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(54) Title: PROTEASE TRIGGERED RELEASE OF MOLECULES FROM HYDROGELS

(57) Abstract: The invention relates to compositions comprising (i) biocompatible hydrogel and (ii) one or more therapeutic agents contained within said hydrogel; wherein the hydrogel is cross-linked utilizing a cross-linker comprising a peptide sequence that is capable of being degraded by an enzyme; the therapeutic agent being effective as a treatment of a condition related to the presence of the enzyme.



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PROTEASE TRIGGERED RELEASE OF MOLECULES FROM HYDROGELS

RELATED APPLICATIONS

[0001] The present application claims benefit of U.S. Provisional Patent Application No. 61/356,800, filed June 21, 2010, the disclosure of which is incorporated herein in its entirety.

TECHNICAL FIELD

[0002] The present invention concerns the use of hydrogels to locally deliver pharmaceuticals/factors based on elevated local enzyme levels.

BACKGROUND

[0003] Cardiac problems are a major global health concern. According to the American Heart Association, 1.26 million people suffer from heart attacks annually. If the patient survives, they are at a high risk for developing heart failure. Left ventricular remodeling contributes to heart failure, which in 1995, affected 2 million people (Schocken *et al*, J Am Coll Cardiol. 1992 Aug;20(2):301-6). The incidence and death by heart failure has been steadily increasing for years, suggesting that the potential patient population may continue to grow significantly over time. Many therapeutic approaches, both pharmacologic and surgical, have been developed to treat heart failure. Most therapies are directed at patients who have already developed symptoms. Few if any are directed at patients in the early post myocardial infarction time period before symptoms develop. None are directed at limiting extracellular matrix destruction by matrix metalloproteinases. Typically, a patient suffering a heart attack is given a cocktail of medicines that can be difficult to titrate and manage. Efficacy is often not achieved. The population of heart failure patients continues to grow in spite of the current therapeutic armamentarium.

[0004] In a paper published in Circulation (June 2003, p 2857), Wilson *et al* determined that certain matrix metalloproteinases (MMP), such as MMP-13 are upregulated post-MI, perhaps resulting in the left ventricular remodeling that adversely affects heart function. Further, they found that the antagonist to MMP-13, TIMP, is down-regulated. In particular, this study demonstrated increased levels of MMP-13 and MT1-MMP after MI, which may have particular significance with respect to pathological remodeling. Specifically, MMP-13 is increased in end-stage cardiomyopathies and aggressive breast carcinomas. MMP-13 degrades fibrillar collagens and therefore may contribute to myocardial extracellular remodeling. Increased MT1-MMP

levels within the transition and MI regions may have particular significance, for two reasons. First, MT1-MMP degrades a wide range of extracellular matrix proteins. Second, MT1-MMP can proteolytically process soluble pro-MMPs, such as pro-MMP-13,2 and thereby amplify local proteolytic activity. The LV regions in which this local induction of MT1-MMP and MMP-13 occurred were paralleled by decreased TIMP levels. The present study demonstrated that increased MT1-MMP levels and decreased TIMP-4 levels were correlated to the extent of regional LV remodeling. This regional imbalance between these specific MMPs and TIMPs probably contributed to continued regional expansion in the post-MI myocardium.

[0005] There is a need in the art for treatments to minimize left ventricular remodeling associated with MI. In addition to LV remodeling uses, there is also a need in the art to provide regional delivery of MMP inhibiting therapy that would be active only where MMP's are active.

SUMMARY

[0006] In some aspects, the invention concerns compositions comprising a biocompatible hydrogel; and a therapeutic agent contained within the hydrogel. The hydrogel is cross-linked utilizing a cross-linker comprising a peptide sequence that is capable of being degraded by an enzyme; said therapeutic agent being effective as a treatment of a condition related to the presence of said enzyme. In some embodiments, the therapeutic agent is a tissue inhibitor of matrix metalloprotease, a growth factor, or a cell homing factor. In certain embodiments, such therapeutics include tissue inhibitor of matrix metalloprotease contained within the hydrogel and the hydrogel is cross-linked utilizing a cross-linker comprising a peptide sequence that is capable of being degraded by a matrix metalloprotease; the matrix protease being inhibited by said tissue inhibitor of matrix metalloprotease.

[0007] In some compositions, the hydrogel comprises one or more of hyaluronic acid and polyethylene glycols.

[0008] Certain compositions have the peptide sequence incorporated into the cross-linker via reaction of thiol groups of cysteines with acrylates or methacrylates. Some compositions have a cross-linker that comprises the peptide sequence and at least one of hyaluronic acid or polyethylene glycol. Some compositions consist of reaction of an aldehyde-containing molecule with a hydrazide group on the end of the peptide.

[0009] In some embodiments, the tissue inhibitor of matrix metalloprotease is TIMP-3. In certain embodiments, the matrix metalloprotease is MMP-13 or MMP-2.

[0010] Another aspect of the invention concerns methods for treating myocardial infarction comprising administering to a patient in need of such treatment a composition

disclosed herein. In some embodiments, the patient is a mammal. In some preferred embodiments, the patient is a human.

[0011] Yet another aspect of the invention concerns methods of delivery of an inhibitor of matrix metalloprotease comprising: (i) administering a hydrogel of disclosed herein to a patient; (ii) allowing the hydrogel to contact matrix metalloprotease; and (iii) the contact resulting in the release of at least a portion of said tissue inhibitor of matrix metalloprotease. In some embodiments, the delivery is accomplished through a syringe or catheter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] **Figure 1** illustrates synthesis of HA-aldehyde (Synthesis 1) for use in forming a hydrogel.

[0013] **Figure 2** presents analytical analysis of the HA-aldehyde shown in Figure 1.

[0014] **Figure 3** illustrates synthesis of HA-peptide hydrazide for use in forming the hydrogel. The product has a hyaluronic acid backbone modified with either an aldehyde or a peptide with a hydrazide end.

