Atom-economical, One-pot, Self-initiated Photopolymerization of Lactose Methacrylate for Biobased Hydrogels

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Abstract

An excess of lactose and lactose-rich milk permeate is produced by the dairy industry. The use of these waste products has been investigated for the preparation of sugar-based hydrogels. An environmentally friendly, atom-economical reaction conducted in water with minimal waste was successfully applied in the synthesis of lactose methacrylate. Lactose methacrylate was copolymerized with the methacrylic acid generated as a byproduct of the initial synthesis using photoinduced polymerization to yield hydrogels. The photopolymerization was facilitated by a low intensity UV-light (365 nm) without the need of exogenous photoinitiator. Hydrogels with varied water uptake, rheological, and mechanical properties could be prepared by the use of different methacrylic anhydride loadings in the synthesis of lactose methacrylate.

Keywords: lactose, dairy waste, milk permeate, hydrogel, gelation, methacrylic anhydride

Introduction

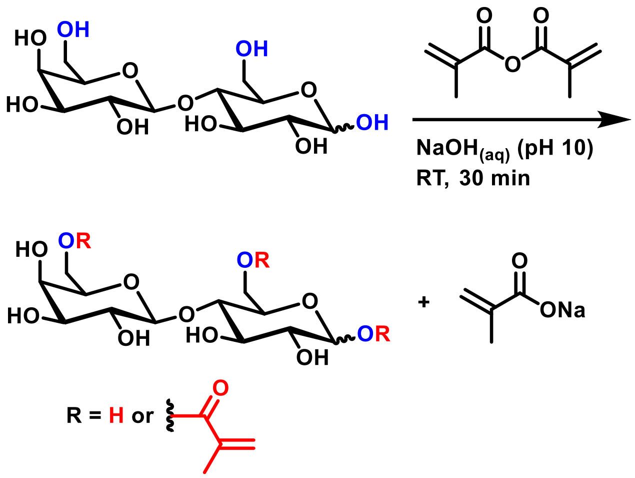
Lactose is a disaccharide composed of a galactose unit covalently bound to a glucose unit. Lactose can exist as α- or β-anomers depending on whether the configuration of anomeric hemiacetal carbon of the glucose unit is *trans*- or *cis*- with respect to the -CH_2OH group in the glucose ring, respectively. Lactose is attractive as a feedstock for the preparation of hydrophilic materials due to its rich hydroxy functionality imparting aqueous compatibility and enabling easy functionalization. The main source of lactose is from whey, a byproduct of dairy processing, which is composed of ~60% lactose on a solids basis with the remainder being largely made up of proteins and minerals. Approximately three billion kilograms on a solids basis of whey are produced annually in the United States. From this, only slightly more than half of the whey is further processed into useful commodities while the remainder is treated as waste.[1,2] This waste stream contains an abundance of lactose that could be exploited as a useful chemical feedstock. The potential to utilize this surplus of lactose provides clear motivation for new chemistry and methods for the development of functional materials. In this work, we aim to use lactose as a principal constituent in the synthesis of hydrogels.

Hydrogels are hydrophilic polymer networks that are swollen with water and are typically capable of absorbing water at loadings many times greater than their dry mass.[3] The network structures are commonly formed with covalent bonds between polymer chains but can also be constructed with physical crosslinks arising from chain entanglement, electrostatic interactions, and associations via strong hydrogen bonding or van der Waals interactions.[4,5] These materials have potential use for biomedical applications,[6,7] pharmaceuticals,[8] agriculture,[9] and personal hygiene products (e.g., diapers).[10] The incorporation of carbohydrates in the polymer structure is a viable strategy to introduce the hydrophilicity necessary for the preparation of hydrogels.[11] This has been demonstrated with a variety of mono- and disaccharides such as sucrose,[12,13,14] and trehalose,[15] in addition to various polysaccharides.[16,17,18,19] Lactose containing polymers have also been shown to function as hydrogels via polymer chemistries including incorporation into polyureas,[20] phenolics,[21] and free radical polymerization of styrenic[22,23,24,25] and acrylamide[26,27,28,29] derivatives. These previous works have successfully demonstrated the utility of lactose-containing polymers for preparing hydrogels, however they generally rely on multi-step synthesis of monomers often involving protecting group chemistry and organic solvents.

