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Modifiable Hyperbranched Polyester Drug Delivery Systems

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MODIFIABLE HYPERBRANCHED POLYESTER DRUG DELIVERY SYSTEMS

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By:

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Dorothy Ogden ENTITLED Modifiable Hyperbranched Polyester Drug Delivery Systems BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science**.**

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ABSTRACT

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Modifiable Hyperbranched Polyester Drug Delivery Systems.

This work encompassed synthesis and characterization of biocompatible hyperbranched polyester drug delivery systems prepared with fumaric acid, glycerol and polyethylene glycol. The polymers were manufactured in the melt utilizing $A_2 + CB_2$ polymerization. The ratio of A_2:CB_2 was modified and excess B was added to end-cap the polymers to avoid cross-linking. Fumaric acid was selected as the A_2 monomer because the double bond provided a site for polymer backbone modification or covalent attachment of active pharmaceutical ingredients. Acetaminophen and Ondansetron Hydrochloride were added to evaluate feasibility of using the polyesters as drug delivery systems. The weight average molecular weight of the $A_2 + CB_2$ polymer systems with the end-capping agent ranged from 5100 to 8500 Da with PDI values between 1.3 and 1.7. The polymers containing Acetaminophen appeared to degrade while the polymers with Ondansetron were determined to be immediate-release dosage forms.

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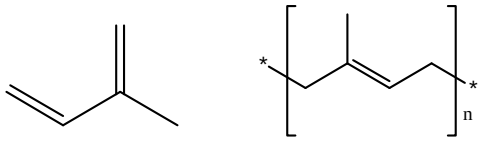
I. INTRODUCTION

The main objective of this project was to study modifiable $A_2 + CB_2$ hyperbranched polyester polymers. Naturally occurring polymers are prevalent throughout the world and include cotton, latex, starch, proteins, DNA and cellulose. Some common synthetic polymers include Bakelite, Teflon, Nylon and Kevlar. Polymers are large molecular weight compounds composed of repeat unit(s) called monomers. A polymer can be composed of a single repeating monomer (homopolymer) or multiple repeating monomers (copolymer). For instance, natural rubber is a homopolymer containing repeat isoprene units. Just to clarify, monomers become the repeat units; poly(isoprene) is polymerized isoprene.

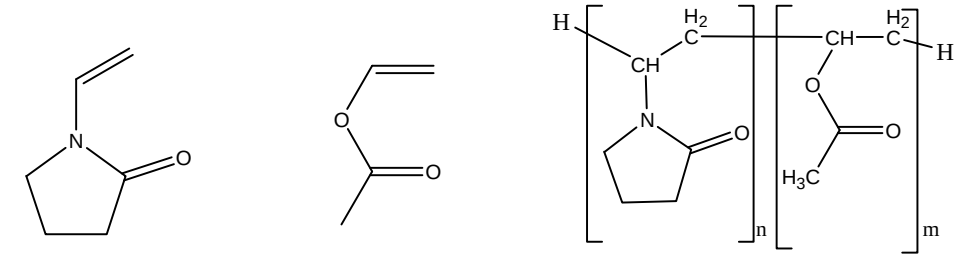
Figure 1: Natural rubber homopolymer.



isoprene natural rubber

Copovidone is a copolymer used in the pharmaceutical industry for controlled drug release. It is prepared from 1-vinyl-2-pyrrolidone and vinyl acetate monomers.[1]

Figure 2: Copovidone copolymer.

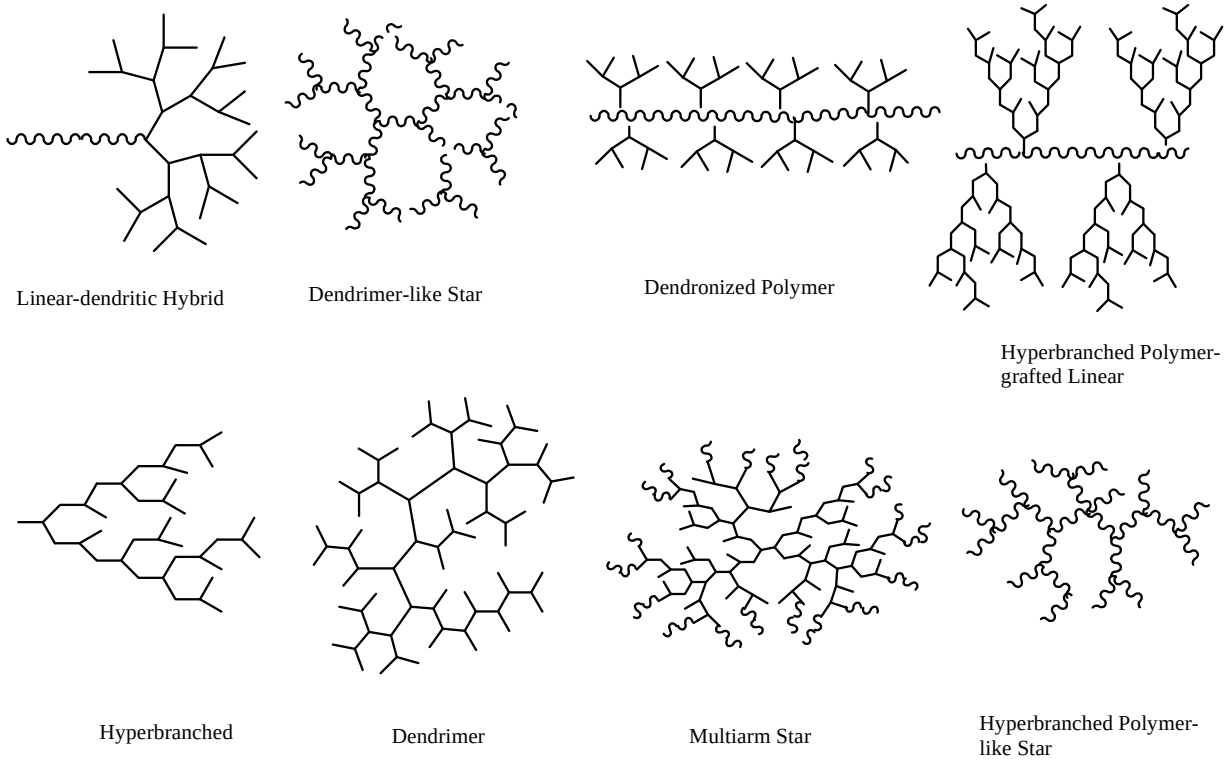


1-vinyl-2-pyrrolidone vinylacetate copovidone

Hyperbranched polymers are one of eight basic types of branched polymers. A perfectly branched or 100% branched polymer is a dendrimer. Dendrimers are perfectly symmetrical and

spherical with functional groups on the surface and/or inside the sphere. This makes dendrimers ideal for drug delivery, along with many other uses, since they can be created to be water soluble and also to contain binding sites for an active pharmaceutical ingredient (API). Variations of the dendrimer are linear-dendritic hybrids, dendronized polymers, dendrimer-like star macromolecules (DendriMacro), hyperbranched polymers, multiarm star polymers, hyperbranched polymer-like star macromolecules (HyperMacro) and hyperbranched polymer-grafted linear macromolecules.[2]

Figure 3: Branched polymers (adapted from Gao et al.).[2]

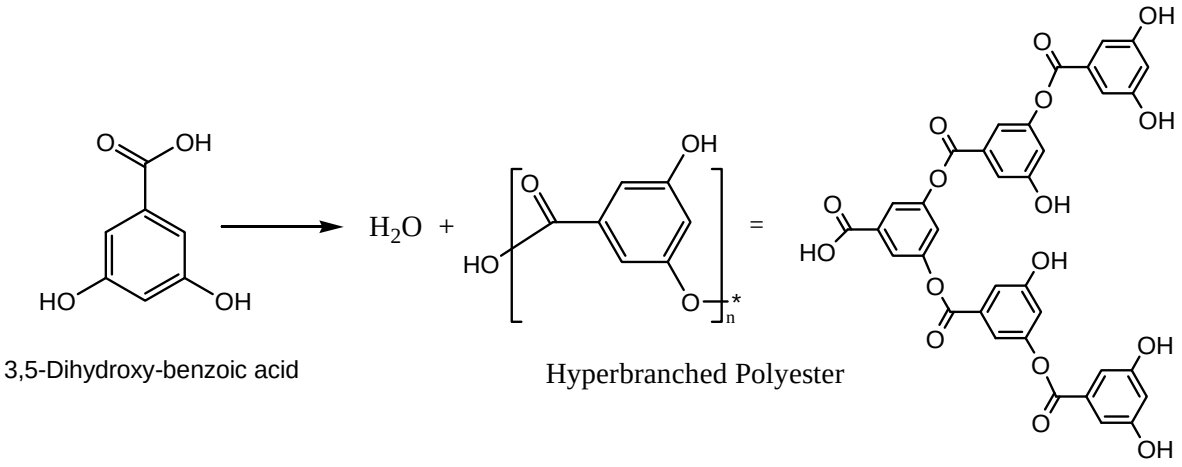


Hyperbranched polymers have become increasingly popular over the last twenty to thirty years due to their inherent physical properties. These properties include good solubility, low solution viscosity, thermal stability and a multitude of end groups.[3] In the 1980s, Kim and Webster used the terminology hyperbranched polymers to describe macromolecules with random branch-on-branch configurations.[4] Such macromolecules contain structural irregularities and are composed of linear, dendritic and terminal repeat units. While dendrimers are typically synthesized using tedious multistep

methods, hyperbranched polymers are often produced via a one-pot synthesis which is conducive to large scale manufacturing.

Hyperbranched polymers can be prepared via numerous methods. These include, but are not limited to, condensation, ring-opening multibranching (ROMBP), proton-transfer, atom transfer radical (ATRP) and reversible addition-fragmentation chain transfer (RAFT).[5,6] Condensation polymerization is a step-growth process in which monomers are joined one at a time to form dimers, trimers, tetramers, pentamers, etc. These small units then join to form larger ones and eventually become a polymer. Typically, each monomer in condensation polymerization has at least two functional groups and as the functional groups interact, a small molecule such as water is released. For instance an acid group on 3,5-dihydroxy-benzoic acid can react with an alcohol on another molecule of 3,5-dihydroxybenzoic acid to form an ester and water. This undergoes subsequent condensations to form a hyperbranched polyester.[7]

Scheme 1: Polycondensation to form polyester.



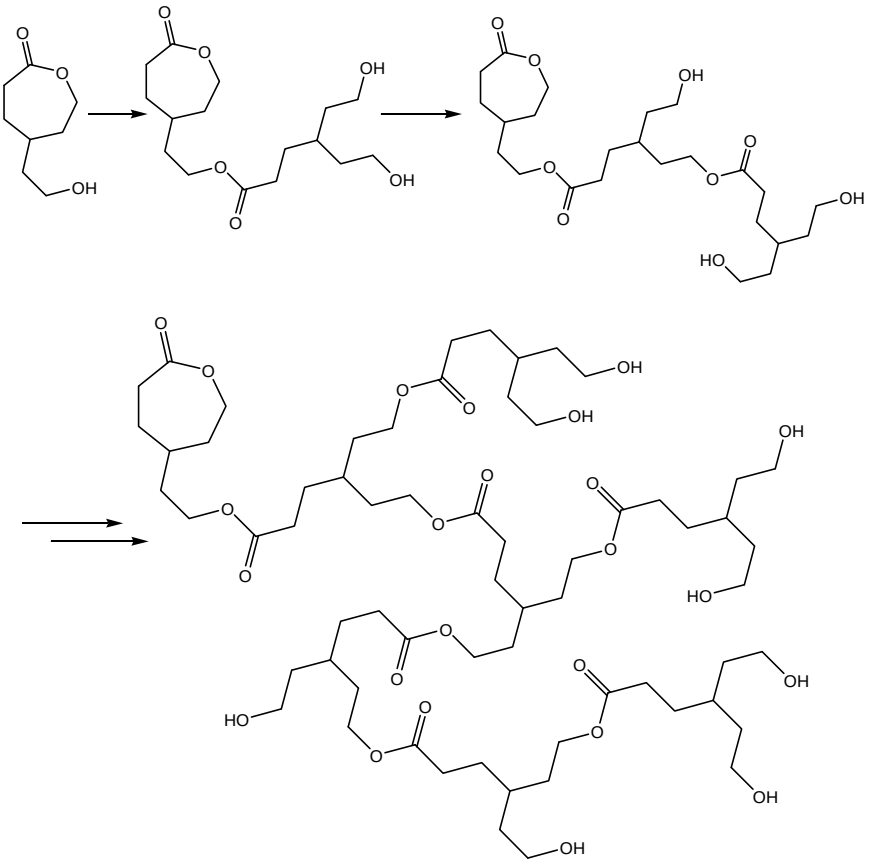
3,5-Dihydroxy-benzoic acid

Hyperbranched Polyester

ROMBP is a chain-growth process which typically involves initiation, ring opening, propagation and termination. In chain-growth polymerization, the molecule grows link by link to form a polymer. Liu et al. developed a procedure for preparing 4-(2-hydroxyethyl)-epsilon-caprolactone which employs a

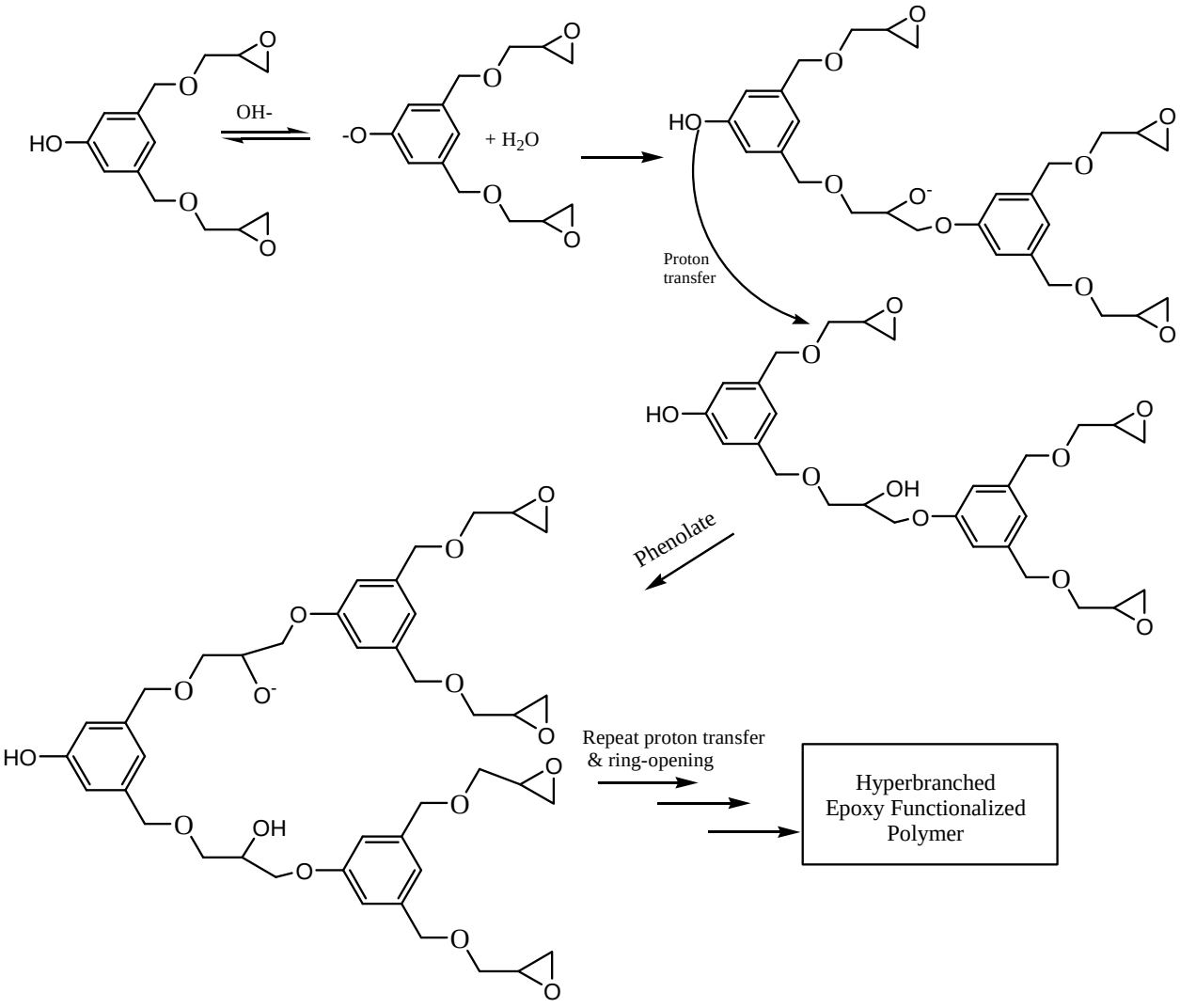
primary alcohol to initiate ring opening via the carbonyl group. Primary alcohols on the resulting dimer open additional rings to obtain a trimer, tetramer, etc. until a polymer is formed.[8]

Scheme 2: Ring-opening multibranching polymerization (adapted from Liu et al.).[8]



