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Ibuprofen Derived Supramolecular Topical Gel for Self Delivery Applications

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Abstract: A new small molecule–drug conjugate (SMDC) derived from the non-steroidal anti-inflammatory drug (NSAID) ibuprofen has been synthesized through an amidation reaction with the biogenic molecule 5-aminoisophthalic acid, with the objective of transforming the native nongelator ibuprofen into a sustainable supramolecular gelator for self-delivery applications. The resulting small molecule–drug conjugate exhibited efficient gelation in methyl salicylate, a widely used component in topical gel formulations. Comprehensive characterization, including tabletop and dynamic rheological measurements, confirmed the mechanical stability of the gel, while HR-TEM imaging revealed an entangled fibrous network characteristic of supramolecular self-assembly. Overall, the strategic modification of ibuprofen into a small molecule–drug conjugate demonstrates a promising pathway for developing NSAID-based supramolecular gels for controlled topical drug-delivery systems.

Keywords: Topical gel; SAFiNs; Supramolecular gels; Self drug delivery

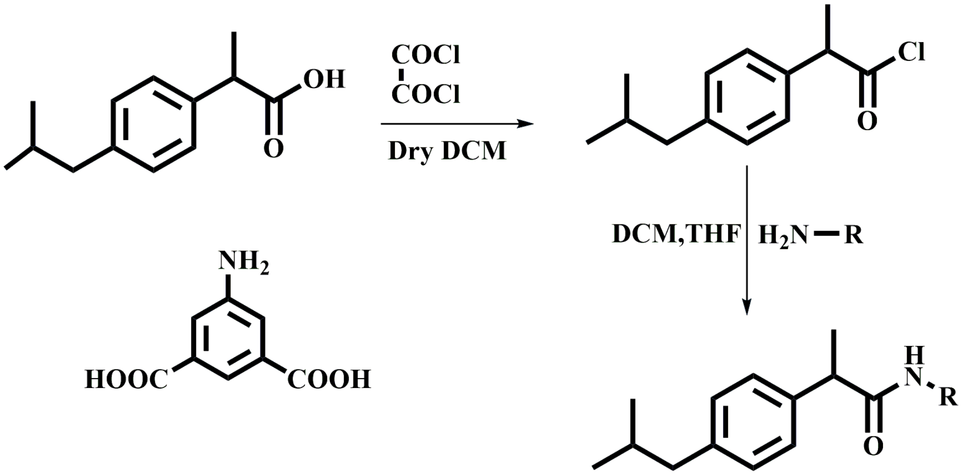
Introduction

Low-molecular-weight gelators (LMWGs) [1–5] are small molecules, typically with molecular weights below 3000 Da, capable of forming gels in a broad range of organic and aqueous media. Extensive studies employing microscopy and X-ray diffraction have established that LMWGs generally self-assemble into one dimensional supramolecular structures that further entangled through various non covalent weak intermolecular interactions such as hydrogen bonding, π–π stacking, van der Waals forces, hydrophobic effects, and charge-transfer interactions in order to generate three-dimensional self-assembled fibrillar networks (SAFiNs) [6]. Within these 3D networks, solvent molecules become immobilized, giving rise to gel formation. Supramolecular gels derived from LMWGs have attracted substantial interest due to their wide-ranging applications in optics and photonics [7], sensing [8], cosmetics [9], structure-directing soft materials [10], art conservation [11], catalysis [12], and biomedical fields [13–16]. More recently, their potential as controlled drug-delivery systems has gained prominence [17,18]. Drug delivery refers to the process by which an active pharmaceutical ingredient reaches its target site and produces a therapeutic effect. Although numerous administration routes such as oral, topical, transmucosal, and inhalation have been developed for drug delivery purposes, protein and peptide-based drugs often face rapid enzymatic degradation, thereby limiting their stability and efficacy. Conventional delivery systems typically rely on external carriers, which can pose challenges including complex synthesis, restricted drug-loading capacity, uncontrolled release, and potential cytotoxicity [19]. In contrast, self delivery systems [20] offer a sustainable alternative, wherein the drug molecule itself is transformed into a supramolecular hydrogel / topical gel capable of delivering the active agent directly to the affected site. This strategy avoids carrier-related drawbacks while enabling localized, efficient, and environmentally benign drug administration. The present work aims to develop supramolecular topical gel for self-delivery applications with inherent anti-inflammatory functionality. For this purpose, Ibuprofen, widely used NSAID and a nongelator in its native form was chosen as the parent drug molecule. However, due to poor water solubility [21] and resulting low bioavailability often require