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Development of Rapid Dispersible Tablet Preparations Using Synthetic and Natural Superdisintegrant Disintegrants: Comparative Performance Analysis

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ABSTRACT

Rapid dispersible tablets (RDTs) are patient-friendly oral dosage forms designed to disintegrate rapidly in the oral cavity or in the presence of a small amount of water, thereby improving patient compliance, particularly among pediatric, geriatric, and dysphagic populations. The performance of RDTs is highly dependent on the type and concentration of superdisintegrants used, as these excipients play a critical role in governing tablet disintegration behavior, wetting characteristics, mechanical strength, and drug release kinetics. Synthetic superdisintegrants such as croscarmellose sodium (CCS) and crospovidone (CPVP) are widely utilized due to their high swelling capacity and capillary action, whereas natural superdisintegrants like Plantago ovata husk (ispaghula husk) have gained increasing interest as eco-friendly and biocompatible alternatives. However, comparative information regarding the efficiency of synthetic and natural superdisintegrants in high-dose drug formulations remains limited. In this study, metformin hydrochloride (500 mg), a high-dose and highly water-soluble antidiabetic drug, was formulated into RDTs using different superdisintegrants via direct compression. The results demonstrated that the optimized formulation containing crospovidone exhibited the fastest disintegration time of 29.1 seconds, along with rapid tablet breakup and efficient drug release, compared to formulations containing croscarmellose sodium and Plantago ovata husk.

Keywords: *Rapid Dispersible Tablet, Superdisintegrant, Croscarmellose Sodium, Crospovidon, Plantago Ovata,*

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INTRODUCTION

Oral solid dosage forms, particularly conventional tablets and capsules, remain the most widely accepted and commercially dominant pharmaceutical dosage forms globally. However, a significant subset of patient populations - including pediatric patients who lack the swallowing reflex development, elderly patients with dysphagia associated with neurological degeneration, psychiatric patients requiring observed medication administration, and bedridden patients - experience considerable difficulty swallowing conventional tablets. The World Health Organization (WHO) reports that approximately 35% of the global population experiences swallowing difficulties to some degree, with the incidence rising sharply to 50-70% in institutionalized elderly populations. Rapid dispersible tablets (RDTs), also termed orally disintegrating tablets (ODTs), fast-dissolving tablets, or mouth-dissolving tablets in the literature, represent an innovative patient-centric dosage form strategy designed to circumvent swallowing difficulties. As defined by the European Pharmacopoeia (EP 8th Edition), RDTs are "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed" with a disintegration time of no more than 3 minutes when tested using the conventional disintegration apparatus. The US Food and Drug Administration (FDA) Guidance for Industry (2008) sets a more stringent target of disintegration within 30 seconds when tested using a modified disintegration method.

The fundamental technological challenge in RDT development lies in achieving an optimal balance between two apparently contradictory requirements: (1) achieving sufficiently rapid and complete disintegration within seconds upon contact with minimal saliva or water, while (2) maintaining adequate mechanical integrity (hardness and friability resistance) to withstand the stresses of manufacturing, packaging, transportation, and handling. This inherent paradox arises because the excipient strategies used to accelerate disintegration - such as incorporating highly porous, hydrophilic, and hygroscopic superdisintegrants - simultaneously tend to reduce compact mechanical strength.

Superdisintegrants are a specialized class of excipients characterized by their ability to cause rapid and complete tablet disintegration at relatively low use concentrations (2-10% w/w) through mechanisms that include: (a) rapid water absorption and consequent swelling to many times their original volume, (b) recovery of elastic deformation upon wetting ('rebound' mechanism), (c) capillary action through wicking or wetting, and (d) deformation recovery of particles compressed into non-equilibrium states. Three categories of superdisintegrants are currently available commercially and in routine pharmaceutical use: crosslinked carmellose sodium derivatives (croscarmellose sodium, CCS), crosslinked polyvinylpyrrolidone (crospovidone, CPVP), and modified starch/natural polymer derivatives such as sodium starch glycolate (SSG) and natural gums.

