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Short Research Article

The design of radiolabeled carbon-14 polymers†

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Abstract: This paper outlines three methods for the incorporation of carbon-14 radiolabels into polymers. The first method discussed used the radiolabeled starting material, [1,6-^{14}C]hexamethylenediamine **2**. The reaction of **2** with sodium dicyanamide led to a carbon-14 polybiguanide **3** with a wide molecular weight distribution. An improvement to this reaction was to react **2** with biguanide. This produced **3** with a tighter molecular weight distribution. Modification of side chains in polymers provides a facile route to incorporate carbon-14 labels. This is illustrated in the formation of [^{14}C]carboxymethyl cellulose **6** which resulted in near perfect molecular weight distribution. Another method to incorporate carbon-14 into polymers was the reaction between the sodium salt of polyethylene glycols (PEGs) with [U-^{14}C] ethylene oxide. This resulted in oligomer formation and random labeling in the polymer. This was circumvented by synthesizing carbon-14 PEG esters from the reaction of carbon-14 labeled 2-bromoethyl esters with PEG. This method retained the polydispersity ratio on the reduction of the ester to release the carbon-14 labeled PEG. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: molecular weight distribution; end labeling; side chain derivatization

Introduction

Polymers are often required to have radiolabels incorporated into their structure to be used as pharmaceutical drugs or in drug delivery devices. Synthetic routes are required to incorporate these radiolabels such as carbon-14 into the polymer. This paper will outline a variety of methods which will focus on the molecular weight distributions of the carbon-14 radiolabel polymers.

Results and discussion

Method 1: monomer labeling

The aim was to produce a carbon-14 labeled polybiguanide with a similar molecular weight distribution to an unlabeled polybiguanide which was supplied by the customer. The first step was to produce a monomer unit that was easy to synthesize and purify to high radiochemical purity. For this we required a synthetic route to the radiolabeled starting material, [1,6-^{14}C] hexamethylenediamine **2**.

[1,6-^{14}C]Adiponitrile **1** was synthesized by the reaction of potassium [^{14}C]cyanide (55 mCi/mmol) with dibromobutane. The target monomer **2** was reduced using lithium aluminum hydride (Scheme 1). The reduced product [1,6-^{14}C]hexamethylenediamine was purified to high radiochemical purity using silica flash chromatography. This purification eliminated the by-product [1,6-^{14}C]-5-aminopentylacetonitrile. The presence of this by-product during the polymerization would terminate the polymer chains and therefore affect the molecular weight distribution.

At GE Healthcare we have investigated two approaches to initiate the polymerization of the radiolabeled substrate, [1,6-^{14}C]hexamethylenediamine **2**. The progress of the polymerization was monitored by using the technique gel permeation chromatography (GPC). This approach enabled the polymerization to be tailored around our molecular weight specifications and thus leading to a simplification in the purification process.

The first method involved a 'melt' polymerization at 150°C on [1,6-^{14}C]hexamethylenediamine and sodium dicyanamide to afford the carbon-14 polybiguanide **3**

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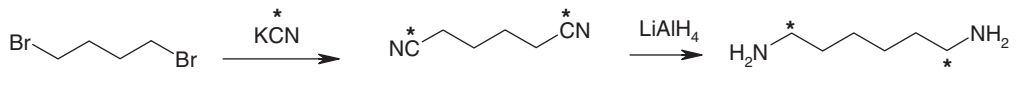
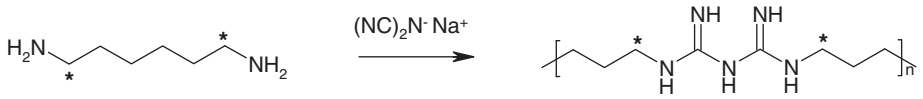
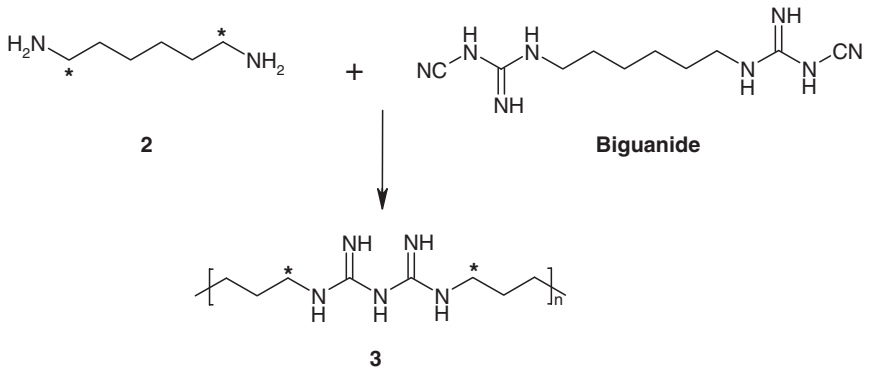


