

Natural–Synthetic Binary Superdisintegrant Systems in Orodispersible Tablets

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Abstract

Background: Fast-dissolving tablets are intended to disintegrate rapidly in the oral cavity without water. Fexofenadine hydrochloride is a bitter, second-generation antihistamine; a rapidly disintegrating dosage form may improve ease of administration. A hybrid disintegrant system combining the swelling action of *Plantago ovata* (isabgol) mucilage with the wicking action of croscopovidone was therefore investigated.

Objective: To formulate, statistically optimise and evaluate 60 mg fexofenadine hydrochloride fast-dissolving tablets prepared by direct compression using *Plantago ovata* mucilage and croscopovidone.

Methods: Nine 200 mg tablet batches (F1–F9) were prepared using a 3² full factorial design. *Plantago ovata* mucilage (4%, 7% and 10% w/w) and croscopovidone (2%, 4% and 6% w/w) were the independent variables. Blends and tablets were evaluated for micromeritic properties, physical quality, wetting, water uptake, dispersion, disintegration and dissolution. Drug–excipient compatibility was examined by FTIR and DSC. The selected batch was compared with a marketed conventional tablet and stored for three months at 40 ± 2°C/75 ± 5% RH.

Results: All blends exhibited good flow and all tablet batches complied with the specified mechanical and assay limits. F5, containing 7% mucilage and 4% croscopovidone, gave a hardness of 3.5 ± 0.2 kg/cm², friability of 0.62%, drug content of 99.6 ± 0.4%, wetting time of 16 ± 1 s, disintegration time of 22 ± 2 s and 96.8% drug release at 10 min. Its ten-minute release exceeded the marketed conventional tablet (41.6%). The factorial models were significant ($p \leq 0.0014$), and prediction errors for F5 were below 1.5%. After three months of accelerated storage, F5 retained 98.5% drug content, disintegrated in 25 s and released 95.7% at 10 min.

Conclusion: The combination of 7% *Plantago ovata* mucilage and 4% croscopovidone produced a mechanically acceptable fast-dissolving fexofenadine tablet with rapid disintegration and early drug release. Formal taste testing, longer-term stability, scale-up and in-vivo evaluation remain necessary.

Keywords: Croscopovidone; factorial design; fast-dissolving tablet; fexofenadine hydrochloride; *Plantago ovata*; psyllium mucilage.

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Introduction

Orally disintegrating tablets are solid dosage forms designed to disintegrate rapidly on the tongue.

The United States Food and Drug Administration recommends that products designated as orally disintegrating tablets should generally have an in-vitro disintegration time of approximately 30 s or less and a tablet weight not exceeding 500 mg. [1]

Such products may be useful when swallowing conventional tablets or taking water is inconvenient.[2] Fexofenadine hydrochloride is a

second-generation peripheral H₁-antihistamine used in allergic rhinitis and chronic urticaria. [3] Development of a fast-dissolving tablet requires a balance between rapid water penetration, prompt tablet breakup, acceptable strength, low friability and taste acceptability.

Plantago ovata mucilage has previously shown disintegrant potential in directly compressed tablets; a published formulation containing 8% mucilage produced an in-vitro dispersion time of

approximately 8 s and faster release than a conventional comparator. [4]

Crospovidone promotes capillary uptake of aqueous fluid, whereas Plantago ovata mucilage hydrates and swells. Combining these mechanisms may provide rapid breakup while the natural polymer contributes binding strength.

This study used a 3^2 factorial design to determine the effects of both components and to identify a balanced formulation rather than simply selecting the batch with the shortest disintegration time.

Materials and Methods

Materials: Fexofenadine hydrochloride, Plantago ovata husk, crospovidone, mannitol, microcrystalline cellulose, aspartame, talc, magnesium stearate, potassium dihydrogen phosphate, sodium hydroxide, methanol, acetone and potassium bromide were of pharmacopoeial or analytical grade. A marketed conventional fexofenadine tablet was used as the dissolution comparator.

Table 1: Materials and functions in the formulation

Material	Function
Fexofenadine hydrochloride	Active pharmaceutical ingredient
Plantago ovata mucilage	Natural swelling disintegrant/binder
Crospovidone	Synthetic wicking superdisintegrant
Mannitol	Diluent and mouth-feel enhancer
Microcrystalline cellulose	Dry binder/filler
Aspartame	Sweetener
Talc	Glidant
Magnesium stearate	Lubricant

Isolation of Mucilage: Plantago ovata husk was soaked in distilled water (approximately 1:20) for 24 h, heated gently and squeezed through muslin cloth. The filtrate was treated with acetone (approximately 3:1 acetone: filtrate) to precipitate the mucilage.

