

**POLYMER COMPOSITION COMPRISING A THERMOGELLING
POLYMER AND A TYROSINE KINASE INHIBITOR, AND RELATED
METHODS THEREOF**

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TECHNICAL FIELD

The present disclosure relates broadly to a polymer composition comprising a thermogelling polymer and a tyrosine kinase inhibitor (TKI), and related methods thereof.

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BACKGROUND

Presently, providing sustained release of biologics at specific sites to treat various diseases remains a challenging area. This includes treatment of disease such as retinal neovascular diseases, cancer, etc., where there still exists an unmet clinical need to provide an effective sustained delivery solution as an alternative to current treatment methods.

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For instance, the current gold-standard treatment for ocular neovascular diseases or posterior eye segment proliferative vascular diseases such as Age-Related Macular Degeneration (AMD) and Diabetic Retinopathy (DR), involves costly, invasive, and inconvenient monthly or bi-monthly anti-vascular endothelial growth factor (anti-VEGF) injections that result in poor patient compliance. This frequent injection regimen places a significant burden on both patients and caregivers.

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For diseases that currently rely on oral administration of a drug, long term oral administration may result in the development of overall drug resistance and/or overall drug toxicity experienced by the patient. For instance, in diseases such as cancers that require long term tyrosine kinase inhibitor (TKI) treatment, TKIs can be orally applied for more than a period of 2 years. As a result, such

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patients are reported to have developed drug resistance 8 months after treatment and experiencing the toxic effect caused by long term oral supplements.

In view of the above, there is a need to address or at least ameliorate the above-mentioned problems. In particular, there is a need to provide an injectable drug depot capable of providing localized drug release over a sustained period.

SUMMARY

According to one aspect, there is provided a polymer composition comprising:

- a multi-block thermogelling polymer comprising a hydrophilic poly(alkylene glycol), a hydrophobic polymer, and a polyether or polyester chemically coupled together by at least one of urethane/carbamate, carbonate, ester, carbamide, an amide, ether, amine, triazole, linkages or combinations thereof; and
- a tyrosine kinase inhibitor (TKI) intermixed with the multi-block thermogelling polymer.

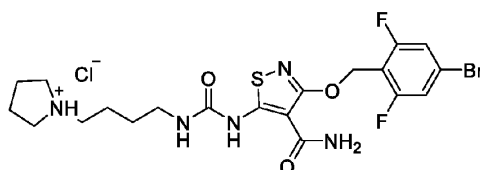
In one embodiment, the TKI interacts with the multi-block thermogelling polymer to facilitate gelation of the multi-block thermogelling polymer.

In one embodiment, the TKI increases the viscosity of the polymer composition at least 10 times as compared to when the TKI is absent.

In one embodiment, the TKI comprises a VEGFR inhibitor (e.g., VEGFR-2 inhibitor) and/or FGFR inhibitor.

In one embodiment, the TKI comprises one or more of the following:

- i. CP-547632, analogs thereof, or pharmaceutically acceptable salts thereof;
- or
- ii. a compound of Formula (I),



Formula (I).

In one embodiment, the hydrophilic poly(alkylene glycol) comprises
 5 poly(ethylene glycol) (PEG).

In one embodiment, the hydrophobic polymer is selected from the group
 consisting of poly(propylene glycol) (PPG), poly(lactic-co-glycolic acid) (PLGA),
 polylactic acid (PLA), poly(N-isopropylacrylamide) (PNIPAAm), polypeptides, or
 10 combinations thereof.

In one embodiment, the polyether or polyester comprises one or more of
 polycaprolactone (PCL), polytetrahydrofuran (PTHF), polyhydroxybutyrate
 (PHB), poly(lactic-co-glycolic acid) (PLGA), and polylactic acid (PLA).
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In one embodiment, the concentration of TKI in the polymer composition
 is no less than about 10 mg/L.

In one embodiment, the molar ratio of the hydrophilic poly(alkylene glycol)
 20 to the hydrophobic polymer is 1-10:1.

In one embodiment, the polyether or polyester is present in an amount
 falling in the range of from 1 wt% to 10 wt% in the multi-block polymer.

25 In one embodiment, the molar ratio of the hydrophilic poly(alkylene glycol)
 to the hydrophobic polymer to the polyether or polyester in the multi-block
 polymer is in the range of about 1 – 10: 1: 0.01 – 1.5.

In one embodiment, the multi-block polymer is present at an amount of up to 30% w/v in an aqueous medium.

In one embodiment, the pH of the composition falls in the range of from
5 7.1 to 7.4.

In one embodiment, the polymer composition has a critical gelation temperature of no less than 4 °C.

10 In one embodiment, the polymer composition further comprises one or more pharmaceutically active ingredient that is different from the TKI.

In one embodiment, the pharmaceutically active ingredient that is different from the TKI is selected from the group consisting of aflibercept, sunitinib malate
15 and combinations thereof.

In one embodiment, the polymer composition has a drug release profile of no less than 2 months.

20 In one embodiment, the polymer composition has a drug release profile of no less than 12 months.

According to another aspect, there is provided the polymer composition as disclosed herein for use in medicine.
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According to another aspect, there is provided the polymer composition as disclosed herein for use in treating or preventing an eye condition, for treating or preventing tumour, treating or reducing angiogenesis, and/or treating cancer.

30 According to another aspect, there is provided use of the polymer composition as disclosed herein in the manufacture of a medicament for

treating or preventing an eye condition, for treating or preventing tumour, treating or reducing angiogenesis, and/or treating cancer.

According to another aspect, there is provided a method of treating or preventing an eye condition, treating or preventing tumour, treating or reducing angiogenesis, and/or treating cancer, the method comprises administering to a subject in need thereof, the polymer composition as disclosed herein.

In one embodiment, the eye condition is selected from the group consisting of neovascular retinal diseases, age related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RV).

In one embodiment, the cancer is selected from the group consisting of breast cancer, leukemia, gastrointestinal cancer, kidney cancer, lung cancer (e.g., non-small cell lung cancer), non-Hodgkin lymphoma, melanoma, ovarian cancer, fallopian tube cancer, ocular cancer.

According to another aspect, there is provided a method of preparing the composition as disclosed herein, the method comprising:

providing a multi-block thermogelling polymer comprising a hydrophilic poly(alkylene glycol), a hydrophobic polymer, and a polyether or polyester chemically coupled together by at least one of urethane/carbamate, carbonate, ester, carbamide, an amide, ether, amine, triazole, linkages or combinations thereof; and

mixing a tyrosine kinase inhibitor (TKI) with the multi-block thermogelling polymer.

DEFINITIONS

The term "substantially transparent" when used herein to describe an object is to be interpreted broadly to mean that 50% or more of the incident light normal to surface of the object can be transmitted through the object. In some

examples, the object that is substantially transparent to light allow 60% or more, 65% or more, 70% or more, 80% or more, 85% or more, 90% or more, or 95% or more of the incident light normal to surface of the object to be transmitted. In one example, the object that is substantially transparent to light allow above 70% of the incident light normal to surface of the object to be transmitted.

The terms "coupled" or "connected" as used in this description are intended to cover both directly connected or connected through one or more intermediate means, unless otherwise stated.

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The term "alkyl" as a group or part of a group refers to a straight or branched aliphatic hydrocarbon group having 1 to 20 carbon atoms, 1 to 10 carbon atoms, 1 to 6 carbon atoms, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms. Examples of suitable straight and branched alkyl substituents include methyl, ethyl, n-propyl, 2-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, hexyl, amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, pentyl, isopentyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, 2-ethylpentyl, 3-ethylpentyl, heptyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, 5-methylheptyl, 1-methylheptyl, octyl, nonyl, decyl and the like. The group may be a terminal group or a bridging group.

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The term "and/or", e.g., "X and/or Y" is understood to mean either "X and Y" or "X or Y" and should be taken to provide explicit support for both meanings or for either meaning.

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Further, in the description herein, the word "substantially" whenever used is understood to include, but not restricted to, "entirely" or "completely" and the like. In addition, terms such as "comprising", "comprise", and the like whenever

used, are intended to be non-restricting descriptive language in that they broadly include elements/components recited after such terms, in addition to other components not explicitly recited. For example, when "comprising" is used, reference to a "one" feature is also intended to be a reference to "at least one" of that feature. Terms such as "consisting", "consist", and the like, may in the appropriate context, be considered as a subset of terms such as "comprising", "comprise", and the like. Therefore, in embodiments disclosed herein using the terms such as "comprising", "comprise", and the like, it will be appreciated that these embodiments provide teaching for corresponding embodiments using terms such as "consisting", "consist", and the like. Further, terms such as "about", "approximately" and the like whenever used, typically means a reasonable variation, for example a variation of +/- 5% of the disclosed value, or a variance of 4% of the disclosed value, or a variance of 3% of the disclosed value, a variance of 2% of the disclosed value or a variance of 1% of the disclosed value.

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Furthermore, in the description herein, certain values may be disclosed in a range. The values showing the end points of a range are intended to illustrate a preferred range. Whenever a range has been described, it is intended that the range covers and teaches all possible sub-ranges as well as individual numerical values within that range. That is, the end points of a range should not be interpreted as inflexible limitations. For example, a description of a range of 1% to 5% is intended to have specifically disclosed sub-ranges 1% to 2%, 1% to 3%, 1% to 4%, 2% to 3% etc., as well as individually, values within that range such as 1%, 2%, 3%, 4% and 5%. The intention of the above specific disclosure is applicable to any depth/breadth of a range.

