Temperature and pH-responsive hydrogels were prepared with the combination of various monomers such as N-isopropylacrylamide (NIPAAm), acrylamide(AAm), n-butoxymethylacrylamide (nBMA), poly(ethylene glycol) methyl ether methacrylate (PEG), and acrylic acid (AAc). 2,4-Dichlorophenoxyacetic acid was chosen as the herbicide loaded into hydrogel. Volume transition, swelling behavior and release property of temperature and pH-responsive hydrogels by copolymerization

Abstract

Temperature and pH-responsive hydrogels were prepared with the combination of various monomers such as N-isopropylacrylamide (NIPAAm), acrylamide (AAm), n-butoxymethylacrylamide (nBMA), poly(ethylene glycol) methyl ether methacrylate (PEG), and acrylic acid (AAc). 2,4-Dichlorophenoxyacetic acid was chosen as the herbicide loaded into hydrogel. Volume transition, swelling behavior and release property of temperature and pH-responsive hydrogels by copolymerization

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1. Introduction

Hydrogels are crosslinked polymeric networks that can absorb large amounts of water. They are used in a variety of applications, including biomedical devices, drug delivery systems, and tissue engineering. In recent years, there has been growing interest in developing hydrogels that respond to external stimuli, such as changes in temperature or pH, to regulate their properties and functions. This type of smart hydrogel can be used in applications where responsive behavior is desired, such as in controlled drug delivery, tissue regeneration, and soft robotics.

1.1 Materials

NIPAAm (Aldrich) is hexene-1 and used to prepare N-isopropylacrylamide, a monomer used in the synthesis of N-isopropylacrylamide hydrogels. Acrylamide (AAm) is a monomer used in the synthesis of acrylamide hydrogels. n-Butoxymethylacrylamide (nBMA) is a monomer used in the synthesis of n-butoxymethylacrylamide hydrogels. Poly(ethylene glycol) methyl ether methacrylate (PEG) is a monomer used in the synthesis of poly(ethylene glycol) methyl ether methacrylate hydrogels. Acrylic acid (AAc) is a monomer used in the synthesis of acrylic acid hydrogels. 2,4-Dichlorophenoxyacetic acid is a herbicide used in the synthesis of 2,4-Dichlorophenoxyacetic acid hydrogels. 2-Methyl-2,4-dinitrophenol is a reducing agent used in the synthesis of 2-Methyl-2,4-dinitrophenol hydrogels. 4-Methylimidazole is a catalyst used in the synthesis of 4-Methylimidazole hydrogels. 3-Ethyl-1-methylimidazolium chloride is a catalyst used in the synthesis of 3-Ethyl-1-methylimidazolium chloride hydrogels. 1-Ethyl-3-methylimidazolium chloride is a catalyst used in the synthesis of 1-Ethyl-3-methylimidazolium chloride hydrogels. 1-(1-Methylpyrazol-1-yl)ethan-1-one is a catalyst used in the synthesis of 1-(1-Methylpyrazol-1-yl)ethan-1-one hydrogels. Acrylonitrile (AN) is a monomer used in the synthesis of acrylonitrile hydrogels.

2. Synthesis

2.1 Materials

NIPAAm (Aldrich) was used as the crosslinking monomer. Acrylamide (AAm) was used as the crosslinking monomer. n-Butoxymethylacrylamide (nBMA) was used as the crosslinking monomer. Poly(ethylene glycol) methyl ether methacrylate (PEG) was used as the crosslinking monomer. Acrylic acid (AAc) was used as the crosslinking monomer. 2,4-Dichlorophenoxyacetic acid was used as the crosslinking monomer.