The material was separated, washed, dried below 50°C, powdered, passed through sieve no. 80 and stored in a desiccator. Yield, pH, swelling index,

viscosity, loss on drying, ash values, microbial count and micromeritic properties were determined.

Analytical Method: Fexofenadine hydrochloride was quantified by UV spectrophotometry at 259 nm in phosphate buffer pH 6.8. Standards of 2–20 µg/mL were measured in triplicate. The method was evaluated for linearity, accuracy, intra-day and inter-day precision, limits of detection and quantification.

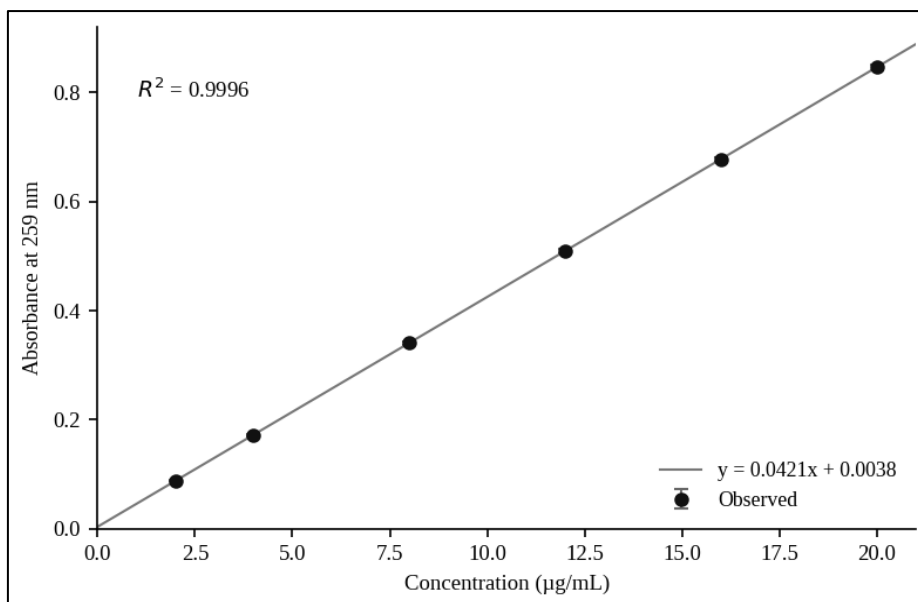


Figure 1: Calibration curve of fexofenadine hydrochloride at 259 nm in phosphate buffer pH 6.8.

Compatibility studies: FTIR spectra of the drug, mucilage, crospovidone, mannitol and the complete physical mixture were recorded over 4000–400

cm⁻¹. DSC thermograms were obtained for the drug, excipients and physical mixture. Retention of diagnostic bands and the drug melting endotherm

without a new spectral or thermal event was taken

as evidence of compatibility.

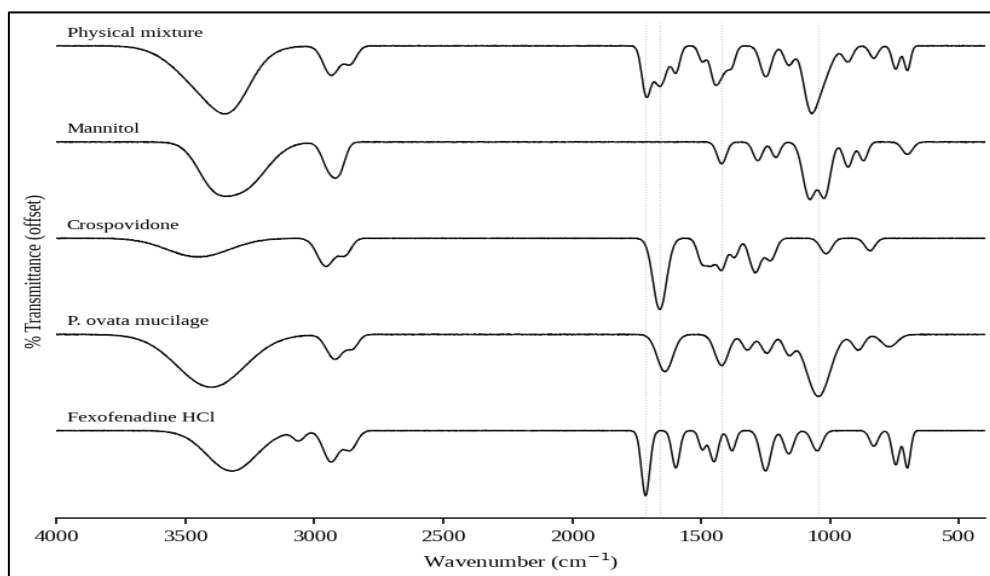


Figure 2: Overlaid FTIR spectra of the drug, selected excipients and physical mixture.

