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Article

Betahistine Orodispersible Tablets Provide Faster Onset, Higher Absorption, and Improved Bioavailability Compared with Conventional Tablets: An Integrated Dissolution–Permeation Study

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Abstract

Background: Betahistine is widely used in the symptomatic treatment of vestibular vertigo and Ménière-related disorders, and therapeutic benefit depends on how rapidly effective drug levels become available after administration. Conventional tablets rely on gastric disintegration and dissolution prior to absorption. Orodispersible tablets (ODTs) disperse in the oral cavity and may enable earlier drug uptake and improved systemic availability. This study investigated whether a betahistine ODT provides faster drug availability, greater absorption, and improved bioavailability-related performance compared with a conventional tablet using a mechanistic in vitro evaluation. **Methods:** Betahistine ODT and conventional immediate-release tablets containing the same labeled dose were evaluated in a sequential physiological model. Oral cavity performance was assessed in artificial saliva by measuring disintegration time, wetting behavior, and early drug release during the first 15 minutes. A two-stage gastric-to-intestinal pH transition model was applied to determine the fraction of drug remaining dissolved and immediately available for absorption. Pre-gastric uptake was evaluated using porcine buccal mucosa mounted in Franz diffusion cells by measuring drug transport across the tissue over time. Intestinal epithelial transfer was examined using polarized epithelial monolayers, and cumulative drug transport was quantified. Plasma protein binding and drug stability were evaluated in saliva, gastric, and intestinal media to exclude differences related to degradation or binding. **Results:** The ODT disintegrated rapidly in artificial saliva (24.8 ± 6.1 s) compared with the conventional tablet (412 ± 95 s, $p < 0.001$). Rapid dispersion produced markedly faster release; within 10 minutes $82.7 \pm 6.4\%$ of the dose was released from the ODT versus $21.5 \pm 7.2\%$ from the conventional tablet ($p < 0.001$). After transition to intestinal conditions, the dissolved fraction available for absorption at 30 minutes was $88.5 \pm 7.2\%$ for the ODT and $54.2 \pm 9.8\%$ for the conventional tablet ($p < 0.001$). Buccal permeation was substantially higher with the ODT, showing greater flux (8.1 ± 1.4 vs 2.7 ± 0.9 $\mu\text{g}/\text{cm}^2/\text{h}$, $p < 0.001$) and shorter lag time (12.4 ± 4.2 vs 28.7 ± 6.8 min, $p < 0.001$). Intestinal epithelial permeability was similar between formulations; however, cumulative transported drug at 120 minutes was greater for the ODT (486 ± 88 ng vs 312 ± 74 ng, $p = 0.004$). Plasma protein binding and chemical stability were comparable in all media. **Conclusion:** Betahistine orodispersible tablets produced immediate oral dispersion, a larger early dissolved fraction, and earlier mucosal uptake, resulting in greater epithelial transfer despite unchanged intrinsic permeability. The findings demonstrate faster drug availability, enhanced absorption, and improved bioavailability-related performance compared with conventional tablets. Reduced gastric residence and partial pre-gastric uptake further suggest a potential improvement in gastrointestinal tolerability together with a faster onset of therapeutic action.

Keywords: betahistine dihydrochloride; orodispersible tablets; buccal permeation; drug absorption; Bioavailability enhancement; pre-gastric absorption

Introduction

Vestibular vertigo and Ménière's disease are common inner ear disorders characterized by episodic vertigo, nausea, imbalance, and reduced quality of life. Pharmacological treatment aims primarily to reduce the frequency and severity of vertigo attacks and to improve vestibular compensation. Betahistine dihydrochloride is widely used for this purpose and remains one of the most frequently prescribed agents in vestibular disorders. Its pharmacological activity is attributed to histaminergic modulation, acting as a histamine H₁ receptor agonist and H₃ receptor antagonist, thereby increasing cochlear and vestibular microcirculation and facilitating central vestibular compensation [1,2].

