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Synthesis of Poly(Alkyl Cyanoacrylates) as Biodegradable Polymers for Drug Delivery Applications

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Summary: Poly(alkyl cyanoacrylates) are biodegradable and biocompatible polymers. Ethyl, n-butyl and octyl cyanoacrylate have been approved in the last decades by the US Food and Drug Administration (FDA) and novel applications are continuously appearing. Recently, such polymers have been proposed as raw materials for the synthesis of nanoparticles aimed to drug delivery. In the literature, such nanoparticles have been always produced through heterogeneous polymerization processes in water. In this work, the anionic polymerization of ethyl, n-butyl and octyl-cyanoacrylate in water is systematically investigated. Optimum conditions for the process are identified by changing reaction temperature and solution pH. It is found that an aqueous dispersion medium at pH around 5 and 65 °C gives the best results in terms of polymer molecular weight for all monomers, even if the process exhibits the dominant production of low molecular weight (LMW) polymer. On the other hand, the amount of high molecular weight polymer becomes noticeable at room temperature.

Keywords: biopolymers; cyanoacrylates; drug delivery; nanoparticles; polymerization

Introduction

Cyanoacrylates are acrylic monomers which rapidly polymerize in the presence of water following an anionic or zwitterionic polymerization mechanism. For this reason, water or even natural moisture in the air can activate the polymerization process, thus forming long chains of poly(alkyl cyanoacrylates) (PACA). From the early 1960s, several cyanoacrylates have been studied for possible use in the biomedical field, for example as tissue adhesives and suture materials, with several advantages over conventional materials in soft-tissue surgery. Cyanoacrylates are commonly used as adhesives, in particular for non-porous materials or in presence of small traces of water. In this field possible applications are for example the assembling of prototype electronics or flying model aircraft. The capability of cyanoacrylate glues to bond metals is also remarkable while, on the contrary, they are not recommended for use with glass.[1]

If medical use of cyanoacrylate glues goes back to the half of the last century especially for military applications, US Food and Drug Administration (FDA) approved some classes of cyanoacrylates as bio-compatible compounds only in the last two decades. Accordingly, many developments of novel biomedical employments of PACA have been recently reported. Studies in this field have shown that such polymers are excellent skin adhesives, surgical glues and embolitic materials.[2–5] With this respect, examples are the use of cyanoacrylate tissue adhesives for skin closure in plastic surgery or the osteosynthesis with liquid ethyl cyanoacrylate polymerized with ultrasounds.[6,7] Further applications are the therapeutic embolization of cerebral arterio-venous malformations and the employment of cyanoacrylate glue in gastric variceal bleeding or corneal perforations.[8,9] More recently PACA polymers have been proposed as raw materials for the synthesis of nanoparticles

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aimed to drug delivery.[10] In all these applications and especially in PACA use for nanoparticles production, an important role is played by the polymer synthesis. In literature the most common methodology proposed is the anionic polymerization in aqueous solution.[11–14] The aim of this work is to investigate the anionic polymerization of PACA in water in order to optimize the operative conditions of the process. In particular, different reaction temperatures and pH values of the aqueous solution are studied to evaluate their influence on the molecular weight of the polymer produced.

Experimental Part

The monomers used in this work are ethyl, n-butyl and octyl-cyanoacrylate kindly supplied by Henkel (Henkel Biomedical, Dublin, Ireland). Reactions have been performed in a batch reactor at constant temperature. Polymers are produced in aqueous solutions at different pH: 2, 3, 5, 7, 9 and 11, respectively. Reaction temperatures taken into consideration at each value of pH are: 0, 25, and 65 °C. The reaction mixture is mixed by a magnetic stirrer at 650 rpm. Distilled water is loaded into the reactor and the selected temperature and pH conditions are established (in the latter case, by adding HCl or NaOH). Monomer was injected directly into the stirred aqueous solution using a syringe as reported in the literature,[11-13] typically at 1% w/v (1 g/100 ml). After two hours of reaction at constant conditions, the reaction products are isolated from the suspension by centrifugation at 20,000 rpm and then dried under vacuum and stored in refrigerator.

