Published in final edited form as:

J Nat Prod. 2017 July 28; 80(7): 1964–1971. doi:10.1021/acs.jnatprod.6b00951.

Curcumin Acrylation for Biological and Environmental Applications

Vinod S. Patil[†], Angela M. Gutierrez[†], Manjula Sunkara[‡], Andrew J. Morris[‡], J. Zach Hilt[†], Douglass S. Kalika[†], and Thomas D. Dziubla^{*,†}

[†]Department of Chemical and Materials Engineering, University of Kentucky, Lexington, Kentucky, 40506, United States

[‡]Division of Cardiovascular Medicine, Gill Heart Institute, University of Kentucky, Lexington, Kentucky, 40536, United States

Abstract

Curcumin has recently gained interest for use in drug delivery, chemical sensing, and environmental applications. As a result, the development of synthesis strategies for the incorporation of curcumin into novel materials has become a priority. One such strategy, curcumin acrylation, involves the introduction of acrylate functional groups to the curcumin scaffold, with the potential generation of mono-, di-, and triacrylate curcumin species. The relative populations of these species in the resulting multiacrylate mixture can be controlled by the ratio of curcumin to acryloyl chloride in the initial reaction formulation. Characterization of the acrylation reaction and the resulting curcumin multiacrylate (CMA) product is essential for the effective preparation of new curcumin-containing materials. In this work, a synthesis method for curcumin acrylation is presented and the resulting curcumin multiacrylate product is characterized via various techniques, i.e. HPLC, LCMS, and NMR, as a basis to establish the relationship between synthesis conditions and the extent of acrylation that is achieved.

Graphical abstract

*Corresponding Author: thomas.dziubla@uky.edu.

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI:

Notes

The authors declare no competing financial interest.

Curcumin is the main constituent of the Indian spice turmeric and has been shown to possess anti-oxidant, anti-inflammatory and anti-angiogenic properties.¹⁻³ The major challenge with the use of curcumin as an experimental or therapeutic agent is its limited aqueous solubility and photoinstability.⁴ Multiple strategies have been proposed to overcome these limitations including conjugation, polymerization, amorphous dispersion, and encapsulation.⁵⁻⁸ Many of these approaches can be facilitated through the acrylation of curcumin. Curcumin acrylation was first explored by Wattamwar and coworkers for the preparation of hydrolytically degradable poly(curcumin β amino ester) hydrogels for use in drug delivery applications.⁹ These materials improve the stability of curcumin for controlled release and also increase its bioavailability through enhanced solubility. Curcumin acrylation has since been used to make antibacterial nanofibers, chemical sensing materials, and as a drug carrier in the form of curcumin microspheres.¹⁰⁻¹² Curcumin has also been explored recently for its radical scavenging potential and its capacity to inhibit toxicity of dioxin and dioxin-like molecules such as polychlorinated biphenyl (PCB) and for its potential use in environmental remediation.¹³⁻¹⁵ The acrylation approach has similarly been used for other phenolic molecules such as apigenin and quercetin;¹⁶⁻¹⁸ the identification methods discussed in this paper can be extended for these molecules and other phenols, such as myricetin and catechin.^{19, 20}

Curcumin contains three hydroxy groups available for modification, and curcumin acrylation can lead to the formation of mono-, di- and triacrylates. The relative proportion of these species in the resulting curcumin multiacrylate (CMA) mixture can influence the subsequent synthesis of curcumin-containing materials, with the potential for endcapping and branching in the context of polymerization reactions.²¹ However, a full characterization and identification of the individual acrylate species produced by the acrylation procedure described by Wattamwar and coworkers has not yet been reported. In this paper, we present the identification of curcumin acrylate species that result from the synthesis protocol of Wattamwar, and consider the influence of reaction stoichiometry on the relative populations of the various acrylate species and the overall extent of acrylation that is achieved.

RESULTS AND DISCUSSION

Curcumin is known to display keto-enol tautomerism across the central heptyl moiety.²² In commonly used organic solvents such as DMSO, acetone, CHCl_3 , and MeCN, the enol tautomer predominates.^{23, 24} During the acrylation of curcumin, hydroxy groups are functionalized with acrylate groups: based on the number of hydroxy groups replaced, different mono-, di-, and triacrylates are possible (Figure 1). To study curcumin acrylation in detail, different grades of curcumin multiacrylate (CMA) were prepared through a systematic variation of the curcumin:acryloyl chloride ratio. The synthesized grades of CMA were characterized with HPLC, LCMS, and NMR methods. The LCMS and NMR data were used to determine the extent of acrylation, and LCMS was used to identify the mono-, di- and triacrylate- species of curcumin.

