Ring-Opening Polymerization of Epoxy End-Terminated Polyethylene Oxide (PEO) as a Route to Cross-Linked Materials with Exceptional Swelling Behavior

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ABSTRACT: We report here studies directed toward the synthesis and characterization of cross-linked poly(ethylene oxide) gels for use as drug delivery platforms. These gels were prepared by anionic ring-opening polymerization of diepoxy PEO_{400}, PEO_{3400}, and PEO_{8000} using *t*-BuOK as the initiator. The diepoxy PEO_{3400} and PEO_{8000} derived gels were found to swell to 20× and 30× their initial masses in water, falling in the category of superadsorbants. Evaluation of their behavior as disintegrants using lactose and calcium phosphate, in comparison with commercial disintegrant croscarmellose sodium, showed the diepoxy PEO_{3400} gel to be twice as fast in disintegrating a tablet. The diepoxy PEO_{3400} and PEO_{8000} derived gels were characterized by XRD, DSC, and TGA. and compared with the linear versions of the same materials. XRD powder patterns for all materials are very similar, albeit those for the gels are less intense likely because of packing disorders near cross-links. DSC data indicate that both T_m and T_c are consistently lower by 5−10 °C in the cross-linked systems. The lower the T_m and T_c, the greater the degree of swelling. Although the PEO_{3400} gels swell less than the PEO_{8000} gels, they swell faster as judged by disintegrant studies. One interpretation of these results suggests a potential new mechanism for the design of hydrogels and superadsorbants wherein cross-linking creates higher energy forms than found in the linear polymers. Such higher energy forms would melt and crystallize at lower temperatures. Likewise higher energy forms would solvate and swell more rapidly.

Introduction

The rapid and efficient oral delivery of drugs depends on several physical and chemical factors. Desirable physical features include high surface area forms of the drugs to be delivered, to ensure rapid (but controlled and even) dissolution/release. These high surface area drug powders must then be dispersed uniformly in a binder that dissolves or simply releases the drug in a controlled fashion in the body (e.g., in gastric media). These requirements mandate chemical properties wherein the binder must (1) be hydrophilic and water-soluble, (2) be nontoxic, (3) offer controllable dissolution properties to permit either immediate or timed release, and (4) permit facile processing of tabular/capsule forms, without recourse to large solvent volumes that must be removed following processing or high processing temperatures that degrade either the binder or the drug, and offer exceptional shelf life.[1−4]

Numerous methods are used to disperse drugs in solid, innocuous binders that range from eutectic mixtures, to solid solutions, to amorphous precipitates in a crystalline (or amorphous) carrier.[1,2] One particularly useful method is to combine the drug with a binder that has a low enough T_g (softening temperature) or T_m (melt temperature), typically in the 120 to 180 °C range, to allow the drug to be mixed effectively and efficiently and then extruded. This solves two problems at once: it eliminates the costly step of removing solvents used to mix binders with drugs, and it allows the direct injection molding or extrusion of tablets or filling of gel caps. Note that the lower temperature (≥120 °C) is defined by processing limits and the upper temperature (≤180 °C) by drug stability limits.

An alternate approach uses a polymer that does not dissolve or melt but is highly swellable. Such materials, especially hydrogels, can be swollen to many times their normal volume with an innocuous solvent containing the drug to be delivered and then dried to encapsulate the drug within for later release by swelling with a suitable solvent-including saliva. Alternately, the same type of polymer can be used in small amounts as a binder that is physically, but intimately, mixed with the drug of interest and compounded in tabular form. The resulting tablet, in the presence of a suitable solvent, swells rapidly, leading to disintegration of the tablet and "instant" release of a high surface area form of the drug.

We begin here a series of papers whose objectives are to introduce novel forms of functionality to well-known drug delivery systems at an early stage in the synthesis that greatly expand the utility of those systems without compromising their biocompatibility. We begin with efforts to develop functional poly(ethylene oxide)s that can be cross-linked to realize novel hydrogel-like behavior and unusually rapid drug delivery.[5−11]

Some precepts that guide our efforts include the following: (1) identifying functionality that provides access to tailored, nontoxic, hydrophilic, and highly water miscible (swellable) derivatives, and (2) developing simple functionalized poly(ethylene oxide) (PEO) derivatives that are inexpensive to synthesize and

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process, yet offer enhanced properties compared with commercial materials.

Within these guidelines, we sought to introduce PEO chain end functionalization such that the functional groups provide access to novel branch, graft, star, and cross-linked polymer systems.[12−19] A further constraint was that the functional groups must produce innocuous (see below) chain-linkers following polymerization. We report here on the use of glycidyl units and their anionic ring-opening polymerization to form hydrogel-like materials. These functional groups ring open polymerize to give glycerol cross-link units. Characterization data suggest that the high density of cross-links affects the energetics of chain segment packing such that solvation is highly favored, leading to rapid and exceptional swelling and therefore excellent distintegrant behavior.

