

Beyond Nicotine: Buccal Films for Multi-Drug Delivery in Smoking Cessation

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ABSTRACT

Smoking cessation remains a significant global health challenge, with current pharmacotherapies often yielding suboptimal long-term abstinence rates due to complex withdrawal symptoms and varied individual responses. This review explores the innovative potential of mucoadhesive buccal films for multi-drug delivery as a sophisticated approach to enhance smoking cessation outcomes. While nicotine replacement therapies (NRTs) address physical dependence, their limitations, coupled with the side effect profiles and inconsistent efficacy of non-nicotine pharmacotherapies like bupropion and varenicline, highlight an unmet need for more integrated and patient-centric solutions. Buccal films, by leveraging the oral mucosa's unique characteristics—high vascularization, bypass of first-pass metabolism, and direct systemic absorption—offer a versatile platform for delivering multiple active pharmaceutical ingredients (APIs). This article provides a comprehensive overview of the rationale for combination therapy, the challenges in co-formulating disparate drugs into mucoadhesive buccal films, advancements in polymer science and formulation techniques, and the critical in vitro/ex vivo characterization methods. It critically discusses the synergistic potential of co-delivering nicotine with agents like bupropion or varenicline to address both physical cravings and neuropsychological aspects of addiction. Furthermore, the review identifies current hurdles in optimizing multi-drug buccal film formulations, ensuring their stability, and facilitating their clinical translation, outlining future research directions to realize their full therapeutic promise in combating tobacco dependence.

Keywords: Smoking cessation, Nicotine, Buccal film.

I. INTRODUCTION

Smoking cessation is a critical global public health imperative, yet nicotine addiction remains a leading cause of preventable disease and mortality worldwide [1]. Despite decades of research and the availability of various pharmacotherapies, sustained abstinence rates following a quit attempt often remain disappointingly low, typically ranging from 15% to 25% at one year [2]. This persistent challenge underscores the complex interplay of physical nicotine dependence, psychological factors, and behavioral cues that characterize tobacco addiction.

Current pharmacotherapeutic options include nicotine replacement therapies (NRTs) such as patches, gums, lozenges, and inhalers, which aim to alleviate withdrawal symptoms by providing exogenous nicotine. While effective, NRTs often face limitations related to inconsistent nicotine delivery, variable patient adherence, and an inability to fully mimic the rapid onset of nicotine delivery from cigarettes, which contributes to acute craving management [3, 4]. Furthermore, non-nicotine pharmacotherapies like bupropion, an antidepressant that acts as a norepinephrine-dopamine reuptake inhibitor, and varenicline, a partial agonist of nicotinic acetylcholine receptors, offer alternative mechanisms of action. However, these drugs are associated with systemic side effects and may have a delayed onset of therapeutic effect when administered orally, further impacting patient compliance and long-term success [5, 6].

The multifaceted nature of nicotine addiction suggests that a single-agent approach may be insufficient for a significant proportion of smokers. Combination pharmacotherapy, such as combining an NRT with bupropion or varenicline, has shown superior efficacy over monotherapy in clinical trials, indicating a potential synergistic benefit in addressing both physical withdrawal and motivational aspects of quitting [7, 8]. However,

administering multiple agents orally often involves complex dosing regimens, potential drug-drug interactions, and additive gastrointestinal side effects, which can deter patient adherence.

To overcome these inherent limitations of conventional oral administration and enhance the efficacy of combination therapies, mucoadhesive buccal drug delivery systems have emerged as a highly promising and patient-centric alternative. The buccal mucosa, characterized by its rich blood supply and direct access to systemic circulation, offers a unique opportunity to bypass hepatic first-pass metabolism and avoid gastrointestinal degradation, leading to improved drug bioavailability and a potentially faster onset of action [9, 10]. Furthermore, the ability of mucoadhesive films to adhere to the mucosal surface prolongs the contact time, facilitating sustained drug absorption and potentially allowing for lower total daily doses, thereby minimizing systemic adverse effects [11].

II. LIMITATIONS OF CURRENT SMOKING CESSATION PHARMACOTHERAPIES AND THE RATIONALE FOR COMBINATION THERAPY

Current pharmacotherapies, while foundational to smoking cessation efforts, still face substantial hurdles that contribute to the high rates of relapse. Understanding these limitations is crucial for appreciating the value of advanced delivery systems and combination approaches.