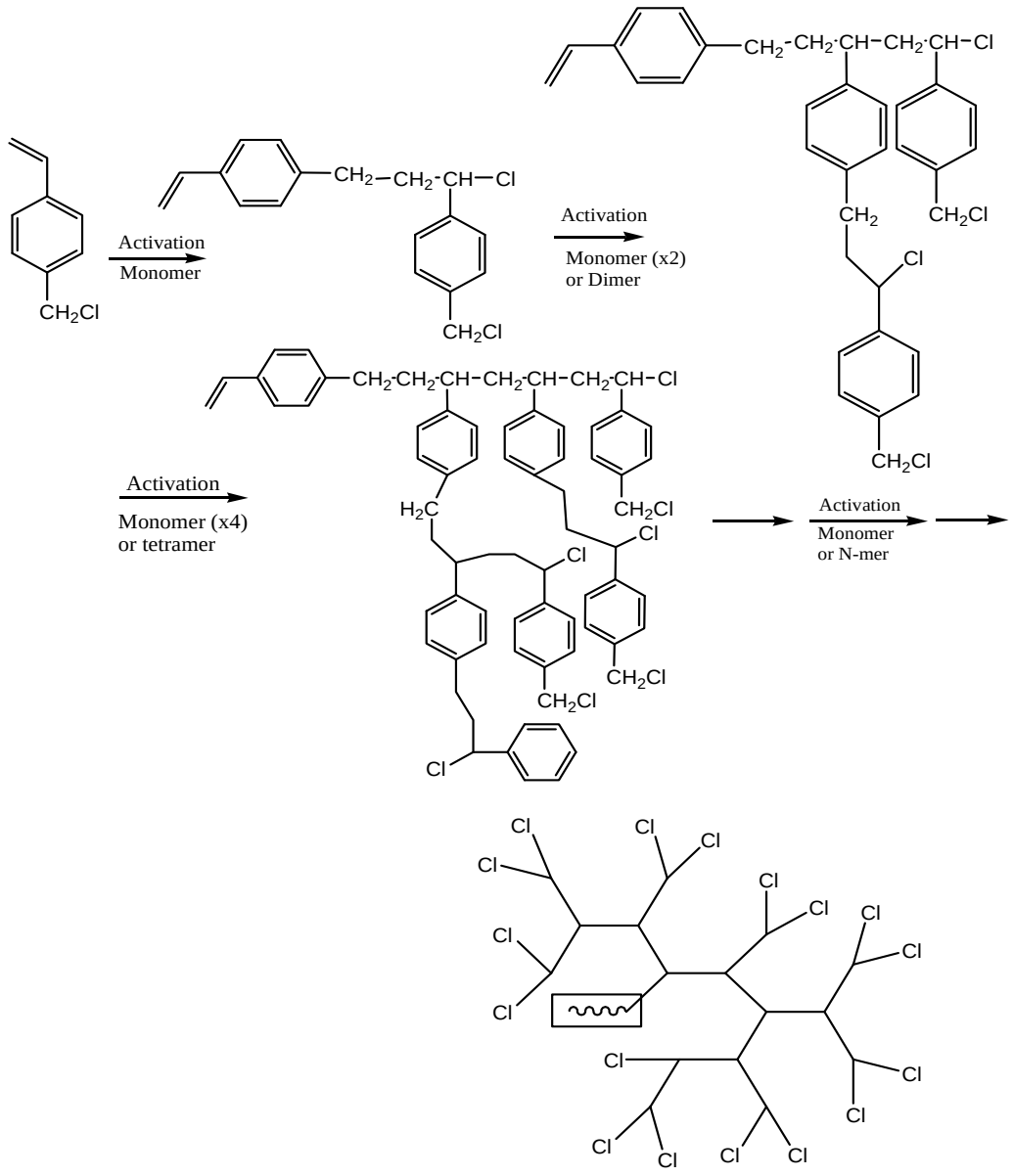
Proton transfer polymerization is another means for preparing hyperbranched polymers. It is a chain-growth process that involves deprotonation, nucleophilic attack and rapid proton exchange. This polymerization is similar to ROMBP and was reported by Chang and Fréchet in 1999.[9]

Scheme 3: Proton-transfer polymerization (adapted from Chang et al.)[9]



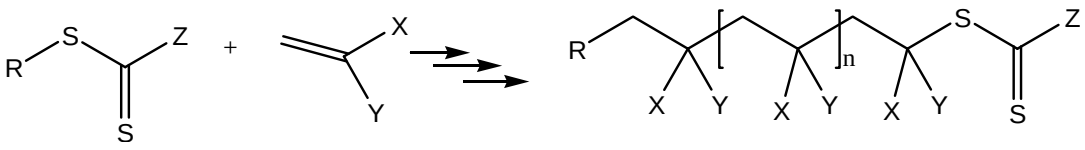
Atom transfer radical polymerization (ATRP) is a chain growth process and was reported by Gaynor et al. in 1996.[10] The one-pot synthesis involves using *p*-(chloromethyl)styrene as both the initiator and the monomer. The process occurs by homolytical cleavage of the chlorine on the styrene by Cu(I) to form Cu(II)Cl and a radical. The radical attacks the double bond on another styrene molecule to form a polymer with pendant groups. The pendant groups can also react to form a hyperbranched molecule.

Scheme 4: ATRP synthesis (adapted from Gaynor et al.).[10]



RAFT or reversible addition-fragmentation chain transfer polymerization is another chain growth process. In this mode, polymerization is reversible and occurs via chain transfer. Moad et al. described a process in which carbon sulfur bonds were broken and monomer was inserted.[11] The resulting molecule serves as the RAFT agent as presented in Scheme 5. Polymerization proceeds by chain transfer, reinitiation, chain equilibration and then termination.

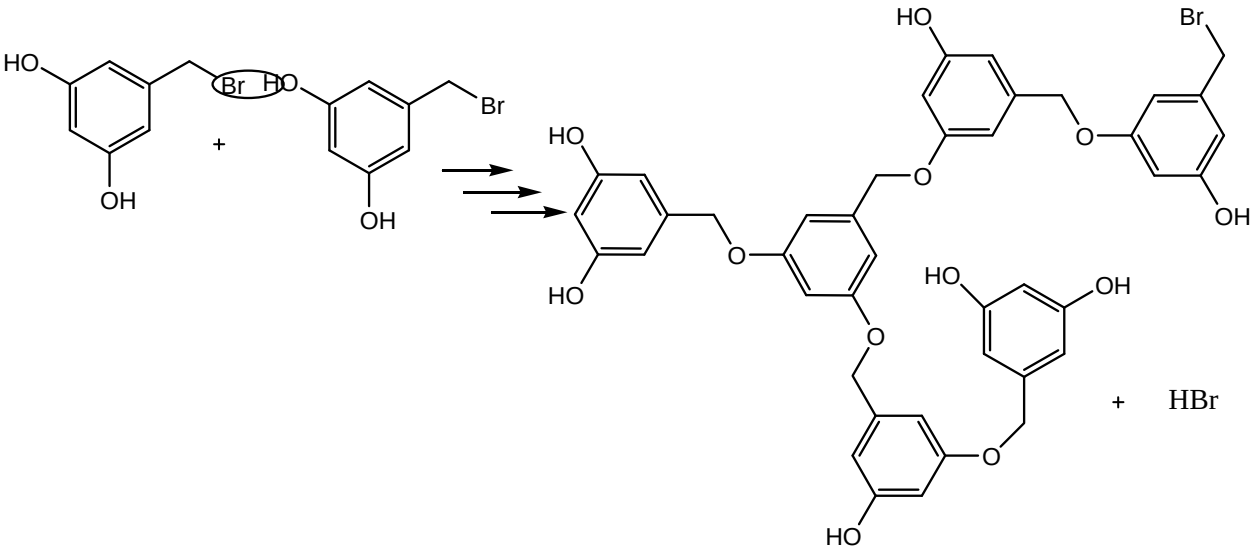
Scheme 5: RAFT agent synthesis (adapted from Moad et al.).[11]



An overview of several modes for preparing hyperbranched polymers has been presented. Focus will now be directed to polycondensation polymerization since it is one of the simplest and straightforward methods for preparing polymers.

One of the most famous works regarding polycondensation theory is that of Flory in which he described synthesis of branched polymers.[12] He theorized that a condensation of two monomers, one with a single A functional group and one with two or more B functional groups (AB_x), could be performed to create a highly branched polymer without gelation. Gelation occurs when polymer chains cross-link by forming intermolecular covalent or ionic bonds. This typically results in a polymer with undesirable physical properties such as low solubility and limited to no end-group functionality. According to Flory, the probability that an A functional group has been incorporated in a branching unit is $\alpha=\rho_A$ and the probability that a B group has been reacted is $\alpha=\rho_B$. By definition, the number of A groups incorporated must equal the number of B groups incorporated, so in an AB_f system, $\rho_B(f-1)=\rho_A$. Furthermore, $\alpha=\rho_A/(f-1)$ or $\alpha=\rho/(f-1)$. Thus, the probability that a functional group is incorporated into a branch unit will always be less than $\rho/(f-1)$ for AB_x polymers. This equates to the possibility of non-cross-linked polymers that can be made in a one-step polycondensation reaction. A multitude of such AB_x hyperbranched polymers were developed throughout the late 1980s and 1990s. These include, but are not limited to, polyamides, polyphenylenes and polyethers.

Scheme 6: Polycondensation to form polyether.[13]



However, the AB_n systems do not come without significant drawbacks: cyclization can occur and the monomers can be too reactive, expensive or not readily available.[3,14] In 1999, Jikei et al. reported the synthesis of a hyperbranched polyamide using an $A_2 + B_3$ system.[15] Emrick et al. followed with $A_2 + B_3$ polyethers that contained highly functional end groups.[16] The advantages of the $A_2 + B_3$ systems are that the monomers are readily available and soluble and three dimensional hyperbranched polymers may be attained as long as gelation is controlled.[15] Flory described $A_2 + B_3$ systems in the early 1940s when he discussed gelation and the degree of polymerization.[17] Flory theorized there was a critical condition in which a polymer would cross-link and presented calculations to predict the critical points. Stockmayer furthered Flory's work and compared gelation to the condensation of a saturated vapor.[18] Both Flory and Stockmayer stated that the critical point of gelation, ρ_c, is related to the number of functional groups on the monomer as given in Equation 1.

$$\rho_c = \frac{1}{(f-1)}$$

Equation 1

When two monomers are present, the critical point of gelation becomes inversely proportional to the functionality of both monomers as detailed in Equation 2. Where χ_a = molar functionality of the A monomer and χ_b = molar functionality of the B monomer.

$$\rho_c = \frac{1}{[(x_a - 1)(x_b - 1)]^{1/2}}$$

Equation 2

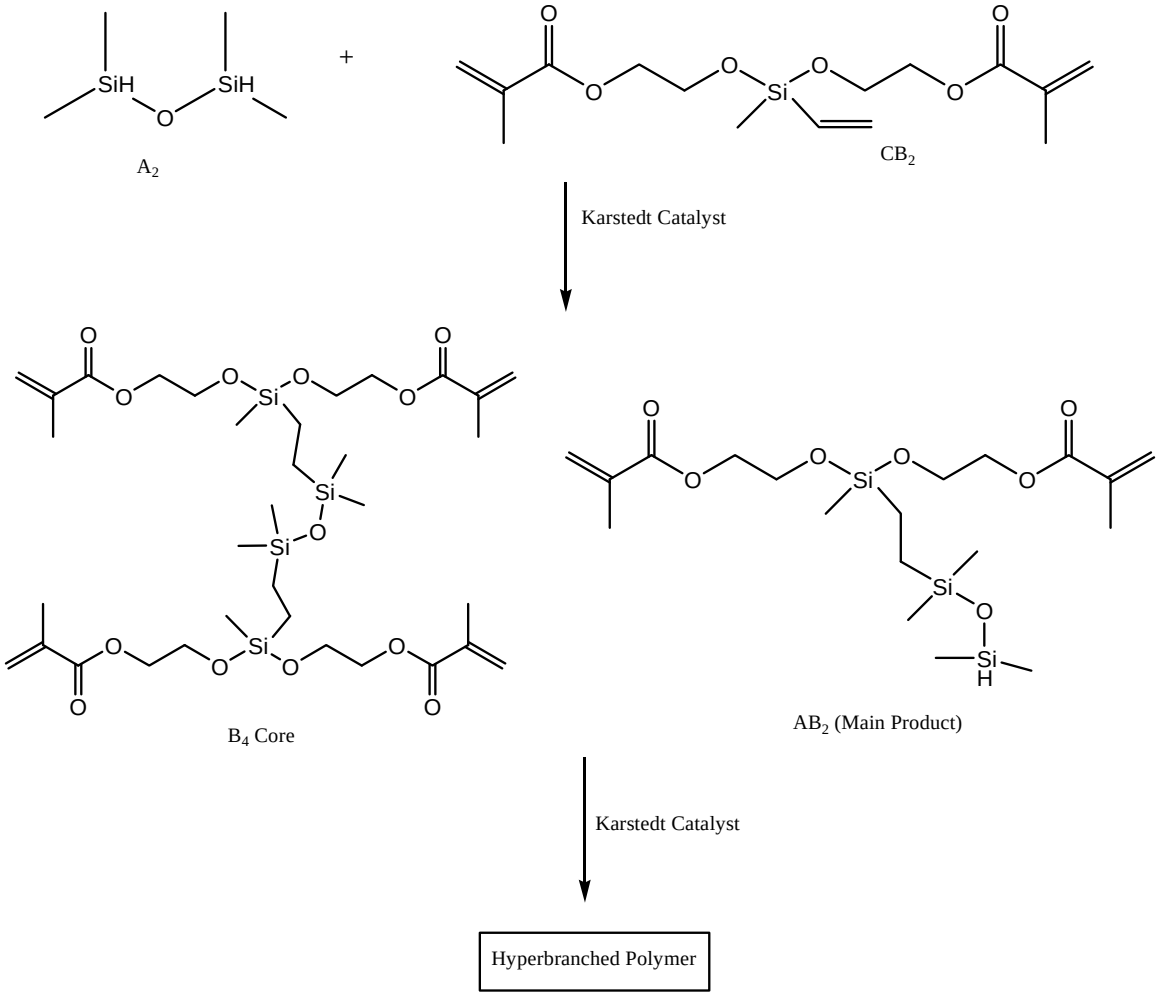
Therefore, for $A_2 + B_3$ polymerization with the monomers at a molar ratio of 1:1, $\rho_c = \frac{1}{[(1)(2)]^{1/2}} = 0.71$. When the molar ratio of A:B is 1:1.5, $\rho_c = 0.85$.

Obviously, gelation is a concern in the $A_2 + B_3$ system where it is not an issue at all in the AB_n reactions. Fortunately, the gelation problem can be dealt with by three major means: allow cyclization to occur in an opportunistic manner, stop the reaction before the reaction reaches the critical conversion point or allow the polymerization to reach a higher conversion rate by adding additional species such as excess A or B or another functional group such as C. Lin and Long overcame gelation when they prepared hyperbranched poly(aryl ester)s by making dilute solutions of each monomer and then slowly adding the A_2 monomer solution to the B_3 monomer solution.[19] Jikei et al. avoided gelation while forming aromatic polyamides by controlling the ratio of A to B functional groups.[15] Stumbé and Bruchmann avoided gelation by closely monitoring and controlling the rate of reaction in the synthesis of hyperbranched polyesters.[20] If gelation is restricted, $A_2 + B_3$ polymerization systems offer an easy and cost-effective means for preparing hyperbranched polymers.

Within the last couple of years, $A_2 + CB_2$ polymerization has gained some attention. In this system, the C functional group has a different reactivity than the B_2 functional groups. In 2009, Zhou et al. presented a model for $A_2 + CB_2$ systems in which C was significantly more reactive than B_2.[21] They proposed that during early stages of synthesis, the C would react rapidly with one of the A groups which would then leave the second A group to react with the two B groups. They also speculated that the AB_2

intermediate could react with the CB_2 monomer and result in A being attached to four B groups. This entity could serve as a "core" for polymerization which could potentially lead to a hyperbranched polymer with a very narrow molecular weight distribution. Wang et al. prepared hyperbranched polysiloxysilanes using A_2 + CB_2 systems.[22] They described the B_4 core and also varied monomer ratios to control physical properties (i.e. molecular weight, viscosity) of the polymer without gelation occurring.

Scheme 7: A_2 + CB_2 synthesis of polysiloxysilanes (adapted from Wang et al.).[22]



A_2

CB_2

B_4 Core

AB_2 (Main Product)

Another important aspect of hyperbranched polymers is the degree of branching (DB). DB corresponds closely with the physical properties of the polymer such as chain entanglement, glass-transition temperature, mechanical strength, etc. of the polymer.[2] While dendrimers are perfectly

branched (100%), hyperbranched polymers are not. In 1991, Hawker et al. defined the degree of branching for AB_2 systems as being equal to the sum of dendritic (D) and terminal (T) units divided by the total number of units (dendritic, terminal and linear (L)): DB = (D+T)/(D+T+L).[23] For AB_2 polymers with high molecular weights, the number of terminal units is practically equal to the number of dendritic units. Therefore, the maximum degree of branching is equal to 2D/(2D+L), which correlates to 50% branching for AB_2 systems. For $A_2 + B_3$ polymerization, the degree of branching becomes that as described in Equation 3.[24]

$$DB = \frac{2D}{2D + L} = \frac{2\,[b_3]}{2[b_3] + \,[Bb_2]}$$

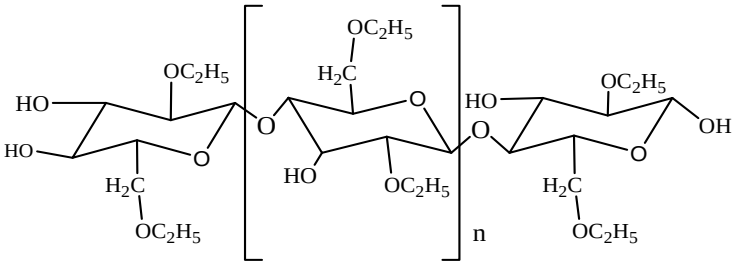
Equation 3

Here, $[b_3]$ is equal to the dendritic B groups and $[Bb_2]$ is equal to the linear B groups. DB can be controlled for $A_2 + B_3$ systems by modifying the feed ratio or by the order of addition of the monomers.[3] When the concentration of A_2 increases, the DB increases. This results in a highly branched polymer and a DB of 0.93 (i.e. 93% branching), can be attained.[24] A polymer with this high degree of branching will tend to have physical properties similar to a dendrimer but without the tedious synthesis steps.

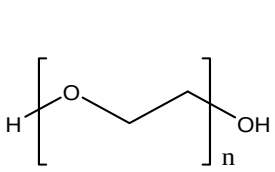
As previously mentioned, hyperbranched polymers have some good physical properties: solubility, viscosity and stability. The abundance of highly functionalized end groups also makes them good candidates for drug delivery. Polymers have been in pharmaceuticals for decades and there are numerous ones that have been deemed GRAS (Generally Recognized As Safe) by the Food & Drug Administration (FDA). GRAS ingredients do not require extensive toxicological evaluation so they are the ingredients of choice if given options. Polymethacrylates are GRAS and are used in enteric coatings of solid oral dose tablets to control release in the gastrointestinal tract.[1] Ethylcellulose (see Figure 4) has many uses in the pharmaceutical industry but is most commonly used for extended release of oral

drugs. Polyethylene glycol (PEG) is typically found as a suspending agent, solubility enhancer or film coating. Poloxamer is a GRAS triblock copolymer that is employed as a surfactant, emulsifier, solubilizer and stabilizer. These are just four examples of polymers used in pharmaceuticals. However, it should be noted that none of these examples include covalent or ionic bonding of the drug to the polymer to control drug delivery. The polymers merely enhance the performance of the formulations.

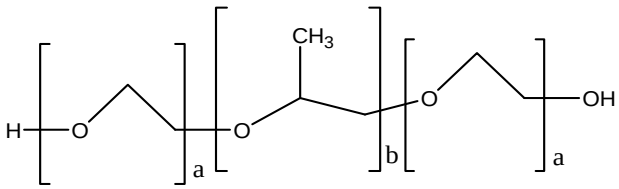
Figure 4: GRAS polymers.



Ethylcellulose



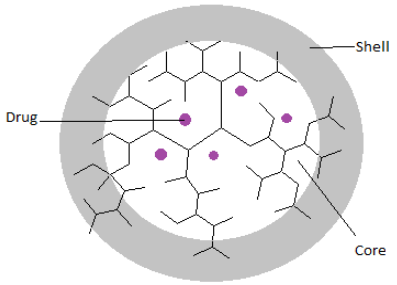
Polyethylene glycol



Poloxamer

Hyperbranched polymers, along with dendrimers, offer functional terminal end groups, an inner core and linear as well as branched repeat units connecting the core to the end groups. [25] This enables a drug to react with an end group, interact with the core such as in the case of a micelle or network with the linear repeat units (Figure 5). These characteristics are ideal for proteins, gene therapy drugs and anti-cancer drugs because the drug can be imbedded or attached in the polymer and then transported to the desired location in the body. This has become a widely studied area of polymer chemistry during the last decade.

