Surface-Eroding Drug Delivery Films for Sequential and/or Intermittent Release of Psychoactive Drugs

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SURFACE-ERODING DRUG DELIVERY FILMS FOR SEQUENTIAL AND/OR INTERMITTENT RELEASE OF PSYCHOACTIVE DRUGS

By
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A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College.

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ABSTRACT
JASON BLAKE PRICE: Surface-Eroding Drug Delivery Films for Sequential and/or Intermittent Release of Psychoactive Drugs

For patients with psychiatric diseases, adherence to medication schedules, medication errors, and abuse are common issues. Promising new forms of therapy for these patients, such as micro-dosed lysergic acid diethylamide (LSD), where patients receive 10-20% of a full dose every third day, present further drug delivery challenges. Sequential or intermittent release of drugs from an implanted device could ensure long-term drug compliance, automate drug dosing during the life of the implant, and eliminate potential for abuse and medication errors. To this end, we generated polymeric films composed of cellulose acetate phthalate (CAP) and Pluronic F-127 (P) polymers that can co-encapsulate a wide variety of drug molecules. We generated CAPP films via a slow solvent evaporation method, where CAP and P were dissolved – along with one of two model drugs Fluorescein or Rhodamine B – in acetone and left to dry at 4 degrees Celsius. The films slowly re-dissolve in Phosphate-buffered saline (PBS) via surface erosion to allow controlled drug release. Single layer CAPP films were eroded using 300, 600, 900, 1200, 1600, and 1800 mg polymer mass groups to study the relationship between polymer thickness and erosion rate. Based off that analysis, polymer thickness and erosion rate had a positive correlation that increased linearly. Drug release profiles were quantified from single layer devices to establish the connection between film thickness and drug concentration release. Based off release profiles generated from the analysis of single layer devices, multilayered devices were fabricated to achieve controlled, intermittent release of the model drugs. We found that the multilayered devices could successfully release Fluorescein and Rhodamine B in a sequential and/or intermittent order with a delay of 48-72 hours between release. To further tailor the films, polymer concentration, layer order, and
encapsulated drugs can be varied in a modular manner. Thus, CAPP films are a promising technology for long-term, sequential and/or intermittent release of psychiatric agents from an implantable device, and the device will be further optimized to achieve ideal release profiles for the micro-dosing of LSD in patients with treatment-resistant depression.
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Introduction

For patients with psychiatric disorders, adherence to medication schedules, medication errors, and medication abuse are common issues that need to be addressed by healthcare providers [Bellack 1, Brown 2]. Psychiatric disorders are becoming more prominent as awareness grows and more patients seek help for their conditions at a higher rate than they have in previous decades [Mental Health America 3]. However, it is still difficult for people with disorders to come forward as mental health stigma remains. As reported by the World Health Organization (WHO), mental or psychiatric disorders affect one in four people at some point during their lives and nearly half of all adults in the United States (US) will experience a mental illness [WHO 4, Mental Health First Aid 5]. This puts psychiatric disorders among the leading causes of health conditions in, not only the US, but also the world [WHO 4]. Although the US has many affected people, only about 41 percent of patients in the US receive healthcare for their disorder [Mental Health First Aid 5].