Scheme 1



Scheme 2

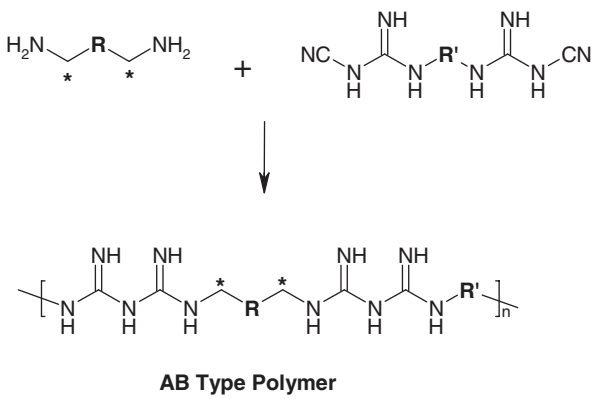


Scheme 3

as shown in Scheme 2. This produced a very wide molecular weight distribution which did not meet the customer's specifications.

The second method (Scheme 3) was to employ a 'melt' polymerization which was carried out with [1,6-^{14}C]hexamethylenediamine **2** and the commercially available biguanide to give the carbon-14 biguanide polymer **3**. This was performed using the same conditions as the previous method above (Scheme 2) and gave a much tighter molecular weight distribution for **3** when analyzed by GPC.

GPC analysis was used to follow and terminate the polymerization at the correct point. A simple work up afforded a matched molecular weight distribution without any further purification. Hence, this method should also provide an easy route to the production of simple copolymers of the AB type (Scheme 4).



Scheme 4

Method 2: side chain derivatization

The modifications to the side chains of polymers can provide a simpler route for the incorporation of more than one carbon-14 label into the final polymer. This methodology allows the molecular weight distribution of the product to be governed by the donor polymer. A good example of this method was the labeling of cellulose **5** to produce, [^{14}C]carboxymethyl cellulose **6**. This was produced by reacting cellulose with chloro [2-^{14}C]acetic acid (Scheme 5).

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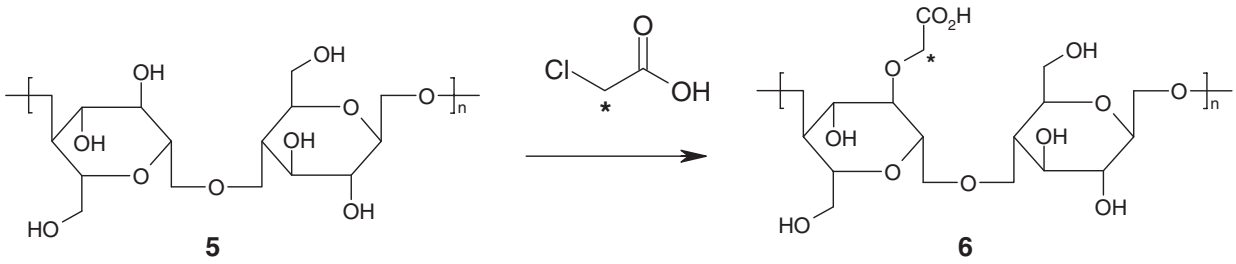
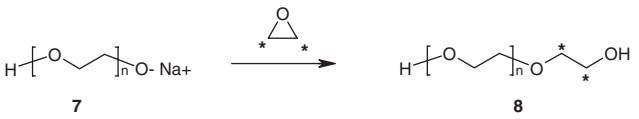


5 **6**

Scheme 5



7 **8**

Scheme 6

A major advantage of this type of reaction is that fragmentation is avoided. Another important advantage is that the percentage incorporation of activity can be varied and the molecular weight distribution is governed by the donor polymer. Hence, a perfect molecular weight match can be achieved with this approach.