Experimental Section

Materials. All chemicals were bought from standard vendors and used as received or purified as specified. THF and hexane were distilled under N_2 from benzophenone/Na. Acetone was used without further purification. Me_3SiCl (TMS chloride) and hexamethyldisilazane (HMDS) were distilled prior to use. Poly(ethylene glycol)s (PEOs) with M_ns of 400, 3400, and 8000 were purchased from Aldrich and used without further purification. Molecular weights and distributions were verified by GPC (see below). Sodium hydride (NaH), and epichlorohydrin used in the epoxidation of PEG were purchased from Aldrich and used as received without purification. Potassium *tert*-buoxide (*t*-BuOK) used in the polymerization of PEO as a catalyst was also purchased from Aldrich and used without further purification. KH used in the production of the initiator was purchased form Aldrich as a 30% oil suspension. Lactose monohydrate (Fast Flo), dicalcium phosphate (Di-Tab), and croscarmellose sodium (AcDisol) used in the disintegration tablets were purchased from Foremost, Rhodia, and FMC, respectively.

Analytical Techniques. NMR Analyses. All ^1H and ^{13}C NMR analyses were done in $CDCl_3$ or acetone-d_6 and recorded on a Varian INOVA 300 and 400 spectrometer. ^1H NMR spectra were collected at 300.0 and 400.0 MHz using $CDCl_3$ or acetone-d_6 as an internal reference at 7.24 and 2.05 ppm, respectively.

X-ray diffraction analyses (XRD) were performed on a Rigaku rotating anode goniometer (Rigaku Denki Co., Ltd., Tokyo, Japan). Powder samples (20−40 mg) were packed on a glass specimen holder. XRD scans were made from 10 to 60° in 2θ, using a scan rate of 2°/min in 0.05° increments and Cu Kα radiation (1.542 A°) operating at 40 kV and 100 mA.

Thermal gravimetric analysis—differential thermal analysis (TGA—DTA) was performed on a SDT 2960 simultaneous DTA−TGA (TA Instrument, Inc., New Castle, DE). The instrument was calibrated with gold supplied by Perkin-Elmer. Measurements were performed under a continuous flow of air (100 mL/min). Samples (100 mg) were heated at 10 °C/min to 1000 °C and then allowed to cool to ambient at 20 °C/min. Other runs were made using a ramp rate of 10 °C/min to 850 °C and then 1, 2, or 5 °C/min to 800 °C.

DSC studies were performed on a DSC 2910 differential scanning calorimeter (TA instrument, Inc., New Castle, DE). Measurements were performed under a continuous flow of nitrogen (110 mL/min). Two heating−cooling cycles at 1 °C/min were recorded for each sample from 25 to 100 °C unless otherwise noted.

Synthetic Methods. Synthesis of DiepoxyPEOs. PEO_{400}, PEO_{3400}, and PEO_{8000} were used as starting materials. In a typical reaction, 50 g of PEO was added to a dry 2000 mL flask previously vacuum-dried for 2 h and then purged using three cycles of N_2 and vacuum. Then, 500 mL of dried THF was added to the flask. To aid solvation, the flask was heated to 40 °C until the PEO dissolved to form a colorless solution and then cooled to room temperature. Then, 2.2 equiv of NaH was added based on the moles of PEO used. The solution was stirred at room temperature for 6 h. Then, 10 equiv of epichlorohydrin, based on PEO, was added and the reaction was left stirring for 20 h and then filtered through a funnel equipped with a glass wool/Celite filter to remove NaCl and byproducts. The filtered solutions were slowly precipitated into hexanes. After precipitation, the filtered products were vacuum-dried at room temperature and then stored in a refrigerator. PEO_{400} was recovered from the precipitation step as a viscous oil. After purification through precipitation, excess solvent was removed under vacuum and the product stored in a refrigerator.

The yields are typically >90% with 95% conversion. ^1H NMR ($CDCl_3$): 3.61 [m 36.6H (PEO_{400}), 328H (PEO_{3400}) 764H (PEO_{8000})], 3.35 (m 2H), 3.1 (m 2H), 2.71 (m 2H), 2.53 (m 2H). DSC: PEO_{3400}, T_m = 58.7 °C; PEO_{8000}, T_m = 61.4 °C. NMR data for the starting materials are found in Supplemental Table 1 in the Supporting Information.

Ring-Opening Polymerization (ROP) of diepoxyPEO Using *t*-BuOK. A reaction system consisting of a 100 mL r/b flask with a magnetic stir bar and a reflux condenser was dried by heating under vacuum using a heat gun. The system was then placed under N_2 flow. Potassium *tert*-butoxide (0.01, 0.10, 0.25, 0.5, or 1.0 equiv) was introduced to the system and then 3 g of diepoxyPEO was added. The mixture was left under N_2 for 30 min. Then varying volumes of dry THF were added through a septum using a dry syringe at room temperature. The reaction mixture was heated immediately to 70 °C with an oil bath and then kept at temperature. After complete dissolution, 0.1, 0.25, 0.5, 0.75, or 1.0 equiv of potassium *tert*-butoxide, based on the total number of end groups, was added.

Changes in molecular weight and polydispersity of the ROP products and starting materials as a function of time were followed by GPC. One milliliter samples of reaction solution were removed at 0.5, 1, 2, 5, 10, and 20 h using a dry syringe and placed in a nitrogen-filled vial (10 mL) with a stir bar. Then, 1.2 equiv of Me_3SiCl [or $(Me_3Si)_2NH$] was added to the extracted sample and the mixture allowed to react at room temperature for 30 min with stirring. The resulting mixture was then added dropwise to a vial containing 10× the amount of hexane to terminate the reaction and precipitate the product. Polymer precipitates were collected by decantation and rinsed 3× with hexane. The product was vacuum-dried for ≥2 h, sealed, and stored at 0 °C. The product texture varied, depending on the amount of equivalent potassium *tert*-butoxide and time elapsed, from a viscous liquid to a gel. Final samples were dried under vacuum and stored in a desiccator for swelling experiments. Characterization data for varying conditions can be found in the discussion below.