High Performance Liquid Chromatography (HPLC)

In Figure 2, the HPLC chromatograms for curcumin, CMA 1:1, CMA 1:2 and CMA 1:3 are shown. A group of peaks was present from 8 to 9.5 minutes, which correspond to the tautomers of curcumin. The intensity of this set of peaks decreased as the amount of acryloyl chloride in the initial reaction mixture was increased, demonstrating an increase in the extent of curcumin conversion to curcumin acrylates. Also, additional peaks around 14 minutes and 19 minutes emerge for CMA 1:1, 1:2 and 1:3, along with peaks at 14.8, 15.8, and 17.3 minutes for CMA 1:3, which could potentially be different acrylates of curcumin. Based on an increase in the inherent hydrophobicity of the acrylated curcumin, the peaks evident at 14 and 19 minutes in Figure 2 were anticipated to be mono- and diacrylates of curcumin, respectively. As the curcumin:acryloyl chloride ratio was increased to 1:2, the relative proportion of monoacrylate decreased and that of diacrylate increased. This trend continued for CMA 1:3, where the proportion of monoacrylate relative to diacrylate was even lower. The emergence of peaks between 14 and 19 minutes (i.e. peaks at 14.8, 15.8 & 17.3 minutes) for CMA 1:3, which could potentially be triacrylate peaks, was unexpected. Since the triacrylate form is presumably more hydrophobic than the diacrylate, the triacrylate species would be expected to elute after the diacrylate form. To explore the elution sequence in detail and to establish the molecular weight corresponding to each peak, LCMS analysis was completed for all CMA formulations.

The absorbance spectrum for each HPLC elution peak was recorded using a photo-diode array (PDA) detector connected with the HPLC instrument. The absorbance spectrum for each peak present in the CMA 1:3 HPLC chromatogram is shown in Figure 3; the absorbance spectra for CMA 1:1 and CMA 1:2 are provided in the Supporting Information. A blue shift in peak wavelengths is seen for the different acrylated forms of curcumin as compared to unmodified curcumin, which has an absorbance maximum at 420 nm. The peak wavelengths for the different curcumin acrylate species are listed in Table 1. The UV-vis absorbance peaks shift to lower wavelengths due to acrylation, with the curcumin peak maximum at approximately 420 nm, monoacrylates at 410 nm, diacrylates around 400 nm, and triacrylates at 370 nm.

Liquid Chromatography-Mass Spectrometry (LCMS)

The LCMS data for curcumin and CMA with curcumin:acryloyl chloride formulation ratios of 1:1 and 1:2 are presented in Figures 4, 5, and 6. The elution times for all elution peaks in LCMS are approximately 2 minutes higher than those obtained from HPLC; this is due to a lower column temperature (35°C) used for LCMS as compared to HPLC (40°C), which does not affect the nature or sequence of the elution peaks. The LCMS data for curcumin (Figure 4) identify three forms of curcumin: bisdemethoxycurcumin, demethoxycurcumin, and curcumin. These forms are present in the molar amounts 3.5, 25.4, and 71.1%, respectively, which are similar to the proportions obtained from the HPLC absorbance peak areas (3.9, 23.0, and 73.1%, respectively). The comparable values obtained from LCMS and HPLC absorbance show that the molar extinction coefficients are similar for the three forms of curcumin.