Natural polymer-based superdisintegrants have attracted increasing interest in recent pharmaceutical research as sustainable, biodegradable, and potentially cost-effective alternatives to synthetic superdisintegrants, particularly for formulations intended for markets in developing countries where synthetic excipient costs may be prohibitive. Plantago ovata seed husk (Ispaghula or psyllium husk), a natural mucilaginous polysaccharide composed predominantly of arabinoxylan (approximately 85% of the dry weight), exhibits high water-binding capacity and can form viscous gels upon hydration, properties theoretically suitable for superdisintegrant applications. However, the mucilaginous gel-forming tendency of Ispaghula husk may paradoxically retard drug release from the disintegrated mass, a critical consideration in comparative performance evaluation.

Metformin hydrochloride, the first-line pharmacological therapy for type 2 diabetes mellitus (T2DM) recommended universally by the American Diabetes Association (ADA) and the International Diabetes Federation (IDF), was selected as the model drug for this study. With a water solubility of approximately 300 mg/mL at 25 degrees C and BCS Class III classification (high solubility, low permeability), Metformin HCl is an ideal candidate for RDT formulation because rapid dissolution from the disintegrated mass is not expected to be the rate-limiting step, allowing the superdisintegrant's intrinsic performance characteristics to be directly compared without confounding factors. The present study aims to systematically develop and comparatively evaluate RDT formulations of Metformin HCl 500 mg incorporating CCS, CPVP, and Ispaghula husk at three concentration levels each, using direct compression technology.

METHODS

Metformin hydrochloride (pharmaceutical grade, purity 99.8%) was obtained from PT. Kimia Farma (Bandung, Indonesia). Croscarmellose sodium (Ac-Di-Sol, FMC BioPolymer), crospovidone (Kollidon CL, BASF), and microcrystalline cellulose PH-101 (Avicel PH-101, FMC BioPolymer) were gifted by PT. Brataco Chemika (Jakarta, Indonesia). *Plantago ovata* husk (Ispaghula husk, pharmacopeial grade) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Lactose monohydrate (Pharmatose 200M, DFE Pharma), mannitol (Pearlitol 200 SD, Roquette), aspartame (NutraSweet), magnesium stearate (Mallinckrodt), and colloidal silicon dioxide (Aerosil 200, Evonik) were obtained from commercial suppliers, while all other reagents and solvents were of analytical grade. Phosphate buffer pH 6.8 was prepared according to USP specifications. Preformulation compatibility between metformin HCl and individual excipients was evaluated using differential scanning calorimetry (DSC, DSC 214 Polyma, NETZSCH, Germany) and Fourier-transform infrared spectroscopy (FTIR, Shimadzu IRAffinity-1S). Binary physical mixtures of metformin HCl with each excipient at a 1:1 (w/w) ratio were analyzed. DSC thermograms were recorded from 25 to 350 °C at a heating rate of 10 °C/min, while FTIR spectra were recorded in the 400–4000 cm^{-1} range using the KBr pellet method. The absence of new thermal events or significant FTIR peak shifts between the pure drug and physical mixtures indicated compatibility.

Eight rapid dispersible tablet (RDT) formulations (F1–F8) were prepared by direct compression method. All powders were passed through a 60-mesh sieve to break aggregates.

Metformin HCl, superdisintegrant (croscarmellose sodium, crospovidone, or *Plantago ovata* husk at specified concentrations), microcrystalline cellulose PH-101, lactose monohydrate, mannitol, and aspartame were co-blended in a polypropylene container using a Y-cone blender for 15 minutes at 20 rpm. Magnesium stearate and colloidal silicon dioxide were then added and blended for an additional 3 minutes. The resulting blends were compressed using a single-punch tablet press (Manesty Unipress, UK) fitted with 12 mm flat-faced punches at a compression force of 10 kN, producing 100 tablets per batch, and the full formulation matrix is presented in Table 1.

Pre-compression powder properties were evaluated through bulk and tapped density measurements (100 taps, USP apparatus), from which Carr's Compressibility Index and Hausner's Ratio were calculated, while angle of repose was determined using the fixed-funnel method, and flowability was classified according to USP <1174>. Tablet quality attributes including thickness (n = 10), hardness (n = 10), friability (USP <1216>, 25 rpm, 4 min, n = 20 tablets), weight variation (n = 20), and drug content uniformity (10 tablets dissolved in 0.1 M HCl and analyzed at 233 nm, R^2 = 0.9999) were evaluated using standard pharmacopeial procedures.

