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Rheological analysis of hybrid hydrogels during polymerization processes

Abstract: Development of new implant coatings with temperature-controlled drug release to treat infections after device implantation can be triggered by highly elastic hydrogels with adequate stability and adhesive strength in the swollen state. By using an ionic liquid (IL $[\mathrm{ViPrIm}]^+[\mathrm{Br}]^-$) as additive to N-isopropylacrylamide (NIPAAm) unique effects on volumetric changes and mechanical properties as well as thermoresponsive drug release of the obtained hybrid hydrogels were observed. In this context, rheological measurements allow the monitoring of gelation processes as well as chemical, mechanical, and thermal treatments and effects of additives. Hybrid hydrogels of pNIPAAm and poly (ionic liquid) (PIL) were prepared by radical emulsion polymerization with N,N′-methylenebis(acrylamide) as 3D crosslinking agent. By varying monomer, initiator and crosslinker amounts the multi-compound system during polymerization was monitored by oscillatory time sweep experiments. The time dependence of the storage modulus (G′) and the loss modulus (G″) was measured, whereby the intersection of G′ and G″ indicates the sol-gel transition. Viscoelastic behavior and complex viscosity of crosslinked and non-crosslinked hydrogels were obtained. Within material characterization rheology can be used to determine process capability and optimal working conditions. For biomedical applications complete hydrogelation inter-connecting all compounds can be received providing the possibility to process mechanically stable, swellable implant coatings or wound closures.

Keywords: hydrogel; crosslinking; gelation; N-vinyl-imidazolium; polymeric ionic liquids

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1 Introduction

Recent desires for new implant coatings with controlled or responsive drug release to treat infections after device implantation are increasingly shifting the focus to the development of novel hybrid or multi-compound systems.

Regarding requirements in the medical field, in particular the indispensability of biocompatibility for usage in the human body the discovery of new synthetic oligo- or polymers is limited. Thus, most of the synthetic water absorbable polymers like poly(acrylic acid) (PAA) as super absorbers cause skin irritations [1] and requires protection by non-woven materials for e.g. diapers. However, other swellable polymers are already successfully used non-invasive as wound dressings [2,3], ultrasound gels or contact lenses [4,5] for a short or limited time. The demand on new implantable polymeric materials is even more complex, due to possibility of degradation during prolonged stay. Some medical devices should be selectively degraded without leaving toxic metabolites and if applicable replaced by human tissue after a certain time. Others should remain permanently without causing foreign body reactions or biofouling.

To treat an infection caused by biofilm formation or through mechanical irritation on e.g. cardiac pacemaker housings a second surgical intervention is currently required. Accordingly, one focus of our research is on the development of smart hybrid hydrogel coatings to avoid such an intervention. Their soft and often very elastic properties together with a controlled local drug release even after a certain time can be used to respond effectively to inflammations. Still, published research is of mainly academic nature, since preclinical testing and clinical trials for selected product candidates bear high risks with associated time and cost.

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The radical emulsion polymerization with N,N′-methylenebis(acrylamide) (MBAA) for crosslinking generally involves additional risks. But the unique properties of new highly elastic hydrogels [6] with adequate stability and adhesive strength in the swollen state might be worth using them as implant coatings. Apart from this rheological analysis can be used for further material characterization, more specifically to analyze the hydrogelation, determining processing capability and optimal working conditions.

We previously reported an hybrid hydrogel system prepared from an ionic liquid ([ViPrIm]$^+$[Br]$^-$) as additive to N-isopropylacrylamide (NIPAAm) supplementary crosslinked with MBAA [7]. Herein strong effects on volumetric changes and mechanical properties as well as thermoresponsive drug release were observed. The current rheological measurements allow the monitoring of gelation processes as well as chemical, mechanical, and thermal treatments and effects of additives. A complete polymerization interconnecting all compounds and uniform gelation process for biomedical applications can be received providing the possibility to process mechanically stable, thermosensitive swellable implant coatings or wound closures.