[0015] **Figure 4** illustrates synthesis of HA-hydrazide (Synthesis 2). The example depicted in the figure has 33% modification.

[0016] **Figure 5** illustrates formation of a hydrogel by mixing precursors containing a hyaluronic acid backbone modified with either an aldehyde or a peptide with a hydrazide end. By using a peptide that is MMP sensitive, the gel will form an enzyme sensitive hydrogel.

[0017] **Figure 6** illustrates gel formation through mixing of Synthesis 1 and Synthesis 2: hydrazone formation via hydrazide-aldehyde reaction. Gelation/properties can be controlled by HA modification and ratio of HA-aldehyde to HA-hydrazide.

[0018] **Figure 7** illustrates a MMP-specific gel with a peptide crosslinker that responds to MMP-1, MMP-2.

[0019] **Figure 8** illustrates mass loss with the gel of Figure 7 as a function of time upon exposure to MMP (at day 1 or day 3).

[0020] **Figure 9** illustrates the crosslinking of an acrylated hyaluronic acid with a peptide (containing thiols on each end).

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0021] The present invention may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures and examples, which form a part of this disclosure. It is to be understood that this invention is not limited to the

specific devices, methods, applications, conditions or parameters described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed invention. Also, as used in the specification including the appended claims, the singular forms “a,” “an,” and “the” include the plural, and reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise. The term “plurality”, as used herein, means more than one. When a range of values is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another embodiment. All ranges are inclusive and combinable.

[0022] It is to be appreciated that certain features of the invention which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any subcombination. Further, reference to values stated in ranges include each and every value within that range.

[0023] Hydrogels containing degradable cross-linkers can be utilized in the delivery of therapeutic and/or diagnostic agents to a specified site within a patient. In the present invention, the cross-linkers comprise a peptide sequence that is degradable by particular enzymes. When one utilizes a hydrogel containing a therapeutic agent to a condition that is associated with the presence of a particular enzyme, one can selectively deliver the agent to a specified target within the patient because the enzyme will cause degradation of the cross-links which will result in release of the agent.

[0024] Any peptide sequence containing linking group that is capable of being degraded by the desired enzyme can be utilized. In some embodiments, the peptide is at least two units in length. While the peptide has no maximum length so long as it is degradable by the desired enzyme, in certain embodiments, the peptide is up to 20, 30, 50 or 100 units in length. Some peptides are at least 5 or 10 units in length. Each of these upper and lower limits are intended to be combinable to reflect some preferred peptide lengths. Examples of suitable peptides include GCRDGPQGIWGQDRCG, GGPQGIWGQGCG, and GCGQGWIQPGGG.

[0025] One application concerns treatment of myocardial infarction (MI). Left ventricular (LV) remodeling after myocardial infarction, for example, is a common structural event and contributes to increased morbidity and mortality. Matrix metalloproteases (MMPs) have been demonstrated to contribute to LV remodeling after MI by contributing to the

breakdown of interstitial matrix proteins like collagen and elastin. We have demonstrated that upregulation of MMPs and down regulation of their naturally occurring inhibitors, tissue inhibitors of matrix metalloproteinases (TIMPs), occur in a type, region and temporal specific manner within the myocardium after MI. The use of a broad spectrum, systemically delivered MMP inhibitor is associated with significant adverse reactions. The ability to inhibit specific MMPs in specific regions of the heart at specific times after MI will lead to improved outcomes after MI for a large number of patients.

[0026] Regional delivery of MMP inhibiting therapy that would be active only where MMP's are active can also be utilized in treatments of other conditions. Arthritis is an example of another disease where this approach could be useful. Any disease state where localized release of therapeutics where certain MMPs exist may be treated by the hydrogel systems of the invention.

[0027] One concept that is disclosed herein is the use of synthetic hydrogels that incorporate peptide sequences that degrade in the presence of certain enzyme/proteases. The degradation or breaking of these crosslinks in the hydrogel alters the crosslinking density, which in turn alters the material properties (*i.e.* mechanics), which alters the diffusion of molecules through the hydrogel and hence delivery into the affected tissue. One area where this approach would be important is in disease processes where there are region specific changes in the levels of MMPs. An important example of such a pathologic phenomenon is post-MI LV remodeling. There may be target molecules (*e.g.*, TIMPs) that can alter MMP activity and treat or prevent this disease. With a material such as this, the release of these molecules will be locally dependent on the level of protease activity at those sites. For example MMP-13 is known to be up-regulated in the peri-infarct region in the first 8 weeks after MI and TIMP-3 (an inhibitor of MMP-13) down regulated during this time period; a hydrogel that is degraded only in the presence of MMP-13 and released TIMP-3 locally as it was degraded would likely have a beneficial effect on LV remodeling.

[0028] Hydrogels are well known in the art and are generally formed by the reaction of a macromer having a biocompatible backbone with a cross-linking agent. Any suitable hydrogel may be utilized. Types of materials that could be used for this purpose include crosslinked synthetic hydrogels that are based on molecules like hyaluronic acid or polyethylene glycols. Suitable hydrogels also include those constructed using polyesters, polyurethanes, polysaccharides, proteins, and combinations thereof. Polyesters, poly(ethylene oxide) (PEO), proteins and the like are also suitable polymeric materials can also be used as a polymeric

component of the hydrogel. General synthetic methods for making hydrogels can be found, for example in Burdick, *et al*, *Soft Matter*, 2009, 5, 1601–1606.

[0029] A partial listing of polysaccharides that are useful in the claimed invention includes hyaluronic acid, amylase, amylopectin, glycogen, cellulose, heparin, agarose, alginate, and the like. In some embodiments, hyaluronic acid or any combination thereof is particularly suitable for use in the instant invention. In some embodiments – such as those embodiments that include hyaluronic acid – the biocompatible backbone unit is capable of enzymatic degradation.