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Additionally, when describing some embodiments, the disclosure may have disclosed a method and/or process as a particular sequence of steps. However, unless otherwise required, it will be appreciated that the method or process should not be limited to the particular sequence of steps disclosed. Other sequences of steps may be possible. The particular order of the steps disclosed herein should not be construed as undue limitations. Unless otherwise required,

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a method and/or process disclosed herein should not be limited to the steps being carried out in the order written. The sequence of steps may be varied and still remain within the scope of the disclosure.

5 Furthermore, it will be appreciated that while the present disclosure provides embodiments having one or more of the features/characteristics discussed herein, one or more of these features/characteristics may also be disclaimed in other alternative embodiments and the present disclosure provides support for such disclaimers and these associated alternative embodiments.

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It will also be appreciated that where priority is claimed to an earlier application, the full contents of the earlier application is also taken to form part of the present disclosure and may serve as support for embodiments disclosed herein.

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DESCRIPTION OF EMBODIMENTS

Exemplary, non-limiting embodiments of a polymer composition, methods of preparing the polymer composition, and related use of the polymer composition are disclosed hereinafter.

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Polymer composition

In various embodiments, there is provided a polymer composition comprising a multi-block thermogelling polymer and a tyrosine kinase inhibitor (TKI) intermixed with the multi-block thermogelling polymer. Advantageously, the polymer composition is capable of serving as a drug depot for slow release of a drug or a pharmaceutically active ingredient (e.g., when disposed in the human or animal body). The inventors have found that TKI encapsulation delayed the dissociation or dissolution of hydrogel. Without being bound by theory, it is believed that the TKI interacts with the multi-block thermogelling polymer synergistically to result in a further crosslinked structure that allows prolonged

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period of drug release. Advantageously, the long-term release profile of the TKI-gel composition may provide a longer therapeutic effect, preventing the need for repeated treatment.

5 In various embodiments, the TKI interacts with the multi-block thermogelling polymer to facilitate gelation of the multi-block thermogelling polymer. In various embodiments, the interaction between the TKI and the multi-block thermogelling polymer may involve hydrogen bonding and hydrophobic interactions, which may induce secondary gelation. In various embodiments, the
10 gelation induced by the TKI does not alter the thermosensitive properties of the multi-block thermogelling polymer. For example, in various embodiments, the TKI-gel composition is still injectable at 4 °C and gel at body temperature. The polymer composition may be thermosensitive and changes its physical state based on temperature changes.

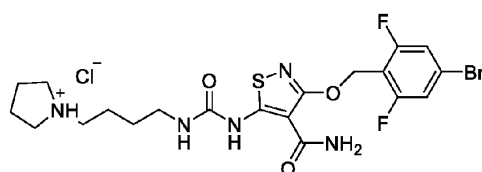
15 In various embodiments, the presence of TKI increases the viscosity of the composition to at least about 10 times, at least about 15 times, at least about 20 times, at least about 25 times, at least about 30 times, at least about 35 times, at least about 40 times, at least about 45 times, at least about 50 times, at least
20 about 55 times, at least about 60 times, at least about 65 times, at least about 70 times, at least about 75 times, at least about 80 times, at least about 85 times, at least about 90 times, at least about 95 times, at least about 100 times, at least about 150 times, at least about 200 times, at least about 250 times, at least about 300 times, at least about 350 times, at least about 360 times, at least about 370
25 times, at least about 380 times, at least about 390 times, at least about 400 times as compared to when the TKI is absent/not present.

 In various embodiments, the TKI comprises a VEGFR inhibitor (e.g., VEGFR-2 inhibitor) and/or FGFR inhibitor.

30 In various embodiments, the TKI comprises a small molecule, for example a molecular weight of less/no more than about 1000 Da, less/no more than about

900 Da, less/no more than about 850 Da, less/no more than about 800 Da, less/no more than about 750 Da, less/no more than about 700 Da, or less/no more than about 650 Da.

- 5 In various embodiments, the TKI comprises one or more of the following:
- i. CP-547632, analogs thereof, or pharmaceutically acceptable salts thereof (e.g., HCl, trifluoroacetate, etc.); or
 - ii. a compound of Formula (I),



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Formula (I).

- In various embodiments, using a small molecule like CP-547632 hydrochloride (CP-HCl) is advantageous compared to biologics/proteins such as aflibercept or bevacizumab. This is because those biologics do not self-assemble to form gels on their own and therefore cannot enhance the thermogel polymeric matrix in the same way as CP-HCl. As a result, when aflibercept or bevacizumab are used in place of CP-HCl, the release of aflibercept or bevacizumab from the hydrogel occurs much faster compared to when CP-HCl is used.

- In various embodiments, the CP-HCl has increased water solubility. It allows more soluble drug to interact with the polymer and form secondary gelation. In various embodiments, the TKI is CP-547632 HCl which is soluble in water in contrast to water insoluble drugs such as paclitaxel which is highly insoluble in water. When CP-HCl is encapsulated in multi-block thermogelling polymer such as poly(PEG/PPG/PCL urethane), it is partially encapsulated into the micellar core and it also simultaneously forms a secondary gel matrix to enhance the polymeric matrix of the thermogel. This secondary gel matrix

significantly reduces the rate of gel erosion and this allows the CP-HCl multiblock thermogel combination to achieve an extended release of more than 1 year. In contrast, when CP-HCl is replaced with paclitaxel, the release of paclitaxel lasted only about 30 days as paclitaxel does not contribute to gel matrix enhancement.

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In various embodiments, the concentration of TKI (e.g., CP-HCl) is no less than about 10 mg/L, no less than about 20 mg/L, no less than about 30 mg/L, no less than about 40 mg/L. Advantageously, it was found that when a TKI (e.g., CP-HCl) with a concentration of about 40 mg/mL was used in the polymer composition, a one-year sustained release of the drug may be achieved.

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In various embodiments, the TKI (e.g., CP-HCl) is substantially homogeneously intermixed with the polymer. Advantageously, long-term sustained drug release may be achieved from a homogeneous, thermosensitive hydrogel as compared to a drug powder-loaded hydrogel.

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In some embodiments, the TKI (e.g., CP-HCl) is the only pharmaceutically active ingredient in the polymer composition.

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In various embodiments, the TKI (e.g., CP-HCl) has a release profile of no less than about 2 months, no less than about 3 months, no less than about 4 months, no less than about 5 months, no less than about 6 months, no less than about 7 months, no less than about 8 months, no less than about 9 months, no less than about 10 months, no less than about 11 months, or no less than about 12 months.

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In various embodiments, the polymer composition may further comprise one or more pharmaceutically active ingredients which are different from the TKI (e.g., CP-HCl). In various embodiments, the pharmaceutically active ingredient that is different from the TKI (e.g., CP-HCl) is selected from the group consisting of aflibercept, sunitinib malate.

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In various embodiments, the multi-block thermogelling polymer comprises a hydrophilic poly(alkylene glycol), a hydrophobic polymer, and a polyether or polyester chemically coupled together by at least one of urethane/carbamate, carbonate, ester, carbamide, an amide, ether, amine, triazole, linkages or combinations thereof. In various embodiments, the selection of different types of polymer chains in the multi-block thermogelling polymer is based on achieving desirable thermogel properties. The combination of the hydrophilic and hydrophobic polymers may advantageously facilitate self-assembly to form gels at the desired temperature and environment, thereby providing a structure that can serve as a favourable drug depot under the right conditions.

In various embodiments, the thermogel is made up of one or more multi-block copolymers, which are tri-component multi-block polymers. For example, the multi-block thermogelling polymer comprises three different types of polymeric segments. In various embodiments, the multi-block thermogelling polymer comprises essentially of A: hydrophilic poly(alkylene glycol), B: the hydrophobic polymer, and C: the polyether or polyester. In various embodiments, the multi-block polymer may have at least one unit of the following structural sequence A-B-C. It may be appreciated that in some embodiments, the positions of A, B and C may be interchanged among themselves. In various embodiments, the multi-block polymer may comprise a plurality the hydrophilic poly(alkylene glycol) blocks, a plurality of the hydrophobic polymer blocks, and/or a plurality of the polyether or polyester blocks. In various embodiments, the multi-block copolymer comprises more than 3 polymeric blocks. The blocks may be randomly distributed/arranged within the polymer. In various embodiments, the polymeric blocks in the copolymer are connected to one another by a linkage selected from the group consisting of a carbamate, a carbonate, a carbamide, an ester, an amide, an ether, an amine, a triazole, and any combinations thereof.

In some embodiments, the hydrophilic poly(alkylene glycol) comprises hydrophilic poly(ethylene glycol) (PEG) and the hydrophobic polymer comprises a second poly(alkylene glycol), such as poly(propylene glycol) (PPG),

poly(butylene glycol), or the like or combinations thereof. In various embodiments, the hydrophobic polymer comprises a temperature responsive/thermo-sensitive polymer.

- 5 In various embodiments, the polyether or polyester comprises one or more of polycaprolactone (PCL), polytetrahydrofuran (PTHF), polyhydroxybutyrate (PHB), polylactic-co-glycolic acid (PLGA), and polylactic acid (PLA).

