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Smart Thermosensitive Poly (N-vinylcaprolactam) Based Hydrogels for Biomedical Applications

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ABSTRACT

Photopolymerisation is an attractive technique used in biomedical applications as it can provide rapid reaction rates with excellent temporal and spatial control features and unique tuneable properties. This fabrication technique provides the potential to reduce invasiveness and cost for biomedical and biotechnological applications. In this study physically crosslinked hydrogels based on N-vinylcaprolactam with different weight percentages of photoinitiator were prepared via free radical polymerisation. These temperature responsive polymers were characterised in terms of glass transition, lower critical solution temperature (LCST) and swelling properties. Results showed that photoinitiator concentration had minimal effect on phase transition temperature as LCST was ~31°C for samples tested. Swelling studies results showed that hydrogen bonding dominates below its LCST as the polymers dissolved within 5hrs.This was compared to above its LCST where both hydrogen bonding weakens and the hydrophobic components dominate in the system. Finally, the photoinitiator concentration altered the glass transition temperature of the hydrogels where values ranged from 89-118 °C.

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INTRODUCTION

Photocuring of monomers is a common method that involves the use of a photoactivator system that is capable of absorbing ultraviolet or visible radiation wavelengths to convert a monomer into a cross linked system[1]. This system is used in a broad range of commercial and biological applications such as dentistry, optical materials and blood vessel adhesives[2]. It's versatility is due to the simplistic procedure, as it provides a cost effective and user-friendly operation process, exhibits fast curing rates at room and physiological temperatures, produces minimal heat and is an environmentally friendly technique[3].

Smart hydrogels or stimuli responsive polymers are three dimensional hydrophilic networks which are composed of a polymer back bone, water and cross linking agent. These polymers are capable of absorption and desorption of large quantities of solution which is triggered by environmental changes such as temperature, pH or ionic strength. Consequently this behaviour can be utilised in a broad range of applications such as drug delivery, gene delivery and tissue engineering. One stimuli responsive polymer of interest in biomedical applications is poly (N-vinylcaprolactam) (PNVCL).PNVCL contains hydrophilic carboxylic and amide groups, where the amide group is directly connected to the hydrophobic carbon-carbon backbone chain. PNVCL is a non-ionic, water soluble, non-toxic thermo sensitive polymer with a phase transition in the region of physiological temperature (31-38 °C) [4-6]. Its characteristics of water-solubility, non-adhesiveness, thermally sensitivity and biocompatibility allow it to be used as a new biomedical material, such as in the binding and release of medicines and as a liquid embolic material to cure cerebral arteriovenous malformation (AVM) endovascular [7]. PNVCL can also be used as a UV-curable adhesive, synthetic resin in hair and skin care products [7].

Previous studies have shown that photoinitiator concentration can affect the polymerisation rate of hydrogels. In the case of insufficient photoinitiator, this results in the incomplete curing of the hydrogels which can compromise the physical properties, mechanical properties, colour stability and thermal properties[2]. However, in the presence of high concentration of initiator this may lead to the formation of undesirable toxic contaminants trapped in the polymer matrix which may leach out into biomedical devices [8]. In light of this,

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the goal of this research was to investigate the effect of different wt% of photoinitiator and subsequently to evaluate the physical and mechanical properties of PNVCL based hydrogels.

MATERIALS AND METHODS

Materials:

N-Vinylcaprolactam (NVCL) was obtained from Sigma Aldrich which has a molecular weight of 139.19 g/mol and storage temperature of 2-8 °C (Figure 1). 1-hydroxycyclohexylphenylketone (Irgacure® 184) was obtained from Ciba speciality chemicals (Figure 2).

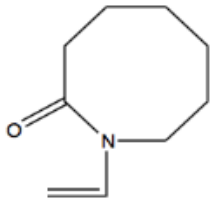

Fig. 1: Chemical structure of NVCL.

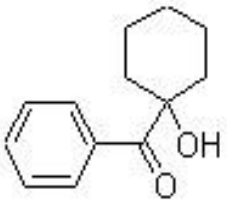

Fig. 2: Chemical structure of Irgacure® 184.