2 Material and methods

2.1 Hydrogel preparation

As model ionic liquid 1-vinyl-3-isopropyl-imidazolium bromide ([ViPrIm]$^+$[Br]$^-$), hence abbreviated as IL, was used. In a first step the IL was synthesized with a yield of 84% following a procedure already described in [8]. Hydrogel samples have been prepared by using NIPAAm, IL or a hybrid of IL/NIPAAm 5/95wt% (see **Figure 1**). Modified parameters concern the addition or omission of the crosslinking agent. For all crosslinked systems the MBAA amount was kept constant with 1.3% related to the amount of IL or NIPAAm. Tetramethylethylenediamine (TEMED) is used with ammonium persulfate (APS) to catalyze the polymerization and was added subsequently. Defined masses were mixed and dissolved in distilled water as described in detail in [7]. The amount of TEMED was further doubled, but no significant effect on gelation was observed.

All used materials and chemicals have been purchased from Sigma-Aldrich (St Louis, MO, USA) and used as received.

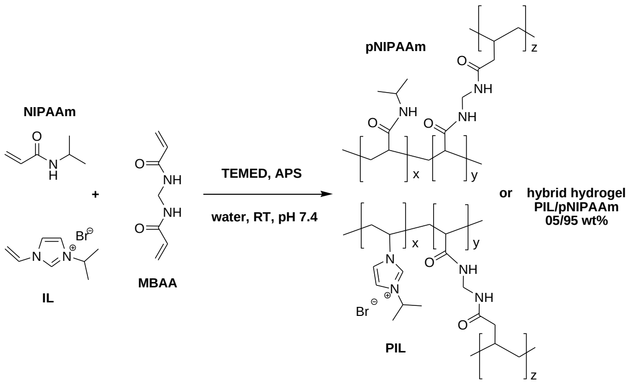

Figure 1: Poly-IL (PIL) or/and pNIPAAm hydrogel formation by vinyl addition copolymerization initiated by TEMED/APS in phosphate buffered saline solution (PBS).

2.2 Rheological characterization

Rheological properties of the multi-compound system during polymerization were monitored over time. Three different hydrogel samples were investigated by varying the monomer, initiator and crosslinker amounts. For analysis a RheoStress 1 rheometer (Thermo Haake GmbH, Karlsruhe, Germany) with a cone-plate C 20/1° Ti system was used. Immediately after TEMED addition and rapid mixing of all components, the sample was loaded as a thin layer between a stationary and a movable setup component and an oscillatory time sweep experiment was started. Conditions: distance between cone-plate 0.054 mm, controlled stress (CS) mode; test parameters: 100 Pa, frequency f = 1 Hz; temperature T = 21 ± 0.5°C and measurement time t = 3000 s. The sample volume was 40 µL. Measurements were run in triplicates for each composition.

3 Results and discussion

Oscillatory rheology is used quite frequently to characterize viscoelastic materials and to investigate curing reactions of multi-compound systems, where the sample is going through a liquid to solid phase transition. Parameters such as start of chemical reaction (t_0), type and strength of hydrogelation, final complex dynamic viscosity (η^*), as well as gel point (t_{Gel}), can be used to compare different network formulations and to evaluated novel hybrid hydrogels. **Figure 2** shows representative rheological measurements of crosslinking reaction within the initial ten minutes performed with single and mixed hydrogel reagents in the presence of 1.3% MBAA. In general, the start of vinyl addition polymerization is initiated by free radicals from persulfate, whereby TEMED

