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Review Article

A Review of Rational Design of Fast Dissolving Tablets Using Binary Superdisintegrants: Isabgol Mucilage and Crospovidone

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Abstract:
Dysphagia affects approximately 15–22% of the global population, with substantially higher prevalence among pediatric (20–30%), geriatric (35–40%), and institutionalized patients (up to 60%), representing a major barrier to oral drug administration. Fast dissolving tablets (FDTs) provide a rational pharmaceutical solution by disintegrating in the oral cavity within 30–60 seconds without requiring water or chewing. Despite advances in superdisintegrant technology, single-agent systems face limitations including inconsistent disintegration times (>45 seconds) and suboptimal drug release profiles (<85% in 15 minutes). Binary superdisintegrant systems combining mechanistically distinct agents offer synergistic performance improvements. This review critically evaluates FDT formulation using Isabgol mucilage (Plantago ovata Forsk.) and crospovidone as binary superdisintegrants, focusing on mechanistic synergy, excipient functionality (advantages and disadvantages), formulation optimization strategies, and cardiovascular drug applications (amlodipine besylate, carvedilol). Optimized Isabgol:crospovidone blends at 1:1 to 2:1 ratios achieve disintegration times of 7–11 seconds with >98% drug release in 15 minutes. The sublimation technique using camphor as a complementary manufacturing strategy, fast dissolving films as an allied dosage form, and stability considerations under ICH guidelines are also discussed. Challenges of moisture sensitivity, batch-to-batch variability of natural excipients, taste masking, and manufacturing scalability are addressed.
Keywords: Fast dissolving tablets; Isabgol mucilage; Crospovidone; Binary superdisintegrants; Plantago ovata; Orally disintegrating tablets; Sublimation technique; Fast dissolving films; Amlodipine besylate; Carvedilol; Patient compliance.

Introduction

The oral route remains the most widely preferred route for drug administration, accounting for approximately 60–70% of all marketed pharmaceutical products. However, dysphagia affects 15–22% of the general population, with substantially higher prevalence among pediatric patients (20–30%), geriatric patients (35–40%), institutionalized elderly (up to 60%), bedridden patients, and individuals with neurological disorders such as stroke, Parkinson's disease, and cerebral palsy. This condition leads to poor medication compliance, therapeutic failure, and

increased healthcare costs. Fast dissolving tablets (FDTs), also termed orally disintegrating tablets (ODTs) or mouth dissolving tablets (MDTs), were developed to address these clinical needs. According to the European Pharmacopoeia, FDTs are solid dosage forms that disintegrate or disperse in the mouth within 3 minutes, while the FDA defines them as tablets that disintegrate within 30 seconds when placed on the tongue. These dosage forms offer multiple therapeutic advantages: (i) rapid onset of action through pre-gastric absorption, (ii) partial avoidance of first-pass hepatic metabolism, (iii) improved bioavailability for certain drugs, (iv) enhanced patient compliance particularly in acute conditions, and (v) convenience in situations where water is unavailable.

The disintegration efficiency of FDTs is critically governed by the type, concentration, and combination of superdisintegrants employed. [1]

Superdisintegrants are specialized excipients effective at low concentrations (typically 2–10% w/w) that promote rapid water uptake, swelling, and tablet matrix disruption. Both natural (Isabgol mucilage, guar gum, fenugreek mucilage) and synthetic (crospovidone, croscarmellose sodium, sodium starch glycolate) superdisintegrants have been extensively investigated. Binary superdisintegrant systems combining two agents with complementary mechanisms have demonstrated superior performance compared to single-agent formulations, achieving additive or synergistic effects in disintegration time reduction, dissolution enhancement, and mechanical strength optimization. This review critically synthesizes current knowledge on FDT formulation employing the binary combination of Isabgol mucilage (a natural swelling-based disintegrant) and crospovidone (a synthetic wicking-based disintegrant), with emphasis on cardiovascular drug applications and allied fast-dissolving delivery systems.

Mechanism of Drug Release from Fast Dissolving Tablets

Superdisintegrant-Mediated Disintegration Mechanism

In FDTs formulated by direct compression, the tablet must rapidly break down into fine particles upon contact with saliva or a small volume of water. Drug release from FDTs occurs in two sequential phases: (i) rapid disintegration of the tablet matrix into primary particles driven by superdisintegrant action, and (ii) dissolution of drug particles or granules exposed after disintegration. For poorly water-soluble drugs (BCS Class II), dissolution is the rate-limiting step even after rapid disintegration necessitating solubility-enhancement strategies in addition to efficient disintegrant selection.

