Negative Temperature Sensitive Hydrogels in Controlled Drug Delivery

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Summary: PVP/PNIPAAm copolymers exhibit a temperature sensitive nature that makes them an attractive candidate for controlled drug delivery devices. Diclofenac sodium was added to the monomeric mixture, which included an initiator and crosslinking agent (where appropriate), prior to UV photopolymerisation. It was found that the xerogels retained similar properties as the original samples (not containing drug) at lower levels of drug integration. In all cases, drug dissolution analysis showed that the active agent was released at a slower rate at temperatures above the Lower Critical Solution Temperature (LCST). Interestingly, the drug release trends were almost identical for both the physically and chemically crosslinked hydrogels, when the decrease in transition temperature caused by the incorporated crosslinking agent is taken into consideration. It is believed that both types of copolymers reached a constant maximum swollen weight at a set of temperatures above their transition temperatures. When this swollen plateau is attained, the hydrophilic-hydrophobic interactions are balanced, thus the gel does not swell or shrink further and the drug diffuses out at a constant rate.

Keywords: drug delivery systems; hydrogels; lower critical solution temperature; photopolymerisation; physical entrapment

Introduction

Polymers have gained in importance in the pharmaceutical industry as both drug encapsulants and vehicles for drug carriage. Polymers employed to delay drug dissolution aim to slow the rate at which drug molecules are exposed to water from the aqueous environment surrounding the drug delivery system.[1] Hydrogels formed by chemical or physical crosslinking are a special class of polymers that imbibe a considerable amount of water while maintaining their shape. The research on hydrogels with respect to drug delivery and biomedical devices has been extensive over the last few decades because of their biocompatibility properties and easy control of solute transport.[2–4] Physical entrapment is probably one of the simplest methods used for incorporating active agent into hydrogels that are intended for controlled drug delivery applications. With physical entrapment, the active agent is contained within the hydrogel, which has a tight enough structure to inhibit diffusion of the drug into the surrounding environment, i.e. there must be sufficient crosslinking or entanglements to ensure the solute remains in the hydrogel.[5] There are two general methods of physical entrapment used for loading hydrogels with active agent, as discussed in a review article by Kim et al.[6] Briefly, the first involves placing a previously prepared hydrogel in a suitable drug solution until it swells to equilibrium, thus allowing the active agent to diffuse into the

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polymer. The drug-loaded hydrogel is then dried and the device is obtained. The equilibrium swelling technique has recently been used to load hydrogels with drugs such as 5-fluorouracil[7] and theophylline.[8,9] In the second approach, the hydrogel monomer(s) are mixed with drug, an initiator, with or without a crosslinker, and allowed to polymerise, thus trapping the drug within the matrix.[6] This technique continues to be popular and has recently been carried out using drugs such as theophylline,[5,10] proxyphylline,[11] aspirin and paracetamol.[12]

Preparation of Samples

In previous works by our research group, both physically and chemically crosslinked hydrogels based on *N*-isopropylacrylamide (NIPAAm) and 1-vinyl-2-pyrrolidinone (NVP), with phase transition temperatures in the region of 37 °C, have been synthesised and characterised.[13–16] In this contribution, diclofenac sodium was incorporated into the hydrogels, and the role that the LCST plays on the rate of drug release is explored. The active pharmaceutical ingredient was incorporated using the second method outlined in the introduction, whereby the drug was added to the monomeric mixture that included the initiator and crosslinking agent (where appropriate) prior to the UV photopolymerisation process. Drug loadings of 25wt%, 10wt%, 5wt%, 2.5wt% and 1wt% of the total monomer content were examined and its effect on the curing time and integrity of the resulting xerogels is discussed. At higher drug loadings of diclofenac sodium, the negative temperature sensitive copolymers exhibited similar curing behaviour. For example, at 5wt% drug and above, the xerogels were discarded, as they had not cured satisfactorily even after 48 hrs. There was a marked improvement with samples containing 2.5wt% drug, and at 1wt% drug incorporation the copolymers cured to a standard comparable to that of the original samples synthesised without drug. The samples however took approximately four times longer to cure and appeared a shade darker in colour than the original xerogels (this is not uncommon as yellowing is often exhibited by polymers produced by UV curing and the darker colour is likely due to the longer exposure to the UV light). Longer curing times remains a common drawback when integrating drug into xerogels using this technique.[5,11] Scott and Peppas suggest that active agent may act as a retarding agent over the course of the radical polymerisation, by scavenging free radicals available for the polymerisation.[11] The drug release analysis in this investigation was carried out using both physically and chemically crosslinked A1(L1) samples (see Table 1), with diclofenac sodium incorporated at 1wt% of the total monomer content. As diclofenac sodium is reported to be freely water soluble,[17] it is ideal for this assessment.