2.2 Synthesis of NIPAAm hydrogels

NIPAAm was synthesized by free radical polymerization. The reaction mixture containing NIPAAm, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

2.3 Synthesis of AAm hydrogels

AAm was synthesized by free radical polymerization. The reaction mixture containing AAm, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

2.4 Synthesis of nBMA hydrogels

nBMA was synthesized by free radical polymerization. The reaction mixture containing nBMA, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

2.5 Synthesis of PEG hydrogels

PEG was synthesized by free radical polymerization. The reaction mixture containing PEG, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

2.6 Synthesis of AAc hydrogels

AAc was synthesized by free radical polymerization. The reaction mixture containing AAc, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

2.7 Synthesis of 2,4-Dichlorophenoxyacetic acid hydrogels

2,4-Dichlorophenoxyacetic acid was synthesized by free radical polymerization. The reaction mixture containing 2,4-Dichlorophenoxyacetic acid, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

2.8 Synthesis of 2-Methyl-2,4-dinitrophenol hydrogels

2-Methyl-2,4-dinitrophenol was synthesized by free radical polymerization. The reaction mixture containing 2-Methyl-2,4-dinitrophenol, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

2.9 Synthesis of 4-Methylimidazole hydrogels

4-Methylimidazole was synthesized by free radical polymerization. The reaction mixture containing 4-Methylimidazole, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

2.10 Synthesis of 3-Ethyl-1-methylimidazolium chloride hydrogels

3-Ethyl-1-methylimidazolium chloride was synthesized by free radical polymerization. The reaction mixture containing 3-Ethyl-1-methylimidazolium chloride, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

2.11 Synthesis of 1-Ethyl-3-methylimidazolium hydrogels

1-Ethyl-3-methylimidazolium was synthesized by free radical polymerization. The reaction mixture containing 1-Ethyl-3-methylimidazolium, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

2.12 Synthesis of Acrylonitrile hydrogels

Acrylonitrile was synthesized by free radical polymerization. The reaction mixture containing Acrylonitrile, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

2.13 Synthesis of 1-(1-Methylpyrazol-1-yl)ethan-1-one hydrogels

1-(1-Methylpyrazol-1-yl)ethan-1-one was synthesized by free radical polymerization. The reaction mixture containing 1-(1-Methylpyrazol-1-yl)ethan-1-one, initiator, and crosslinker was heated to a predetermined temperature. The reaction mixture was then reacted for a predetermined time. The resulting hydrogel was washed and dried to obtain the final product.

3. Results and Discussion

The synthesized hydrogels were characterized using various techniques, such as gel permeation chromatography (GPC), Fourier transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC). The results showed that the hydrogels had good swelling properties and were responsive to changes in temperature and pH.

3.1 Swelling Properties

The swelling properties of the synthesized hydrogels were evaluated by measuring the weight of the hydrogel before and after swelling in water at different temperatures. The results showed that the hydrogels had good swelling properties and were responsive to changes in temperature.

3.2 Thermoresponsiveness

The thermoresponsiveness of the synthesized hydrogels was evaluated by measuring the weight of the hydrogel before and after changing the temperature. The results showed that the hydrogels had good thermoresponsiveness and were responsive to changes in temperature.

3.3 pH Responsiveness

The pH responsiveness of the synthesized hydrogels was evaluated by measuring the weight of the hydrogel before and after changing the pH. The results showed that the hydrogels had good pH responsiveness and were responsive to changes in pH.

4. Conclusion

In conclusion, the synthesized hydrogels had good swelling properties and were responsive to changes in temperature and pH. These properties make them potential candidates for use in various applications, such as drug delivery systems and tissue engineering.

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References

NIPAAm은 전체 반응액의 17wt%를 파우더 형태로 사용했고 nBMA는 deionized water(DW)에 용해시켜 25wt%의 농도로 제조하였으며 가교제는 단량체의 2mol%(AAc를 graft시킬때는 2.7mol%)를 사용하였고, 광개시제는 단량체의 4.6wt%로 하여 이들을 서로 금연하게 혼합한 평균 절반 반응액을 제조하였다. 판형의 하이드로젤을 합성하기 위해서 두께가 1mm인 테프론 개스 케이 장착된 유리 주형에 중합반응액을 주입한 후 자외선(365nm)을 3분간(AAc를 graft시킬때는 30분간) 조사하였다. 제조된 하이드로젤의 미량반응을 제거하기 위해 우선 메탄올에 24hr동안 항원체로 하이드로젤을 폐용시키면서 미량반응물을 충분히 용합시켰다. 이렇게 처리된 하이드로젤을 DW에 넣고 온도를 상온과 60°C로 교대로 바꿔주면서 하이드로젤을 폐용 및 수축시켜 생애에 포함된 전부 미량반응물을 제거하였다.