[0030] In other embodiments, the biocompatible backbone is capable of hydrolytic degradation. Those embodiments are considered useful where a user may desire a degradable macromer whose degradation is dependent primarily on exposure to aqueous medium without the additional complication of a macromer that is also susceptible to enzymatic degradation. In some embodiments, the macromer is capable of both enzymatic and hydrolytic degradation.

[0031] The macromers may include a range of polymerizing moieties, such as acrylates, methacrylates, and the like. In some embodiments, the polymerizing moiety includes a carbon-carbon double or triple bond. The moiety is suitably polymerized by photopolymerization, by free radical-initiation, or by other methods of polymerization known to those of skill in the art.

[0032] The peptide moieties can be incorporated into the cross-linkers by reaction of active hydrogen atoms. In some embodiments, the active hydrogen atoms can be part of hydroxy, thiol, or amine groups (including hydrazine). In some embodiments, the peptide can be incorporated as crosslinks through the addition reaction of thiols in cysteines in the peptides with acrylate or methacrylates, vinyl sulfones, or maleimides on these molecules.

[0033] Any useful therapeutic agent can be utilized with the present invention. In some embodiments, growth factors (vascular endothelial growth factor (VEGF), for example), stem cell homing factors (SDF-1 α , for example), or tissue inhibitor of matrix metalloprotease (TIMP-1, TIMP-2, TIMP-3, and TIMP-4, for example).

[0034] In some embodiments, the therapeutic molecule may be directly encapsulated during the gelation process by mixing the molecule with the pre-cursor solutions.

[0035] The compositions of the instant invention may be administered by methods well known to those skilled in the art. Such methods include local or systemic administration. In some embodiments, administration is topical. Such methods include ophthalmic administration and delivery to mucous membranes (including vaginal and rectal delivery), pulmonary (including inhalation of powders or aerosols; intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous,

intraperitoneal or intramuscular injection or infusion; or intracranial (including intrathecal or intraventricular, administration).

[0036] Pharmaceutical compositions and formulations for topical administration include but are not limited to ointments, lotions, creams, transdermal patches, gels, drops, suppositories, sprays, liquids and powders. Utilization of conventional pharmaceutical carriers, oily bases, aqueous, powder, thickeners and the like may be used in the formulations.

[0037] The pharmaceutical compositions may also be administered in tablets, capsules, gel capsules, and the like.

[0038] Penetration enhancers may also be used in the instant pharmaceutical compositions. Such enhancers include surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants. Such enhancers are generally described in U.S. Patent No. 6,287,860, which is incorporated herein by reference.

[0039] In addition to treatment of diseases or other conditions, compositions disclosed herein may also be useful prophylactically.

[0040] In some preferred embodiments, the hydrogels can be delivered locally either via implantation or as an injection procedure, potentially through syringes or catheters.

[0041] Due to the variety of therapeutic agents that can be utilized with the cross-linked hydrogel systems, a wide variety of diseases and disorders can be treated with the technology described herein. Post MI remodeling is one application of the proposed therapeutic approach. In addition, the disclosed concept could be applied in any ailment in which MMPs contribute to the pathophysiology of the disease. Treatment methods comprise administration of the instant compositions by any appropriate method to a patient in need of such treatment. In some embodiments, the patient is a mammal. In certain preferred embodiments, the patient is a human.

[0042] The invention is illustrated by the following examples which are intended to be illustrative and not limiting in scope.

Examples

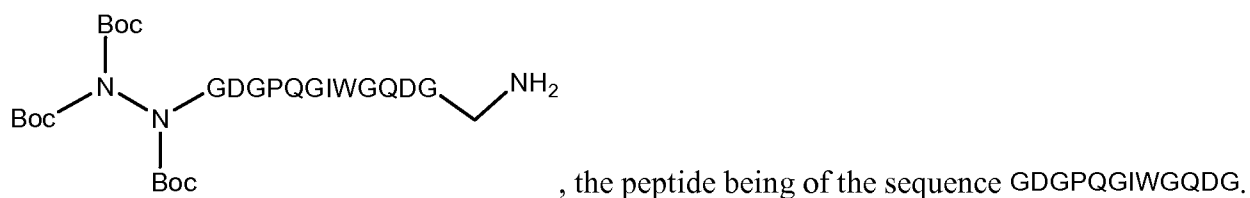
[0043] Unless noted otherwise, all percentages are by weight.

Example 1: Synthesis of HA-aldehyde

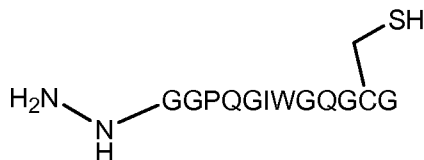
[0044] Hyaluronic acid (HA) is contacted with NaIO_4 to produce the aldehyde derivative (Synthesis 1) depicted in **Figure 1**. **Figure 2** presents analytical data for the HA-aldehyde.

Example 2: Synthesis of HA-peptide hydrazide

[0045] Hyaluronic acid (HA) is contacted with EDC/HoBT at pH 6.8 for 12-14 hours to produce the intermediate depicted in **Figure 3**. The intermediate is then contacted with trifluoroacetic acid (TFA, 49%), trisopropyl silane (TIS, 1%), and water (50%) for 4 hours to produce the hydrazide depicted in **Figure 3**. EDC is ethyl-(N',N'-dimethylamino) propylcarbodiimide hydrochloride (EDC). HoBT is 1-hydroxybenzotriazole. One peptide that could be used is GCRDGPQGIWGQDRCG, which cleaves in the presence of MMP-2, but somewhat nonspecifically. In the example, the cross-linker utilized was of the formula:

**Example 3: HA-hydrazide synthesis**

[0046] HA-hydrazide synthesis (Synthesis 2) having 33% modification was performed as depicted in **Figure 4**. The peptide utilized was of the formula:



which is represented by the shorthand



[0047] Analytical analysis of the product is also presented in **Figure 4**.