Drug Release

The drug dissolution experiments were carried out as detailed in a previous work.[12] Physically crosslinked A1(L1) has a phase transition temperature onset value of 36.80 °C and peak maximum value of 38.90 °C in distilled water, as detected using modulated DSC.[14] In pH 6.8 buffer solution, the copolymer has LCST onset and peak maximum values of 33.05 and 35.24 °C respectively, as the salts incorporated in the preparation of the buffer media cause a 'salting out' effect.[16] The drug release behaviour of the negative temperature sensitive pseudogels containing diclofenac sodium was investigated in distilled water and pH 6.8 buffer media at a number

Table 1.
Name and composition of hydrogel synthesised for drug dissolution analysis.

Hydrogel Name	NVP (wt%)	NIPAAm (wt%)	Distilled water (wt%)
A1 (L1)	15	65	20

of different temperatures. In distilled water, the entrapped drug was released from the copolymer after approximately 12 hrs at a temperature of 30 °C, as can be seen in Figure 1. Surprisingly, the release rate was almost identical at 37 °C, which corresponds to the phase transition temperature onset value of the copolymer in distilled water. This was most likely because the temperature was not high enough for the hydrophobic interactions to dominant sufficiently, and significantly slow the rate of water sorption. With negative thermosensitive polymers, it is believed that a small fraction of the gel begins to undergo its phase transition at the onset temperature, while the bulk undergoes the transition at the peak maximum value. At both lower test temperatures, it was noted that the gels had disintegrated but not fully dissolved after the release of the drug. Hydration studies carried out at corresponding temperatures show that these gels swelled 3.5 to 4 times their initial mass, attained maximum swollen weight between 24 and 48 hrs and took between 96 and 120 hrs to fully dissolve.[14] Taking into consideration the greater volume of dissolution media, the aggressive environment and drug incorporation, the accelerated break down of the gels is not unexpected.

At 40 °C, the negative temperature dependant capabilities of the copolymers became clearer. As shown in Figure 1, the drug takes an extra 7 hrs to release with a 3 °C increase in test temperature. When the temperature was further elevated to 44 °C, the active agent was still not completely released even after 24 hrs. Also when examined after the analysis, the samples were observed not to have disintegrated to the same degree as they had at the lower temperatures. In fact, after inspection at the highest test temperature, samples were found to have excellent stability while imbibing roughly twice their initial weight in water, and when dried had a gel fraction of approximately 73%. For this reason, a diffusional process is believed to have played a predominant role in the release of drug from these samples particularly at most elevated analysis temperature. As the dissolution environment is approximately 5 °C higher than the LCST peak maximum value of the copolymer, the water sorption rate is lessened considerably, and thus the samples take longer to release the active agent and to disintegrate.

For analysis carried out on the pseudo-gels in pH 6.8 buffer, the drug release properties are again closely dependent on the temperature conditions prevailing in the dissolution vessel as illustrated in Figure 2. At all temperatures there was a slight burst release of drug followed by a period of more sustained release, principally due to surface drug being freed more rapidly. The gels studied in distilled water also exhibited this trend. As expected at 30 °C, the samples exhibited a similar drug

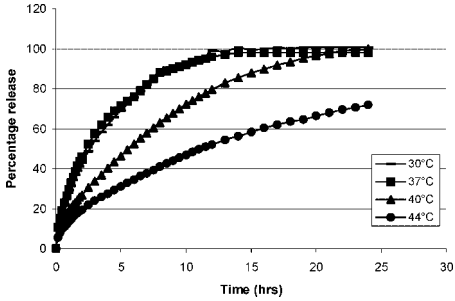

Figure 1.
Effect of temperature on the release rate from physically crosslinked A1(L1) diclofenac sodium drug carriers in distilled water.

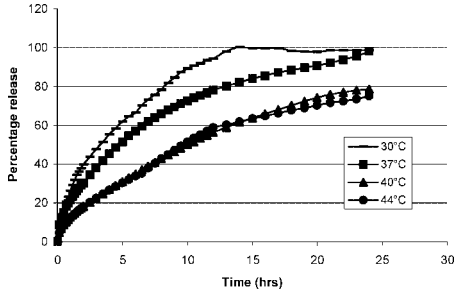

Figure 2.
Effect of temperature on the release rate from physically crosslinked A1(L1) diclofenac sodium drug carriers in pH 6.8 buffer solution.

release profile as they did in distilled water, as the LCST of the samples in the buffer media remained a few degrees Celsius higher than the test temperature. When the copolymers are examined at 37 °C, which is above their LCST peak maximum value in the pH buffer solution, the active agent takes a further 11 hrs to be completely released. Notably in the pH buffer environment, the release profiles at 40 and 44 °C are almost identical with about 78% of the diclofenac sodium released after 24 hrs. Following testing at these temperatures, the copolymers retained excellent integrity while hydrated, and exhibited a gel fraction of 73%. The release profile for samples tested at 44 °C in distilled water is also nearly indistinguishable from those exhibited by the pseudogels at the two highest test temperatures in the buffer media. It is believed that the copolymers may have reached a constant maximum swollen weight at a set of temperatures above their LCST. Therefore, the samples hydrate at a similar rate and to a comparable volume over this range of temperatures, and as result the drug release profiles remain very alike.

