ARx TECHNICAL PAPER

HOW DRUGS ARE DELIVERED TRANSMUCOSALLY AND THE MECHANISMS THAT MAKE IT WORK

Most pharmaceutical companies know that transmucosal delivery bypasses first-pass metabolism. What they don't know is precisely how drugs cross mucosal barriers, which compounds make good candidates, and why certain formulations succeed while others fail commercially.

The mechanisms matter because they determine everything: which molecules can cross membranes, which formulation strategies work, how much intellectual property you can generate, and whether your product can resist generic competition.

Understanding the science separates successful development from the costly trial-and-error approach.

WHAT MAKES MUCOSAL MEMBRANES DIFFERENT

Mucosal tissues lining the mouth, nose, rectum, and vagina evolved as selective barriers. They allow nutrient absorption while blocking pathogens and toxins. This selectivity creates both opportunity and challenge for **transmucosal drug delivery.**

These membranes consist of epithelial cell layers on a basement membrane, beneath which lies a network of capillaries. Epithelial thickness varies dramatically—the buccal mucosa measures approximately 500-800 micrometers thick, while sublingual tissue measures only 100-200 micrometers. This difference matters because thinner tissue allows for faster absorption.

The capillary networks beneath these membranes drain directly into systemic circulation, with buccal and sublingual vessels feeding into the jugular vein. This anatomy **explains why transmucosal routes avoid first-pass metabolism** that metabolizes drugs absorbed through the intestine.

TWO ROUTES DRUGS CAN CROSS IN MUCOSAL BARRIERS

The Transcellular Route Goes Through Cells

Epithelial cells of the buccal mucosa are non-keratinized stratified squamous cells. Most drugs cross barriers by passing directly through epithelial cells. The drug dissolves in aqueous mucosal fluids, partitions into the lipid-rich cell membrane, diffuses through the cell's interior, exits through the opposite membrane, and enters the capillary bed beneath.

This pathway favors drugs with moderate lipophilicity, logP values between 1 and 3. If they're too hydrophilic, molecules can't penetrate membranes. If they're too lipophilic, they won't dissolve or release from formulations.

Molecular size also matters, as small molecules with a molecular weight under 500 Daltons cross membranes more readily; however, modern **formulation approaches** are expanding what's possible.

The Paracellular Route Goes Between Cells

The paracellular route permits small, low-molecular-weight hydrophilic compounds to permeate through the extracellular amphipathic lipid matrix via passive diffusion. Some drugs cross barriers by squeezing between epithelial cells through gap junctions. These protein complexes seal spaces between adjacent cells. This pathway typically restricts molecules to under 1000 Daltons and favors hydrophilic compounds.

Gap junctions are enriched with desmosomes and hemidesmosomes, which typically permit limited drug passage. But permeation enhancers open these junctions by interacting with the specialized proteins known as cadherins, or by altering the lipid environment, creating gaps for drug passage.

This route offers promise for peptides and other hydrophilic drugs that struggle with transcellular transport.

THREE DELIVERY ROUTES WITH DISTINCT MECHANISMS

Buccal Delivery

Buccal delivery systems are placed between the cheek and gum, where they must cross relatively thick mucosal tissue while resisting removal by the flow of saliva, tongue movement, and swallowing. The tissue is non-keratinized, with excellent blood flow, and has an approximately 50 square centimeter surface area.

READ MORE: *Everything You Need to Know About Buccal Thin Films*

The key benefit lies in extended contact time. Modern films utilize **mucoadhesive polymers** that hydrate upon contact with saliva and form bonds with the charged mucin glycoproteins coating the tissue. These interactions create forces that resist clearance for hours while controlling release.

The challenge lies in balancing requirements. Strong adhesion prevents premature clearance but can cause discomfort during removal. Rapid release achieves a fast onset but may cause side effects due to high peak concentrations.

Lingual Delivery

Lingual films are placed on the surface of the tongue, where they offer distinct advantages compared to sublingual and buccal routes. The tongue's dorsal surface offers approximately 60-70 square centimeters of absorptive tissue with rich vascularization, providing a larger area than sublingual delivery while maintaining faster absorption than buccal placement.

This route strikes a balance between rapid absorption and ease of administration. The tissue thickness varies across the tongue, allowing for moderate absorption rates, while the flexible surface accommodates larger film sizes than sublingual placement. Patients find tongue placement more comfortable than sublingual positioning, improving compliance.

Technical considerations include taste masking, as drugs remain in direct contact with taste receptors during dissolution. Films must dissolve quickly enough to prevent discomfort but slowly enough to ensure adequate absorption. Formulations typically use moderately fast-dissolving polymers combined with flavoring agents.

Sublingual Delivery

Sublingual films are placed under the tongue, where the sublingual mucosa provides the thinnest and most permeable tissue in the oral cavity. This tissue is characterized by exceptional blood flow that rapidly clears absorbed drugs into systemic circulation.