higher dosages, thereby increasing the risk of adverse effects such as renal impairment, gastrointestinal irritation, and cardiovascular complications [22]. Converting ibuprofen drug into a supramolecular topical gel provides a promising strategy to overcome all these limitations by enabling localized drug delivery and minimizing systemic toxicity. A topical gel can be applied direct onto the affected site. Recent systematic efforts in this field highlight the potential of NSAID derived supramolecular gels for self-delivery, facilitated primarily through covalent modification. It is noteworthy that the commercially available anti-inflammatory formulation Volini gel contains diclofenac sodium as the active pharmaceutical ingredient, with methyl salicylate serving as a solvent component and menthol functioning as a cooling agent. For instance, Kim and co-workers developed an enzyme-responsive ibuprofen–peptide hydrogel for controlled release [23]. In this context, the main objective of the present work was to convert ibuprofen into a topical gel. Herein, we report synthesis and characterization of a small molecule–drug conjugate based gelator for self-delivery. The resulting drug conjugate further formed gel in methyl salicylate a common ingredient for commercially available topical gel. This gel was further characterized with rheological experiments and TEM morphology. Furthermore, we formulated menthol containing methyl salicylate topical gel of the bioconjugate.

Results & Discussion

Synthesis

The ibuprofen–conjugate was synthesized according to a reported procedure with minor modifications as shown in Scheme 1. A time-efficient route was employed in which oxalyl chloride (90 µL) was added dropwise to a solution of ibuprofen (1 mmol, 206 mg) in 20 mL of dry DCM containing a catalytic amount of DMF. The mixture was stirred at room temperature for 8 hours, after which the solvent was removed to yield a yellow intermediate. This activated species was dissolved in 10 mL of dry DCM and added dropwise to a solution of 5-aminoisophthalic acid (190 mg, 1 mmol) in 10 mL of dry THF. The resulting mixture was stirred for 30 minutes at room temperature and then refluxed for 8 hours. Evaporation of the solvent yielded 295 mg of a cream-colored solid (~80% yield); which was subsequently characterized by mass spectrometry, IR spectroscopy, and ^{1}H NMR.



Scheme 1: Synthetic procedure of ibuprofen–conjugate.

Methyl salicylate Gel formulation

Approximately 20 mg of the ibuprofen–conjugate was placed in a test tube and mixed with 0.50 mL of methyl salicylate (M.S). The mixture was heated until a clear solution was obtained and subsequently allowed to cool to room temperature, resulting in gel formation. This M.S was further confirmed by the standard test-tube inversion method. The M.S gel was found to be thermoreversible in nature. Moreover, the gel displayed a minimum gelator concentration (MGC) of 4 wt% and a gel dissociation temperature (T_{Gel}) of 69 °C.

The T_{Gel} values at different gelator concentrations were determined using the dropping-ball method. In this procedure, a 420 mg glass ball was carefully placed onto 0.5 mL of the gel inside a test tube, which was then immersed in an oil bath and heated gradually. The temperature at which the ball reached the bottom of the tube was recorded as T_{Gel}. The resulting T_{Gel} with respect to concentration plot further revealed a steady increase in T_{Gel} value with rising gelator concentration. Therefore, multiple noncovalent interactions such as hydrogen bonding, π–π stacking, and C–H···π interactions play crucial roles in stabilizing and strengthening the supramolecular gel network (Figure 1).