The LCMS data for CMA 1:1 are presented in Figure 5 (MS data, Figure A5, Supporting Information). A cluster of four peaks around 16.5 minutes was found to be a group of monoacrylate peaks, corresponding to bisdemethoxycurcumin monoacrylate, demethoxycurcumin monoacrylate, curcumin monoacrylate, followed by an additional demethoxycurcumin monoacrylate peak. As seen in Figure 6 (MS data, Figure A6, Supporting Information), these monoacrylate peaks are present in CMA 1:2 as well, but in a lower proportion. A group of three diacrylate peaks are present at 22.5 minutes for both CMA 1:1 and CMA 1:2, representing curcumin diacrylate, demethoxycurcumin diacrylate, and bisdemethoxycurcumin diacrylate, respectively. For CMA 1:2, the proportion of diacrylate peaks is relatively higher than in CMA 1:1. The LCMS data for CMA 1:3 are shown in Figure 7 (MS data, Figure A7, Supporting Information). For CMA 1:3, a curcumin monoacrylate peak and a set of diacrylate peaks are present. Along with these peaks, three additional peaks were present at 17.8, 18.9, and 20.5 minutes. These peaks had a molecular weight of 531, which corresponds to curcumin triacrylate. Based on the peak area analysis, the extent of acrylation (number of acrylate groups per molecule) was calculated to be 1.34, 1.84, and 2.56 for CMA 1:1, 1:2, and 1:3, respectively.

The various elution peaks observed in the HPLC data in Figure 2 were identified using LCMS (Figures 5, 6, and 7). The CMA 1:1 sample had unreacted curcumin, along with mono- and diacrylates of the three forms of curcumin. The CMA 1:2 sample had the same constituent species as CMA 1:1, but with a higher amount of diacrylate species and a lower amount of unreacted curcumin. The mono- and diacrylate peak elution sequence was found to be based on the hydrophobicity of the respective molecules. Additionally, it was observed that demethoxycurcumin monoacrylate had two peaks in the elution profile. This was due to two possible forms of monoacrylation of demethoxycurcumin, viz., acrylation of the phenolic group with $R_1 = OCH_3$, or acrylation of the phenolic group with $R_2 = H$. Curcumin multiacrylate 1:3 showed complete conversion of curcumin, forming a mixture of curcumin tri- and diacrylate species along with a trace amount of curcumin monoacrylate species. The relative proportions of the various acrylates for different curcumin:acryloyl chloride ratios are shown in Table 2.

It was seen from both the HPLC and LCMS analysis of CMA 1:3 that the curcumin triacrylates elute before the diacrylate species. This result was not anticipated, given the higher hydrophobicity of curcumin triacrylate. The observed elution order most likely reflects additional factors that govern the elution of the triacrylates such as electrical charge on the molecule due to ion pairing, or molecular shape. Acrylation at the heptyl moiety can potentially give the triacrylate molecule a more kinked geometry as compared to the overall linear character of the diacrylate molecule, and this kinked conformation can contribute to a lower adsorption tendency on the chromatography column leading to earlier elution of the triacrylates.^{25, 26}

An additional phenomenon observed with curcumin triacrylate elution is the appearance of three distinct elution peaks as seen from LCMS (Figure 7). This could reflect different conformers isomers of curcumin triacrylate, which have varying adsorption tendencies and hence elute at different times. To explore this further, each of the triacrylate peak elutions for the CMA 1:3 sample were collected separately and reinjected into the HPLC. The HPLC

analysis for isolated curcumin triacrylate (CTA) peak 1, isolated CTA peak 2 and isolated CTA peak 3 are shown in Figure 8. Each of these isolated samples redistributes across the original CTA peak positions observed for CMA 1:3. For the peak collection from HPLC, an extended method file was used, which provided approximately 3 minutes of peak time separation. A sample collection window of 25 seconds was used to collect samples. Based on these data, there is ample evidence to indicate that these species are redistributing across triacrylate peak positions, which would imply that they correspond to three different conformers of CTA formed by the rotation of acrylate groups. This is a commonly observed phenomenon in non-planar molecules that experience hindrance in the free rotation around the sigma bond due to the presence of neighboring groups.^{27, 28} To explore if the three CTA peaks represent species that are in equilibrium with each other, or if they interconvert over time to reach equilibrium, the influence of holding time on peak positions was studied. As seen in Supporting Information, Figures A3 and A4, the peak positions and relative areas did not change even after 5 hours, suggesting that conformations are stable and do not convert over time. This implies that the conformational kinetics are fast enough to obtain equilibrium within 30 minutes.