These common psychiatric disorders include post-traumatic stress disorder, schizophrenia, treatment resistant depression, and anxiety disorders [Medline Plus 6]. Of those remaining 59 percent, there are several obstacles that the healthcare provider must go through to properly treat a patient with a mental disorder. Psychiatric patients struggle with psychological treatments because a high number of patients are unable to adhere to a medication schedule [Iseselo 7]. In studies of psychiatric patients, poor medication adherence and refusal is quite common in a rehabilitation center [Marrero 8, Kasper 9]. Also, other patients' challenges include availability and affordability of these psychiatric drugs, as well as, patients who do not benefit from medications that already exist [Iseselo 7]. Because most psychiatric patients experience chronic
symptoms, chronic treatment regimens open the door for increasingly poor compliance [Brown 2]. Another common issue is medication abuse, as substance abuse disorders are significant issues associated with drug usage, which are increased within psychiatric patient populations [Giguère 10, Dunn 11]. Battling these issues with psychiatric patients and their treatments have led to the development of novel therapeutic strategies, including long-term implantable drug delivery system [Puleo 12]. However, new technologies must be well perceived for it to be an effective treatment. Because of its novelty, it needs the demand and support of the patients, as well as, the healthcare providers. In a study of patients and their close family members, the likelihood of these patients endorsing and using these novelty medication devices were 50 percent, while their family member’s approval for the patient’s treatment was 75 percent [Dankert 13]. This is a promising response to new technology that can be the future of therapeutic regimens for psychiatric patients. These devices would be implanted intramuscularly underneath the skin much like Nexplanon, a long-term birth control [Nexplanon 14]. Along with new delivery methods for these patients, there are also new forms of medication being studied as well.

Currently, a promising therapeutic agent being studied for psychiatric patients is lysergic acid diethylamide (LSD), which is a potent psychedelic drug that was first synthesized in 1938 by Albert Hofmann [Drugs.com 15]. The effects of the drug include: alterations of perception, emotion, cognition, and stimulation of one’s imagination [Drugs.com 15]. The most known reason as to how LSD and other psychedelic drugs alter the state of mind in such a unique manner is by attaching to a serotonin receptor known as 5-HT_{2A} [Dankert 13]. This receptor is the target for some atypical antipsychotic drugs such as olanzapine and clozapine, which are both on the market today [Dankert 13]. Recent studies have stemmed from a phenomenon known as “microdosing,” which is the administration of LSD in low doses that fall in a therapeutic window without the
hallucinogenic properties of the drug [Polito 16, Chen 17]. Microdosing has been studied only a few times in humans, but multiple articles agree that thirteen micrograms is the therapeutic limit for LSD administration, and more experiments at this dosage should be further studied [Polito 16, Bershad 18]. Most notably, in a survey of 98 regular recreational microdosers, their findings suggested that LSD improved mood, psychological function, and cognition, while also reducing anxiety, stress, and depression [Polito 16]. While there are benefits, there have been some concerns about the use of LSD.

The lack of clinical studies of acute effects of LSD leads clinicians to the fact that more studies need to be conducted to understand human behavior while being medicated in this novel fashion [Polito 16]. There have been promising rat and mice controlled experiments [Winter 19]. One study showed that stimulus control of LSD in mice was possible, as well as citing another experiment where rats had shown stimulus control for hallucinogens [Winter 19]. These are the reasons that LSD has increasing interest in clinical studies for psychiatric patients as well as breakthroughs with the Food and Drug Administration (FDA) in the last few years for treating depression, schizophrenia, and other psychiatric disorders [Blevins 20]. Also, in the last few years, psychedelic mushrooms have been decriminalized in Denver, CO, the FDA gave 3,4-methylenedioxymethamphetamine (MDMA) a breakthrough therapy designation, and a new form of ketamine, esketamine, has been made into a nasal spray for depression [Blevins 20]. This shows promise that psychedelic drugs research is growing to combat the US’ mental health crisis and opens the door for LSD to be the next drug designated for therapy. Currently, the problem with LSD is most studies have not been in a controlled clinical environment, so they lack the validation needed to solidify these effects on humans [Polito 16]. Also, the administration of psychoactive drugs to a psychiatric patient is an issue. LSD is a Schedule I narcotic, so administration of this
drug is illegal, but through future research, FDA break throughs, and validation, LSD may become a legal drug with accepted medicinal uses soon [Drugs.com 15]. The issue of giving any prescription medicine to a patient, especially an ill-adhering patient, like a psychiatric patient, is trusting that patients will not abuse their medication [National Institute on Drug Abuse 21]. Unfortunately, abuse happens. In 2017, an estimated 18 million people misused prescription drugs [National Institute on Drug Abuse 21]. The psychiatric patients mentioned earlier are at a higher risk to abuse their medication, so a solution must be developed [Brown 2].

