# Reversibly Cross-Linked Asymmetric Hybrid Open-Polysilsesquioxane Films Enhancing Clotrimazole Bioavailability and Anti-*Candida* Mature Biofilm Activity for Vaginal Therapy

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Streszczenie

Vulvovaginal candidiasis, primarily caused by *Candida albicans*, presents a significant therapeutic challenge due to fungal biofilm formation and the poor aqueous solubility of azole antifungals like clotrimazole, CLT. Films are increasingly favored as antimicrobial drug carriers due to their capacity to provide prolonged vaginal retention, extended shelf life, and simplified storage compared to traditional drug forms. Current film formulations, however, often suffer from nonuniform drug distribution, uncontrolled drug release, and compromised structural integrity. To overcome these limitations, we developed novel, water-swellable polymeric networks designed for enhanced clotrimazole bioavailability and potent anti-*Candida* biofilm activity. Our strategy involved the reversible cross-linking of unique asymmetric open-Polyhedral Oligomeric Silsesquioxane (POSS) cages, functionalized with both hydrophobic, i.e., phenyl (**IC-POSS$^{Ph}$**) or isobutyl (**IC-POSS$^{iBu}$**) groups and bearing hydrophilic 1,2-diol moieties, with poly(dimethylacrylamide-2-acrylamidephenylboronic acid) (P(DMAM-2-AAPBA)) copolymers. We tailored the copolymer composition to achieve precise control over the network cross-linking density. Comprehensive characterization, including $^{11}$B NMR spectroscopy, differential scanning calorimetry, rheology, and SEM-EDS (scanning electron microscopy-energy dispersive X-ray spectroscopy), elucidated the structure–property relationships. We demonstrated that **IC-POSS$^{Ph}$** cages intrinsically prevent CLT crystallization, likely via π–π-stacking interactions, facilitating homogeneous drug distribution. Conversely, while **IC-POSS$^{iBu}$** cages showed less inherent drug compatibility, the P(DMAM-2-AAPBA) copolymers were crucial for achieving uniform CLT dispersion within these networks. Our studies revealed that higher 2-AAPBA content in the copolymer increased network cross-linking density, leading to

slower drug release. Moreover, π–π interactions between **IC-POSS$^{Ph}$** cages in the networks contributed to a reduced swelling capacity and evidently slower drug release. Crucially, biological evaluations confirmed that these CLT-loaded polymeric films significantly enhanced antifungal efficacy against both planktonic *C. albicans* strains (ATCC 10231 and SC5314) and mature *Candida* biofilms, outperforming free CLT. This superior performance is attributed to the networks' ability to maintain CLT in the molecular state and enable its controlled release, thereby improving its bioavailability at the target site. The elaborated films also exhibited good cytocompatibility. This work highlights how subtle structural modifications in network components are crucial to achieving desired biological functions, representing a promising advance for antifungal drug delivery and, in general, hydrophobic drug carriers in various biomedical applications.

Słowa kluczowe

Antimicrobial agents, Biofilms, Copolymers, Drug release, Nucleic acid structure, network, film formulation, antifungal intravaginal therapy, boronic ester, incompletely condensed POSS cage, cross-linkable open-POSS cage, swelling ratio, Candida biofilm inhibition



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