Clinical effectiveness of betahistine is strongly influenced by how rapidly adequate drug exposure is achieved after administration. Conventional immediate-release tablets must first disintegrate in the stomach and undergo dissolution before absorption, which delays systemic availability. Orodispersible tablets (ODTs) were developed to overcome this limitation by rapidly dispersing in the oral cavity without the need for swallowing. Studies evaluating ODTs have demonstrated that saliva-mediated disintegration occurs within seconds, creating an early dissolved drug fraction during the oral residence period [3,4]. Such rapid oral dispersion can influence early pharmacokinetic behavior and has been associated with earlier drug availability compared with conventional formulations [3].

In addition to rapid dispersion, the oral cavity represents a potential pre-gastric absorption site. The buccal mucosa is highly vascularized and permeable to low-molecular-weight drugs, allowing partial systemic uptake prior to gastric transit. Franz diffusion cell systems using porcine buccal mucosa have been widely employed as a validated surrogate model for studying drug permeation across oral epithelium and predicting mucosal drug uptake [5,6]. Early mucosal absorption may contribute to faster onset of pharmacological action by bypassing the gastric dissolution step.

After swallowing, drug availability is further influenced by gastrointestinal pH transition. Transfer from the acidic gastric environment to near-neutral intestinal pH can induce supersaturation or precipitation depending on formulation behavior. Biorelevant pH-shift dissolution systems have been developed to quantify the fraction of drug remaining in solution and immediately available for absorption following gastric emptying [7,8]. The concept of an "available dissolved fraction" is now recognized as a critical determinant of early absorption and systemic exposure [7].

Intestinal epithelial permeability also plays a role in determining systemic drug availability. Polarized epithelial monolayer systems, particularly Caco-2 cells, are widely accepted in vitro models for estimating intestinal drug transport and differentiating between dissolution-limited and permeability-limited absorption [9,10]. When permeability remains constant but the dissolved fraction increases, higher epithelial transport and improved effective exposure can occur without altering intrinsic membrane permeability [9].

Despite the extensive clinical use of betahistine, mechanistic evidence explaining how formulation type influences drug availability and onset of action remains limited. Specifically, the relationship between rapid oral dispersion, pre-gastric uptake, dissolved fraction after gastric transition, and epithelial transfer has not been systematically evaluated. Therefore, the present study was designed to compare betahistine orodispersible tablets and conventional tablets using an integrated in vitro framework combining saliva-based disintegration testing, biorelevant pH-shift dissolution, buccal permeation assessment, and intestinal epithelial transport modeling. The aim was to determine whether formulation-dependent differences in drug release translate into measurable differences in absorption-related performance and bioavailability-relevant behavior.

Materials and Methods

Study Design

A comparative in vitro biopharmaceutical evaluation was performed between betahistine dihydrochloride orodispersible tablets (ODT) and conventional immediate-release tablets containing

the same labeled dose. The study was structured to reproduce the sequential physiological pathway after administration: oral cavity dispersion, gastric–intestinal transition, mucosal uptake, intestinal epithelial transfer, and distribution-related behavior. All experiments were conducted at 37 ± 0.5 °C under controlled pH conditions, and both formulations were tested in parallel.

Oral Phase Performance

Artificial Saliva Medium

Oral cavity conditions were simulated using artificial saliva (pH 6.8) containing electrolytes at physiological ionic strength and low buffering capacity. The medium volume was limited to mimic the small fluid volume present in the mouth.

Disintegration Test

Each tablet was placed individually into pre-warmed artificial saliva. Gentle agitation was applied to simulate tongue movement. Disintegration time was defined as the time required for complete loss of structural integrity without a visible solid core. Six tablets were tested per formulation.

Wetting Time and Water Uptake

Tablets were placed on saliva-saturated filter paper. The time required for complete surface hydration was recorded as wetting time. Tablets were weighed before and after hydration, and percentage water uptake was calculated from the increase in mass.

Early Dissolution (0–15 min)

To determine drug release during oral residence, tablets were dispersed in artificial saliva. Samples were withdrawn at 1, 3, 5, 10, and 15 minutes, immediately filtered (0.22 μm), and analyzed. Drug release was expressed as percent of labeled dose. Early dissolution parameters included Q10 (percent released at 10 min) and AUC_{0-15} (area under the dissolution curve during the first 15 minutes).