ROP of diepoxyPEOs at Scale. A 1000 mL r/b reactor equipped with a magnetic stir bar and a reflux condenser, was first heated under vacuum using a heat gun. After heating, the system was placed under N_2 flow. Then 50 g of diepoxyPEO was added and kept under N_2 for 30 min, and then 330 mL of dry THF was added by syringe. The reaction mixture was then heated to 70 °C. After complete dissolution, 0.5 equiv of potassium *tert*-butoxide was added, and then after 5 h of reaction time, an additional 0.25 equiv was added. The viscosity of the reaction solution slowly increased after 3 h.

After heating for 7 d, transparent and mostly colorless gels were obtained. The obtained gels were washed with water, by immersion, for 1 d, vacuum-dried for 7 d at 35 °C, and stored in a desiccator for evaluation of the swelling behavior. The yields were essentially quantitative.

PEO gel swelling experiments were conducted using 0.1−0.04 g of gel. Samples were cut from gelled material previously vacuum-dried at room temperature and stored as described above. Gel samples were weighed and submerged in distilled water for 24 h at room temperature. The samples were then washed briefly with acetone on a Büchner funnel to remove surface water. The samples were turned during washing to ensure that all surfaces were exposed. The samples were then dried in flowing N_2 and then weighed.

Disintegrations in model systems were performed with PEO gels. A Spex 6800 freezer/mill was used to reduce the

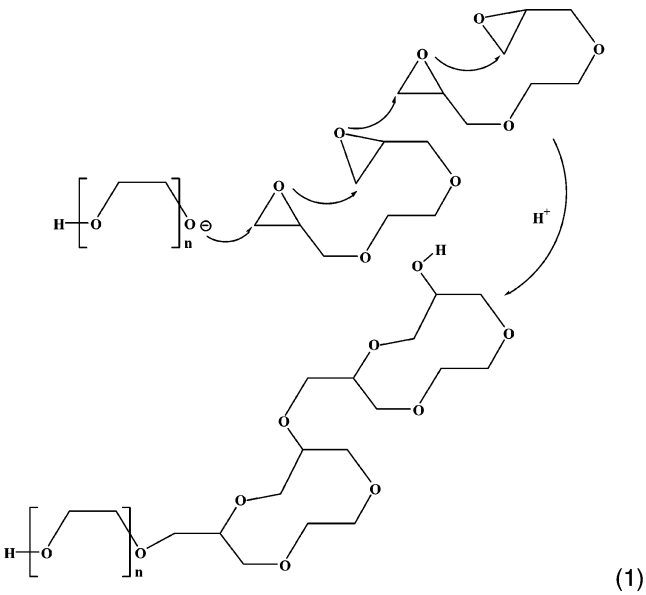
particle size, and the milled dry gel was screened using a Sonic sifter. The hydrogel was placed in a milling container. The whole container was submerged in liquid nitrogen and cryo-milled. An impactor inside the container breaks the frozen hydrogel into powder. Five percent gel with less than 150 mm particle sizes was used to make 500 mg tablets with 95% of either lactose or dicalcium phosphate. A Carver Laboratory Press model C with a $^3/_8$ biconcave round punch was used to form tablets, with 5% magnesium stearate in methanol used as lubricant and applied to the die prior to compaction. Tablet hardness was measured using a Distek hardness tester HC97. Disintegration testing was performed in 900 mL of USP water (37 °C) using Pharma-Test Type PTZ3EH with standard screen (size #10 mesh) basket. Disintegration time was monitored with a stop watch.

Results and Discussion

The pivotal point in our approach to PEO-based hydrogels was the search for anionic initiators and cross-linkers that (1) were likely to be innocuous in vivo, (2) provide a high degree of cross-linking, (3) were easily accessible synthetically, and (4) were similar in chemistry to PEO. We initially identified glycerol and glycolic acid as potential initiators and cross-linkers that meet these parameters. We later recognized that ethylene glycol used as an anionic initiator or cross-linker also provides the same opportunities even though ethylene glycol by itself is toxic.

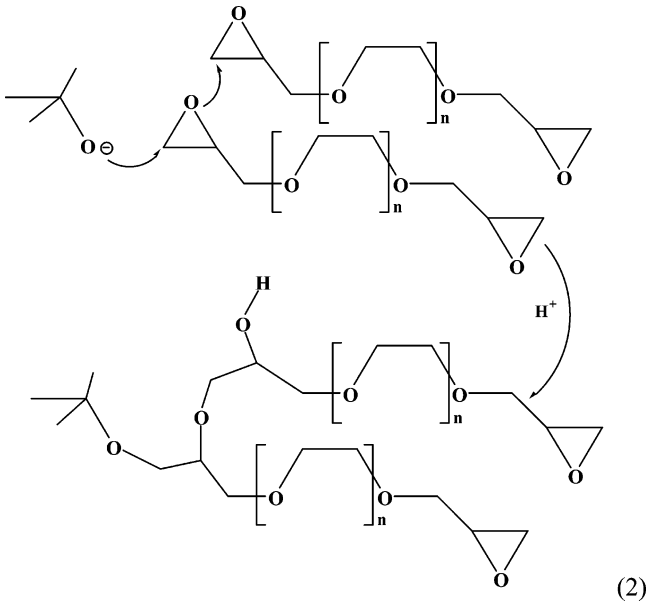
On the basis of our experience with epoxy resins, we realized that oxygenate anion promoted ring-opening polymerization of glycidyl epoxides will form glycerol cross-linkers.[12] Thus, if we used the above-noted initiators, also deemed innocuous, then materials that comply with the above four points appeared to be accessible. Furthermore, a search of the literature indicated that this approach might be used to produce the desired hyperbranched, star, and hydrogel-like materials, although no reports directly overlapped with our approach.[13−17]