Polymer properties of all samples were measured by gel permeation chromatography (GPC). The device (Agilent, 1100 series, Germany) is equipped with two detectors in series (ultraviolet (UV) and

Table 1.
Average Molecular Weight of short- (LMW) and long-chain (HMW) polymer obtained at three different temperatures as a function of pH for: a) ethyl cyanoacrylate (ECA), b) n-butyl cyanoacrylate (BCA) and c) octyl cyanoacrylate (OCA).

		Temperature 65°C		Temperature 25°C		Temperature 0°C	
	pH	HMW (Da)	LMW (Da)	HMW (Da)	LMW (Da)	HMW (Da)	LMW (Da)
ECA	2	–	1256	2.21×10^5	1256	–	2957
	3	–	1449	4.30×10^5	1449	–	2910
	5	–	540	7.13×10^5	1534	1.47×10^5	554
	7	–	548	2.94×10^5	1632	5.38×10^5	545
	9	4.08×10^5	541	2.08×10^5	1327	7.21×10^5	581
	11	4.56×10^5	509	3.05×10^5	1044	7.10×10^5	580

		Temperature 65 °C		Temperature 25 °C		Temperature 0 °C	
	pH	HMW (Da)	LMW (Da)	HMW (Da)	LMW (Da)	HMW (Da)	LMW (Da)
BCA	2	–	411	–	398	–	741
	3	–	608	–	475	–	760
	5	–	719	8.28×10^5	986	–	887
	7	1.51×10^6	745	9.71×10^5	350	3.52×10^5	801
	9	6.62×10^5	694	5.46×10^5	376	6.52×10^5	955
	11	4.29×10^5	744	9.60×10^5	349	6.18×10^5	628

		Temperature 65 °C		Temperature 25 °C		Temperature 0 °C	
	pH	HMW (Da)	LMW (Da)	HMW (Da)	LMW (Da)	HMW (Da)	LMW (Da)
OCA	2	–	720	4.15×10^5	738	–	–
	3	5.61×10^6	691	2.21×10^6	723	–	–
	5	–	730	3.71×10^5	754	–	–
	7	7.38×10^5	695	3.42×10^5	726	4.42×10^5	748
	9	–	719	3.30×10^5	729	6.77×10^5	734
	11	5.60×10^5	735	-	692	1.07×10^5	735

differential refractive index (RI)), three PLgel columns (Polymer laboratories Ltd., UK; two with pore sizes of MXC type and one oligopore; column length: 300 mm; column diameter: 7.5 mm) and a pre-column. THF was used as a solvent with 1 mL/min flow rate and temperature of 30 °C.

Results and Discussion

PACAs are synthesized following the recipe reported above. Average Molecular Weight (MW) values of PACAs obtained at different temperatures are summarized in Table 1. Reported results are in agreement with those found in the literature for poly(n-butyl cyano acrylate) (PBCA).[13] Moreover, a variation of the temperature does not have any influence on the average MW.

Experimentally it has been found a drastic decrease of the reaction rate, especially at low pH values for poly(octyl cyanoacrylate) (POCA), when changing the experimental conditions. This behavior is quite evident for POCA obtained at 0 °C where, at pH values of 2 and 3, the octyl cyanoacrylate monomer does not polymerize at all. This is a very important result, indicating a distinct reactivity difference with respect to the more reactive ethyl and n-butyl cyanoacrylates, where the monomer is completely converted into polymer in a few seconds.

In Figure 1, the GPC chromatograms obtained for POCA produced at different pH values and at 25 °C are reported: such behavior is equally representative of all the other monomers under examination. The first peak on the left corresponds to polymers with high molecular weight (in the order of 300,000 Da) while the second one to much shorter chains, with an average MW in the order of 700 Da. All the other peaks come from the solvent (THF) and therefore they do not need to be considered.