- 10 In various embodiments, the molar ratio of the hydrophilic poly(alkylene glycol) to the hydrophobic polymer is 1-10:1. For example, the molar ratio of the hydrophilic poly(alkylene glycol) to the hydrophobic polymer may be about 1:1, about 2:1, about 3:1, about 4:1, about 5:1, about 6:1, about 7:1, about 8:1, about 9:1 or about 10:1, preferably about 4:1.

- 15 In various embodiments, the polyether or polyester is hydrophobic. In various embodiments, the polyether or polyester is present in an amount falling in the range of from 1 wt% to 10 wt% the multi-block polymer. For example, the polyether or polyester may be in an amount/concentration of about 1 wt%, about 2 wt%, about 3 wt%, about 4 wt%, about 5 wt%, about 6 wt%, about 7 wt%, about 20 8 wt%, about 9 wt%, or about 10 wt% of the multi-block polymer, preferably from about 1 wt% to about 3 wt%.

- 25 In various embodiments, the molar ratio of the hydrophilic poly(alkylene glycol) to the hydrophobic polymer to the polyether or polyester in the multi-block polymer is in the range of about 1 – 10: 1: 0.01 – 1.5.

- 30 In various embodiments, the multi-block polymer is present at an amount of up to 30% w/v in an aqueous medium. In various embodiments, the polymer composition comprises about 1% to about 30% w/v of the multi-block thermogelling polymer in an aqueous medium. In various embodiments, the composition comprises an amount of up to about 30% w/v of the polymer in water/aqueous solution/buffer solution, or from about 1% w/v, about 2% w/v,

about 3% w/v, about 4% w/v, about 5% w/v, about 6% w/v, about 7% w/v, about 8% w/v, about 9% w/v, about 10% w/v, about 11% w/v, about 12% w/v, about 13% w/v, about 14% w/v, about 15% w/v, about 16% w/v, about 17% w/v, about 18% w/v, about 19% w/v, about 20% w/v, about 21% w/v, about 22% w/v, about 23% w/v, about 24% w/v, about 25% w/v, about 26% w/v, about 27% w/v, about 28% w/v, about 29% w/v, or about 30% w/v of polymer in water/aqueous solution/buffer solution.

In various embodiments, the aqueous medium may be a balanced salt solution. In various embodiments, the balanced salt solution is a solution having a physiological pH and isotonic salt concentration. In various embodiments, the balanced salt solution comprises at least one of sodium, potassium, calcium and magnesium salts such as calcium chloride, potassium chloride, magnesium chloride, sodium acetate, sodium citrate, and sodium chloride.

In various embodiments, the polymer composition may have a high water content of more than about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, or about 99% by weight. Accordingly, the material may be a water-based polymer.

In various embodiments, the pH of the composition falls in the range of from 7.1 to 7.4. In various embodiments, the pH of the composition has a pH value that is substantially similar to physiological pH value ranging from about pH 7.1 to about pH 7.7, from about pH 7.2 to about pH 7.6, from about pH 7.3 to about pH 7.5, or about pH 7.4.

In various embodiments, the polymer composition has a critical gelation temperature/thermo-reversible sol-gel transition temperature/converts from a liquid/flowable state to a non-flowable/gel-like state at a temperature that is no less than about 4°C, no less than about 5 °C, no less than about 6 °C, no less than about 7 °C, no less than about 8 °C, no less than about 9 °C, no less than about 10 °C, no less than about 15°C, no less than about 20°C, no less than

about 25°C, no less than about 30°C, no less than about 31°C, no less than about 32°C, no less than about 33°C, no less than about 34°C, no less than about 35°C, no less than about 36°C, no less than about 36.5°C, up to about 37°C or at a temperature that is substantially similar to living human body temperature at
5 about 36.5°C or at about 37°C. In some embodiments, the conversion from a liquid/flowable state to a gel-like state is reversible.

In various embodiments, the polymer composition is injectable using needles (e.g., 18G and above) because it is a sol at low temperatures.
10 Advantageously, less tissue damage is expected as the use of larger bore instruments is not required. In various embodiments, the polymer composition may be intravitreal (IVT) injected for posterior segmental diseases or intratumorally injected for local drug delivery in cancer treatment. Advantageously, the injectability of polymer composition allows the treatment to
15 be carried out in a less invasive way as compared to implants.

In various embodiments, the polymer composition is substantially devoid of solvent contaminants. For example, the composition or multi-block polymer may be substantially devoid of benzene and/or carbon tetrachloride and/or 1,2-
20 dichloroethane and/or 1,1-dichloroethene and/or 1,1,1-trichloroethane and/or acetonitrile and/or chlorobenzene and/or chloroform and/or cyclohexane and/or 1,2-dichloroethene and/or dichloromethane and/or 1,2-dimethoxyethane and/or N,N-dimethylacetamide and/or N,N-dimethylformamide and/or 1,4-dioxane and/or 2-ethoxyethanol and/or ethyleneglycol and/or formamide and/or hexane
25 and/or methanol and/or 2-methoxyethanol and/or methylbutylketone and/or methylcyclohexane and/or N-methylpyrrolidone and/or nitromethane and/or pyridine and/or sulfolane and/or tetrahydrofuran and/or tetralin and/or toluene and/or 1,1,2-trichloroethene and/or xylene (m-, p-, o-isomers) and/or acetic acid and/or acetone and/or anisole and/or 1-butanol and/or 2-butanol and/or butyl
30 acetate and/or tert-butylmethyl ether and/or cumene and/or dimethyl sulfoxide and/or ethanol and/or ethyl acetate and/or ethyl ether and/or ethyl formate and/or formic acid and/or heptane and/or isobutyl acetate and/or isopropyl acetate

and/or methyl acetate and/or 3-methyl-1-butanol and/or methylethylketone and/or methylisobutylketone and/or 2-methyl-1-propanol and/or pentane and/or 1-pentanol and/or 1-propanol and/or 2-propanol and/or propyl acetate.

5 In various embodiments, the polymer or composition is biocompatible and/or non-toxic and/or does not elicit an inflammatory or adverse immune response in the body of an animal or human, particularly in the eye of an animal or human.

10 In various embodiments, the multi-block thermogelling polymer is substantially transparent and/or exhibits a high degree of optical clarity and/or a refractive index substantially similar to that of naturally occurring vitreous humour, such as from about 1.20 to about 1.48, from about 1.21 to about 1.47, from about 1.22 to about 1.46, from about 1.23 to about 1.45, from about 1.24 to about 1.44,
15 from about 1.25 to about 1.43, from about 1.26 to about 1.42, from about 1.27 to about 1.41, from about 1.28 to about 1.40, from about 1.29 to about 1.39, from about 1.30 to about 1.38, from about 1.31 to about 1.37, from about 1.32 to about 1.36, from about 1.33 to about 1.35, from about 1.339 to about 1.349, from about 1.338 to about 1.348, from about 1.337 to about 1.347, from about 1.336 to about
20 1.346, from about 1.335 to about 1.345, or from about 1.334 to about 1.344.

 In various embodiments, the entire polymer or at least one or more of the blocks within the polymer or the composition is/are biodegradable and/or can be broken down naturally (in some examples, all the polymeric blocks are
25 biodegradable).

 In various embodiments, the polymer composition is capable of being degraded/dissolved naturally in the human/animal body within about 16 months, within about 15 months, within about 14 months, within about 13 months, or within
30 about 12 months.

In various embodiments, the polymer composition may fully degrade/dissolve in the human/animal body in no less than about 50 days, no less than about 60 days, no less than about 70 days, no less than about 80 days, no less than about 90 days, no less than about 100 days, no less than about 110 days, no less than about 120 days, no less than about 130 days, no less than about 140 days, no less than about 150 days, no less than about 160 days, no less than about 170 days, no less than about 180 days, no less than about 190 days, no less than about 200 days, no less than about 210 days, no less than about 220 days, no less than about 230 days, no less than about 240 days, no less than about 250 days, no less than about 260 days, no less than about 270 days, no less than about 280 days, no less than about 290 days, no less than about 300 days, no less than about 310 days, no less than about 320 days, no less than about 330 days, no less than about 340 days, no less than about 350 days, no less than about 360 days, or no less than about 365.

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In various embodiments, the polymer composition comprises/ consists essentially of/ consists of the multi-block polymer disclosed herein; the TKI disclosed herein; water/aqueous medium/aqueous buffer; optionally a pharmaceutically active ingredient that is different from the TKI, and optionally pharmaceutically acceptable excipients.

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In various embodiments, the polymer composition may exist as a drug depot or a pharmaceutical formulation.

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In various embodiments, there is also provided a polymer composition as disclosed herein for use in medicine. In various embodiments, there is provided a drug depot comprising a multi-block thermogelling polymer comprising poly(ethylene glycol) (PEG), poly(propylene glycol) (PPG), and poly(caprolactone) (PCL) chemically coupled together by at least a urethane linkage, a drug composition intermixed with the multi-block thermogelling polymer, the drug composition comprising CP-547632 or pharmaceutically acceptable salts thereof (e.g., HCl).

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In various embodiments, there is also provided a polymer composition as disclosed herein for use in drug delivery in the eye.

5 In various embodiments, there is also provided a polymer composition as disclosed herein for use in treating or preventing an eye condition and/or an ocular disorder, for treating or preventing tumour, treating or reducing angiogenesis, treating or reducing tumour migrations and recurrence, treating cancer, and/or preventing or reducing the frequency of IVT injection.

