Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
NLM (National Library of Medicine): ID: (101671502)
Index Copernicus Value 2024: 84.28
Volume 15, Issue 3; 2026, 181-187

ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

Review Article

Natural–Synthetic Binary Superdisintegrant Systems in Orodispersible Tablets

Jakki Imam[1], Ashutosh Sharma[2], Vishal Choudhary[3]

[1]Research Scholar, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur Rajasthan
[2]Associate Professor, Jaipur College of Pharmacy, Jaipur, Rajasthan
[3]HOD - Production, ASPO Pharmaceutical LLP, Baddi (H.P)

Article Info: Received: 10-03-2026 / Revised: 14-04-2026 / Accepted: 30-04-2026
Corresponding Author: Jakki Imam
DOI: https://doi.org/10.32553/jbpr.v15i3.1472
Conflict of interest statement: No conflict of interest

Abstract:
Fexofenadine hydrochloride is a second-generation, non-sedating H1-receptor antagonist prescribed for seasonal allergic rhinitis and chronic idiopathic urticaria. Despite BCS Class III status with high solubility and low permeability, conventional tablets have Tmax of 1–3 hours and require water for swallowing, which delays symptom relief and limits use in pediatric, geriatric, and dysphagic patients. Fast dissolving tablets (FDTs) that disintegrate within 30 seconds in the oral cavity without water enable rapid onset via pregastric absorption and improve compliance. This review analyzes formulation of fexofenadine HCl FDTs using a binary superdisintegrant system of natural mucilage from Plantago ovata, Lepidium sativum, Moringa oleifera, or Ocimum basilicum and synthetic crospovidone. Natural mucilage provides rapid water uptake and three-dimensional swelling with swelling index 15–25 mL/g, generating disruptive hydrostatic force, while crospovidone functions by wicking with high capillary activity and porosity, ensuring water penetration without gel formation. The synergistic combination at 4–10% w/w mucilage plus 2–8% w/w crospovidone achieves disintegration time 12–28 seconds, wetting time under 40 seconds, and more than 90% drug release in 5 minutes. Direct compression with mannitol as cooling diluent, microcrystalline cellulose PH 102 as binder, aspartame as sweetener, magnesium stearate as lubricant, and talc as glidant produces tablets with hardness 3–4 kg/cm² and friability below 0.8%. Bitter taste of fexofenadine is masked by a mannitol–aspartame–menthol combination. Challenges of mucilage hygroscopicity, microbial load, and batch variation are addressed through co-processing, moisture control below 10%, and gamma irradiation. QbD via 3^2 factorial design identifies mucilage: crospovidone ratio and compression force as critical parameters. This natural–synthetic binary system meets IP 2022 and USFDA FDT criteria and offers a cost-effective, biocompatible platform for rapid management of allergic symptoms.
Keywords: Fexofenadine HCl; Fast dissolving tablets; Natural mucilage; Crospovidone; Binary superdisintegrants; Plantago ovata; Taste masking; Allergy.

Introduction

Allergic rhinitis and chronic urticaria affect up to 30% of the global population. Fexofenadine HCl, the active carboxylic acid metabolite of terfenadine, is a preferred second-generation antihistamine due to selective peripheral H1-blockade and absence of sedation. It is a

substrate for P-glycoprotein efflux at the blood–brain barrier, preventing CNS penetration and psychomotor impairment. It also inhibits histamine-induced expression of adhesion molecules and release of IL-6, IL-8, and GM-CSF, providing additional anti-inflammatory effects.

Despite clinical efficacy, conventional fexofenadine tablets 60 mg twice daily or 180 mg once daily have limitations. Onset of action is about 60 minutes with Tmax 1–3 hours, which is inadequate for acute allergic episodes. The drug is intensely bitter, and oral bioavailability is only around 33% due to P-gp efflux in the gut. Bioavailability further reduces by 36–72% with fruit juices due to OATP1A2 inhibition. Pediatric and geriatric patients with dysphagia face swallowing difficulties, reducing adherence.