Disintegration time was determined in triplicate using USP Disintegration Apparatus I (ERWEKA ZT 322) in 900 mL phosphate buffer pH 6.8 at 37 ± 0.5 °C. Although RDTs are intended to disintegrate in minimal saliva volume, the USP method was used to ensure pharmacopeial comparability and reproducibility across formulations. Wetting time was evaluated using the Petri dish method, while water absorption ratio was calculated based on weight gain after wetting. Dispersibility was assessed by dispersing a tablet in 100 mL water at 20 ± 5 °C, followed by sieve analysis (710 μm) and classification into Grade A or B. Drug release was performed using USP Apparatus II (paddle method, ERWEKA DT700, 900 mL phosphate buffer pH 6.8, 50 rpm, 37 ± 0.5 °C), with sampling at predetermined time intervals up to 45 minutes, followed by UV spectrophotometric analysis at 233 nm.

Release kinetics were analyzed using Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models, and the release exponent (n) was used to determine the mechanism of drug release. The optimized formulation (F5) was subjected to accelerated stability testing according to ICH Q1A(R2) guidelines at 40 ± 2 °C and 75 ± 5% RH for 6 months using HDPE packaging with desiccant, with evaluation at 0, 1, 3, and 6 months for physical appearance, hardness, disintegration time, drug content, dissolution, and moisture content using Karl Fischer titration. All data were expressed as mean ± standard deviation, and statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test with significance set at $p < 0.05$, while Pearson correlation analysis was used to evaluate relationships between superdisintegrant concentration and key response variables.

RESULTS

1. Preformulation Compatibility Study

DSC thermograms of pure Metformin HCl revealed a sharp endothermic melting peak at 232.4 °C (literature value: 232–236 °C), confirming the identity and crystalline purity of the drug. In binary physical mixtures of Metformin HCl with each excipient, the characteristic melting peak was

retained without significant shifting (less than 2 °C) and without the appearance of additional endothermic or exothermic events, indicating the absence of solid-state chemical interactions. FTIR analysis further confirmed the physicochemical compatibility, as the characteristic absorption bands of Metformin HCl, including N–H stretching vibrations at 3371 and 3290 cm^{-1}, C=N stretching at 1626 cm^{-1}, and symmetric bending at 1566 cm^{-1}, were preserved in all binary mixtures without notable shifts or intensity changes. Collectively, these results demonstrate that Metformin HCl is compatible with all excipients used in the formulation and suitable for further development into rapid dispersible tablets.

2. Formulation Composition

Eight RDT formulations were designed using a direct compression approach. Table 1 summarizes the complete compositional matrix. Superdisintegrants were incorporated at three concentration levels (2.5%, 5.0%, and 7.5% w/w) for CCS (F1-F3) and CPVP (F4-F6), and at two levels for Ispaghula husk (2.5% and 5.0%; F7-F8), as pilot studies indicated that Ispaghula concentrations above 5% resulted in unacceptably long disintegration times due to gel barrier formation. MCC PH-101 served as both a direct compression diluent and a disintegration facilitator. Mannitol was included to provide a mild sweetness and enhance the sensation of freshness. Aspartame (0.5 mg) was added as an intense sweetener to mask the bitter taste of Metformin HCl.

Table 1. Composition of Rapid Dispersible Tablet Formulations (per tablet, mg)

Ingredient / Excipient	F1	F2	F3	F4	F5	F6	F7	F8
Active (Metformin HCl, mg)	500	500	500	500	500	500	500	500
Croscarmellose Sodium / CCS (mg)	25	50	75	--	--	--	--	--
Crospovidone / CPVP (mg)	--	--	--	25	50	75	--	--
Plantago ovata Husk (Ispaghula, mg)	--	--	--	--	--	--	25	50
MCC PH-101 (mg)	100	100	100	100	100	100	100	100

Ingredient / Excipient	F1	F2	F3	F4	F5	F6	F7	F8
Lactose Monohydrate (mg)	q.s.*	q.s.*	q.s.*	q.s.*	q.s.*	q.s.*	q.s.*	q.s.*
Mannitol SD (mg)	50	50	50	50	50	50	50	50
Aspartame (mg)	5	5	5	5	5	5	5	5
Magnesium Stearate (mg)	5	5	5	5	5	5	5	5
Colloidal Silicon Dioxide (mg)	3	3	3	3	3	3	3	3
Total Tablet Weight (mg)	**800**	**825**	**850**	**800**	**825**	**800**	**800**	**825**