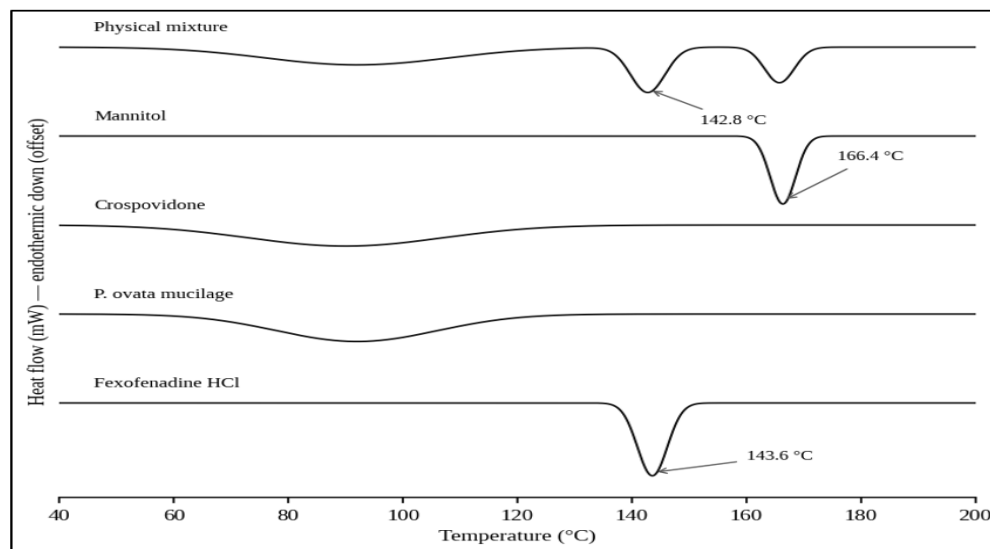


Figure 3: DSC thermograms of the drug, selected excipients and physical mixture.

Formulation design: A three-level, two-factor full factorial design was used. Plantago ovata mucilage was varied at 4%, 7% and 10% w/w, and crospovidone at 2%, 4% and 6% w/w. The

responses were disintegration time, wetting time, friability and cumulative release at 10 min. Each tablet contained 60 mg fexofenadine hydrochloride and had a target weight of 200 mg.

Table 2: Composition of fexofenadine hydrochloride fast-dissolving tablets (mg/tablet)

Batch	Drug	Mucilage	CP	MCC	Asp.	Mannitol	Talc	MgSt	Total
F1	60	8	4	30	4	91	2	1	200
F2	60	8	8	30	4	87	2	1	200
F3	60	8	12	30	4	83	2	1	200
F4	60	14	4	30	4	85	2	1	200
F5	60	14	8	30	4	81	2	1	200
F6	60	14	12	30	4	77	2	1	200
F7	60	20	4	30	4	79	2	1	200
F8	60	20	8	30	4	75	2	1	200
F9	60	20	12	30	4	71	2	1	200

CP, crospovidone; MCC, microcrystalline cellulose; Asp., aspartame; MgSt, magnesium stearate.

Tablet preparation: All ingredients were passed through sieve no. 60. The drug was geometrically blended with mucilage, crospovidone, mannitol, microcrystalline cellulose and aspartame for 15 min. Talc was mixed for 5 min and magnesium stearate for a final 2 min. The blends were compressed with flat-faced punches to a target hardness of 3–4 kg/cm².

Evaluation: Pre-compression testing included angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Tablets were evaluated for appearance, thickness, weight variation, hardness, friability and drug content. Rapid-release testing included wetting time, water absorption ratio, dispersion time and compendial disintegration in phosphate buffer pH 6.8 at 37 ± 0.5°C.

Dissolution was performed with USP apparatus II at 50 rpm in 900 mL phosphate buffer pH 6.8 at 37 ± 0.5°C. Samples were withdrawn at 1, 2, 3, 5, 10, 15, 20 and 30 min and analysed at 259 nm. The selected formulation was compared with a marketed conventional tablet under identical conditions. Difference and similarity factors were calculated using the model-independent approach

introduced by Moore and Flanner and subsequently analysed by Shah et al. [5, 6]

Statistics and Stability: Results are reported as mean ± standard deviation for the replicate numbers specified. Quadratic polynomial models were fitted to the factorial responses and tested by analysis of variance, with $p < 0.05$ considered significant.