Fast dissolving tablets are defined by IP 2022 as uncoated tablets that disperse within 3 minutes in water, while USFDA recommends disintegration time below 30 seconds for orally disintegrating tablets. FDTs disintegrate in saliva, allowing dispersion of drug particles for rapid dissolution and potential buccal absorption. This bypasses tablet disintegration and gastric emptying, accelerating onset to approximately 15–20 minutes. For fexofenadine, rapid onset is critical to control sneezing, rhinorrhea, and pruritus.

Superdisintegrants govern FDT performance. Synthetic agents like crospovidone provide rapid wicking but increase cost. Natural mucilages from Plantago ovata, Lepidium sativum, Moringa oleifera, and Ocimum basilicum offer biocompatibility, biodegradability, and low cost, but may show slow action or batch variation. Binary systems combining natural and synthetic superdisintegrants provide mechanistic synergy and reduce total excipient load.

This review integrates detailed drug and excipient profiles with 2015–2025 literature to provide a comprehensive M.Pharm standard reference for fexofenadine HCl FDTs. [1]

Summary of Literature Review

Extensive literature from 2015–2025 reveals that fast dissolving tablets of fexofenadine HCl have been investigated using single and binary superdisintegrant systems to overcome delayed onset and bitter taste of conventional tablets.

Single Superdisintegrant Approaches

Early studies employed synthetic superdisintegrants alone. Patel et al., 2018 reported crospovidone 6% w/w achieving disintegration time of 35 seconds, but required high diluent levels that increased tablet weight. Croscarmellose sodium 5% gave disintegration in 42 seconds with slight gelling at tablet surface, delaying dissolution. Sodium starch glycolate 8% showed 38 seconds but caused gritty mouth feel. These studies confirmed that single synthetic agents often fail to meet USFDA <30 second disintegration criterion for high-dose 60–180 mg fexofenadine tablets. [2]

Natural Mucilage as Superdisintegrant

To reduce cost and improve biocompatibility, researchers evaluated plant mucilages. Sharma et al., 2020 used Plantago ovata mucilage 8% w/w and achieved disintegration in 41 seconds with swelling index 18 mL/g. Lepidium sativum mucilage 10% by Kumar et al., 2021 gave 44 seconds but showed batch variation in swelling. Moringa oleifera gum 7% by Rao et al., 2019 gave 39 seconds with good taste masking due to demulcent property. However, natural mucilages alone exhibited hygroscopicity, microbial growth risk, and slower water penetration versus synthetics, limiting use in humid conditions.

Binary Natural-Synthetic Systems: Recent work 2021–2025 focuses on synergy. Patel et al., 2021 combined Plantago ovata mucilage 6% + crospovidone 4% and reported disintegration time 19 seconds, wetting time 24 seconds, and 93.2% release in 5 minutes. The mucilage provided swelling pressure while crospovidone ensured rapid wicking without gel barrier. Singh et al., 2022 used Ocimum basilicum mucilage 5% + crospovidone XL-10 5% with

disintegration 16 seconds and Tmax 1.1 h vs 2.4 h for marketed tablets. Kumar et al., 2019 optimized fenugreek mucilage 4% + crospovidone 6% giving 22 seconds and taste score 4.1/5. These studies establish that binary systems reduce total superdisintegrant load to 8–12% w/w, improve compressibility, and meet <30 second criterion. [3]

Taste Masking and Excipients

Bitter taste of fexofenadine remains a challenge. Mannitol 30–50% w/w is consistently used for cooling effect and bulk sweetness. Aspartame 1–2% provides immediate sweetness. Menthol 0.5–1% enhances palatability. MCC PH-102 15–25% balances hardness and wicking. Sodium stearyl fumarate 0.6% is preferred over magnesium stearate to avoid disintegration retardation. Co-processing of mucilage with mannitol by spray drying improves flow from angle of repose 42° to 28°, enabling direct compression.

QbD and Regulatory Findings

3^2 factorial designs by Mahesh et al., 2023 and Singh et al., 2022 identify mucilage:crospovidone ratio and compression force 4–6 kN as critical parameters. Interaction plots confirm synergy at 1:1 to 2:1 ratios. ICH stability studies show binary FDTs stable for 6 months at 40°C/75% RH in Alu-Alu pack with desiccant. IP 2022 and USFDA criteria of disintegration <30 seconds and dissolution >80% in 15 minutes are met by optimized batches. [4]

Research Gap

Despite promising results, no study has compared different botanical mucilages with crospovidone in a single design for fexofenadine HCl. Impact of nano-sized mucilage, as reported by Mehta et al., 2026 for basil seed mucilage in fexofenadine FDTs, on disintegration kinetics of 60–180 mg tablets remains underexplored. Long-term stability of natural mucilage in humid Indian conditions and pediatric taste preference data are limited.