In this report we describe the implementation of green chemistry principles for the straightforward preparation of hydrogels composed of lactose containing polymers. This was achieved by the synthesis of lactose based methacrylic monomers and their subsequent copolymerization to yield hydrophilic crosslinked materials via an atom-economical, one-pot process in aqueous media. Photopolymerization was used to facilitate hydrogel formation which further contributes to the green chemistry aspect of this work as it enables synthesis at ambient temperature, is energy efficient, and can facilitate high polymerization rates.[30,31] In our approach, lactose was derivatized with methacrylic anhydride (MAH) to simultaneously install methacrylate groups (Scheme 1) for reactivity under free radical polymerization conditions and to introduce methacrylic acid (and/or the corresponding salt) as a comonomer. The resulting monomer mixture in aqueous solution was then directly utilized for subsequent photopolymerization into hydrogels. We demonstrate that the mechanical properties and water uptake of the resulting hydrogels could be easily tailored by simply varying the ratio of methacrylic anhydride to lactose. This enabled the preparation of hydrogels with equilibrium water contents (i.e., the mass of water in a swollen hydrogel sample divided by the mass of polymer multiplied by 100%, see Supporting Information Equation 3) ranging from 80% to 260% and compressive moduli between 12 kPa and 735 kPa.

Additionally, the water content could be increased up to 4000% upon lyophilization and rewetting. Finally, the robustness of this method for preparing lactose-based hydrogels was demonstrated by its successful implementation with the direct utilization of milk permeate (as received from a cheese processing plant) in place of reagent grade lactose.

Scheme 1. Synthesis of lactose methacrylate hydrogel precursor mixture.



Results and Discussion

Synthesis and Photopolymerization of Lactose Methacrylate Hydrogel Precursor Mixtures. Lactose was functionalized with methacrylate groups by esterification with methacrylic anhydride in aqueous solution under basic conditions (pH ≈ 10) maintained with the slow addition of aqueous sodium hydroxide (Scheme 1). The resulting aqueous solution of lactose methacrylates and sodium methacrylate generated as a byproduct of the esterification and as a result of hydrolysis was then neutralized to pH = 7 yielding a hydrogel precursor mixture. By ESI-MS we observed the presence of lactose mono-, di-, and trimethacrylate in the hydrogel precursor solution (Figure S2). Attempts to separate and quantify the various lactose methacylate species with chromatographic techniques

(HPLC-MS and HPAEC) were unfortunately unsuccessful. The use of ^{1}H NMR spectroscopy to quantify the extent of methacrylation and determine the relative distribution of lactose mono-, di-, and higher methacrylates was also challenging due to considerable overlapping resonances in the NMR spectrum, although it was possible to observe signals for the olefinic protons from methacrylate groups attached to lactose (Figure S3). Difficulty in direct determination of the lactose methacrylate composition was compounded by the possibility of esterification occurring at any of the eight free hydroxyls. However, functionalization of the hydroxyl at the anomeric position was assumed to be the most favorable under alkaline conditions due to the higher acidity (pKa = 12–14) relative to the other hydroxyls (pKa = 16–18).[32,33] While a complete and precise picture of the exact structures of the lactose methacrylates resulting from this process is still emerging, the resulting monomer mixture was successfully used to synthesize hydrogels.

A series of hydrogel precursor mixtures were prepared with various molar ratios of lactose and methacrylic anhydride to target compositions with increasing amounts of lactose di- and trimethacrylate which serve as crosslinkers during polymerization. This was of interest to investigate the properties of hydrogels with varying degrees of crosslinking. Three compositions with low, medium, and high methacrylic anhydride feeds were investigated corresponding to lactose:methacrylic anhydride molar ratios of 1:0.5, 1:1, and 1:2 respectively.

Photoinduced copolymerization of lactose methacrylate and sodium methacrylate was carried out by irradiating the as-prepared hydrogel precursor mixtures with UV light (365 nm, 3.8 mW/cm^2) (Figure 1). The methacrylic monomer mixture was self-initiating and that gelation could be achieved without the addition of an exogenous photoinitiator. UV-curing rheology was used to compare the formation of hydrogels upon UV irradiation in the presence (0.5 wt% of Irgacure 2959) and absence of added photoinitiator (Figure S5). The storage modulus (G') reflects the elastic response and the loss modulus (G’’) reflects the viscous response. Prior to gelation the viscoelastic response is dominated by G” and in the crosslinked state the response is dominated by G’. We define the crossover point of G” and G’ during crosslinking as the gel point or gel time. Our experiments were conducted with and without photoinitiator to explore any differences in the gel time. However, no significant difference was observed in the gel time as indicated by the crossover of storage (G’) and loss (G’’) moduli was and thus all photopolymerizations were conducted without added photoinitiator. The photoinduced self-initiating polymerization of (meth)acrylate derivatives is a known phenomenon and postulated to occur by excitation of the monomer species to a triplet state with subsequent hydrogen abstraction leading to initiating radical species.[34,35,36,37,38] Additionally, a control experiment was conducted to establish that UV light was necessary for polymerization at ambient temperature. This was done by monitoring the rheological behavior of the medium MAH precursor solution for 30 min without UV-light exposure (Figure S6). Over the entire 30 min G” was greater than G’ and both values were low and constant showing that the hydrogel precursor retained liquid-like behavior and no gel was formed.