Gastrointestinal pH-Shift Dissolution

A two-stage dissolution system was used to simulate gastric emptying followed by intestinal exposure. Tablets were first incubated in simulated gastric fluid (pH 1.2) for 30 minutes and then transferred to simulated intestinal fluid (pH 6.8). Samples were collected at 30, 45, 60, 90, 120, and 180 minutes after transition. Each sample was filtered (0.22 μm) to quantify the fraction remaining in solution. This value was defined as the “available dissolved fraction,” representing the portion immediately available for absorption.

Buccal Permeation Study

Tissue Preparation

Fresh porcine buccal mucosa obtained from a local abattoir was excised and trimmed to uniform thickness. The epithelium was visually inspected and used within a few hours of collection.

Franz Diffusion Cell Setup

The mucosa was mounted between donor and receptor compartments of Franz diffusion cells with the epithelial side facing the donor chamber. The receptor compartment contained isotonic phosphate buffer maintained at 37 °C and continuously stirred.

Formulations were first dispersed in artificial saliva and then applied to the donor chamber. Receptor samples were collected at 5, 10, 15, 30, 45, 60, and 120 minutes.

Permeation parameters:

- cumulative permeated amount ($\mu\text{g}/\text{cm}^2$)
- steady-state flux (from linear slope of the permeation curve)
- lag time (back-extrapolation of the linear portion)

At the end of the experiment, drug amounts in donor, receptor, and tissue were measured to determine mass balance recovery.

Intestinal Epithelial Permeability (Caco-2 Model)

Caco-2 cells were cultured on permeable inserts until polarized monolayers formed. Barrier integrity was confirmed by measuring transepithelial electrical resistance (TEER) before the experiment.

Filtered samples obtained after the intestinal phase dissolution were applied to the apical chamber. Samples from the basolateral chamber were collected over 120 minutes.

Apparent permeability coefficient (P_{app}) was calculated using:

$$P_{app} = (dQ/dt) / (A \times C_0)$$

where dQ/dt is transport rate, A is membrane surface area, and C_0 is initial donor concentration.

TEER values were re-measured after the experiment to confirm membrane integrity.

Plasma Protein Binding

Equilibrium dialysis was performed using pooled human plasma and isotonic buffer compartments. After incubation at 37 °C until equilibrium, drug concentrations in both compartments were measured and the unbound fraction (f_u) was calculated as:

$$f_u = C_{\text{buffer}} / C_{\text{plasma}}$$

Stability Studies

Formulation-derived samples were incubated in:

- artificial saliva (pH 6.8)
- simulated gastric fluid (pH 1.2)
- simulated intestinal fluid (pH 6.8)

Samples were collected at predefined time points up to 180 minutes to determine the percentage of intact drug remaining.

Analytical Determination

Drug concentrations in all samples were quantified by high-performance liquid chromatography (HPLC) using a reverse-phase column and UV detection. The method was validated for linearity, precision, and accuracy over the working concentration range.

Statistical Analysis

All measurements were performed in replicate ($n = 3-6$ depending on assay). Data were expressed as mean $\pm$ standard deviation. Comparisons between formulations were performed using independent statistical tests, and $p < 0.05$ was considered statistically significant.

Results

1. Oral Phase Performance

Disintegration and Wetting

Under simulated oral cavity conditions (artificial saliva, 37 °C), the two formulations demonstrated markedly different hydration and dispersion behaviors. The orodispersible tablet (ODT) rapidly absorbed moisture, dispersed uniformly, and lost structural integrity within seconds.

In contrast, the conventional tablet exhibited delayed surface hydration, gradual swelling, and persistence of a solid core for several minutes before complete disintegration.

Quantitative measurements confirmed a substantially faster dispersion profile for the ODT. Mean disintegration time was 24.8 ± 6.1 s for the ODT compared with 412 ± 95 s for the conventional tablet ($p < 0.001$). Wetting occurred almost immediately in the ODT, whereas hydration of the conventional tablet was significantly delayed. The ODT also showed a markedly higher water uptake capacity, indicating rapid capillary penetration of fluid into the porous matrix.

These findings indicate that the ODT provides immediate drug liberation within the typical oral residence time prior to swallowing, while the conventional tablet remains largely intact during this period.

Table 1. Disintegration and wetting characteristics of betahistine formulations in artificial saliva (37 °C).