Binary Superdisintegrant Mechanism: Swelling and Wicking

When Isabgol mucilage and crospovidone are combined, both disintegration mechanisms operate simultaneously.

Isabgol mucilage absorbs water rapidly through hydrogen bonding and swells 10–14-fold, generating internal hydrostatic pressure that disrupts the tablet matrix. Crospovidone, through its porous particle structure, wicks water rapidly into the tablet interior via capillary channels and then undergoes elastic deformation recovery upon hydration, releasing stored elastic energy that further disrupts interparticulate bonds.

This dual mechanism produces more rapid and complete disintegration than either polymer alone: optimized Isabgol:crospovidone binary combinations achieve disintegration times of 7–11 seconds, representing a 30–50% reduction compared to single agents at equivalent total concentrations.

Excipient Profile and Functional Role in Fast Dissolving Tablets

Superdisintegrants are the most critical components of FDTs. Both natural and synthetic superdisintegrants are commonly employed, individually or in binary combination, to achieve the desired rapid disintegration profile. The following section provides a critical review of

each excipient used, including its mechanism, advantages, disadvantages, and specific role in Isabgol–crospovidone FDT formulations. [2]

Isabgol Mucilage (Plantago ovata Forsk.)

Isabgol mucilage is the most widely investigated natural superdisintegrant derived from the seed husk of Plantago ovata Forsk. (Family Plantaginaceae). It is a complex arabinoxylan polysaccharide with a branched backbone of β-(1→4)-linked D-xylopyranose residues bearing arabinosyl and xylosyl side chains, and a molecular weight of the order of 10^6 Da. Numerous hydroxyl groups allow extensive hydrogen bonding with water, leading to rapid and extensive three-dimensional water uptake the molecular basis of its disintegrant action.

Advantages:

- Produces rapid, high-magnitude swelling (swelling index 10–14 mL/g), the highest among commonly used natural mucilages
- Natural origin: biodegradable, biocompatible, non-toxic, and patient-acceptable; GRAS status
- Cost-effective: approximately 3–5× cheaper than synthetic superdisintegrants
- Dual functionality: can serve as both superdisintegrant (at low levels, 2–10% w/w) and binder (at moderate levels) in direct compression
- Pharmacopoeial acceptance: listed in IP, USP, BP, EP; excellent safety profile
- Optimized formulations achieve disintegration times of 7–8 seconds and >98% drug release in 15 minutes

Disadvantages:

- Batch-to-batch variability: swelling index and viscosity depend on botanical source, extraction conditions, and storage
- Moisture-sensitive and hygroscopic: requires controlled humidity during manufacturing (<60% RH) and moisture-protective packaging
- Gel formation at concentrations >15% w/w may retard rather than accelerate disintegration
- Microbial risk: natural polysaccharide requires stringent microbial quality control and preservatives
- Slightly mucilaginous mouthfeel at concentrations >10 mg/tablet may require taste-masking

Role in FDT: At 4–14 mg/tablet (approximately 4–10% w/w), Isabgol mucilage generates the primary swelling-based disintegration force. Chlorpheniramine maleate FDTs containing Isabgol mucilage at 14 mg/tablet achieved the lowest disintegration time (7 seconds) and the highest cumulative drug release (98.85%). The optimal range for FDT applications is 4–14 mg/tablet below this, swelling force is insufficient; above 15 mg, gel formation may retard drug release. [3]

Crospovidone: Crospovidone (INN: crospovidonum) is a water-insoluble, non-ionic, cross-linked poly(1-vinyl-2-pyrrolidone) produced by a special "popcorn" polymerization technique that yields highly porous particles with irregular surface morphology and high degree of cross-linking. Commercial grades include Kollidon® CL and CL-F (BASF) and Polyplasdone® XL, XL-10, and INF-10 (Ashland), which differ mainly in particle size distribution, bulk density, and hydration capacity.