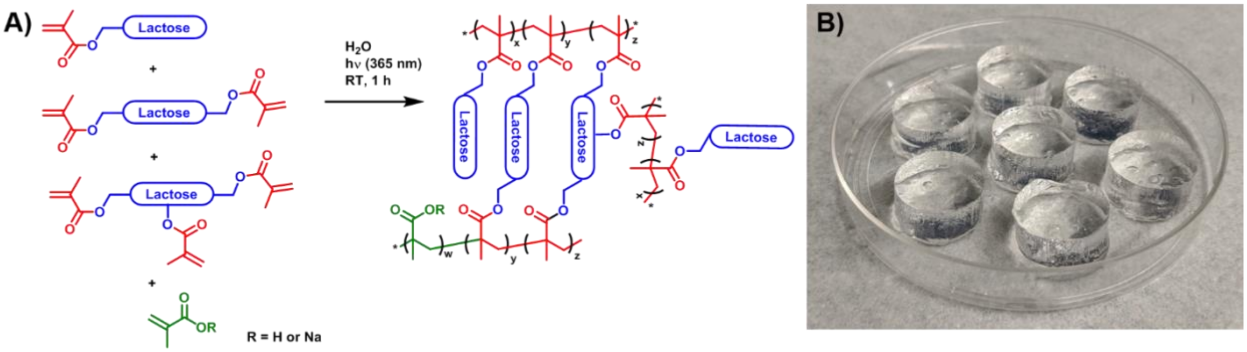


Figure 1. A) Scheme of the synthesis of lactose-based hydrogels by photoinduced copolymerization of lactose methacrylate and sodium methacrylate mediated by UV irradiation in

an aqueous environment. B) Photograph of representative hydrogels as prepared after photopolymerization.

Rheological characterization during UV Irradiation. UV-curing rheology was also used to characterize the formation of hydrogels from precursor mixtures prepared with different initial MAH loadings and to determine gelation times (Figure 2). Hydrogel precursor mixtures were irradiated with UV light (365 nm; 3.8 mW/cm^2) and the storage (G') and loss (G'') moduli were measured over the course of 60 min. Early in the course of UV irradiation the values of G' and G" were relatively low and G" > G' which is characteristic of liquid-like behavior and was expected as the samples were loaded as solutions. As the UV exposure time increases, the viscosity increases due to polymer formation and eventual gelation. For all the experiments, the UV-light was turned on after one minute (as indicated in Figure 2). The crossover between G' and G" during UV exposure indicates a transition from liquid-like behavior to solid gel-like behavior and allows for determination of gelation time (t_{gel}).[39] This transition is due to the formation of a network structure as monomer is converted into polymer. Gelation time of the low MAH precursor was ~12 min. Comparatively, the medium, and high MAH precursors were found to have shorter gelation times of about 6 min. This can be attributed to the medium and high MAH composition hydrogels precursor solutions containing a higher content of lactose di- and trimethacrylate. The higher content of multifunctional monomers leads to network formation at lower extents of monomer conversion and thus a faster onset of increases in G'.