Although some formulations reached a total tablet weight of up to 850 mg, this is primarily attributed to the high-dose nature of Metformin HCl (500 mg), which significantly limits the extent to which total excipient content can be reduced in rapid dispersible tablet (RDT) design. In high-dose RDT formulations, increased tablet mass is commonly observed due to the need to accommodate the active pharmaceutical ingredient together with functional excipients such as superdisintegrants, directly compressible diluents, lubricants, and taste-masking agents, while still ensuring acceptable mechanical strength and rapid disintegration performance. Despite the relatively high tablet weight, the optimized formulation maintained rapid disintegration behavior, achieving a disintegration time of 29.1 seconds, which confirms that tablet performance was not compromised by the increased mass. Therefore, the higher tablet weight reflects a formulation constraint associated with high drug loading rather than a limitation of the rapid dispersible tablet system.

3. Pre-compression Powder Flow Properties

The flow properties of powder blends are critical determinants of tablet weight uniformity and tableting process efficiency. Results of powder characterization are presented in Table 2. The CPVP-containing blends exhibited the best overall flow, with Carr's Index values of 19.6 +/- 1.5% (classified as 'Good') and Hausner's Ratio of 1.24 +/- 0.02, compared to CCS blends (CI 22.2 +/- 1.8%, 'Passable') and Ispaghula husk blends (CI 25.5 +/- 2.1%, 'Passable', borderline 'Poor'). The superior flowability of CPVP blends is attributable to the spherical particle morphology and low moisture

sorption characteristics of crosslinked polyvinylpyrrolidone, which minimizes inter-particulate cohesion and electrostatic adhesion. In contrast, Ispaghula husk particles are irregularly shaped and hygroscopic, leading to increased inter-particle friction and cohesion that impair flowability. Angle of repose values ranged from 30.1 deg (CPVP) to 35.8 deg (Ispaghula), all within the acceptable range for direct compression (<40 deg). Colloidal silicon dioxide (0.3% w/w) was incorporated as a flow enhancer across all formulations.

Table 2. Pre-compression Powder Flow Properties of RDT Blends (mean +/- SD, n=3)

Parameter	CCS Group (n=3)	CPVP Group (n=3)	Ispaghula Group (n=2)
Bulk Density (g/mL)	0.42 +/- 0.03	0.45 +/- 0.02	0.38 +/- 0.04
Tapped Density (g/mL)	0.54 +/- 0.02	0.56 +/- 0.03	0.51 +/- 0.03
Carr's Index (%)	22.2 +/- 1.8	19.6 +/- 1.5	25.5 +/- 2.1
Hausner's Ratio	1.29 +/- 0.03	1.24 +/- 0.02	1.34 +/- 0.04
Angle of Repose (deg)	32.4 +/- 1.6	30.1 +/- 1.4	35.8 +/- 2.3
Flow Classification	Passable	Good	Passable

4. Post-compression Tablet Physical Characteristics

Physical characterization results for all eight formulations are presented in Table 3. Tablet thickness ranged narrowly from 3.19 to 3.28 mm across all formulations, indicating consistent die fill and compression force. Hardness values ranged from 48.6 N (F7, Ispaghula 2.5%) to 57.4 N (F6, CPVP 7.5%), all within the clinically acceptable range of 40-80 N for conventional oral tablets. A general trend of increasing hardness with superdisintegrant concentration was observed for CCS and CPVP groups, which may be attributed to increased particle interlocking and compaction efficiency at higher excipient levels. Notably, Ispaghula husk formulations showed slightly lower hardness compared to corresponding CCS and CPVP formulations, likely due to the elastic deformation characteristics of mucilaginous particles that partially recover after compaction.

Friability values for all formulations were below the USP/BP acceptable limit of 1.0%, ranging from 0.43% (F6) to 0.61% (F7). Drug content uniformity was within the 90-110% acceptance criterion for all formulations (97.8-99.7%), indicating satisfactory blend homogeneity and content uniformity. Weight variation results showed all tablets within the USP weight variation limits (less than 5% for tablets over 300 mg), confirming excellent flowability of the blends during tableting.

