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ORAL FILM DRUG DELIVERY SYSTEMS FOR BETAHISTINE DIHYDROCHLORIDE: CURRENT PERSPECTIVES AND FUTURE DIRECTIONS

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Abstract
The development of fast-dissolving oral thin films has recently followed the progression of dosage forms from straight forward ordinary tablets and capsules to modified release tablets and capsules, oral disintegrating tablets, and wafers. A hydrophilic polymer used in fast- dissolving oral thin films quickly hydrates or adheres when applied on the tongue or in buccal cavity. These films melt or disintegrate in a matter of seconds, releasing the active ingredient without need for drinking or chewing. A drug-containing thin film with surface area of 5 to 20 cm^2 is called an oral dissolving film. The maximum single dose of the drugs that can be loaded is 30mg. As opposed to tablets, several pharmaceutical companies are now producing oral thin films that dissolve quickly. Films combine the benefits of liquid dosage forms with those of tablets, such as exact dose and simple administration (easy swallowing, rapid bioavailability. At the same time, it gives a general overview of crucial formulation design factors that have an impact on thin films, such as thin film design, anatomical and physiological constraints, choice of the best manufacturing processes, characterization techniques, and the physicochemical properties of drugs and polymers. Fast-dissolving or al thin films can be used for a variety of purposes, including sublingual and gastro-retentive delivery systems in addition to buccal fast-dissolving systems. Future uses might involve employing laminated multilayer films to combine incompatible active medicinal components into a single product.

Keywords: *Fast Dissolving drug delivery system, Oral Thin Film, Super disintegrants, Dissolution, Disintegration.*

Introduction

1. Background and Rationale

Oral drug delivery remains the most widely accepted and preferred route of administration due to its convenience, pain-free nature, ease of use, and improved patient compliance.[1] Traditional oral dosage forms such as tablets and capsules dominate the pharmaceutical market; however, they present challenges including swallowing difficulty, slow onset of action, and first-pass metabolism which can limit bioavailability. To overcome these limitations, novel drug delivery systems have been developed, among which **Oral Film Drug Delivery Systems (OFDS)** have gained significant attention in recent years.[2]

Figure 1 The advantages of using oral films [2]

OFDS—also known as orally disintegrating films, strip films, or oral thin films—are thin, flexible strips designed to rapidly disintegrate and dissolve when placed in the mouth, releasing the active pharmaceutical ingredient (API) for absorption either buccally or through gastro-intestinal (GI) tract after swallowing the dissolved film. Their unique properties offer advantages such as rapid onset, improved bioavailability, ease of administration (especially for pediatric, geriatric, and dysphagic patients), and reduced dosing frequency. The integration of OFDS with APIs that have absorption challenges is a promising frontier in drug delivery research.[3-4]

Betahistine dihydrochloride (BDH), an anti-vertigo agent widely used for the management of Ménière's disease and vestibular vertigo, presents specific challenges that make it a suitable candidate for OFDS formulation. Its conventional oral administration is characterized by frequent dosing due to rapid metabolism and variable bioavailability. The application of advanced delivery platforms such as OFDS has the potential to address these limitations and enhance therapeutic outcomes for patients requiring consistent plasma levels and improved compliance.[5]

2. Betahistine Dihydrochloride: Physicochemical and Pharmacological Profile[6-12]

2.1 Chemical Identity and Properties

Betahistine dihydrochloride is a synthetic histamine analogue chemically described as **1–[2–(methylamino)ethyl]–1,3-diethyl–2,3,4,5-tetrahydro-1H-benzimidazole dihydrochloride**. As a dihydrochloride salt, it exists as a highly water-soluble compound, yet its physicochemical profile imposes constraints on absorption kinetics when administered conventionally. BDH has a molecular weight of approximately 269.2 g/mol and exhibits stability challenges under variable pH conditions which can influence its release and absorption in the GI environment.

2.2 Mechanism of Action and Pharmacodynamics

BDH acts primarily through modulation of histaminergic pathways and vestibular compensation mechanisms. It

exerts **partial agonist activity at H1 receptors** and antagonistic activity at presynaptic H3 receptors, thereby increasing histamine turnover in the central nervous system (CNS). This dual action enhances blood flow in the inner ear and vestibular structures, reducing symptoms such as vertigo, tinnitus, and hearing loss associated with Ménière's disease and vestibular dysfunction.

The pharmacodynamic effects of BDH contribute to improved vestibular compensation, reduction in spontaneous nystagmus, and restoration of equilibrium. However, the therapeutic benefit is dependent on maintaining effective plasma concentrations, which is a challenge with conventional oral dosing due to first-pass metabolism and short elimination half-life (reported between 3.5–4 hours). Consequently, frequent dosing (typically 3–4 times daily) is recommended, posing adherence challenges for many patients.