2.1. Limitations of Existing Monotherapies

Nicotine Replacement Therapies (NRTs): NRTs deliver nicotine without the harmful chemicals found in tobacco smoke, mitigating withdrawal symptoms [3]. However, their effectiveness is often limited by several factors:

- **Variable Nicotine Delivery:** Absorption kinetics can vary significantly between different NRT formulations and individuals. For instance, nicotine gum or lozenges require proper administration technique for optimal absorption, which is often not adhered to in real-world settings [4]. Patches provide a relatively steady release but may not adequately address acute cravings.
- **Compliance Issues:** Daily adherence to NRTs can be challenging. Users may find lozenges or gums inconvenient, or experience localized irritation, taste issues, and gastrointestinal

disturbances (e.g., nausea from swallowed nicotine) [12].

- **Incomplete Craving Management:** While NRTs reduce baseline cravings, they may not provide the rapid nicotine surge that smokers are accustomed to from cigarettes, making it harder to manage acute, intense cravings [13].

Non-Nicotine Pharmacotherapies: Bupropion and varenicline offer alternative mechanisms to reduce nicotine withdrawal and cravings:

- **Bupropion:** As a norepinephrine-dopamine reuptake inhibitor, bupropion reduces withdrawal symptoms and appears to blunt the rewarding effects of nicotine [5]. However, it has a delayed onset of action, requiring treatment initiation prior to a quit date, and is associated with systemic side effects such as insomnia, dry mouth, and, rarely, seizures, which can limit its use [14]. Oral bioavailability is relatively low (around 5-20%) due to extensive hepatic metabolism [15].
- **Varenicline:** This partial agonist of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor reduces craving and withdrawal symptoms while also blocking nicotine's rewarding effects [6]. Despite its efficacy, varenicline can cause neuropsychiatric side effects, including mood changes, depression, and suicidal ideation, though the causal link remains debated [16]. Nausea, insomnia, and abnormal dreams are common [17]. Varenicline is primarily renally excreted with minimal metabolism, suggesting potential for interactions in patients with renal impairment [18].

2.2. Rationale for Combination Pharmacotherapy

The complexity of nicotine addiction, involving both physiological dependence and psychological/behavioral components, often benefits from a multi-pronged approach. Clinical evidence supports the superiority of **combination pharmacotherapy** over monotherapy for smoking cessation [7].

- **Synergistic Mechanisms:** Combining agents that act on different pathways can lead to more comprehensive craving and withdrawal management. For example, a sustained-release NRT patch can provide continuous nicotine levels, while a rapid-delivery NRT (like a buccal film) can manage acute cravings. Simultaneously, bupropion or varenicline can

target central nervous system mechanisms to reduce the reinforcing effects of smoking [8].

- **Addressing Diverse Symptoms:** Quitting smoking can manifest in a wide array of withdrawal symptoms (e.g., irritability, anxiety, difficulty concentrating, increased appetite) [2]. A combination approach can more effectively mitigate this broader spectrum of symptoms, enhancing comfort and reducing the likelihood of relapse.
- **Improved Efficacy:** Meta-analyses consistently show that combination therapies (e.g., nicotine patch plus short-acting NRT, or NRT plus bupropion/varenicline) significantly increase abstinence rates compared to single pharmacotherapy or placebo [7, 8].

Despite the proven benefits, current combination therapies administered orally or via multiple routes can suffer from complexity in dosing regimens, leading to reduced patient adherence. This highlights a significant unmet need for integrated, patient-friendly multi-drug delivery systems.

III. BUCCAL DRUG DELIVERY: A PROMISING PLATFORM FOR ENHANCED SMOKING CESSATION

The **buccal route** offers unique physiological advantages that make it an ideal candidate for overcoming the limitations of conventional oral and even other NRT delivery systems, especially for multi-drug formulations in smoking cessation.

3.1. Anatomy and Physiology of the Buccal Mucosa

The buccal mucosa, lining the inner cheek, is composed of a **non-keratinized stratified squamous epithelium** about 500-600 μm thick [9]. This thin, relatively permeable membrane is highly vascularized, with a rich blood supply drained directly into the systemic circulation via the jugular vein. Key features supporting its utility for drug delivery include:

- **Bypass of First-Pass Hepatic Metabolism:** Drugs absorbed through the buccal mucosa enter the systemic circulation directly, circumventing the liver's metabolic processes that often reduce the bioavailability of orally ingested drugs [10]. This is particularly advantageous for drugs like bupropion, which undergoes extensive first-pass metabolism [15].