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 In various embodiments, there is also provided a polymer composition as disclosed herein for use in the manufacture of a medicament for treating or preventing an eye condition and/or an ocular disorder, for treating or preventing tumour, treating reducing angiogenesis, treating or reducing tumour migrations and recurrence, treating cancer, and/or preventing or reducing the frequency of IVT injection.

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 In various embodiments, there is also provided a method of treating or preventing an eye condition and/or an ocular disorder, treating or preventing tumour, treating reducing angiogenesis, treating or reducing tumour migrations and recurrence, treating cancer, and/or preventing or reducing the frequency of IVT injection using a polymer composition as disclosed herein. In various embodiments, the method comprises administering to a subject in need thereof, the polymer composition as disclosed herein. In various embodiments, the step of administering the polymer composition comprises injecting the polymer composition into the subject in need thereof.

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 In various embodiments, the eye condition is selected from the group consisting of neovascular retinal diseases, age related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RV).

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In various embodiments, the cancer is selected from the group consisting of breast cancer, leukemia, gastrointestinal cancer, kidney cancer, lung cancer (e.g., non-small cell lung cancer), non-Hodgkin lymphoma, melanoma, ovarian cancer, fallopian tube cancer, ocular cancer.

5

Method of preparing the polymer composition

In various embodiments, there is also provided a method of preparing the polymer composition as disclosed herein, the method comprising providing a
10 multi-block thermogelling polymer comprising a hydrophilic poly(alkylene glycol), a hydrophobic polymer, and a polyether or polyester chemically coupled together by at least one of urethane/carbamate, carbonate, ester, carbamide, an amide, ether, amine, triazole, linkages or combinations thereof; and mixing a tyrosine kinase inhibitor (TKI) with the multi-block thermogelling polymer.

15

In various embodiments, the TKI and the polymer is mixed at a temperature of no more than about 30 °C, no more than about 25 °C, no more than about 20 °C, no more than about 15 °C, no more than about 10 °C, no more than about 5 °C or no more than about 4 °C, for a period of no less than about 20
20 hours, no less than about 24 hours, no less than about 25 hours no less than about 30 hours, no less than about 35 hours, no less than about 40 hours, no less than about 45 hours, no less than about 48 hours, no less than about 50 hours, no less than about 55 hours, no less than about 60 hours, no less than about 65 hours, no less than about 70 hours, no less than about 72 hours or no
25 less than about 75 hours.

In various embodiments, the TKI is provided in a buffer (e.g., AMO buffer, phosphorated buffer saline (PBS), or the like). In various embodiments, the buffer is aqueous based. The presence of additives may be adjusted based on need in
30 the aqueous based buffer.

In various embodiments, the step of providing a multi-block thermogelling polymer comprises a step of mixing a hydrophilic poly(alkylene glycol), a hydrophobic polymer, and a polyether or polyester with a coupling agent in the presence of a metal catalyst and a suitable solvent to form said polymer. The metal catalyst may comprise a tin catalyst selected from the group consisting of alkyltin compounds, aryltin compounds and dialkyltin diesters such as dibutyltin dilaurate, dibutyltin diacetate, dibutyltin dioctanoate and dibutyltin distearate. The solvent may comprise an anhydrous solvent selected from the group consisting of toluene, benzene, and xylene. The hydrophilic poly(alkylene glycol), the hydrophobic polymer and the polyether or polyester may be mixed in a molar ratio of about 1–10: 1: 0.01 – 1.5. In some embodiments, the amount of coupling agent added is equivalent to the number of reactive groups in the composition.

The mixing of the hydrophilic poly(alkylene glycol), the hydrophobic polymer and the polyether or polyester with the coupling agent may be performed at an elevated temperature of from about 70°C to about 150°C, from about 72°C to about 148°C, 74°C to about 146°C, from about 76°C to about 144°C, from about 78°C to about 142°C, from about 80°C to about 140°C, from about 82°C to about 138°C, from about 84°C to about 136°C, from about 86°C to about 134°C, from about 88°C to about 132°C, from about 90°C to about 130°C, from about 92°C to about 128°C, from about 94°C to about 126°C, or from about 96°C to about 124°C, from about 98°C to about 122°C, from about 100°C to about 120°C, from about 102°C to about 118°C, from about 104°C to about 116°C, from about 106°C to about 114°C, from about 108 °C to about 112°C, or about 110°C.

The mixing of the hydrophilic poly(alkylene glycol), the hydrophobic polymer and the polyether or polyester with the coupling agent is carried out for at least about 12 hours, at least about 14 hours, at least about 16 hours, at least about 18 hours, at least about 20 20 hours, at least about 22 hours, at least about 24 hours, at least about 26 hours, at least about 28 hours, at least about 30 hours, at least about 32 hours, at least about 34 hours, at least about 36 hours, at least

about 38 hours, at least about 40 hours, at least about 42 hours, at least about 44 hours, at least about 46 hours, or at least about 48 hours.

In various embodiments, the mixture of the hydrophilic poly(alkylene glycol), the hydrophobic polymer, and the polyether or polyester is dissolved at a temperature of about 110 °C for no more than about 10 minutes.

The mixing of the hydrophilic poly(alkylene glycol), the hydrophobic polymer, and the polyether or polyester with the coupling agent may be performed in the absence of air and/or water/moisture and/or in the presence of an inert gas such as nitrogen. The coupling agent may comprise an isocyanate monomer that contains at least two (two or more) isocyanate functional groups. In various embodiments, the coupling agent is a diisocyanate selected from the group consisting of hexamethylene diisocyanate, tetramethylene diisocyanate, cyclohexane diisocyanate, tetramethylxylene diisocyanate, dodecylene diisocyanate, tolylene 2,4-diisocyanate, and tolylene 2,6-diisocyanate.

In various embodiments, the method further comprises removing the multi-block polymer off/from contaminants; and solubilizing the multi-block polymer in aqueous medium to form a multi-block thermogelling polymer. The step of removing the multi-block polymer off/from contaminants may comprise purifying and/or washing the multi-block polymer. The step of solubilizing the multi-block polymer in aqueous medium may comprise redissolving the polymer (e.g., final polymer powder) in a balanced salt solution (BSS). In various embodiments, BSS is water-based.

In various embodiments, the method also comprises the step of removing the multi-block polymer off/from contaminants which comprises dialysis to remove unreacted reactants, solvents and catalyst (e.g., extensive dialysis to remove unreacted PEG, solvents, and metallic catalyst, etc.).

It may be appreciated that the multi-block thermogelling polymer may be obtained or prepared through one or more of the methods and steps disclosed in Singapore Patent application no. 10202001798R, the contents of which are fully incorporated herein.

5

BRIEF DESCRIPTION OF FIGURES

FIG. 1 are graphs showing the drug release profiles of Aflibercept (A), Sunitinib Malate (STB) and CP547682-HCl (CP) from 20 wt% of different hydrogel depots: (1) Pluronic F127 with 20 wt% of hydrogel concentration (F127),
10 (2) poly(ethylene glycol (PEG)/polypropylene glycol (PPG)/polycaprolactone (PCL) urethane) with 1 % PCL content and 20 wt% of hydrogel concentration (20 wt% EPC1), and (3) poly(PEG/PPG/PCL urethane) with 3 % PCL content and 20 wt% of hydrogel concentration (20 wt% EPC3) in accordance with various
15 embodiments disclosed herein. **FIGS. 1A-1C** show the tunable in vitro drug release profiles of the three different drugs using the three different hydrogel depots. The numbers in the brackets represent the concentration of drugs in mg/mL encapsulated within the hydrogels. For instance, A(10)-EPC1 indicates that the EPC1 hydrogel contains 10 mg/mL of drug A. **FIG. 1D** shows the in vitro
20 release profile of the three different drugs, A, STB and CP, from the same hydrogel depot (20 wt% EPC1), which suggested that the nature of drugs also plays an important role in drug release. **FIG. 1E** shows the in vitro release profile of 10 mg/mL of CP from the three different hydrogel-depots. When concentration of CP reduced from 40 mg/mL (**FIG. 1C**) into 10 mg/mL (**FIG. 1E**), the complete
25 drug release was shortened significantly, suggesting the important role of CP concentration in the hydrogel depots in sustained drug release.

FIG. 2 is a graph showing the drug release profiles of CP from three different hydrogel depots F127, EPC1, and EPC3 containing CP at
30 concentrations of 40 mg/mL or 10 mg/mL, in accordance with various embodiments disclosed herein. The numbers in the brackets represent the

concentration of drugs in mg/mL encapsulated within the hydrogels. For instance, CP(10)-EPC1 indicates that the EPC1 hydrogel contains 10 mg/mL of drug CP.

FIG. 3 are graphs showing the mass loss (%) of three types of hydrogel depots F127, EPC1, and EPC3 after incubation in PBS at pH 7.4 and 37 °C on shaker at 50 rpm in accordance with various embodiments disclosed herein. **FIG. 3A** shows the mass loss (%) of the hydrogel depots prepared in AMO at a 10 wt% hydrogel concentration. **FIG. 3B** shows the mass loss (%) of the hydrogel depots prepared in AMO at a 20 wt% hydrogel concentration. **FIG. 3C** shows the mass loss (%) of the hydrogel depots prepared at a 20 wt% hydrogel concentration with 40 mg/mL CP solutions in AMO.