Anionic polymerization of the diepoxyPEOs can be envisioned to followed several pathways depending on the PEO segment length, the degree of functionality of the initiator, and its concentration. Two likely cross-linking scenarios are depicted in reactions 1 and 2. The

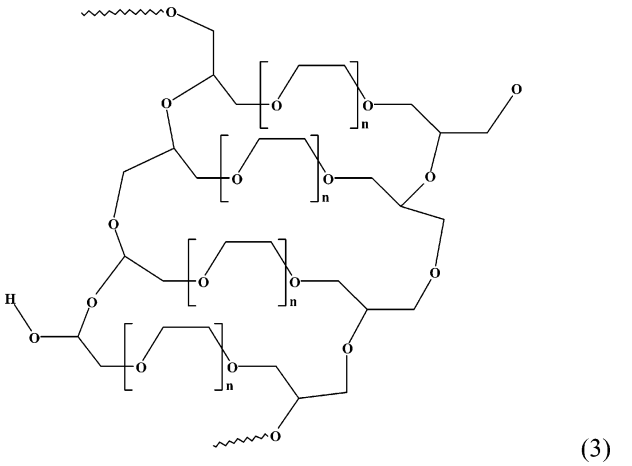


(1)

final outcome of reaction 2 is the product shown in (3). Note that in reaction 2 the anionic initiator is *t*-BuO$^-$.



(2)



(3)

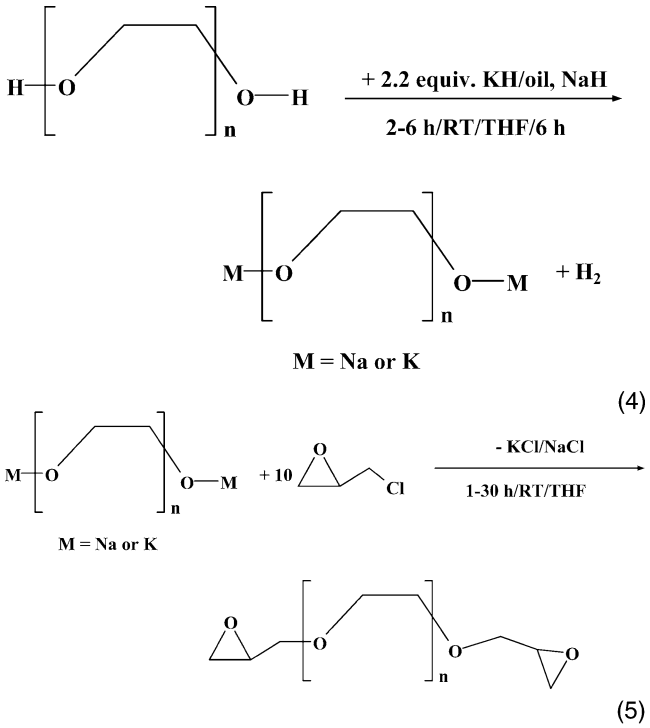
As noted below, we chose this initiator for model studies because we assumed it would be visible by ^{1}H NMR during the polymerization process and allow us to follow polymerization spectroscopically. Unfortunately, polymerization is sufficiently rapid that most of the tBu groups appear to become part of the insoluble component in these systems and solution ^{1}H NMR cannot be used to follow the polymerization process. The polymerization process is also essentially quantitative. Recovered yields of gels washed repeatedly with water and then vacuum-dried extensively appear to be within the limits of mechanical losses quantitative.

On the basis of the above scenarios, we chose a set of three PEOs that would allow us to access materials likely to form the species shown in (1) or (3) and that were available commercially. Furthermore, for ease of processability, it was desirable to keep the molecular weights below PEO_{10000}. Thus, our set included PEO_{400}, PEO_{3400}, and PEO_{8000}.

The first synthetic step was to identify optimal reaction conditions simply for producing the diepoxy-PEOs. Next, we conducted model ring-opening polymerization studies to identify optimal conditions for preparing PEO hydrogels with reproducible properties. Finally, we were able to develop a set of methods for characterizing the resulting hydrogels. The following sections detail our efforts in this order.

DiepoxyPEO Synthesis Studies. Although no reports on glycerol-linked PEO hydrogels appear in the literature;[13−18] for reproducible properties, pure starting materials are essential. For example, the starting diepoxyPEOs must be formed in high conversion to ensure the high degree of uniform cross-linking necessary for reproducible swelling behavior and limit contributions from chain transfer events.

All diepoxyPEOs used here were prepared by nucleophilic coupling of the PEO dianion with epichlorohydrin per reactions 4 and 5.[8−12] The products were characterized by GPC and ^{1}H NMR (Supporting Information, Supplemental Table 1).



