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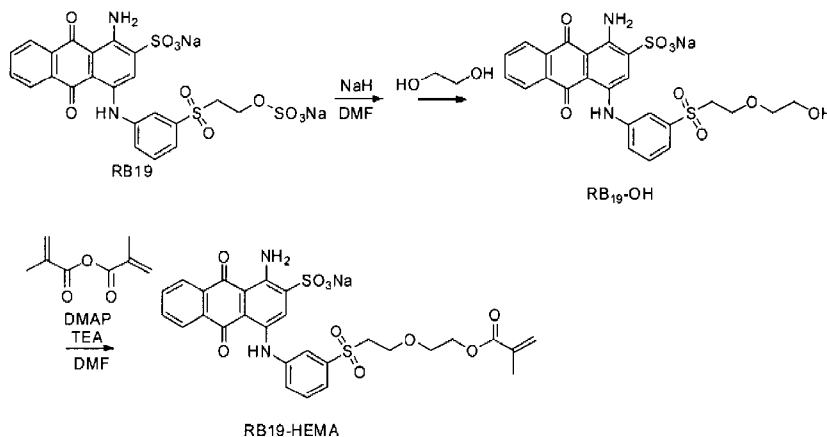
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(54) Title: POLYMERIZABLE DYES FOR CONTACT LENSES



(57) Abstract: A polymerizable dye for use in contact lens formulations is prepared by combining a reactive dye comprising a sulfonateoxyethylsulfonyl group with a linking agent having at least two functional groups to form an intermediate dye comprising at least one pendant functional group to which is attached a polymerizable group.

POLYMERIZABLE DYES FOR CONTACT LENSES

BACKGROUND

[001] The field of the invention is polymerizable dyes for contact lenses.

[002] Dyes used to tint soft contact lenses can often leach during the manufacturing process when the lenses are subjected to hydration, extraction, and sterilization conditions, or they may leach during prolonged storage. To address this problem, polymerizable groups can be covalently attached to a dye so that the dye becomes an integral part of the polymeric matrix of the contact lens. For example, it is known that a reactive dye containing a sulfonatoxyethylsulfonyl group, such as Reactive Blue 19 (RB19), can be reacted with hydroxyethyl methacrylate (HEMA) to prepare a polymerizable reactive dye, RB19-HEMA. However, previously described reactions have not been commercially practical because when scaled up the reaction yields are low and/or impurities are high.

[003] Disclosed herein is an improved method of making a polymerizable dye for use in contact lenses. Background publications include U.S. Pat No. 4,468,229, U.S. Pat No. 4,559,059, U.S. Pat No. 5,470,932, U.S. Pat. No. 5,944,853, U.S. Pat. No. 6,149,692, U.S. Pat. No. 7,105,688, U.S. Pat. No. 7,216,975 and U.S. Pat. No. 7,659,325.

SUMMARY

[004] Provided herein is a method for making a polymerizable dye suitable for use in contact lens formulations. The method comprises combining a reactive dye comprising a sulfonatoxyethylsulfonyl group, a linking agent having at least a first and a second functional group, and a base under conditions in which the first functional group of the linking agent covalently attaches to the reactive dye to form an intermediate dye comprising the second functional group. The first and second functional groups are independently selected from $-OH$, $-SH$, $-NH_2$, and $-SiH_3$. The intermediate dye is then covalently attached to a monomer to form the polymerizable dye. In a specific example, the reactive dye is RB19, the linking agent is ethylene glycol, and the monomer is methacrylic anhydride or methacryloyl chloride.

[005] The polymerizable dye prepared using the methods described herein can be used to manufacture a contact lens in a method comprising polymerizing a formulation comprising the polymerizable dye and at least one additional polymerizable monomer to form a contact lens.

In a specific example the polymerizable dye is RB19-HEMA and is used as a tinting agent in a silicone hydrogel contact lens.

BRIEF DESCRIPTION OF THE FIGURE

[006] **FIG. 1** depicts a reaction scheme for making RB19-HEMA in accordance with the present disclosure.