Table 3. Post-compression Tablet Physical Characteristics (mean +/- SD, n=10 unless stated)

Parameter	F1	F2	F3	F4	F5	F6	F7	F8
Thickness (mm)	3.21	3.24	3.28	3.20	3.23	3.27	3.19	3.22
Hardness (N)	52.3	54.1	55.8	53.7	55.2	57.4	48.6	50.3
Friability (%)	0.58	0.52	0.48	0.55	0.49	0.43	0.61	0.57
Weight Variation (mg)	801+/- 4.2	826+/- 3.8	851+/- 4.5	802+/- 3.9	827+/- 4.1	851+/- 3.7	800+/- 4.6	826+/- 4.3
Drug Content (%)	98.6	99.1	98.9	99.3	99.7	99.5	97.8	98.4

5. Disintegration Time, Wetting Time, and Water Absorption Ratio

The results of disintegration, wetting, and water absorption evaluation are presented in Table 4, representing the most critical performance parameters for RDT characterization. Highly significant differences ($p < 0.001$, one-way ANOVA) were observed among formulations for all three parameters.

Among all synthetic superdisintegrant formulations, CPVP at 5% w/w (F5) exhibited the shortest disintegration time of 29.1 +/- 1.8 seconds, significantly outperforming both the best CCS formulation (F2: 38.7 +/- 2.5 seconds) and the best Ispaghula formulation (F7: 72.5 +/- 4.1 seconds). This superior performance of CPVP is mechanistically explained by its rapid and extensive three-dimensional water absorption through the porous crosslinked polymer network, generating significant swelling pressure that ruptures tablet compacts from within. CPVP's insolubility in water is a critical advantage: unlike soluble disintegrants that can dissolve to form viscous solutions retarding tablet break-up, CPVP maintains its solid particulate form while swelling, creating physical disruption of the tablet matrix.

The superiority of CPVP 5% over CPVP 7.5% (F6: 35.8 seconds) is a notable finding and follows a well-established 'concentration-optimum' behavior of superdisintegrants. At concentrations above the optimum, superdisintegrant particles begin to compete for the limited tablet pore space, potentially forming a continuous gel-like network that paradoxically impedes water penetration into the tablet interior, slowing rather than accelerating disintegration. This optimum concentration phenomenon was also observed for CCS, where F1 (2.5%) showed 58.4 seconds, F2 (5.0%) showed the best performance at 38.7 seconds, and F3 (7.5%) showed an intermediate result of 47.6 seconds.

Ispaghula husk formulations displayed the longest disintegration times across corresponding concentrations, a finding consistent with the mucilage-forming mechanism of psyllium husk hydration. Upon contact with water, Ispaghula husk particles rapidly form a viscous gel layer at the tablet surface that acts as a diffusion barrier, slowing water penetration to the tablet core and paradoxically retarding the overall disintegration process. The high water absorption ratio (WAR) of F7 (84.7%) and F8 (91.2%), approaching or exceeding that of CCS formulations, confirms that Ispaghula does absorb substantial water; however, the mechanism of water retention in a gel matrix rather than swelling-driven tablet rupture accounts for the extended disintegration times.

Table 4. Disintegration Time, Wetting Time, Water Absorption Ratio, and Dispersibility Grade (mean +/- SD, n=3)

Formulation	Disintegration Time (sec)	Wetting Time (sec)	Water Absorption Ratio (%)	Dispersibility Grade
F1 (CCS 2.5%)	58.4 +/- 3.2	46.2 +/- 2.8	71.3 +/- 3.5	A
F2 (CCS 5.0%)	38.7 +/- 2.5	31.5 +/- 2.1	82.4 +/- 2.9	A
F3 (CCS 7.5%)	47.6 +/- 2.9	38.9 +/- 2.4	76.1 +/- 3.1	A
F4 (CPVP 2.5%)	44.3 +/- 2.7	35.8 +/- 2.2	79.8 +/- 2.7	A
F5 (CPVP 5.0%)	29.1 +/- 1.8	23.6 +/- 1.5	91.6 +/- 2.4	A
F6 (CPVP 7.5%)	35.8 +/- 2.1	29.4 +/- 1.9	88.2 +/- 2.6	A
F7 (Ispaghula 2.5%)	72.5 +/- 4.1	61.3 +/- 3.6	84.7 +/- 3.8	A
F8 (Ispaghula 5.0%)	89.3 +/- 5.2	78.4 +/- 4.8	91.2 +/- 4.2	B

Dispersibility Grade A: Complete dispersion within 3 minutes with no residue on 710-um sieve; Grade B: Partial dispersion with residue on sieve. All formulations except F8 achieved Grade A.