An experimental treatment could be performed using a novel polymeric drug delivery product that has gained some momentum in recent years. This new technology being studied aims to mimic naturally occurring release of hormones, but instead with a tissue-engineered association polymer structure using cellulose acetate phthalate (CAP) and Pluronic F-127 (P) [Puleo 22]. This new technology could change the field of drug delivery as we know it because the human body has many complex, time-dependent patterns of hormonal secretion, which is essentially a naturally occurring drug release profile [Puleo 22]. However, this profile is perfectly timed, with the correct dosage, and over time instead of taking a drug all at once such as pills. CAP is commonly used as a coating around enteric devices, and with daily food intake does not have toxicity issues or adverse effects up to 30 percent [Puleo 22]. Pluronic F-127 is widely used in the topical gel industry, as well as, in parenteral formulations to extend delivery times [Puleo 22]. Pluronics have been given to rats intravenously at 4 g/kg and 1 g/kg for two and four weeks respectively, and the only side effect was the uptake of type II macrophages noticed in the lungs [Puleo 22]. The use of Pluronic F-127 material as a polymeric drug delivery device is promising, while the intermuscular use of Pluronic F-127 is further studied.

These polymers are unique, for they are surface-eroding polymers. These special polymers
are currently made by the association of CAP and P which is done in a 70/30 weight ratio [Puleo 12, Puleo 22]. This association is done by dissolution of the two polymer components in an acetone solvent through hydrogen bonding of the carboxylic groups in CAP and the ether oxygen groups in P [Puleo 22]. After the solution is made, the polymers are then poured into a flat-bottomed dish, which can range in diameters depending on desired device circumference. Then the polymers are put in a refrigerator or vacuumed dry using a slow solvent evaporation technique overnight creating films within the dishes. This new technology should be readily available and affordable for all future patients due to ease of development and affordability of common ingredients. The CAPP polymer degrades by hydrolysis, so the erosion can be tailored with increasing or decreasing the hydrophobicity of the polymer [Puleo 22]. Also, the polymer tailorability, non-toxicity, and erosion method are making it a strong candidate for an intermuscular drug delivery implant.

Also, the polymers can encapsulate a variety of drugs within their matrix, and with many psychiatric patients taking multiple drugs per treatment regimen, the polymers would be a promising technique to accomplish multi-drug delivery. The way that the CAPP polymer system can do so is by multilayering the polymers [Puleo 22]. In this way of drug delivery, when the top layer, drug A, erodes, then the blank, drug-less layer, then drug B would start eroding, which would automate a multi-drug treatment regimen for psychiatric patients. However, if the patient does not have a multi-drug treatment regimen, then the device could only encapsulate drug A, but with blank layers between drug concentrated layers.

Single drug CAPP delivery methods have already been studied that have promising outlooks about the tailorability of the CAPP systems [Puleo 22]. This engineered drug release schedule would increase adherence to medication, alleviate medication errors, and abuse, and provide continuous, controlled therapy for the lifespan of the implant. With an initial drug
concentration within the polymer films, the drug concentration, release, and stimulus can be in a controlled environment when erosion rate and effects of encapsulated drugs are thoroughly studied. This sequential or intermittent optimization of the CAPP system could make it a viable drug delivery method in the future. In one study, the group designed CAPP devices so that intermittent release of simvastatin could be produced [Puleo 12]. It had positive responses to osteoblast and bone formation during this multilayered treatment regimen [Puleo 23]. Furthermore, the group conducted similar studies of intermittent release of two drugs in the CAPP polymer system, that resulted in positive responses as well [Puleo 12]. Another study of the multilayer drug delivery method shows films would suit the sequential delivery of a multi-drug treatment regimen [Puleo 23]. The same group conducted mathematical modeling of single layer films with metronidazole, simvastatin, and doxycycline revealing no substantial differences in the release profiles of the calculated models and that of the experimental models [Puleo 12]. Along with that, the group successfully conducted an experimental multilayer device using a four-layer CAPP polymer system with alternating metronidazole loaded layers and blank layers [Puleo 12]. This CAPP system showed that sequential or intermittent release of drug concentrated layers could be successfully delayed due to blank layers [Puleo 12, Puleo 23].