Example 4: Hydrogel formation

[0048] Hydrogel formed by mixing the aldehyde of Example 1 with the hydrazide of Example 2 to form the hydrogel depicted in **Figure 5**.

Example 5: Gel formation through mixing of Synthesis 1 and Synthesis 2

[0049] Gel was formed through a mixing of the products of synthesis 1 and synthesis 2 as presented in **Figure 6**. Gelation/properties can be controlled by HA modification and ratio of

HA-aldehyde to HA-hydrazide. Differences in time are illustrated by the plots presented in **Figure 6**.

Example 6: MMP-specific gel synthesis

[0050] **Figure 7** shows a MMP-specific gel with a peptide crosslinker that responds to MMP-1, MMP-2. In this example, the peptide has the sequence GCGQGWIGQPGGG. Response to MMP of this gel is illustrated in **Figure 8**.

Example 7: Crosslinking of an Acrylated Hyaluronic Acid

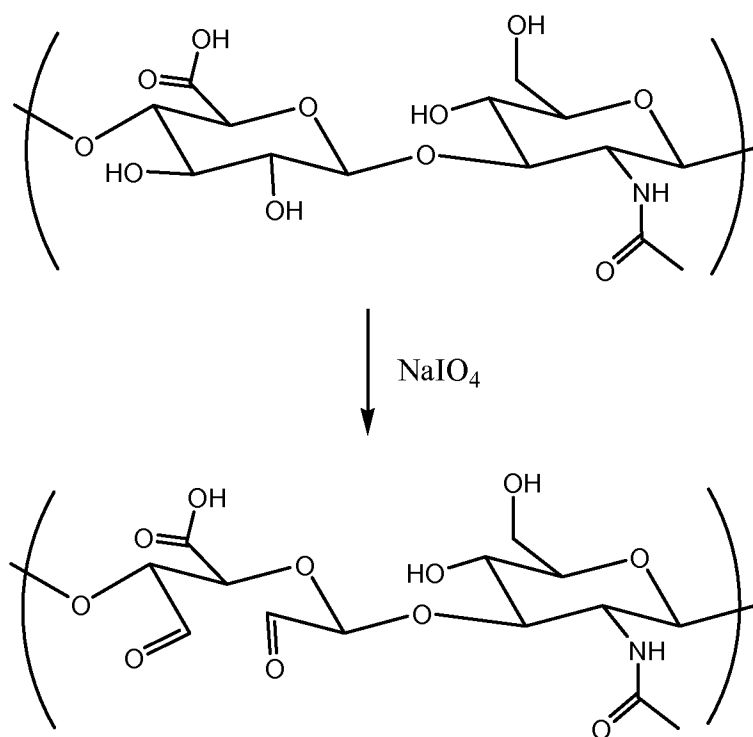
[0051] Schematic of the crosslinking of an acrylated hyaluronic acid with a peptide (containing thiols on each end) is depicted in **Figure 9**.

What is Claimed:

1. A composition comprising:
biocompatible hydrogel; and
a therapeutic agent contained within said hydrogel;
wherein said hydrogel is cross-linked utilizing a cross-linker comprising a peptide sequence that is capable of being degraded by an enzyme; said therapeutic agent being effective as a treatment of a condition related to the presence of said enzyme.
2. The composition of claim 1, wherein said therapeutic agent is a tissue inhibitor of matrix metalloprotease, a growth factor, or a cell homing factor.
3. The composition of claim 1, wherein said therapeutic is a tissue inhibitor of matrix metalloprotease contained within said hydrogel and said hydrogel is cross-linked utilizing a cross-linker comprising a peptide sequence that is capable of being degraded by a matrix metalloprotease; said matrix protease being inhibited by said tissue inhibitor of matrix metalloprotease.
4. The composition of claim 3, wherein said hydrogel comprises one or more of hyaluronic acid and polyethylene glycols.
5. The composition of claim 3, wherein said peptide sequence is incorporated into the cross-linker via reaction of thiol groups of cysteins with acrylates or methacrylates.
6. The composition of claim 3, where said tissue inhibitor of matrix metalloprotease is TIMP-3.
7. The composition of claim 3, wherein said matrix metalloprotease is MMP-13 or MMP-2.
8. The composition of claim 1, wherein said cross-linker comprises said peptide sequence and at least one of hyaluronic acid or polyethylene glycol.
9. The composition of claim 1, wherein said hydrogels comprise at least one of hyaluronic acid and polyethylene glycols.

10. A process for treating myocardial infarction comprising administering to a patient in need of such treatment a composition of claim 1.
11. The process of claim 10, wherein said patient is a mammal.
12. The process of claim 10, wherein said patient is a human.
13. The process of claim 10, wherein said peptide sequence is incorporated into the cross-linker via reaction of thiol groups of cysteins with acrylates or methacrylates.
14. The process of claim 8, wherein said hydrogels comprise at least one of hyaluronic acid and polyethylene glycols.
15. A process for delivery of an inhibitor of matrix metalloprotease comprising:
 - administering a hydrogel of claim 1 to a patient;
 - allowing said hydrogel to contact matrix metalloprotease;
 - said contact resulting in the release of at least a portion of said tissue inhibitor of matrix metalloprotease.
16. The process of claim 15, wherein said tissue inhibitor of matrix metalloprotease is TIMP-3.
17. The process of claim 15, wherein said matrix metalloprotease is MMP-13 or MMP-2.
18. The process of claim 15, wherein the delivery is accomplished through a syringe or catheter.