Photopolymerisation:

NVCL monomer was preheated in a hot water bath at 70 °C for approximately 60 minutes prior to use due to the monomers precipitating state. The monomer was of analytical grade and was used as received. Different wt% of photoinitiator Irgacure 184, specified in Table 1 was weighed out using a sartorius scales and transferred into a 25 ml beaker along with the monomer once in aqueous form. Once both components were in the beaker the solution was stirred using a magnetic bar and stirrer at 50 °C until the solution was homogeneous.1ml of the solution was then quickly pipetted into disc shape silicone moulds with dimensions of 23 mm diameter by 2.2 mm thickness. Once the solution was in the disc mould it was placed into the UV curing system (Dr.Gröbel UV-Electronik GmbH) and cured for 30 minutes. This particular irradiation chamber is a controlled radiation source with 20 UV-tubes that provide a spectral range of between (315-400nm) at an average intensity of (10-13.5mW/cm^2).

Table 1: Composition of PNVCL containing different weights of Irgacure 184.

Sample name	NVCL (%)	Irgacure 184 (wt%)
NVCL (1)	100	0.1
NVCL (2)	100	0.3
NVCL (3)	100	0.5

Swelling Studies:

The swelling and dissolution characteristics of the polymers were investigated in triplicate at different temperatures. Prior to analysis the xerogels were transferred into a 40 °C oven for 24 hrs to remove any moisture. Once the xerogels were dried their dry mass was weighed and recorded using a sartorius scales. Samples of cured polymer with a mass 1.2±0.35g were placed into a petri dish containing 25ml of distilled water. The hydrogels were tested at both ambient (21 °C) and above its LCST at 40 °C. Periodically, the polymer was carefully removed after predetermined time intervals. The samples were blotted free of excess water with filter paper before weighing, the wet sample weight was then weighed and recorded. The samples were then re-submerged into solution and the procedure was repeated until the polymer was completely solubilised. The polymers swelling ratio was calculated by using Eq1 illustrated below.

Swelling Ratio (%) = $(W_t/ W_0) \times 100$ (Equation 1)

W_t is the weight of the gel at a predetermined time and W_0 is the dry mass weight of the polymer. In order to give a clear demonstration of the swelling behaviour of the polymers, photographs were taken after various time points.

Cloud point analysis:

Cloud point analysis was used to identify the lower critical solution temperature of the polymers. 1, 2 and 3 wt% polymer was added to known amounts of water and transferred intocapped 75mm glass test tubes. A 200ml beaker was filled with distilled water and placed onto a hot plate with a starting temperature of 20 °C. The test tubes were then placed into the beaker and once the temperature reached 20 °C, the temperature was manually increased by 1 °C/min. Once the polymer changed colour the temperature was recorded at the onset of turbidity.

Thermal analysis of PNVCL hydrogels:

Differential scanning calorimetric (DSC) analysis was carried using the TA Instruments DSC 2920 Modulated DSC (AGB Scientific Ltd.). Samples were prepared by weighing out dry samples ranging from 8-12mg using the Sartorius scale having a resolution of 0.01mg. The measurement was carried out using crimped aluminium hermetic pans, wherean empty pan was used as the reference sample. Before thermal analysis was carried out, the cell was cleaned using a glass fibre brush and burned off at 400 °C for 5 minutes. The Instrument was then calibrated using indium as standard. Samples in sealed hermetic pans were then carefully placed into the cell and scanned at a rate of 10 °C/min from 20 to 150 °C to remove the thermal history and cooled down to 20 °C. They were then reheated at a rate of 10 °C/min from 20 to 200 °C. All DSC analysis was carried out under a nitrogen atmosphere to prevent oxidation of the samples.

RESULTS AND DISCUSSIONS

Preparation of PNVCL:

NVCL batch polymerisation was first studied by Solomon *et al.*(1968) using azobisisobutyronitrile, terl-butyl perbenzoate, and tert-butyl peroxide as initiators [4,8]. The aforementioned study observed the kinetic behaviours of NVCL hydrogels in a nitrogen and air atmosphere by varying the initiators, temperatures and molecular weights [9]. The polymerisation of these polymers occurs through the vinyl back bone in the presence of initiators by chain polymerisation [10]. Essentially the free radical attacks a double bond on a monomer and the electron moves on to another monomer, the process is continued until the end result is a chain of cyclic amide groups which is attached to the hydrophobic back bone [11].

In this study PNVCL polymers were prepared using free radical photopolymerisation. Photopolymerisation has several advantages over conventional polymerisation techniques such as solvent casting, particular leaching and freeze drying. These include spatial and temporal control over the polymerisation, fast curing times, minimal heat production and adjusting temperature and pH close to physiological temperature. Initial studies were carried out to analyse the effect of photoinitiator concentrations (0.1, 0.3 and 0.5wt%) on the hydrogels properties by curing them for 20 minutes. From a biocomptability point, the concentration levels of photoinitiator should be kept to a minimum given that previous studies have shown that minimising photoinitiator concentration levels serves to increase biocompatibility of the hydrogel, though it also increases curing time [12,13].