Conclusion of Literature Review: The collective evidence indicates that binary systems of natural mucilage 4–10% w/w and crospovidone 2–8% w/w are the most effective, economical, and patient-friendly approach for fexofenadine HCl FDTs, providing disintegration 12–28 seconds and onset within 15–20 minutes. Co-processing, taste masking, and QbD are essential for robust formulation. This justifies the present review's focus on natural mucilage–crospovidone systems for development of fexofenadine HCl FDTs. [5]

Drug Profile: Fexofenadine Hydrochloride

Chemical and Pharmacological Data

Fexofenadine hydrochloride is chemically designated as 2-[4-[1-hydroxy-4-[4-(hydroxy diphenylmethyl)piperidin-1-yl]butyl]phenyl]-2-methylpropanoic acid hydrochloride, with molecular formula $C_{32}H_{39}NO_4 \cdot HCl$ and molecular weight 538.12 g/mol (CAS number 153439-40-8). It is the active carboxylic acid metabolite of terfenadine and exists as a racemic mixture. The molecule has a piperidine ring, diphenylmethyl group, and propionic acid moiety, giving zwitterionic character at physiological pH. This zwitterionic nature contributes to low passive permeability across the blood–brain barrier.

Pharmacologically, it is a second-generation antihistamine and selective peripheral H1-receptor antagonist with negligible affinity for muscarinic, alpha-adrenergic, or serotonergic receptors, and is classified as non-sedating. The mechanism involves competitive binding to H1 receptors on vascular endothelium, bronchial smooth muscle, and sensory nerves, blocking histamine-mediated vasodilation, increased permeability, pruritus, and bronchoconstriction. As a P-glycoprotein substrate, it is actively effluxed from the CNS. It also exhibits anti-inflammatory activity by inhibiting histamine-induced adhesion molecules and cytokine release. [6]

Physicochemical Properties

Fexofenadine HCl is a white to off-white crystalline powder that is odorless with intensely bitter taste. It is freely soluble in methanol and ethanol, sparingly soluble in water at 25 °C with solubility around 0.5 mg/mL, and practically insoluble in hexane. Solubility is pH dependent due to its zwitterionic nature, with pKa1 4.25 for the carboxylic acid and pKa2 9.53 for the piperidine nitrogen. Melting point is 195–198 °C with decomposition. Log P is approximately 2.81 and log D at pH 7.4 is about 1.7. It is non-hygroscopic under normal storage and exists in both anhydrous and monohydrate forms. BCS Class III classification indicates high solubility and low permeability, making rapid disintegration and dissolution critical for FDTs.

Pharmacokinetic Profile

Absorption is rapid after oral administration, with oral bioavailability about 33% due to P-gp-mediated efflux in the gut. Food reduces Cmax by about 15% but does not significantly affect AUC. Co-administration with fruit juices decreases bioavailability by 36–72% via OATP1A2 inhibition. Tmax is 1–3 hours post-dose. Volume of distribution is 5.4–5.8 L/kg. Plasma protein binding is 60–70%, mainly to albumin and alpha1-acid glycoprotein.

Minimal distribution into the CNS occurs. Only about 5% undergoes hepatic metabolism and it is not significantly metabolized by CYP450 isoenzymes. Approximately 80% is eliminated unchanged in feces via biliary excretion and about 11% in urine. Active secretion is mediated via P-gp and OATP transporters. Elimination half-life is 11–15 hours in healthy adults, prolonged to around 19 hours in renal impairment, and total body clearance is approximately 3.4 mL/min/kg.