The optimised formulation was packed in aluminium blister strips and stored for three months at 40 ± 2°C/75 ± 5% RH. ICH Q1A(R2) describes 40 ± 2°C/75 ± 5% RH as the general accelerated condition and recommends longer formal studies for registration. [7]

Results

Mucilage and UV Method: The mucilage yield was 22.4% w/w. It was a light cream-to-pale brown amorphous powder that swelled to a translucent gel in water. The swelling index was 19.6 ± 0.4 mL/g and the 1% dispersion viscosity was 28.4 ± 1.2 cP. The powder showed good flow, with an angle of repose of 31.8 ± 0.6°, Carr's index of 14.60% and Hausner's ratio of 1.17.

Table 3: Standardisation of isolated Plantago ovata mucilage

Parameter	Observed value	Inference
Yield	22.4% w/w	Within thesis reference range
pH (1% dispersion)	6.4	Complies
Swelling index	19.6 ± 0.4 mL/g	High swelling capacity
Viscosity (1%)	28.4 ± 1.2 cP	Complies
Loss on drying	6.8%	Complies
Total ash	3.2%	Complies
Acid-insoluble ash	0.6%	Complies
Angle of repose	31.8 ± 0.6°	Good flow

The UV method was linear over 2–20 µg/mL, with the equation $y = 0.0421x + 0.0038$ and $R^2 = 0.9996$. Mean recovery was 99.2–100.6%, intra-day precision was 1.2% RSD, inter-day precision was 1.6% RSD, and LOD and LOQ were 0.31 and 0.94 µg/mL, respectively.

Compatibility: The diagnostic bands of fexofenadine hydrochloride were retained in the physical mixture. The carboxylic carbonyl shifted only from 1715 to 1713 cm⁻¹, and no new band appeared. Pure drug showed a DSC peak at

143.6°C, while the mixture retained the event at 142.8°C. These small shifts did not indicate a detectable incompatibility under the test conditions.

Blend and tablet quality: The nine blends showed angles of repose of 27.2–30.2°, Carr's indices of 12.40–14.23% and Hausner's ratios of 1.14–1.17.

All batches compressed without capping or lamination. Tablet weight remained near 200 mg, hardness was 3.1–4.0 kg/cm², friability was 0.44–0.86%, and drug content was 97.9–99.6%.

Table 4: Post-compression evaluation of tablet batches

Batch	Thickness (mm)	Weight (mg)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)
F1	3.12 ± 0.03	199.4 ± 1.2	3.6 ± 0.2	0.58	98.2 ± 0.6
F2	3.15 ± 0.02	200.2 ± 1.4	3.4 ± 0.2	0.71	98.6 ± 0.5
F3	3.18 ± 0.03	199.8 ± 1.6	3.1 ± 0.3	0.86	97.9 ± 0.7
F4	3.14 ± 0.02	200.6 ± 1.3	3.8 ± 0.2	0.51	99.1 ± 0.4
F5	3.17 ± 0.03	200.1 ± 1.1	3.5 ± 0.2	0.62	99.6 ± 0.4
F6	3.20 ± 0.02	199.6 ± 1.5	3.2 ± 0.3	0.78	98.8 ± 0.6
F7	3.17 ± 0.03	200.4 ± 1.4	4.0 ± 0.2	0.44	98.4 ± 0.5
F8	3.21 ± 0.02	199.9 ± 1.2	3.7 ± 0.2	0.55	99.2 ± 0.4
F9	3.24 ± 0.03	200.3 ± 1.7	3.4 ± 0.3	0.69	98.1 ± 0.6

Rapid-release performance: Disintegration time decreased from 42 ± 3 s in F1 to 19 ± 1 s in F6. Seven batches disintegrated within 30 s. Increasing crospovidone strongly reduced wetting time, whereas increasing mucilage increased water uptake and helped maintain mechanical strength.