We examined several methods of forming the PEO dianion because our early results were not reproducible. Initial studies used KH dispersed in mineral oil to form the dianion. Although this KH is ostensibly quite pure and ROP of diepoxyPEOs gave gels with high degrees of swelling, the gels often appeared dark brown, most likely because of impurities in the KH starting material. To some extent, this was anticipated because scenario 1 suggests the potential to form crown-ether-like repeat units, presumably for shorter chain PEOs such as PEO_{400}. Such species might be anticipated to form stable complexes with trace metals in the environment leading to colored species as seen for related diacrylatePEOs complexed and polymerized with transition metals.[19]

Further support for this supposition comes our failure to remove this color using reprecipitation, membrane dialysis, or even passage of the diepoxy through columns of silica and alumina. Furthermore, once the KH dispersion was washed with hexanes, the coloration mostly disappears. Optimization studies were conducted as follows.

The conversions of PEO dianion (formed using either KH or NaH) to the diepoxy following reaction with epichlorohydrin were determined from ^{1}H NMR and are presented in the Supporting Information (Supplemental Table 2). Two variables were studied: One was the effect of reaction time between PEO_{8000} and KH/NaH before epichlorohydrin addition. The other was the effect of reaction time after adding epichlorohydrin.

As expected reaction times before and after addition greatly affect conversions. For dianion formation times of 6 h with KH or NaH, conversions were >90% at 20 h. However for NaH, conversion was 95% at 10 h. In addition to shorter reaction times and better yields, the products were also cleaner. The overall conclusion was that NaH provides cleaner and quicker conversions to product. Therefore, NaH was used to generate the starting materials for the ROP studies.

Ring-Opening Polymerization of diepoxyPEOs. As noted above, *t*-BuO^- anion was used as the initiator in these model studies under the assumption that we would be able to see the products and examine them by ^{1}H NMR using *t*-Bu as a marker. Unfortunately, gelation was sufficiently rapid that soluble samples were found not to be representative of the hydrogel but likely consisted of small chain oligomers or cyclization products (low molar masses by GPC). We noted above that full cross-linking was not expected given that at some point in the cross-linking process, epoxide units within the network structure would become inaccessible for anionic ROP. These trapped units are potentially worrisome in terms of our "innocuous" goals but can opened to glycerol units by simple acid-catalyzed ring opening in water. However, the isolated mass of the products was very close to theory suggesting that any trapped, unreacted groups are still incorporated into the cross-linked polymer by ROP at the other chain end.

A related issue concerns residual monofunctional expoxyPEO species containing a hydroxyl group. Because chain transfer processes are very likely to occur, these positions will also serve as initiation points. Hence, even without complete epoxidation in the first step, reproducible products are expected to be the norm rather than the exception. Thus, in all cases the resulting hydrogels offer good-to-excellent swelling behavior, as discussed below.

Gelation was expected for all experiments with initiator concentrations less than or equal to stoichiometric amounts given that most alkali-metal alkoxides form aggregate species that do not offer 100% activity.[8,19] To optimize ROP in terms of product properties, we again conducted studies on the effects of variations in conditions, reaction rates and product properties. These efforts begin with *t*-BuOK concentration studies. All reactions were run in THF at 70 °C to ensure that *t*-BuOK dissolved fully.

***t*-BuOK Initiator Studies.** Model studies were run using a set of standard conditions (see Experimental Section). For analytical purposes, 3.0 g of diepoxyPEO*xx* (synthesized from NaH) was dissolved in varying amounts of THF providing samples for concentration studies. The reaction mixtures were heated immediately to 70 °C in a thermostated oil bath. After complete dissolution; 0.1, 0.25, 0.5, 0.75, or 1.0 equiv of *t*-BuOK was added. Note that the total number of epoxide rings per mass of chain is much smaller for diepoxyPEO_{3400} and diepoxyPEO_{8000}; hence, lower mass amounts of *t*-BuOK were added accordingly. It is important to note that when the total equivalents of *t*-BuOK become sufficiently small, trace amounts of impurities (e.g., proton sources) can compete for formation of active initiator materials. Hence the data in some instances are likely affected by trace impurities. Extensive efforts were made to minimize adventitious hydroxyl sources,

but the monofunctional epoxyPEOs become initiators themselves by chain transfer processes. Rates of polymerization from the diepoxyPEO$_{3400}$ experiments were followed by GPC, but these results only reflected the soluble portion of the materials in solution, which was very small. Consequently, how they reflect on the actual polymerization process cannot be clearly delineated.

The end results of multiple ROP experiments were to identify optimal ROP conditions that provide hydrogels with exceptional degrees of swelling (20−30 times initial mass). Representative data for *t*-BuOK studies with diepoxyPEO$_{3400}$ and diepoxyPEO$_{8000}$ polymerized with *t*-BuOK at 70 °C are provided in the Supporting Information.

It was found that solutions to which were added 0.1, 0.25, and 1.0 equiv of initiator did not gel completely even after 5 d despite further addition of 0.25 equiv of *t*-BuOK. However, in the case where 0.5 equiv was added, the reaction gave macroscopic gels but the reaction was slow. In contrast, the 0.75 equiv reaction was too fast and gave brown products. However, if an additional 0.25 equiv of initiator is added to the 0.5 equiv reactions after 5 h, ROP proceeds to form colorless macroscopic gels after 7 d.

Above, it was noted that KH tended to give a high degree of coloration particularly with the PEO$_{400}$ system. Colored product was also obtained when 0.75 equiv of *t*-BuOK was added to promote initiation. Colored products also result simply on heating the various PEOs with these bases. Perhaps, at high base concentrations, some form of deprotonation (e.g., of C−H bonds adjacent to C−O linkages) and disproportionation occurs, leading to coloration. That this can be avoided by slow addition of initiator is the most important observation here.