Clinical Use and Safety

Fexofenadine HCl is indicated for seasonal allergic rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria in adults and children older than 6 months. Adult dose is 60 mg twice daily or 180 mg once daily. Pediatric dose is 30 mg twice daily for 6–11 years and 15 mg twice daily for 6 months to 2 years with CIU. In renal impairment, 60 mg once daily is recommended for creatinine clearance below 80 mL/min. The drug should be administered with water on an empty stomach and not with fruit juices; aluminum or magnesium antacids should be separated by at least 2 hours. Common adverse effects include headache (~7.2%), drowsiness (~1.3%), dizziness, nausea, and dyspepsia; rare effects include hypersensitivity, angioedema, and anaphylaxis. It is contraindicated in known hypersensitivity, and plasma levels are increased by co-administration with erythromycin and ketoconazole. Fexofenadine is categorized as Pregnancy Category C. [7]

Excipient Profiles for FDTs

Natural mucilage

Plant mucilages (Plantago ovata, Lepidium sativum, Moringa oleifera, Ocimum basilicum) are arabinoxylan-rich hydrocolloids with swelling index about 15–25 mL/g and near-neutral pH. In FDTs they promote rapid water uptake and 3D swelling, generating disruptive forces that aid disintegration. Typical use is 4–10% w/w, but their moisture and microbial sensitivity require controlled storage; they are GRAS, biodegradable, and non-toxic.

Crospovidone

Crospovidone is a crosslinked, porous povidone that is insoluble but highly wettable. It acts mainly by capillary wicking, rapidly drawing water into the tablet without forming a gel. Effective levels are 2–8% w/w. It is chemically inert, non-ionic, compatible with most APIs, and not absorbed from the GI tract. [8]

Binary system rationale: Mucilage alone can gel and slow water ingress, while crospovidone alone provides limited swelling force. Combining 4–10% mucilage with 2–8% crospovidone exploits swelling plus wicking, typically giving 12–28 s disintegration with lower total superdisintegrant load and better compressibility. Ratios around 1:1–1:2 (crospovidone:mucilage) are frequently optimal.

Mannitol

Mannitol is a non-hygroscopic polyol used at 20–60% w/w as diluent and sweetener. It dissolves quickly, creates porosity, and provides cooling sweetness that helps mask fexofenadine bitterness. It is chemically stable and GRAS.

Microcrystalline cellulose PH 102

MCC PH 102 is a directly compressible cellulose used at about 5–25% w/w to impart hardness and improve flow. Its porous structure supports water penetration and disintegration. It is stable, GRAS, and not absorbed. [9]

Aspartame

Aspartame (0.5–3% w/w) supplies high-intensity sweetness and works synergistically with mannitol for taste masking. It is stable in the dry state but unsuitable for patients with phenylketonuria, requiring label warning.

Magnesium stearate

Magnesium stearate (0.25–1% w/w) is a hydrophobic lubricant that minimizes sticking. Excess level or mixing time, however, can slow wetting and prolong disintegration, so its use must be tightly controlled.

Talc

Talc (0.5–2% w/w) acts as a glidant and anti-adherent, improving flow and reducing sticking with minimal effect on disintegration. It is inert and orally safe, though dust inhalation should be minimized during processing. [10]

Formulation and Evaluation Strategies

Manufacturing by Direct Compression

Direct compression is the method of choice for fexofenadine HCl FDTs due to the drug's stability and the need to avoid premature moisture activation of natural mucilage. The typical process involves: sifting fexofenadine HCl, mannitol, MCC PH 102, aspartame, natural mucilage, and crospovidone through #40 mesh; blending in geometric dilution for about 15 minutes; adding talc and mixing for 5 minutes; then adding magnesium stearate and mixing for not more than 3 minutes to prevent over-lubrication. The blend is compressed using 8–10 mm flat-faced punches at 4–6 kN to achieve hardness 3–4 kg/cm², with target tablet weight 150–250 mg for 30–60 mg fexofenadine dose. This approach minimizes processing steps, is compatible with moisture-sensitive mucilage, and supports scale-up using standard high-speed tablet presses. [11]

Optimization by QbD

A 3^2 factorial design is commonly used, with X1 representing natural mucilage (4–10% w/w) and X2 representing crospovidone (2–8% w/w). The main responses are disintegration time (Y1), wetting time (Y2), and percent drug release at 5 minutes (Y3). ANOVA typically shows that crospovidone level (X2) has a stronger effect on disintegration time, whereas mucilage level (X1) more markedly influences wetting time and water absorption. Desirability function optimization often identifies a formulation containing approximately 6% mucilage and 4% crospovidone as optimal, yielding disintegration time around 18 seconds, wetting time about 26 seconds, and Q5min near 94–95%. Compression force between 4 and 6 kN is critical; forces above 7 kN reduce porosity and increase disintegration time up to 38 seconds. Similarly, lubrication time beyond 5 minutes can increase disintegration time by about 40% due to formation of a more continuous hydrophobic film of magnesium stearate on particle surfaces.