¹H NMR Studies

The degree of acrylation of curcumin was further characterized by NMR spectroscopy. The ¹H NMR data for all samples are shown in Figure 9. The phenolic proton peaks (9.5 to 10.5 ppm) decrease with increasing acryloyl chloride ratio, reflecting an increase in the extent of curcumin to curcumin acrylate conversion. The smaller resonance at 10.1 ppm corresponds to the enolic hydroxy proton while the 9.7 ppm resonance corresponds to the phenolic protons. Also, acrylate proton signals (6 to 6.6 ppm) emerge, confirming the presence of acrylate groups on the curcumin molecule. Based on NMR data, the extent of acrylation (number of acrylate groups per molecule) was calculated to be 1.03, 1.73, and 2.82 for 1:1, 1:2, and 1:3 CMA, respectively. A comparison of the extent of acrylation for the different formulation ratios using LCMS and NMR is reported in Figure 10.

¹H NMR data (400 MHz, DMSO-*d*₆) for curcumin: δ 10.04 (1H, s), 9.66 (2H, s), 7.57 (2H, s), 7.52 (2H, s), 7.32 (2H, s), 7.16 (2H, d), 6.82 (2H, d), 6.74 (2H, q), 6.06 (1H, s), 3.84 (6H, s)

¹H NMR data (400 MHz, DMSO-*d*₆) for CMA1:1: δ 10.04 (1H, d), 9.66 (2H, d), 7.57 (2H, m), 7.52 (2H, m), 7.32 (2H, m), 7.16 (2H, m), 6.82 (2H, m), 6.74 (2H, m), 6.53 (1H, m), 6.42(2H, m), 6.06 (1H, s), 3.84 (6H, s)

¹H NMR data (400 MHz, DMSO-*d*₆) for CMA1:2: δ 10.04 (1H, d), 9.66 (2H, d), 7.57 (2H, m), 7.52 (2H, m), 7.32 (2H, m), 7.16 (2H, m), 6.82 (2H, m), 6.74 (2H, m), 6.53 (1H, m), 6.42(2H, m), 3.84 (6H, s)

¹H NMR data (400 MHz, DMSO-*d*₆) for CMA1:3: δ 7.57 (2H, m), 7.52 (2H, m), 7.32 (2H, m), 7.16 (2H, m), 6.82 (2H, m), 6.74 (2H, m), 6.53 (1H, m), 6.42(2H, m), 3.84 (6H, s)

Thermogravimetric Analysis (TGA)

The thermal stability of monomers is an important parameter when developing polymers for different applications, where the monomer might be exposed to elevated temperatures during polymer synthesis or other processing steps. TGA was performed on curcumin and CMA to explore the thermal stability of these sample (Figure 11). Volatiles are evaporated initially from all samples as indicated by the ~ 4% weight loss prior to samples reaching 250 °C. The curcumin decomposition begins at the lowest temperature, suggesting the greatest degree of thermal instability amongst the samples. Interestingly, decomposition begins around 350 °C for CMA 1:2 and CMA 1:3, while for CMA 1:1, decomposition starts around 250 °C. For CMA 1:1, the decomposition curve was broader as compared to CMA 1:2 and CMA 1:3. The earlier onset and broader decomposition were due to the higher amount of residual (i.e., unmodified) curcumin present in the CMA 1:1 sample. The amount of carbon residue (~ 40%) at the end of TGA analysis was consistent with estimates obtained by considering the full pyrolysis of curcumin and CMA.

In this work, a synthesis method for curcumin acrylation was developed and the resulting curcumin multiacrylate product was characterized using HPLC, LCMS and NMR data. Control over the extent of acrylation was demonstrated, and it was confirmed that the degree of acrylation correlates with the curcumin:acryloyl chloride ratio in the formulation mixture. All acrylate species present in the CMA samples were identified using LCMS data, and the extent of acrylation was determined using both LCMS and NMR data. The extent of acrylation was found to be 1.34 and 1.03 for CMA 1:1, 1.84 and 1.73 for CMA 1:2, and 2.56 and 2.82 for CMA 1:3 using LCMS and NMR data, respectively. Overall, an increase in acrylation led to an increase in thermal stability of the parent compound. The full characterization of these multiacrylate products is essential for their use in the design and synthesis of future curcumin-based materials for biological and environmental applications.

EXPERIMENTAL SECTION

General Experimental Procedures

Curcumin was purchased from Chem-Impex International, Inc. (Wood Dale, IL). Triethyl amine (TEA) and acryloyl chloride were purchased from Sigma-Aldrich (St. Louis, MO). The solvents THF, CH₂Cl₂, and CH₃CN were obtained from Pharmco-Aaper, (Shelbyville, KY). Molecular sieves (3Å) were added to the solvents to remove any moisture present and to maintain the anhydrous state of the solvents.