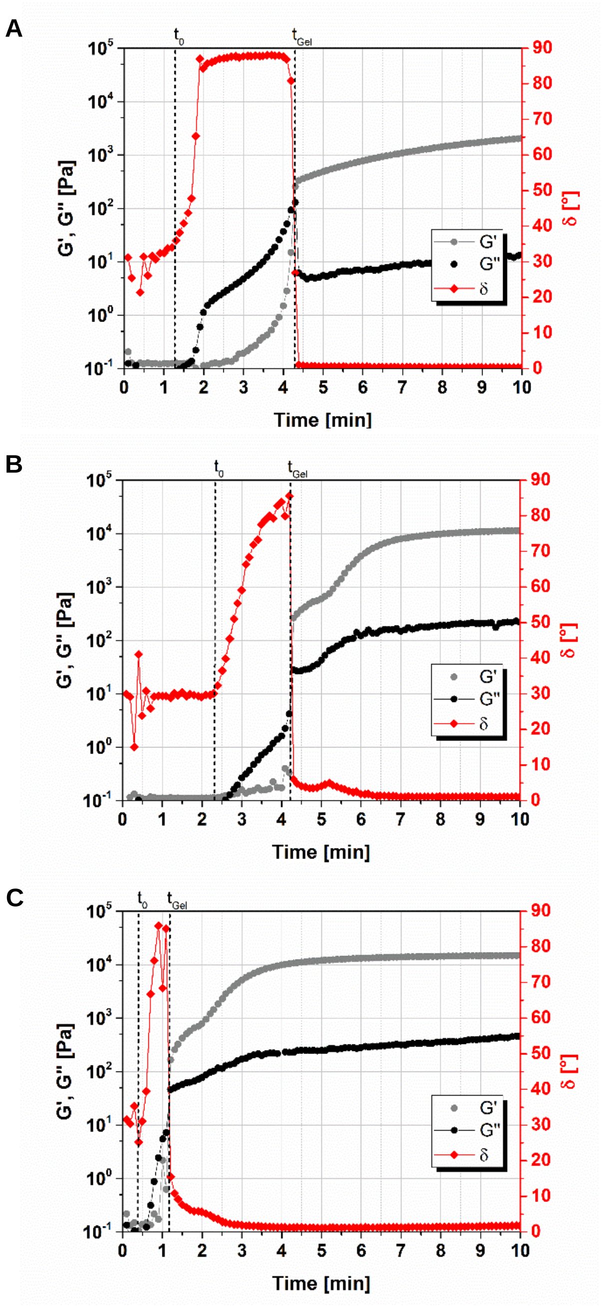

Figure 2: Representative storage modulus G′, loss modulus G″ and phase angle δ as a function of time for crosslinked (A) IL/ MBAA, (B) NIPAAm/MBAA and (C) IL/NIPAAm/MBAA at 21 ± 0.5 °C (n = 3). *Insert:* Start of chemical crosslinking reaction is denoted as t_{CR} and the gelation point as t_{Gel}.

accelerates the rate of their formation. The radicals convert vinyl monomers to free radicals which react with non-activated monomers to start radical chain reaction. The elongating polymer chains are randomly crosslinked by MBAA, resulting in a 3D network. All observed hydrogelations are very fast, as it seems independent of different vinyl compounds. At the beginning, with G′ lower than G″, all exhibited the behavior of a viscous fluid (sol). Both moduli elevated rapidly as hydrogelation proceeded, whereas the increase of G′ was much higher than that of G″, due to the occurrence of crosslinking. Besides, the complex viscosity changed over time as well as the final strength. The results obtained from several oscillatory tests are summarized in **Table 1**.

The intersection of G′ and G″ (t = t_{Gel}, see **Figure 2**) indicates the sol-gel transition. The gel point (t_{Gel}) differed from 4.6 ± 0.3 min for **A** IL/MBAA to approximately 3.1 ± 1.1 min for **B** NIPAAm/ MBAA and 1.5 ± 0.3 min for the 5/95 hybrid system **C** IL/ NIPAAm/MBAA at 21°C. Surprisingly, the initiated polymerization of two different vinyl monomers besides the MBAA crosslinking is much faster. Subsequent G′ and G″ leveled off, whereby G′ reached a value of 4 kPa for crosslinked PIL and 5 kPa for cross-linked pNIPAAm, implying a soft and very flexible structure. All three formations resulted in homogenous 3D networks within a few minutes.

Characterization of single hydrogel reagents without MBAA exhibited significant differences (**Figure 3**). No gelation point was observed for non-crosslinked pNIPAAm (see **Figure 3, C**). In contrast, a gelation of the PIL without crosslinker occurred and can be affected by raising temperature shown in **Figure 3, A/B**. The gelation time of non-crosslinked IL was shortened by more than 80% through a temperature increase of 20°C. A decrease of crosslinking time ($t_{Gel\ 1}$) from 58 min to 10 min allows an adjustment of the polymerization and curing process, so that a homogenous gelation of different reagents can be achieved, which might be useful for in-situ hydrogelations on implant surfaces, whereby body temperature could act as catalyst.