The primary benefit is speed. These systems dissolve completely within seconds to minutes, making them ideal for drugs requiring a rapid onset. Nitroglycerin for acute angina, certain opioids for breakthrough pain, and anti-anxiety medications for panic attacks benefit from this route, where timing significantly impacts outcomes.

Films must be designed to dissolve quickly and be robust enough to handle manufacturing and packaging. They use rapidly dissolving polymers such as pullulan or Hypromellose. The limited space beneath the tongue restricts film size, necessitating the use of low-dose drugs or highly potent compounds.

HOW PERMEATION ENHANCERS WORK

Mechanisms of Action

Permeation enhancers improve transport through several mechanisms. Some disrupt lipid organization in cell membranes, increasing fluidity. Surfactants and fatty acids work this way. Others open gap junctions between cells by interacting with specialized junction proteins or by altering the lipid environment surrounding these connections.

Cyclodextrins improve drug solubility through molecular complexation within their internal cavity, though cavity size limitations restrict their use to drugs below specific molecular weight thresholds. Some enhancers work through multiple mechanisms. Bile salts increase both transcellular and paracellular transport.

Safety and Optimization

The challenge lies in achieving sufficient enhancement while maintaining safety. The enhancement must be reversible, and the enhancers shouldn't cause irritation or damage with repeated use.

Intellectual Property Opportunities

This optimization creates intellectual property opportunities. Enhancer selection, concentration, and combinations can be protected through patents that extend beyond the expiration of the compound patent.

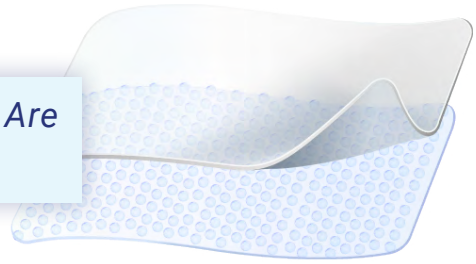
WHY MUCOADHESIVE TECHNOLOGY MATTERS

Absorption requires intimate contact between formulation and tissue. But the oral cavity constantly works to clear foreign materials. Saliva production ranges from 0.5 to 2 liters daily. Tongue movement, swallowing, eating, and drinking all promote clearance.

Mucoadhesive polymers adhere to surfaces through hydrogen bonds with mucin glycoproteins, electrostatic attractions, or physical entanglement in the mucus layer. Effective systems combine multiple bonding mechanisms and create flexible interfaces that conform to tissue contours.

Strength must be optimized. Insufficient adhesion leads to premature clearance and dose loss. Excessive adhesion causes discomfort during removal.

READ MORE: *6 Advanced Adhesive Technologies That Are Transforming Modern Drug Delivery Systems*



WHICH DRUGS MAKE GOOD CANDIDATES

Several factors predict success:

- Molecular weight under 500 Daltons performs best. LogP values between 1 and 3 provide the balance needed for membrane transport while maintaining solubility. Low-dose requirements, typically under 20-30 mg, allow for practical formulation sizes.
- Drugs requiring a rapid onset benefit from sublingual delivery. Compounds with extensive first-pass metabolism gain an advantage from bypassing the liver. Molecules with short half-lives become more practical as extended-release formulations.
- Chemical stability in the oral environment is essential, though formulations can incorporate pH buffering to optimize absorption conditions beyond saliva's natural pH of 6-7. For oral routes, taste becomes a critical factor. Bitter or unpleasant compounds require masking strategies.

WHY DEVELOPMENT REQUIRES SPECIALIZED EXPERTISE

Development demands capabilities most pharmaceutical companies lack internally. Understanding membrane transport requires specialized knowledge. Working with mucoadhesive polymers requires expertise in polymer science that extends beyond traditional formulation.

Manufacturing processes for transmucosal films differ significantly from those for tablet production. **Specialized partners** bring libraries of mucoadhesive polymers, validated permeation enhancer systems, and proven manufacturing processes that scale from development through commercial production across multiple compounds and **therapeutic areas.**

CONCLUSION

The difference between a successful transmucosal product and a failed development program often comes down to understanding mechanisms before you start. How molecules cross barriers. Which enhancers work for your compound. What adhesive strength you need.

These points all determine formulation strategy, development timeline, manufacturing approach, and the intellectual property you can generate to protect market position.

Companies that understand the science identify good candidates early, predict challenges accurately, and build defensible competitive advantages. Those that don't spend years and millions learning through expensive mistakes, what the right **development partner** could have told them at the start.

ARx is a patient-friendly, novel drug delivery partner. We specialize in oral thin film, buccal film, topical and transdermal patch strategies, all backed by tailored, full-scale development services. Contact us today to find the right delivery system for your API.

CONTACT

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