- **Avoidance of Gastrointestinal Degradation:** The buccal route protects drugs from enzymatic degradation in the stomach and intestines, as well as exposure to acidic pH conditions, enhancing the stability of sensitive compounds [10].
- **Rapid Onset of Action:** The high vascularity and direct systemic access can lead to a quicker onset of therapeutic effect compared to oral ingestion, which is crucial for managing acute nicotine cravings [13].
- **Patient Compliance and Ease of Administration:** Buccal formulations are non-invasive, easy to self-administer, and can be removed if adverse effects occur. Their discreet nature and potential for prolonged adherence contribute to higher patient compliance compared to frequent dosing of multiple oral tablets [11].
- **Potential for Sustained Release:** The adhesive nature of buccal films allows for extended contact time with the mucosa, enabling controlled and sustained drug release over several hours. This can help maintain therapeutic drug levels and reduce dosing frequency.

3.2. Principles of Mucoadhesion

Mucoadhesion refers to the adhesion between a natural or synthetic polymer and a mucous membrane [19]. In the context of buccal films, mucoadhesion is paramount for ensuring the dosage form remains at the absorption site for a sufficient duration, allowing for optimal drug release and permeation.

- **Mechanisms of Mucoadhesion:** The process of mucoadhesion typically involves several stages, including contact, wetting, and consolidation. Key theories explaining mucoadhesion include:
 - **Electronic Theory:** Proposes electron transfer between the polymer and mucin surfaces, leading to attractive electrostatic forces [19].
 - **Adsorption Theory:** Suggests that mucoadhesion results from surface forces such as hydrogen bonding, van der Waals forces, and hydrophobic interactions between the polymer and mucus glycoprotein [19].
 - **Wetting Theory:** Relates to the ability of the polymer to spread and establish intimate contact with the moist mucosal surface [20].
 - **Diffusion Interpenetration Theory:** States that polymer chains and mucin glycoproteins interpenetrate and entangle, forming a strong

adhesive bond, especially for flexible polymer chains [20].

IV. MATERIALS AND METHODS

4.1. Key Components of Buccal Film Formulations

The selection of excipients is critical for achieving desired film properties and drug delivery characteristics.

- **Film-Forming and Mucoadhesive Polymers:** These are the backbone of the film, providing structural integrity and adherence to the buccal mucosa.
 - **Natural Polymers:**
 1. **Chitosan:** A cationic polysaccharide known for its excellent mucoadhesive properties, biocompatibility, and permeation-enhancing capabilities due to its ability to transiently open tight junctions [21]. Its solubility can be modified by salification (e.g., chitosan-ascorbate) to optimize film properties.
 2. **Hydroxypropyl Methylcellulose (HPMC):** A widely used semi-synthetic polymer with good film-forming, swelling, and mucoadhesive properties. Different viscosity grades (e.g., HPMC K4M, K100M) can modulate drug release rates [22].
 3. **Sodium Carboxymethyl Cellulose (Na CMC):** An anionic cellulose derivative known for its good mucoadhesion and gelling properties.
 4. **Hydroxypropyl Cellulose (HPC):** Another cellulose derivative offering good film-forming and mucoadhesive characteristics.
 - **Synthetic Polymers:**
 1. **Polyethylene Oxide (PEO):** High molecular weight PEO can provide excellent flexibility and mucoadhesion, forming strong hydrogen bonds with mucin [23].
 2. **Polyvinylpyrrolidone (PVP):** Often used as a binder and film-former, contributing to film flexibility and drug dissolution. PVP K-30 is a common grade [22].
 3. **Carbopol (Polyacrylic acid):** Known for its strong mucoadhesive properties due to carboxylic groups that interact with mucin [24].
 - **Polymer Combinations:** Blending different polymers (e.g., HPMC and Na CMC, Chitosan and PEO) can create synergistic effects,

optimizing film strength, flexibility, mucoadhesion, and drug release profiles [25].

