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Thorough investigation on the encapsulation of drugs with different wettability in thermosensitive micellar hydrogels

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INTRODUCTION: Injectable hydrogels for the targeted release of therapeutics are a promising tool in the treatment of a wide variety of pathologies. In order to optimize gel design, a thorough understanding of gel/therapeutic interactions is required to predict payload release timing and effects on gel properties. Herein, we designed thermosensitive micellar gels based on an amphiphilic poly(ether urethane) (PU), that were loaded with ibuprofen (IBU, hydrophobic drug) or ibuprofen sodium salt (IBUSS, hydrophilic salified form of IBU). IBU and IBUSS arrangement within the gels and their interactions with PU micelles were studied by rheology, dynamic light scattering (DLS) and colorimetric assay using 1,6-diphenyl-1,3,5-hexatriene (DPH) as marker of micellization.

METHODS: PU was synthesized starting from the triblock copolymer Poloxamer 407, an aliphatic diisocyanate and 1,4-cyclohexane dimethanol [1]. Hydrogels were prepared in saline solution at a 15% w/v according to [1]. IBU and IBUSS were then loaded (1 mg/ml) and the resulting systems were rheologically characterized by strain sweep, frequency sweep and temperature ramp tests. Swelling and stability to dissolution were also evaluated. Drug/PU micelle interactions were studied by DLS and DPH assay on PU solutions (0.5% w/v) loaded with IBU and IBUSS [1].

RESULTS: Gel loading with IBU resulted in a decreased onset of the gelation process compared to PU_IBUSS and PU gels (9 °C for PU_IBU *vs* 14 °C for PU_IBUSS and PU). This result suggested that IBU hydrophobic nature induces its encapsulation within PU micelles during their nucleation, thus leading to the achievement of the critical micellar volume required for gelation onset [1] at lower temperature compared to the other samples. In fact, PU_IBUSS did not change its gelation onset compared to PU gel, suggesting that this drug is mainly located in the interstitial space among the micelles. DLS further proved this hypothesis, showing that micelles in PU_IBU had a significantly higher hydrodynamic diameter compared to PU_IBUSS and PU solutions (58 nm for PU_IBU *vs* 37 and 40 nm for PU_IBUSS and PU). Additionally, PDH assay showed that the critical micellization temperature of PU_IBU was clearly lower compared to PU and PU_IBUSS solutions (9 °C for PU_IBU *vs* 22 °C for PU and PU_IBUSS). Interestingly, irrespective of the nature of the encapsulated drug, drug-loading seemed to slightly accelerate the kinetics of gel formation and development compared to drug-free PU hydrogels (gelation points in frequency sweep test at 25°C were 58, 50 and 45 rad/s for PU, PU_IBU and PU_IBUSS), thus suggesting that encapsulating either hydrophilic or hydrophobic drugs do not have detrimental effects on the temperature-driven sol-to-gel transition of micellar gels. Additionally, no significant effects were observed in gel swelling and stability to dissolution in aqueous media upon drug encapsulation.

DISCUSSION & CONCLUSIONS: We reported for the first time the potential of rheology, DLS and DPH assay in characterizing drug arrangement within gels and their interaction with micelles.

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