Lower critical solution temperature determination:

The LCST of a polymer is influenced by the hydrophobic, hydrophilic moieties in its molecular chains. In order to manipulate the LCST, hydrophilic or hydrophobic monomers can be incorporated into the polymer. The advantage of this shift in temperature sensitive polymers from 0 <to> 100 °C is that it provides excellent flexibility in tailoring transitions to suit physiological temperature, inheriting great potential in drug delivery. Some polymer's LCST can be dictated by the wt% of the polymer such as PNVCL [14]. There isa number of papers reporting on the LCST shift with increasing molar mass [15]. Common analysis techniques include fluorescence techniques, particularly time resolved anisotropy measurement (TRAMS), DSC and cloud point analysis [15].

In this study cloud point analysis was used to analyse different concentrations of PNVCL solution containing different wt% of photoinitiator. Figure 3 demonstrates a representation of PNVCL polymers above and below their LCST, whereas the data is reported in Table 2. Results show that the LCST also increased proportionally to the polymer concentration. For example, with PNVCL (1) the LCST temperature ranged between 28 and 33 °C with an increase in polymer concentration from 1 to 3 wt% which is in accordance with the literature [16]. This phenomenon of the LCST behaviour is dependent on the enthalpy and entropy of mixing of the polymer with water, as well as being strongly influenced by the concentration of the polymer.

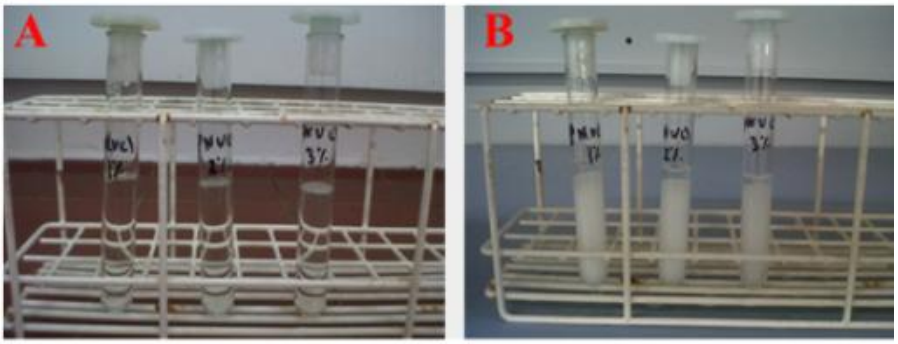

Fig. 3: Different weight percentage of PNVCL in solution below LCST (A) and above LCST (B)

Table 2 illustrates the LCST for the NVCL polymers with different photoinitiator concentration. Results show that the photoinitiator concentration had little effect on the phase transition of the polymer as the values ranged between 28-31 °C for all samples tested.

Table 2: Cloud point analysis results

PNVCL (1) Polymer concentration (wt%)	Temperature (°C)
1	28
2	31
3	33
PNVCL (2)Polymer Concentration (wt %)	Temperature (°C)
1	29
2	31
3	31
PNVCL (3)Polymer Concentration (wt %)	Temperature (°C)
1	30
2	30
3	31

Swelling Studies:

Swelling analysis of PNVCL polymers were performed in a petri dish containing 25ml of distilled water and tested at 20 and 40 °C. Figures4-5 demonstrates how different temperatures dictate the absorption and dissolution behaviour of PNVCL containing varied wt% photoinitiator. In Figure 4 (above LCST), it shows a gradual increase in swelling ratio. However in Figure 5 (belowits LCST) the opposite transition occurred. This is dictated by the LCST of the polymer, essentially below the LCST the enthalpy term related to the hydrogen bonding between the polymer and the water molecules is responsible for the polymer dissolution [11]. Referring to swelling behaviour of PNVCL above its LCST, this lack of dissolution is due to the LCST of the polymer. Most physically crosslinked polymers increase their water solubility as the temperature increase. However, polymers with LCST undergo the opposite behaviour decreasing their water solubility as the temperature increases. This is due to the weakening of the hydrogen bonds and domination of hydrophobic groups leading to precipitation of polymer.