HR-TEM analysis was carried out to investigate the internal morphology of the methyl salicylate gels. For imaging, highly diluted samples of the gelator were drop-cast onto carbon-coated Cu (300 mesh) TEM grids, followed by overnight drying under vacuum. The recorded micrographs revealed well-defined supramolecular architectures characterized by entangled fibrous networks, along with tape-like structures ranging in width from approximately ~300 nm. These observations further confirm the formation of an extended, self-assembled gel network (Figure 2).

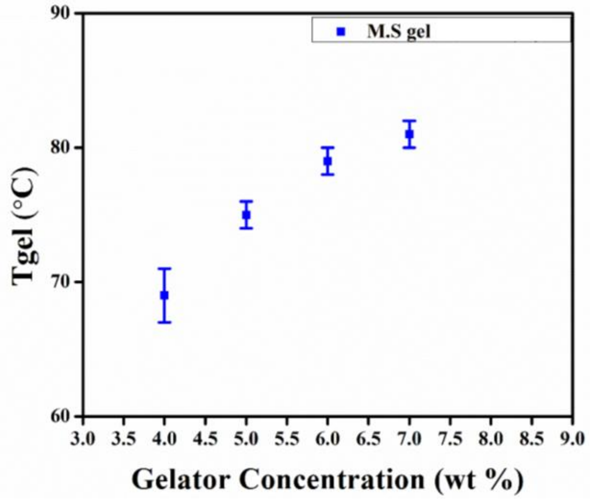


Figure 1. T_{gel} *vs* [gelator] plot.

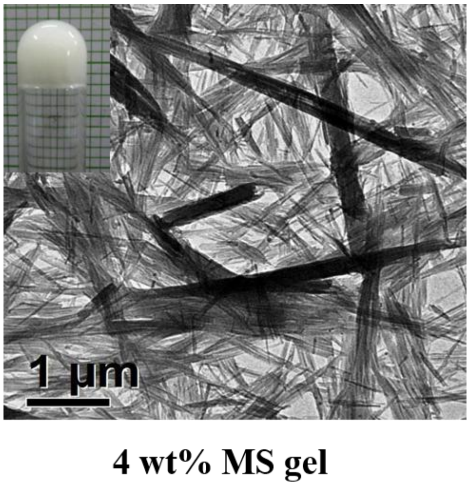


Figure 2. TEM morphologyof 4 wt% methyl salicylate gel.

Next, we checked the viscoelastic properties of the MGClevel gel (4 wt%). For this purpose,various dynamic rheological experiments were performed. A strain sweep experiment was conducted to determine the linear viscoelastic (LVE) region of the gel. In this experiment, increasing oscillatory strain was applied at a constant frequency to evaluate structural stability as well as identifying the Linear Viscoelastic Region (LVR) where G′ exceeds G″. This strain sweep experiment furthermore determines the critical strain at which the gel network begins to break down. In a typical experiment, 20 mL of 4 wt% methyl salicylate gel was subjected to rheological analysis using a PP-25 plate geometry on an Anton Paar rheometer. Figure 3a clearly indicated that, elastic modulus (G′) gradually decreased with increasing strain and eventually dropped below the viscous modulus (G″) at a strain value of 4.35%(critical strain), thereby indicating a characteristic gel–sol transition typical of supramolecular gels. Based on the identified LVE range, a frequency sweep was then performed at a constant strain of 0.1%. The methyl salicylate gel exhibited pronounced viscoelastic behavior, since the storage modulus (G′) remaining significantly higher than that of loss modulus (G″) and showing minimal dependence on frequency across the entire range. This frequency invariance further confirms the formation of a stable, well defined supramolecular network (Figure 3).