Taste Masking

Fexofenadine HCl has an intensely bitter taste, making taste masking essential for pediatric and geriatric acceptability. A multi-pronged approach is typically used: mannitol at 30–50% provides bulk sweetness and a cooling effect; aspartame at 1–2% offers high-intensity immediate sweetness; menthol at 0.5–1% adds a mint flavor and enhances cooling sensation. Fast disintegration (below 30 seconds) further minimizes the duration of contact between dissolved drug and taste buds. For more severe bitterness, the drug can be pre-processed by coating with Eudragit EPO or forming a drug–resin complex with weak cation exchange resins

such as Indion 234 or Kyron T-314 before blending into the FDT formulation, as reported in taste-masked ODT studies. [12]

Evaluation Parameters

Pre-compression parameters

Flow properties of the powder blend are assessed via angle of repose, Carr's index, and Hausner ratio. An angle of repose of 25–30° indicates good flow with talc and co-processed mucilage present, while Carr's index 12–18% and Hausner ratio 1.14–1.22 denote fair to good flow behavior suitable for direct compression. Co-processing mucilage with mannitol or MCC has been shown to reduce angle of repose from about 41° to 27°, improving die filling and uniformity.

Post-compression parameters

Tablet hardness in the range of 3.2–4.5 kg/cm² ensures sufficient mechanical integrity whilst allowing rapid disintegration. Friability between 0.32 and 0.78% satisfies the USP requirement of less than 1%. Weight variation within ±5% and drug content 98.2–101.6% indicate acceptable dose uniformity. MCC PH 102 at 15–20% w/w generally provides adequate hardness without significantly retarding disintegration.

Disintegration time

The USP disintegration test (without disc) is performed in 900 mL pH 6.8 phosphate buffer at 37 °C. IP 2022 specifies not more than 3 minutes for orodispersible tablets, and USFDA guidance recommends less than 30 seconds for ODTs. Binary mucilage–crospovidone systems typically achieve disintegration times of 14–28 seconds, whereas formulations with single crospovidone 6% give around 35 seconds, and single mucilage 8% about 42 seconds, confirming synergy between swelling and wicking mechanisms. In vivo oral dispersion time in human volunteers (18–32 seconds) correlates well with in vitro disintegration.

Wetting time and water absorption ratio

Wetting time is measured by placing the tablet on tissue paper in a petri dish containing 6 mL water dyed with amaranth. Wetting times of 15–38 seconds and water absorption ratios of 65–88% are typical; higher water absorption correlates with increased mucilage content. Water absorption ratio is calculated as $(Wf-Wi)/Wi\times100(Wf-Wi)/Wi\times100$,
where WiWi and WfWf are initial and final tablet weights, respectively.

In vitro dissolution

Dissolution testing is usually conducted using USP Apparatus II (paddle) at 50 rpm in 900 mL pH 6.8 phosphate buffer or simulated salivary fluid at 37 °C. IP specifies not less than 80% drug release in 15 minutes. Fexofenadine FDTs with optimized binary superdisintegrants often show 91–98% release within 5 minutes, reflecting rapid disintegration and high aqueous solubility. Dissolution efficiency at 5 minutes ranges from about 74–86%, and similarity factor f_2 values above 50 versus marketed Allegra ODT suggest comparable or superior release profiles. Owing to the drug's high solubility, release generally follows first-order kinetics.

Stability studies

ICH accelerated stability testing at 40 °C/75% RH for 6 months in Alu–Alu blisters with desiccant typically shows no significant change in disintegration time, assay, dissolution, or physical appearance. To prevent sticking and caking, mucilage moisture content must be controlled below 10%.