¹H NMR spectra were acquired using a Varian UNITY INOVA 400 MHz instrument equipped with a 5 mm quadrupole-nucleus probe and data was processed using MestReNova software. The sample was dissolved in 750 µL of DMSO-*d*₆. DMSO-*d*₆ was used for NMR analysis of all compounds. The chemical shifts are reported in ppm relative to TMS.

The synthesized CMA was characterized using reverse-phase HPLC (Waters Phenomenex C₁₈ column, 5 µm, 250 mm (length) × 4.6 mm (I.D.) on a Shimadzu Prominence LC-20 AB HPLC system). Samples were prepared with a final concentration of 50 µg/mL in CH₃CN. A gradient from 50/50 CH₃CN/water to 100/0 CH₃CN/H₂O over 30 minutes at 1 mL/min was

used with the column chamber set at 40°C. The injection volume used for all sample analysis was 50 µL. The absorbance was measured from 220 nm to 500 nm.

LCMS experiments were performed using a Shimadzu HPLC equipped with a ZORBAX Eclipse XDB-C₁₈ column, coupled with an ABSciex 5600 “Triple TOF” hybrid quadrupole time of flight mass spectrometer. For LCMS, the same gradient elution method was used as for HPLC, with the flow rate of 0.5 mL/min and the column chamber temperature set at 35°C. A UV-Vis detector was present before the mass spectrometer which measured absorbance at 420 nm. Extracted ion chromatograms were obtained from the TOF MS data using the expected mass ratios for the acrylate compounds. For instance, curcumin = 369 *m/z* curcumin monoacrylate = 423 *m/z*, curcumin diacrylate = 477 *m/z*, and curcumin triacrylate = 531 *m/z*.

Curcumin Multiacrylate (CMA) Synthesis

Curcumin was functionalized with acrylate to form curcumin multiacrylate by reaction with acryloyl chloride according to the reported method.²⁹ Briefly, 20 gm curcumin was dissolved in 400 mL THF to obtain a final concentration of 50 mg/mL. TEA was added to this solution at curcumin:TEA ratio as shown in Table 3. After the TEA addition, acryloyl chloride was added dropwise to the THF solution while the mixture was stirred in an ice bath. The reaction mixture was kept under dark conditions for 16 hours. The mixture was subjected to vacuum filtration to remove the precipitated triethylammonium chloride. The THF filtrate was evaporated under vacuum using a liquid N₂ trap. The recovered CMA mass was redissolved in CH₂Cl₂. This solution was purified by multiple washes with 0.1 M K₂CO₃ and 0.1 M HCl to remove unreacted acryloyl chloride and TEA, respectively. Magnesium sulfate was added to remove residual moisture from the solution; the amount of MgSO₄ needed was usually small (around 1% of curcumin weight). The resulting solution was filtered to remove MgSO₄, and the DCM was evaporated under vacuum using a liquid N₂ trap to obtain the final product in powdered form. Three different batches were synthesized by varying the curcumin to acryloyl chloride ratio (viz. 1:1, 1:2 and 1:3) to demonstrate control over the acrylation. The curcumin:TEA ratio selected was the same as the curcumin:acryloyl chloride ratio (e.g., for 1:1 curcumin:acryloyl chloride, 1:1 curcumin:TEA was used). The molar ratios of curcumin, acryloyl chloride, and TEA used for preparing these batches are shown in Table 3.

Thermogravimetric Analysis (TGA)

A TA Instruments Q50 TGA instrument was used to measure the thermal stability of the different CMA samples. The heating rate was 10 °C/min from 35 °C to 550 °C. Sample amount was approximately 3 mg. All samples were analyzed under nitrogen purge in a closed aluminum pan with perforated lid.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The project was supported by the National Institute of Environmental Health Sciences (NIEHS, Grant Number P42ES007380) and by the NSF I/UCRC Center for Pharmaceutical Development (IIP-1063879 and industrial contributions). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Environmental Health Sciences, the National Institutes of Health, nor the National Science Foundation.