Table 5: Rapid-release properties of tablet batches

Batch	Wetting time (s)	Water absorption (%)	Dispersion time (s)	Disintegration time (s)
F1	28 ± 2	68.4 ± 1.8	48 ± 3	42 ± 3
F2	21 ± 2	76.2 ± 1.6	39 ± 2	34 ± 2
F3	17 ± 1	82.5 ± 1.5	33 ± 2	29 ± 2
F4	24 ± 2	79.6 ± 1.7	36 ± 2	31 ± 2
F5	16 ± 1	88.3 ± 1.4	26 ± 2	22 ± 2
F6	13 ± 1	92.7 ± 1.3	23 ± 1	19 ± 1
F7	22 ± 2	86.1 ± 1.6	33 ± 2	28 ± 2
F8	15 ± 1	93.5 ± 1.2	25 ± 2	21 ± 1
F9	13 ± 1	96.2 ± 1.1	24 ± 1	20 ± 1

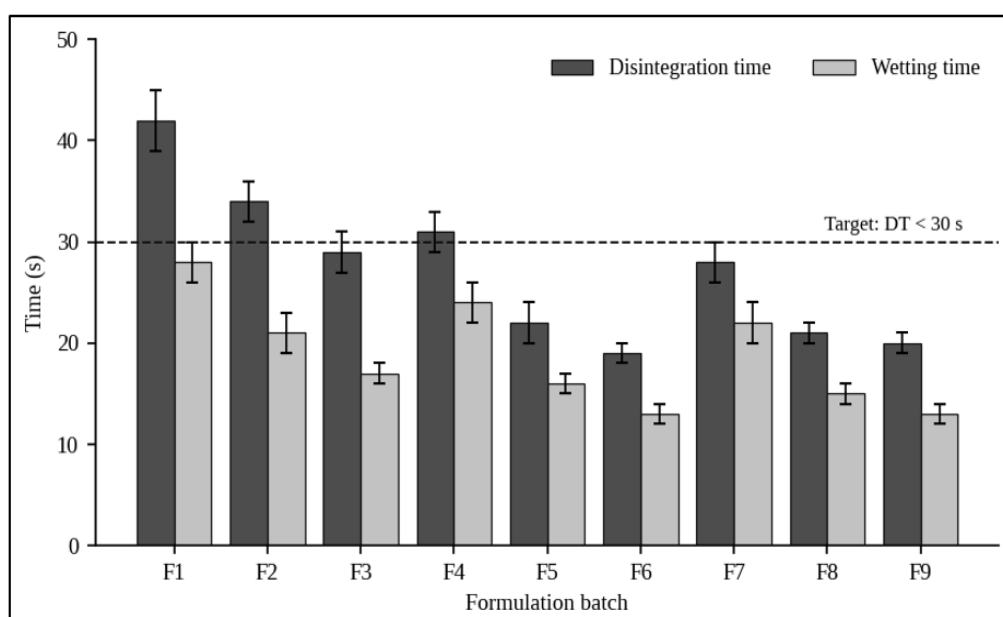


Figure 4: Disintegration and wetting times of batches F1–F9 (mean ± SD).

Dissolution performance: Drug release at 10 min increased from 82.4% in F1 to 98.1% in F9. F5 released 96.8% at 10 min and 99.6% at 30 min. The complete profiles are presented in below.

Table 6: Cumulative in-vitro drug release (%) in phosphate buffer pH 6.8

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	18.6	22.4	25.8	24.1	34.2	36.5	26.9	35.1	37.2
2	31.4	37.8	42.6	40.2	52.8	55.1	44.3	53.6	56.4
3	44.2	51.6	57.3	54.8	68.4	70.2	58.9	69.1	71.3
5	62.8	70.2	75.4	72.6	84.6	86.3	76.8	85.2	87.1
10	82.4	88.6	92.1	89.3	96.8	97.9	91.2	97.4	98.1
15	89.6	94.1	96.4	95.2	98.9	99.2	96.1	99.0	99.3
20	93.2	96.3	97.8	97.1	99.4	99.5	97.6	99.4	99.6
30	95.1	97.2	98.4	97.9	99.6	99.7	98.2	99.6	99.8