The general reaction conditions examined in an effort to optimize the properties of the PEO gels prepared with *t*-BuOK in THF are presented in the Supporting Information (Supplemental Tables 3−6). Note that most of the reactions were run to 7 d, even though gelation appeared complete at times of 3 days or less, because this time was used as a standard.

Following these initial studies, we scaled the most promising reaction conditions to produce 50 g batches of those PEO gels exhibiting degrees of swelling of 20−30×. As in the model studies, a second addition of initiator provided materials with improved gel properties compared with single addition products in terms of swellability and color.

The as-synthesized gels were washed thoroughly with water by swelling and replacement of the water several times followed by extensive vacuum-drying at 60 °C. The yields were typically greater than 95%. Multiple swelling experiments (Supporting Information) indicated that the PEO$_{8000}$ samples absorbed an average of 30 times their mass on immersion in water. In contrast, the PEO$_{3400}$ samples swelled to an average of 20 times their mass under similar conditions.

Characterization Studies

In this section, we develop general methods of characterization that are used as standards for forthcoming papers. Thus, in addition to the characterization of gels by swelling experiments as presented above, their physical properties were assessed using DSC, TGA, and X-ray diffraction. The results of these studies are discussed below.

Table 1. Thermal Properties of PEOs, DiepoxyPEOs, and PEO Gels (DSC in N_2/1 °C/min)

		PEG		diepoxyPEO		PEO gel	
sample properties		3400	8000	3400	8000	3400	8000
2nd scan	T_m (°C)	58	62	58	61	52	56
	ΔH_m (J/g)	182	155	144	149	65	74
	T_{cc} (°C)	40	46	40	47	39	43
	ΔH_{fc} (J/g)	156	142	133	145	61	68

The thermal behavior of the PEOs, diepoxyPEOs, and PEO gels was measured by heating at 1 °C/min/N_2. Two continuous heating−cooling scans were run to ensure reproducibility. As expected from the literature, except for the very low MW materials, the PEO properties were not greatly affected by molecular weight distribution.

Data were obtained for the starting materials (PEG$_{400}$, PEG$_{3400}$, PEG$_{8000}$), the diepoxyPEOs, and PEO gels in the range 25−100 °C. The melting transitions and enthalpies and the crystallinity were evaluated by comparing the enthalpy of melting with that of single PEO crystal (8.65 kJ/mol).[4] We also measured cooling crystallization to examine the effects of thermal history on the PEO gels. DSC data are presented in Supplemental Figures 1−3 in the Supporting Information

The DSC peaks for PEO$_{3400}$ and PEO$_{8000}$ in the first heating cycle exhibit melting endotherms at 55−60 °C. In the subsequent cooling cycle they exhibited crystallization exotherms at 40−45 °C. In the second cycle, an additional endotherm is seen at 50 °C in the PEO$_{3400}$ and at about 55 °C in the PEO$_{8000}$. The key observations are that these materials were highly crystalline and recrystallize easily from the melt. The double peak seen for PEO$_{3400}$ has been suggested to be a consequence of chain-folded lamellae.[20]

The DSC curves of the diepoxyPEOs show essentially the same melting endotherms and recrystallization exotherms as the starting PEOs, suggesting that endcapping has no particular effect on their properties. The ROP gels of these diepoxyPEOs following water washing and vacuum-drying also display melting endotherms and recrystallization exotherms in the same temperature range as that found for the starting PEOs, albeit smaller and broader.

Details of the thermal properties extracted from the DSC curves are given in Table 1. T_ms for PEO$_{3400}$ and PEO$_{8000}$ were 58 and 62 °C, respectively. The T_m of PEO$_{8000}$ was a little higher than that of PEO$_{3400}$. However, the ΔH_m and ΔH_c values are quite different as discussed in the section on polymer morphology at the end.

Typically, T_m and T_g (not measured) are affected by MW and size distribution, which likely translates to the density of chain ends or here the cross-link density.[20] One might expect PEO$_{3400}$ and PEO$_{8000}$ to have different crystallinities and crystallite sizes. Cold crystallization temperatures (T_{cc}) and cold crystallization (ΔH_{fc}) of PEO$_{3400}$ and PEO$_{8000}$ were about 40 and 46 °C and 155 and 140 J/g for the second scan, respectively. T_{cc} and ΔH_{fc} for the diepoxys also showed similar trends. The T_m of the diepoxyPEOs changes very little, but H_f decreases from that of the starting PEOs. *However, the T_ms and ΔH_ms of the PEO gels decrease significantly*. This means that cross-linking between the epoxide rings affects the crystallization process and is likely important in their interaction with solvents. Note that the T_ms recorded in Supplemental Figure 3 (Supporting Information) and in Table 1 for the hydrogels most likely

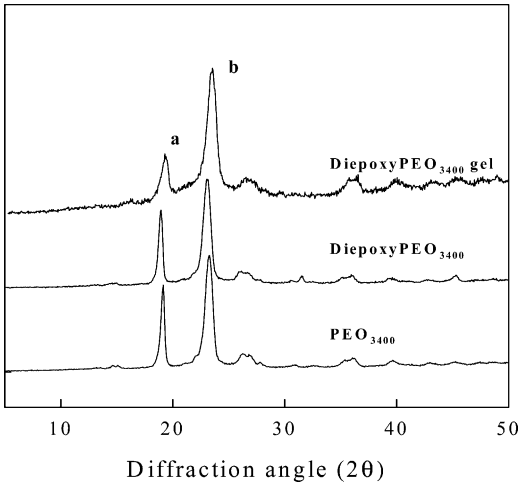


Figure 1. XRD patterns for the PEO_{3400}, diepoxyPEO_{3400}, and diepoxyPEO_{3400} gel.

