the mixture comprising ejectable thermochromic substance is applied on the skin, invasive operation can be made by entering into the blood vessel via a device like an injector, by means of the pores found in the hydrogel formed on the skin surface.

The mixture (1) ensuring blood vessel imaging via gelling or polymerizing after being applied on the skin surface, can also be easily separated from the application surface.

Since the blood vessel temperature felt over the skin surface may vary from person to person and according to the environment, the mixture (1) for blood vessel imaging according to the invention can be prepared for variable blood vessel temperatures and can be formed of thermochromic components that change colour at different temperatures (28-40℃). Moreover, the ejectable thermochromic substance can be applied on all skin areas, on which invasive application would be made, for imaging of vascular accesses in invasive applications.

When the ejectable thermochromic substance is applied on the skin, the gel formed on the skin surface comprises pores, into which injectors or catheters used in invasive applications can enter.

The mixture (1) for blood vessel imaging according to the invention further comprises antibiotic, antiseptic, and analgesic substances, besides the biocompatible polymers or monomers, thermochromic components, and redox couples.

The mixture (1) for blood vessel imaging according to the invention is also used in different fields than blood vessel imaging, such as early diagnosis of cancers such as skin and breast cancer by making use of the thermal difference that occur between the cancerous tissue and normal tissue, since cancerous tissues have more blood vessels than normal tissues.

The mixture (1) for blood vessel imaging according to the invention is easily applicable. In children with blood vessel imaging problems, obese individuals, and individuals having thin vasculature, it provides great convenience in imaging vascular accesses.

The invention is not limited to the above disclosed embodiments and persons skilled in the related art can easily form other embodiments of the invention. These embodiments shall be evaluated according to the scope of protection claimed in the claims part of the invention.

CLAIMS

1. An ejectable or sprayable mixture (1) for blood vessel imaging, characterized in that; it comprises at least two ejectable and sprayable solutions comprising thermochromic components, redox couples, monomer and/or polymers and/or biocompatible monomers and/or polymers.

2. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 1, characterized in that; it comprises at least one redox couple, which is polymerized by cross-linking and rapid polymerization reaction, and in which each oxidizing agent is found in a solution, while each reducing agent is found in another solution.

3. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 2, characterized in that; it comprises at least two solutions, each of which comprising monomer and/or polymer structures and/or biocompatible monomers and/or polymers, thermochromic components, and a redox couple, and the thermochromic components have the characteristic of changing colour according to temperature difference.

4. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 3, characterized in that; it comprises a redox couple found in two separate solutions, in which the oxidizing agent is found in one solution and the reducing agent is found in another solution for being preserved at two separate media and combined at the moment of application on the skin.

5. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 4, characterized in that; it comprises a reaction initiating agent in the first solution and a reduction agent in the second solution as the redox couple.

6. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 5, characterized in that; the redox couples are selected from metal ions used as oxidizing agents or reducing agents, peroxydiphosphate systems, organic-inorganic redox couples (For instance oxidation via Ce^{+4}), and besides the redox type, thermal free radical initiators that cause initiation at low temperatures.

7. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 6, characterized in that; the metal ions that can be used as oxidizing agents or reducing agents are selected from Ferric/Ferrous, Cupric/Cuprous, Seric/Serous, Cobalt (II)/Cobalt (III), Vanadate (V)/Vanadate (VI), permanganate, Manganic/Manganese, and peroxygen-containing compounds, for instance, peroxides and hydrogen peroxides, benzyl peroxide, t-butyl hydroperoxide, t-butyl peroxide, benzoyl peroxide, and cumyl peroxide.

8. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 7, characterized in that; the biocompatible polymer and/or monomer and/or polymers and/or monomers found in the solutions are selected from polymers and/or monomers that are suitable for physical and/or chemical cross linking.

9. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 8, characterized in that; the polymer and/or monomer and/or biocompatible polymers and/or monomers found in the solution are selected from polymers with ionic structure suitable for physical cross linking, metal ions with divalent cationic structure, poly(styrene), poly(caprolactone), poly(oxyethylene), poly(butadiene), poly(n-alkylacrylamide) etc. other block and graft copolymers of water soluble and insoluble polymers, some natural polymers such as gelatine and glucosaminoglycans, and pH-sensitive polymers and/or monomers.

10. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 9, characterized in that; the ionic-structure polymers are selected from alginates, xanthan gums, gum acacia, natural gum, agar, agarose, seaweed, fucoidane, furcellarane, laminarane, hypnea, eucheuma, karaya gum, arabinogalactan, pectin, and amylopectin.