2.3 폐용도 측정
온도변화에 따른 하이드로젤의 폐용도는 완충액내에서 각 온도에서 20분간 보관한후 하이드로젤은 건져내어 표면에 묻어있는 수분을 제거한후 무게를 측정하여 다음의 식으로부터 구하였다.

Swelling ratio = weight of hydrogel / weight of dried hydrogel

2.4-D 방출량 측정
2.4-D를 20wt%의 농도로 ethanol에 용해시킨 용액을 stock solution로 하여 하이드로젤을 3°C, 2.4-D stock solution에서 하루동안 폐용시키며 2.4-D를 담지 시켰다. 2.4-D가 담지된 하이드로젤은 각각의 온도에서 10min, 30min, 1hr, 2hr, 4hr, 8hr, 16hr 동안 순차적으로 옴겨지면서 2.4-D를 방출시켰다. 방출된 2.4-D를 합유하고 있는 ethanol solution을 UV spectrophotometer로 측정하였을 때 299.5nm에서 최대 흡광도를 나타내었다. 미리 구한 결함선을 이용하여 방출된 양을 얻었다.

3. 결과 및 도론
3.1 PEG 그래프 변성 하이드로젤
Poly(NIPAAm)을 기본 물질로 하는 하이드로젤에 생체 적합성과 훈수성을 부여할 수 있는 PEG세를 도입하기 위해서 PEG의 평균분자량이 2,000인 poly(ethylene glycol)methyl ether methacrylate를 NIPAAm과 nBMA와 함께 혼합하여 공중합시키고, 분자량이 20,000인 PEG를 semi-IPN형태로 poly(NIPAAm-co-nBMA)사이에 함유시켰다. 얻어진 공중합체는 PEG세가 그래프된 형태의 변성 하이드로젤이 되고 semi-IPN형태의 것은 poly(NIPAAm-co-nBMA)의 그 물질 구조에 실 가치형태로 잡혀있는 모습이 된다. 공중합에 사용된 poly(ethylene glycol)methyl ether methacrylate와 semi-IPN제조에 사용된 PEG의 여러 함량에 따라 제조된 하이드로젤의 측정 반진이 온도와 폐용 거동을 Fig. 1과 2에 나타내었다. Poly(ethylene glycol)methyl ether methacrylate를 그래프한 경우 훈수성 PEG세의 함양이 증가함수록 상전이 온도가 증가하였다. 이는 물과 하이드로젤 분자간의수소결합에 의해 폐용이 되는 하이드로젤의 특성에 따른 것으로 poly(NIPAAm)분자와 추가로 도입된 PEG분자의 함량이 증가함에 따라 상전이 온도 및 폐용도가 증가하는 것이 확인되었다.

![Fig. 1. Variation on the swelling ratio of slab gels of poly(NIPAAm-co-nBMA-g-PEG) of various PEG contents, depending on the temperature. (NEBA : 2 mole% to monomers, PEG : Mw=20,000)](image1)

![Fig. 2. Variation on the swelling ratio of slab gels of semi-IPN poly(NIPAAm-co-nBMA) with various PEG contents, depending on the temperature. (NEBA : 2 mole% to monomers, PEG : Mw=20,000)](image2)
가교제로 사용된 NEBA의 함량에 따른 하이드로젤의 체적 상변이 온도와 폐용도의 변화를 Fig. 3에 나타내었다. 하이드로젤의 형태 유지와 기계적 강도를 고려하여 NEBA는 단량체의 1~6 mole% 범위에서 변화시켰다. NEBA의 함량이 증가함수록 가교밀도가 증가하여 하이드로젤내의 공간이 감소하여 폐용도가 크게 감소하였다. NEBA 1 mole% 사용하였을 때는 폐용도가 상당히 크게 증가하였지만 폐용 상태에서 하이드로젤의 기계적 강도가 매우 약해서 반복적으로 사용될 약물 출입도 소재로는 적합하지 않았다. 이는 가교밀도가 크지 않아 폐용시 함유된 물의 양을 저하시키는 하이드로젤 메트릭스의 강도가 부족하기 때문인 것으로 판단되었다. 따라서 NEBA 2 mole%의 조건이 PEG가 그래프트된 하이드로젤의 제조에 있어서 적합한 조건인것으로 판단되었다. 가교제의 함량에 차이가 나타라도 체적 상변이 온도는 거의 변화가 없었다. 이는 물과의 수소결합을 이루는 하이드로젤 구성 고분자의 친수성 정도가 상변화를 일으키는 주된 요소이기 때문이다.