DETAILED DESCRIPTION

[007] Described herein is an improved method for making a polymerizable dye for use in contact lens formulations. The method comprises combining a reactive dye comprising a sulfonatoxyethylsulfonyl group with a linking agent having at least two functional groups to form an intermediate dye comprising at least one pendant functional group. A polymerizable group is then attached to the pendant functional group of the intermediate dye to provide a polymerizable dye. The method is scalable and can be used to produce a polymerizable dye suitable for use as a tinting in the manufacture of contact lenses, thus providing a significant improvement over prior methods.

[008] Exemplary reactive dyes that comprise a sulfonatoxyethylsulfonyl group include Reactive Black B, Reactive Orange 16, Reactive Yellow 14, Remazol red B, and Reactive Blue 19 (RB19). In a specific example, the reactive dye is RB19. Frequently, commercially available reactive dyes are less than 90% by weight (i.e. 90 wt.%) pure or even less than 80 wt.% pure and contain significant amount of inorganic salts. The reactive dye may be used as-is, or may be purified before use in the method to a purity of at least 90 wt.%. In an exemplary purification, such as described in Example 1, the reactive dye is purified using a methanol wash in which the dye is mixed with methanol at a weight ratio of about 1:5 up to about 1:50, respectively, for at least 1 hour, filtered and dried. The methanol wash time can be increased and/or the wash repeated to increase the dye purity level. The reactive dye may be purified to achieve a purity of at least 85 wt.%, 90 wt.%, or 95 wt.%, as determined by peak area of an HPLC read-out. In a specific method, the reactive dye is RB19 having a purity of at least 85 wt.%, 90 wt.%, or 95 wt.%. Throughout this disclosure, when a series of values is presented with a qualifier preceding the first value, the qualifier is intended to implicitly precede each value in the series unless context indicates otherwise. For example, in the above-mentioned

purity levels it is intended that the qualifier “at least” implicitly precedes the values of 90 wt.% and 95 wt.%. Further, throughout this disclosure a reference to “examples”, “an example” or “a specific example” or similar phrase, is intended to introduce a feature or features of the method of making the polymerizable dye, or the polymerizable dye itself (depending on context) that can be combined with any combination of previously-described or subsequently-described examples (i.e. features), unless a particular combination of features is mutually exclusive, or if context indicates otherwise.

[009] The reactive dye is combined with a linking agent comprising at least two functional groups and a base. In the presence of the base the sulfonatoxyethylsulfonyl group is converted into a vinyl sulfone group which then reacts with a first functional group of the linking agent to form an intermediate dye comprising a second functional group. Typically, the first and second functional groups are independently selected from $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, and $-\text{SiH}_3$. In various examples, the linking agent is a straight-chain or branched alkyl or alkoxy comprising two or more pendant functional groups independently selected from $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, and $-\text{SiH}_3$. In one example, the linking agent is a C2-C12 alkyl or alkoxy. In a further example, the linking agent comprises two to four functional groups. In specific examples, the linking agent comprises at least one hydroxyl (i.e. $-\text{OH}$) group. In further examples, the linking agent is a diol or a triol. Exemplary diols include glycols such as ethylene glycol, diethylene glycol, 1,3 propylene glycol and 1,2 propylene glycol. Exemplary triols include glycerol and 1,3,5 pentanetriol. Other exemplary linking agents include 2-mercaptoethanol, 1,2 ethanedithiol, ethanolamine, ethylenediamine, and 2-silylethylsilane.

[010] The reactive dye and the linking group are typically combined in amounts to provide a number ratio of sulfonatoxyethylsulfonyl groups to molecule of linking agent of about 2:1 to about 5:1, respectively. Typically, the reactive dye is dissolved in an anhydrous solvent, such as dimethylformamide (DMF), at a ratio of about one liter of solvent for every 100 to 200 g of reactive dye. The linking agent is then added to the reactive dye. In one example, the entire amounts of the reactive dye and the linking agent are combined to form a mixture of the reactive dye and the linking agent prior to addition of the base.

[011] Any base can be used which is capable of facilitating the conversion of the sulfonatoxyethylsulfonyl group into a vinyl sulfone group which reacts with the linking agent to formation the intermediate dye, such as an alkali metal containing base or alkali metal salt.