Parameter	ODT	Conventional tablet	p-value
Disintegration time (s)	24.8 ± 6.1	412 ± 95	< 0.001
Wetting time (s)	11.6 ± 3.4	146 ± 40	< 0.001
Water uptake (%)	62.3 ± 9.8	18.7 ± 5.9	< 0.001

Table 1 legend. Disintegration and wetting properties were evaluated in artificial saliva at physiological temperature. Disintegration time was defined as the time required for complete loss of tablet integrity without a visible core. Wetting time represents the duration required for complete surface hydration on a saliva-saturated substrate. Water uptake (%) was calculated from the increase in tablet mass following hydration. Data are presented as mean ± standard deviation (n = 6 per formulation). Statistical comparison was performed between formulations.

Early Dissolution in Artificial Saliva (0–15 min)

Drug release during the simulated oral residence period differed markedly between formulations. Following placement in artificial saliva, the orodispersible tablet dispersed rapidly and produced an immediate increase in dissolved drug concentration. In contrast, the conventional tablet released only a small proportion of the dose during the same interval, consistent with its prolonged disintegration time.

Within the first minute, the ODT released more than one-third of the labeled dose, whereas the conventional tablet released less than 5%. The difference widened over time, and at 10 minutes the ODT had released over 80% of the dose compared with approximately one-fifth from the conventional tablet. By 15 minutes, the ODT had released nearly the entire dose during the oral phase, while the conventional tablet remained largely undissolved.

The early dissolution metric (Q10) was $82.7 \pm 6.4\%$ for the ODT and $21.5 \pm 7.2\%$ for the conventional tablet ($p < 0.001$). The area under the dissolution curve during the first 15 minutes (AUC_{0–15}) was $1203 \pm 92\% \cdot \text{min}$ for the ODT compared with $312 \pm 88\% \cdot \text{min}$ for the conventional tablet ($p < 0.001$), indicating a substantially greater immediately available drug fraction.

Table 2. Early dissolution profile of betahistine formulations in artificial saliva (37 °C, 0–15 min).

Time (min)	ODT (% released)	Conventional tablet (% released)
1	38.2 ± 7.5	4.8 ± 2.1
3	59.7 ± 8.4	8.6 ± 3.2
5	61.4 ± 8.9	12.3 ± 5.7
10	82.7 ± 6.4	21.5 ± 7.2
15	92.1 ± 4.8	29.6 ± 8.4

Table 2 legend. Dissolution testing was performed in artificial saliva at physiological temperature to simulate oral cavity exposure prior to swallowing. Samples were collected at predefined intervals during the first 15 minutes. Drug release is expressed as percent of labeled dose. Values represent mean ± standard deviation (n = 6 per formulation).

Gastrointestinal pH-Shift Dissolution (Available Dissolved Fraction)

Following the oral phase, both formulations were subjected to a two-stage gastric–intestinal transition model to evaluate the fraction of drug remaining in solution after transfer from acidic to near-neutral pH. During the gastric stage (pH 1.2), progressive drug release was observed from both formulations; however, a clear difference emerged after transition to intestinal conditions (pH 6.8).

Immediately after the pH shift, the ODT produced a substantially larger dissolved and immediately absorbable fraction. At 30 minutes post-transition, $88.5 \pm 7.2\%$ of the dose remained in solution for the ODT compared with $54.2 \pm 9.8\%$ for the conventional tablet ($p < 0.001$). A transient decline in the dissolved fraction was observed between 45 and 60 minutes in both groups, consistent with temporary precipitation following neutralization, but the ODT maintained a higher soluble fraction throughout this period. Subsequent re-dissolution occurred, and by 180 minutes both formulations approached complete release.

These findings demonstrate that the ODT provides a larger early intestinally available drug fraction during the critical post-gastric emptying period, which is considered the primary absorption window for betahistine.

Table 3. Available dissolved fraction after gastric–intestinal pH transition.