Advantages:

- Effective at low concentrations (2–8% w/w), minimizing impact on tablet size and formulation cost
- Multi-modal mechanism (wicking + deformation recovery + particle repulsion) ensures rapid and uniform tablet hydration
- Does not form a viscous gel upon hydration ensures rapid drug dissolution post-disintegration (key advantage over sodium starch glycolate)
- pH-independent performance: consistent disintegration across pH 1–8 (stomach to colon)
- Non-ionic: no electrolyte sensitivity; excellent compatibility with cationic, anionic, and neutral drugs

- Pharmacopoeial acceptance: listed in USP, EP, JP, IP

Disadvantages:

- Higher cost compared to natural superdisintegrants (approximately 3–5× cost of Isabgol mucilage)
- Limited swelling: disintegration relies more on wicking than swelling pressure, which may be less effective in very low-porosity matrices compressed at high forces
- Requires good powder flow and uniform distribution for consistent disintegrant performance
- Potential for static charge accumulation during processing, necessitating humidity control (40–50% RH)

Role in FDT: At 2–8% w/w, crospovidone provides wicking-mediated rapid water distribution throughout the tablet interior, ensuring that the entire compact hydrates uniformly. FDTs of amlodipine besylate using crospovidone (Kollidon CL) at 6% w/w combined with camphor sublimation achieved a disintegration time of 11 seconds and 97.19% drug release in 10 minutes. Neither swelling (Isabgol alone) nor wicking (crospovidone alone) achieves optimal performance; the binary combination exploits both mechanisms simultaneously.

Mannitol

Mannitol is a polyol diluent widely used in FDTs owing to its unique combination of properties that directly support fast-dissolving performance.

Advantages: Pleasant sweet taste and cooling sensation (negative heat of solution of −28.9 cal/g) enhances palatability; directly compressible grade (Pearlitol®) provides adequate hardness; non-hygroscopic (moisture uptake <0.2% at 80% RH); compatible with moisture-sensitive superdisintegrants including Isabgol mucilage; synergizes with sublimation techniques by providing the solid matrix around subliming agent particles

Disadvantages: Higher cost than lactose; may cause osmotic diarrhea at high doses (>10 g/day); poor compressibility when used as sole diluents requires co-processing or combination with MCC.

Role in FDT: Used at 30–60% w/w as the primary diluent and taste-masking agent in both amlodipine besylate and prochlorperazine maleate FDT formulations. [4]

Microcrystalline Cellulose (MCC PH 101/PH 102)

MCC is a partially depolymerized cellulose used as a directly compressible diluent providing excellent mechanical strength through plastic deformation.

Advantages: Outstanding compressibility ensuring hardness >4 kg/cm² at moderate compression forces (4–8 kN); chemically inert; promotes uniform drug distribution; widely pharmacopoeially accepted.

Disadvantages: Slightly hygroscopic; in high concentrations (>40% w/w) may slightly retard water penetration through capillary absorption; does not contribute to disintegrant activity.

Role in FDT: Used at 15–40% w/w as the mechanical backbone. Ensures hardness 4.0–5.5 kg/cm² and friability <1% without compromising the rapid disintegration profile.

Colloidal Silicon Dioxide

Colloidal silicon dioxide (Aerosil® 200; surface area >200 m²/g) functions as a glidant by coating excipient particles and reducing interparticulate friction, which is essential in cohesive Isabgol-containing blends.

Advantages: Highly effective glidant at 0.25–1.0% w/w; reduces angle of repose from ~38° to ~26°; prevents blend segregation; chemically inert; does not affect drug release.

Disadvantages: Over-glidation at >1.0% w/w may reduce tablet hardness; fine particles require GMP handling precautions; does not function as a lubricant.

Role in FDT: At 0.5–1.0% w/w, essential for achieving acceptable flow and die-filling uniformity in cohesive Isabgol-crospovidone blends.

Magnesium Stearate

Magnesium stearate is a hydrophobic lubricant used at 0.5–1.0% w/w to reduce die-wall friction during tablet compression.

Advantages: Highly effective lubricant at low concentrations; prevents sticking and picking; pharmacopoeially accepted in all major compendiums.

Disadvantages: Over-lubrication (>1.0% w/w or blending >3 minutes) creates hydrophobic barriers that retard wettability and reduce water penetration, increasing disintegration time by up to 25%; blending time is therefore a critical **process parameter** that must be validated.

Role in FDT: Used at 0.5–1.0% w/w with strictly controlled blending time of 2–3 minutes an identified critical process parameter that must be monitored and controlled in production. [5]

Evaluation of Fast Dissolving Tablets

Pre-compression Parameters

Good powder flow is critical for uniform die filling and tablet weight consistency. Target values for Isabgol–crospovidone FDT blends are summarized below:

Carr's Compressibility Index (CI):

CI (%)=TD−BDTD×100CI (%)=TDTD−BD ×100

Where TD = tapped density and BD = bulk density. CI < 15%: excellent flow; 16–20%: good flow; >35%: very poor flow.