Examples of suitable bases include NaH, NaNH₂, NaOH, and K₂CO₃. In one example the base is a sodium salt (e.g. NaH, NaNH₂, NaOH, etc.). In another example a base is used that results in formation of an intermediate dye that is essentially free of *in situ*-formed water. Examples of such bases include NaH and NaNH₂. As used herein, a reaction product that is essentially free of *in situ*-formed water comprises less than 0.5 wt.% *in situ* formed water. When a base is used that results in *in situ* formation of water, a drying agent, such as anhydrous Na₂SO₄, may be added to the reaction to keep reaction conditions substantially anhydrous. By substantially anhydrous reaction condition, it is meant that the reaction mixture comprises less than 2 wt.% water, or less than 1 wt.%, or 0.5 wt.% water. In some examples, especially for exothermic reactions, the base is added incrementally over a period of time, for example in roughly equal increments about every 2 to 10 minutes over a period of about 30 to 90 minutes. Additionally, the reaction may be carried out at a reduced temperature, for example less than about 10° C typically about 0° C. The reaction may be monitored by chromatography. Additional base can be added in increments until the reaction is complete. Further, increasing the reaction temperature towards the end of the reaction to room temperature or above can facilitate complete conversion of the reactive dye. After the reaction, the intermediate dye is typically collected by filtration, washed in an organic solvent, and then filtered and dried. Preferably, the intermediate dye is purified to at least 95 wt.% prior to reaction with a monomer to form the polymerizable dye. In various examples, the yield of intermediate dye relative to the amount of reactive dye is at least 50%. For example, if 500g of reactive dye is used in the reaction, the yield of intermediate dye is at least 250g. In various examples, the yield of intermediate dye is at least 55 wt.%, 60 wt.% or 65 wt.%. In a specific example, the reactive dye is RB19, the linking agent is ethylene glycol, and the base is NaH.

[012] The intermediate dye is dissolved in a suitable solvent prior to reaction with the monomer, typically at a ratio of about one liter of solvent for every 100 to 200 g of reactive dye. Exemplary suitable solvents are dimethylformamide (DMF). As used herein, the term monomer means any compound that can covalently attach to the functional group of the intermediate dye to provide a polymerizable moiety. Typically, the polymerizable moieties of components of contact lens formulations are independently selected from an acrylate group (i.e. CH₂CHC(O)O⁻), a methacrylate group (i.e. CH₂C(CH₃)C(O)O⁻), or a vinyl group (i.e. CH₂CHCH₂⁻). In examples where the reactive dye has a single sulfonatoxyethylsulfonfyl

group, such as RB19, and the linking agent has two functional groups, such as ethylene glycol, the resulting intermediate dye will have a single pendant functional group. The intermediate dye can then be reacted with a monomer that results in a polymerizable dye having a single polymerizable moiety. In another example, a polymerizable dye comprising two or more polymerizable moieties can be made using the methods described herein, and thus act as a cross-linking agent in a polymerizable formulation. For example, a reactive dye, such as Reactive Black 5, which comprises two sulfonatoxyethylsulfonyl groups can be reacted with a linking agent, such as ethylene glycol which has two functional groups, resulting in a cross-linkable, polymerizable dye comprising two polymerizable groups. Another way to prepare a cross-linkable dye is to select a linking agent having three or more functional groups. After being attached to a sulfonatoxyethylsulfonyl group of the reactive dye, two (or more) pendant functional groups will remain available for linking to the monomer providing the polymerizable group. For example, the linking agent 1, 3, 5 pentanetriol comprises three functional groups and thus can be used to prepare a cross-linkable dye in accordance with the methods described herein.