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Synthesis 1: HA-Aldehyde
Synthesis

Figure 1

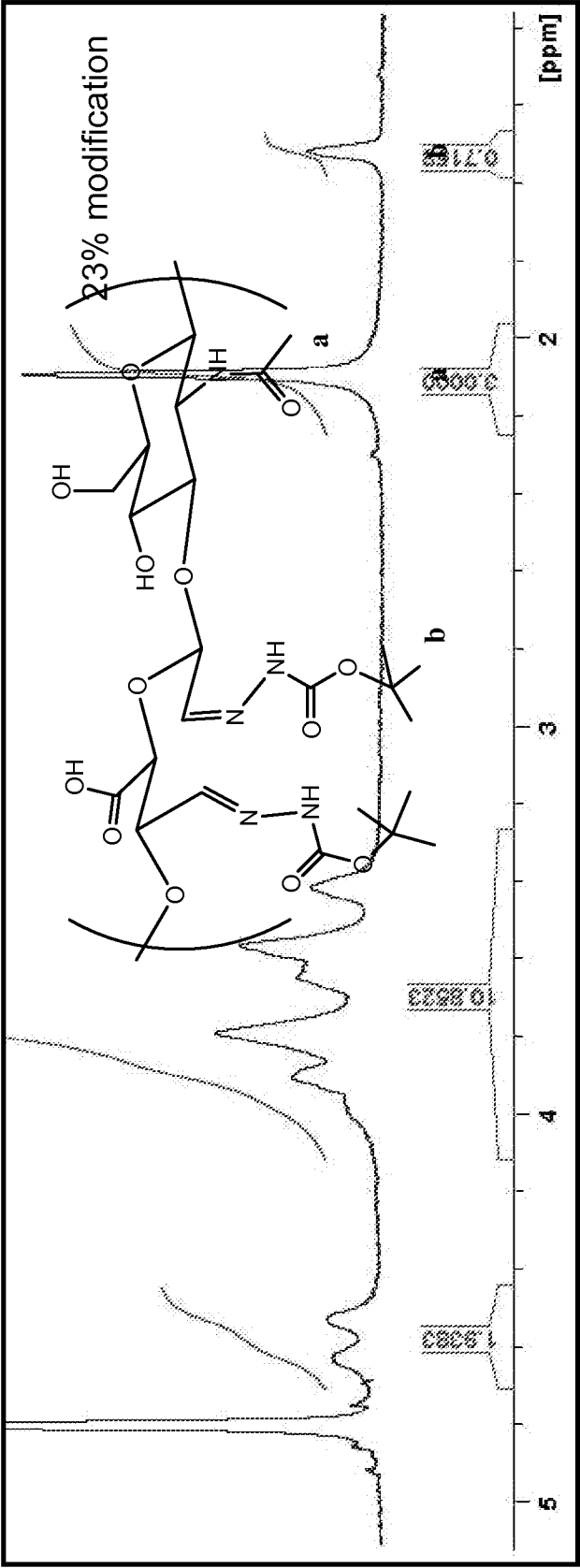


Figure 2

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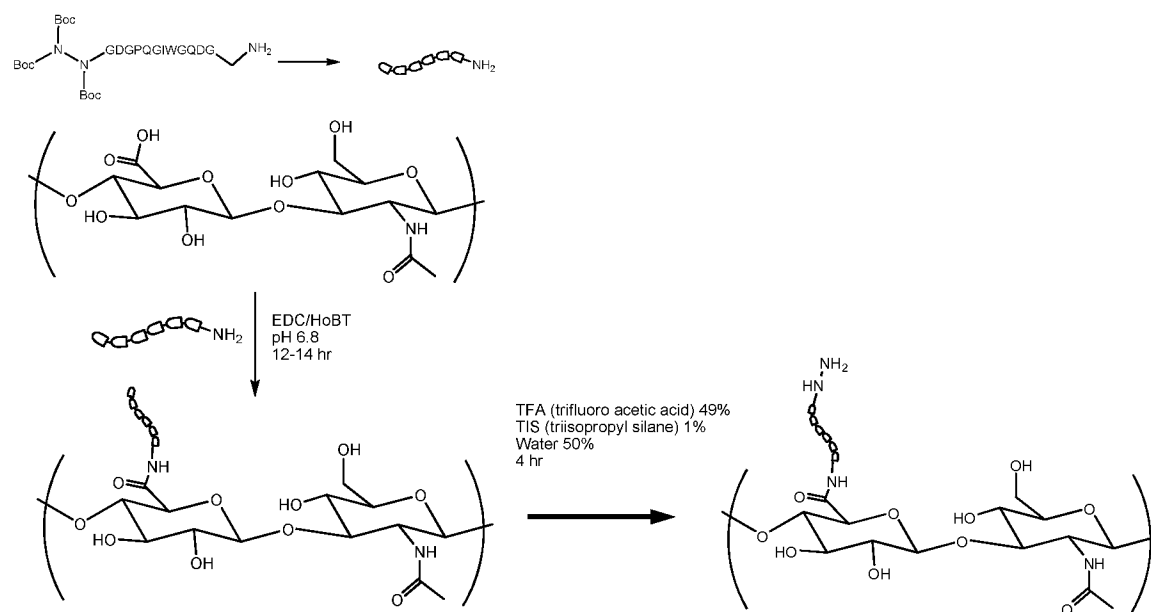