FIG. 4 are graphs showing the flow behaviour of different hydrogels that are in accordance with various embodiments disclosed herein, represented by viscosity as a function of oscillation strain rate. **FIG. 4A** shows the flow behaviour of EPC1 and its corresponding STB (10 or 20 mg/mL) and CP (10 or 40mg/mL) complexes. **FIG. 4B** shows the flow behaviour of EPC3 and its corresponding STB (10 or 20 mg/mL) and CP (10 or 40mg/mL) complexes. **FIG. 4C** shows the flow behaviour of F127 and its corresponding STB (10 or 20 mg/mL), CP (10 or 40 mg/mL) complexes.

FIG. 5 are Fourier Transform Infrared Spectroscopy (FT-IR) spectra of the copolymers (i.e., EPC1, EPC3, and F127) and their corresponding CP-gel depots (i.e., EPC1+CP, EPC3+CP, and F127+CP) in accordance with various embodiments disclosed herein, plotted separately from 1800 - 4000 cm^{-1} and 1200 - 1800 cm^{-1} for clarity. The FT-IR spectrum of CP547682-HCl (CP) was used as a reference.

FIG. 6 are Scanning Electron Microscopy (SEM) images of hydrogels EPC1 and EPC3 before and after the incorporation of CP at a concentration of 40 mg/mL or STB at a concentration of 20 mg/mL in accordance with various embodiments disclosed herein. The figure includes overview and cross-sectional

images of the hydrogels and their corresponding gel depots with drug incorporation. All gels were prepared in deionized (DI)-water at 20 wt% with and without of drug incorporation. SEM images were taken on the lyophilized hydrogel residues. The SEM images of the drugs alone (CP at 40 mg/mL and STB at 20 mg/mL) were used as references.

FIG. 7 are graphs and schematics related to the in vitro bioactivity characterization of in vitro gel-released CP and STB in accordance with various embodiments disclosed herein. **FIG. 7A** shows Human Umbilical Vein Endothelial Cells (HUVECs) death dependent on the concentrations of the drugs STB or CP. **FIG. 7B** is a schematic diagram of the experimental design including two aspects: 1) Drug concentration quantification after harvesting the released drug from the hydrogels; and 2) Cell exposure to the drug that has been diluted 10 times from its in vitro released concentration. **FIG. 7C** shows the detected CP concentration of CP40, which was initially encapsulated at 40 mg/mL, released from F127, EPC1, and EPC3 at pre-determined dates. **FIG. 7D** shows the detected STB concentration of STB10, which was initially encapsulated at 10 mg/mL, released from F127, EPC1, and EPC3 at pre-determined dates. **FIGS. 7E-7F** shows the cytotoxicity of in vitro released CP and STB from EPC1, EPC3, and F127, respectively, against HUVECs.

FIG. 8 are images and graphs showing that intravitreal (IVT) application of in vitro released CP from EPC1 hydrogel causes choroidal neovascularization (CNV) regression in a laser-induced mouse model in accordance with various embodiments disclosed herein. **FIG. 8A** are the Fundus Fluorescein Angiography (FFA) images taken from a representative eye on Day 7 and Day 14 after model establishment. PBS: phosphate buffer saline used as a control; A: 10 mg/mL in PBS; CP: CP-HCl at 10 mg/mL in PBS; DX: "X" represents the number of days when the image was taken. **FIG. 8B** is a graph showing the fluorescence leakage degree in choroidal lesion area (n = 6) quantified by ImageJ, based on the FFA images. The reduction in leakage area was calculated using following formula: (leakage area on the day of IVT injection: Day 0 – leakage area on Day 7 after

IVT injection)/7 days. *p < 0.05, **P < 0.01, *** P < 0.001 versus PBS control.

FIG. 8C is a graph of Isolectin B4 staining quantification by ImageJ on the choroidal flat mounts, indicating an overall reduction in the size of CNV lesions after treatment.

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FIG. 9 are images and a graph showing that intratumorally injected CP-EPC1 depot regresses the orthotopic breast tumour and retards further growth in accordance with various embodiments disclosed herein. **FIG. 9A** are In Vivo Imaging System (IVIS) images taken to monitor tumour volume in tumour-bearing
10 nude mice injected with PBS, CP at 40 mg/mL (CP40), EPC3, and 40 mg/mL of CP encapsulated in EPC3 (CP-EPC3). Tumour injections were performed on Day 0, gel injections on Day 8, and the mice were euthanized on Day 22. The images were taken on Day 7, 15, and 21. A PBS solution was used as a control. **FIG. 9B** is a graph showing the changes in tumour volume quantified from the Luciferase
15 reporter signal expressed over time as radiance. The larger the tumour, the stronger the radiance emitted in respect to volume.

FIG. 10 are images showing the ulceration in mouse models treated with different hydrogel or drug compositions (i.e., CP at 40 mg/mL (CP40), EPC3, and
20 40 mg/mL of CP encapsulated in EPC3 (CP-EPC3)) in accordance with various embodiments disclosed herein. In the experiments where CP is present, it is administered intratumorally. A PBS solution was used as a control.

FIG. 11 are immunofluorescence (IF) staining images of cells treated with
25 different thermogel or drug compositions (i.e., CP at 40 mg/mL (CP40) and 40 mg/mL of CP encapsulated in EPC3 (CP-EPC3)) in accordance with various embodiments disclosed herein. The staining includes DAPI for nuclear visualization, Ki67 to assess cell proliferation, and CD31 to evaluate endothelial cells and angiogenesis. The images demonstrate the inhibition of angiogenesis.
30 The blood vessels appear white in the images. A PBS solution was used as a control.

FIG. 12 is a schematic of preparing a biodegradable 3-block copolymeric thermosensitive hydrogel made from poly(ether ester urethane)-Poly(ethylene glycol)-Poly(propylene glycol) (EPC: PEG-PPG-PCL) as an injectable drug depot in accordance with various embodiments disclosed herein. This hydrogel
5 dissolves in aqueous environments and facilitates easy drug encapsulation. It remains in a liquid state when injected at 4°C, forming a gel upon reaching body temperature (approximately 37°C). The gel then undergoes bio-erosion, allowing for controlled and sustained drug release.

10 **EXAMPLES**

Example embodiments of the disclosure will be better understood and readily apparent to one of ordinary skill in the art from the following examples, tables and if applicable, in conjunction with the figures. It should be appreciated
15 that other modifications related to structural, biological, and/or chemical changes may be made without deviating from the scope of the invention. Example embodiments are not necessarily mutually exclusive as some may be combined with one or more embodiments to form new example embodiments. The example embodiments should not be construed as limiting the scope of the disclosure.

20

Example 1. List of drugs and hydrogel types used in this study.

Three types of thermosensitive hydrogels were included in this study (Table 1), which are commercially available Pluronic F127, EPC1 and EPC3.
25 EPC1 and EPC3 are the in-house prepared polyurethane, made up with random multi-block copolymer with PEG : PPG ratio of 4 to 1 ratio, and containing additional 1% or 3% PCL, respectively. F127 is a commercially available thermosensitive hydrogel. It is included because of its chemical similarity, which composed by tri-block copolymer (PEG-PPG-PEG) with PEG : PPG molar ratio
30 of 40 : 13 and its thermogel property.

Table 1. Summarized the polymer types used for the drug release study and the corresponding conditions used for gel preparation.

Hydrogel	Polymer backbone	PCL content	PEG to PPG ratio	Hydrogel conc. (wt%)	Buffer to prepare gel solution
EPC1	PEG/PPG/PCL	1%	4:1	20	PBS ± drug
EPC3	PEG/PPG/PCL	3%	4:1	20	PBS ± drug
F127	PEG-PPG-PEG	0%	40:13	20	PBS ± drug

A series of drugs: Aflibercept (A), tyrosine kinase inhibitors (TKIs) like sunitinib malate (STB) and CP547682-HCl were included in this work (Table 2). Those drugs are commonly used to treat cancer and some ocular diseases, like age related macular degeneration (AMD) because of their angiogenic inhibition mechanism.

Table 2. Types and concentration of the drugs used in this study.

Drugs	Abbreviation	Category	Drug Conc. In gel (mg/mL)
Aflibercept	A	Anti-VEGF macromolecule	10
CP-547682-HCl	CP	TKI	40 and 10
Sunitinib Malate	STB	TKI	20

Briefly, all drug solutions are directly dissolved or dispersed in AMO buffer and added into polymer powder for gel incorporation. To facilitate dissolution, the solutions will be left at 4°C for 3 nights with vortexing and centrifugation.

Example 2. Preparation and characterizations of hydrogel and drug-gel interaction.

2.1. Synthesis of random multi-blocked poly(PEG/PPG/PCL urethane)s copolymer.

Table 3. Molecular composition of EPC1 and EPC3.