[013] In specific examples, the monomer is an acrylating agent selected from methacrylic anhydride, methacryloyl chloride, acrylic anhydride, methacrylic anhydride, 2-isocyanatoethyl methacrylate, itaconic acid, or itaconic anhydride. As used herein, an “acrylating agent” is a compound that can react with the intermediate dye to attach one or more methacrylate or acrylate groups. In a specific example the reactive dye is RB19, the linking agent is ethylene glycol, and the monomer is methacrylic anhydride or methacryloyl chloride, which forms RB19-HEMA, as depicted in Figure 1. With previous methods of forming RB19-HEMA, in which RB19 and HEMA are combined in the presence of a base, an undesirable side reaction in which vinyl sulfone is hydroxylated rather than methacrylated. In some prior methods, as much as 50% or more of the final product is hydroxylated, and column purification is needed to separate the hydroxylated product, remaining RB19-vinylsulfone intermediate, and other impurities from the RB19-HEMA, which is not practical on a commercial scale. In one example using the methods described herein, a hydroxylated intermediate, e.g. RB19-OH, is purposefully formed as an intermediate compound, not as an undesirable side reaction. The RB19-OH is then reacted with the monomer to form the polymerizable dye. Conventional reaction conditions can be used to link the monomer to the intermediate dye. For example, as

shown in Figure 1, the intermediate dye with a pendant hydroxyl group (e.g. RB19-OH) is reacted at room temperature with methacrylic anhydride in the presence of an esterification catalyst (e.g. 4-dimethylaminopyridine) and triethylamine. In other examples the monomer comprises one or more vinyl groups, such as ally ether or ethylene glycol divinyl ether, which is reacted with the intermediate dye using conventional methods to result in a polymerizable dye comprising a vinyl group. In various examples, the intermediate dye and the monomer are combined under substantially anhydrous reaction conditions.

[014] As previously noted, an advantage of the methods disclosed herein is that they can be used to produce large batches of polymerizable dyes in high purity compared to previous methods. In specific examples, the purity of the polymerizable dye produced by the method disclosed herein is at least 90 wt.%, 92 wt.%, or 95 wt.%. The yield of polymerizable dye obtained in a single batch relative to the amount of intermediate dye is preferably at least 10%. For example, if 500g of intermediate dye is used in a reaction, the amount of polymerizable dye obtained is at least 50g. In a specific example, the polymerizable dye is RB19-HEMA having a purity of at least 95% and in an amount of at least 50 g produced from single batch. In a further example, the method forms RB19-HEMA at a purity of at least 90% or 95% without column purification.

[015] The polymerizable dye is suitable for use as a colorant of polymerized medical devices, including ophthalmic devices such as silicone hydrogel contact lenses or traditional HEMA-based hydrogel contact lenses. The polymerizable dye can be directly added to a polymerizable composition comprising at least one additional polymerizable monomer, which is then polymerized so that the polymerizable dye becomes an integral part of the resulting polymer, imparting color to it. The polymerizable dye is typically added to a polymerizable formulation in an amount of about 0.001 wt.% to about 0.5 wt.%, relative to the weight of all polymerizable ingredients in the formulation. For silicone hydrogel contact lens formulations, the polymerizable dye may be added to the formulation in an amount of about 0.005 wt.% to about 0.05 wt. %. Examples of polymerizable formulations for silicone hydrogel contact lenses are described in US Pat. No. 7,750,079, US Pat No. 7,572,841, and US Publ. No. 2012/0220689, incorporated herein by reference. The tints used in the formulations described in these patents may be replaced by the polymerizable dye described herein. Thus, provided herein is a method of manufacturing a contact lens comprising: (i) making a polymerizable

formulation comprising a polymerizable dye prepared as described herein and at least one additional polymerizable monomer; and (ii) polymerizing the polymerizable formulation to form a contact lens. In a specific example, the polymerizable dye is RB19-HEMA, and the at least one additional polymerizable monomer is a Si-O containing monomer.

[016] The following Examples illustrate certain aspects and advantages of the present invention, which should be understood not to be limited thereby. Unless otherwise stated, any % amounts provided herein are based on total weight. Further the term or phrase “a” or “an” is meant to encompass “one or more” such as two, three, four or more.

[017] Example 1: Purification of RB19

[018] In a 10-L flask, 7 liters of anhydrous methanol and 1 kg of RB19 were combined and stirred overnight. The solid was collected by filtration and then mixed together with 7 liters of methanol for at least 8 hours. The solid was collected by filtration and dried in a vacuum drying oven (50° C, about 0.08 MPa, 24 hours). The yield was 600 g of purified RB19 (purity 92%).