6. In Vitro Drug Release Study and Kinetic Modeling

Cumulative percent drug release profiles at selected time points and Korsmeyer-Peppas kinetic parameters are presented in Table 5. All formulations achieved the USP dissolution requirement for immediate-release tablets (>80% drug released within 30 minutes). However, marked differences existed in the rate and extent of early drug release, particularly at the 15-minute sampling point.

Formulation F5 (CPVP 5%) demonstrated the most rapid drug release profile, releasing 63.8% within 5 minutes and achieving quantitative release (>99%) within 30 minutes. This exceptionally fast drug release is directly correlated with its shortest disintegration time (29.1 seconds), confirming that for a highly water-soluble BCS Class III drug like Metformin HCl, disintegration is the rate-limiting step governing drug dissolution from RDTs. Once the tablet matrix is disrupted by the superdisintegrant action, dissolution of the drug is virtually instantaneous given its high aqueous solubility.

A statistically significant linear correlation (Pearson $r = -0.918$, $p < 0.001$) was found between disintegration time and drug release at 15 minutes across all formulations, confirming the mechanistic link between superdisintegrant efficiency and drug bioavailability. Ispaghula husk formulations (F7, F8) showed notably slower and incomplete drug release profiles, particularly in the early time points (F7: only 28.6% at 5 minutes; F8: 22.1% at 5 minutes). This is attributed to the mucilage barrier formed around Metformin HCl particles within the disintegrated mass, which impedes drug diffusion into the dissolution medium despite the overall high water absorption.

Korsmeyer-Peppas modeling revealed that CCS and CPVP formulations (F1-F6) followed Fickian diffusion mechanisms (n values 0.38-0.48, all below 0.45), indicating drug release primarily controlled by simple diffusion through the swollen polymer network. In contrast, Ispaghula husk formulations exhibited non-Fickian (anomalous) transport (n = 0.52-0.56), consistent with a combined diffusion and polymer relaxation/swelling mechanism. The higher n values for Ispaghula formulations reflect the gel-controlled release kinetics characteristic of mucilaginous natural polymers. Good model fits were obtained for all formulations ($R2 = 0.985$-0.998).

Table 5. In Vitro Cumulative Drug Release (%) and Korsmeyer-Peppas Kinetic Parameters (mean, n=3)

Formula	5 min (%)	10 min (%)	15 min (%)	30 min (%)	45 min (%)	Release Mechanism (Korsmeyer-Peppas)
F1	32.4	58.7	73.2	88.6	95.1	n=0.48, R2=0.991 (Fickian)
F2	45.6	72.3	88.4	96.7	99.2	n=0.44, R2=0.994 (Fickian)
F3	41.2	65.8	81.5	93.4	98.1	n=0.46, R2=0.993 (Fickian)
F4	52.3	78.1	91.6	98.2	99.8	n=0.41, R2=0.996 (Fickian)

Formula	5 min (%)	10 min (%)	15 min (%)	30 min (%)	45 min (%)	Release Mechanism (Korsmeyer-Peppas)
F5*	63.8	89.4	97.2	99.6	100.0	n=0.38, R2=0.998 (Fickian)
F6	58.4	83.6	94.3	99.1	100.0	n=0.40, R2=0.997 (Fickian)
F7	28.6	51.4	68.9	83.2	91.7	n=0.52, R2=0.989 (Non-Fickian)
F8	22.1	44.7	62.3	78.9	88.6	n=0.56, R2=0.985 (Non-Fickian)

F5 identified as optimal formulation. n = release exponent; R2 = coefficient of determination. Fickian diffusion: n <= 0.45; Non-Fickian (Anomalous) transport: 0.45 < n < 0.89.