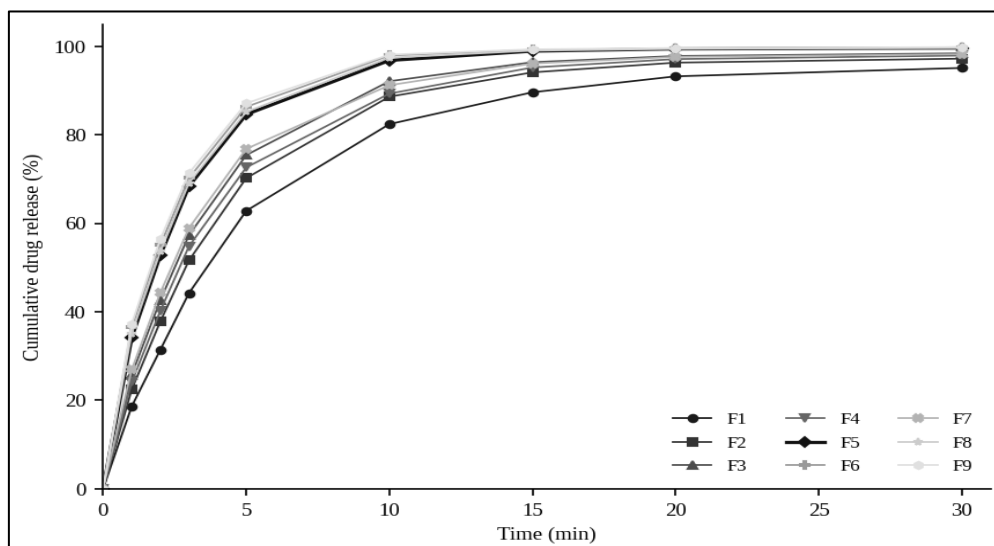


Figure 5: In-vitro cumulative drug release profiles of batches F1–F9.

Marketed comparison: F5 released 34.2%, 84.6% and 96.8% at 1, 5 and 10 min, respectively, whereas the marketed conventional tablet released 4.2%, 22.8% and 41.6%. The reported fit factors

were $f_1 = 116.5$ and $f_2 = 17.5$, indicating dissimilar profiles; this dissimilarity reflected the intentionally faster release from F5 rather than equivalence to the conventional product. [5,6]

Table 7: Comparative dissolution of F5 and marketed tablet

Time (min)	F5 (%)	Marketed (%)	Difference
1	34.2	4.2	30.0
2	52.8	8.6	44.2
3	68.4	13.4	55.0
5	84.6	22.8	61.8
10	96.8	41.6	55.2
30	99.6	78.9	20.7

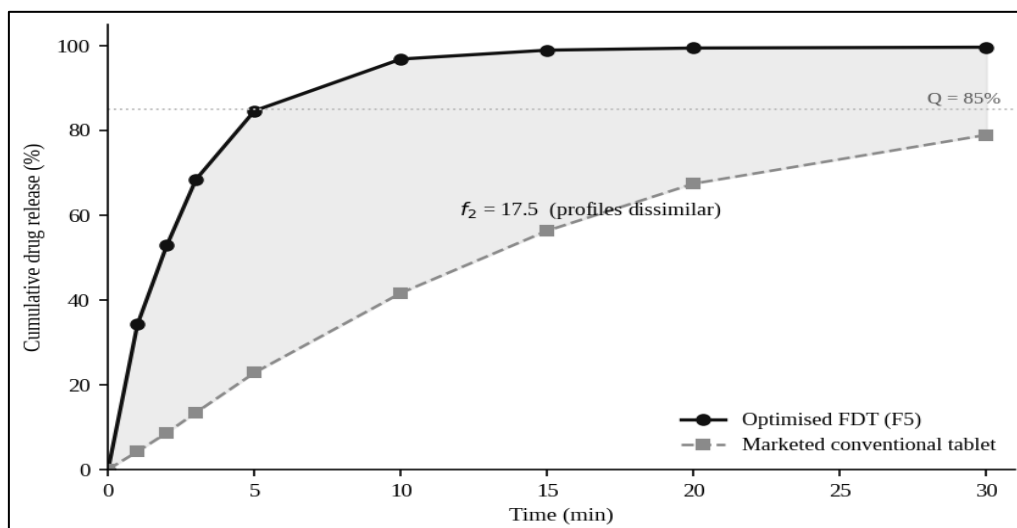


Figure 6: Comparative dissolution profiles of F5 and the marketed conventional tablet.

Factorial optimisation: All four quadratic models were significant. Disintegration time was influenced by both mucilage and croscopvidone, wetting time was influenced more strongly by croscopvidone, and friability showed opposing

factor effects: it decreased as mucilage increased and increased as croscopvidone increased. Release rose toward a broad central-to-upper design region but showed diminishing returns at the highest total disintegrant load.