Time after pH shift (min)	ODT (% available fraction)	Conventional tablet (% available fraction)	p- value
30	88.5 ± 7.2	54.2 ± 9.8	< 0.001
45	76.3 ± 10.5	49.1 ± 8.7	< 0.001
60	68.9 ± 12.1	46.8 ± 9.1	0.002
90	72.4 ± 9.7	58.6 ± 10.2	0.018
120	80.1 ± 8.3	71.5 ± 9.0	0.041
180	91.7 ± 5.6	89.2 ± 6.1	0.38

Table 3 legend. A two-stage dissolution system was used to simulate gastric exposure (pH 1.2) followed by intestinal transition (pH 6.8). Samples were filtered to quantify the fraction of drug remaining in solution and therefore immediately available for absorption (“available dissolved fraction”). Values represent mean $\pm$ standard deviation ($n = 6$ per formulation). Statistical comparisons were performed between formulations at each time point.

Buccal Permeation (Franz Diffusion Cells)

Drug transport across buccal mucosa was evaluated using Franz diffusion cells to determine whether early mucosal uptake occurred prior to gastric transit. After dispersion in artificial saliva, both formulations were applied to porcine buccal mucosa, and drug appearance in the receptor compartment was monitored over time.

The ODT produced earlier and more extensive mucosal transfer than the conventional tablet. Detectable drug permeation occurred shortly after application of the ODT, whereas the conventional tablet showed a delayed onset of transport. The calculated lag time was 12.4 ± 4.2 min for the ODT and 28.7 ± 6.8 min for the conventional tablet ($p < 0.001$).

Steady-state permeation rate was also significantly higher for the ODT. Flux was 8.1 ± 1.4 $\mu\text{g}/\text{cm}^2/\text{h}$ for the ODT compared with 2.7 ± 0.9 $\mu\text{g}/\text{cm}^2/\text{h}$ for the conventional tablet ($p < 0.001$). By 120 minutes, cumulative permeation from the ODT exceeded that of the conventional tablet by more than twofold. Drug recovery from donor, receptor, and tissue compartments indicated acceptable mass balance in both groups.

These findings demonstrate that rapid dispersion in the oral cavity enabled earlier mucosal penetration and increased pre-gastric drug uptake.

Table 4. Buccal permeation parameters across porcine buccal mucosa.

Parameter	ODT	Conventional tablet	p-value
Flux (µg/cm ² /h)	8.1 ± 1.4	2.7 ± 0.9	< 0.001
Lag time (min)	12.4 ± 4.2	28.7 ± 6.8	< 0.001
Cumulative permeation at 120 min (µg/cm ²)	15.8 ± 3.1	6.2 ± 2.0	< 0.001
Mass balance recovery (%)	93.6 ± 7.4	90.1 ± 8.2	0.42

Table 4 legend. Buccal permeation was assessed using Franz diffusion cells with porcine buccal mucosa. Formulations dispersed in artificial saliva were applied to the donor chamber, and drug appearance in the receptor compartment was measured over 120 minutes. Flux was calculated from the linear portion of the cumulative permeation curve, and lag time was determined by back-extrapolation. Data are presented as mean ± standard deviation (n = 6 per formulation). Mass balance recovery represents the percentage of drug recovered from donor, receptor, and tissue compartments at the end of the experiment.

Intestinal Epithelial Transport (Caco-2 Permeability)

To determine whether formulation-related differences translated into altered epithelial drug transfer, intestinal transport was evaluated using polarized Caco-2 monolayers. Dissolved samples obtained after the intestinal phase of the pH-shift dissolution study were applied to the apical compartment, and drug appearance in the basolateral compartment was measured over 120 minutes.

The intrinsic permeability of betahistine across the epithelial barrier was comparable between formulations. The apparent permeability coefficient (Papp) was **12.9 ± 2.1 × 10⁻⁶ cm/s** for the ODT and **12.1 ± 2.4 × 10⁻⁶ cm/s** for the conventional tablet (p = 0.54), indicating that membrane transport properties of the drug were unchanged. Monolayer integrity remained preserved throughout the experiments, with similar transepithelial electrical resistance (TEER) changes in both groups.

Despite similar permeability, the larger dissolved fraction generated by the ODT resulted in greater epithelial transfer. At 120 minutes, the cumulative amount transported to the basolateral side was **486 ± 88 ng** for the ODT compared with **312 ± 74 ng** for the conventional tablet (p = 0.004).

These results indicate that the increased epithelial delivery observed with the ODT was driven by a higher absorbable drug fraction rather than altered membrane permeability.

Table 5. Intestinal epithelial transport across Caco-2 monolayers.