Figure 3

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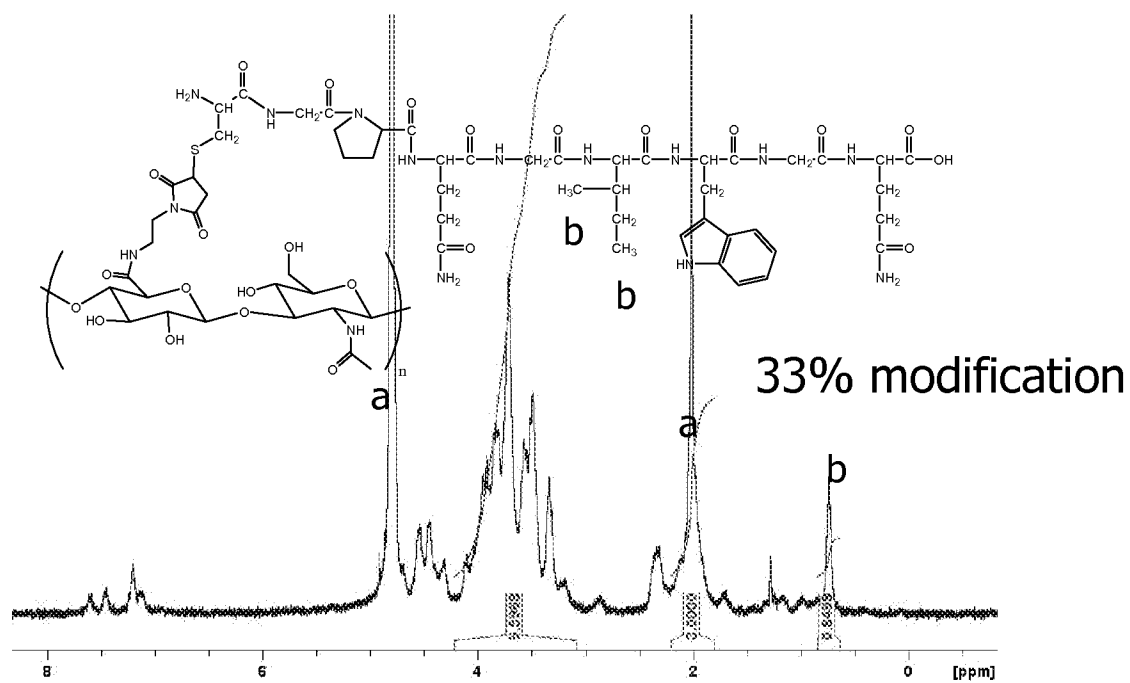
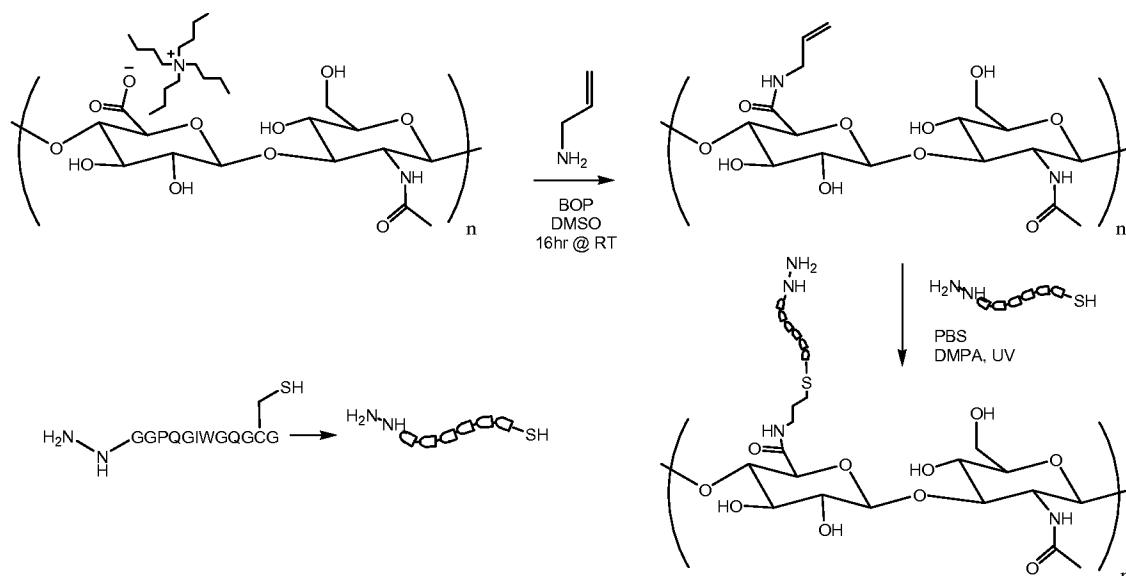
Synthesis 2: HA-Hydrazide
Synthesis