The CAPP system is a promising technology for automation of medication schedules and ensuring patient compliance with long-term drug regimens. This would benefit many ill-adhering patient groups such as psychiatric patients, adolescents, and the elderly.

The successful study of erosion rates in the CAPP polymer systems are key to the current research being done. The erosion rates have shown to be quantifiable and substantially accurate in the single layer models previously mentioned [Puleo 22]. Multilayer CAPP device studies should validate the technology behind this device, which shows promise to be more efficient, automatic,
and adherable than current drug delivery methods [Puleo 12, Puleo 23]. To that end, it will reduce the public health issues and errors of treatment of psychiatric patients, while increasing the adherence and completion of therapeutic cycles prescribed. The proper rehabilitation of these patients further reduces governmental costs to provide for these patients.

The reason for new studies is because a microdose of LSD combined with the novel technology of the CAPP polymer system may solve the problem with completion of therapy, medication adherence, and medication abuse within the psychiatric patient community. New, various drugs such as microdosed LSD or other 5HT2A agonists can be studied for singular and/or multiple drug encapsulations for erosion rate results, which so far each drug studied has an alteration to the erosion rate in the CAPP polymer system. In turn, the drug encapsulation is yet another way of the tailorability of the CAPP polymer system. Further studies moved to the optimization of multilayer devices with Fluorescein and Rhodamine B. A three-layer device, as seen in Figure 1, contains a Fluorescein top layer, a blank middle layer, and a Rhodamine B bottom layer.

This configuration was used to perform multilayer experiments. The multi-drug encapsulation ability of CAPP polymers can be used for therapeutic scheduling that requires a multi-drug therapy
over any amount of time required. This ensures that the patient adheres to their drug schedule, gets optimal therapeutic delivery, and completes their prescribed therapy. Some error remains and further optimization of the multilayer device will be critical in the next step of CAPP film usage and research.

For the future, the creation of a sufficient capsule for the multilayer device shall be created, so that it can be implanted, reduce error, and provide ease of use for the CAPP film feasibility. This capsule would have to be able to erode at a much slower rate than the CAPP films ensuring the integrity of the device and that it releases encapsulated drugs in an ordered fashion. The capsule would also lengthen the longevity of the CAPP implant lifespan. The capsule would make the implant an easy procedure during the introduction of the implant into the patient, much like Nexplanon.

The project aims to optimize and thoroughly investigate the capabilities of the CAPP polymer system, which include polymer mass/thickness, multi-drug encapsulation, varying erosion rates, and polymer order in a multilayer device. While the use of a microdose amount of LSD within CAPP films is a future goal, there are mitigants surrounding the use of LSD as a drug treatment therapy. First, the fact that LSD is a Schedule I narcotic means that rescheduling of LSD, or an FDA therapy designation would have to happen to allow for the novel drug to be implanted within a CAPP polymer system. However, the safety risk of LSD is low, as it and other psychedelics are generally known as non-habit forming narcotics [Chen 17, Blevins 20]. To that end, the approved medicinal use of other previously outlawed narcotics includes Tetrahydrocannabinol (THC), marijuana, ketamine, and Gamma-Hydroxybutyric acid (GHB), which opens the door for LSD to be rescheduled or designated a therapy treatment by the FDA [Blevins 20]. Also, improper use or adherence could be an issue, but the street amount of LSD
within the implant would be unsubstantial, as well as, optimization of the CAPP polymer system would reduce these issues.