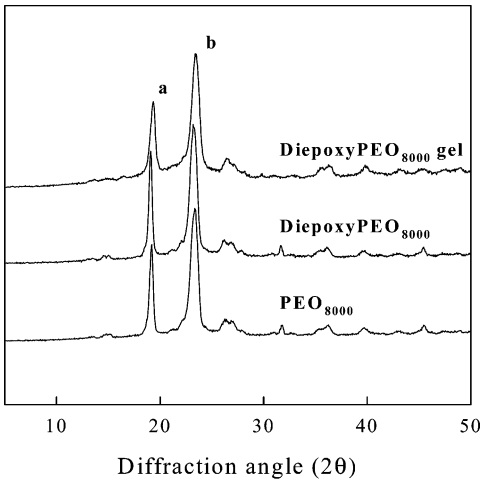


Figure 2. XRD patterns for the PEO_{8000}, diepoxyPEO_{8000}, and diepoxyPEO_{8000} gel.

correspond to chain segmental motion in the highly cross-linked network.

Supplemental Figures 4 and 5 in the Supporting Information provide the TGA curves for PEO, diepoxy-PEO, and PEO gels in N_2. As expected from the DSC results, all of the samples exhibited the same decomposition temperature onset at about 350 °C and similar trends in mass loss.

Figures 1 and 2 show the XRD patterns of the solid PEOs, diepoxyPEOs, and PEO gels. All of the materials have very similar powder patterns. However the PEO gels exhibit somewhat lower crystallinity, most likely because of the cross-links. Coincidentally, there appears to be an amorphous component underlying the peaks in the powder pattern. Thus, the data suggest that at least some of the gel material is amorphous or sufficiently disordered as to limit the long-range periodicity needed to provide narrow and strong X-ray powder peaks. Supplemental Table 6 in the Supporting Information records the 2θ values, d spacing, and fwhm for two main peaks in the range of 17−25° in 2θ.

Taken as a whole, these data represent a detailed characterization of these model gel systems which serve as the basis for efforts to make materials using "innocuous" initiators such as glycolic acid, as will be described at a later date.

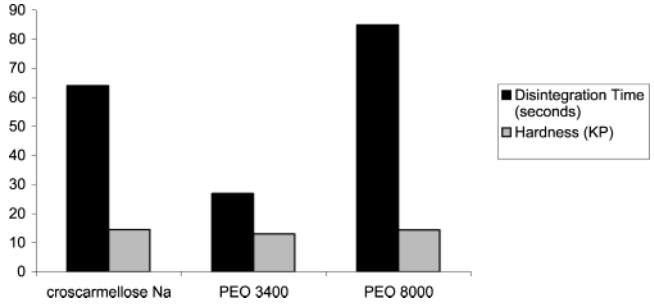


Figure 3. Disintegration time and hardness for lactose tablets (n = 3) made with croscarmellose sodium and PEO3400 and PEO8000 gels.

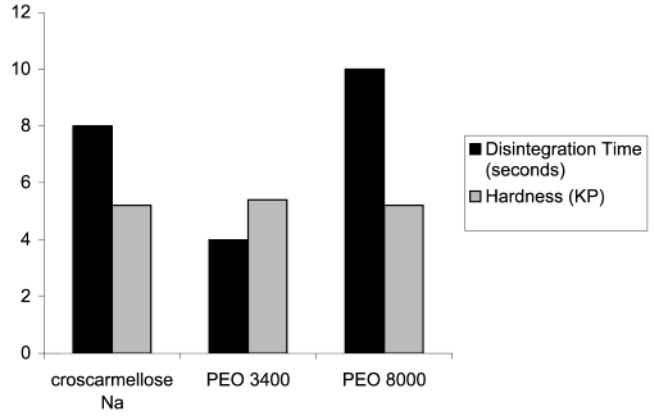


Figure 4. Disintegration time and hardness for dicalcium phosphate tablets (n = 3) made with croscarmellose sodium and PEO3400 and PEO8000 gel.

Disintegrations in Model Systems. Dosage form disintegration time is used in the pharmaceutical industry to evaluate the speed of drug dispersion, which enables its active ingredient to become available for absorption. Disintegrants are used to facilitate this dispersion and their mechanism of action is primarily due to wicking and swelling.[22] PEO_{3400} and PEO_{8000} gels are promising new disintegrants based on their swelling behavior. Tablets made with these PEO gels and either water-soluble lactose or water-insoluble dicalcium phosphate were compared with tablets made with croscarmellose sodium, a standard pharmaceutical disintegrant. Compaction pressures of 10-20 MPa were used to obtain tablet hardnesses between 12 and 16 kp (1 kp = 1 kg of force, 9.81 N) for lactose tablets and 4−6 kp for dicalcium phosphate tablets. The results are listed in Table 2 and presented in Figures 3 and 4.

