# Multilayer Polymer Films for Interval Delivery of 5HT2A Agonists

**Thomas Werfel[1, 2, 3], Mehjabeen Hossain[3], Suresh Sulochana[3], Chalet Tan[3], John Rimoldi[3], Glenn Walker[1]**
Departments of [1]Biomedical Engineering, [2]Chemical Engineering, [3]BioMolecular Sciences
University of Mississippi, University, MS, USA

**Statement of Purpose:** Mental illnesses such as anxiety disorder, post-traumatic stress disorder (PTSD), and major depressive disorder (MDD) impact millions daily. Existing treatments include psycho- and pharmaco-therapy, but these therapies are not effective in as many as 50% of MDD patients. 5HT2A agonists (*e.g.*, lysergic acid diethylamine (LSD) and psilocybin) have shown therapeutic promise for treating depression, leading to their designation as a "Breakthrough Therapy" by the U.S. Food and Drug Administration (FDA) in 2018.[1, 2] But although 5HT2A agonists show significant promise for treating depression, a rigorous clinical setup is required to administer these therapies and poor patient compliance is a consequence of the many follow-up visits that are required for these therapies. Thus, there is an urgent unmet medical need for improved strategies to ensure patients suffering from depression and other mental illness have access to safe and efficacious therapies. Here, we seek to address this gap in treatment by developing a polymeric drug delivery device for precise, safe, and long-term interval delivery of 5HT2A agonists to alleviate the symptoms of chronic mental illness without the need for repeated administration of compounds in a clinical setting.

**Methods:** We constructed polymer films composed of a 70:30, 80:20, and 90:10 weight ratios of cellulose acetate phthalate (CAP) and Pluronic F-127® (P) polymers, henceforth referred to as CAPP films.[3] Films were prepared either unloaded (Blank), loaded with Rhodamine B (model drug), or loaded with the 5HT2A agonists (±)-2,5-Dimethoxy-4- iodoamphetamine hydrochloride (DOI) and 4-acetoxy-N,N-Dimethyltryptamine (4-acetoxy DMT). The 90:10 CAPP films degrade via surface erosion, whereas 80:20 and 70:30 films degrade by bulk erosion, enabling tunability of drug release profiles based on the CAPP polymer ratio. Thus, by layering multiple films and coating on all but one side, sequential and/or intermittent drug release can be achieved based on the layering of the films. Here, we designed films that release a single drug every 72 hours for up to one week as proof-of-concept by alternating 70:30 drug-loaded CAPP films (for burst drug release) and 90:10 blank CAPP films (for delayed release). Physicochemical characteristics of the devices were characterized, followed by the quantification of drug release kinetics by measuring fluorescence of supernatant releasates on a microplate reader (for Rhodamine B) and performing high-performance liquid chromatography (for DOI, 4-acetoxy DMT).

**Results:** Films of consistent thicknesses varying from 0.1 to 0.4 mm were produced and confirmed by caliper measurements. The correlation of thickness to drug release was then established, where 0.1, 0.2, 0.3, 0.4 mm thick films released drug completely at 24, 42, 72, and 98 hours respectively (**Fig. 1A**). Therefore, burst release of drug could be achieved from 0.1 mm thick 70:30 CAPP films loaded with Rhodamine B, whereas controlled release was seen particularly in 0.3 mm and 0.4 mm thick films. Parallel to the model drug Rhodamine B, DOI and 4-acetoxy DMT were also encapsulated in 0.1 mm thick CAPP films. Both DOI and 4-acetoxy DMT showed a burst release (similar to Rhodamine B) from 0.1 mm thick CAPP films (**Fig. 1B**). Next, we began to assemble multilayer films for long-term interval release as can be visualized in **Fig. 1C**. The multilayer films were composed of alternating drug-loaded, 0.1 mm 70:30 CAPP films and Blank, 0.4 mm 90:10 CAPP films. This initial design demonstrated pulsed drug release, with the peak of each drug pulse occurring ~72 hrs apart (**Fig. 1D**).

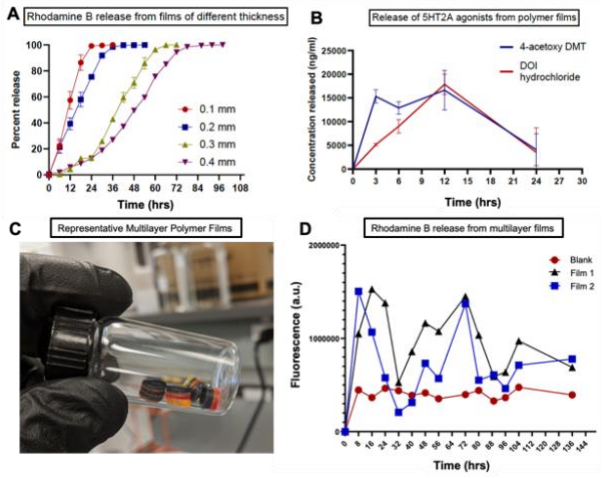


**Figure 1. Drug Release from Multilayer CAPP Polymer Films. (A)** Rhodamine B release from single-layer CAPP films of varying thicknesses. Rate of drug release is correlated to film thickness. **(B)** Release kinetics of two 5HT2A agonists from 0.1 mm thick CAPP films. **(C)** Representative multilayered CAPP films – thickness increased and dyes included for effect. (D) Rhodamine B release from a 5-layer CAPP film with the following layering pattern: 1) Rho, 2) Blank, 3) Rho, 4) Blank, 5) Rho. Pulsatile drug delivery is achieved with ~72 hours between pulse peaks.

**Conclusions:** The prototype multilayered film developed here shows promise for achieving consistent every-third day interval dosing from a safe and biodegradable material platform that could radically improve compliance to pharmacotherapies for depression and other mental illness. Future studies will focus on pulsed delivery of 5HT2A agonists and extending the lifetime of the devices for long-term outcomes.

**References:** [1] Carhart-Harris et al., Lancet Psychiatry, 2016. [2] Carhart-Harris et al., Psychopharmacology, 2018. [3] Jeon et al., Int. J. Pharm., 2007.

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