In conclusion, drug release profiles were quantified from single layer devices to establish the connection between film thickness and drug release rate. Based on release profiles generated from the analysis of single layer devices, multilayered devices were fabricated to achieve controlled, intermittent and/or sequential release of the model drugs. The study found that the multilayered devices could successfully release Fluorescein and Rhodamine B in sequential order and intermittently with a delay of 48-72 hours between each release. Sequential or intermittent release of drugs from an implanted device could ensure long-term drug compliance, automate drug dosing during the life of the implant, and eliminate potential for abuse and medication errors. The dosing schedule would be customizable to the patient due to the CAPP polymer erosion rate and drug release can be altered by several factors including; polymer mass, thickness, drug concentration, and layer ordering. Also, the stimulus effects of LSD provide promising new forms of therapy for patients with psychiatric disease [Chen 17]. A psychiatric patient with chronic treatment-resistant depression would receive a microdose of LSD to rehabilitate or alleviate symptoms over the lifetime of the implant. Thus, CAPP films are a promising technology for long-term, sequential and/or intermittent release of psychiatric agents from an implantable device, and the device will be further optimized to achieve ideal release profiles for the microdosing of LSD in psychiatric patients with treatment-resistant depression, schizophrenia, PTSD, and other psychiatric disorders.
1. CAPP Materials and Methods

The polymeric devices fabricated were from a family of surface-eroding polymers. The devices fabricated comprised of cellulose acetate phthalate (CAP) and Pluronic F-127 (P). Their chemical structures can be seen in Figure 2.

![Chemical Structures of Cellulose Acetate Phthalate (top) and Pluronics F-127 (bottom)](image)

Figure 2- Chemical Structures of Cellulose Acetate Phthalate (top) and Pluronics F-127 (bottom)

CAP is a cellulose derivative that replaces hydrogen atoms from the alcohol group on carbon six with either acetyl or phthalyl to form esters, while Pluronic F-127 is an ABA triblock copolymer comprised of polyethylene oxide (PEO) and poly-propylene oxide [Puleo 22]. The CAPP films are made using a slow solvent evaporation technique. CAP and Pluronic F-127 are mixed in a 70:30 weight ratio, respectively, and dissolved in acetone creating a polymer solution, as seen in Figure 3 [Puleo 12, Puleo 22].
The interaction that stabilizes this blend between the two polymers is that of hydrogen bonding, which is between the hydrogens on the carboxylic groups of CAP and the ether oxygens in Pluronic F-127 [Puleo 22]. Rhodamine B and Fluorescein was added at 1% weight into the acetone-polymer solution and stirred thoroughly until completely dissolved. The resulting drug-polymer solution was poured into muffin tins as seen in Figure 4 and left to store in the refrigerator at 4 degrees Celsius for 24 hours for slow-solvent evaporation.

Blank, drug-less, CAPP films were prepared using the same method, but without the addition of drugs, respectively. Upon allowing the CAPP films to dry overnight, the stock CAPP films were complete, as seen in Figure 5.
Figure 5- Stock CAPP film devices containing Rhodamine B (top, red) and Fluorescein (bottom, yellow)

For study, samples were punched out of the stock CAPP films that are roughly 6 mm in diameter, as seen in Figure 6, so the CAPP films would fit into the plate wells.

Figure 6- Samples punched out of stock films to fit into plate wells 6mm in diameter

There were variations of single layer and multi-layer CAPP devices, therefore, the study used polymers of varying mass to better understand their release kinetics. The study included masses of; 300, 600, 900, 1200, 1600, and 1800 milligram polymers.

The fabrication of multi-layer CAPP films were designed for intermittent and or sequential release of the study drugs. The multi-layer devices are put in order of the desired sequence and 5 microliters of acetone were placed between each layer. After the application of acetone, compression bonds the layers together. For sequential release of both Rhodamine B and Fluorescein, a three-layered CAPP device was fabricated using the Fluorescein and Rhodamine B samples with a blank film between the two layers, as seen in Figure 1. The multi-layered CAPP
devices were loaded into a 6-mm polystyrene well in a plate, which acts as a barrier to better enable unidirectional release of the study drugs and erosion of the CAPP films.
2. Fluorescence Imaging and Drug Release