Figure 5: Micelle-like polymer (adapted from Gao et al.).[2]



In 2005, Dailey et al. presented applications of biodegradable poly (vinyl alcohol) and poly (lactic-*co*-glycolic acid) branched polyesters in drug delivery.[26] They prepared neutral, negatively charged and positively charged polymers and then evaluated them for delivery of different drugs. The neutrally charged species (Figure 6) appeared to be promising for drug delivery of three proteins. The negatively charged polymers (Figure 7) seemed to be suitable for delivery of tetanus toxoid vaccines. The positively charged macromolecules (Figure 8) were good candidates for DNA vaccines and peptides and proteins. The positively charged species also seemed good candidates for use in nebulized suspensions to be used for pulmonary drug delivery.

Figure 6: Neutral polymer.

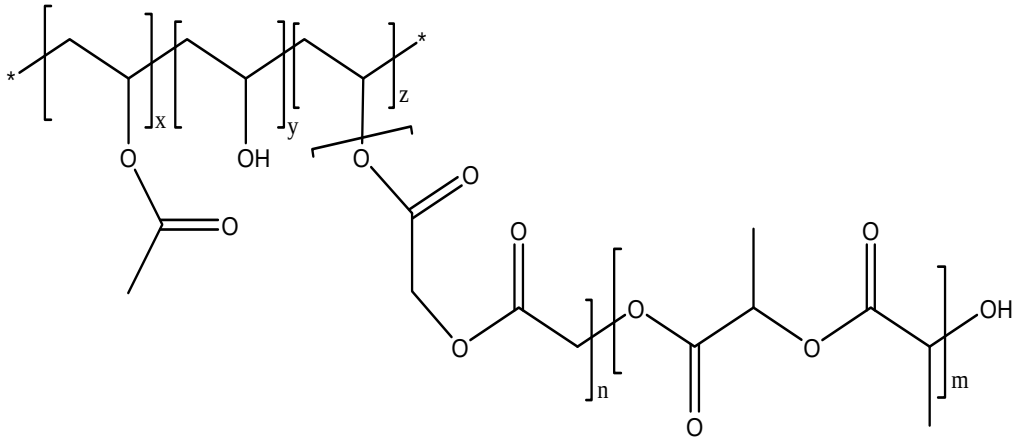


Figure 7: Negatively charged polymer.

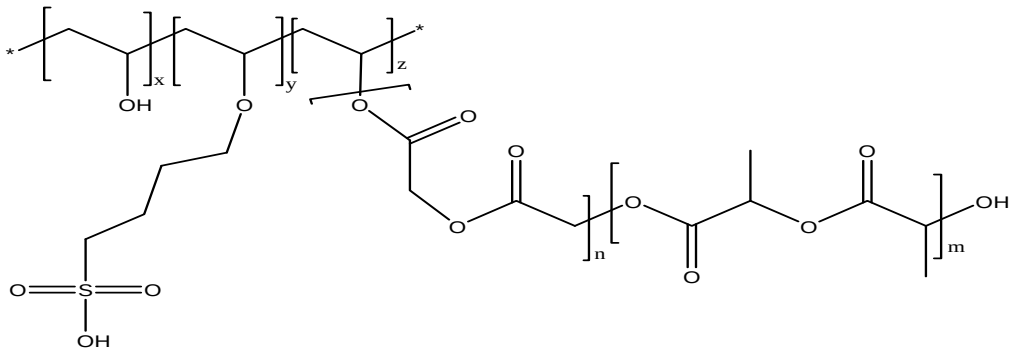
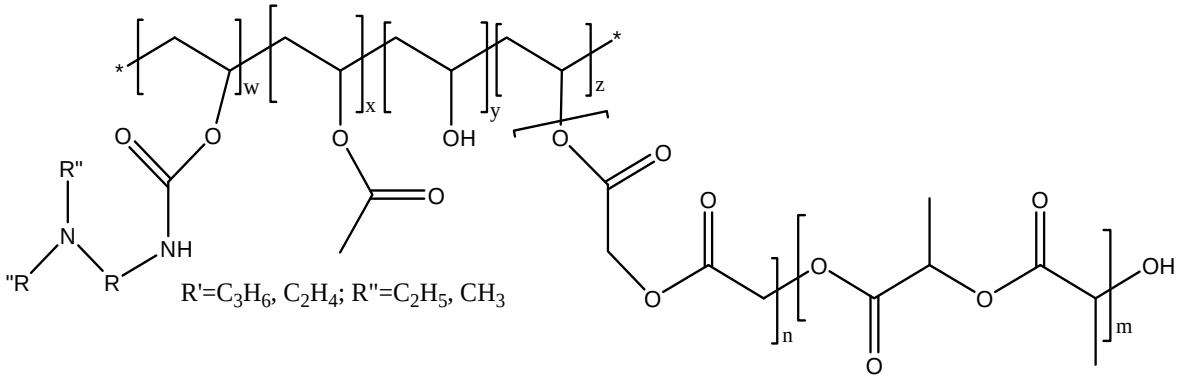


Figure 8: Positively charged polymer.



Pang et al. examined hyperbranched polymers containing polyethylene glycol and glycidyl methacrylate.[27] They coupled the polymer to methotrexate (Figure 9) and showed *in vitro* that the drug delivery system was pharmacologically active. Ye et al. developed hyperbranched polyglycerols for cisplatin drug delivery.[28] They modified commercially available polyglycerols to change the carboxylic acid density of the functional groups. The modified polymers were bound to cisplatin (Figure 10) and demonstrated controlled release and *in vitro* activity.

Figure 9: Methotrexate.

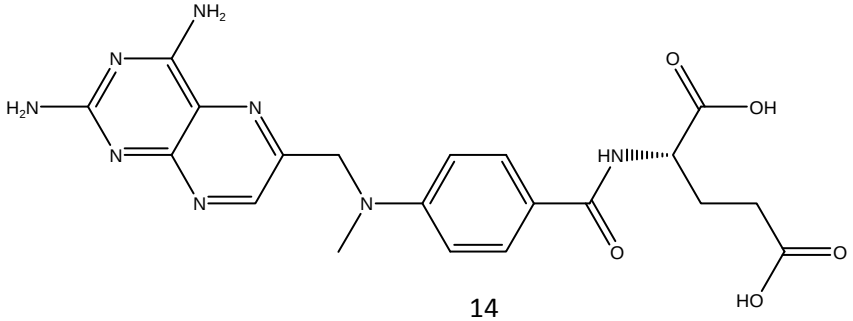
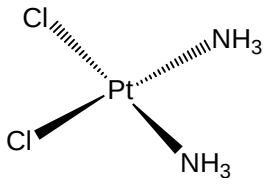
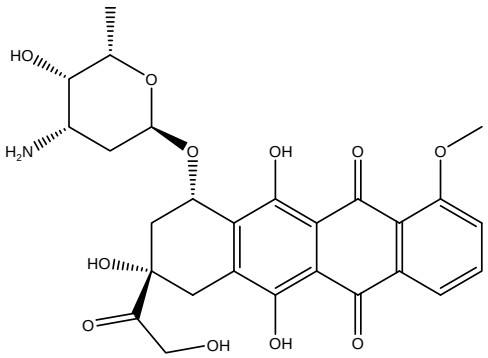


Figure 10: Cisplatin.



One additional example of hyperbranched polymers in drug delivery is that recently published by Chen et al. in which they used a negatively charged polysulfonamine.[29] The polysulfonamine was used to deliver doxorubicin (Figure 11) to human epidermoid tumor cells. Release of the drug was controlled by pH and had a low cytotoxicity in normal cells.

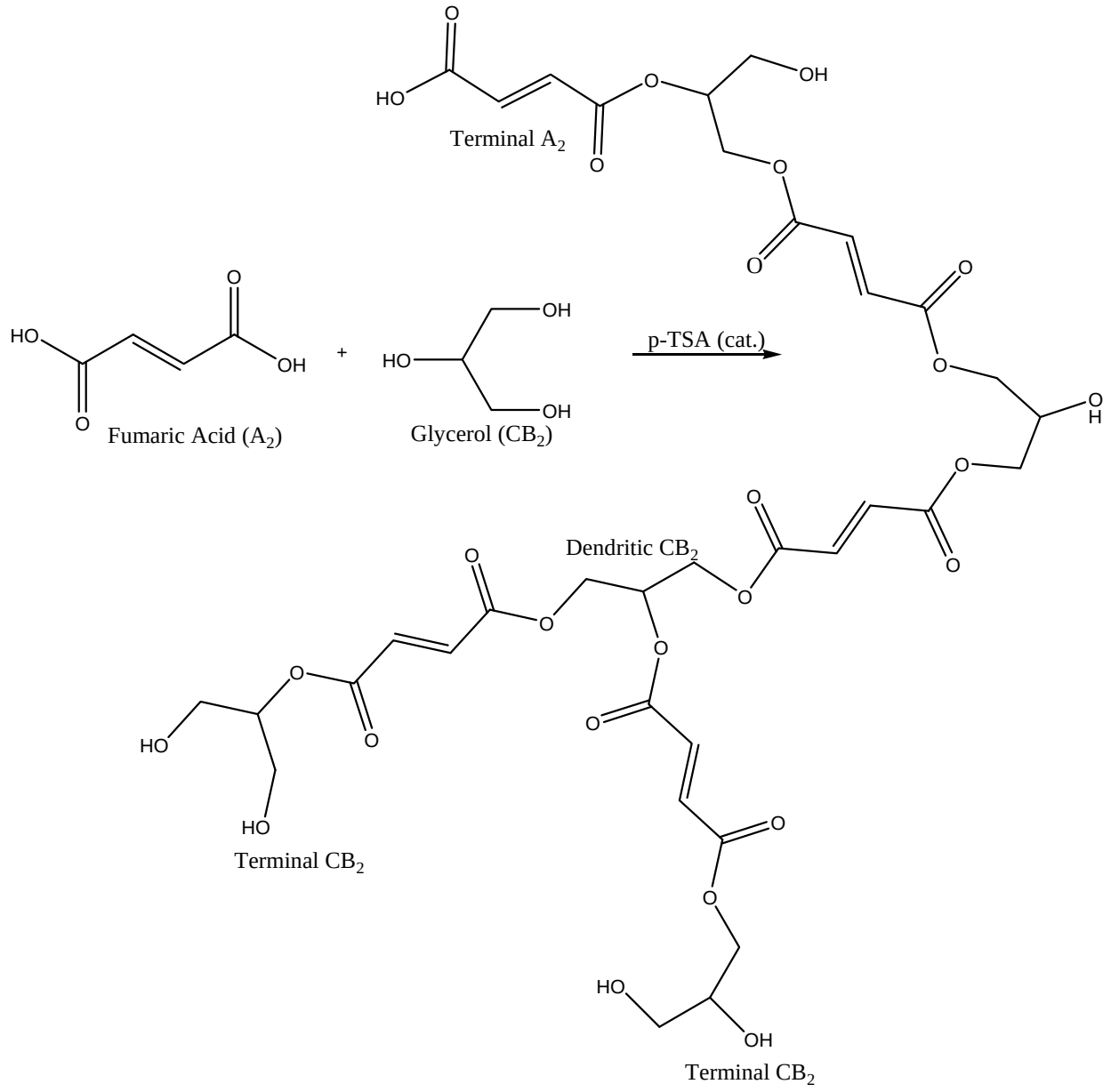
Figure 11: Doxorubicin.



The purpose of this work is to further the research of biocompatible hyperbranched polyesters prepared by Werry in 2007.[30] Werry synthesized hyperbranched polymers via the $A_2 + B_3$ polycondensation of fumaric acid (A_2) and glycerol (B_3). Werry experienced gelation issues during his research and examined the effect that temperature and the molar ratio of A_2:B_3 had on cross-linking. He found that a lower temperature caused the reaction to proceed at a slower rate, which enabled the reaction to be terminated before cross-linking occurred. Werry observed that gelation was delayed as the molar ratio of A_2:B_3 was decreased (i.e. when the glycerol concentration was increased while maintaining the fumaric acid concentration). Werry also investigated valeric acid as an end-capping agent and claimed the valeric acid delayed gelation even though it was not soluble in the

glycerol/fumaric acid solution. It should be noted that glycerol in Werry's system can be considered a CB_2 monomer since the secondary alcohol is more sterically hindered than the primary alcohols. This results in different reactivities. Therefore, the monomer is composed of two equivalent B functional groups and one C functional group. The research herein involves evaluation of varying the A_2:CB_2 monomer ratio and adding a third monomer (polyethylene glycol monomethyl ether or acid terminated polyethylene glycol) as a means to control gelation (see Scheme 8 and Scheme 9). The polyethylene glycol methyl ether (PEG) molecular weight was also varied to examine the effect of size on end-capping effectiveness. The PEG and acid terminated polyethylene glycol serve as end-capping agents which will prohibit intramolecular covalent bonding of the terminal monomer. These agents were chosen because they are considered GRAS and are frequently used in the pharmaceutical industry. Additionally, they are water soluble which can be advantageous in biological systems.

Scheme 8: A_2 + CB_2 polymerization.



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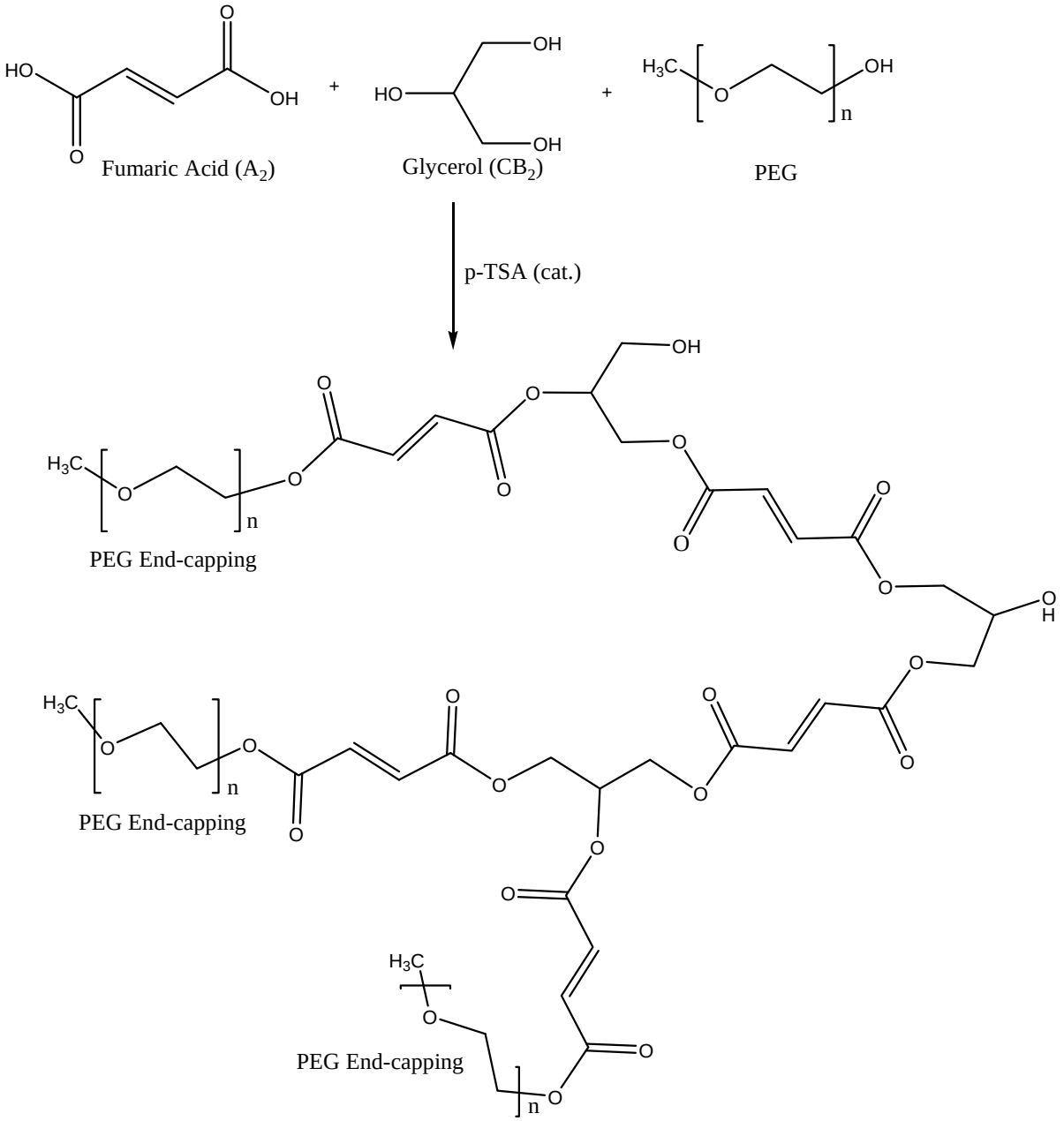
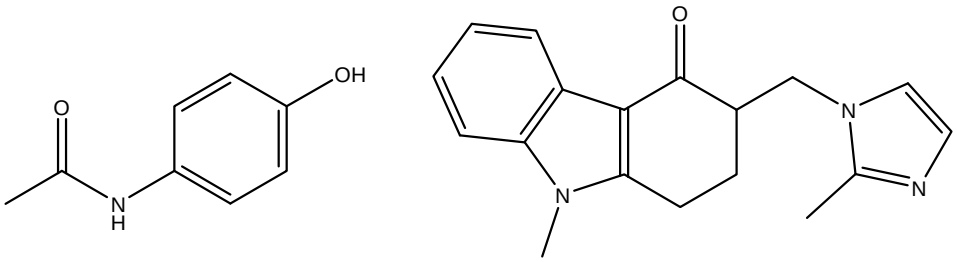
Scheme 9: PEG end-capping.



According to Werry, the fumaric acid entity in the hyperbranched polymer contains an alkene which provides a nucleophilic site.[30] However, it should be noted that the alkene is in conjugation and is therefore only a weak nucleophile at best. In this project, two active pharmaceutical ingredients (APIs), Acetaminophen and Ondansetron, were added to the hyperbranched polymer to evaluate drug delivery possibilities.

Figure 12: Acetaminophen and Ondansetron.