Figure 4

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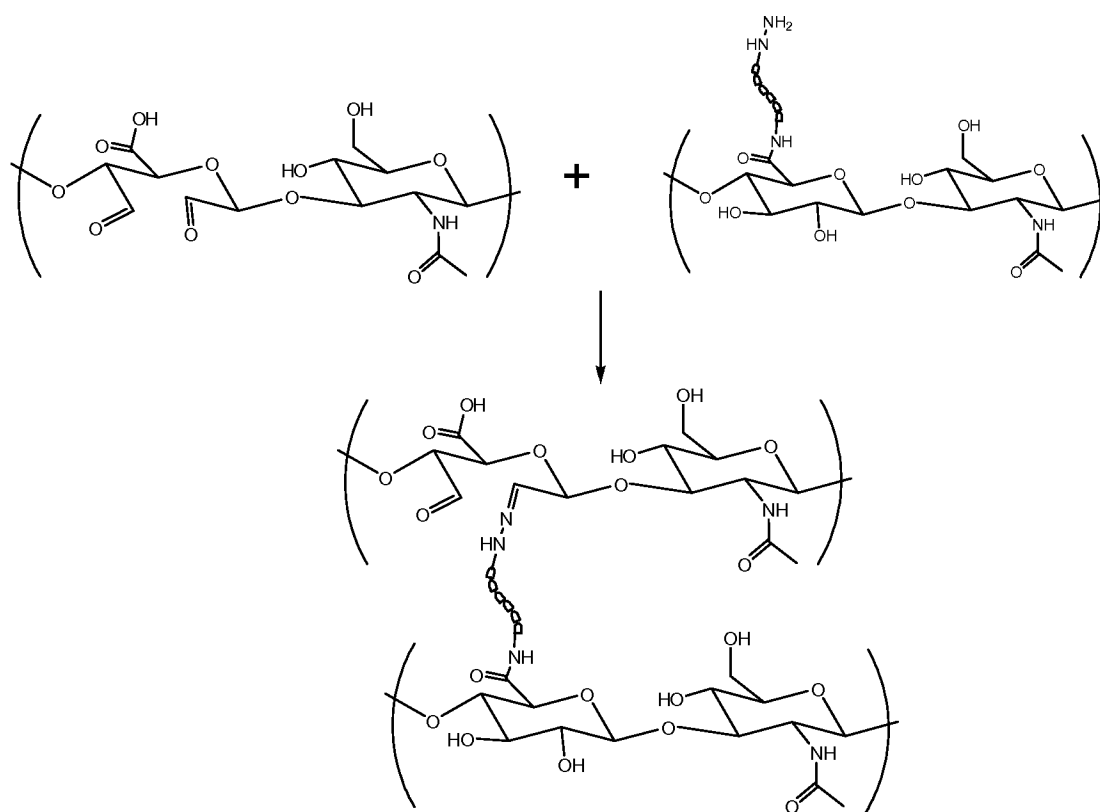
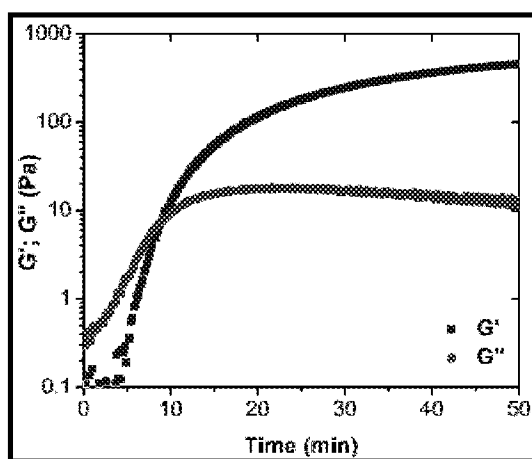
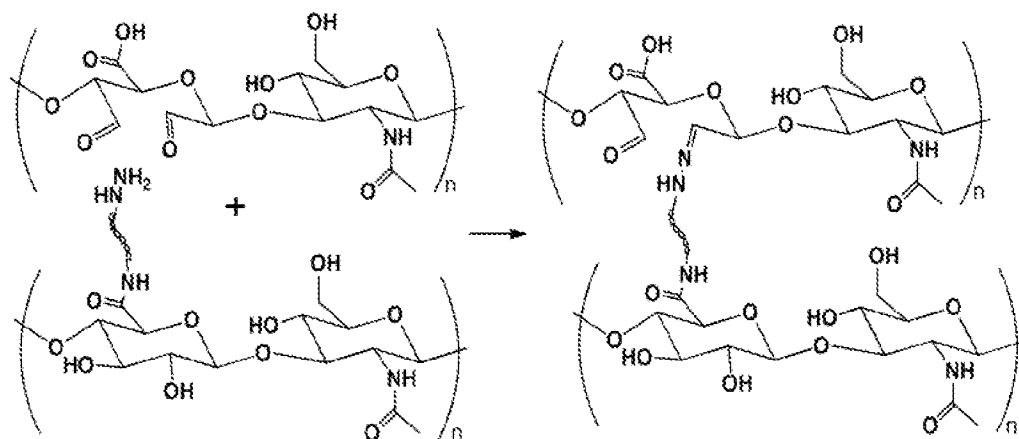


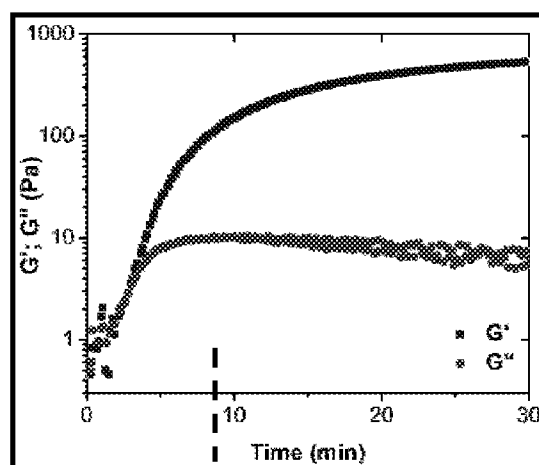
Figure 5

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Gel formation through mixing of Synthesis 1 and Synthesis 2:
Hydrazone formation via Hydrazone-Aldehyde reaction