In Table 1, the average MW of the two peaks corresponding to the polymer chains with low and high MW, respectively, are collected for all examined monomers. Even if the average MW values are very similar one to the other, the highest MW value is found at pH around 5 for all of the three reaction temperatures and for all the monomers. On the other hand, analyzing LMW data, it is clear that the MW of poly(ethyl cyanoacrylate) (PECA) constantly decreases at 0 °C, reaching minimum values in the pH range 5–11. Moreover, for the other monomers, data drastically differ from case to case because of the influence of temperature on reaction rate, especially for POCA.

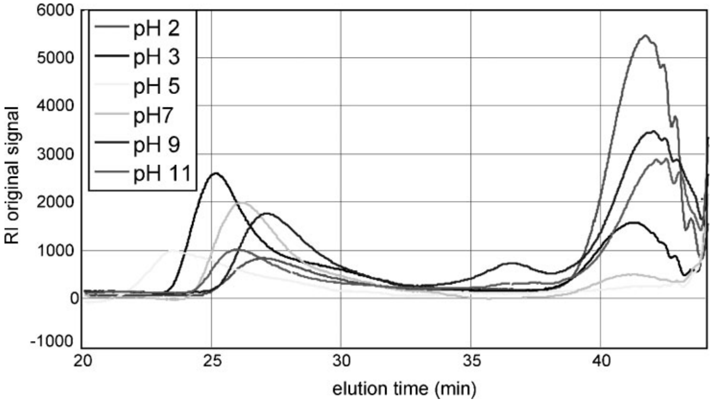

Figure 1.
POCA Molecular Weight Distributions obtained at 25 °C and at different pH values.

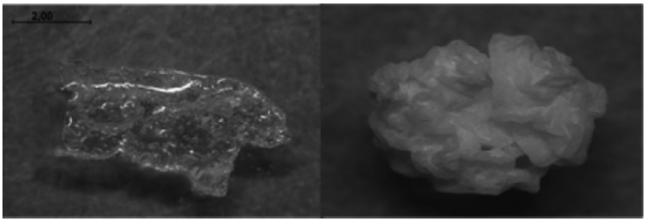

Figure 2.
Precipitated solid PECA polymer produced at 25 °C at pH 3 (left side) and pH 7 (right side).

As reported in literature the presence of two different peaks in all the chromatograms is representative of two parallel mechanisms able to produce both long and short polymer chains (depolymerization-repolimerization processes, DPRP).[13–15] In particular, the values of the average MW of these long-chains (see Table 1) span over about one order of magnitude, ranging from 208,000 to 2,000,000 Da. These results show that highest MWs for this fraction of polymer were found in the reactions carried out with BCA at pH 7 and OCA at pH 3. The mechanism leading to the formation of long polymer chain is not yet understood but it represents an important chemical pathway since the weight percentage of polymer with higher MW can be as large as 50%.

A final consideration has to be made about the morphology of the polymer. Actually, the final product is recovered in two different forms: the major part as a bulky, solid material settled down on the bottom of the reactor vessel (see Figure 2), while the rest is suspended as stable particles in aqueous solution. A correlation between conversion rate and final form of the polymer can be proposed: in the reactions carried out at low pH, the reaction rate is slower and the amount of suspended polymer is notably larger than the precipitated one. Vice versa, reactions carried out at neutral and higher pH values instantaneously lead to the formation of bulky, precipitated polymer, while the suspended polymer is only a small fraction of the total.

Conclusion

In the present work, the effect of pH and temperature on PACA MW distribution has been studied. Minor effects on the polymer MW at all explored pH values were measured. Carrying out the reactions in aqueous media, the best results in terms of polymer average molecular weight have been found at 65 °C and pH 3 for POCA and pH 7 for PBCA. Most of the polymer exhibits low molecular weight, even though a fractional amount at high MW becomes noticeable at room temperature. Finally, it was found that low temperature and pH conditions inhibit the reaction, especially in the case of POCA.

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