	PEO (g)	PPG (g)	PCL-diol (g)	HMDI (mL)	DBTL (μL)
EPC1	8	2	0.10	0.80	10
EPC3	8	2	0.30	0.81	10

The poly(PEG/PPG/PCL urethane)s, namely EPC1 and EPC3, are synthesized by the polyaddition of the macromonomer-diols with hexamethylene diisocyanate (HMDI) in the presence of dibutyltindilaurate (DBTL) catalyst. The listed quantities of PEG (M_n 2,050 g mol⁻¹), PPG (M_n 2,000 g mol⁻¹), and PCL-diol (M_n 2,000 g mol⁻¹) required for the synthesis of EPC1 and EPC3 are weighed into separate clean 250 mL round bottom flasks. The macromonomer-diols are dissolved in 20 mL of anhydrous toluene at 60 °C and dried by 2 rounds of azeotropic distillation. Inert dry argon is introduced into the reaction flasks and 60 mL anhydrous toluene is added before heating up to 110 °C. 10 uL of DBTL catalyst is added followed by the required amount of HMDI. Reaction duration of EPC1 is 1 h while the reaction time of EPC3 is 30 mins, this is because EPC3 may become insoluble after synthesis if the copolymers are too long. The reactions are quenched by the addition of 5 mL of absolute ethanol. The crude copolymers are obtained by precipitating into anhydrous diethyl ether and are then further purified by dialysis. For dialysis, 10 g of crude copolymer was dissolved in 100 mL of CMOS-grade isopropyl alcohol at 60 °C and filled into regenerated cellulose dialysis tubing with 3500 Da molecular weight cut-off. Dialysis is performed against 2 L deionised water for 3 days with 2 changes of water per day. The dialysed copolymer solution is frozen and lyophilised to obtain the purified copolymers (typical yield ≈ 90 %).

2.2. Molecular characterization.

Apparent molecular weights of the copolymers were determined by Gel Permeation Chromatography (GPC) using Agilent 1260 Infinity II. The GPC system was equipped with 1260 Vial-sampler, 1260 Iso-Pump, 1260 Refractive Index Detector (RID), and an Agilent PLgel 5 μm MIXED-D column with molecular weight range of 200 Da to 400,000 Da. The system was circulated with THF of

HPLC grade at 1 mL min⁻¹ and 40 °C. Monodispersed polystyrene standards were used to obtain a calibration curve. Copolymers samples were injected at 5 mg mL⁻¹ and 20 µL for GPC measurements. ¹H nuclear magnetic resonance (NMR) spectra were recorded using a JEOL 500 MHz NMR spectrometer (Tokyo, Japan) at room temperature and chemical shifts were referred to the solvent peak of deuterated chloroform (CDCl₃, δ = 7.26 ppm). The acquisition time was 4.37 seconds, pulse repetition time was 9.37 seconds, pulse width was 90°, and 64 scans were performed per sample.

2.3. Drug encapsulation and releasing.

Aflibercept stock solution was diluted into 10 mg/mL in AMO buffer, STB was prepared at 20 mg/mL as a suspension in AMO and CP were prepared at 10 and 40 mg/mL as a suspension in AMO buffer. Copolymers, Pluronic F127, EPC1 and EPC3 (20 mg) were placed in a 1.5 mL centrifuge tube, then 100 µL of drug solution was added. For control tubes, AMO (100 µL) was used instead of drug solutions. The solutions were mixed thoroughly and allowed to stay at 4 °C for 3 nights to form drug encapsulated hydrogel-depots. The prepared drug-gel depots were transferred to 37 °C, 1 mL of pre-warmed fresh PBS was added in half hour to initiate drug release. The tubes were kept at 37 °C while shaking at 50 rpm. At certain intervals, 500µL of supernatants were collected followed by addition of an equal volume of pre-warmed fresh PBS. The collected supernatants were kept at - 20 °C for drug concentration quantification. Released aflibercept was quantified using the Pierce microBCA protein Assay kit (Thermo Fisher Scientific, Waltham, MA). STB and CP were quantified based on their typical absorbance at 426 and 261 nm using a Quartz cuvette. Quantitation of drug amount was based on a calibration curve, obtained with the corresponding stock solutions, prepared in a serial concentration range.

Aflibercept (A) is a hydrophilic anti-vascular endothelial growth factor (anti-VEGF) protein, with molecular weight of 119 kDa. It is used as the standard intravitreal injected anti-VEGF treatment for age related macular degeneration

(AMD). Both sunitinib malate (STB) and C547682-HCl (CP) belongs to tyrosine kinase inhibitor, which are synthetic small molecular drugs (< 1000 Da). STB is FDA approved, used to treat Gastrointestinal stromal tumor. It is also formulated into a microparticulate-depot to sustain release STB for wet-AMD treatment, which is under clinical trial phase 2b. PAN-90806 is the eyedrop formulation of CP-HCl for wet-AMD, under phase 1/2 clinical trial currently.

Hydrogel matrices play an important role in drug release through diffusion or matrix degradation manners. For example, A (FIG. 1A) and STB (FIG. 1B) displayed the same drug release patterns, that arranged from fastest to slowest gel matrix is F127 >> EPC3 > EPC1, despite the significant drug difference. This trend was found to agree with the gel dissociation speed as shown in FIG. 3A & B, that the complete dissolution/degradation of 20 wt% gels: F127, EPC3 and EPC1 were about 10 days, about 30 days and 30 - 40 days, respectively. Interestingly, this drug release trend changed when CP incorporated into the gel at 40 mg/mL. Firstly, the drug release trend changed into F127 >> EPC1 > EPC3. Secondly, the drug release term was significantly extended from 2-months into 1-year. This drug release trend was found to be perfectly in agreement with the gel dissociation speed (FIG. 3C), that the gel dissociation was slowed down and the trend changed into F127 >> EPC1 > EPC3 when CP were incorporated within the gel at 40 mg/mL. The release profile of A, STB and CP40 from EPC1 (20 wt%) were displayed in FIG. 1D, further disclosing the drug type effect on the release rate. The low initial burst release of A is contributed to the electrostatic interaction between A and EPC gel and its high protein molecular weight. The high burst release from STB was contributed to its small molecular nature and the improved water solubility by adopting the malate form. However, different from the expectation, CP40 displayed a low initial burst release and a long sustained release, despite its enhanced water solubility by using the CP-HCl form in this study and its small molecular weight. When CP concentration was reduced to 10mg/mL from 40mg/mL (FIG. 1E), the release trend becomes the same as A and STB and release term was significantly shortened.

2.4. Hydrolytic degradation of hydrogels and the corresponding drug depot.

Using the same design as drug release test, 20 wt% copolymers +/- drug (100 μ L) were prepared in PBS in 1.5 mL centrifuge tubes, mixed and equilibrated 3 nights at 4°C. PBS (1 mL) was added into each hydrogel samples when the temperature was equilibrated at 37 °C. Samples were then incubated and shaken at 50 rpm at 37 °C. The PBS buffer solution was replaced with fresh ones at predetermined time intervals. The process was allowed to proceed for up to one year. The experiments were done in triplicate. At various time points, the tubes were lyophilized and weighted. The mass loss of the copolymer gels after dissolution and degradation was defined as

$$\text{Mass loss (\%)} = [1 - (W_t/W_0)] \times 100\%,$$

where W_0 and W_t were the initial weight and the weight of the copolymer left at the tube after dissolution or/ and degraded at time t , respectively.

Table 4. Mass loss (in mg or %) of hydrogel depots EPC1, CP40+EPC1, EPC3, CP40+EPC3, F127, and CP40+F127 over 200 days.

[illegible]

The hydrolytic erosion process was accompanied by the mass loss of the hydrogel, as shown in FIG. 3. F127 hydrogel was found to degrade/dissolve the fastest under all circumstance, regardless gel concentration (FIG. 1A & B) and drug incorporation (FIG. 3B & C). Increased hydrogel concentration reduced the rate of weight loss, especially at the early time points (< 20 days, FIG. 3B). This contributes to increased crosslinking degree within hydrogel when the polymer concentration increased. FIG. 3C suggests that when CP was incorporated within 20 wt% polyurethane gels, the weight loss only started to happen 20 days after the initiation of drug release. 100 % gel dissolution happened at about 50 days for pure 20 wt% polyurethane gels, EPC1 and EPC3. However, less than 6 0% weight loss was observed at 100 days when CP was incorporated at 40 mg/mL.

2.5. Drug-gel interaction quantified by rheology measurements, infrared spectroscopy (FT-IR), and scanning electron microscopy (SEM).

2.5.1. Rheological measurements

Steady and dynamic rheological experiments were performed on an AR-G2 stress-controlled rheometer (TA Instruments, Newark, DE). The steady shear flow behavior of samples was evaluated in strain-controlled mode and at 60 °C. Shear-rate sweeps were conducted from 0.001 to 100 s⁻¹.

Flow curves (steady shear flow) describe the viscosity of a hydrogel as a function of applied shear rate, which determines the tendency of a material to flow (FIG.4). During the application of low shear rate from 0.0006 to 0.06 S⁻¹, the viscosity of hydrogel remained relative stable, which was mainly the influence of Brownian forces. Comparing across hydrogel and the corresponding drug complexes, CP40 complexed EPC showed the highest viscosity increasement, which are 370 times and 20 times higher than EPC3 and EPC1, respectively. But such increasement was not found in F127, which is only about 1.5 times after complexed with CP40 than F127.

2.5.2. Infrared Spectroscopy (FT-IR)

FT-IR spectral analysis of the hydrogels and drug-gel composites were performed on a Perkin Elmer Spectrum 2000 FT-IR spectrometer. All hydrogel
5 and drug-gel complexes were prepared in aqueous solution and lyophilized. Samples were run either by pelleting with spectroscopic grade KBr, or using a zinc selenide optical crystal for attenuated total reflectance (ATR).