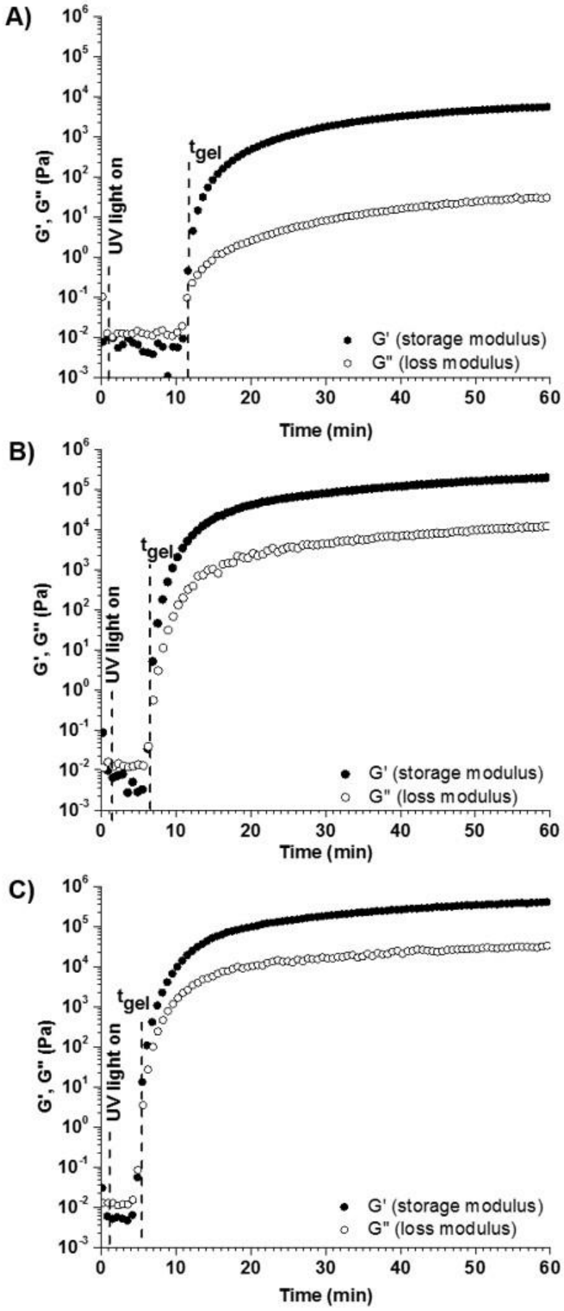


Figure 2. Storage modulus (G') and loss modulus (G") as function of UV (365 nm; 3.8 mW/cm2) exposure time at 0.1 Hz and 0.01% strain at 25 °C for hydrogel precursor mixtures with different MAH loading molar equivalents relative to lactose of A) 0.5, B) 1.0, and C) 2.0.

After the gelation point, a plateau region with higher G' relative to G'' was observed which is consistent with the formation of an elastic network with solid-like behavior.[40] After 60 min of UV treatment the low MAH composition hydrogel exhibited a plateau G' value of 5 kPa (Figure 2A). Increases in the initial MAH loadings of the hydrogel precursors resulted in relatively higher plateau G' values of 200 kPa for the medium MAH composition (Figure 2B) and 400 kPa for the high MAH composition (Figure 2C). The plateau modulus increases as the crosslink density increases and indicated that higher degrees of crosslinking are present in hydrogels prepared from the precursors with higher initial MAH loadings. This also further suggests higher lactose di- and trimethacrylate content in those mixtures.

Gel Fractions of Lactose Methacrylate Hydrogels. Gel-fractions were determined by first lyophilizing the as-prepared hydrogels and obtaining an initial dry mass. The dried samples were soaked in an excess of water which was replaced multiple times over ~66 h to ensure any soluble components were removed. The hydrogels were then lyophilized a second time and the percentage of the remaining mass relative to the initial dry mass was taken as the gel fraction. Hydrogels prepared with low initial MAH loading had an average gel fraction of 39 wt% compared to 47 wt% for medium MAH and 55 wt% for high MAH (Figure 3). These results corroborate the rheology data indicating that the relative degree of crosslinking is positively associated with initial MAH content of the precursor mixture. The sol fraction was composed of lactose and unpolymerized sodium methacrylate as determined by ^1H NMR spectroscopy (Figure S4).

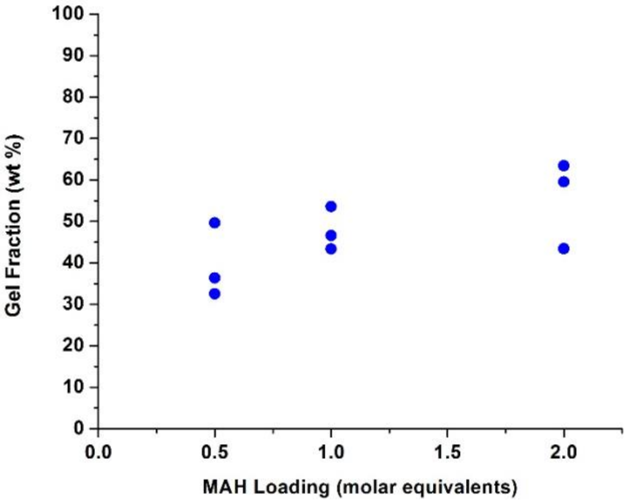


Figure 3. Plot of gel fraction versus molar equivalent of MAH relative to lactose in the hydrogel precursor solution. The analysis was performed in triplicate and all the data for each sample are shown.

Water Uptake. Hydrogels can swell with water to an equilibrium state while maintaining their shape. Immediately after photopolymerization, all of the hydrogels have an initial water content of ca. 65% regardless of initial MAH content as the same concentration of water was utilized for all precursor formulations (Figure S7). The hydrogels are capable of accommodating additional water inside their network structure upon addition of excess water. The hydrogels then reach an equilibrium water content dictated in part by the degree of crosslinking in the hydrogel. Water uptake kinetics were measured for each of the hydrogel compositions (Figure 4). The hydrogels were immersed in water immediately after photopolymerization for a determined time, at different time points the hydrogels were removed from the water, the excess of water on the surface of hydrogels was wiped off with paper towel and the swollen hydrogel was weighed again. The high MAH hydrogel reached an equilibrium water content in the shortest amount of time (~4 hours) and exhibited the lowest equilibrium water content of ~80 wt%. The medium MAH and low MAH hydrogels required a considerably longer time of 20 hours to reach equilibrium and exhibited equilibrium water contents of more than 220 wt%.