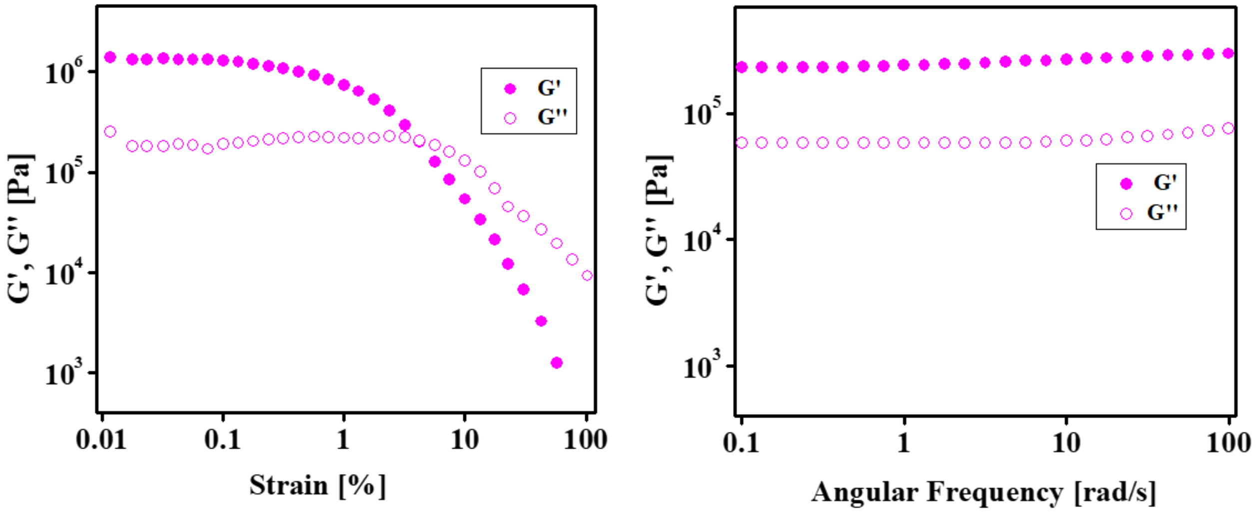


Figure 3. a) strain sweep and b) frequency sweep experiment of the methyl salicylate gel.

Topical gel formulation

After successfully converting ibuprofen into its gelator form, we further extended our study towards the development of a topical gel formulation. In this regard, menthol was incorporated as a common excipient, as it provides a cooling sensation and induces vasodilation, thereby enhancing the penetration of the active component through the skin. Interestingly, 1 % menthol containing methyl salicylate topical gel retained its gelling behavior displaying MGC at 4.2wt% and gel dissociation temperature at 68°C.

Conclusion

The present study reports the design, synthesis, and characterization of a new small molecule–drug conjugate derived from the NSAID ibuprofen, prepared via a straightforward amidation reaction with 5-aminoisophthalic acid. The resulting small molecule–drug conjugate exhibited efficient gelation in methyl salicylate, a key component of many commercial topical formulations. Microscopic analyses revealed an entangled fibrous network characteristic of supramolecular gel structures, while rheological measurements confirmed the viscoelastic behaviour expected for a stable gel system. Furthermore, a menthol-containing methyl salicylate–based topical gel formulation was successfully developed using this gelator. Overall, the small molecule–drug conjugate derived supramolecular gel offers a promising platform for advanced drug-delivery applications, combining effective therapeutic potential with improved patient compliance.

Experimental Section

Materials

All the chemicals including were purchased from TCI chemicals and used without further purification. Analytical reagent (AR) grade solvents were purchased from local market.

Methods

FT-IR spectra of the compounds were carried out using Shimadzu FT-IR 8300 instrument. Transmission Electron Microscopy (TEM) images were recorded using a JEOL instrument with 300 mesh copper TEM grid. Rheological experiments were carried out using SDT Q series advanced rheometer AR 2000.