Lactose and dicalcium phosphate tablets made with PEO_{3400} gel showed disintegration times that were at least two times faster than those tablets made with croscarmellose sodium. Even though both PEO_{3400} and PEO_{8000} gels exhibited swelling of 20−30× after 24 h as shown in the swelling experiments, differences in their microstructure likely contribute to their varied disintegration behavior over a short period as in the disintegration test.

Given that we see that the PEO_{3400} gel shows lower melting and crystallization temperatures than PEO_{8000} gels, these results seem to support our contention that its packing is higher in energy than in the linear PEO precursors, leading to more rapid swelling, which alleviates this condition.

Polymer Morphology and Swelling Behavior. The above observed swelling behavior was not antici-

Table 2. Formulation and Disintegration of Lactose and Dicalcium Phosphate Tablets

formulation	pressure (psi)	hardness (KP)	disintegration time (s)
lactose (95%)	1500	14.5	61
croscarmellose sodium (5%)			62
			68
lactose (95%)	2000	13.1	26
PEO_{3400} gel (5%)			27
			27
lactose (95%)	1500	14.4	84
PEO_{8000} gel (5%)			85
			85
dicalcium phosphate (95%)	3000	5.2	8
croscarmellose sodium (5%)			8
			8
dicalcium phosphate (95%)	3000	5.4	4
PEO_{3400} gel (5%)			4
			4
dicalcium phosphate (95%)	2000	5.2	10
PEO_{8000} gel (5%)			10
			9

pated. However, based on the DSC and XRD data and work published recently, it is possible to offer some explanation of these results with the view toward using them to make still better materials.

Recent work by Mather et al.[20] and Wunder et al.[21] concern the synthesis of poly(ethylene oxide)s (PEOs) end-capped with silsesquioxanes. The work reported in these papers was directed toward understanding how massive end-caps affect segmental behavior. Some of the results appear relevant to the current work where one might assume that each cross-link point represents something akin to a massive end-cap.

Wunder et al. find that, for very short segments (e.g., $PEO_n \approx 12$ units), the presence of a silsesquioxane unit prevents or greatly retards crystallization and gives a T_m of 11 °C and $\Delta H_m = 68$ J/g. Mather et al. worked with a number of end-capped PEO materials including PEO_{1000}, PEO_{2000} PEO_{3400}, and PEO_{8000}. The PEO_{3400} and PEO_{8000} materials were crystalline and gave T_ms of 21 and 50 °C with $\Delta H_m \approx 40$ and 100 J/g, respectively. The shorter chain PEOs gave only amorphous products. The Mather et al. work reports T_cs of −13 and +16 °C for the PEO_{3400} and PEO_{8000} systems with $\Delta H_c = 95$ and 100 J/g.

For comparative purposes, in our hands, the T_ms of pure PEO_{3400} and PEO_{8000} were 58 and 62 °C and ΔH_ms = 180 and 155 J/g. T_cs were 40 and 46 °C with ΔH_c = 155 and 140 J/g. Thus, massive end-caps appear to inhibit crystallization and lower T_ms and T_cs. Likewise, they reduce ΔH_m and ΔH_c significantly.

Here, we see PEO_{3400} and PEO_{8000} gels with (second DSC cycle) T_ms of 52 and 58 °C and $\Delta H_m = 65$ and 74 J/g, respectively. We find T_cs of 39 and 30 °C for the PEO_{3400} and PEO_{8000} systems with $\Delta H_c = 61$ and 68 J/g. Thus, cross-links appear to lower the T_ms and T_cs somewhat while substantially lowering the ΔH_m and ΔH_cs. The XRD data for the gels do suggest an amorphous component but not to the point where it is clearly visible as the major phase.

Thus, we have not changed the periodicity of segment packing but we have changed the thermodynamics of melting and crystallization. The same is true in the Mather et al. system where it appears that the presence of massive silsesquioxane end-caps controls the nucleation and growth patterns in this system.[20] In the present systems, the ΔH_ms and ΔH_cs are generally lower than those observed in the Mather et al. systems.

These observations indicate that melting requires less energy and crystallization is less favorable meaning that the crystalline state is higher in energy in the gels than in the linear chains. Indeed, it appears that in the PEO_{3400} gels it is less favorable than in the PEO_{8000} gels. If this assumption is correct, then any process that drives volume changes (e.g., solvation) in the dry gels will be highly favored in the PEO_{3400} and PEO_{8000} gels, but most favored in the PEO_{3400} gels. This would then relate directly to the rate of solvation. One would predict, on this basis, that the PEO_{3400} gels will solvate faster and provide better disintegrants than linear PEOs. Although the PEO_{8000} gel swells to a greater degree than the PEO_{3400} gel, it appears that the rate of swelling is more important. At this point, it is premature to use the above interpretations to develop general methods of preparing highly packed, cross-linked systems that exhibit superior swelling.

Conclusions

One immediate conclusion is that the PEO_{3400} gels demonstrate the potential to be good disintegrants with properties superior to croscarmellose sodium. These results, if proved general, suggest a potential new mechanism for the design of hydrogels and superadsorbants[13] wherein cross-linking may create higher energy forms of the linear polymers. In turn, the higher energy form will solvate and swell more rapidly.

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Supporting Information Available: Tables of ^{1}H NMR data, conversion of dianionic PEO8000, degree of swelling of PEO_{3400} gels, degree of swelling of PEO_{8000} gels, synthesis conditions vs degree of swelling, and 2θ values, d spacings, and fwhm for gels and figures showing DSC plots and TGA curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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