Microbial limits total aerobic microbial count less than 1000 CFU/g and total yeast and mold count less than 100 CFU/g can be met by subjecting the mucilage to about 5 kGy gamma irradiation or appropriate ethylene oxide treatment. [13]

Challenges

Hygroscopicity of natural mucilage can cause moisture uptake and tablet softening during storage, especially at higher relative humidity. This is mitigated by co-processing mucilage with mannitol or MCC, using Alu–Alu blister packaging, and including silica gel desiccants in secondary packs. Natural materials also carry a

risk of microbial contamination, necessitating suitable sterilization steps and, for aqueous systems, preservatives. Batch-to-batch variability in swelling index (typically 15–25 mL/g) requires routine characterization and adjustment of mucilage level within 4–10% to maintain consistent disintegration behavior.

The intense bitterness of fexofenadine demands robust taste masking strategies, such as sweetener–flavor combinations or drug-resin complexes. Over-lubrication with magnesium stearate (above 1% w/w or mixing beyond 5 minutes) can significantly retard disintegration by forming hydrophobic films, so tight control of lubricant level and blending time is essential.

Regulatory Considerations

The IP 2022 monograph for Fexofenadine Orodispersible Tablets stipulates disintegration time not more than 3 minutes and dissolution not less than 80% in 15 minutes. USFDA guidance for ODTs recommends in vitro disintegration time not more than 30 seconds and encourages clinical swallowability studies to demonstrate patient acceptability. The GRAS status of plant mucilage, mannitol, and crospovidone supports their regulatory acceptance in FDT formulations. However, the use of aspartame requires a phenylketonuria warning on product labeling. For binary superdisintegrant systems, regulators increasingly expect clear identification of critical material attributes (e.g., mucilage swelling index, crospovidone particle size) and their linkage to critical quality attrib utes such as disintegration and dissolution. [14]

References

1. Indian Pharmacopoeia 2022. Vol III. Government of India, Ministry of Health and Family Welfare. Ghaziabad: Indian Pharmacopoeia Commission; 2022.
2. Patel DM, et al. Formulation and evaluation of fexofenadine HCl orodispersible tablets using Plantago ovata mucilage. Int J Pharm Sci Res. 2021;12(3):1420–1428.
3. US Food and Drug Administration. Guidance for Industry: Orally Disintegrating Tablets. Center for Drug Evaluation and Research, Pharmaceutical Quality/CMC; 2008.
4. European Pharmacopoeia 10.0. Orodispersible Tablets. Strasbourg: European Directorate for the Quality of Medicines & HealthCare (EDQM); 2019.
5. Sharma S, et al. Natural superdisintegrants in fast dissolving tablets: A review. Int J Pharm Sci Rev Res. 2020;60(1):45–52.
6. Patel DM, et al. Formulation and evaluation of fexofenadine HCl orodispersible tablets using Plantago ovata mucilage. Int J Pharm Sci Res. 2021;12(3):1420–1428.
7. Kumar R, et al. Crospovidone and natural mucilage as binary superdisintegrants in fast dissolving tablets. Drug Dev Ind Pharm. 2019;45(8):1295–1304.
8. Singh A, et al. QbD approach for optimization of fexofenadine orally disintegrating tablets. AAPS PharmSciTech. 2022;23(4):142.
9. Rao CB, et al. Taste masking techniques for bitter antihistamines in orodispersible tablets. Int J Appl Pharm. 2018;10(5):22–29.
10. Mahesh TG, et al. Stability of natural mucilage-based fast dissolving tablets under ICH conditions. J Drug Deliv Sci Technol. 2023;80:104123.
11. Rowe RC, Sheskey PJ, Quinn ME, editors. Handbook of Pharmaceutical Excipients. 9th ed. London: Pharmaceutical Press; 2020.
12. United States Pharmacopeia 43 – National Formulary 38 (USP 43–NF 38). Rockville (MD): United States Pharmacopeial Convention; 2020.
13. Allen LV, Ansel HC, Popovich NG. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 11th ed. Philadelphia: Wolters Kluwer; 2018.
14. Ghosh PK, et al. Recent advances in orodispersible tablets: A review. Int J Pharm Investig. 2024;14(1):1–12.