Characterization Data

Physico-chemical Data: FT- IR (NEAT): 3300 (s, amide N-H stretch), 1740 (b, acid C = O stretch), 1660 (amide C=O stretch) cm^{-1} (Figure S1). **HR-MS, ESI (MeOH) m/z (100%):** calculated for $[C_{21}H_{23}NO_5 + H]^+$ is 370.16. Found 370.31. $[C_{21}H_{23}NO_5 + Na]^+$ is 392.40. Found 392.31. ^{1}H NMR (400 MHz, DMSO-d_6, 25°C): δ=8.42(s, ,2H, aromatic H of isophthalic acid), 8.12(s, ,1H, aromatic H of isophthalic acid), 7.29-7.27(d, 2H,8Hz, aromatic H of ibuprofen), 7.11-7.09(d, ,2H,8Hz, aromatic H of ibuprofen), 3.79-3.77 (m, 1H, chiral hydrogen of ibuprofen), 2.39-2.38(d, 2H, CH_2 of ibuprofen), 1.79-1.77(m, 1H, CH next to isopropyl group of ibuprofen,), 1.40-1.39 (d, 3H,4Hz, alkyl hydrogen of ibuprofen), 0.83-0.82(d, 6H, 4Hz, isopropyl methyl hydrogen of ibuprofen) (Figure S2).

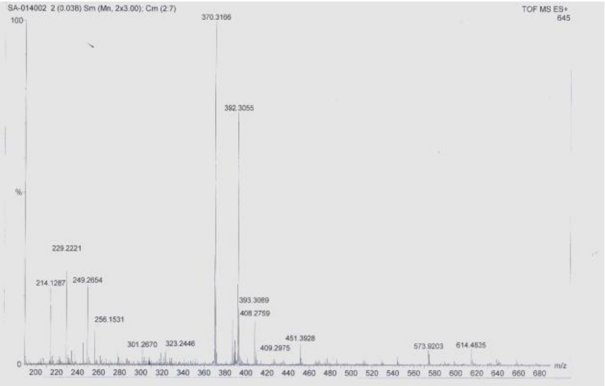


Figure S1. Mass spectra of small molecule–drug conjugate.

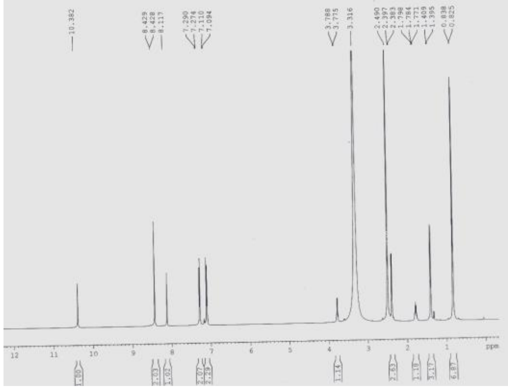


Figure S2. ^{1}H NMR spectra of small molecule–drug conjugatein DMSO-d6.

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Reference

1. Terech, P, Weiss, RG. Low Molecular Mass Gelators of Organic Liquids and the Properties of Their Gels. Chemical Reviews 1997, 97(8):3133–3160.
2. Suzuki, M, Hanabusa, K. L-Lysine-based low-molecular-weight gelators. Chemical Society Reviews 2009, 38(4):967–975.
3. Weiss, RG, Terech, P (eds.). Molecular Gels. 2006, .
4. Jones, CD, Steed, JW. Gels with sense: supramolecular materials that respond to heat, light and sound. Chemical Society Reviews 2016, 45(23):6546–6596.
5. Tomasini, C, Castellucci, N. Peptides and peptidomimetics that behave as low molecular weight gelators. Chemical Society Reviews 2013, 42(1):156–172.
6. George, M, Weiss, RG. Molecular Organogels. Soft Matter Comprised of Low-Molecular-Mass Organic Gelators and Organic Liquids. Accounts of Chemical Research 2006, 39(8):489–497.

