Synthesis and non-covalent interaction investigation of metformin-conjugated poly(methyl acrylate)

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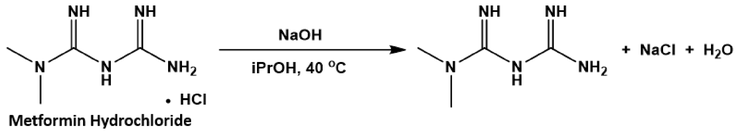
Abstract

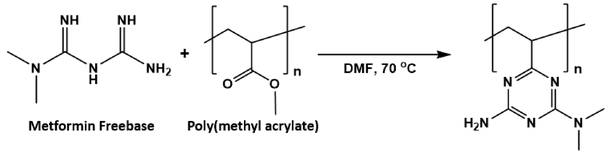
In this study, we report the post-synthetic functionalization of poly(methyl acrylate) (PMA) using metformin. By reacting the methyl ester side chains of PMA with metformin, biguanide groups were successfully introduced into the polymer, as verified through nuclear magnetic resonance (NMR) spectroscopy. This chemical modification is anticipated to convert the originally hydrophobic PMA into an amphiphilic polymer capable of self-assembling into micellar structures in aqueous environments. These metformin-functionalized micelles are expected to act as drug carriers by encapsulating therapeutic agents through non-covalent interactions. Moreover, the presence of metformin units within the polymer structure may contribute inherent pharmacological activity, adding a therapeutic role to the carrier itself. This dual-purpose system—integrating drug delivery capability with potential bioactivity—demonstrates a promising strategy for the design of multifunctional drug delivery platforms. Ultimately, such an approach could enhance the performance and adaptability of polymer-based delivery technologies by consolidating multiple functional benefits into a single material.

Introduction

Polymeric materials are essential in drug delivery due to their adaptability, biological compatibility, and therapeutic versatility [1]. Poly(methyl acrylate) (PMA) is notable for its mechanical strength and chemical tunability, but its inherent hydrophobicity restricts biomedical use [2]. To address this, we chemically conjugated hydrophilic metformin to PMA by reacting methyl ester groups with metformin's biguanide moieties, creating an amphiphilic polymer. Structural confirmation via ^{1}H, ^{13}C NMR, and 2D HSQC spectroscopy demonstrated successful metformin grafting. This modification improved aqueous solubility and introduced therapeutic functionality, making metformin-functionalized PMA promising for advanced multifunctional drug delivery systems.



Scheme 1. Synthetic scheme of metformin freebase



Scheme 2. Synthetic Scheme of PMA-MET

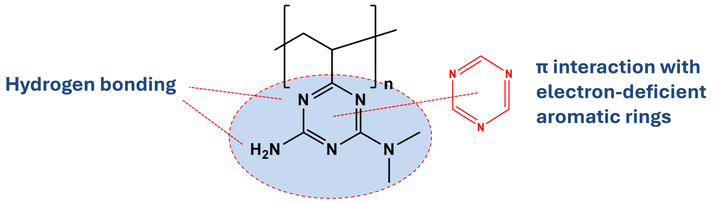


Figure 1. Potential non-covalent molecular interaction of side chain in PMA-MET

Materials and methods

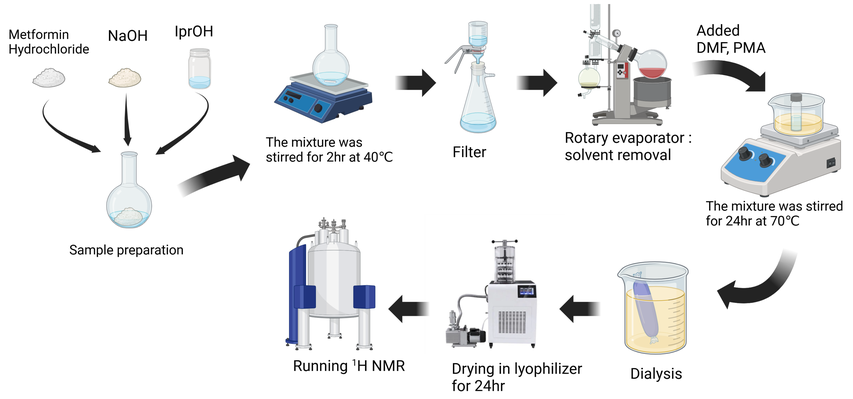


Figure 2. Synthesis of metformin free base, PMA-MET and purification of the polymer

Results

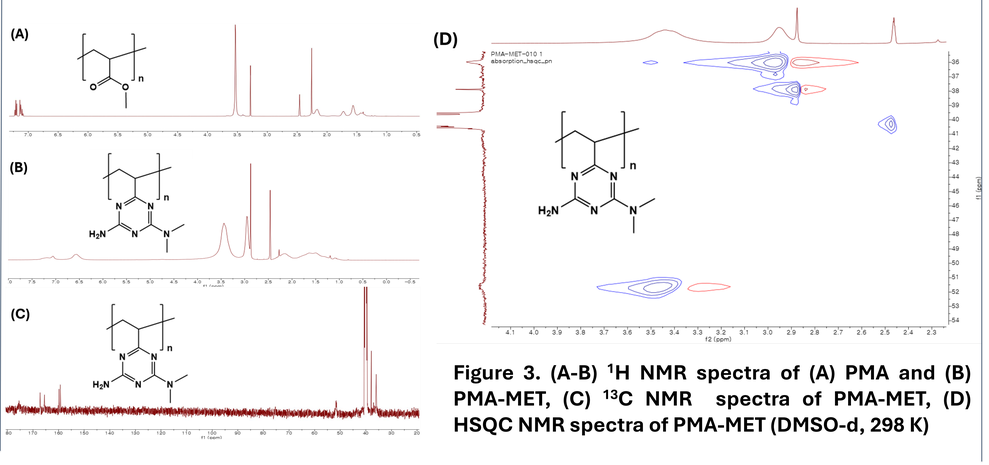


Figure 3. (A-B) ^{1}H NMR spectra of (A) PMA and (B) PMA-MET, (C) ^{13}C NMR spectra of PMA-MET, (D) HSQC NMR spectra of PMA-MET (DMSO-d, 298 K)

Result

Reagent	Molecular weight (g/mol)	Equiv. (mmol)
Poly(methyl acrylate)	40,000	0.47
Metformin Hydrochloride	165.63	4.7
Sodium Hydroxide	40	6.6

Table 1. Reagents in the polymer synthesis

Conclusion

In this study, we modified poly(methyl acrylate) (PMA) with metformin, yielding an amphiphilic polymer that can self-assemble into micelles in aqueous environments. Structural confirmation using ^{1}H, ^{13}C, and HSQC NMR spectroscopy revealed new chemical shifts and cross-peaks, indicating covalent bonding between metformin and the PMA backbone. This structural and functional modification may enhance PMA's utility in biomedical applications by combining drug delivery capability with the therapeutic nature of metformin. However, additional studies are necessary to assess the micelle stability, drug encapsulation and release kinetics, and biocompatibility under physiological conditions. Incorporating other bioactive compounds or targeting groups could further expand the system's versatility. Altogether, PMA-MET represents a promising dual-functional platform for next-generation drug delivery systems.

Reference

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2. Paul, M., et al. "Physicochemical characteristics of pentamidine-loaded polymethacrylate nanoparticles: implication in the intracellular drug release in Leishmania major infected mice." *Journal of drug targeting* 5.6 (1998): 481-490.
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Acknowledgement

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT). (Grant No.: RS-2023-00210769)