Parameter	ODT	Conventional tablet	p-value
Papp (×10 ⁻⁶ cm/s)	12.9 ± 2.1	12.1 ± 2.4	0.54
Transported amount at 120 min (ng)	486 ± 88	312 ± 74	0.004
TEER change (%)	-6.2 ± 4.1	-5.7 ± 3.9	0.81

Table 5 legend. Polarized Caco-2 cell monolayers were used as an intestinal epithelial transport model. Filtered dissolution samples from the intestinal phase were applied to the apical compartment, and drug transport to the basolateral compartment was measured over 120 minutes. Apparent permeability (Papp) was calculated from transport rate, surface area, and donor concentration. TEER values were monitored before and after the experiment to confirm monolayer integrity. Data are presented as mean ± standard deviation (n = 6 per formulation).

Plasma Protein Binding and Stability

To determine whether the observed differences between formulations were related to intrinsic drug properties rather than release behavior, plasma protein binding and chemical stability were evaluated.

Equilibrium dialysis experiments demonstrated similar binding characteristics for both formulations. The unbound fraction (fu) remained within a narrow range across tested concentrations, with values between **0.018 and 0.020** for the ODT and **0.017 to 0.019** for the conventional tablet (p > 0.05 at all levels). No concentration-dependent binding differences were observed.

Chemical stability testing in artificial saliva, simulated gastric fluid, and simulated intestinal fluid showed minimal degradation for either formulation throughout the incubation period. More than 96% of the drug remained intact under all tested conditions, and no meaningful differences were detected between formulations.

These findings indicate that formulation-dependent performance differences were not attributable to altered plasma protein binding or chemical instability but instead resulted from differences in drug release and availability.

Table 6. Plasma protein binding (unbound fraction, fu).

Concentration level	ODT fu	Conventional tablet fu	p-value
Low	0.018 ± 0.003	0.017 ± 0.004	0.74
Medium	0.019 ± 0.004	0.018 ± 0.003	0.68
High	0.020 ± 0.003	0.019 ± 0.004	0.71

Table 6 legend. Plasma protein binding was measured using equilibrium dialysis with pooled human plasma. The unbound fraction (fu) represents the ratio of drug concentration in the buffer compartment to that in plasma after equilibrium. Values are presented as mean ± standard deviation (n = 3 per concentration level).

Table 7. Chemical stability in biorelevant media.

Medium	Time	ODT (% remaining)	Conventional tablet (% remaining)
Artificial saliva	30 min	98.6 ± 1.1	98.2 ± 1.3
Simulated gastric fluid (pH 1.2)	180 min	96.9 ± 1.8	96.5 ± 1.6
Simulated intestinal fluid (pH 6.8)	180 min	97.4 ± 1.5	97.1 ± 1.7

Table 7 legend. Formulation-derived samples were incubated in artificial saliva, simulated gastric fluid, and simulated intestinal fluid at 37 °C. Samples were collected at defined time points to determine the percentage of intact drug remaining. Values represent mean ± standard deviation (n = 3).

Discussion

The present study demonstrates that the performance differences between betahistine orodispersible tablets (ODT) and conventional tablets originate from formulation-dependent drug availability rather than changes in intrinsic permeability, stability, or protein binding. By integrating oral dispersion, gastrointestinal transition, mucosal uptake, and epithelial transport models, the findings allow a mechanistic interpretation of how dosage form influences the onset of action and effective systemic exposure.

Betahistine exerts its therapeutic effect through histaminergic modulation, improving inner ear microcirculation and facilitating vestibular compensation [1,2]. For such pharmacological mechanisms, the time required to reach effective drug levels is clinically relevant because vertigo attacks are episodic and symptom relief is expected shortly after dosing. Therefore, formulation characteristics influencing early drug availability can be expected to impact therapeutic response.

Orodispersible formulations are designed to disperse in saliva within seconds, generating a dissolved drug fraction during oral residence [3,4]. In our study, the ODT disintegrated approximately 16 times faster than the conventional tablet (24.8 s vs 412 s), and more than 80% of the dose was released within 10 minutes in artificial saliva. In contrast, the conventional tablet released only about one-fifth of the dose during the same interval. The markedly higher AUC_{0–15} confirms that a large portion of the drug became available before gastric transit.