Acetaminophen Ondansetron

II. EXPERIMENTAL

All ^{1}H and ^{13}C NMR spectra were generated using a Bruker AVANCE 300 MHz NMR operating at 300 and 75.5 MHz, respectively. Samples were dissolved in deuterated dimethyl sulfoxide (DMSO-d_6) obtained from Sigma-Aldrich. Gel Permeation Chromatography (GPC) data were obtained using a Viscotek Model 300 TDA GPC with refractive index, viscosity and light scattering detectors and two Polymer Laboratories 5 µm PLGel Mixed C columns. The columns were maintained at 40°C and mobile phase containing N-methylpyrrolidone (0.5% LiBr) was pumped at 0.80 mL/min using a Thermoseparation Model P1000 HPLC pump. GPC analyses were also performed using a Viscotek GPC with a 270 Dual (viscosity and light scattering) Detector, a VE3580 RI detector and two Agilent PLGel HPLC columns. The columns were maintained at 40°C and mobile phase containing dimethylformamide (0.5% LiBr) was pumped at 0.80 mL/min using a PerkinElmer 200 HPLC pump. A VanKel VK7000 dissolution apparatus with a VK8000 autosampler was used for dissolution studies. The dissolutions were conducted using USP apparatus 2 (paddle) at 50 rpm. A Hitachi HPLC 7000 High Performance Liquid Chromatograph (HPLC) with UV/Vis detection (216 nm) was employed for assay and impurity analyses. The separation was performed using a Zorbax SB-CN column (250 x 4.6 mm, 5 µm particle size) from Agilent with a mobile phase (0.02M Phosphate buffer (pH 2.0):CH_3CN, 80:20, v:v) flow rate of

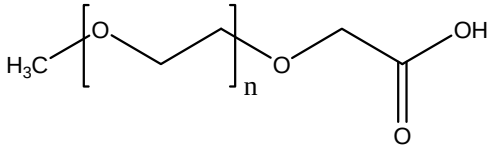
1.5 mL/min. Differential Scanning Calorimetry (DSC) data were obtained on TA Instruments DSC Q200 from -60°C to 200°C at 10°C/min.

All reagents were used as received. Fumaric acid, glycerol, *p*-toluenesulfonic acid (*p*-TSA) and *t*-butyl chloroacetate were procured from Sigma-Aldrich. Poly (ethylene glycol) monomethyl ether (PEG) M_n750 and M_n2000 were also received from Sigma-Aldrich. PEG M_n 350 was received from Sigma. Potassium *t*-butoxide was obtained from Fluka and *t*-butyl chloroacetate (*t*-BCA) was purchased from Sigma-Aldrich. Chloroform, isopropyl alcohol (IPA) and ethyl ether were received from BDH, EMD and Fisher, respectively. Methanol and Karl Fischer Reagent were received from EMD.

A. Synthesis of Acid-Terminated PEG

Following a literature procedure,[31] PEG (M_n 2000) was modified to contain a terminal acid group. Approximately 5 g PEG M_n2000 (2.2 mM) was added to a 250-mL round bottom flask. Toluene (~ 100 mL) was added and the vessel was fitted with a Dean-Stark trap and a condenser with N_2 flow. The flask was heated at 150°C for 1 hour and then cooled to room temperature. Potassium *t*-butoxide (0.6 g) was added and the mixture was stirred for 1.5 hours at room temperature. An aliquot (2.2 g) *t*-butyl chloroacetate (end-capping agent) was added and the reaction was stirred for an additional hour at room temperature. The solvent was removed under vacuum at 100°C. The precipitate was re-precipitated using chloroform, IPA and ether to obtain an acid-terminated PEG (see Figure 13).

Figure 13: Acid-terminated PEG.



B. A_2 + CB_2 Polymerization (1:1 Ratio)

The A_2 + CB_2 polymerizations with A_2:CB_2 at a 1:1 molar ratio were typically performed by adding fumaric acid (5 g) and glycerol (4 g) to a 100-mL three neck round bottom flask equipped with a gas inlet and outlet. The mixture was heated (either 140°C or 150°) while stirring under N_2 until the fumaric acid dissolved. An aliquot of *p*-TSA (~20-25 mg) was then added. The reaction was allowed to proceed until the gelation point was almost reached (i.e. the stir bar stopped stirring). The resulting polymer was a clear, viscous gel-like material. Since the polymer was prepared in the melt in a single vessel, the reaction yield was not determined and was assumed 100%.

C. A_2 + CB_2 Polymerization (1:1 Ratio) with Acid-Terminated PEG

Fumaric acid (5 g), glycerol (4 g) and Acid-Terminated PEG (1 g) were added to a 100-mL three neck round bottom flask and heated to 145°C while stirring under N_2. After the fumaric acid dissolved, *p*-TSA (~27 mg) was added and the reaction was allowed to proceed for 2.5 hours until near the gelation point. The polymer was clear and highly viscous. Once again, overall yield was not determined.

D. A_2 + CB_2 Polymerization with PEG End-Capping (1:1:0.1 Ratio)

In general, the polymerizations with PEG end-capping at a A_2:CB_2:PEG molar ratio of 1:1:0.1 were performed by combining fumaric acid (5 g), glycerol (4 g) and PEG M_n350 (3 g) in a 100-mL three neck round bottom flask. The mixture was heated at 150°C under N_2 while stirring until the fumaric acid dissolved. The *p*-TSA catalyst (~20-25 mg) was added and the reaction was allowed to continue until near gelation. The final product was a clear, viscous gel.

E. A_2 + CB_2 Polymerization with PEG End-Capping (1:1.3:0.2Ratio)

Typically, the reactions with A_2:CB_2:PEG at 1:1.3:0.2 molar ratio were performed by adding fumaric acid (4 g), glycerol (4 g) and PEG M_n350 (3 g) to a 100-mL three neck round bottom flask. The combination was stirred under N_2 at 150°C until the fumaric acid dissolved. An aliquot (~20-25 mg) *p*-

TSA was added. The reaction was allowed to continue until the gelation point was almost reached. The resulting polymer was clear and viscous.

F. A_2 + CB_2 Polymerization with PEG End-Capping (1:0.6:0.1 Ratio)

The basic procedure for preparing polymerization with the A_2:CB_2:PEG at a molar ratio of 1:0.6:0.1 was to combine fumaric acid (5 g), glycerol (3 g) and PEG M_n350 (3 g) in a 100-mL three neck round bottom flask. The mixture was stirred under N_2 at 150°C. Once the fumaric acid dissolved, *p*-TSA (~20-25 mg) was added to the vessel. Polymerization was allowed to occur until the reaction was near gelation and a clear, viscous gel-like liquid was obtained. ^{1}H NMR (DMSO, δ): 2.50, 3.24, 3.31, 3.51, 3.67, 4.06, 4.19, 4.29, 4.98, 6.63, 6.71, 6.82. ^{13}C NMR (DMSO, δ): 57.96, 62.37, 63.03, 69.04, 69.50, 69.71, 71.20, 72.41.

G. A_2 + CB_2 Polymerization with Varied Molecular Weight PEG

Polymers were prepared at an A_2:CB_2:PEG molar ratio of 1:1:0.2. This was done by adding fumaric acid (5 g), glycerol (4 g) and PEG (~0.2 – 0.25 moles) of M_n 350, 750 or 2000 to a 100-ml three neck round bottom flask. The contents were heated at 150°C while stirring under N_2 or argon until the fumaric acid dissolved. The *p*-TSA catalyst (~20-25 mg) was added and the reaction was allowed to proceed until near the gelation point. The final products were gel-like and were clear, opaque and off-white to yellow for the polymers prepared with PEG M_n 350, 750 and 2000, respectively. ^{1}H NMR (DMSO, δ): 2.51, 2.55, 2.73, 2.89, 3.22, 3.49, 3.66, 4.18, 6.70, 6.81, 7.93. ^{13}C NMR (DMSO, δ): 57.98, 59.30, 59.63, 60.16, 62.31, 62.96, 64.32, 65.77, 65.89, 66.67, 67.96, 69.02, 69.49, 69.70, 71.19, 72.17.

H. A_2 + CB_2 Polymerization with CB_2 Added in Portions

The A_2 + CB_2 syntheses containing the various molecular weights of PEG end-capping agent were repeated where only approximately half of the CB_2 monomer was added initially. After approximately two hours the remaining glycerol was added. The polymerization was allowed to continue until the

polymer approached gelation. The polymers resembled those obtained with all the CB_2 monomer added initially. ^{1}H NMR (DMSO, δ): 2.55, 2.73, 2.88, 2.98, 3.22, 3.49, 3.74, 4.03, 4.18, 4.26, 6.63, 6.70, 6.81. ^{13}C NMR (DMSO, δ): 57.96, 59.28, 59.62, 60.16, 62.29, 62.94, 64.30, 65.76, 65.89, 66.65, 67.96, 69.01, 69.48, 69.69, 71.18, 72.14, 72.32.

III. RESULTS AND DISCUSSIONS

A. Glycerol Water Content

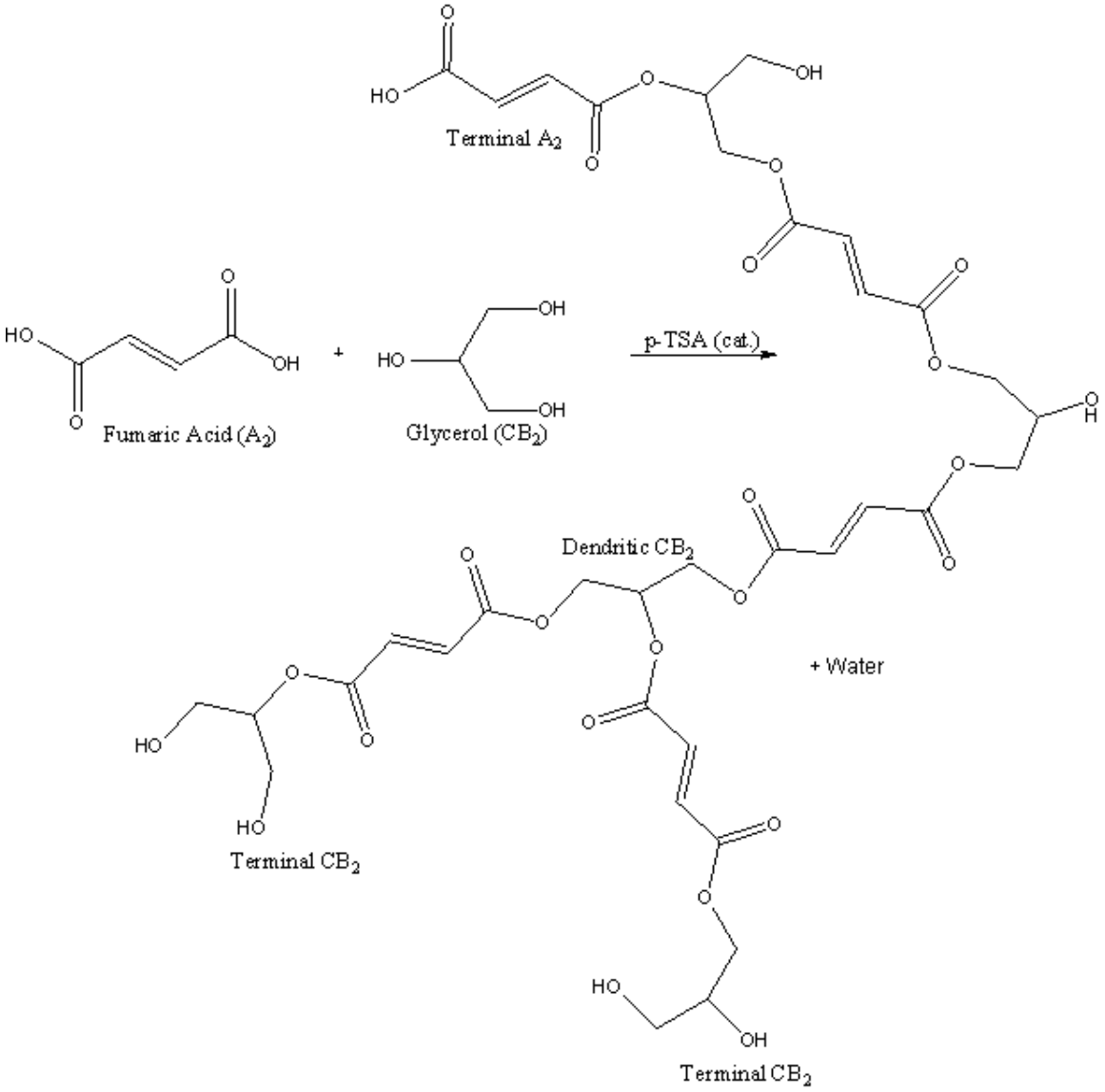
Since glycerol is a liquid at room temperature and the material used in this research was stored in a plastic bottle with a rubber stopper, water uptake was a possibility. A significant amount of water could lead to stoichiometric imbalance and affect the degree of polymerization. The water content of the CB_2 monomer was determined in duplicate by Karl Fischer (Mettler DL35) titration. Approximately 0.5 mL glycerol was added to a vessel containing previously rendered anhydrous methanol. The vessel was titrated with Karl Fischer Reagent after a two-minute stir time. The average water content of the glycerol used in these studies was determined to be 0.5% w/w. Since the water content was less than 1% w/w, no correction factor was applied to the glycerol molecular weight before use.

B. A_2 + CB_2 Polymerization at a 1:1 Molar Ratio

Two syntheses with fumaric acid and glycerol at approximately a 1:1 molar ratio were performed at 150°C under N_2 on different days. One reaction did not crosslink, or gel, until after about 5 hours while the other reaction gelled after just 2.5 hours. These observations demonstrated that there is great difficulty in controlling the onset of gelation in A_2 + CB_2 reactions in the melt phase. Additionally, the reaction rate did not appear to be reproducible on a day to day basis. This apparent lack of control is most likely attributed to variability in the N_2 flow rate, the temperature of the reaction vessel and slight differences in the molar ratios. The effect of changes in molar ratio has been previously discussed and the potential effect from changes in the temperature of the reaction vessel is obvious: if the

temperature is erroneously high, the reaction should proceed faster, if it is erroneously low, the reaction should proceed slower. However, the effect of variability in the nitrogen flow rate may not be as apparent. One can surmise though that at higher N_2 rates, the water from the reaction vessel should be removed faster. This would push the equilibrium towards the products and therefore increase the polymerization reaction rate (See Scheme 10).

Scheme 10: Fumaric acid + glycerol polymerization.



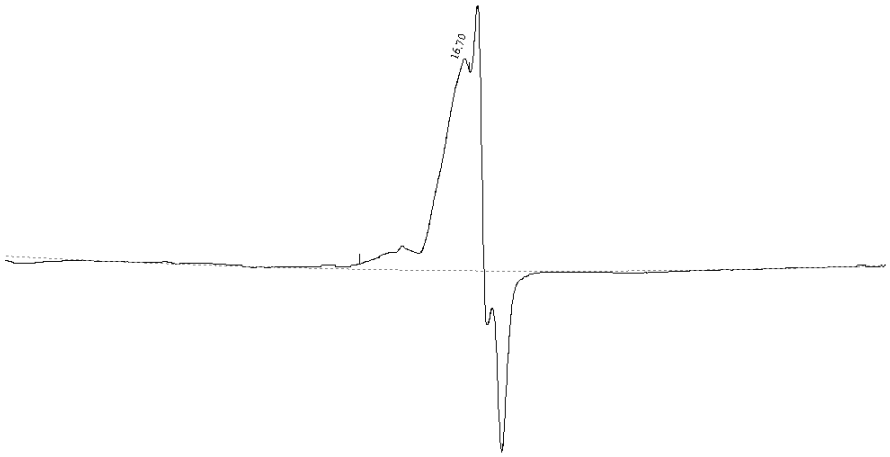
The 1:1 molar ratio polymerization was repeated two more times, but with the temperature reduced to 145°C. One reaction cross-linked within an hour while the other reached the gelation point around an hour and a half.

The polymerization was repeated again, but the temperature was reduced to 140°C and 143°C (fumaric acid did not fully dissolve at 140°C so the temperature was increased). This time the polymers gelled around 3.5 and 1.5 hours, respectively. The need for better control of gelation was obvious.

C. $A_2 + CB_2$ with Acid-Terminated PEG

The acid-terminated PEG represented an $A_2 + CB_2$ polymerization with excess A functionality. Although the acid-terminated PEG was suspected to have a different reactivity than that of fumaric acid, it was expected that the acid group on the PEG would react with the CB_2 monomer to reduce cross-linking. The synthesis using this design employed approximately a 0.02 molar equivalent of the acid-terminated PEG and was performed at 145°C. The critical point of gelation was reached after approximately 2.5 hours. It is suspected that not enough PEG was present to prevent cross-linking. An aliquot of the sample was dissolved in NMP and analyzed by GPC. A chromatogram is depicted in Figure 14. The weight average molecular weight (M_w) was approximately 7800 Daltons (Da) while the number average molecular weight (M_n) was about 2700 Da which corresponded to a polydispersity index (PDI) of 2.8. This strategy was aborted at this point because PEG with excess B functionality was readily available and more cost effective.

Figure 14: Polymer with acid-terminated PEG.



D. A_2 + CB_2 with PEG

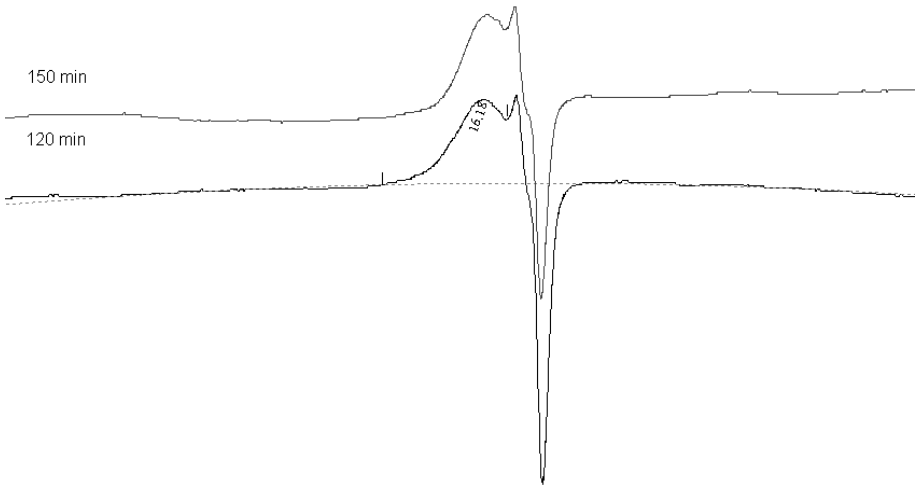
Initial end-capping studies with polyethylene glycol methyl ether (PEG) involved maintaining a 1:1 ratio of A_2 and CB_2 monomers in the presence of three different molecular weight PEGs (M_n = 350, 750 and 2000 Da). The amount of PEG added ranged from 0.01 to 0.09 molar ratios in comparison to the monomers. The syntheses were allowed to proceed until the polymers approached the gelation point (i.e. when the stir bar could no longer move). The reaction time ranged from 75 minutes to 4.5 hours and there was no apparent correlation between the PEG amount present and the time to reach gelation. Nor was there a direct relationship between the size of PEG used and the gelation point. A summary of the data may be found in Table 1.

Table 1: Gelation summary.