[019] Example 2: Preparation of RB19-OH

[020] 600 g of purified RB19 was added to 4 liters of DMF, then 172.5 mL of ethylene glycol (grade: AR) was added and stirred for 30 min. 29.4 g of NaH (60% in mineral oil) was added in 11 portions (2~3 grams per portion) at intervals of about 5 minutes over the course of about one hour with stirring. An ice bath was used to keep the temperature at about 0° C. After the last portion of NaH was added, the mixture was stirred at room temperature for 3 hours, then for 1 more hour at 50° C. The reaction was monitored by TLC. The reaction mixture was diluted by a mixture of 4 L of ethyl acetate (EA) and 40 L of petroleum ether (PE) (v/v= 1/10) and stirred for about 2 hours. The solid was collected by filtration (LC-MS purity >93%). The solid was washed with 1.4 L of mixture of EA/EtOH/PE (v/v/v=1/1/5) for several times, until the purity was over 95%. The solid was collected by filtration and dried in a vacuum drying oven (50°C, about 0.08 MPa, 24 hours). The yield was 400 g of RB19-OH (purity >95%).

[021] Example 3: Preparation of RB19-HEMA

[022] 400 g of RB19-OH was added to 2.5 liters of DMF, then 196 mL of triethylamine, 0.05 g of dimethylaminopyridine (DMAP), and 253 mL of methacrylic anhydride were added. The mixture was stirred at room temperature overnight and monitored by LC-MS until RB19-OH was completely consumed. 2.2 liters of saturated brine was added to reaction mixture and the precipitate was collected by filtration. The solid was washed with 1.8 L of DI water/EtOH (v/v=1:8) overnight, to remove inorganic salt. The solid was then collected by filtration and washed again overnight with 1.8 L of DI water/EtOH (v/v=1:8). The solid was collected by filtration, then washed with EA/EtOH (1.8L, v/v=8/1) for 8 hours and filtered for several times. The solid was then washed with 500 mL of DI water for 2 hours, filtered, and dried in vacuum oven (50°C, about 0.08 MPa, 3 days). The yield was 55 g of RB19-HEMA (purity >95%).

[023] Although the disclosure herein refers to certain illustrated examples, it is to be understood that these examples are presented by way of example and not by way of limitation. The intent of the foregoing detailed description, although discussing exemplary examples, is to be construed to cover all modifications, alternatives, and equivalents of the examples as may fall within the spirit and scope of the invention as defined by the additional disclosure.

[024] A number of publications and patents have been cited hereinabove. Each of the cited publications and patents are hereby incorporated by reference in their entireties.

[025] From the foregoing, it will be appreciated that the invention further provides each of the combinations described in the following paragraphs:

[026] 1. A method for making a polymerizable dye comprising: combining a reactive dye comprising a sulfonatoxyethylsulfonyl group, a linking agent having at least a first and a second functional group, and a base under conditions in which the first functional group of the linking agent covalently attaches to the reactive dye to form an intermediate dye comprising the second functional group, wherein the first and second functional groups are independently selected from -OH, -SH, -NH₂, and -SiH₃; and combining the intermediate dye with a monomer under conditions in which the second functional group of the intermediate dye covalently attaches to the monomer to form the polymerizable dye.

[027] 2. The method of 1, wherein the reactive dye is RB19.

[028] 3. The method of 1 or 2, wherein the linking agent has at least one hydroxyl group.