11. An ejectable or sprayable mixture (1) for blood vessel imaging according to any one of Claims 8 to 10, and it is characterized in that; the biocompatible polymers and/or monomers are selected from large monomers and polymers comprising all small or polymerizing groups such as acrylic acid and vinylprolactam that can form a biocompatible surface coating via chemical and/or physical cross linking.

12. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 11, characterized in that; the biocompatible monomers and/or polymers are selected from acrylic acid, vinylcaprolactam, polyethylene glycol diacrylate, ethylene, polymers comprising unsaturated

groups, PVA (Polyvinyl alcohol) and derivatives, PVP (Polyvinylpyrrolidone) and derivatives, polyacrylic acid and derivatives, polyacrylamides and derivatives, hydroxypropyl methacrylamide and derivatives, divinyl ether anhydride and derivatives, polyoxazoline and derivatives, polyphosphates and derivatives, polyphosphazenes and derivatives, polyethylene glycol and derivatives.

13. An ejectable or sprayable mixture (1) for blood vessel imaging according to any one of Claims 1 to 12, characterized in that; the thermochromic components are selected from thermochromic dye and ink, liquid crystals (e.g. cholesteryl pelargonate, cholesteryl benzoate, cholesteryl oleyl carbonate etc.), other thermochromic materials or polymers that can change colour with the impact of heat such as NIPAAM.

14. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 13, characterized in that; it may also comprise antibiotic, antiseptic, and analgesic substances, besides the monomers and/or polymers and/or biocompatible monomers, thermochromic components, and redox couples.

15. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claims 13 or 14, and it is characterized in that; it comprises thermochromic components that change colour at different temperatures (28-40℃) for variable blood vessel temperatures.

16. An ejectable or sprayable mixture (1) for blood vessel imaging according to any one of the above claims, characterized in that; the thermochromic components, monomers and/or polymers and/or biocompatible monomers and/or polymers, and redox couples found in both of the solutions have suitable characteristics for chemical, mechanical, or electronic ejection methods, by which the solution would be transformed into sprayable forms.

17. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 16, characterized in that; it has a form that can turn into a hydrogel layer on the skin in 1 to 120 seconds, after it is applied on the skin.

18. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 17, characterized in that; following application, the thickness of the gel to be formed on the skin is between 0.001 to 10 mm.

19. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 18, characterized in that; following application, the thickness of the gel to be formed on the skin is between 0.1 mm to 4 mm.

20. An ejectable or sprayable mixture (1) for blood vessel imaging according to Claim 18 or Claim 19, characterized in that; when the ejectable or sprayable mixture (1) is applied on the skin, the gel formed on the skin surface comprises pores, into which injectors or catheters used in invasive applications can enter.

21. An ejectable or sprayable mixture (1) for blood vessel imaging according to any one of the above claims, characterized in that; it further comprises antibiotic, antiseptic, and analgesic substances, besides the monomers and/or polymers and/or biocompatible monomers, thermochromic components, and redox couple.

22. An ejectable or sprayable mixture (1) for blood vessel imaging according to any one of the above claims, characterized in that; it is also used in other fields such as early diagnosis of cancers such as skin and breast cancer by making use of the thermal difference that occur between the cancerous tissue and normal tissue, since cancerous tissues have more blood vessels than normal tissues.

23. An ejectable or sprayable mixture (1) for blood vessel imaging according to any one of the above claims, characterized in that; it is used for determining the blood vessel location.

24. A container (S) comprising at least two sections (R) containing an ejectable or sprayable mixture (1) for blood vessel imaging according to any one of Claims 1 to 22, and a spray that ensures spraying.