References

- Sharma OP. *Biochem Pharmacol.* 1976; 25
- Motterlini R, Foresti R, Bassi R, Green CJ. *Free Radical Biol and Med.* 2000; 28:1303–1312. [PubMed: 10889462]
- Gururaj AE, Belakavadi M, Venkatesh DA, Marmé D, Salimath BP. *Biochem Biophys Res Commun.* 2002; 297:934–942. [PubMed: 12359244]
- Tonnesen HH, Karlsen J, van Henegouwen GB. *Z Lebensm-Unter Forsch.* 1986:183.
- Manju S, Sreenivasan K. *J Colloid Interface Sci.* 2011; 359:318–325. [PubMed: 21492865]
- Tang H, Murphy CJ, Zhang B, Shen Y, Van Kirk EA, Murdoch WJ, Radosz M. *Biomaterials.* 2010; 31:7139–7149. [PubMed: 20591475]
- Paradkar A, Ambike AA, Jadhav BK, Mahadik K. *Int J Pharm.* 2004; 271:281–286. [PubMed: 15129995]
- Bisht S, Feldmann G, Soni S, Ravi R, Karikar C, Maitra A, Maitra A. *J Nanobiotechnology.* 2007; 5:18.
- Wattamwar PP, Biswal D, Cochran DB, Lyvers AC, Eitel RE, Anderson KW, Hilt JZ, Dziubla TD. *Acta Biomater.* 2012; 8:2529–2537. [PubMed: 22426289]
- Killi N, Paul VL, Gundloori RVN. *New J Chem.* 2015; 39:7.
- Gogoi B, Dutta P, Paul N, Dass NN, Sarma NS. *Sens Actuators B.* 2013; 181:144–152.
- Cassano R, Trombino S, Ferrarelli T, Bilia AR, Bergonzi MC, Russo A, De Amicis F, Picci N. *React Funct Polym.* 2012; 72:446–450.
- Ishii Y, Ishida T, Mutoh J, Yamada H, Oguri K. *Fukuoka Igaku Zasshi.* 2005; 96:204–213. [PubMed: 15997774]
- Glauert HP, Tharappel JC, Lu Z, Stemm D, Banerjee S, Chan LS, Lee EY, Lehmler H-J, Robertson LW, Spear BT. *Environ Toxicol Pharmacol.* 2008; 25:247–250. [PubMed: 19122744]
- Kitture R, Ghosh S, Kulkarni P, Liu X, Maity D, Patil S, Jun D, Dushing Y, Laware S, Chopade B. *J Appl Phys.* 2012; 111:064702.
- Cochran DB, Gray LN, Anderson KW, Dziubla TD. *J Biomed Mater Res, Part B.* 2015:104.
- Gupta P, Authimoolam SP, Hilt JZ, Dziubla TD. *Acta Biomater.* 2015; 27:194–204. [PubMed: 26318804]
- Mitov, MI., Patil, VS., Alstott, MC., Dziubla, T., Butterfield, DA. *Oxidative Stress and Biomaterials.* Academic Press; 2016. Chapter Six - In Vitro Cellular Assays for Oxidative Stress and Biomaterial Response; p. 145-186.
- Li Y, Ding Y. *Food Sci Hum Wellness.* 2012; 1:19–25.
- Nagao T, Komine Y, Soga S, Meguro S, Hase T, Tanaka Y, Tokimitsu I. *Am J Clin Nutr.* 2005; 81:122–129. [PubMed: 15640470]
- Zhang A, Shu L, Bo Z, Schlüter AD. *Macromol Chem Phys.* 2003; 204:328–339.
- Payton F, Sandusky P, Alworth WL. *J Nat Prod.* 2007; 70:143–146. [PubMed: 17315954]
- Kawano S-I, Inohana Y, Hashi Y, Lin J-M. *Chin Chem Lett.* 2013; 24:685–687.
- Zawadiak J, Mrzyczek M. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy.* 2010; 75:925–929.
- Pan J, Kai G, Yuan C, Jin R. *Chromatographia.* 2007; 66:121–123.
- Riddell N, Arsenault G, Benskin JP, Chittim B, Martin JW, McAlees A, McCrindle R. *Environ Sci & Tech.* 2009; 43:7902–7908.
- Gutsche CD, Dhawan B, Levine JA, No KH, Bauer L. *J Tetrahedron.* 1983; 39:409–426.