Analysis of the CAPP devices was done by the incorporation of study fluorescent drugs, Rhodamine B and Fluorescein, respectively. To analyze the CAPP films after fabrication, the single layer and multi-layer devices were eroded in a solution of Phosphate-buffered saline (PBS) at 37 degrees Celsius in 6 mm wells in a polystyrene plate. The resulting supernatant solution on top of the continuously eroding CAPP film was collected every hour for the first 6 hours and then every 6 hours until complete erosion of the CAPP film. Upon collection of the supernatant solution, 200 microliters of fresh PBS would be injected back into the polystyrene wells to continue the erosion of the CAPP films. The measuring of the supernatant solution was done by fluorescent imaging using a plate reader. Initially, PBS is loaded into a black polystyrene plate with no other solutions or chemicals to evaluate the relative fluorescence units (RFUs) of PBS for background signal. Henceforth, the imaging was done with the supernatant solutions collected. The imaging of fluorophores, a general name for a fluorescent molecule, is done by exciting the fluorescent molecule at a range of wavelengths and the RFUs recorded are at a relative range of emission wavelengths using the plate reader. For the study molecules Rhodamine B and Fluorescein, their excitation wavelengths were 546 nm and 491 nm, respectively [Bioquest 24, Bioquest 25]. In the beginning of study, Rhodamine B and Fluorescein samples with known concentrations are measured in the plate reader for their RFUs. Using this information, a linear line of best fit was used to analyze future data. The linear line of best fit was used to calculate the concentration of future experimental samples by using known RFUs. Therefore, the RFUs measured give an indication of the concentration of study drugs that are in each sample of supernatant solution. The concentrations are used to analyze the release rates of CAPP films over time and create release
profiles, which are used to evaluate if the polymers are within the therapeutic window, as seen in Figure 7.

Figure 7- The Ideal Therapeutic Window for CAPP devices

The window has a threshold concentration, which until that concentration is met the drug will have no effect. However, it also has a maximum concentration that cannot be exceeded or the patient will have side effects or toxicity issues. The ideal kinetics fall between this range as a constant therapeutic release, which is a motive behind the study of CAPP films and their release kinetics.

3. Effect of Polymer Mass
During the study of CAPP films, polymer mass, along with other factors, were studied to show the tailorable capabilities of CAPP films. During the fabrication of CAPP films, multiple masses of CAP and P were made to study the relationship of polymer mass with erosion time and polymer thickness. The weight ratios remained the same throughout the CAPP films fabrication. The CAPP films studied were polymer masses of 300, 600, 900, 1200, 1600, and 1800 milligrams. After fabrication, the thickness of various polymer stock films was measured by using a digital caliper with a sample size of 5 per film mass group. The average polymer thickness recorded for each polymer mass group can be seen in Figure 8.

![Polymer Mass vs Thickness](image)

**Figure 8- Polymer Mass verse Thickness**

In Figure 8, increasing polymer mass increases the polymer thickness at a constant rate, which shows a very high positive correlation between the two. Also, the rate of increase is highly calculable and using the line of best fit method a R² value of .99161 was obtained. This not only shows that it is increasing constantly, but that the thickness needed for an unknown polymer can be found using theoretical calculations using the linear trend line in Figure 8 with little error. Along with polymer thickness, another variable of CAPP films that is effected by polymer mass variation
is polymer erosion time. The erosion time was a variable studied to determine if the CAPP films could be easily tailored to fit custom patient doses and drug schedules. The erosion time increased with polymer mass and thickness showing a highly correlated relationship between the variables as well. Increasing the polymer mass and thickness made for a longer erosion time for the CAPP films, as seen in Figure 9.

![Polymer Erosion Time Chart](image)