PEG M_n (Da)	Molar Ratio (A_2:CB_2:PEG)	Gelation Time (hours)
350	1:1:0.07	2.0
750	1:1:0.03	3.0
750	1:1:0.09	2.5
2000	1:1:0.01	1.3
2000	1:1:0.03	4.5

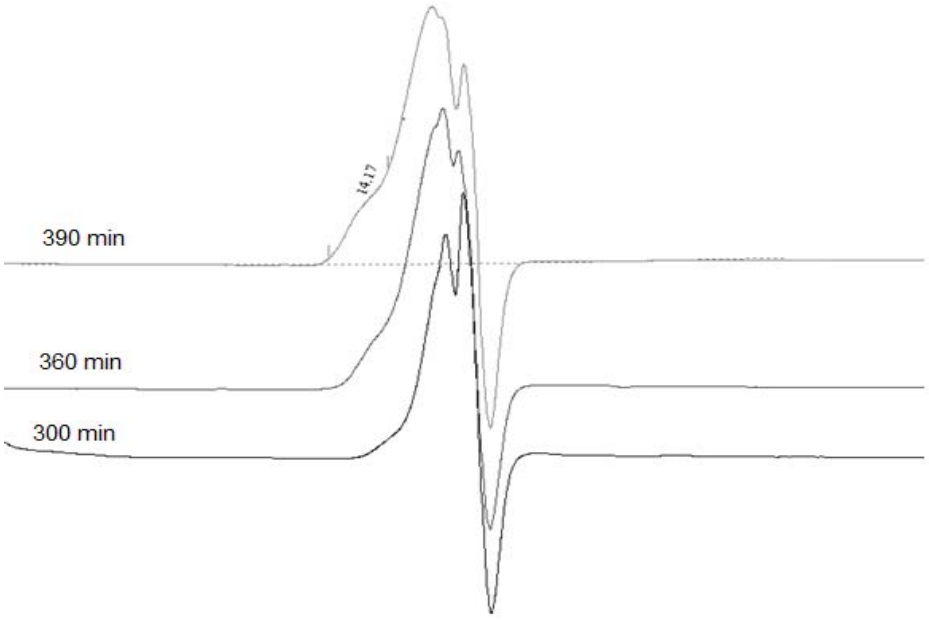
The molecular weights of the polymers were determined by removing aliquots during the reaction and analyzing by GPC. The M_w ranged from approximately 5000 to 7700 Da. Representative chromatograms for PEG M_n 750 at a molar ratio of 0.03 in relation to the monomers are presented in Figure 15.

Figure 15: GPC overlay (1:1:0.03 A_2:CB_2:PEG 750).



The ultimate goal of these end-capping studies was to reproducibly obtain the highest molecular weight polymers possible while controlling gelation. In addition, the end-capped polymers should be economic to prepare and be suitable for formulating finished drug products. Since cross-linking was not controlled, further syntheses were conducted using PEG M_n 350 at a molar ratio of 0.2 with respect to the A_2 and CB_2 monomers. Synthesis was conducted under the same conditions as used for previous studies and gelation was delayed until approximately 5 to 8 hours into the reaction. Aliquots were removed during the reaction and analyzed by GPC for molecular weight determination. The typical M_w was around 4400 Da while the M_n was approximately 2700 Da which corresponded to a PDI of 1.6. An overlay of representative GPC chromatograms is depicted in Figure 16.

Figure 16: GPC overlay for polymer with PEG M_n 350 at a 0.2 molar ratio.



Since the gelation point was extended by increasing the molar ratio of PEG to 0.2, the next goal of this project was to attempt to improve the granularity of the polymers. This was desirable so the polymers could be better processed with APIs. Initially PEG M_n 350 was added to the reaction vessel at a molar ratio of 1:1:0.2 (A_2:CB_2:PEG). After five hours the polymer was transferred to a polytetrafluoroethylene (PTFE) sheet and placed into a vacuum oven at approximately 28 inches Hg and 110°C for about 15 hours. The polymer was removed from the PTFE sheet and broken into pieces. At this point, the polymer was still pliable. The above experiment was repeated at a 1:1.3:0.2 (A_2:CB_2:PEG) molar ratio. After five hours the polymer was dried under vacuum at 12 inches Hg and 60°C for one hour. After one hour the oven was increased to 27 inches Hg and 100°C and the polymer was heated for another 30 minutes. This second polymer was also somewhat pliable when removed from the PTFE sheet. However, both of these macromolecules were insoluble in numerous solvents: isopropanol, acetone, methanol, acetonitrile, diethyl ether, water, NMP and DMF. The first polymer was slightly soluble in 1,4-dioxane. It is suspected that additional polymerization occurred in the vacuum oven and

the polymers became infinitely large. While this physical property may be desirable for some applications, it is not advantageous for pharmaceuticals.

The next set of syntheses involved adding only half of the CB_2 monomer at the beginning of the synthesis. This was done in an attempt to allow the PEG to react with the A_2 monomer to optimize the end-capping. In the first reaction, fumaric acid and glycerol were combined with PEG M_n 350 at 1:0.6:0.2 molar ratios and heated at 150°C under nitrogen for two hours. An aliquot was removed and titrated with 0.01N NaOH to determine how much unreacted A_2 monomer was present. It was determined that approximately 21 meq free acid groups remained around 2 hours into the reaction which corresponds to approximately 49% of the initial acid groups. An additional 0.5 molar equivalent of glycerol was added to the reaction vessel and polymerization was allowed to continue for another 2.5 hours. Aliquots were removed and placed in DMF and DMSO-d_6 for GPC and NMR analyses, respectively. The polymer was readily soluble in DMSO-d_6 but only partially soluble in DMF. The remaining polymer was transferred to a PTFE sheet and placed at room temperature overnight. The polymer was then dried in a vacuum at 60°C for four days. The PTFE sheet was removed from the oven and the polymer film was lifted from the sheet, turned over and returned to the vacuum oven for another three days. This process produced a flexible non-tacky polymer but the final product was not soluble in DMF or DMSO-d_6. It was suspected that cross-linking occurred during the drying step so the reaction was repeated and the resulting polymer was dried for only two hours under vacuum at room temperature. The dried polymer was not soluble in DMF or DMSO-d_6 but it was suspected this was due to nitrogen and argon issues that were encountered during synthesis (the gas cylinders were turned off during the reaction) rather than from over drying the polymer.

The approach above was also performed using PEG M_n 750 at a 1:0.6:0.04 A_2:CB_2:PEG molar ratio. An additional 0.4 molar equivalents of glycerol was added after one hour. The polymer

approached the gelation point after another 2 hours so the reaction was stopped. The polymer was transferred to a PTFE sheet and placed in the vacuum oven at room temperature for 2.5 hours. The polymer was only marginally soluble in DMF and DMSO-d_6. In order to further investigate the solubility issues encountered with this polymerization system, two side by side syntheses were performed. One reaction contained a molar ratio of A_2:CB_2:PEG M_n 350 at 1:0.6:0.1 while the other was at 1:1:0.1. Both were heated at 150°C under nitrogen. After one hour, an additional 0.5 molar equivalent CB_2 was added to the vessel containing only 0.6 molar equivalents of glycerol to start. The polymer gelled within 10 minutes and was not usable for further analyses. The polymer at the1:1:0.1 molar ratios was transferred to a petri dish and dried under vacuum at room temperature for 2 hours. Aliquots of this polymer were placed in various solvents to evaluate solubility. While the polymer was slightly soluble in toluene, it was insoluble in DMF, isopropanol, ethyl acetate, acetone, methanol and chloroform.

Gelation was still an issue so the PEG molar equivalent ratio was increased to about 0.3 with respect to the A_2 and CB_2 monomers. Six additional reactions were performed using fumaric acid, glycerol and either PEG M_n 350, PEG M_n 750 or PEG M_n 2000. Half of the syntheses were conducted with all of the CB_2 monomer added at the beginning of the reaction while the other half were performed with only half the CB_2 monomer added initially and the remaining monomer added after 90 to 130 minutes. The reactions were conducted at 150°C under either nitrogen or argon. The final composition of each system was at a 1:1:0.3 A_2:CB_2:PEG molar ratio. Polymerization was allowed to proceed for anywhere between 6.5 to 10.5 hours. The increase in PEG concentration was expected to prevent cross-linking by end-capping even more of the A_2 monomers versus reactions that were conducted using only ≤0.2 molar equivalents of PEG.

There was no visible difference between the two polymers that were made with the same molecular weight PEG. However, as expected, there was significant difference in the appearance

between the polymers prepared with different molecular weight PEG: the polymers containing PEG M_n 2000 resembled lip balm while the polymers with M_n 350 were a viscous liquid. The polymers with PEG M_n 750 were somewhere in between. Aliquots of each polymer were dissolved in DMF and DMSO-d_6 for GPC and NMR analyses, respectively.

No significant difference was observed in the GPC data between the two polymers prepared with PEG M_n 350. The M_w and M_n were approximately 5100 and 2900 Da, respectively, with a PDI of 1.7. Refer to Figure 17 for an overlay of the chromatograms. A slight difference was observed in the proton NMR spectra in that the peak at 3.6 ppm in the polymer where all of the CB_2 was added at the beginning of the reaction shifted downfield to about 3.8 ppm in the polymer where only half of the CB_2 was added initially. This is most likely attributed to either residual acetone from cleaning the NMR tube or residual water in the polymer. The spectra are presented in Figure 18. The ^{13}C DEPT spectra of the two polymers containing PEG M_n 350 were nearly identical as shown in Figure 19. It should be noted that the ^{13}C DEPT spectra were similar to those reported by Werry indicating that both linear and dendritic units are present.[30] The dendritic units are formed when each of the three functional groups on the glycerol undergo condensation with the fumaric acid to form ethers. The linear units are formed when only two of the functional groups undergo condensation. The degree of branching was estimated from the intensities of the predicted linear, terminal and dendritic glycerol units in the ^{13}C DEPT spectra. The estimated DBs obtained were 0.66 and 0.69 for the polymers with ½ the CB_2 and all the CB_2 added initially, respectively.

Figure 17: GPC overlay of polymers with PEG M_n 350.

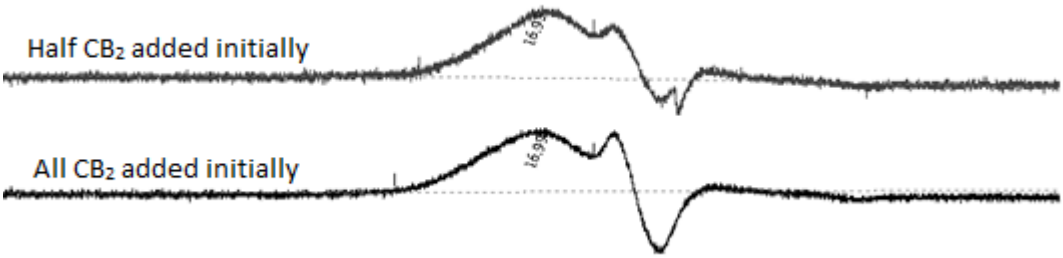


Figure 18: Proton spectra of polymers with PEG M_n 350.

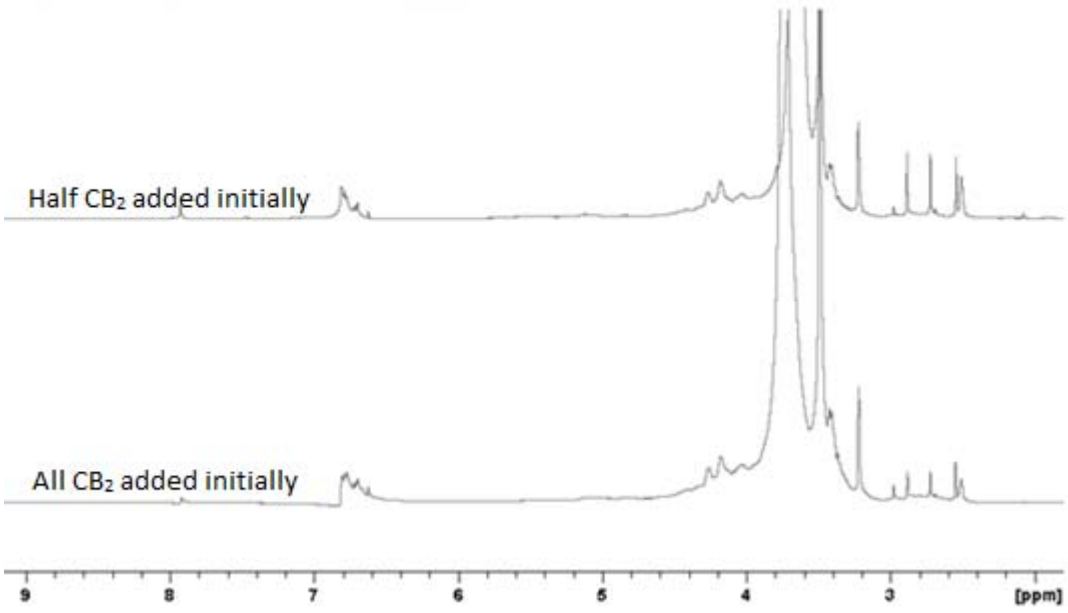
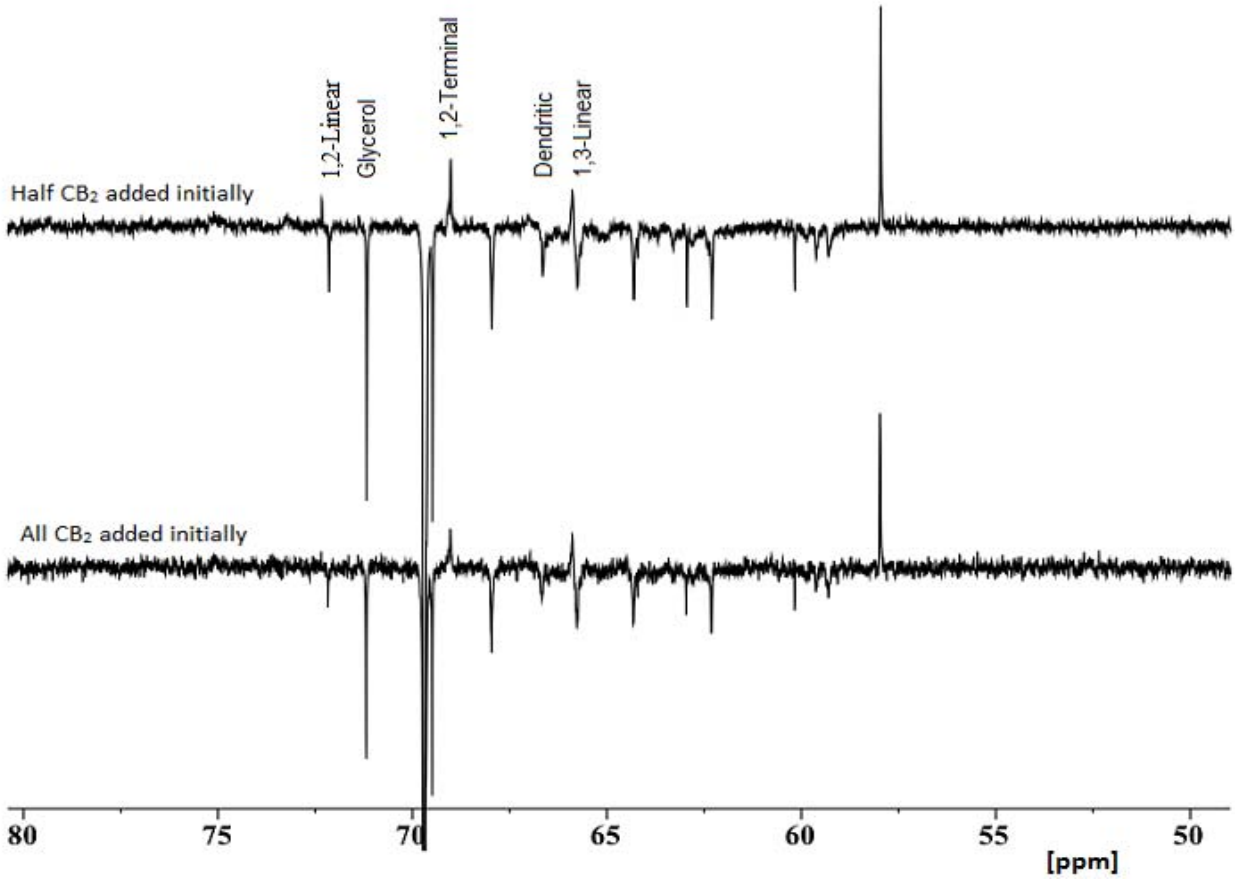


Figure 19: ^{13}C DEPT spectra of polymers with PEG M_n 350.



For the two polymers prepared with PEG Mn 750, there was little difference in the GPC data (Figure 20): M_w and M_n were approximately 5200 and 3200 Da which corresponds to a 1.6 PDI. The proton and ^{13}C spectra were nearly superimposable (Figure 21 and Figure 22). It should be noted that the M_w of these polymers is only approximately 2% more than those prepared with M_n 350 while the M_n is about 10% higher. The estimated DBs were 0.69 and 0.65 for the polymers with ½ the CB_2 and all the CB_2 added initially, respectively.

Figure 20: GPC overlay of polymers with PEG M_n 750.

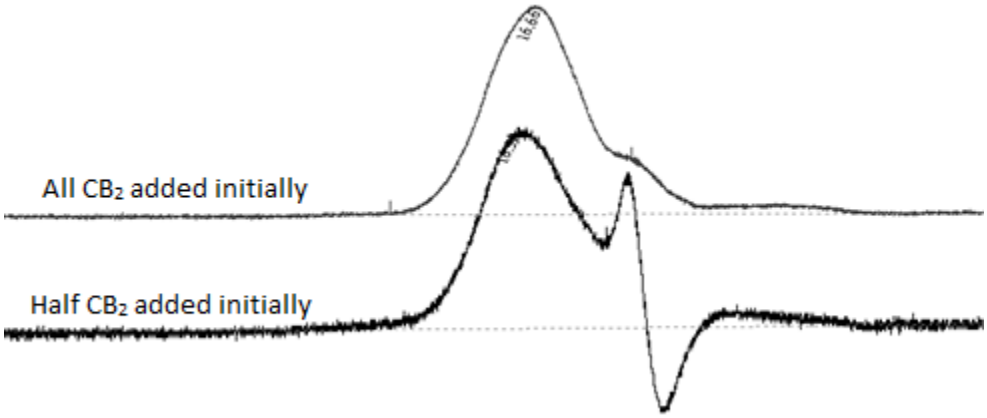


Figure 21: Proton spectra of polymers with PEG M_n 750.