Method 3: end labeling

Carbon-14 labeled polyethylene glycols (PEGs) **8** can be prepared by the formation of the sodium salt of the PEG **7** and the subsequent reaction with [U-^{14}C]ethylene oxide (Scheme 6).

The analysis of the carbon-14 PEG product obtained in this way showed that the polydispersity ratio of carbon-14 labeled PEG was sometimes different to the unlabeled precursor. The product often contained small active labeled fragments. Although these could be easily removed by simple size exclusion chromatography, they were obviously undesirable. It appeared that these were created by [U-^{14}C]ethylene oxide being initiated and forming oligomers.

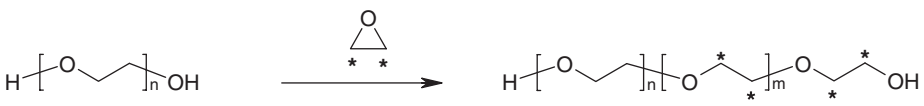
Analysis demonstrated that the molecular weight distribution had often been broadened. The labeled polymer chains were seen to contain more than one carbon-14 labeled monomer unit. It was proposed that the sodium was labile and could migrate down the monomer causing propagation of the polymer chain (Scheme 7).

It would be difficult to use this technique to produce a close match for polymers with a low polydispersity ratio. In order to carbon-14 label PEGs an alternative approach was investigated which would enable the product to retain its polydispersity ratio. It was important that as a result of the labeling process, the monomer was not able to self initiate and generate its own polymer chains. A two stage labeling process was investigated which prevented propagation by producing a stable intermediate such as a carbon-14 PEG ester that could not react any further (Scheme 8).

This carbon-14 PEG ester intermediate can be isolated and purified by traditional methods. Low molecular weight polymers and carbon-14 PEG ester can be separated from unreacted PEG by chromatography methods. This approach proved to be beneficial over the traditional labeling techniques with [U-^{14}C]ethylene oxide. By purifying the carbon-14 PEG ester we could remove the unreacted PEG and ensure that the unreacted PEG does not contaminate the final product. This effectively increases the specific activity of the final carbon-14 PEG.

The carbon-14 PEG ester can be readily reduced to the carbon-14 PEG without any fragmentation. This reduction was achieved using lithium aluminum hydride (Scheme 9). This approach gave several advantages:

- The polymer contains only one labeled carbon-14 monomer unit.
- Also, it was impossible to generate low molecular weight fragments which for low molecular weight PEGs could contaminate the final product.



Scheme 7

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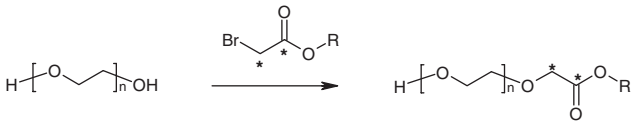
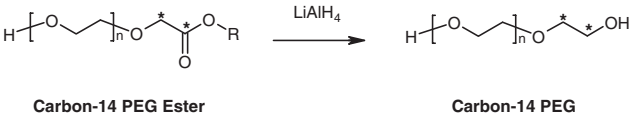


Scheme 8



Scheme 9

- Analysis of polymers of low polydispersity ratios indicated a uniform spread of carbon-14 labeling across the polymer chains, with only one monomer unit added to each chain.

Conclusion

At GE Healthcare we have utilized various strategies to incorporate carbon-14 radiolabels in polymers and to meet a range of customer specifications (specific activity, radiochemical purity, etc.).

Acknowledgement

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