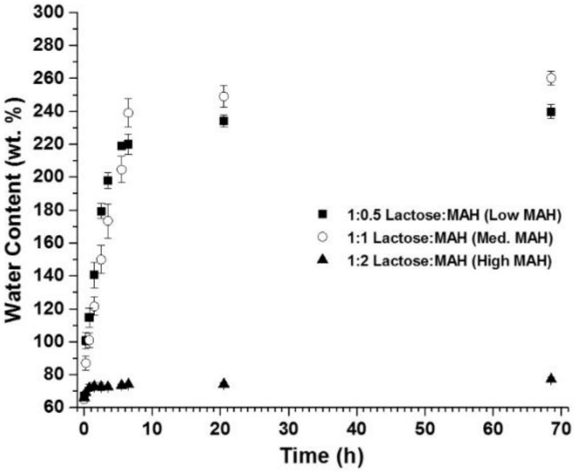


Figure 4. Water content kinetics curves of hydrogels prepared with various lactose:MAH loadings.

For some applications, it is desirable to handle hydrogels in the solid state as dry powder prior to swelling with water. In the powdered state obtained after lyophilization (freeze-drying), the lactose methacrylate-based hydrogels were capable achieving an equilibrium water content in less than 5 minutes. The low MAH composition exhibited a remarkable equilibrium water content of up to 4000 wt% when swelled from a dry powder (Figure 5). Lyophilization of hydrogels is known to impart a porous structure to the materials.[41,42] The freezing process induces phase separation between the polymer component and emerging ice crystals. The ice crystals then act as a template for pores that develop upon removal of the ice via sublimation.[43] The increase in equilibrium water content and faster water uptake kinetics of the powdered hydrogels could be attributed in part to the porous structure established during freeze-drying.[44] A porous structure inherently has a degree of unoccupied volume and this void volume within the hydrogel scaffold could accommodate additional water beyond the water content established by swelling of the polymer network alone. The more rapid establishment of equilibrium water content could be attributed to the incorporation of water into the porous structure via the added action of capillary forces. Furthermore, the considerable increase in surface area to volume with a particulate sample relative to the larger samples tested immediately following photopolymerization would contribute to an increased rate of water uptake.

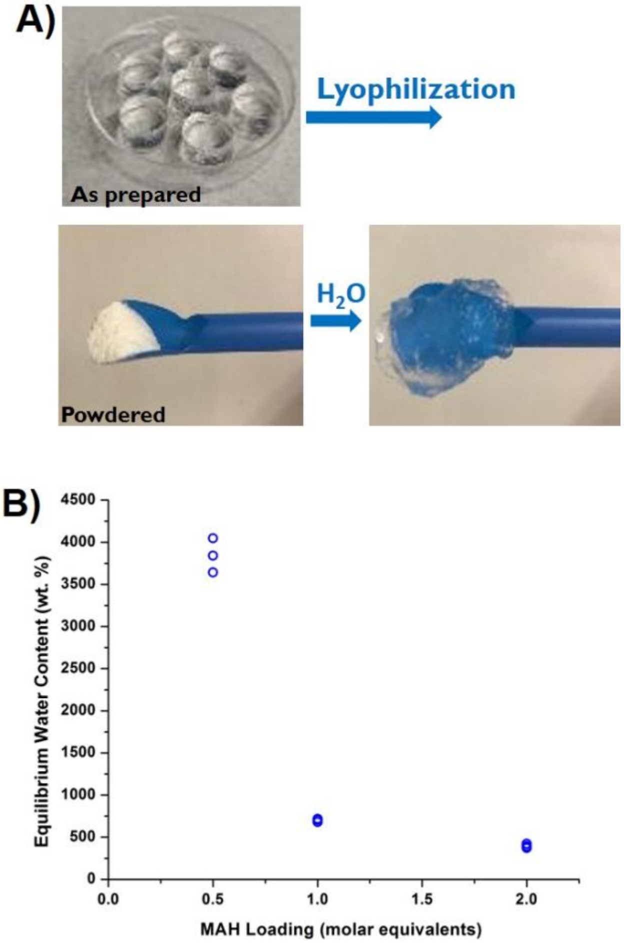


Figure 5. A) Photograph of representative hydrogels as prepared after photopolymerization, powdered hydrogel after lyophilization and swollen powder hydrogel. B) Equilibrium water

content of dry powdered hydrogels (i.e., after lyophilization) as a function of the lactose to MAH ratios of the hydrogel precursor mixture.