7. Prasanthkumar, S, Ghosh, S, Nair, VC, Saeki, A, Seki, S, Ajayaghosh, A. Organic Donor–Acceptor Assemblies form Coaxial p–n Heterojunctions with High Photoconductivity. Angewandte Chemie 2015, 127(3):960–964.
8. Ikeda, M, Fukuda, K, Tanida, T, Yoshii, T, Hamachi, I. A supramolecular hydrogel containing boronic acid-appended receptor for fluorocolorimetric sensing of polyols with a paper platform. Chemical Communications 2012, 48(21):2716–2718.
9. Wynne, A, Whitefield, M, Dixon, A, Anderson, S. An effective, cosmetically acceptable, novel hydro-gel emollient for the management of dry skin conditions. Journal of Dermatological Treatment 2002, 13(2):61–66.
10. Basit, H, Pal, A, Sen, S, Bhattacharya, S. Two-Component Hydrogels Comprising Fatty Acids and Amines: Structure, Properties, and Application as a Template for the Synthesis of Metal Nanoparticles. Chemistry – A European Journal 2008, 14(21):6534–6545.
11. Carretti, E, Bonini, M, Dei, L, Berrie, BH, Angelova, LV, Baglioni, P, Weiss, RG. New Frontiers in Materials Science for Art Conservation: Responsive Gels and Beyond. Accounts of Chemical Research 2010, 43(6):751–760.
12. Escuder, B, Rodríguez-Llansola, F, Miravet, JF. Supramolecular gels as active media for organic reactions and catalysis. New Journal of Chemistry 2010, 34(6):1044–1054.
13. Khademhosseini, A, Langer, R. Microengineered hydrogels for tissue engineering. Biomaterials 2007, 28(34):5087–5092.
14. Li, J, Kuang, Y, Gao, Y, Du, X, Shi, J, Xu, B. D-amino acids boost the selectivity and confer supramolecular hydrogels of a nonsteroidal anti-inflammatory drug (NSAID). Journal of the American Chemical Society 2013, 135(2):542–545.
15. Du, X, Zhou, J, Xu, B. Supramolecular Hydrogels Made of Basic Biological Building Blocks. Chemistry – An Asian Journal 2014, 9(6):1446–1472.
16. Bommel, KJC van, Stuart, MCA, Feringa, BL, Esch, J van. Two-stage enzyme mediated drug release from LMWG hydrogels. Organic & Biomolecular Chemistry 2005, 3(16):2917–2920.
17. Webber, MJ, Matson, JB, Tamboli, VK, Stupp, SI. Controlled release of dexamethasone from peptide nanofiber gels to modulate inflammatory response. Biomaterials 2012, 33(28):6823–6832.
18. Majumder, J, Deb, J, Das, MR, Jana, SS, Dastidar, P. Designing a simple organic salt-based supramolecular topical gel capable of displaying in vivo self-delivery application. Chemical Communications 2014, 50(14):1671–1674.
19. Uhrich, KE, Cannizzaro, SM, Langer, RS, Shakesheff, KM. Polymeric Systems for Controlled Drug Release. Chemical Reviews 1999, 99(11):3181–3198.
20. Li, X, Li, J, Gao, Y, Kuang, Y, Shi, J, Xu, B. Molecular nanofibers of olsalazine form supramolecular hydrogels for reductive release of an anti-inflammatory agent. Journal of the American Chemical Society 2010, 132(50):17707–17709.
21. Lee, S, Von Allmen, P. Tight-binding modeling of thermoelectric properties of bismuth telluride. Applied Physics Letters 2006, 88(2):022107.
22. Silverstein, FE, Faich, G, Goldstein, JL, Simon, LS, Pincus, T, Whelton, A, Makuch, R, Eisen, G, Agrawal, NM, Stenson, WF, Burr, AM, Zhao, WW, Kent, JD, Lefkowith, JB, Verburg, KM, Geis, GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000, 284(10):1247–1255.
23. Bhuniya, S, Seo, YJ, Kim, BH. (S)-(+)-Ibuprofen-based hydrogelators: an approach toward anti-inflammatory drug delivery. Tetrahedron letters 2006, 47(40):7153–7156.