Table 1: Complex viscosity |η*| and gelation point of the key reagents with and without crosslinking at 21± 0.5 °C (n = 3 for each component).

Key component	Viscosity |η*| [Pas]		
	$t_{500\ s}$	$t_{1000\ s}$	t_{end}
PIL (crosslinked)	282 ± 37	671 ± 97	914
pNIPAAm (crosslinked)	1671 ± 76	2098 ± 85	14824
PIL/pNIPAAm (5/95) (crosslinked)	2234 ± 88	2599 ± 136	33212
PIL (non-crosslinked)	0.1 ± 0.1	2.3 ± 1.3	144
pNIPAAm (non-crosslinked)	2590 ± 2253	10220 ± 13129	64982

t_{end}: Time point within 30 min where the highest viscosity is measured before first loss of contact between hydrogel and cone-plate.

4 Conclusion

The control and optimization of time- and temperature dependent hydrogelation process for coatings is a major challenge. Hybrid hydrogels of NIPAAm and IL have been successfully combined with new deviating material properties and a complete hydrogelation towards soft and very flexible hydrogel layers can be assured.

In this study the time dependence of the storage modulus (G′) and the loss modulus (G″) of different hydrogel formulations was measured. The viscoelastic behavior of crosslinked and non-crosslinked PIL hydrogels differs fundamentally from pNIPAAm hydrogels.

For further material characterization rheological studies can be used to analyze the hydrogelation determining processing capability and optimal working conditions. By the use of this method complete polymerization interconnecting all compounds and uniform gelation process for biomedical applications can be received providing the possibility to process mechanically stable, thermosensitive swellable implant coatings or wound closures.

Author's Statement

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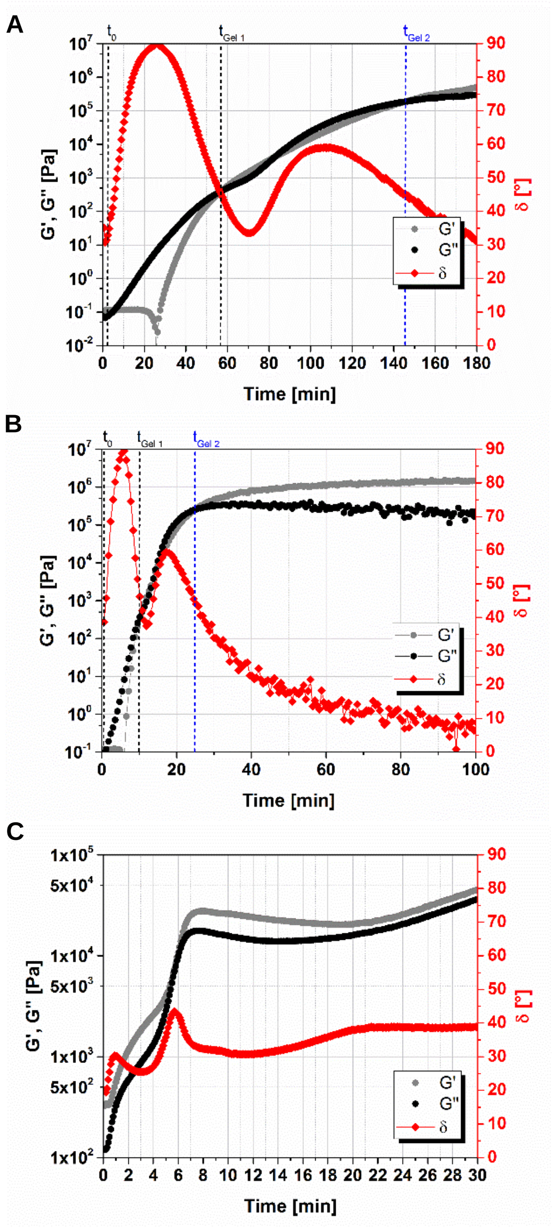

Figure 3: Storage modulus G’, loss modulus G” and phase angle δ as a function of time for (A) non-crosslinked PIL at 21 ± 0.5 °C, (B) non-crosslinked PIL at 40 ± 0.5 °C and (C) non-crosslinked pNIPAAm at 21 ± 0.5 °C (n = 1).

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