Compression testing of hydrogels. Unconfined compression testing was conducted to evaluate the mechanical properties of the lactose containing hydrogels from precursor mixtures with various initial MAH loadings (Figure 6). Cylindrical samples with a diameter of 2 cm and height of about 1 cm were uniaxially compressed at a send speed of 1 mm/min until failure. Testing was completed on hydrogels in their as-prepared state after photopolymerization of the precursor mixture, which all have a nominally equivalent water content of 65%. The compressive elastic modulus was determined from the slope of the stress-strain curve between 10% and 20% strain. Hydrogels prepared with low initial MAH loading (lactose:MAH = 1:0.5) were comparatively flexible and somewhat elastic with a modulus of about 12 ± 2 kPa and failure strain of 57 ± 3%. An increase in the initial MAH loading of the precursor mixture with lactose:MAH molar ratio of 1:1 led to a slightly more rigid hydrogel with a modulus of 29 ± 2 kPa and failure strain of 55 ± 4%. A further increase in initial MAH loading with a lactose:MAH molar ratio of 1:2 yielded hydrogels that were notably more rigid and brittle with a modulus of 730 ± 230 kPa and failure strain of 25 ± 1% The increase in elastic modulus and decrease in failure strain corresponding to higher initial MAH content can be attributed to a greater content of lactose di- and trimethacrylates in the hydrogel precursor mixture resulting in a higher crosslink density.[45]

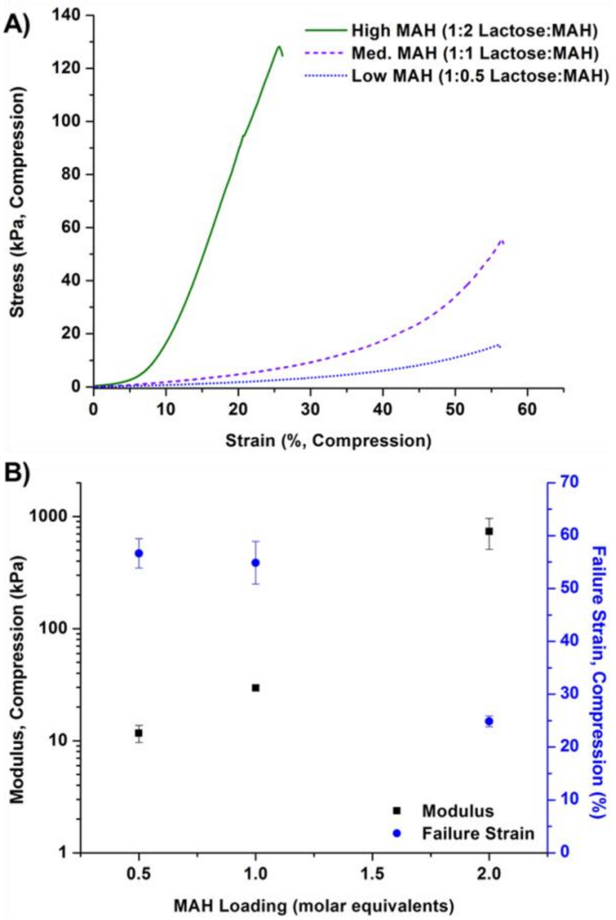


Figure 6. Uniaxial compression testing data of hydrogels synthesized from precursor mixtures prepared with various lactose:MAH loadings. A) Representative stress-strain curves and B) a plot of compressive elastic modulus and failure strain versus MAH loading in molar equivalents relative to lactose. The error bars represent standard deviation with n ≥ 5.

Direct use of Milk Permeate for the Synthesis of Hydrogels. To demonstrate the versatility of the hydrogel synthesis method, milk permeate from a cheese processing facility was used directly as the lactose source in place of purified lactose. Milk permeate is a complex mixture and required analysis by ^{1}H NMR spectroscopy to quantify the lactose content and identify the other metabolites it contains. To determine the percentage of lactose in the milk permeate a calibration curve of lactose (Figure S1) was constructed using different concentrations of lactose in D_2O (15, 30, 45, 60, 150, 250 and 450 mg/mL) and tetrachloroethane as an internal standard according to literature precedent.[46] The set of peaks for lactose in the range 4.05-3.25 ppm was integrated to determine the experimental concentration of lactose. It was determined that the milk permeate utilized was composed of 83% lactose (40% of α-anomer and 60% of β-anomer) and a variety of metabolites including carnitine, choline, creatinine, citrate and *N*-acetylcarbohydrates (Figure S8).[47]