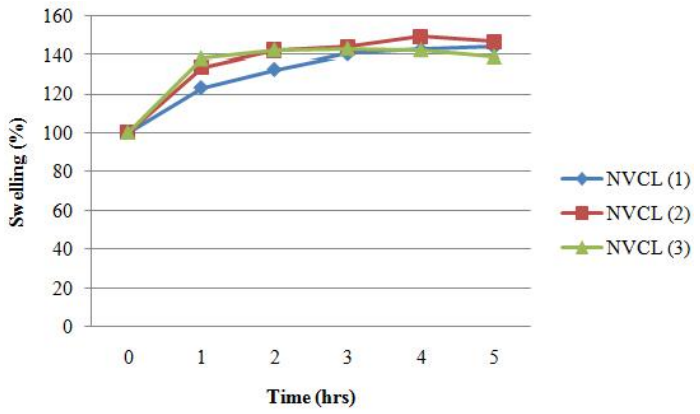

Fig 4 Swelling studies data for PNVCL polymers above their LCST

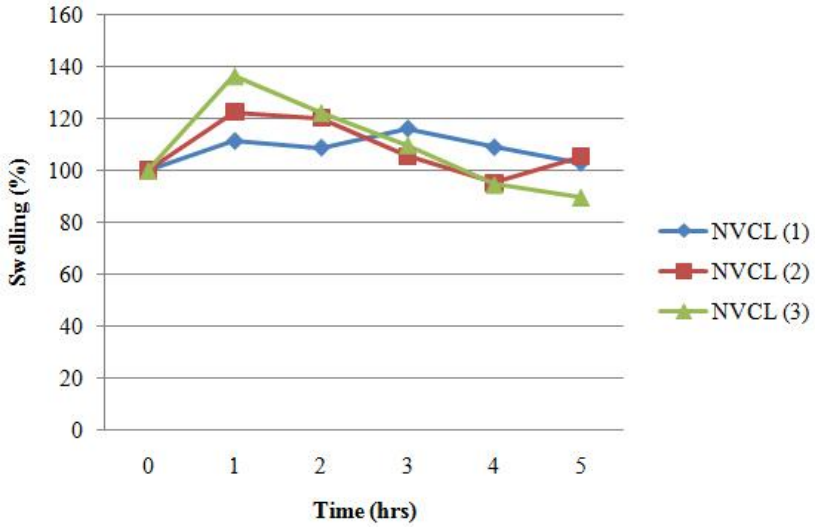

Fig. 5: Swelling studies data for PNVCL polymers below their LCST.

Differential Scanning Calorimetry:

DSC is a widely used thermal analysis technique and employs the use of a linear temperature ramp in order to obtain quantitative calorimetric information. DSC is a technique in which the heat flow difference into the sample and reference sample is measured as a function of temperature [16].The analysis was preformed to identify the glass transition (Tg) of PNVCL. The Tgrepresents the temperature which molecular motion of a glassy amorphous solid is reduced and above which the amorphous materials takes on a rubbery character. DSC was an important technique to perform in order to identify the effects of different percentages of photoinitiator on the thermal characteristics of the hydrogels.

The Tg's for NVCL based polymers areexhibited in Figure5.Results show that the glass transition temperature decreases as the concentration of photoinitiator increases. It was hypothesised that as the photoinitiator increased, so should the Tg and heat capacity due to the degree of crosslinking. The Tgdisplays a decrease in Tgas the photoinitiator decreases and this was perhaps influenced by such factors as molecular weight and molecular weight distribution [16].

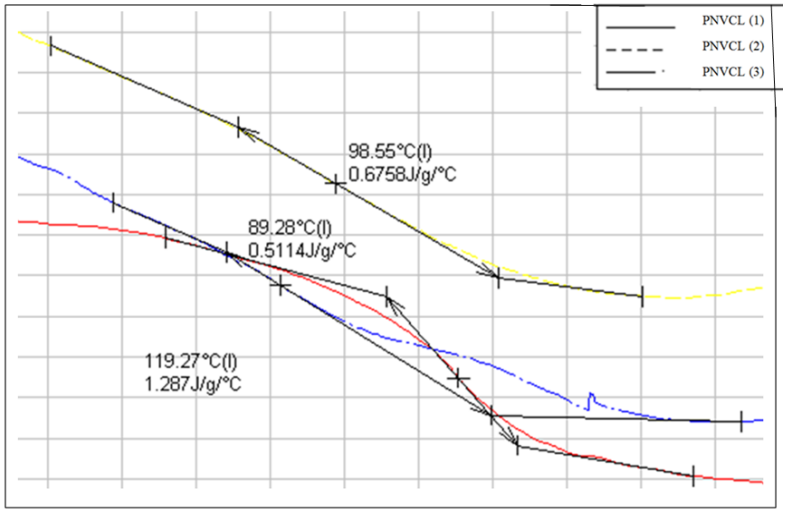

Fig. 5: Thermograph of PNVCL containing different wt% of photoinitiator

Conclusion:

In this study, physically crosslinked hydrogels (NVCL) containing different photoinitiator content (0.1-0.5 wt%) were photo polymerised. Cloud point analysis showed that the aqueous solution exhibited thermo sensitive behaviour. The temperature at which this occurs was dependent on the polymer concentration as values ranged between 28-33°C. Swelling study results demonstrated that below its LCST, hydrogen bonding dominates which resulted in rapid dissolution of the polymers. However, above the LCST, the polymers

remained intact which is due to the dominance of the hydrophobic bonds present in the system. The glass transition temperature could be readily altered with the change in photoinitiator concentration. Based on the results obtained, by increasing the photoinitiator concentration the glass transition temperature can range between 89-118 °C.

REFERENCES

[1] Allen, N., 2003. Photopolymerisation chemistry, Photochemistry and Photobiology, 159: 102-159.
[2] Williams, C.G., A.N. Malik, T.K Kim, P.N. Manson, J.H. Elisseeff, 2005. Variable cytocompatibility of six cell lines with photoinitiators used for polmerizing hydrogels and cell encapsulation, Biomaterials, 11: 1211-1218.
[3] Karaca, N., G. Temel, D.K. Balta, M. Aydin, N. Arsu, 2010. Preparation of hydrogels by photopolymerization of acrylates in the presence of Type 1 and one-component Type 2 photoinitiators, Journal of Photochemistry and Photobiology, 209: 1-6.
[4] Gaballa, H.A., L.M. Geever, J.A. Killion, C.L. Higginbotham, 2013. Synthesis and characterization of physically crosslinked N-vinylcaprolactam, acrylic acid, methacrylic acid, and N,N-dimethylacrylamide hydrogels. Journal of Polymer Science Part B: Polymer Physics, 21: 1555-1564.
[5] Ng, L.T., S. Swami, C.G. Thomson, 2006. Hydrogel synthesised through photoinitiator-free photopolymerisation technique for delivering drugs including a tumour-tracing porphyrin, Radiation Physics and Chemistry, 75: 604-612.
[6] Lee, B., A. Jiao, Y. Seungjung, J.B. You, D.H. Kim, S.G. Im, 2013. Initiated chemical vapour deposition of thermoresponsive poly N- vinylcaprolactam thin film for cell sheet engineering, Acta Biomaterials, 9: 7691–7698.
[7] Shubo, F., L. Shuyuan, Z. Eril, T. Xinliang, 2009. Synthesis on N-vinyl caprolactam, Catalysis Today, 140: 1-6.
[8] Solomon, O.F., M. Corciovei, C. Boghina, 1968. Radical Bulk Polymerization of N-vinylcaprolactam, Applied Polymer Science, 13: 1-2.
[9] Ma, F.L., 2006. Novel Smart Core-Shell Microgels, Synthesis, Characterization and Application, Hong Kong: Hon Kong Polytechnic University.
[10] Qiu, Y., K. Park, 2012. Environment-sensitive hydrogels for drug delivery, Advanced Drug Delivery Reviews, 64: 2-11.
[11] Schroder, W.F., C.I. Vallo, 2007. Effect of different photoinitiator system on conversion profiles of a model unfilled light-cured resin, Dental Materials, 23: 1313-1312.
[12] Studer, K., C. Decker, E. Beck, R. Schwalm, 2003a. Overcoming oxygen inhibition in UV-curing of acrylate coatings by carbon dioxide inerting, Part I. Progress in Organic Coatings, 48: 92-100.
[13] Studer, K., C. Decker, E. Beck, R. Schwalm, 2003b. Overcoming oxygen inhibition in UV-curing of acrylate coatings by carbon dioxide inerting: Part II. *Progress in Organic Coatings*, 48: 101-111.
[14] Meeussen, F., E. Nies, H. Berghmans, S. Verbruggle, E. Goethals, F. Du Prez, 2000. Phase Behaviour of poly N vinylcaprolactam in water, Polymer, 41: 8597-8602.
[15] Chee, C.K., S. Rimmer, I. Soutar, L. Swanson, 2006. Fluorescence investigations of the conformational behaviour of Poly (N-vinylcaprolactam), Reactive and Functional Polymers, 66: 1-11.
[16] Ward, M.A., T.K. Georgiou, 2011. Thermoresponsive Polymers for Biomedical Applications, Polymers, 3: 1215-1242.