- [029] 4. The method of 3, wherein the linking agent is a diol or a triol.
- [030] 5. The method of 1 or 2, wherein the linking agent is selected from ethylene glycol, 1,3 propylene glycol, 1,2 propylene glycol, glycerol, or 1,3,5 pentanetriol.
- [031] 6. The method of 1 or 2, wherein the linking agent is ethylene glycol.
- [032] 7. The method of any one of 1 to 6, wherein the monomer is selected from methacrylic anhydride, methacryloyl chloride, 2-isocyanatoethyl methacrylate, itaconic acid, or itaconic anhydride.
- [033] 8. The method of any one of 1 to 6, wherein the monomer is methacrylic anhydride or methacryloyl chloride.
- [034] 9. The method of any one of 1 to 8, wherein the base is NaH.
- [035] 10. The method of any one of 1 to 9, wherein the reactive dye, linking agent, and base are combined under substantially anhydrous reaction conditions.
- [036] 11. The method of any one of claims 1 to 10, wherein the intermediate dye and the monomer are combined under substantially anhydrous reaction conditions.
- [037] 12. The method of any one of 1 to 11, wherein the reactive dye has a purity of at least 90 wt.%.
- [038] 13. The method of any one of 1 to 12, comprising purifying the intermediate dye to at least 95 wt.% prior to combining it with the monomer.
- [039] 14. The method of any one of 1 to 13, wherein the method provides a single batch of the polymerizable dye in a batch size of at least 50 grams.
- [040] 15. The method of any one of 1 to 14, wherein the polymerizable dye has a purity of at least 95 wt.%.
- [041] 16. A polymerizable dye prepared by the method of any one of 1 to 15.
- [042] 17. A contact lens manufactured by polymerizing a reaction mixture comprising the polymerizable dye of 16.

[043] 18. A method of manufacturing a contact lens comprising polymerizing a polymerizable formulation comprising the polymerizable dye of 16 and at least one additional polymerizable monomer to form a contact lens.

[044] 19. The method of 18, wherein the at least one additional polymerizable monomer is a Si-O containing monomer.

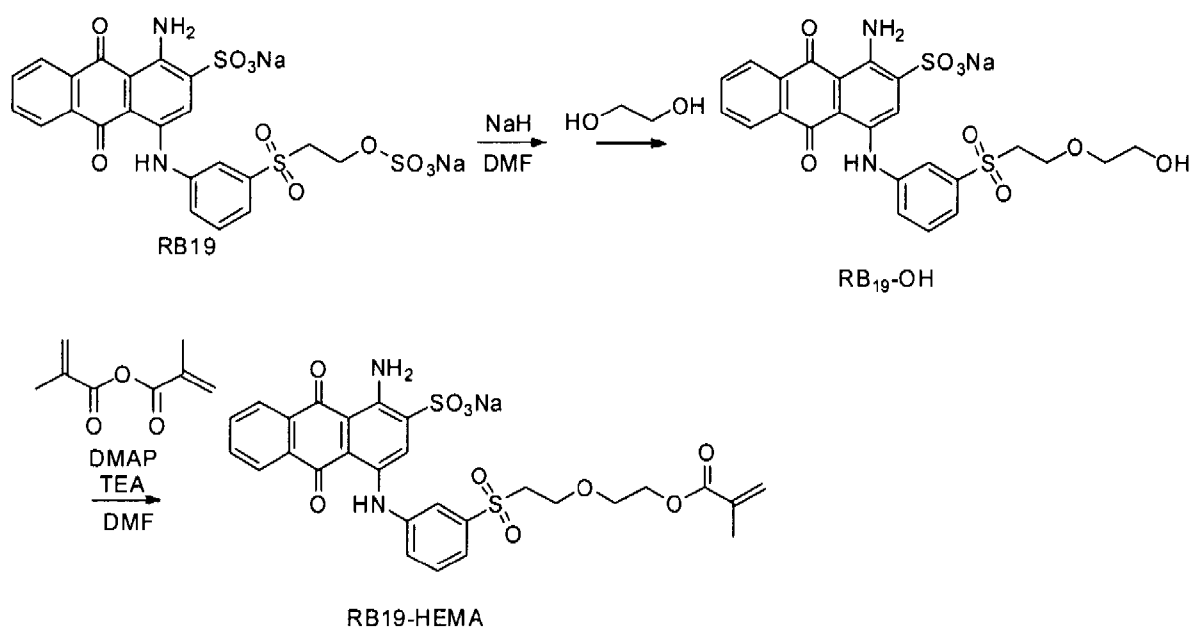
[045] 20. The method of 18 or 19, wherein the polymerizable dye is RB19-HEMA.