The relevant superimposed FTIR spectra of CP40, EPC1, EPC3, and
10 F127 (FIG. 5) show evidence of enhanced supramolecular interactions between CP40 and the EPC polymers compared with F127:

- Extensive hydrogen bonding between CP40 and EPCs are discerned by the considerable broadening of CP40's O-H stretches centred $\sim 3470\text{ cm}^{-1}$. In contrast, the O-H broadening of CP40 in the presence of FTIR is much smaller,
15 indicating smaller extent of hydrogen bonding. This is further supported by the greater perturbations of CP40's C=O stretches in the presence of EPC ($1680 \rightarrow 1695\text{ cm}^{-1}$) compared with F127 ($1680 \rightarrow 1688\text{ cm}^{-1}$).
- Hydrophobic interactions between the aromatic groups of CP40 and the hydrophobic segments of EPC and F127 can be discerned from the
20 perturbations of the aromatic C=C stretch of CP40 from $1540 \rightarrow 1550\text{ cm}^{-1}$. In the solid state, the extents of hydrophobic interactions appear to be similar from the similar shifts of the C=O stretches.

2.5.3. Scanning electron microscopy (SEM)

Surface morphological characters and the pores within hydrogel were observed using SEM (instrument). Hydrogel composite was cryo-cut and fixed on
5 a cylindrical microscope stub covered with a carbon strip, coated with a 100-200 Å-thick layer of gold, and then observed by SEM.

The microstructures of hydrogel were studied using SEM and are shown in FIG. 6. The surface of EPC1 and EPC3 was compact packed, with a mesh-like
10 network from its cross-section image. CP40 alone showed an irregularly crosslinked network structure at 40 mg/mL, suggesting the formation of soft gel by itself at this concentration. By incorporating CP40, EPC1/EPC3+CP40 showed a difference in morphological difference with a regular cage-like crosslinked structure.

15

Example 3. Biological application of TKI-gel depots for neovascular retinal diseases and cancer treatment.

3.1. In vitro bioactivity of released CP & STB with a released drug 20 concentration-dependent cytotoxicity to HUVECs.

Human umbilical vascular endothelial cells (HUVECs, 12,000 cells/well of 96 well plate) were grown in endothelial grown medium (EGM) over night. Both CP and STB stock solutions were prepared at 1mg/mL in EGM and serial diluted
25 to EGM for 0.1, 1, 5 and 10 µg/mL trial concentrations. The media was then replaced with 100 µL of serial diluted drug solutions. Cells directly exposed to EGM were used as negative control. After 24 hours culture, the HUVECs were washed by PBS twice, 50 µL of 10 times diluted lysis buffer from Lactate Dehydrogenase Release (LDH) assay kit was added into each well, followed with
30 50 µL working solution 1 hour after cell lysing. 30 minutes later, stop buffer (50 µL/well) was added and then the absorbance is taken by at 490 nm with 650 nm

was reference using a microplate reader for viable cells. The percentage of viable cells were calculated based on:

$$\% \text{ Viable cells} = 100 \times (\text{Ab test} / \text{Ab control}).$$

5 Long term sustained delivering active therapeutics is important for AMD treatment. Tyrosine kinases are important cellular signalling proteins that have a variety of biological activities including cell proliferation and migration. Multiple kinases are involved in angiogenesis, including receptor tyrosine kinases. Inhibition of angiogenic tyrosine kinases has been developed as a systemic
10 treatment strategy for cancer and under clinical trial for some of angiogenic retinal diseases. In this study, we found a TKI concentration dependent cytotoxicity against HUVECs (FIG. 7A), this method was used to test the bioactivity of in vitro released CP (over 200 days, FIG. 7E) and STB (over 30 days, FIG. 7F) from 20 wt% F127, EPC1 and EPC3. The released CP and STB concentration harvested
15 at a specific date was quantified and recorded in FIG. 7C & D. Notably, the release of CP from F127 at D3 was significantly higher than that from EPC1 and EPC3 (FIG. 7C), which contributed to significant lower cell viability in FIG. 7E. On the other hand, complete release of CP was almost reached from F127 at D40 (FIG. 7C), therefore, a high corresponding cell viability using samples harvested
20 from F127 at D40 (FIG. 7E) was observed. Up to D158, the cytotoxicity of CP released from EPC1 showed higher cytotoxicity than that from EPC3 (FIG. 7E), however, with no significant difference. The same higher CP release on those days were seen in FIG. 7C. Once this release trend reversed on D200, the corresponding changes in the cytotoxicity results on the CP released on D200
25 were observed. The same higher STB release (FIG. 7D) and lower HUVECs viability (FIG. 7F) were observed, which is especially obvious for STB released from F127 gel. The high STB release from F127 on Day 1 result in low cell viability, however, the more than 75% cell viability on D10 and the lateral about 100% cell viability on D20 and D30 corresponding to the low and nearly completed STB
30 release on D10, D20 and D30. This result strongly suggested the in vitro released CP & STB are still bioactive, regardless gel types and the released days.

3.2. Intravitreal injected in vitro released CP is able to reduce vessel leakage in a laser induced CNV mice model.

Male wild-type C57B/6J mice, ranging 6 to 8 weeks old, were obtained from In-vivos (Singapore) and used for in vivo experiments. Mice were anaesthetized using intraperitoneal ketamine (150 mg/kg) & xylazine (10 mg/kg). In these eyes, photocoagulation was induced using an image guided laser system (Micro IV, Phoenix Research Laboratories, Pleasanton, CA). Seven days later after laser treatment, the fundus fluorescein angiography (FFA) images were taken as T = 0 and the mice were divided into 4 groups: PBS, aflibercept at 10 mg/mL in PBS (A), CP-HCl at 10 mg/mL in PBS (CP) and in vitro harvested CP released from EPC1 hydrogel at pre-determined time points. The 4 group samples were intravitreal injected (1 μ L) into the vitreous of the eye immediately after image taken on T = 0. Seven days later after IVT, FFA images of T = 7 were taken. The mice were then euthanized and enucleated for choroidal flat mount. Eyes were fixed in 4% paraformaldehyde in PBS overnight at 4°C. The eyecups were incubated with isolectin B4 at 4 °C for choroidal vessel staining before 3 cycles of PBS wash. After making four incisions radial to the optic nerve, the tissue was flat-mounted, and Z-stack images of the CNV lesions were taken with the confocal microscope (LSM700, Zeiss, Thornwood, NY). The angiograms and Z-stack images were imported into imageJ. The maximal border of the CNV lesion on each image was manually delineated under magnification, with the area quantified as the number of pixels per 100 μ m. The fluorescence intensity of the CNV lesions was graded using ImageJ (National Institutes of Health, Bethesda, MD) by 2 independent graders with single blinding. The results are shown in FIG. 8.

The bioactivity of released CP was further confirmed using a mouse model of laser induced CNV. When PBS buffer was IVT injected, the reduction in leakage was 17.4%, which was the smallest.

3.3. Intra-tumoral injection of CP-EPC1 depot regresses orthotopic breast cancer xenograft mice model.

The application of CP as a localized drug release depot was further tested in an in vivo orthotopic xenograft breast cancer model of NCr-Foxn1 nude mice. Orthotopic breast cancer model of MCF7-Luciferase reporter cell line (MCF7-Luc) was generated by injecting MCF7-Luc into both the abdominal mammary gland pads of nude mice. After the confirmation of solid tumour formation via IVIS at Day 0 (FIG. 9A), CP-EPC1 was injected intra-tumourally at one contralateral mammary gland site. The other site of the tumour serves as a negative control (Phosphate Buffer Saline, intra-tumourally injection). Day 7 post injection, IVIS imaging observed regression for the CP-EPC1 injection site. The significant regression or grow retardation was observable even at 14 days post injection.

Example 4. Summary and Discussion

In the foregoing examples, three types of thermosensitive hydrogels: commercially available pluronic F127, EPC1 and EPC3 were prepared at 20wt% and used to contain drugs. Those polymers have fixed PEG to PPG ratio at 4 to 1 but vary in PCL content from 0 to 1% to 3%, respectively. When the hydrogel contains no drug, complete hydrogel (20wt%) dissolution happens at ~10 days for F127, ~40 days for EPC3 and ~50 days for EPC1.

Three types of anti-VEGFs, aflibercept (anti-VEGF macromolecule) and two small molecular TKIs, sunitinib malate (STB) and CP, are directly incorporated into hydrogels by dissolving polymer powder in the desired drug solution in phosphate buffer saline (PBS). When CP concentration is 20mg/mL, the release was extended into one year together with significantly delayed gel dissolution in EPC1 and EPC3. Achieving long-term drug release from biodegradable hydrogel depots is typically challenging due to their inherently hydrophilic nature. However, the examples show that more than one-year sustained in vitro release of a tyrosine kinase inhibitor (TKI), CP-547632 (CP), may be achieved from a biodegradable 3-block copolymeric poly(ether ester

urethane)-Poly(ethylene glycol)-Poly(propylene glycol) (EPC: PEG-PPG-PCL) thermosensitive hydrogel.