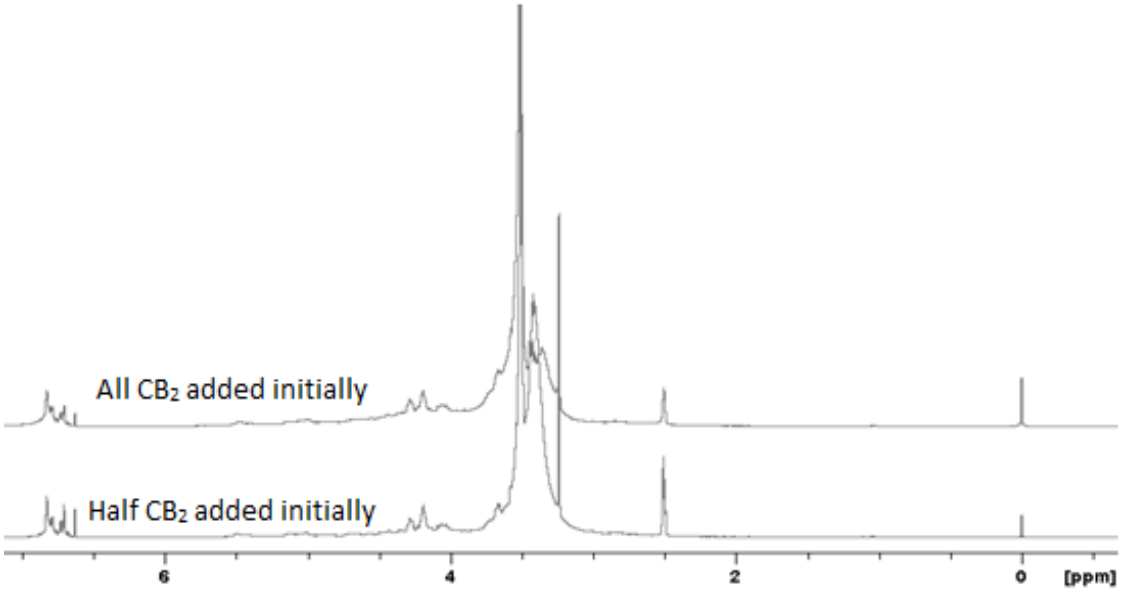
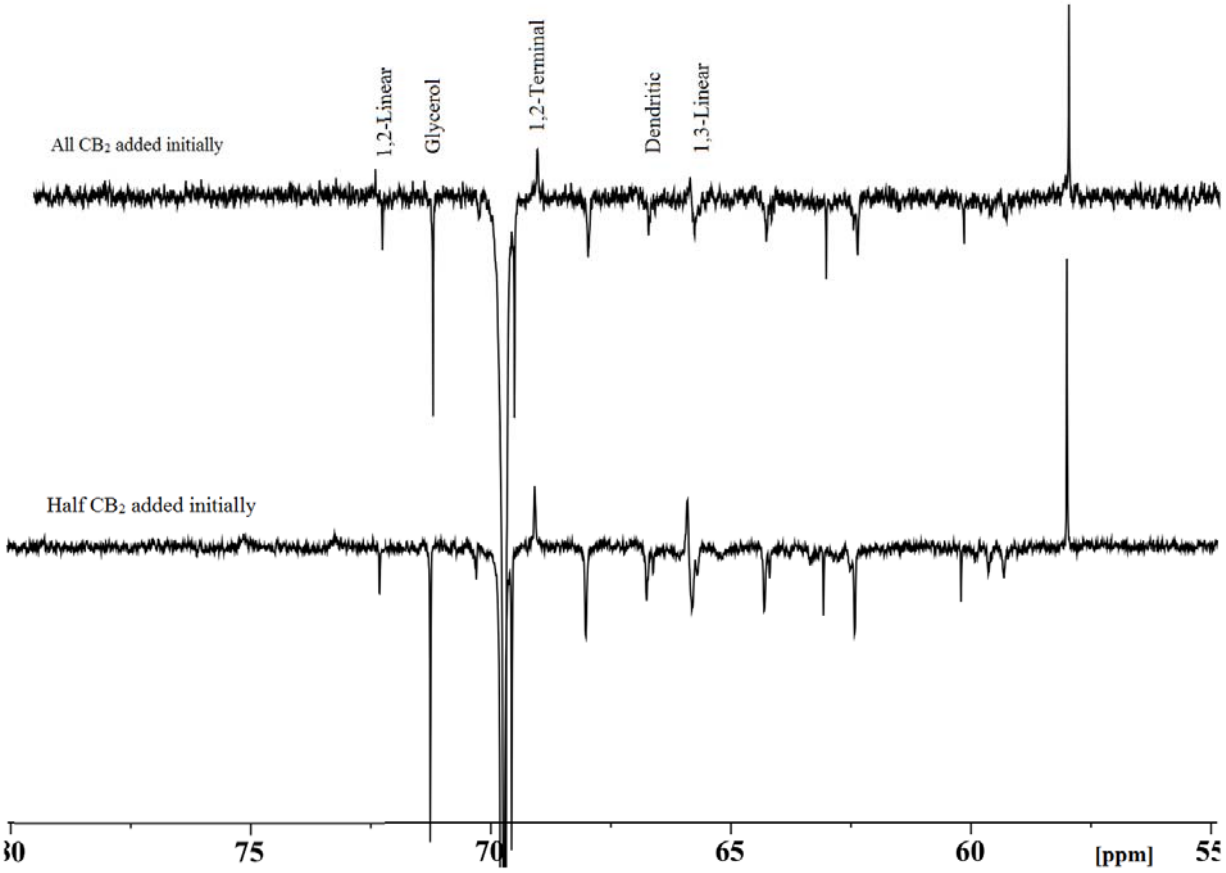


Figure 22: ^{13}C spectra of polymers with PEG M_n 750.



The two polymers prepared with the highest molecular weight PEG (M_n 2000) were also virtually identical. The M_w and M_n were approximately 8500 and 6700 Da, respectively, which corresponds to a PDI of 1.3. An overlay of the GPC chromatograms is depicted in Figure 23. The proton NMR spectra were essentially superimposable as can be seen in Figure 24. The ^{13}C spectra were also very similar. The estimated DBs were 0.65 and 0.49 for the polymers with ½ the CB_2 and all the CB_2 added initially, respectively.

Figure 23: GPC overlay of polymers with PEG Mn 2000.

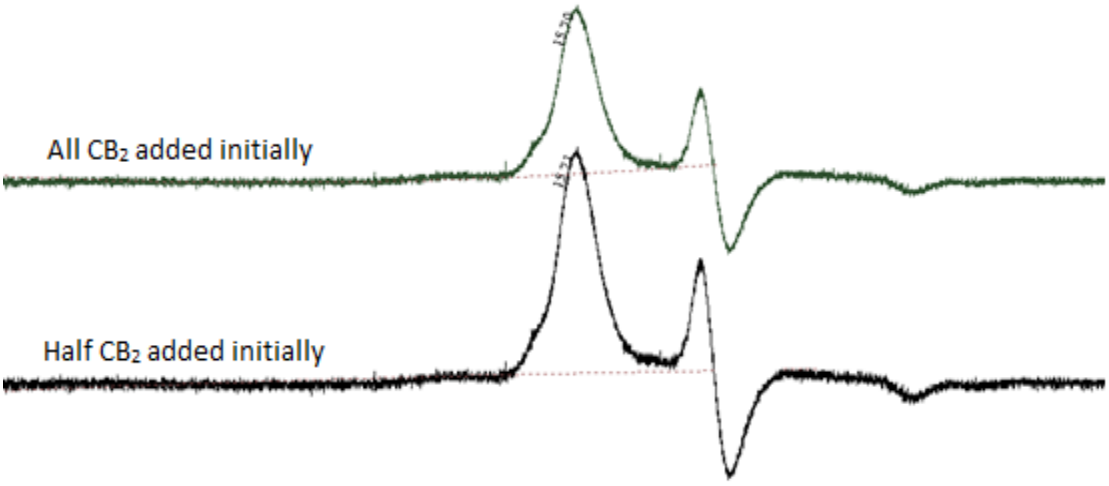


Figure 24: Proton spectra of polymers with PEG M_n 2000.

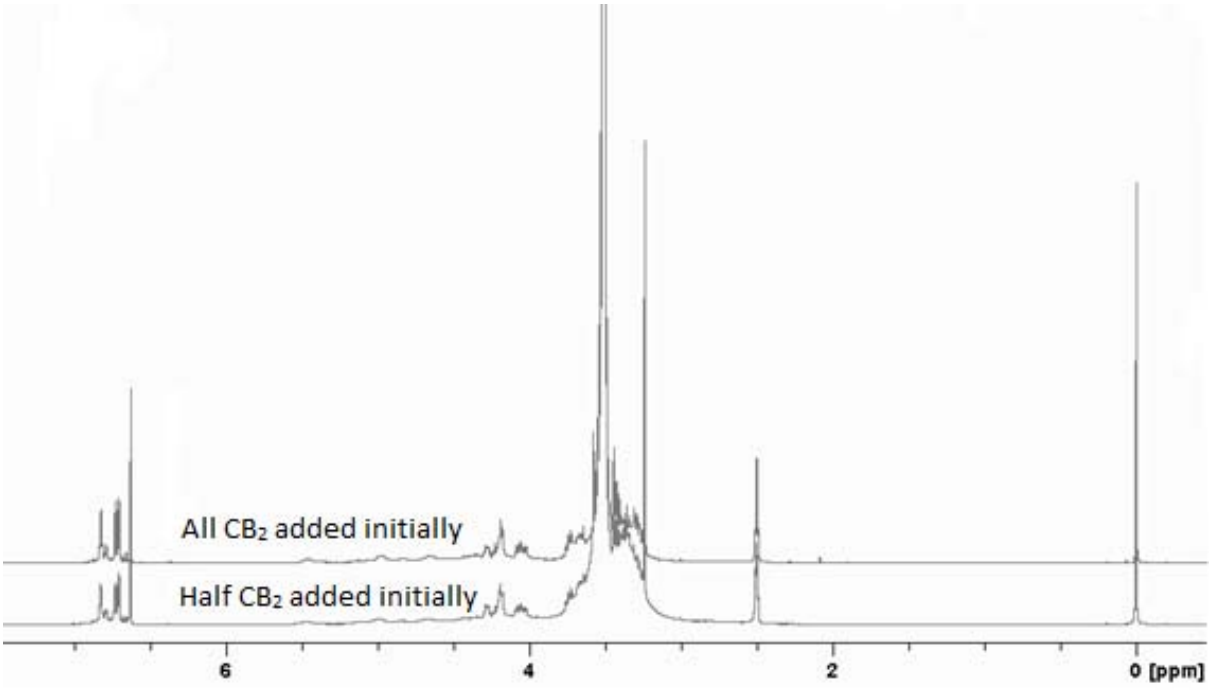
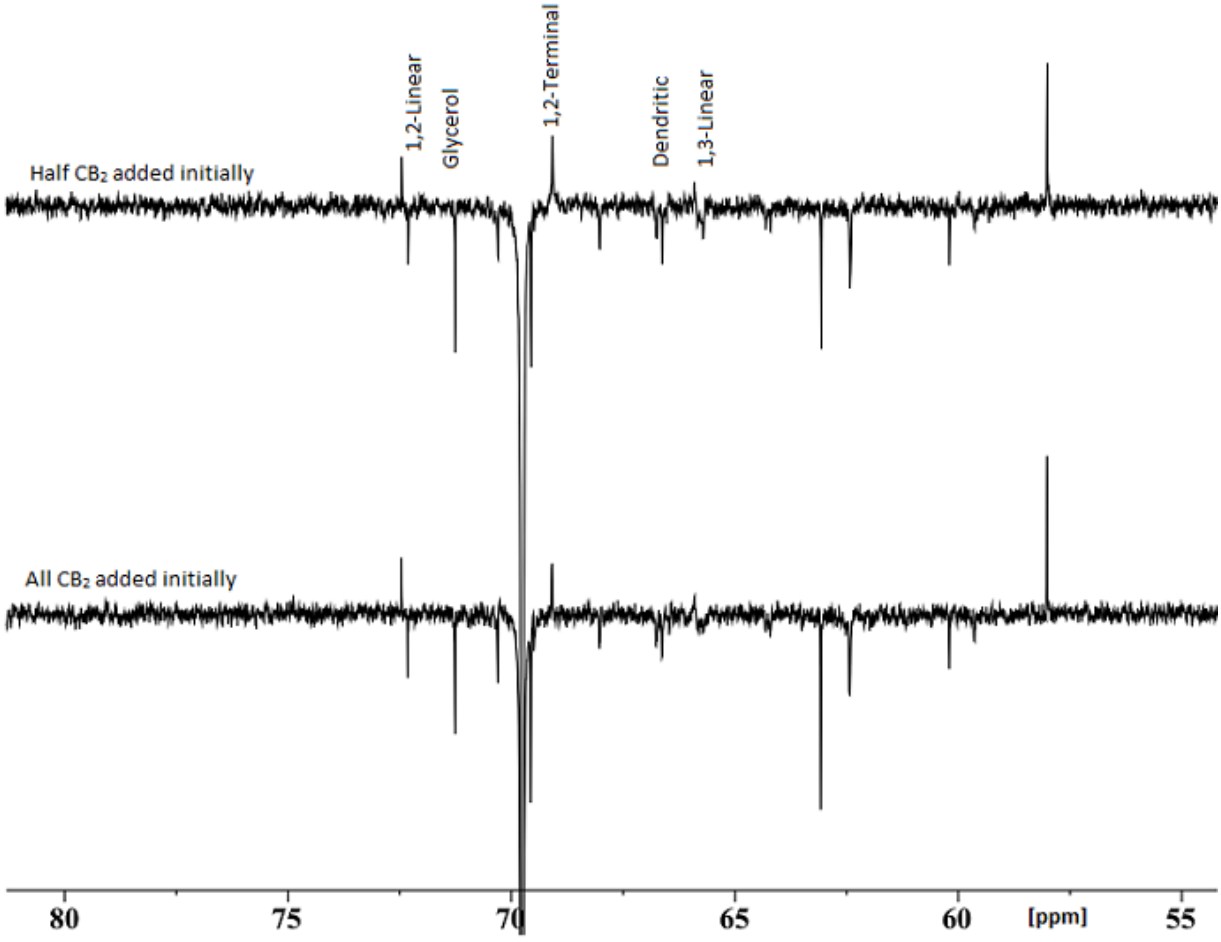


Figure 25: ^{13}C spectra of polymers with PEG M_n 2000.



As has been discussed, no significant differences were observed between the polymers prepared with all of the CB_2 monomer and only half of the CB_2 monomer added initially. As expected, the polymers prepared with the different molecular weight PEGs were different. A summary of the molecular weights is provided in Table 2. There was significant difference in the physical appearance but the ^{13}C DEPT NMR data did not exhibit vast differences as depicted in Figure 27 and Figure 29 for the polymers where half the CB_2 was added initially and where all of the CB_2 was added initially, respectively.

Table 2: Molecular weight summary of polymers with different PEG.

PEG M_n (Da)	M_w (Da)	M_n (Da)	PDI	DB
350	5100	2900	1.7	0.66-0.69
750	5200	3200	1.6	0.65-0.69
2000	8500	6700	1.3	0.49-0.65

Figure 26: Proton spectra of polymers with half CB_2 added initially.

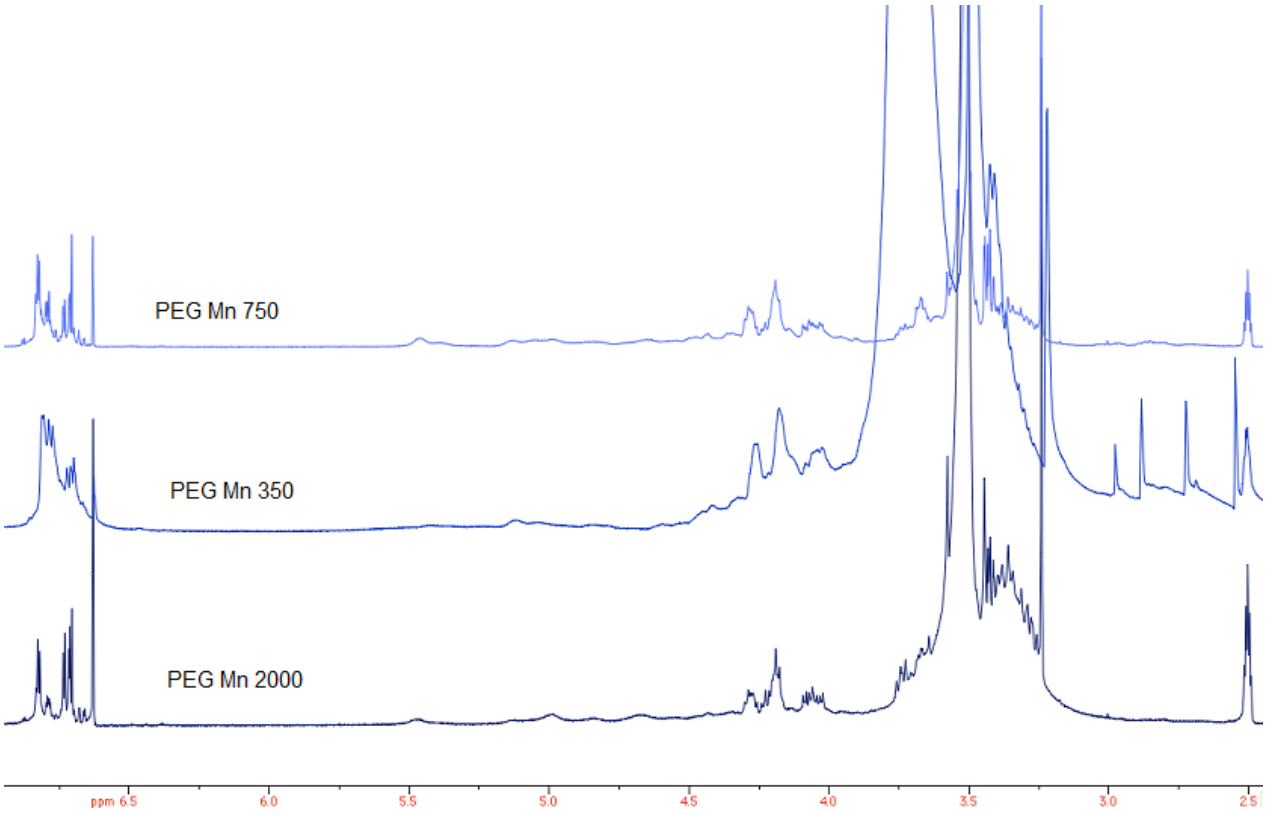


Figure 27: ^{13}C DEPT spectra of polymers with half CB_2 added initially.