- **Plasticizers:** These are essential to improve the flexibility and reduce the brittleness of the films, making them less prone to cracking during handling and application. Common examples include **glycerol, polyethylene glycol (PEG) (various molecular weights), and propylene glycol** [26]. The concentration of plasticizer directly impacts the mechanical strength and elasticity of the film.
- **Permeation Enhancers:** To overcome the buccal mucosa's barrier properties, permeation enhancers can be incorporated to facilitate drug absorption. These agents work by various mechanisms, such as disrupting lipid bilayers, increasing membrane fluidity, or altering tight junctions. Examples include **chitosan (due to its positive charge), fatty acids (e.g., oleic acid), bile salts, and certain surfactants** [27].
- **Active Pharmaceutical Ingredients (APIs):** For smoking cessation, this includes **nicotine**, and potentially **bupropion** or **varenicline**. The choice of API influences solubility, stability, and compatibility within the film matrix.
- **Other Excipients:**
 - **Solvents:** Water, ethanol, or binary mixtures are typically used in the solvent casting method to dissolve polymers and disperse drugs.
 - **Taste Masking Agents:** Crucial for improving patient acceptability, especially for drugs with unpleasant tastes (e.g., nicotine). Sweeteners (sucralose, aspartame) and flavoring agents (mint, fruit) are commonly used [28].
 - **Saliva Stimulants:** Agents like citric acid can temporarily increase saliva production, aiding in film wetting and initial drug dissolution, although excessive saliva can also lead to premature swallowing.

4.2. Formulation Techniques

The **solvent casting method** is the most widely used and versatile technique for preparing mucoadhesive buccal films [29].

• Steps involved in Solvent Casting:

1. **Polymer Dissolution:** Polymers are dissolved in a suitable solvent (e.g., water, ethanol, or a mixture) to form a viscous solution.
2. **Drug Dispersion/Dissolution:** The API(s) and other excipients (plasticizers, permeation enhancers, taste maskers) are dissolved or uniformly dispersed in the polymer solution.

For multi-drug systems, care must be taken to ensure compatibility and stability of all APIs.

3. **De-aeration:** The solution is de-aerated to remove air bubbles, which can affect film uniformity and appearance.
4. **Casting:** The homogenous solution is poured onto a flat, non-stick surface (e.g., a petri dish, glass plate, or mercury surface).
5. **Drying:** The solvent is evaporated slowly under controlled temperature and humidity conditions to form a solid film. This step is crucial to prevent cracking or warping.
6. **Cutting:** The dried film is then cut into desired sizes and shapes for individual doses.
- **Other Techniques:** While less common for buccal films currently, techniques like hot-melt extrusion offer solvent-free manufacturing and better content uniformity for certain formulations [30].

V. CHARACTERIZATION AND EVALUATION OF MULTI-DRUG BUCCAL FILMS

Rigorous characterization is crucial to ensure the quality, efficacy, and safety of multi-drug buccal film formulations.

5.1. Physicochemical and Mechanical Characterization

- **Appearance and Texture:** Visual inspection for smoothness, transparency, and absence of air bubbles or drug agglomerates.
- **Weight Uniformity and Thickness Uniformity:** Essential for consistent dosing. Gravimetric methods and micrometer measurements are used [29].
- **Surface pH:** Measured by placing the film on a pH electrode with a drop of distilled water. A pH compatible with the buccal environment (6.2-7.4) is crucial to prevent irritation [29].
- **Folding Endurance:** Determines the film's flexibility and resistance to breakage during handling. Measured by repeatedly folding the film at the same point until it breaks [26].
- **Tensile Strength and Elongation at Break:** Evaluate the film's mechanical strength and elasticity using a texture analyzer. These properties are vital for handling and in-mouth comfort [26].
- **Swelling Index (SI):** Measures the film's ability to absorb water and swell. Adequate swelling is necessary for mucoadhesion and controlled drug release. It is determined by

monitoring weight increase of the film upon exposure to simulated saliva [29].

- **Moisture Content and Moisture Uptake:** Important for film stability and physical integrity during storage.

5.2. Drug Content Uniformity

Each film unit must contain the precise amount of each API. This is determined by dissolving individual films and analyzing the drug concentration using validated analytical methods like HPLC or UV-Vis spectroscopy. High drug content uniformity (>90-95%) indicates homogeneous distribution of drugs throughout the formulation [31].