It will be appreciated that the long-term release of CP from the EPC hydrogel is attributed to the CP-facilitated gelation process of EPC, which is PCL content-dependent and linearly related to CP concentration. The extended drug release and gel dissolution was not found for aflibercept and STB and it was not found when using F127 gel. The scanning electron microscope (SEM) topography and cross-sectioning images of the gels suggested that the same drug promoted gel crosslinking with the increased pores and reduced pore-size within the CP incorporated EPC1 and EPC3. The surprising technical effect of the TKI promoting further gelation of the hydrogel depot through physical interaction has not been previously known or suggested.

The FT-IR data disclosed the crosslinking mainly contribute to hydrogen bonding formed with hydroxyl group and carbonyl groups and the hydrophobic interaction with alkyls between CP and EPC polymers.

The bioactivity of released STB and CP from hydrogel depot is proved by in vitro HUVEC cytotoxicity. The cell death increase with the increased released drug concentration during the whole drug release course, suggesting the stability of the drug within hydrogel within the one-year drug releasing term and in vivo mouse laser induced choroidal neovascularization (CNV) model.

The potential biological applications of released CP for neovascular retinal diseases was confirmed with the speed up vessel leakage after injecting 1uL of in vitro released CP into the vitreous of CNV treated mice. The anti-cancer activity of the CP-EPC1 depot was proved by the significantly reduced cancer volume 1 & 2 weeks after intratumor injection of the depot using a breast tumor bearing nude mice model.

As far as the inventors are aware, the longest therapeutic effect using the clinical trial product intravitreal axitinib implant OTX-TKI is about 1 year based on results obtained from a clinical trial. Thus, the present technology offers an alternative option which may potentially provide comparable or even longer
5 therapeutic effect than treatment using OTX-TKI.

Indeed, embodiments of the present technology are believed to provide several advantages over existing technologies, which include but are not limited to the following:

- 10 • localized long-lasting release of the active tyrosine kinase inhibitor (TKI) may significantly impact the treatment of retinal diseases, such as age-related macular degeneration (AMD), diabetic macular edema (DME), retinal vein occlusion (RV), etc. and diseases requiring long-term TKI treatment, such as cancers;
- 15 • easy drug encapsulation in aqueous environments;
- injectable polymer composition which minimizes damage to surrounding tissues;
- use of soft tissue nature of material;
- localized drug delivery which helps to minimize side effects, for example, the
20 localized, long-term drug release may help overcome the issue of drug resistance normally reported 8 months after treatment and ease the toxic effects associated with long-term oral supplements;
- the need to validate ocular efficiency and address safety concerns may be mitigated as both the drug (CP) and hydrogel depot (EPC) are well tested for
25 ocular application;
- the CP-loaded hydrogel depot can be achieved by a simple mixing process;
- the gelation process between CP and gel molecule is through physical interaction, therefore, avoiding the use of toxic reactive chemicals and stringent reaction conditions;
- 30 • the gelation process is highly reproducible with high success rate;

- the CP-loaded hydrogel depot may be applied as a transparent implant to treat eye conditions and thus does not adversely interfere with the patient's eyesight; and
 - the sustained release of the TKI may reduce the frequency of bi-monthly
- 5 intravitreal injections of anti-VEGFs to a yearly-based treatment.

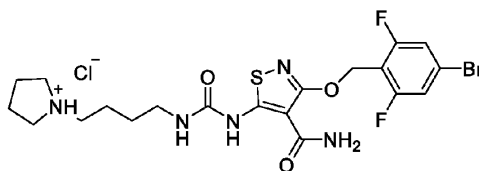
It will be appreciated by a person skilled in the art that other variations and/or modifications may be made to the embodiments disclosed herein without departing from the spirit or scope of the disclosure as broadly described. For

10 example, in the description herein, features of different exemplary embodiments may be mixed, combined, interchanged, incorporated, adopted, modified, included etc. or the like across different exemplary embodiments. The present embodiments are, therefore, to be considered in all respects to be illustrative and not restrictive.

15

CLAIMS

1. A polymer composition comprising:
a multi-block thermogelling polymer comprising a hydrophilic poly(alkylene glycol), a hydrophobic polymer, and a polyether or polyester chemically coupled together by at least one of urethane/carbamate, carbonate, ester, carbamide, an amide, ether, amine, triazole, linkages or combinations thereof; and
a tyrosine kinase inhibitor (TKI) intermixed with the multi-block thermogelling polymer.
2. The polymer composition as claimed in claim 1, wherein the TKI interacts with the multi-block thermogelling polymer to facilitate gelation of the multi-block thermogelling polymer.
3. The polymer composition as claimed in any one of the preceding claims, wherein the TKI increases the viscosity of the polymer composition at least 10 times as compared to when the TKI is absent.
4. The polymer composition as claimed in any one of the preceding claims, wherein the TKI comprises a VEGFR inhibitor (e.g., VEGFR-2 inhibitor) and/or FGFR inhibitor.
5. The polymer composition as claimed in any one of the preceding claims, wherein the TKI comprises one or more of the following:
- CP-547632, analogs thereof, or pharmaceutically acceptable salts thereof; or
 - a compound of Formula (I),



Formula (I).

- 5 6. The polymer composition as claimed in any one of the preceding claims,
wherein the hydrophilic poly(alkylene glycol) comprises poly(ethylene glycol)
(PEG).
- 10 7. The polymer composition as claimed in any one of the preceding claims,
wherein the hydrophobic polymer is selected from the group consisting of
poly(propylene glycol) (PPG), poly(lactic-co-glycolic acid) (PLGA), polylactic
acid (PLA), poly(N-isopropylacrylamide) (PNIPAAm), polypeptides, or
combinations thereof.
- 15 8. The polymer composition as claimed in any one of the preceding claims,
wherein the polyether or polyester comprises one or more of polycaprolactone
(PCL), polytetrahydrofuran (PTHF), polyhydroxybutyrate (PHB), polylactic-co-
glycolic acid (PLGA), and polylactic acid (PLA).
- 20 9. The polymer composition as claimed in any one of the preceding claims,
wherein the concentration of TKI in the polymer composition is no less than
about 10 mg/L.
- 25 10. The polymer composition as claimed in any one of the preceding claims,
wherein the molar ratio of the hydrophilic poly(alkylene glycol) to the
hydrophobic polymer is 1-10:1.
11. The polymer composition as claimed in any one of the preceding claims,
wherein the polyether or polyester is present in an amount falling in the range
of from 1 wt% to 10 wt% in the multi-block polymer.
- 30 12. The polymer composition as claimed in any one of the preceding claims,
wherein the molar ratio of the hydrophilic poly(alkylene glycol) to the

hydrophobic polymer to the polyether or polyester in the multi-block polymer is in the range of about 1 – 10: 1: 0.01 – 1.5.

13. The polymer composition as claimed in any one of the preceding claims,
5 wherein the multi-block polymer is present at an amount of up to 30% w/v in an aqueous medium.
14. The polymer composition as claimed in any one of the preceding claims,
10 wherein the pH of the composition falls in the range of from 7.1 to 7.4.
15. The polymer composition as claimed in any one of the preceding claims,
wherein the polymer composition has a critical gelation temperature of no less than 4 °C.
- 15 16. The polymer composition as claimed in any one of the preceding claims,
further comprises one or more pharmaceutically active ingredient that is different from the TKI.
17. The polymer composition as claimed in claim 16, wherein the
20 pharmaceutically active ingredient that is different from the TKI is selected from the group consisting of aflibercept, sunitinib malate and combinations thereof.
18. The polymer composition as claimed in any one of the preceding claims,
25 wherein the polymer composition has a drug release profile of no less than 2 months.
19. The polymer composition as claimed in claim 18, wherein the polymer
composition has a drug release profile of no less than 12 months.
- 30 20. The polymer composition as claimed in any one of the preceding claims, for use in medicine.

21. The polymer composition as claimed in any one of the preceding claims, for use in treating or preventing an eye condition, for treating or preventing tumour, treating or reducing angiogenesis, and/or treating cancer.
- 5
22. Use of the polymer composition as claimed in any one of the preceding claims, in the manufacture of a medicament for treating or preventing an eye condition, for treating or preventing tumour, treating or reducing angiogenesis, and/or treating cancer.
- 10
23. A method of treating or preventing an eye condition, treating or preventing tumour, treating or reducing angiogenesis, and/or treating cancer, the method comprises administering to a subject in need thereof, the polymer composition as claimed in claims 1 to 19.
- 15
24. The polymer composition of claim 21, the use of claim 22 or the method of claim 23, wherein the eye condition is selected from the group consisting of neovascular retinal diseases, age related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RV).
- 20
25. The polymer composition of claim 21, the use of claim 22 or the method of claim 23, wherein the cancer is selected from the group consisting of breast cancer, leukemia, gastrointestinal cancer, kidney cancer, lung cancer (e.g., non-small cell lung cancer), non-Hodgkin lymphoma, melanoma, ovarian cancer, fallopian tube cancer, ocular cancer.
- 25
26. A method of preparing the composition of any one of claims 1 to 21, the method comprising:
- 30
- providing a multi-block thermogelling polymer comprising a hydrophilic poly(alkylene glycol), a hydrophobic polymer, and a polyether or polyester chemically coupled together by at least one of urethane/carbamate,

carbonate, ester, carbamide, an amide, ether, amine, triazole, linkages or combinations thereof; and

mixing a tyrosine kinase inhibitor (TKI) with the multi-block thermogelling polymer.