Gelation time 8-9 min

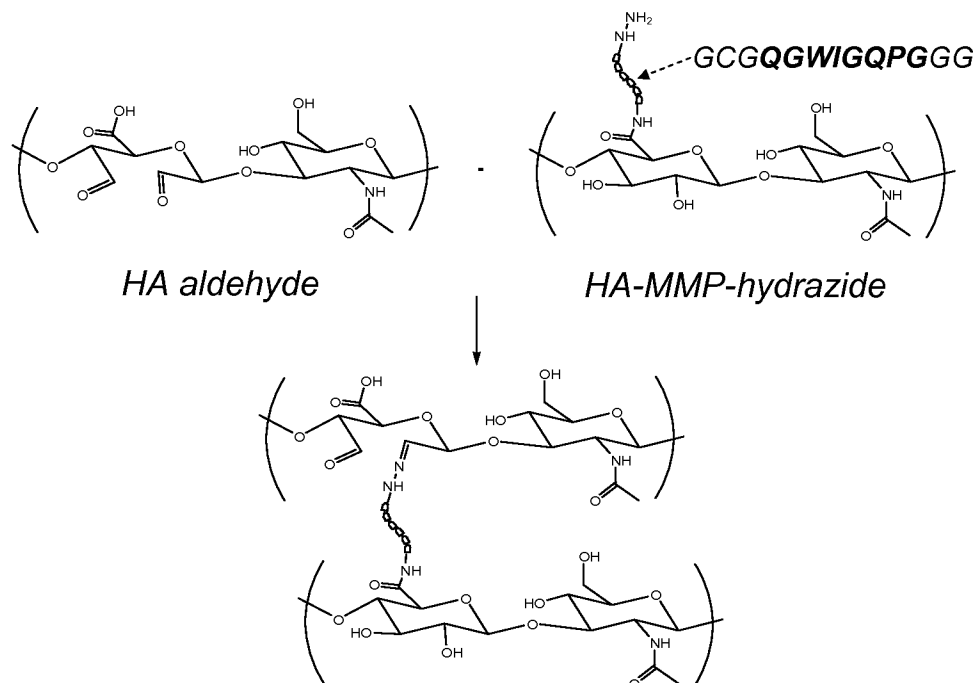


Gelation time 2-3 min

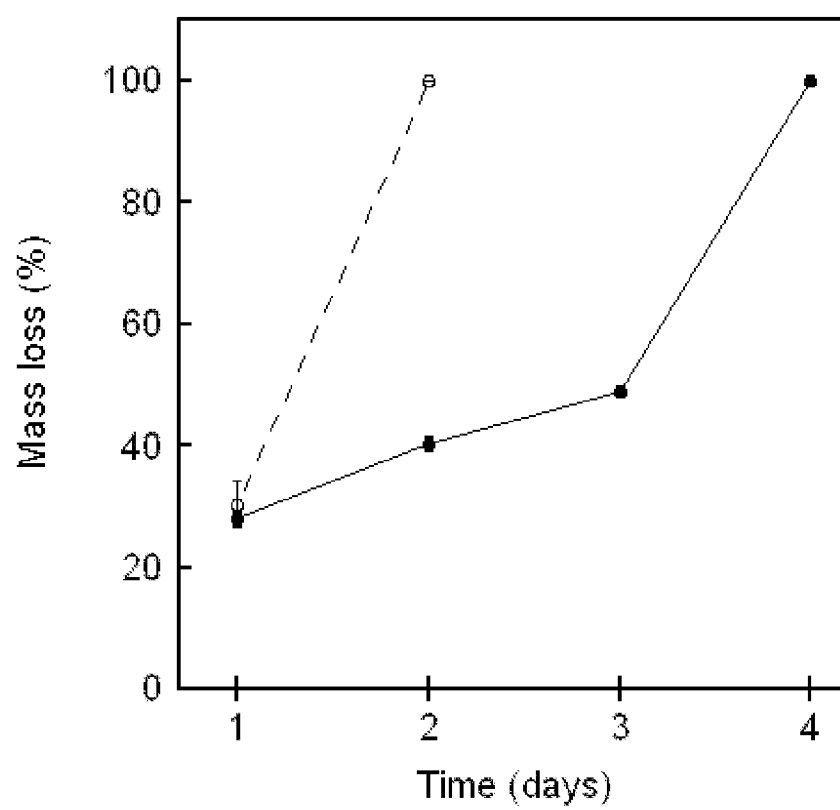
Gelation/properties controlled by HA modification and ratio of HA-Aldehyde to HA-Hydrazide

Figure 6

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MMP-specific gel**Peptide crosslinker that responds to MMP-1, MMP-2****Figure 7**

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Response to MMP**Figure 8**

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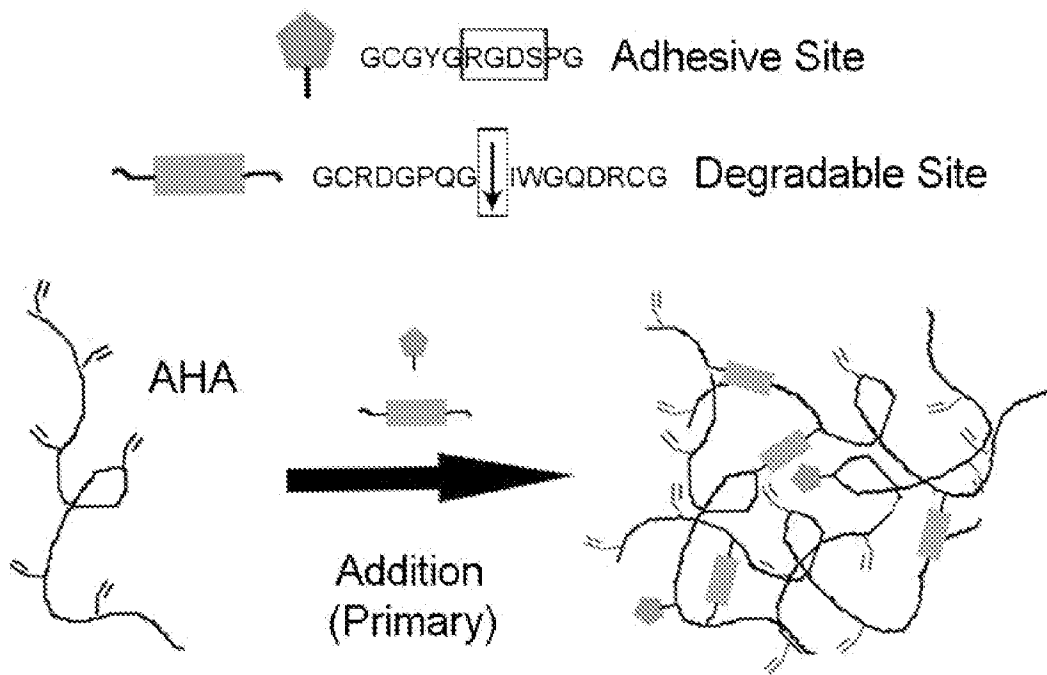


Figure 9