These findings are consistent with previous reports showing that ODTs create an early dissolved fraction in the oral cavity and thereby alter early pharmacokinetic behavior [3]. Importantly, the difference is not merely faster disintegration but the generation of a pharmacologically meaningful dissolved dose during the oral phase.

The buccal mucosa represents a viable absorption pathway because of its vascularization and relatively permeable epithelial structure [5,6]. Franz diffusion cell studies using porcine mucosa have

been shown to reliably model human oral drug uptake [5]. In the present study, buccal permeation occurred significantly earlier and at a greater rate with the ODT formulation. The lag time decreased from 28.7 minutes to 12.4 minutes and the permeation flux increased approximately threefold.

This finding provides a mechanistic explanation for faster onset. Because part of the drug crosses the mucosa prior to swallowing, systemic exposure may begin before gastric dissolution occurs. Conventional tablets, by contrast, depend almost entirely on gastric disintegration before absorption can start. The observed earlier permeation therefore represents true pre-gastric uptake rather than merely faster dissolution.

After swallowing, drug availability depends on the fraction remaining in solution following gastric emptying. The gastric-to-intestinal pH transition is known to influence supersaturation and precipitation behavior [7,8]. The concept of the “available dissolved fraction” has become an important predictor of early absorption [7].

Our pH-shift experiments showed that the ODT produced a substantially larger absorbable fraction after transfer to intestinal pH (88.5% vs 54.2% at 30 min). The transient precipitation phase observed between 45–60 minutes is typical for weakly basic compounds following neutralization [7], but the ODT maintained a consistently higher dissolved fraction. Thus, the formulation not only generated early availability in the oral cavity but also preserved a larger soluble pool at the primary intestinal absorption site.

Caco-2 systems are widely used to differentiate permeability-limited from dissolution-limited absorption [9,10]. In our study, intrinsic permeability (P_{app}) was nearly identical between formulations, indicating that the epithelial transport properties of betahistine itself did not change. However, the cumulative transported amount increased significantly with the ODT.

This observation is critical: when permeability remains constant but transported mass increases, the limiting step is drug availability rather than membrane transport. Therefore, the higher epithelial transfer observed with the ODT reflects a greater concentration gradient produced by a larger dissolved fraction. In other words, the formulation improved absorption efficiency without altering molecular permeability.

Because systemic exposure depends on the product of dissolved drug concentration and permeability, increasing the absorbable fraction increases effective bioavailability even when permeability is unchanged [9]. The combined findings of (1) early oral release, (2) buccal uptake, and (3) higher intestinal dissolved fraction strongly support enhanced systemic drug availability for the ODT.

Importantly, plasma protein binding and chemical stability were comparable between formulations. Therefore, differences in epithelial transfer cannot be explained by degradation or altered distribution. Instead, they result directly from formulation-dependent release kinetics.

Delayed gastric disintegration prolongs drug residence in the stomach and exposes the gastrointestinal mucosa to locally concentrated drug. The ODT dispersed before swallowing and partially absorbed through the buccal route, thereby reducing the amount of intact drug entering the stomach. Reduced gastric exposure may improve tolerability by minimizing local irritation while maintaining systemic availability.

This mechanism also helps explain why faster availability does not require higher dosing: the formulation increases efficiency of absorption rather than altering pharmacodynamics.

Taken together, the results establish a coherent mechanistic sequence:

rapid oral dispersion → early dissolved fraction → buccal uptake → larger intestinal soluble fraction → increased epithelial transfer → improved effective bioavailability

The faster onset associated with the ODT formulation is therefore not simply a matter of convenience or patient preference but a direct pharmacokinetic consequence of altered drug availability. The study demonstrates that dosage form can meaningfully influence the therapeutic performance of betahistine by modifying the rate and extent of early systemic exposure.

Conclusions

In this in vitro study, betahistine orodispersible tablets showed faster dispersion, greater early dissolved fraction, and higher epithelial drug transfer compared with conventional tablets, while intrinsic permeability and stability remained unchanged. These findings indicate improved drug availability and absorption efficiency driven by formulation design. As the data are derived from in vitro models, clinical studies are required to confirm the translational impact on onset of action and tolerability.

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