7. Comparative Performance Analysis

Table 6 presents a head-to-head comparison of the best-performing formulation from each superdisintegrant group (F2: CCS 5%; F5: CPVP 5%; F7: Ispaghula 2.5%) against pharmacopoeial quality standards. This comparative framework allows critical analysis of the relative merits and limitations of each superdisintegrant category in the context of RDT development.

Crospovidone (CPVP) at 5% w/w clearly emerges as the superior superdisintegrant across all evaluated performance criteria, demonstrating statistically significant advantages in disintegration time (29.1 vs. 38.7 vs. 72.5 seconds for CPVP vs. CCS vs. Ispaghula), wetting time, water absorption ratio, and particularly drug release rate at the clinically important 15-minute time point (97.2% vs. 88.4% vs. 68.9%). The performance ranking is unambiguous: CPVP 5% (F5) > CCS 5% (F2) >> Ispaghula 2.5% (F7). All formulations met pharmacopoeial limits for hardness, friability, and drug content. The drug release specification (>75% at 30 minutes, immediate-release criterion) was met by all formulations except F8.

The inferior performance of Ispaghula husk as a superdisintegrant relative to its synthetic counterparts is consistent with the physicochemical limitations of mucilaginous natural polymers. While Ispaghula husk offers potential advantages including natural origin, biodegradability, potential prebiotic effects for the colonic microbiome, and lower cost in tropical markets, these benefits must be weighed against its demonstrably slower disintegration and drug release kinetics. Future formulation strategies incorporating Ispaghula husk could explore chemical modification (e.g., carboxymethylation), cation exchange treatment, or blending with synthetic superdisintegrants to achieve synergistic disintegration performance while retaining the natural polymer advantages.

Table 6. Comparative Performance Analysis: Best Formulation per Superdisintegrant Group vs. Pharmacopoeial Limits

Parameter	Best CCS (F2)	Best CPVP (F5)	Best Ispaghula (F7)	USP/BP Limit
Disintegration Time (sec)	38.7 +/- 2.5	29.1 +/- 1.8 *	72.5 +/- 4.1	< 180
Wetting Time (sec)	31.5 +/- 2.1	23.6 +/- 1.5 *	61.3 +/- 3.6	--
Water Absorption Ratio (%)	82.4 +/- 2.9	91.6 +/- 2.4 *	84.7 +/- 3.8	--
Drug Release at 15 min (%)	88.4 +/- 2.6	97.2 +/- 1.8 *	68.9 +/- 3.1	>75 at 30 min
Drug Release at 45 min (%)	99.2 +/- 1.2	100.0 +	91.7 +/- 2.8	>80
Hardness (N)	54.1 +/- 2.3	55.2 +/- 2.5	48.6 +/- 2.1	40-80 N
Friability (%)	0.52	0.49	0.61	< 1.0%
Drug Content (%)	99.1 +/- 0.8	99.7 +/- 0.6 *	97.8 +/- 1.2	90-110%
Overall Rank	2nd	1st (Optimal)*	3rd	--

The comparative evaluation of the best-performing formulations from each superdisintegrant group demonstrated clear differences in disintegration performance. Although all formulations complied with the United States Pharmacopeia (USP) requirement for orally disintegrating tablets (<180 s), more stringent criteria for orally disintegrating systems, as recommended by the FDA (<30 s), further distinguished their performance. Among all formulations, only the crospovidone-based formulation (F5) achieved a disintegration time of 29.1 ± 1.8 s, thereby meeting the FDA target for rapid disintegration in the oral cavity. In contrast, formulations containing croscarmellose sodium (F2) and *Plantago ovata* husk (F7) did not meet this stricter benchmark, although they still satisfied compendial USP requirements. These findings highlight the superior wicking and capillary action of crospovidone in facilitating rapid tablet breakup, particularly in a high-dose system such as Metformin HCl 500 mg.

8. Accelerated Stability Study (F5 - Optimal Formulation)

Accelerated stability results for the optimized formulation F5 (CPVP 5%) under ICH Q1A(R2) conditions (40 deg C/75% RH, 6 months) are presented in Table 7. Tablets maintained their white appearance throughout the study period, with only a slight off-white tinge noted at 6 months, attributed to minor Maillard reaction between aspartame and trace reducing sugar impurities in lactose under the elevated humidity conditions employed.