5.3. In vitro Mucoadhesion Studies

These tests quantify the adhesive strength of the film to a mucosal surface.

- **Detachment Force Method:** Measures the force required to pull the film away from a model mucosal surface (e.g., porcine buccal mucosa) under controlled conditions [32].
- **Shear Stress Method:** Measures the force required to slide the film off the mucosal surface.
- **In vitro Residence Time:** Determines how long the film can remain adhered to the mucosa under simulated physiological conditions (e.g., simulated salivary flow) [32].

5.4. In vitro Drug Release Studies

These studies predict how the drugs will be released from the film in the oral cavity.

- **Dissolution Apparatus:** USP Dissolution Apparatus I (basket) or II (paddle) modified for films, or specialized Franz diffusion cells can be used.
- **Release Media:** Simulated saliva (pH ~6.7-6.8) at physiological temperature (37°C) is used.
- **Release Kinetics:** Data is analyzed using mathematical models (e.g., Zero-order, First-order, Higuchi, Korsmeyer-Peppas) to understand the release mechanism and rate of each drug from the film matrix [33]. Differential release profiles for multiple drugs should be precisely controlled.

5.5. Ex vivo Permeation Studies

These studies provide a more accurate prediction of in vivo drug absorption.

- **Model Membranes:** Typically conducted using freshly excised porcine buccal mucosa

due to its histological similarity to human buccal mucosa [34].

- **Franz Diffusion Cells:** The film is placed on the mucosal tissue in the donor chamber, and drug permeation into the receptor chamber (containing simulated physiological fluid) is monitored over time.
- **Permeation Flux and Permeability Coefficient:** Calculated to quantify the rate and extent of drug transport across the membrane. These are critical for assessing the effectiveness of permeation enhancers and optimizing drug absorption from multi-drug films.

5.6. Stability Studies

Assessing the long-term stability of multi-drug films is crucial for shelf-life and efficacy.

- **Accelerated Stability Testing:** Films are stored under elevated temperature and humidity conditions (e.g., 40°C/75% RH) for short periods (e.g., 6 months) to predict long-term stability [31].
- **Long-Term Stability Testing:** Films are stored under recommended storage conditions (e.g., 25°C/60% RH) for the proposed shelf-life.
- **Parameters Monitored:** Drug content, physical appearance, mechanical properties, and in vitro drug release profiles are assessed at predetermined intervals.
- **Compatibility Studies:** FT-IR and DSC analyses are used to confirm no chemical interactions or polymorphic changes occur between the drugs and excipients over time [31].

VI. ADVANCEMENTS AND RESEARCH IN MULTI-DRUG BUCCAL FILMS FOR SMOKING CESSATION

Recent research has made significant strides in developing sophisticated buccal film formulations, paving the way for effective multi-drug delivery.

6.1. Co-Delivery of Nicotine with Other Pharmacotherapies

- **Nicotine and Bupropion:** Combining nicotine's direct agonistic effects on nicotinic receptors with bupropion's dopamine and norepinephrine reuptake inhibition offers a powerful synergistic approach to manage both physical withdrawal and mood disturbances

[35]. Buccal films could deliver rapid nicotine for acute cravings and a sustained release of bupropion, bypassing its extensive first-pass metabolism. Research focuses on optimizing the film matrix to accommodate both drugs with different physicochemical properties and desired release profiles [36]. Challenges include bupropion's relatively large molecular weight and hydrophobicity, which might limit its buccal permeation, necessitating efficient permeation enhancers.

- **Nicotine and Varenicline:** While varenicline is a potent nicotinic receptor partial agonist, combining it with exogenous nicotine from a buccal film could potentially provide immediate craving relief while varenicline establishes its therapeutic effects [37]. This combination is less explored in buccal films due to varenicline's existing oral efficacy and high systemic availability (though side effects could be mitigated by buccal delivery if lower doses are possible). Formulation challenges would include managing their distinct pharmacokinetic profiles and potential drug-drug interactions at the absorption site or systemically.
- **Novel Combinations:** Research could also explore co-delivery of nicotine with other compounds that address specific aspects of addiction, such as anxiolytics, appetite suppressants, or neuro-modulators, delivered in a controlled manner via buccal films.