Table 8: Factorial responses and model statistics

Response	Model R ²	F-value	p-value
Disintegration time	0.9963	159.9	0.0008
Wetting time	0.9965	168.7	0.0007
Friability	0.9989	545.2	0.0001
Release at 10 min	0.9945	108.9	0.0014

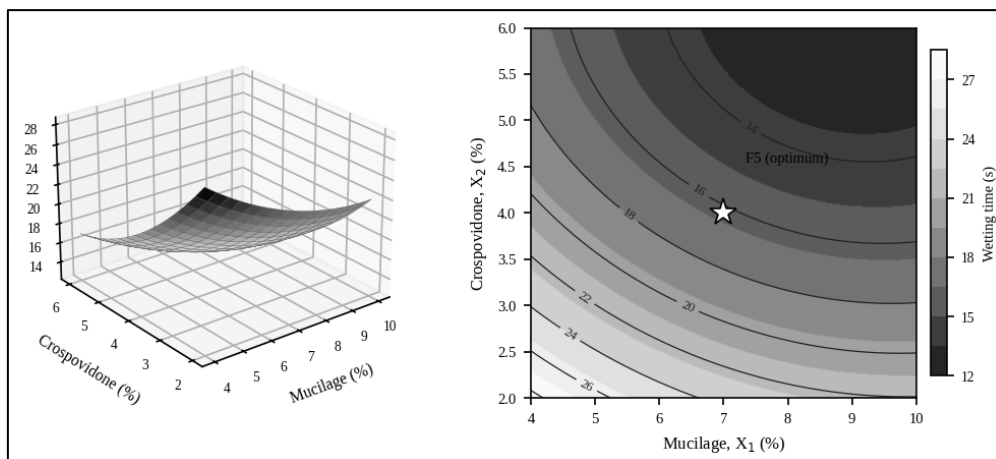


Figure 7: Response surface for disintegration time as a function of mucilage and crospovidone

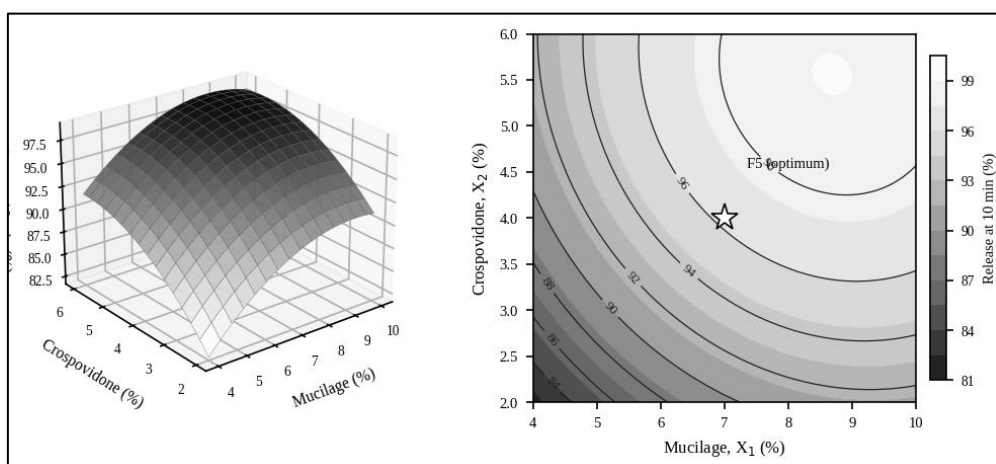


Figure 8: Response surface for drug release at 10 min as a function of mucilage and crospovidone

Selection of F5: F5 was selected because it met all predefined criteria with an overall desirability of 0.89 while using a lower total disintegrant burden than F9. Although F6, F8 and F9 showed marginally faster disintegration or release, F5 retained more mannitol, had lower friability than F6 and F9, and showed the highest drug content. Model-prediction errors for F5 were all below 1.5%.

Table 9: Predicted and observed responses for F5

Response	Predicted	Observed	Prediction error (%)
Disintegration time (s)	22.33	22	1.48
Wetting time (s)	16.22	16	1.36
Friability (%)	0.626	0.62	0.96
Release at 10 min (%)	96.29	96.8	0.53

Accelerated stability: F5 remained white, smooth and intact during three months at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$. Drug content decreased from 99.6% to 98.5%, disintegration time increased from 22 to 25 s, and ten-minute release decreased from 96.8% to 95.7%. These data support short-term accelerated stability only and do not establish a commercial shelf life; ICH Q1A(R2) calls for longer studies and representative batches for registration.[7]

Table 10: Accelerated stability of F5 at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$

Parameter	0 month	1 month	2 months	3 months
Appearance	White, smooth	No change	No change	No change
Hardness (kg/cm ²)	3.5	3.5	3.4	3.4
Friability (%)	0.62	0.64	0.66	0.68
Wetting time (s)	16	16	17	18
Disintegration time (s)	22	23	24	25
Drug content (%)	99.6	99.3	98.9	98.5
Release at 10 min (%)	96.8	96.5	96.1	95.7