To synthesize the hydrogel precursor solution based on milk permeate, the 1:0.5 Lactose:MAH molar ratio composition was chosen as comparison to the low MAH hydrogels prepared with commercial α-lactose. The use of milk permeate as the lactose source required more extensive heating (90 °C) to achieve adequate dissolution in water prior to treatment with methacrylic anhydride. This was attributed to the poorer solubility of the β-anomer of lactose.[48] The soluble part of milk permeate (0.5g/mL) at 90 °C contained 77% lactose as determined using the calibration curve from ^{1}H NMR quantification and this value was used to deliver the appropriate amount of methacrylic anhydride to achieve a molar ratio of lactose:MAH of 1:0.5. Additionally, even with the higher temperature dissolution step there was a minute amount of insoluble material that remained throughout the reaction. This intractable material was not found to adversely affect hydrogel formation, but it could be easily removed prior to photopolymerization via simple gravity filtration in order to improve the clarity of the final hydrogels if desired.

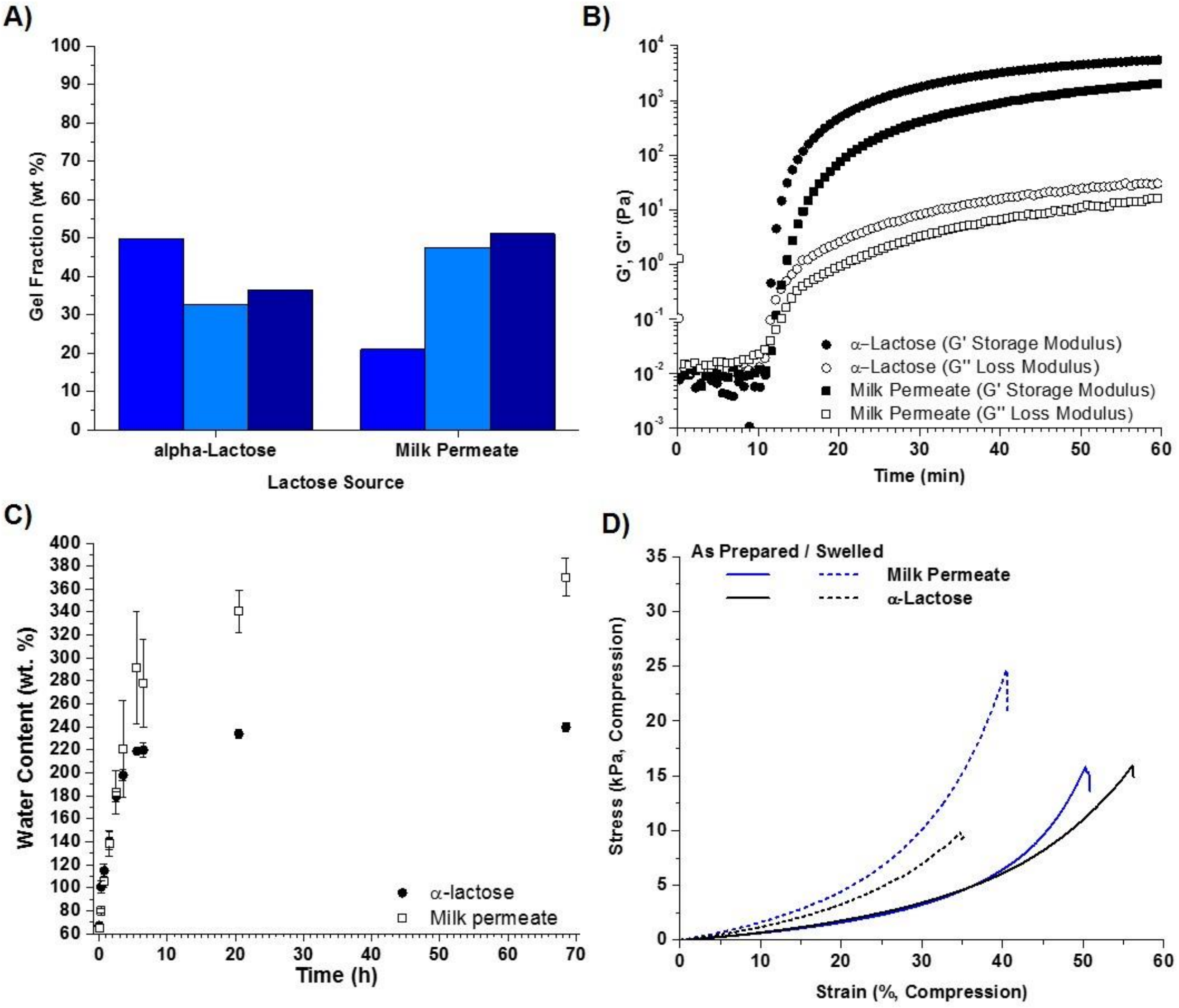


Figure 7. A) Gel fraction, B) UV-curing rheology, C) water content kinetics, and D) representative stress-strain compression testing data comparing hydrogels prepared using milk permeate or commercially available α-lactose.