6.2. Advanced Formulation Strategies

- **Layered Films:** To achieve precise control over the release kinetics of multiple drugs, multi-layered buccal films are being explored. Each layer can contain a different drug or different polymeric compositions, allowing for rapid, sustained, or sequential release profiles [38]. For instance, an outer layer could contain rapidly dissolving nicotine, while an inner layer releases bupropion gradually.
- **Nanotechnology Integration:** Incorporating drug-loaded **nanoparticles or nano-fibers** within the film matrix can enhance drug solubility, improve permeation across the buccal mucosa, and provide highly controlled release. Nanocarriers can also protect sensitive drugs from degradation within the film or during absorption [39].
- **pH-Sensitive and Stimuli-Responsive Polymers:** Development of polymers that respond to the physiological pH of the buccal

cavity (or other stimuli) to trigger drug release. This could allow for more personalized and on-demand delivery, particularly useful for managing unpredictable cravings.

- **Taste Masking and Sensory Improvement:** For multi-drug films, especially those containing nicotine, effective taste masking is crucial for patient acceptability. Innovations in flavoring agents, sweeteners, and formulation techniques to encapsulate bitter drugs are vital for long-term adherence [28].
- **Enhanced Mucoadhesion:** Developing novel mucoadhesive polymers or polymer blends with superior adhesion strength and residence time, capable of withstanding the dynamic environment of the oral cavity.

6.3. Pre-clinical and Clinical Relevance

- **Improved Bioavailability and Reduced Dosing Frequency:** Buccal films promise higher bioavailability for drugs susceptible to first-pass metabolism (like bupropion), potentially allowing for lower total daily doses and reduced systemic side effects [40]. For nicotine, controlled buccal delivery can offer more consistent plasma levels, bridging the gap between current NRTs and the rapid nicotine hit from smoking.
- **Patient-Centric Design:** The discreet nature, ease of application, and potential for reduced systemic side effects of buccal films are expected to significantly improve patient compliance, a major barrier in smoking cessation [11]. The ability to apply a single film containing multiple agents simplifies the regimen compared to taking multiple tablets or using a combination of NRTs.
- **Targeting Acute Craving Episodes:** For both nicotine and other anti-craving agents, rapid-release components within a multi-drug film could provide immediate relief during intense craving episodes, preventing relapse.

VII. CONCLUSION

The pursuit of more effective and patient-centric solutions for smoking cessation continues to drive pharmaceutical innovation. Multi-drug mucoadhesive buccal film formulations stand out as a highly promising strategy to address the complex challenges of nicotine addiction. By intelligently combining multiple pharmacotherapeutic agents within a single, convenient buccal film, this approach offers the potential for enhanced bioavailability, improved

control over drug release, reduction in systemic side effects, and significantly boosted patient compliance.

The unique physiological advantages of the buccal mucosa—bypassing first-pass metabolism and offering direct systemic absorption—make it an ideal site for delivering combination therapies like nicotine with bupropion or varenicline. While significant progress has been made in optimizing film formulation, selecting appropriate polymers, and characterizing these systems in vitro and ex vivo, the path to widespread clinical adoption requires overcoming challenges related to taste, long-term stability, and large-scale manufacturing.

Looking ahead, continued research into advanced material science, nanotechnology integration, and personalized medicine approaches will undoubtedly refine these systems. Ultimately, rigorous clinical trials will be essential to fully establish the therapeutic benefits and safety profiles of these novel multi-drug buccal films. By doing so, we can move beyond existing limitations and provide individuals attempting to quit smoking with a more effective, palatable, and sustainable pathway to long-term abstinence, profoundly impacting global public health.

VIII. FUTURE DIRECTIONS

- **Personalized Medicine Approaches:** Future research could focus on developing buccal films with customizable drug doses or release profiles based on individual patient needs, genetic predispositions, or real-time monitoring of withdrawal symptoms. [42].
- **Biocompatible and Biodegradable Polymers:** Continued exploration of novel polymers that offer superior mucoadhesion, controlled degradation, and excellent biocompatibility, minimizing irritation or long-term effects on the buccal mucosa.
- **Advanced Permeation Enhancement Strategies:** Research into more potent yet safe permeation enhancers, potentially using nanotechnology. [39].
- **Smart Film Technologies:** Developing films with embedded sensors or stimuli-responsive components that could release drugs "on-demand" in response to physiological cues (e.g., increased heart rate during a craving episode) or external triggers (e.g., an app notification).

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