Fig. 3. Variation in the swelling ratio of slab gels of poly(NIPAAm-co-nBMA-g-PEG) of various crosslinker (NEBA) contents, depending on the temperature. (PEG : 10wt%, Mw=2,000)

3.2 AAc 그래프트된 변성 하이드로젤

Poly(NIPAAm-co-nBMA)을 기본 유전으로 하여 하이드로젤에 pH응답성을 부여하기 위해서 AAc 성분을 도입하였다. -COOH 그룹이 -COO⁻와 II'로 이온화되는 pH 5를 기준으로 해서 여러 pH조건에서 폐용도를 측정해서 Fig. 4에 나타내었다. 산성 buffer solution에서 폐용도를 측정한 경우 acid 그룹이 이온화 되지 못하고 인체의 총성 상태로 존재하면서 network내부의 공간이 크게 변화가 일어나지 않아 poly(NIPAAm-co-nBMA)하이드로젤과 별 차이가 없는 체적변이 현상을 나타내었다. 하지만 pH 5 이상의 buffer solution에서 폐용도를 측정했을 때는 두드러한 상변화 온도가 감지되지 않고 완만한 기울기의 직선이 관측되었다. 이는 acid 그룹이 주위의 basic solution에 영향을 받아 이온화 되면서 상호간에 전ach 반방향이 작용하여 network내부의 공간이 넓어지고 더욱 많은 물분자가 내부에 존재할 수 있게 되었기 때문이다. 또한 이온화된 acid 그룹은 물과 더욱 강한 수소결합을 형성하게 된다.

3.3 2,4-D 방출 특성

제조법을 살펴보면 폐용에 흡수되는 과정을 살펴보면 흡수되는 양이 작물에 흡수되는 양보다 될까? 다른 양도 같은 제조법, 2,4-D가 외부의 각각에 의해 적절히 응답해서 방출되도록 한다면 더욱 많은 양의 제조법 응용성이 작물들에 흡수될 수 있을 것이다. 각각 응답 특성을 가지고 있는 하이드로젤을 이러한약물전달 물질의 조절 방출용 소재로 응용하기 위해서는 2,4-D를 담지 약물로 선정하여 온도 변화에 따른 방출 특성을 조사하였다. 하이드로젤 구조안에 포함된 친수성을 부가하는 PEG 분자와 AAc의 함량에 따른 2,4-D 방출 특성을 조사하여 그 결과를 Fig. 5에 나타내었다. PEG와 AAc분자체가 그래프트된 hydrogel의 방출된 경우 전반적으로 2,4-D의 양이 증가하였다. 이는 2,4-D와의 친화성이 높은 PEG와 AAc분자가 하이드로젤 내의 공간에 2,4-D를 담지하기 용이한 조건을 제공하기 때문인 것으로 보여진다.
4. 결론
온도와 pH 변화에 따라 응답특성을 보이는 하이드로젤은 poly(NIPAAm-co-nBMA)를 기본구조로 하여 합성하였다. 이러한 자극 응답 특성 하이드로젤을 약물전달 물질의 발출조정재료로 사용하기 위하여 천수성이 우수한 PEG와 AAc 분자체를 갖도록 변성하였다. 가교되지 않은 poly(NIPAAm-co-nBMA)는 LCST인 23℃이하에서는 물과의 상용성이 우수한 균질상 용액을 형성하지만 가교반응이 진행되면 LCST이하의 온도에서도 부분적 불균일도를 갖는 평온된 가교구조체를 형성하였다.
하이드로젤에서 개질 PEG 함량이 증가할수록 천수성의 증가에 따라 체적 상변이 온도와 평온도가 증가하였다. 또한 2,4-D와의 반응성도 증가함에 따라 하이드로젤의 2,4-D 담취량도 증가하였다. 하지만 하이드로젤을 제조할 때 가교체의 함량이 증가하면 가교밀도가 증가하여 하이드로젤의 평온 상태에서도 기계적 강도가 우수한 반면 평온도가 감소하였다.

참고문헌