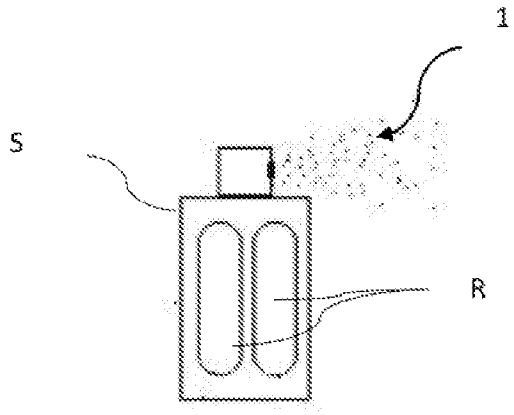

Figure 1

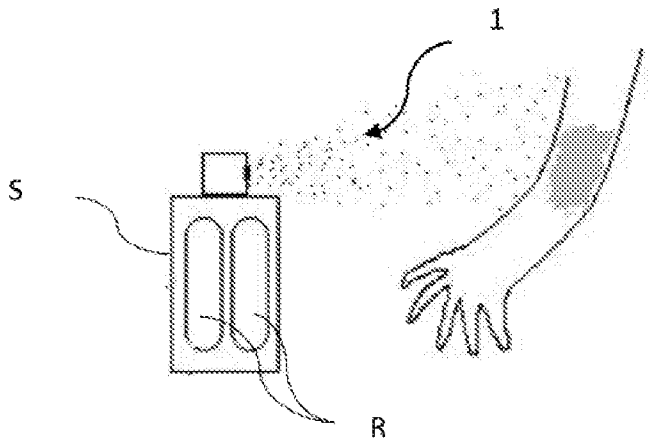

Figure 2

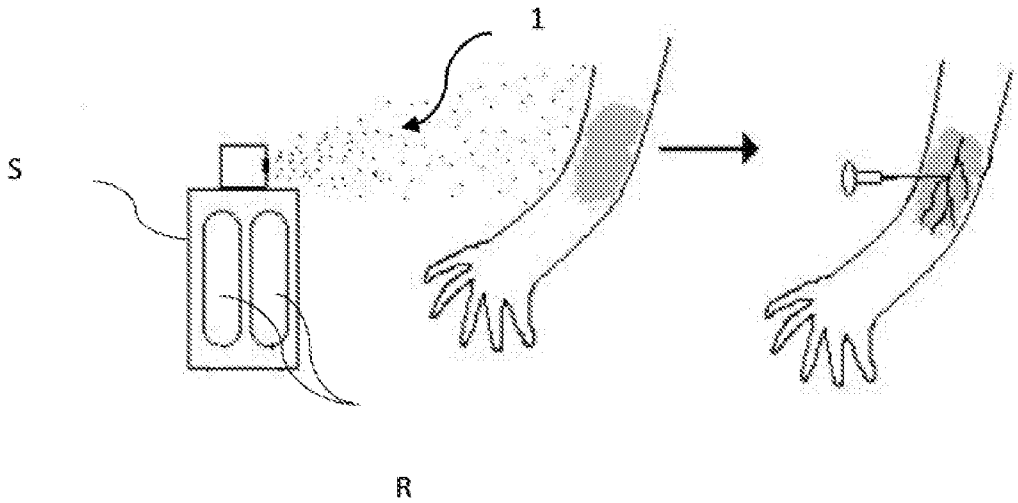

Figure 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2015/050244

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K49/00 A61B5/01
ADD.

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)
A61K A61B

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 practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/039659 A2 (KIMBERLY CLARK CO [US]; YANG SEUNGRIM [KR]; RYU JINHO [KR]; KWON MIYUN) 7 April 2011 (2011-04-07) examples 2,3,4 -& CA 2 772 555 A1 (KIMBERLY CLARK CO [US]) 7 April 2011 (2011-04-07) cited in the application	1-24
A	US 2009/124925 A1 (MACDONALD J GAVIN [US] ET AL) 14 May 2009 (2009-05-14) the whole document	1-24
A	US 6 328 910 B1 (ASKILL IAN N [US] ET AL) 11 December 2001 (2001-12-11) the whole document	1-24

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 2016	22/04/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bliem, Barbara

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2015/050244

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011039659 A2	07-04-2011	AU 2010302372 A1	22-03-2012
		CA 2772555 A1	07-04-2011
		EP 2482717 A2	08-08-2012
		JP 2013506482 A	28-02-2013
		KR 20120082880 A	24-07-2012
		US 2011077527 A1	31-03-2011
		WO 2011039659 A2	07-04-2011
CA 2772555 A1	07-04-2011	AU 2010302372 A1	22-03-2012
		CA 2772555 A1	07-04-2011
		EP 2482717 A2	08-08-2012
		JP 2013506482 A	28-02-2013
		KR 20120082880 A	24-07-2012
		US 2011077527 A1	31-03-2011
		WO 2011039659 A2	07-04-2011
US 2009124925 A1	14-05-2009	AU 2008322352 A1	22-05-2009
		EP 2219529 A2	25-08-2010
		KR 20100075635 A	02-07-2010
		US 2009124925 A1	14-05-2009
		WO 2009063340 A2	22-05-2009
US 6328910 B1	11-12-2001	NONE	