**Figure 9- Erosion Time Difference due to Varying Polymer Mass**

One of the targets of the CAPP film study was to understand and analyze the relationship between these three variables: polymer mass, polymer thickness, and polymer erosion time. Using Figure 8 and 9, the CAPP films were successfully analyzed and can be seen to be easily tailorable for drug schedule optimization and specific patient needs. Also, seen in Figure 9, the encapsulation of the two variable drugs altered the CAPP film erosion time. The CAPP film polymers can co-encapsulate a variety of drugs, which has the potential to reduce drug delivery issues. With the co-
encapsulating capabilities of CAPP films comes challenges as well, which is why the variation of erosion time between the two study drugs was analyzed and measured. The study drugs, Rhodamine B and Fluorescein, can be seen in Figure 9 to have variably different erosion times within the same polymer mass group. The effects are slight at first, but with the increase in polymer mass the Rhodamine B and Fluorescein erosion difference increases within the same polymer mass group. While the erosion time differences range from 2 hours to 22 hours, as seen in Figure 9, the common theme is that the increase of polymer mass increases the difference between the study drugs erosion time. Therefore, depending on the drug selected, a CAPP film study trial would have to be done to quantify an average erosion rate for a new encapsulated drug. The varying drugs used in encapsulation in the CAPP films show how easily the CAPP films can be tailored for specific release kinetic profiles, drug dosing, and drug schedules. The optimization of these 3 variable techniques, polymer thickness, polymer erosion rates, and drug encapsulation would further solidify the CAPP films drug delivering capabilities.

4. **Single and Multi-Layer Release Profiles**

The single layer CAPP films were designed for ideal drug release, so that the drug delivery kinetics would be like the ideal kinetics in Figure 7. The single layer CAPP films were studied to analyze their kinetic release profiles and to interpret the results. For the single layer study, the 6-mm CAPP samples were stamped out into multiples of 5 for each polymer mass group studied.
The polymer mass groups studied for the single layer release profiles were the 300, 600, 900, 1200, and 1600 milligram CAPP films. To measure the data, the single layer CAPP films were eroded in PBS and put into the plate reader to measure their relative RFUs. The resulting graph, seen in Figure 10, shows the timeline of the CAPP films erosion and their range of RFUs recorded for the study drug Fluorescein.

![CAPP Single Layer Kinetics](image)

**Figure 10- CAPP Single Layer Relative RFUs verse Time for Fluorescein**

As seen in Figure 10, the initial release of the single layer polymer kinetics was all similar with no relation to polymer mass or thickness. The duration of the release profiles was the only distinction that polymer mass/thickness changed for the polymer release profiles. Using this data, and the drug concentration trend line found using known concentrations, the graph in Figure 11 was created.
In Figure 11, the release concentration of study drug, Fluorescein, can be seen against time. This graph shows the kinetic release profiles of the various polymer mass groups, which gave the study a comparison against the ideal kinetics profile. Understanding the drug concentration release over time is important for toxicity issues and the drug concentration threshold for therapy. As seen in the ideal polymer kinetics, the drug release profiles of CAPP must stay between the therapeutic threshold and toxicity threshold; however, if a larger concentration threshold is needed, then the weight percentage of the encapsulated drug can be increased for proper dosing or vice versa for lower concentration thresholds. This shows that further study of drug encapsulation and release kinetics for single layer profiles can be made highly tailorable for each patient’s drug scheduling needs.

The multi-layer CAPP film device is the ideal design for therapeutic drug delivery. As stated earlier, the multi-layer device can be an ideal drug delivery method for multi-drug therapy schedules, long-term therapy schedules, or new forms of psychiatric agents, such as micro-dosed Lysergic acid diethylamide (LSD). The multi-layer CAPP film device that was studied was fabricated of three layers consisting of a top layer of Fluorescein, followed by a blank non-drug
layer, and ending in a Rhodamine B bottom layer, as seen in Figure 1. The CAPP film device studied was designed for sequential and intermittent release of Fluorescein and Rhodamine B.

![300mg FBR Multilayer Device](image)