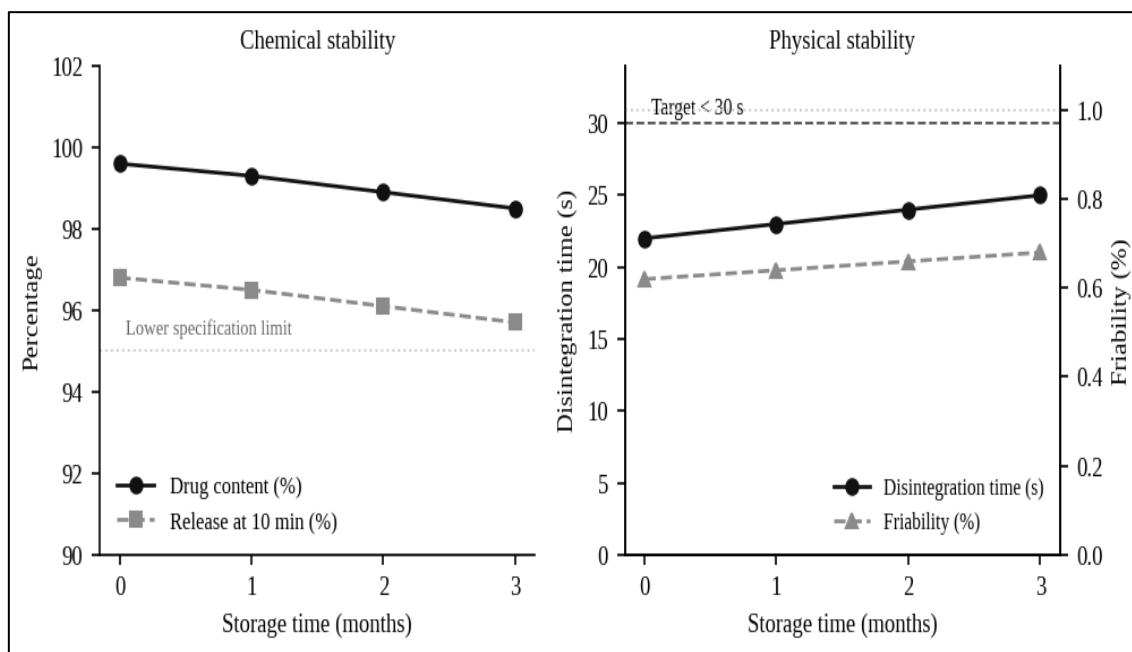


Figure 9: Drug content, disintegration time and drug release of F5 during accelerated storage

Discussion

The results support the proposed complementary roles of the two disintegrants. Crospovidone mainly accelerated fluid penetration, as shown by the strong reduction in wetting time as its concentration increased. Plantago ovata mucilage increased water uptake and also improved tablet strength, shown by higher hardness and lower friability at increasing mucilage concentrations. Previous work has likewise demonstrated that Plantago ovata mucilage can act as an effective disintegrant in directly compressed tablets. [4]

The optimum was not the fastest formulation in isolation. F9 disintegrated two seconds faster than F5 but contained 16% total disintegrants, had less mannitol and showed higher friability. F5 therefore represented a more balanced composition, consistent with multi-response optimisation. Its 22 s disintegration time also falls within the approximately 30 s FDA recommendation for an orally disintegrating tablet. [1]

Rapid disintegration translated into faster early dissolution. The low f_2 value should not be interpreted as bioequivalence or superiority in patients; it only demonstrates that the mean in-vitro profile differed under the specified dissolution

conditions. Likewise, first-order and Korsmeyer–Peppas fitting describe the experimental profile but cannot establish in-vivo absorption. The original Korsmeyer–Peppas work relates release behaviour to diffusion and polymer processes in porous hydrophilic systems. [8]

The study has important limitations. Taste masking was not tested by a validated sensory panel or electronic tongue, no human oral-disintegration or pharmacokinetic study was performed, and accelerated stability was limited to three months in one development batch. Natural mucilage may vary between extraction lots. Consequently, formal taste evaluation, microbial quality controls, batch-to-batch standardisation, stability-indicating chromatography, real-time stability, scale-up validation and in-vivo assessment are required before clinical or commercial claims.

Conclusion

Fast-dissolving tablets of fexofenadine hydrochloride were successfully prepared by direct compression using Plantago ovata mucilage and crospovidone. F5, containing 7% mucilage and 4% crospovidone, provided the best overall balance of tablet strength, friability, wetting, disintegration and early drug release. It disintegrated in 22 s,

released 96.8% drug at 10 min and remained within the predefined quality limits after three months of accelerated storage.

The formulation is a promising laboratory-scale development candidate, but further taste, stability, manufacturing and in-vivo studies are needed.

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