The hydrophilic and hydrophobic balance of polymer side groups in PNIPAAm hydrogels, i.e., –CONH– is hydrophilic and $–CH(CH_3)_2–$ is hydrophobic,[18,19] are responsible for these interesting negative temperature sensitive properties. Any molecules that can form hydrogen bonds to each other can alternatively form hydrogen bonds to water molecules.[20] Because of this competition with water molecules, the hydrogen bonds formed between two molecules dissolved in water are relatively weak. It is generally believed that the phase transition behaviour of PNIPAAm based hydrogels in aqueous solutions is strongly related to the destabilisation of hydrogen bonds between water molecules and amide groups with increasing temperature, probably induced by the presence of the hydrophobic isopropyl group and backbone chain.[21,22] In summary, it is clear that the salts incorporated in making the buffer media have shifted the temperature at which the pseudogels exhibit their negative temperature dependant capabilities. Homopolymers and copolymers of PNIPAAm have been fashioned that are completely hydrophobic at certain temperatures above their LCST. Physically crosslinked PNIPAAm and PNIPAAm/Acrylamide compression coated samples incorporating active agent were found to release no theophylline at temperatures sufficiently above their LCST, thus hydrophobic interactions completely dominated and the polymers were totally insoluble.[23,24]

The volume phase transition temperature of chemically crosslinked A1(L1) was recorded at 33.86 °C (peak onset) and 36.56 °C (peak maximum) in distilled water, which is around 2.5 °C lower than the LCST values exhibited by the physically crosslinked copolymer. The two transition temperatures have been reported to vary slightly depending on the nature of the crosslinking agent.[4] In general, similar drug release behaviour was displayed by the chemically crosslinked hydrogels, when compared with the trends documented for the pseudogels tested in distilled water and buffer media. The primary difference observed was a consequence of crosslinking agent incorporated shifting the temperature at which the copolymers underwent their negative temperature dependent transition. In Figure 3, the drug release profiles

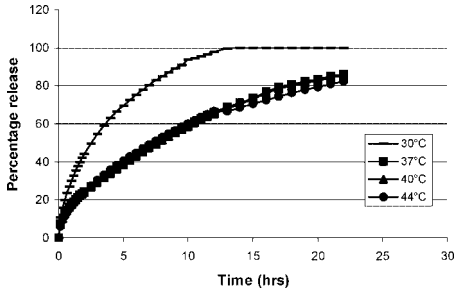

Figure 3.
Effect of temperature on the release rate from chemically crosslinked A1(L1) diclofenac sodium drug carriers in pH 6.8 buffer solution.

for chemically crosslinked A1(L1) in pH 6.8 buffer are plotted over a range of temperatures. Release profiles for both the physically and chemically crosslinked copolymers are almost identical at 30 °C. This is the case throughout this investigation in both dissolution media, as the test temperature is below the LCST of the samples. At the remaining test temperatures, the samples released the incorporated drug in a very similar fashion to one another. This is also comparable to the trends exhibited by the pseudogels, except in this case the test results at 37 °C coincides with the two higher test temperatures, owing to effect of the incorporated crosslinking agent and buffer media on the volume phase transition temperature. Again similar trends were observed for the chemically crosslinked hydrogels analysed in distilled water, when the pH buffer effect on the transition temperature is taken into consideration.

Conclusion

Physically and chemically crosslinked PVP/PNIPAAm hydrogels were synthesised for use as novel controlled drug delivery devices. Drug dissolution analysis in distilled water and pH 6.8 buffer media showed that changes in test temperature had obvious effect on the rate of drug release from the copolymers. In all cases, the diclofenac sodium was released at a slower rate at temperatures above the LCST. It is noted that transition of the copolymer from glassy to rubbery is required to attain diffusion of the drug. Therefore, drug release is delayed for the period of time required for hydration of the matrices. As the hydrophobic interactions become more dominant above the LCST, this significantly slows the rate of water sorption and thus the drug release time. Similar negative temperature dependent drug release behaviour was exhibited in pH buffer solution, although the salts incorporated in the buffer media preparation caused a 'salting out' effect, and so the temperature at which the transition occurred was shifted downwards slightly. Most interestingly, the drug release trends were almost identical for both the physically and chemically crosslinked hydrogels, when the decrease in phase transition temperature caused by the incorporated crosslinking agent is taken into account. It is believed that both types of copolymer reached a constant maximum swollen weight at a set of temperatures above their transition temperatures. When this swollen plateau is attained, the hydrophilic-hydrophobic interactions are balanced, thus the gel does not swell or shrink further and the drug diffuses out at a constant rate. As chemically crosslinked hydrogels are non-biodegradable and the chemical crosslinking agents used in their synthesis are not known to be biocompatible, utilisation of the physically crosslinked device would appear more favourable.

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