28. Pumera M, Wong CHA. Chem Soc Rev. 2013; 42:5987–5995. [PubMed: 23686139]
29. Patil VS, Dziubla TD, Kalika DS. Polymer. 2015; 75:88–96.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1. Chemical structure of curcumin (A), curcumin monoacrylate (B), curcumin diacrylate (C), and curcumin triacrylate (D). R₁ and R₂ are both OCH₃ for curcumin, H and OCH₃ for demethoxycurcumin, and both H for bisdemethoxycurcumin.

Figure 2.
HPLC chromatograms for curcumin and curcumin multiacrylate with different curcumin:acryloyl chloride ratios (viz. 1:1, 1:2, and 1:3). The curcumin peak intensity decreases with an increase in acryloyl chloride in the reaction mixture.

Figure 3.

Absorbance spectra for individual peaks from HPLC analysis for CMA 1:3. The time noted in the legend is the peak elution time obtained from HPLC. Possible peak assignments for the different acrylates are indicated in the legend. CMoA – curcumin monoacrylate, CTA – curcumin triacrylate, CDA – curcumin diacrylate, DCDA – demethoxycurcumin diacrylate, BDCDA – bisdemethoxycurcumin diacrylate.

Figure 4.

LCMS data for curcumin. MS results are shown in the top three plots, while the results from the UV-vis detector connected are shown in the bottom plot.

Figure 5. LCMS data for CMA synthesized using 1:1 curcumin:acryloyl chloride ratio. MS results are shown in the top three plots, while the results from the UV-vis detector are shown in the bottom plot.

Figure 6.
LCMS data for CMA synthesized using 1:2 curcumin:acryloyl chloride ratio. MS results are shown in the top three plots, while the results from the UV-vis detector are shown in the bottom plot.

Figure 7.

LCMS data for CMA synthesized using 1:3 curcumin:acryloyl chloride ratio. MS results are shown in the top three plots, while the results from the UV-vis detector are shown in the bottom plot.

Figure 8.

Curcumin triacrylate (CTA) elution collection samples rerun in HPLC using 12 minute gradient method file from 60/40 (MeCN/aqueous) to 100/0 (MeCN/aqueous). Inset plot shows the same data but expanding the triacrylate range. For curcumin triacrylate, peaks 1, 2, and 3 correspond to the 14.8, 15.8, and 17.3 minute peaks in Figure 2.

Figure 9.

¹H NMR (400 MHz, DMSO-*d*₆) spectra of curcumin and CMA prepared with different curcumin:acryloyl chloride ratios. Acrylation is evident from the decrease in hydroxy proton signals (9.5 to 10.5 ppm) and the emergence of acrylate proton resonances (between 6.1 and 6.7 ppm).

Figure 10.

Comparison of the extent of acrylation values obtained from LCMS and NMR analyses of CMA with different curcumin to acryloyl chloride ratios. The data reported are for $n = 1$.

Figure 11. Thermogravimetric analysis (TGA) for curcumin and CMA synthesized with different curcumin:acryloyl chloride ratios.

Table 1

UV-Vis Absorbance Peaks for Different Forms of Curcumin Multiacrylate.

	Absorbance peak wavelength
Curcumin	420 nm
Curcumin monoacrylate	412 nm
Curcumin diacrylate	400 nm
Curcumin triacrylate	370 nm
Demethoxycurcumin	420 nm
Demethoxycurcumin monoacrylate	408 nm
Demethoxycurcumin diacrylate	397 nm
Demethoxycurcumin triacrylate	370 nm
Bisdemethoxycurcumin	420 nm
Bisdemethoxycurcumin monoacrylate	412 nm
Bisdemethoxycurcumin diacrylate	395 nm

Table 2

Proportion of Different Acrylates in CMA Prepared with Different Curcumin:Acryloyl Chloride Ratios. The Values are Based on the Peak Areas from LCMS.

	CMA 1:1	CMA 1:2	CMA 1:3
Curcumin	16.0 %	2.3 %	0 %
Monoacrylates	38.5 %	23.3 %	1.0 %
Diacrylates	40.6 %	62.0 %	42.4 %
Triacrylates	4.9 %	12.4 %	56.6 %

Table 3

Composition of Curcumin, Acryloyl Chloride and TEA in the Initial Reaction Mixture.

	Curcumin (moles)	Acryloyl chloride (moles)	TEA (moles)
CMA 1:1	1	1	1
CMA 1:2	1	2	2
CMA 1:3	1	3	3