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Hardness showed a progressive but statistically non-significant decrease from 55.2 N (T0) to 52.1 N (T6), remaining comfortably within acceptable limits throughout. Disintegration time exhibited a statistically significant increase from 29.1 seconds at T0 to 38.7 seconds at T6 ($p = 0.032$), attributed to partial hygroscopic softening of the tablet matrix under high humidity, paradoxically reducing mechanical cohesion while simultaneously promoting moisture-induced pre-wetting that slows the explosive swelling mechanism of CPVP. Despite this increase, the 6-month disintegration time (38.7 seconds) remains well within the EP limit of 180 seconds. Drug content and drug release profiles remained within specifications throughout the stability period. Moisture content increased from 2.1% to 3.6% over 6 months, warranting packaging optimization with moisture-barrier materials (aluminum foil blisters) for the final product.

Table 7. Accelerated Stability Study of F5 (CPVP 5%) at 40 deg C / 75% RH - ICH Q1A(R2) (mean +/- SD, n=3)

Parameter (F5 – Optimal)	Initial (T0)	1 Month (T1)	3 Months (T3)	6 Months (T6)
Appearance	White, intact	White, intact	White, intact	Sl. off-white
Hardness (N)	55.2 +/- 2.5	54.8 +/- 2.4	53.9 +/- 2.7	52.1 +/- 3.1
Disintegration Time (sec)	29.1 +/- 1.8	30.6 +/- 2.1	33.4 +/- 2.5	38.7 +/- 3.2
Drug Content (%)	99.7 +/- 0.6	99.3 +/- 0.7	98.8 +/- 0.9	97.9 +/- 1.1
Drug Release at 15 min (%)	97.2 +/- 1.8	96.8 +/- 2.0	95.1 +/- 2.4	92.6 +/- 3.1
Moisture Content (%)	2.1 +/- 0.3	2.4 +/- 0.3	2.9 +/- 0.4	3.6 +/- 0.5
Compliance with Limits	Pass	Pass	Pass	Pass

CONCLUSION

This study systematically developed, characterized, and comparatively evaluated eight rapid dispersible tablet formulations of Metformin HCl 500 mg incorporating synthetic superdisintegrants (croscarmellose sodium and crospovidone) and a natural-origin superdisintegrant (*Plantago ovata* Ispaghula husk) at varying concentrations via the direct compression method. The comprehensive evaluation demonstrated a clear performance hierarchy among the tested formulations, with crospovidone at 5% w/w (F5) showing superior performance, followed by croscarmellose sodium at 5% w/w (F2), and *Plantago ovata* husk at 2.5% w/w (F7), based on disintegration time, wetting behavior, water absorption ratio, and in vitro drug release.

The optimized formulation (F5) exhibited a rapid disintegration time of 29.1 ± 1.8 seconds, drug release exceeding 97% within 15 minutes, and satisfactory mechanical properties including adequate hardness (55.2 N), while complying with all pharmacopoeial quality specifications. Drug release followed Fickian diffusion kinetics, suggesting that tablet disintegration was the primary rate-limiting step for this high-dose, BCS Class III drug system. The superior performance of crospovidone can be attributed to its highly porous, crosslinked structure, rapid capillary water uptake, and lack of gel formation, which collectively facilitate fast tablet disintegration. In contrast, *Plantago ovata* husk, despite its high water absorption capacity, forms a viscous mucilage layer that may impede liquid penetration and delay tablet breakup, limiting its suitability as a primary superdisintegrant in rapid-release formulations.

The optimized formulation also demonstrated acceptable stability under accelerated ICH conditions over 6 months, with no significant changes in physical appearance, drug content, or dissolution behavior. These findings are consistent with recent literature (2021–2026) reporting the superior efficiency of synthetic crosslinked polyvinyl-based superdisintegrants in high-dose orally dispersible systems compared to natural polysaccharide-based alternatives. Overall, this study provides a strong scientific basis for selecting crospovidone as the preferred superdisintegrant for Metformin HCl RDTs prepared by direct compression. Future studies are recommended to explore synergistic superdisintegrant combinations (e.g., crospovidone–Ispaghula blends), advanced porosity enhancement techniques, and in vivo palatability and patient acceptability assessments to further support clinical translation.

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