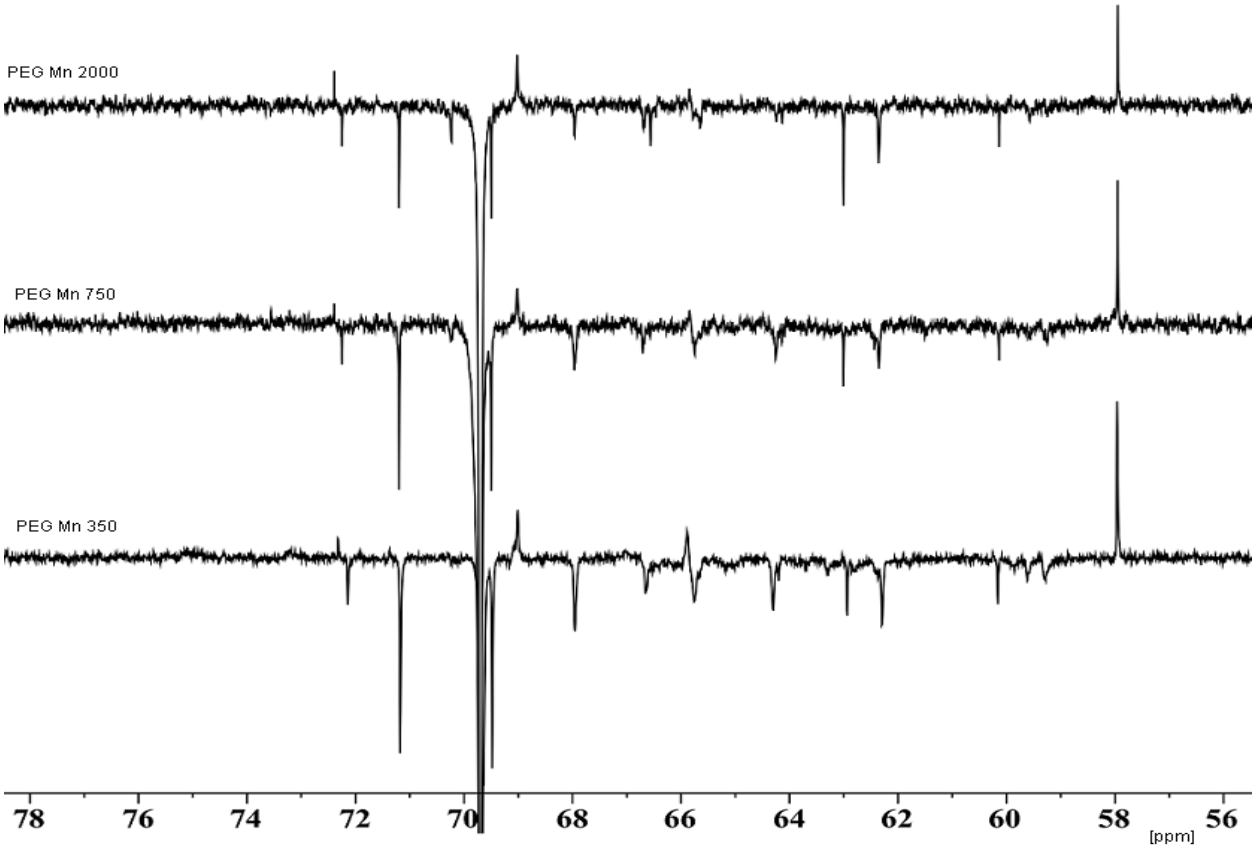


Figure 28: Proton spectra of polymers with all CB_2 added initially.

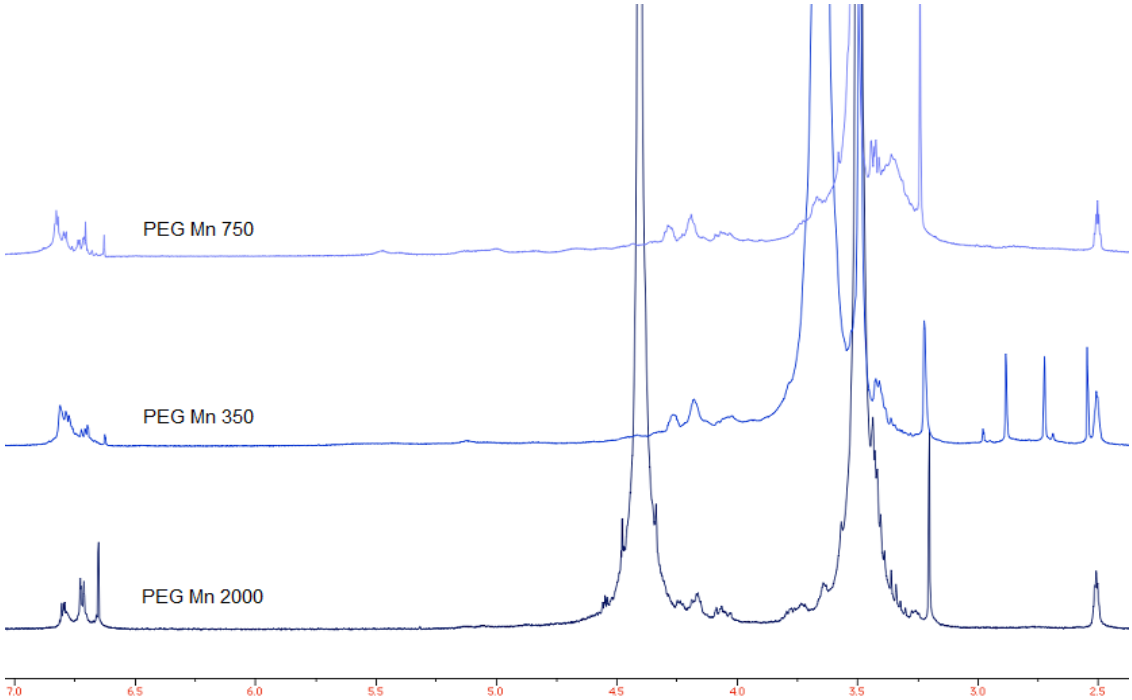
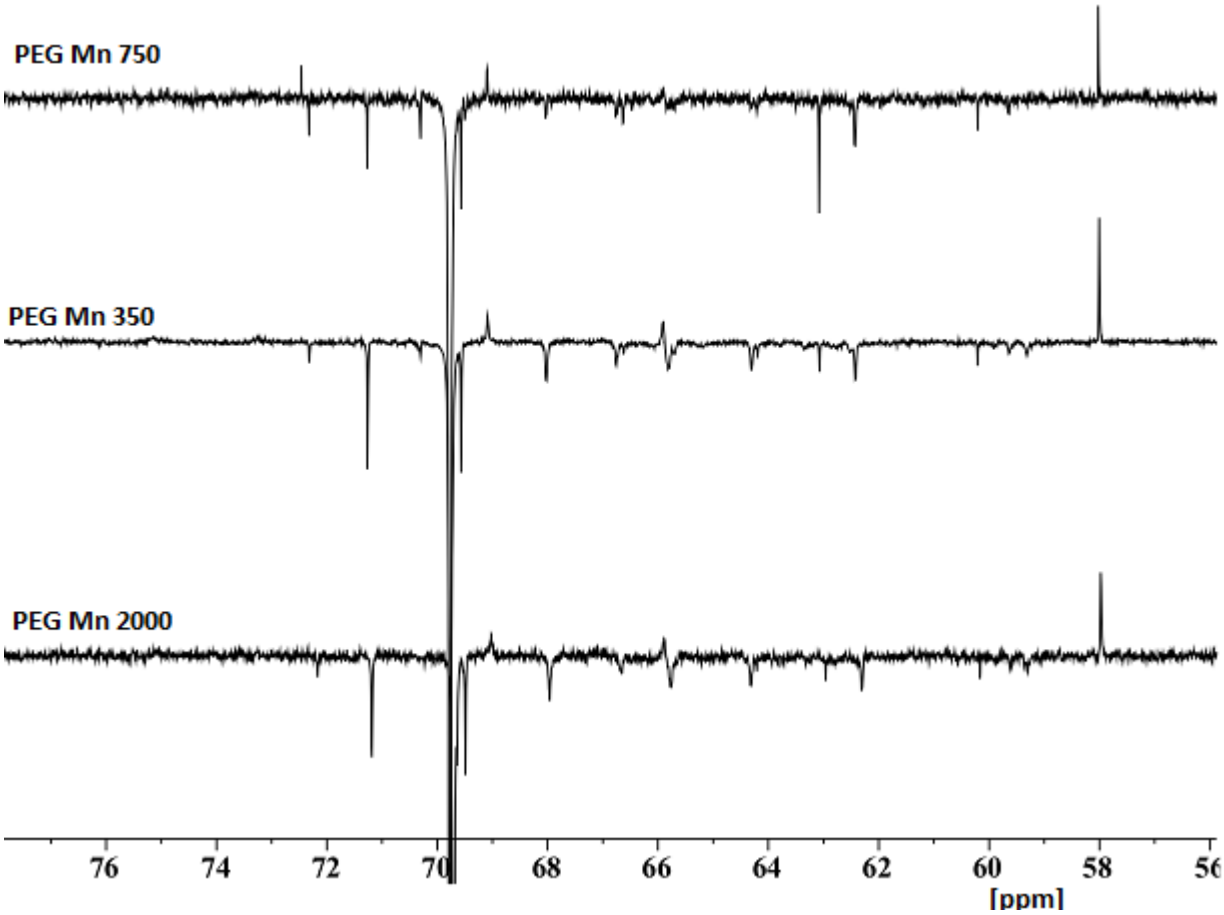


Figure 29: ^{13}C DEPT spectra of polymers with all CB_2 added initially.



The A_2 + CB_2 polymer systems were also evaluated by differential scanning calorimetry (DSC). As anticipated, the two polymers with the same molecular weight PEG had similar thermograms and were characteristic of the corresponding PEG. For instance, the polymers with PEG M_n 350 had a T_m less than 0°C (~-40°C) as shown in Figure 30. The polymers with PEG M_n 750 and M_n 2000 had a T_m of 19-20°C and 46-47°C, respectively (refer to Figure 31 and Figure 32).

Figure 30: DSC of polymers with PEG M_n 350.

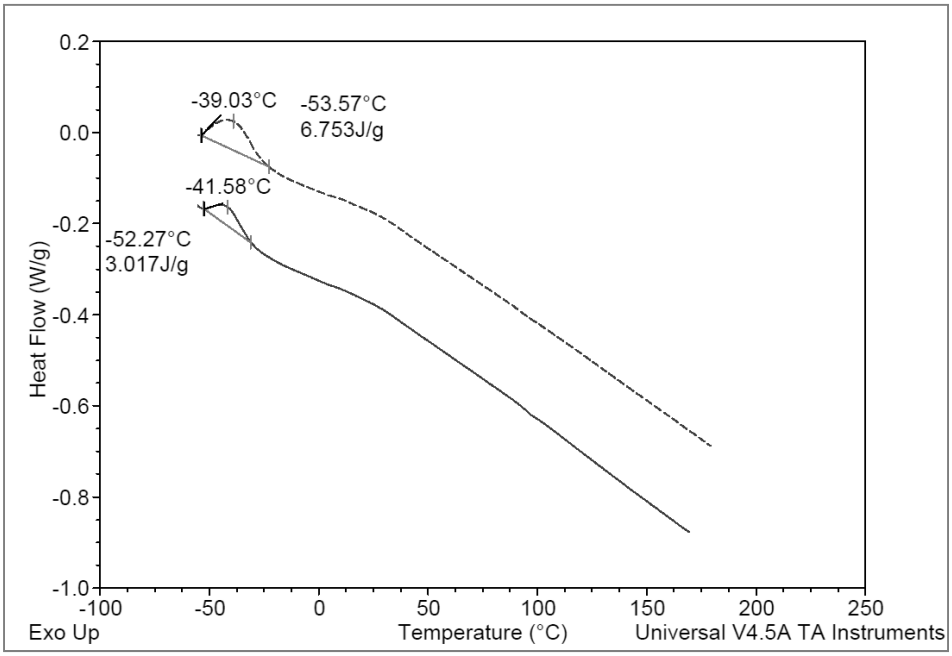


Figure 31: DSC of polymers with PEG M_n 750.

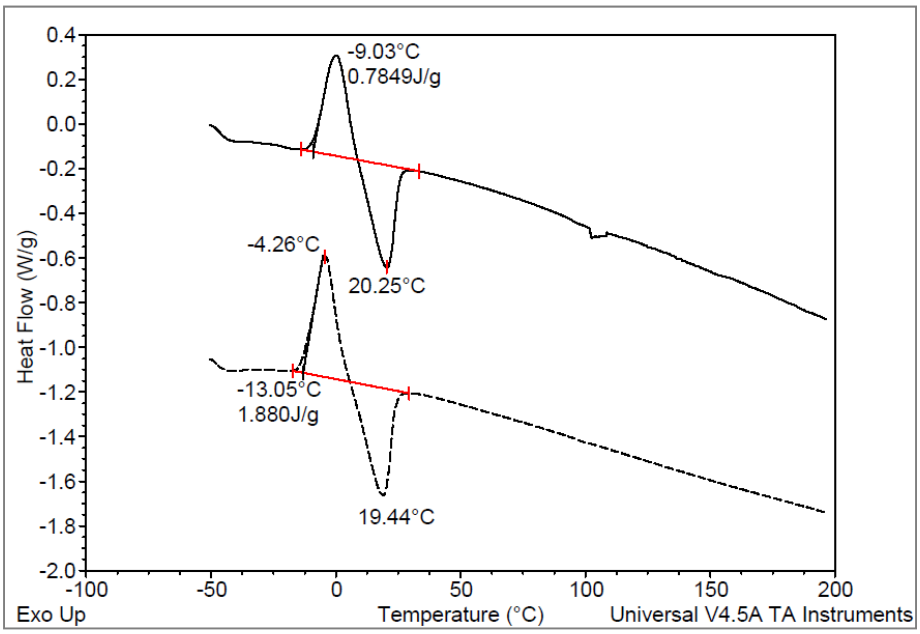
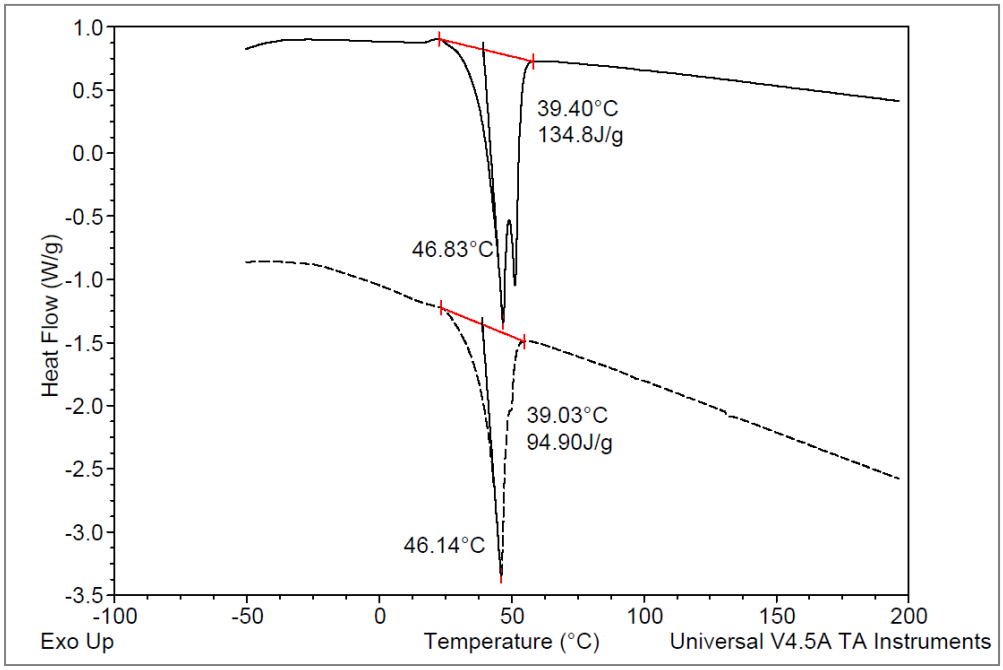
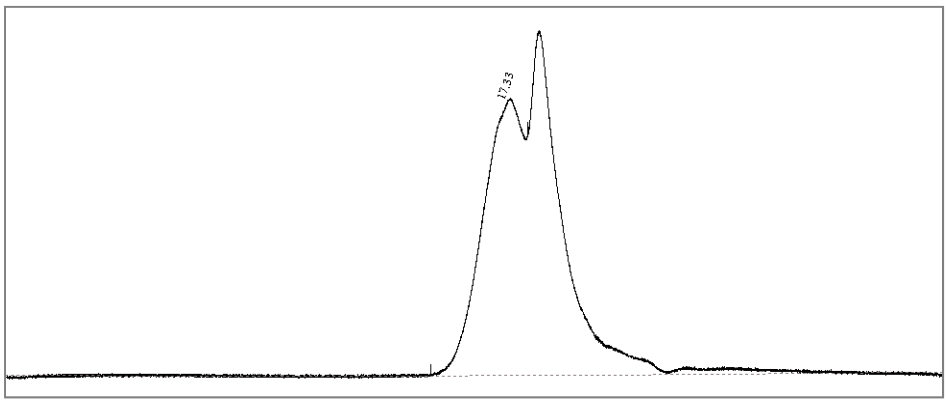


Figure 32: DSC of polymers with PEG M_n 2000.



PEG M_n 350 was chosen as the first end-capping agent for investigation of an A_2 + CB_2 polymer system containing API. Acetaminophen (APAP) was selected as the API since it was readily available. APAP (~1 g) was added to a 1:1:0.3 A_2:CB_2:PEG molar ratio polymer at the end of the four hour synthesis to yield a 7% w/w formulation. The formulation turned a golden yellow. An aliquot was dissolved in DMF and analyzed by GPC. The resulting chromatogram is depicted in Figure 33. The synthesis was repeated using PEG M_n 750 at a 0.2 molar ratio with respect to the A_2 and CB_2 monomers. The APAP was added approximately 2.5 hours after the start of the reaction and the formulation was heated at 150°C for another hour while stirring. This resulted in a 4% w/w APAP formulation which was brown. It was suspected that the APAP degraded in both reactions since APAP has been demonstrated to degrade in solution. [32] Therefore, another API was selected.

Figure 33: Polymer with APAP.