**Figure 12- CAPP Multi-Layer Device RFUs verse Time**

Using Figure 12, the separation of the two fluorescent study drugs by a blank layer provided a barrier between the two during erosion, which created an intermittent drug release schedule. The initial release of RFUs of the study drug Fluorescein can be seen in Figure 12, as well as, the unsubstantial release of Rhodamine B because of the delayed sequential release pattern developed using the CAPP film device. Again, this was accomplished using the blank layer to provide a delay of release of the bottom layer study drug, Rhodamine B, as the RFUs for Rhodamine B did not appear to be substantial until the blank layer started to erode. The Fluorescein layer completely eroded in the drug delivery schedule, noted by the steady decrease of FITC RFUs in Figure 12 over time. Using this information in Figure 12, the CAPP film device can successfully release a multi-drug schedule intermittently or sequentially. The multi-drug encapsulation of CAPP polymers can be used for a therapeutic scheduling that requires a multi-drug therapy over any amount of time required, and the CAPP polymers offer potential in being able to deliver drugs with high-risk challenges such as medication error, abuse, and medication scheduling at a lower
rate of error. The multi-layer CAPP film device could ensure a full completion of the prescribed therapy by the physician to the patient as well, which makes CAPP a promising technology with more optimization.

5. Discussion and Future Directions

The research conducted aimed to develop a CAPP based film device capable of co-encapsulating a variety of drugs, while also being able to deliver them intermittently or sequentially over a broad range of drug schedules. Another research aim was single layer release profiles, which were to give insight into how the fluorescent study drugs, Fluorescein and Rhodamine B, behaved encapsulated in the CAPP film. The profiles were made by placing samples of CAPP films in a polystyrene well for unidirectional erosion, erode in PBS, and then use
fluorescent imaging to quantify the relative RFUs due to the resulting supernatants. Examining the ability of CAPP films to fall within the therapeutic window was an aim of the single layer release profile, as well as, understanding varying erosion time due to different drugs encapsulated and thicknesses of CAPP films. The erosion time differed between the Rhodamine B and Fluorescein with no variation in CAPP polymer thickness making drug selection a therapy variable in drug delivery when using CAPP film devices. The CAPP erosion time increased with CAPP film mass/thickness no matter the study drugs, which shows that the CAPP films can be highly tailorable by the polymer mass variable. CAPP films have potential to be tailored to patient specific drug scheduling and dosing, which would reduce drug delivery issues such as medication error, abuse, and medication scheduling. Building on those ideas, the CAPP multilayered device was fabricated using 5 microliters of acetone between 300 milligram layers of Fluorescein, blank, and Rhodamine B, to fuse together a three-layer device. They were arranged in that order for multilayered studies, which aimed to capitalize on the potential capabilities of CAPP films to release drugs intermittently or sequentially. Intermittent and sequential release of Fluorescein and Rhodamine B during erosion was aided by the separation caused by the blank layer causing the release profile to have a delay of drug release for Rhodamine B. The multilayered CAPP films can be tailored by layer order, polymer mass, and encapsulation of a variety of drugs. These variations in variables prove CAPP could be a long-term solution for drug delivery for a multitude of drug therapies that could include multiple drugs, a long-term therapy, or abusive medicines. Also, in the experiment, increasing temperature made the erosion of the CAPP polymers faster. Therefore, temperature could be a determining factor in selecting the correct CAPP film mass/thickness for drug therapy upon further CAPP optimization. The drugs encapsulated and their release profiles needed for therapy will depend on the patient’s prescribed therapy, drug schedule, and relative
behavior of the drug within the CAPP film device, which calls for further optimization of the CAPP film devices.

6. Conclusion

In conclusion, the fabrication of the CAPP films by using simple solvent-evaporation techniques with acetone show that surface-eroding polymers, such as CAPP, can be easily studied in a laboratory setting, so that new therapeutic drugs and drug delivery issues may be studied and optimized using CAPP films. The CAPP film release profiles are tailorably for therapy based on polymer mass, layer order, and encapsulation of a variety of drugs. The CAPP films could reduce the issues with medication error and abuse, medication scheduling, and completion of therapeutic drug cycles, ultimately increasing drug compliance for patients at a high risk of these issues. Thus, CAPP films are a promising technology for long-term, sequential and/or intermittent release of
psychiatric agents. In the future, studies will begin using a 5HT2A-agonist device that will be placed intra-muscularly on mice to study the effects, toxicity, and long term release of the drug in an environment more suited for human usage of CAPP films. Finally, the device will be further optimized to achieve ideal release profiles for the micro-dosing of LSD in patients with treatment-resistant depression.

7. Bibliography