The properties of hydrogels prepared with milk permeate were generally comparable to hydrogels prepared with commercial α-lactose. The gel fractions of the low MAH milk permeate based hydrogels were ca. 40% and similar to those prepared with α-lactose. Rheological experiments also showed similar behavior for the milk permeate derived hydrogels compared to those prepared with α-lactose in terms of gelation times which were approximately 12 min (Figure

7B). However, the plateau values for G' and G'' were slightly lower for the milk permeate hydrogels indicating a lower crosslinking extent in the hydrogel network (Figure 7B). This apparent difference in crosslinking density could be attributed to a lower content of multifunctional lactose monomers and the incorporation of more monofunctional methacrylate derivatives resulting from the possible reaction of methacrylic anhydride with the various metabolites present in milk permeate. Comparison of the water content corroborates this finding where the milk permeate based hydrogels reached a higher equilibrium water content (~370 wt%) compared to the α-lactose hydrogels (~240 wt%) after 66 h (Figure 7C). In the powdered state (after lyophilization), the equilibrium water content was up to ~4000 wt%. which is comparable to the hydrogels prepared with commercial α-lactose (Figures S9 and S10). Compression testing of the milk permeate hydrogels as-prepared (i.e., 65 wt% water) revealed a slightly lower compressive elastic modulus (9.4 ± 0.5 kPa) and failure strain (52 ± 2%) compared to the α-lactose hydrogels (12 ± 2 kPa, 57 ± 3%). Both hydrogels became more rigid and brittle upon swelling in water for 16 h where the milk permeate hydrogel exhibiting an elastic modulus of 27 ± 3 kPa with a failure strain of 41 ± 2% and the α-lactose hydrogel an elastic modulus of 21 ± 6 kPa with a failure strain of 32 ± 5% (Figures 7D and S11). Overall, these results demonstrated that hydrogels could be successfully prepared by directly utilizing milk permeate in place of commercial α-lactose to produce materials with comparable properties.

Conclusion

Hydrogels based on lactose methacrylate were successfully synthesized using photopolymerization without added photoinitiator in aqueous media according to sustainable/green chemistry principles. Hydrogel precursor mixtures were prepared with an atom economical process by treating lactose with various ratios of methacrylic anhydride to yield a comonomer mixture of lactose methacrylates and methacrylic acid. Rheological analysis showed that increasing the initial MAH loading resulted in the formation of networks with higher degrees of crosslinking. G’ plateau values ranging from 5 kPa to 400 KPa were observed and were attributed to the different content of lactose di- and trimethacrylate species, which act as crosslinkers, resulting from the initial methacrylic anhydride loading in the hydrogel precursor synthesis. The water uptake behavior of the hydrogels also varied with different loadings of methacrylic anhydride used in the precursor formulation. Hydrogels were prepared that had equilibrium water contents up to ~260 wt% in the as-prepared gel state and up to ~4,000 wt% in the powdered state after lyophilization. Mechanical testing showed that hydrogels could be prepared with compressive elastic moduli ranging from 12 kPa to 735 kPa and failure strains ranging from 57 % to 25 % depending on the methacrylic anhydride loading of the precursor mixture. Finally, we demonstrated the use of this hydrogel synthesis methodology with the direct utilization of milk permeate for *in-situ* hydrogel formation. The hydrogels based on milk permeate showed results comparable to hydrogels based prepared using commercial α-lactose.

Acknowledgements

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Supporting Information

Materials, Instrumentation and Methods, Equations, Experimental procedures, Calibration curve of milk permeate by plot of the $_{1}$H NMR integral value versus lactose concentration in D$_{2}$O, ESI-MS of hydrogel precursor mixture, $_{1}$H NMR spectroscopy of hydrogel precursor mixture in

D_2O, G' and G" as function of time in presence and absence of Irgacure 2959 as a photoinitiator for hydrogel precursor mixture, G' and G" as function of time without UV-light for hydrogel precursor mixture, Initial water content percentage of the hydrogels, ^1H NMR of milk permeate in D_2O, Water content kinetics curves of hydrogels as prepared and equilibrium water content of lyophilized hydrogels, Compression testing data, and Equilibrium water content for hydrogels using milk permeate.

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TOC graphic

Lactose methacrylate was synthesized in aqueous solution with minimal waste and photopolymerized to yield hydrogels through a one-pot reaction in the absence of photoinitiator.