Ondansetron Hydrochloride was the next active pharmaceutical ingredient added to the A_2 + CB_2 system. Ondansetron was chosen because it was also readily available. Ondansetron Hydrochloride was added two hours into the synthesis of a 1:1:0.3 A_2:CB_2:PEG M_n 350 polymer at a 15% w/w ratio. The reaction was allowed to proceed for another six hours. The resulting formulation was bright orange which suggests the formulation was highly conjugated. An aliquot was dissolved in DMF for GPC analysis. The M_w and M_n were approximately 4700 and 2900 Da, respectively, which corresponds to a PDI of 1.6. Refer to Figure 34 for the GPC chromatogram. The polymer was also analyzed by HPLC with UV detection at 216 nm. A standard and the sample were diluted in a buffer:acetonitrile (50:50, v:v) solution to yield approximately 0.15 mg Ondansetron HCl per mL. An aliquot (10 µL) was injected into a Hitachi 7000 HPLC system with the column temperature maintained at 35°C. The Ondansetron peak in the sample was quantitated versus that in the standard. The Ondansetron present in the polymer was 4.3% which is equivalent to a loss of 71%. The chromatographic purity based on area percent was 32%. A representative chromatogram is presented in Figure 35. Dissolution testing was performed on the polymer to estimate the time frame in which the drug would be released from the polymer in the gastrointestinal (GI) tract. If Ondansetron was 100% released during the first 60 minutes, the formulation would be considered an immediate-release dosage form[33]. On the other hand, if the drug

was zero to partially released at 1 hour and then fully released at a later time point, it would be considered a modified-release dosage form. The polymer was analyzed in triplicate by adding approximately 140 mg into a dissolution vessel containing 700 mL 0.1N HCl. After two hours 200 mL pH 6.8 buffer modifier was added. Aliquots were removed at 1, 2, 6, 8, 16 and 20 hours and analyzed by HPLC. The samples were compared to a standard containing 21 µg Ondansetron HCl per mL. Assuming a label claim of 4.3% based on the assay above, the polymer released the Ondansetron during the first hour (103% released) and is considered an immediate-release dosage form. A representative chromatogram is depicted in Figure 36.

Figure 34: GPC of polymer with Ondansetron.

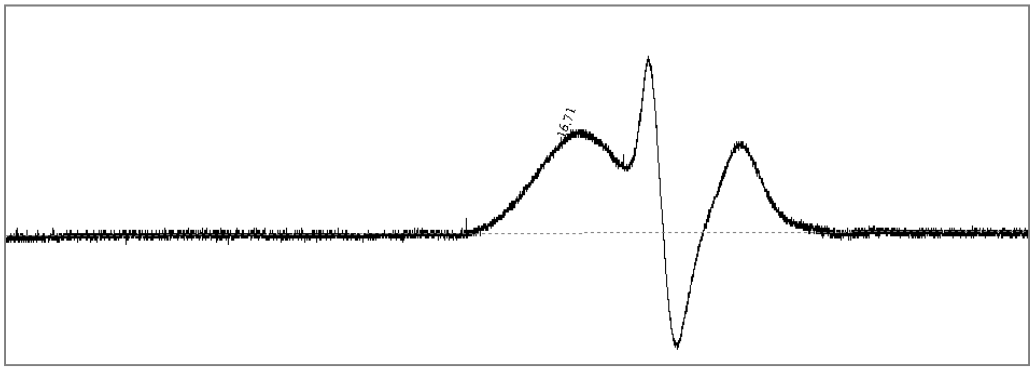


Figure 35: Representative assay/impurity chromatogram for polymer with Ondansetron.

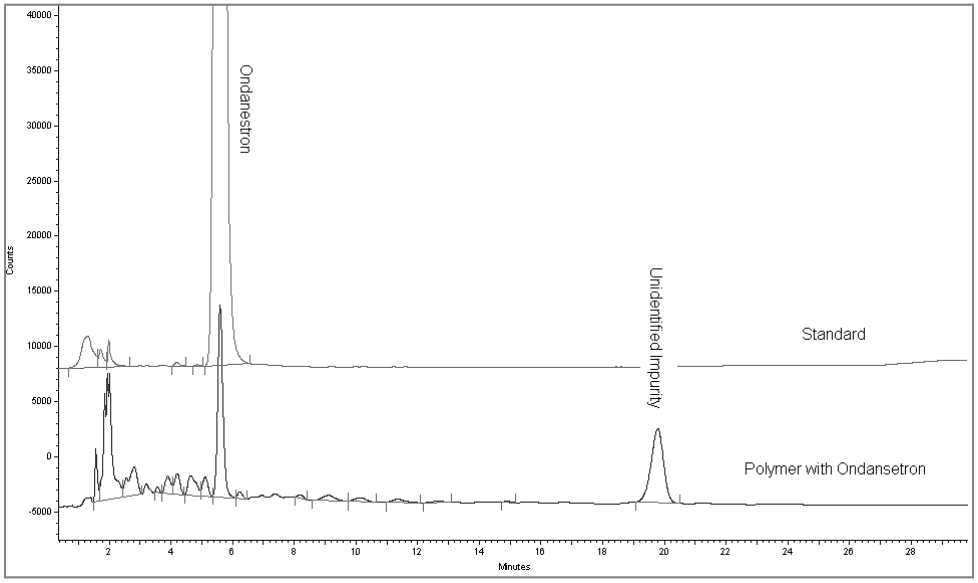
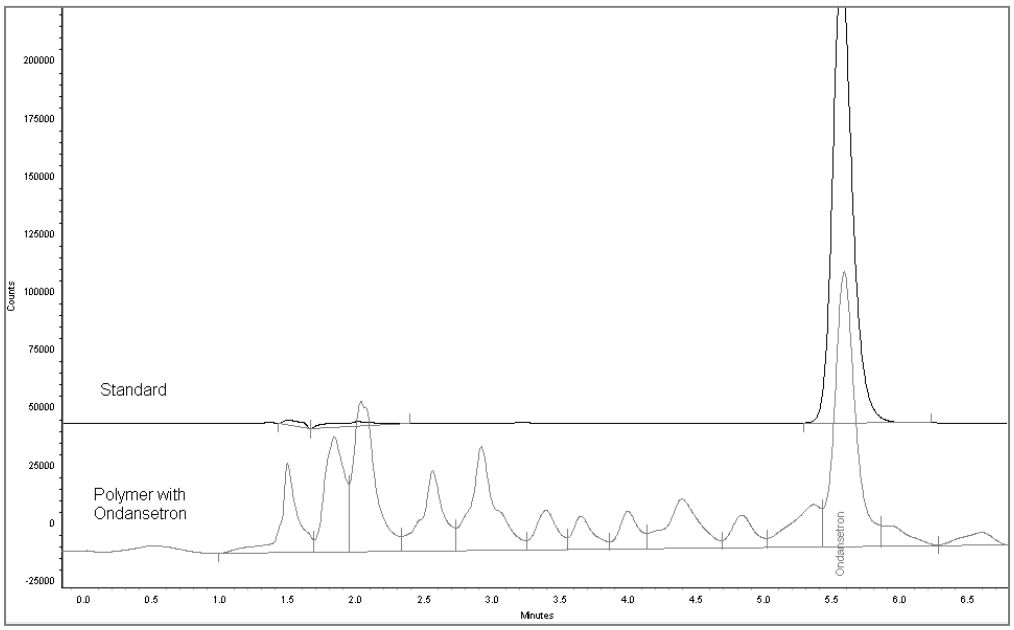


Figure 36: Representative dissolution chromatogram of polymer with Ondansetron.



Due to concern that the efficacy of the API had been compromised, either through degradation or covalent bonding with the polymer, it was decided to repeat the reaction but to add the Ondansetron to the polymer at room temperature after synthesis. The theoretical amount of Ondansetron HCl added was 16% w/w and the final formulation was light tan. Aliquots were dissolved in DMF and DMSO-d_6 for GPC and NMR analyses, respectively. The GPC chromatogram was similar to that found in Figure 34 above. The NMR spectra are presented in Figure 37 and Figure 38. An aliquot of the polymer was assayed by HPLC with UV detection and the Ondansetron amount present in the polymer was determined to be 16% w/w when compared to a standard. This corresponded to 100% of theoretical. Little degradation was observed in the chromatogram (refer to Figure 39). In order to evaluate release of Ondansetron from the polymer in the gastrointestinal tract, dissolution testing was performed. The polymer was analyzed as described above except aliquots were removed from the dissolution vessels at 0.25, 0.5, 1, 1.5, 2, 5 and 20 hours. The Ondansetron was 96% released from the polymer in 15 minutes and was fully released (101%) within 30 minutes. A representative chromatogram is depicted in Figure 40. This corresponds to an immediate release formulation.

Figure 37: Proton NMR spectrum of polymer with Ondansetron.

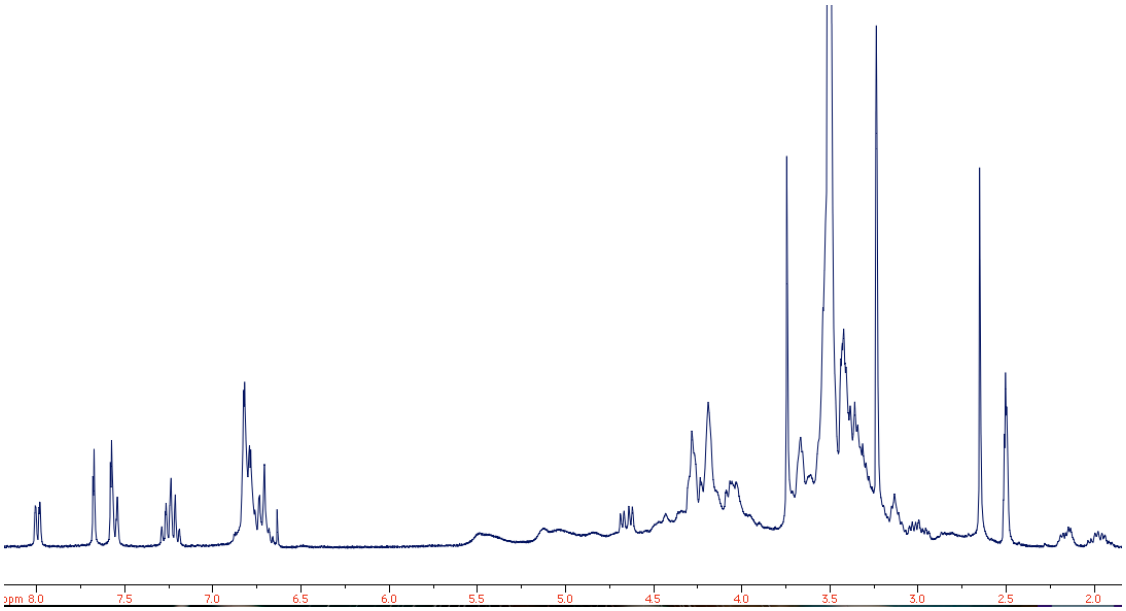


Figure 38: ^{13}C DEPT NMR spectrum of polymer with Ondansetron.

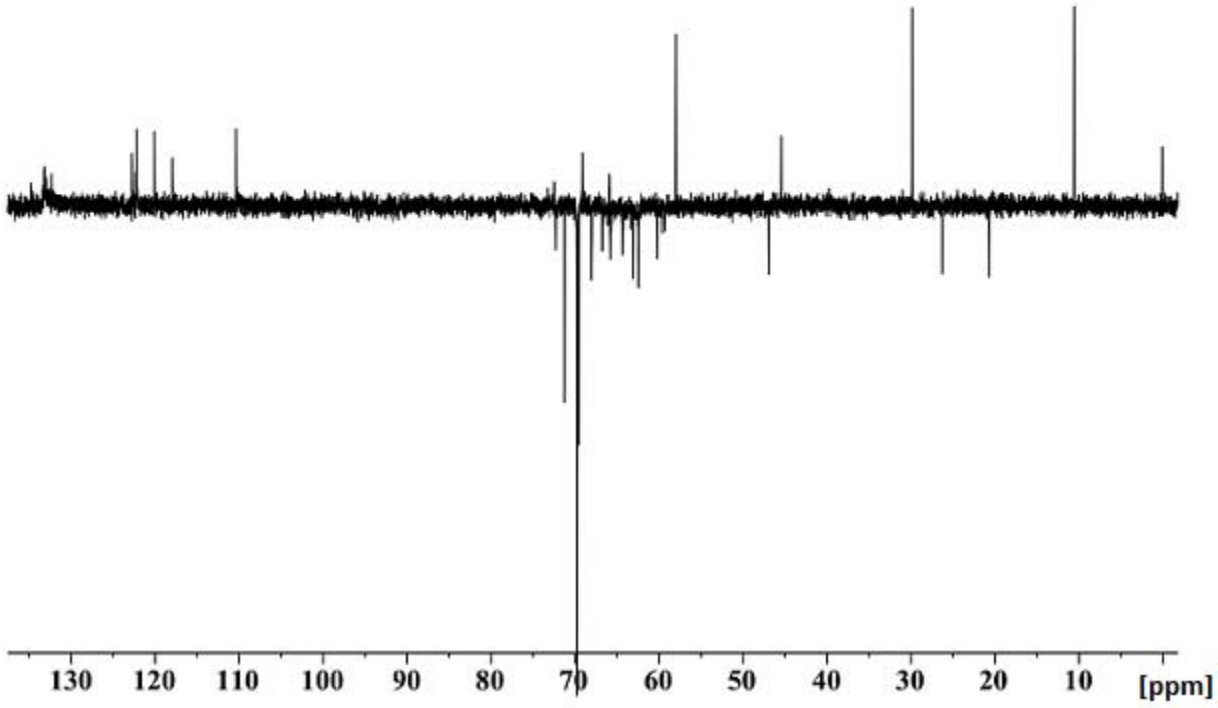


Figure 39: HPLC chromatogram of final polymer with Ondansetron.

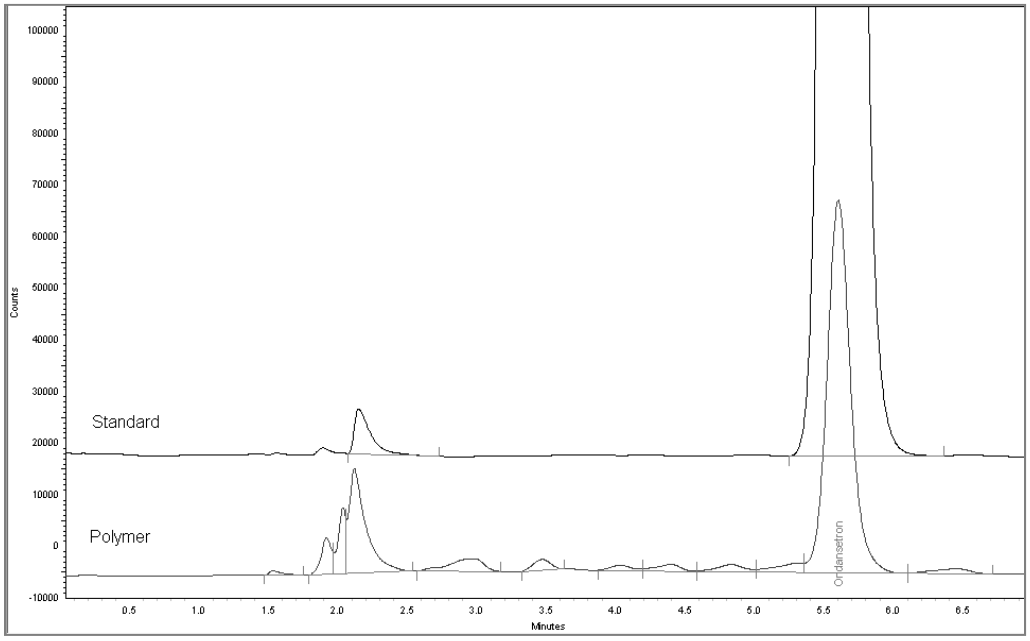
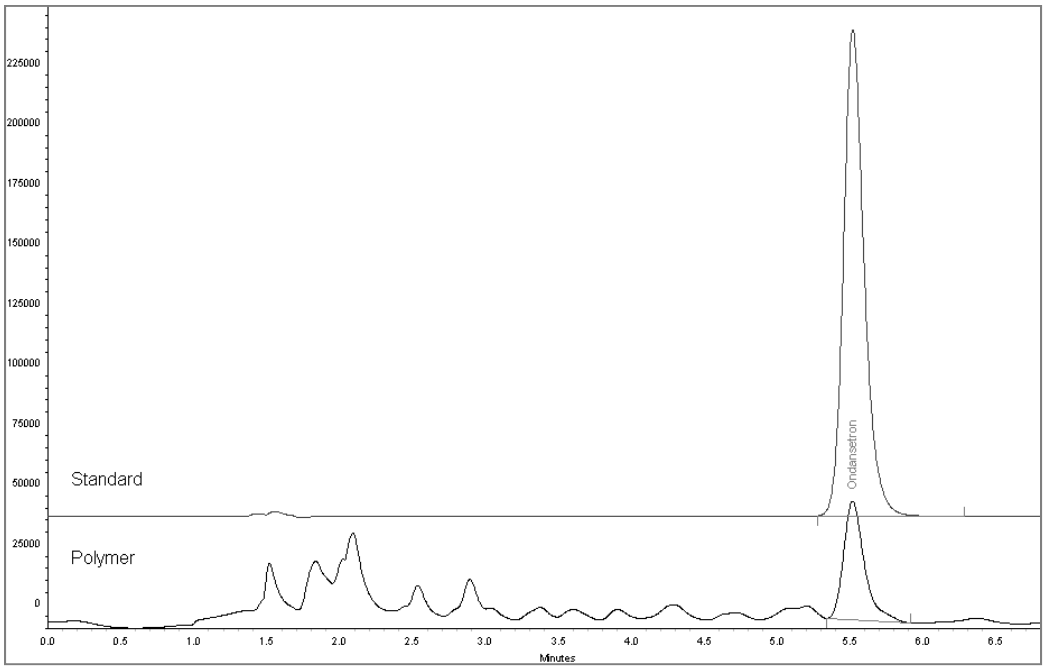


Figure 40: Dissolution chromatogram of final polymer with Ondansetron (30 min).



IV. CONCLUSIONS

Numerous A_2 + CB_2 polymers were made with low levels (≤ 0.09 molar ratio with respect to A_2 and CB_2) of excess B (PEG) added as an end-capping agent. Although these polymers ranged in weight average molecular weights between 5000 and 7700 Da, gelation was difficult to control. As the end-capping agent was increased (~0.2 molar ratio with respect to A_2 and CB_2), gelation was better controlled, but gelling could be attained if the polymers were dried in a vacuum oven. This resulted in insoluble cross-linked polymers. Similar results were obtained when the ratio of A_2:CB_2 was varied in the presence of the same end-capping agent: the vacuum-dried polymer was poorly soluble. Even as the molecular weight of the end-capping agent was increased, the polymers would undergo gelation in the vacuum oven.

When the excess B end-capping agent was increased further (~0.3 molar ratio with respect to A_2 and CB_2) and its molecular weight varied, gelation was better controlled. The resulting A_2 + CB_2 system polymers ranged in weight average molecular weights from ~5100 to ~8500 Da. The hyperbranched polymers exhibited physical properties similar to the PEG end-capping agents from which they were derived. When the biocompatible, end-capped polymer was combined with Ondansetron HCl, it appeared to be a viable immediate-release formulation.

Future work includes conducting a model study of the end-capped system similar to that performed by Werry to confirm the degree of branching.[30] Replacement of the *p*-TSA catalyst with GRAS compounds such as HCl or CH_3COOH is desired. APIs which have a preferred immediate-release need such as sleep aids (i.e. Diphenylhydramine) should be evaluated with the existing A_2 + CB_2 end-capped system. Additionally, attachment of Ondansetron HCl to the polymer should be developed in order to achieve modified-release formulations.

V. REFERENCES

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