WHAT IS CLAIMED IS:

1. A method for making a polymerizable dye comprising:
combining a reactive dye comprising a sulfonatoxyethylsulfonyl group, a linking agent having at least a first and a second functional group, and a base under conditions in which the first functional group of the linking agent covalently attaches to the reactive dye to form an intermediate dye comprising the second functional group, wherein the first and second functional groups are independently selected from $-OH$, $-SH$, $-NH_2$, and $-SiH_3$; and
covalently attaching the second functional group of the intermediate dye with a monomer to form the polymerizable dye.
2. The method of claim 1, wherein the reactive dye is RB19.
3. The method of claim 1, wherein the linking agent has at least one hydroxyl group.
4. The method of claim 3, wherein the linking agent is a diol or a triol.
5. The method of claim 4, wherein the linking agent is selected from ethylene glycol, 1,3 propylene glycol, 1,2 propylene glycol, glycerol, or 1,3,5 pentanetriol.
6. The method of claim 1, wherein the linking agent is ethylene glycol.
7. The method of claim 6, wherein the base is NaH.
8. The method of claim 7, wherein the reactive dye, linking agent, and base are combined under substantially anhydrous reaction conditions.
9. The method of claim 8, wherein the intermediate dye and the monomer are combined under substantially anhydrous reaction conditions.

10. The method of claim 1, wherein the monomer is selected from methacrylic anhydride, methacryloyl chloride, 2-isocyanatoethyl methacrylate, itaconic acid, or itaconic anhydride.
11. The method of claim 1, wherein the monomer is methacrylic anhydride or methacryloyl chloride.
12. The method of claim 1, wherein the reactive dye is RB19, the linking agent is ethylene glycol, and the polymerizable dye is RB19-HEMA.
13. The method of claim 12, wherein at least 50g of the RB19-HEMA having a purity of at least 90 wt.% is produced in a single batch.
14. A polymerizable dye prepared by the method of claim 1.
15. A contact lens manufactured by polymerizing a reaction mixture comprising the polymerizable dye of claim 14.
16. A method of manufacturing a contact lens comprising polymerizing a polymerizable formulation comprising the polymerizable dye of claim 14 and at least one additional polymerizable monomer to form a contact lens.
17. The method of claim 16, wherein the at least one additional polymerizable monomer is a Si-O containing monomer.
18. The method of claim 16, wherein the polymerizable dye is RB19-HEMA.

FIGURE



INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2013/000053

A. CLASSIFICATION OF SUBJECT MATTER

See the extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: D06P 5/-; C09B 1/-; D06P 1/-; G02C 7/-

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)

WPI, EPODOC, CNKI, CNPAT, CAPLUS, REGISTRY: polymer+, dye, contact lenses, reactive blue 19, BR 19, hydroxyethyl methacrylate, HEMA, anhydrous, RN: 2580-78-1, 868-77-9, 1321530-45-3

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/0251929 A1 (HONG, Shinn Guo) 17 November 2005 (17.11.2005), see description, paragraphs [0020] to [0042], embodiment 2	1-18
A	US 2005/0049425 A1 (PEARSON Jason Clay et al.) 3 March 2005 (03.03.2005), see embodiment 3	1-18
A	CN 1090930 A (JOHNSON & JOHNSON VISION PROD. INC.) 17 August 1994 (17.08.1994), see claim 1	1-18
A	US 2006/0252844 A1 (KEY MEDICAL TECHNOLOGIES, INC.) 9 November 2006 (09.11.2006), see embodiments 1 to 10	1-18
A	US 2007/0100018 A1 (HAGTING Joke Geesje et al.) 3 May 2007 (03.05.2007), see embodiment 5	1-18
A	US 4468229 A (CIBA-GEIGY CORPORATION) 28 August 1984 (28.08.1984), see claims 1-14	1-18

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

☒ See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search 25 April 2013 (25.04.2013)	Date of mailing of the international search report 10 Oct. 2013 (10.10.2013)
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer WU,Hongxia Telephone No. (86-10)82246671

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/000053

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
US 2005/0251929 A1	17.11.2005	US 7216975 B2	15.05.2007
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Continuation of : A. CLASSIFICATION OF SUBJECT MATTER

D06P 5/00 (2006.01) i

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