2.3 Pharmacokinetics and Limitations

Upon oral administration, BDH is rapidly absorbed from the GI tract but undergoes extensive first-pass metabolism in the liver, resulting in low systemic bioavailability. Its major metabolite, **2–pyridylacetic acid**, shows limited pharmacological activity, underscoring the need for improved delivery strategies to maximize BDH efficacy.

Key pharmacokinetic limitations associated with BDH include:

- **Variable absorption** due to GI transit variability
- **Extensive first-pass metabolism** leading to reduced available dose
- **Short half-life** necessitating frequent dosing
- **Potential for fluctuating plasma levels** affecting therapeutic consistency

These challenges highlight the need for innovative drug delivery systems that can achieve sustained plasma levels, minimize metabolism-induced loss, enhance patient compliance, and maintain therapeutic efficacy at lower doses or reduced frequency of administration.

Table 1. Physicochemical and Pharmacokinetic Profile of BetahistineDihydrochloride[13-15]

Parameter	Description	Relevance to OFDS
Drug name	Betahistine Dihydrochloride	Anti-vertigo agent suitable for patient-friendly delivery
Chemical class	Histamine analogue	Acts on histaminergic receptors
Molecular weight	~269.2 g/mol	Favorable for mucosal absorption
Solubility	Highly water soluble	Enables rapid dissolution in oral films
pKa	~9.1	Influences ionization and buccal permeability
Bioavailability	Low (oral tablets)	OFDS may enhance systemic availability
Half-life	3.5–4 hours	Requires frequent dosing in conventional forms
First-pass metabolism	Extensive	Buccal OFDS can partially bypass hepatic metabolism
Dose	Low dose (8–24 mg/day)	Suitable for thin film incorporation

3. Oral Film Drug Delivery System (OFDS): Concept and Advantages

3.1 Overview of OFDS

Oral Film Drug Delivery Systems are ultra-thin polymeric films embedded with APIs designed to disintegrate rapidly in the oral cavity. Upon contact with saliva, films hydrate, swell, and disintegrate, releasing the incorporated drug for absorption. Depending on the physicochemical attributes of the API and polymer matrix, absorption may occur through:

- **Buccal mucosa** (direct systemic entry bypassing hepatic metabolism)
- **Sublingual mucosa** (rapid systemic uptake)
- **Swallowed dissolved drug** for GI absorption

OFDS represents a significant advancement in oral delivery technologies, integrating patient-friendly attributes with enhanced pharmacokinetic control.[16]

3.2 Key Benefits of OFDS

- Oral films provide multiple advantages compared with conventional dosage forms:
- **Rapid Disintegration and Dissolution:** OFDS can disintegrate within seconds to minutes, aiding fast onset of action.
- **Improved Patient Compliance:** Easy administration without water enhances acceptability, especially among paediatrics, geriatrics, and those with dysphagia or nausea.
- **Potential for Bypass of First-Pass Metabolism:** When formulated for buccal or sublingual absorption, OFDS can improve bioavailability of APIs prone to extensive hepatic metabolism.
- **Precise Dosing:** Each film can be loaded with exact doses, reducing inter-dose variability.
- **Reduced Dose Frequency:** Controlled release OFDS formulations can sustain drug plasma levels over prolonged periods, minimizing the need for frequent dosing.
- **Convenience and Portability:** Compact and lightweight, films are ideal for on-the-go dosing.

- These benefits align with current regulatory and clinical emphasis on patient-centric formulations and personalized medicine, underlying the decreasing trend toward alternative oral dosage forms beyond tablets and capsules.[17]

4. Rationale for BDH in OFDS

4.1 Need for Improved Delivery of BDH

Given BDH's pharmacokinetic challenges, particularly extensive first-pass metabolism and short half-life, its conventional administration requires frequent dosing which can reduce adherence and therapeutic effectiveness. Chronic conditions like Ménière's disease entail prolonged therapy, making convenience and consistent plasma levels pivotal.

Incorporating BDH into OFDS can potentially:

- **Enhance Bioavailability:** Buccal or sublingual absorption can reduce first-pass metabolism.
- **Improve Onset of Action:** Rapid dissolution and absorption are conducive to faster relief of vertigo symptoms.
- **Reduce Dosing Frequency:** Modified release OFDS can be tailored to sustain release over extended time frames.
- **Increase Patient Adherence:** Ease of use without requirement of water or swallowing reduces barriers to daily dosing.

4.2 Scientific Basis for OFDS Application with BDH

The application of OFDS for BDH is scientifically justified due to:

- **Low dose requirement:** BDH's therapeutic doses are typically low, making them suitable for incorporation into thin polymeric films.
- **Water solubility:** BDH's solubility favours rapid release in the oral cavity.
- **Possibility for Buccal Absorption:** The structure of the drug supports mucosal permeation, which can be enhanced with mucoadhesive polymers and permeation enhancers.

Technological advancements such as hot-melt extrusion, solvent casting, and electrospinning enable precise film fabrication with optimal mechanical and release properties. The integration of permeation enhancers and mucoadhesive agents further supports efficient mucosal uptake.[18-20]

5. Film Formulation Considerations

5.1 Polymers and Excipients

Successful OFDS formulation hinges on the selection of biocompatible polymers that provide appropriate tensile strength, flexibility, and rapid disintegration. Common categories include:

- **Hydrophilic film formers:** Hydroxypropyl methylcellulose (HPMC), pullulan, sodium alginate
- **Plasticizers:** Glycerol, polyethylene glycol (PEG) to improve film flexibility
- **Permeation enhancers:** Cyclodextrins, bile salts to facilitate mucosal entry
- **Sweeteners and flavours:** To improve palatability, especially for bitter APIs[21-23]

Table 2. Key Components Used in Betahistine Dihydrochloride Oral Films[24-25]

Component Category	Examples	Function in OFDS
Film-forming polymers	HPMC, Pullulan, Sodium alginate	Provide structural integrity and rapid disintegration
Plasticizers	Glycerol, PEG-400	Improve flexibility and prevent brittleness
Permeation enhancers	Cyclodextrins, bile salts	Enhance buccal drug permeation
Sweeteners	Aspartame, Sucralose	Improve taste and patient acceptability
Flavoring agents	Mint, orange, strawberry	Mask drug bitterness
Saliva stimulants	Citric acid	Promote rapid film hydration
Stabilizers	Antioxidants	Improve shelf-life and stability

5.2 Release Kinetics and Bioavailability Enhancement

A critical aspect of BDH film development is tailoring release kinetics to achieve therapeutic plasma levels without frequent dosing. Strategies include:

- **Immediate release films** for rapid onset
- **Sustained/modified release films** using polymer blends or layered structures for controlled delivery

- **Mucoadhesive OFDS** to prolong residence time in the oral cavity

5.3 Stability and Packaging

OFDS integrity depends on moisture protection and mechanical robustness. BDH films must be stable against humidity, temperature fluctuations, and mechanical stress. Packaging strategies such as blister packs with desiccants and individual foil wraps are essential to maintain product efficacy.

6. Clinical and Therapeutic Implications

6.1 Improved Therapeutic Outcomes

Transitioning BDH from conventional tablets to OFDS could result in:

- Faster symptom relief due to rapid absorption
- More consistent plasma profiles improving vestibular compensation
- Enhanced quality of life due to convenient dosing and reduced side effects

6.2 Compliance and Patient-Centered Care

Patients with vestibular disorders often experience nausea and difficulty swallowing during episodes of vertigo, making conventional tablets unsuitable. OFDS bypass these barriers and support adherence—a key determinant for chronic therapy success.

6.3 Potential Market and Acceptance

The global market trend toward patient-friendly formulations and the growing demand for rapid onset therapies indicate strong acceptance of OFDS for conditions like vertigo. As OFDS gains traction, BDH films could represent an impactful niche in neuro-otological therapeutics.[26]

7. Challenges and Future Directions

7.1 Formulation Challenges

Key challenges include ensuring uniform drug distribution within films, achieving desired mechanical strength, and optimizing buccal permeation. Addressing stability under varied environmental conditions also remains critical.

7.2 Regulatory and Quality Considerations

Regulatory frameworks for OFDS emphasize stringent control of disintegration time, dose uniformity, and bioequivalence. Producers must validate manufacturing processes and demonstrate clinical efficacy through robust studies.

Table 3. Comparison of Conventional Oral Dosage Forms and Oral Film Drug Delivery Systems [27-29]

Parameter	Tablets/Capsules	Oral Film Drug Delivery System (OFDS)
Mode of administration	Swallowed with water	Placed on tongue/buccal mucosa
Onset of action	Delayed	Rapid
First-pass metabolism	Significant	Reduced (buccal/sublingual absorption)
Patient compliance	Moderate	High
Suitability for dysphagic patients	Poor	Excellent
Dose uniformity	Good	Excellent
Portability	Moderate	High
Risk of choking	Present	Negligible
Application in vertigo	Limited	Highly suitable

7.3 Future Opportunities

Emerging technologies such as nanocarrier-loaded films, smart polymers, and personalized 3D-printed films offer innovative pathways to enhance BDH delivery. Additionally, hybrid OFDS with taste-masking and dual-release profiles can expand therapeutic possibilities.

8. Summary

Betahistine dihydrochloride's potential as an OFDS candidate is rooted in its pharmacokinetic limitations and therapeutic needs. Oral films offer distinct advantages including improved bioavailability, rapid onset, enhanced patient compliance, and tailored release kinetics. The intersection of advanced material science with clinical pharmacology presents a compelling opportunity to reposition BDH within modern, patient-centric drug delivery frameworks.

Conflict of Interest:

We declare that we do not have conflict of interest.

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