Hausner's Ratio (HR):

HR=TDBDHR=BDTD

Values < 1.25 indicate good flow; values > 1.5 suggest poor flow.

Angle of Repose (θ):

tan⁡θ=hrtanθ=rh

Where h = height and r = radius of the powder cone. $\theta \leq 30°$: excellent flow; $\theta > 40°$: poor flow.

Target values for Isabgol–crospovidone blends: angle of repose 25–35°; Carr's index 12–18%; Hausner ratio 1.15–1.25. Colloidal silicon dioxide (0.5–1.0% w/w) is critical for achieving acceptable flow in cohesive mucilage-containing blends. [6]

Post-compression Parameters:

Required post-compression standards for FDTs include:

- **Hardness:** 3.5–6.0 kg/cm² (balance between mechanical strength and rapid disintegration)
- **Friability:** <1.0% weight loss (USP/EP; Roche friabilator, 100 rpm, 4 minutes)
- **Weight variation:** ±7.5% for tablets <80 mg; ±5% for tablets ≥80 mg (IP/USP)
- **Drug content uniformity:** 95–105% of label claim; RSD <2% (n = 10, HPLC or UV spectrophotometry)
- **Thickness:** Consistent within batch (variation <5%)

Optimized Isabgol–crospovidone FDTs typically achieve hardness 4.0–5.5 kg/cm² and friability 0.4–0.8%. [7]

Wetting Time, Water Absorption Ratio, and In Vitro Disintegration

Wetting time is measured by placing a tablet on tissue paper in a Petri dish containing a small volume of purified water with water-soluble dye and recording the time for complete wetting of the upper surface; targets are typically <30 seconds.

Water Absorption Ratio (WAR):

WAR (%)=Wa−WbWb×100WAR (%)=WbWa −Wb×100

Where WaWa = tablet weight after wetting and WbWb = weight before wetting. Higher WAR correlates with faster disintegration and reflects superdisintegrant efficiency.

In vitro disintegration time is measured using USP/IP disintegration apparatus in purified

water or simulated salivary fluid (pH 6.8) at 37 ± 0.5°C. FDTs are expected to disintegrate within 30 seconds (FDA guidance) or as specified in applicable guidelines. Isabgol–crospovidone binary FDTs typically achieve 7–11 seconds — well within guideline requirements. [8]

In Vitro Dissolution

Dissolution testing is performed using USP Apparatus II (paddle), 50 rpm, 900 mL appropriate dissolution medium (pH 6.8 phosphate buffer or pH 1.2 HCl), 37 ± 0.5°C. Target profile for FDTs: >80% drug release within 15 minutes; ideally >95% within 30 minutes. Representative results achieved with optimized Isabgol–crospovidone FDTs include:

- **Chlorpheniramine maleate** (Isabgol 14 mg/tablet): 98.85% in 15 minutes
- **Amlodipine besylate** (crospovidone 6% + camphor sublimation): 97.19% in 10 minutes
- **Prochlorperazine maleate** (Isabgol + crospovidone binary): >95% in 5 minutes. [9]

Fast Dissolving Films: An Allied Dosage Form

Fast dissolving films (FDFs) or oral thin films represent a complementary dosage form with similar patient benefits to FDTs. These thin polymeric strips (typically 2–8 cm^2; 50–150 µm thick) dissolve on the tongue in less than 60 seconds, offering advantages in flexibility, portability, and ease of administration for patients with dysphagia.

FDFs are composed of film-forming polymers (HPMC E5/E15, polyvinyl alcohol, pullulan, maltodextrin), plasticizers (glycerol, PEG 400), sweeteners, flavoring agents, and optionally superdisintegrants at low concentrations (1–3% w/w) to accelerate dissolution. Manufactured primarily by solvent casting, they offer larger surface area for faster dissolution and superior taste-masking potential compared to FDTs. Applications include antihypertensive drugs (amlodipine, losartan), antiemetics (ondansetron), and analgesics (diclofenac). The primary limitations of FDFs are lower drug loading capacity (<30 mg typically), higher manufacturing complexity, and greater production cost compared to FDTs. [10]

Stability Studies

Stability Testing

Stability studies are generally performed according to ICH Q1A(R2) guidelines at the following conditions:

- **Accelerated:** 40 ± 2°C / 75 ± 5% RH; sampling at 0, 1, 2, 3, and 6 months

Recent Advances and Challenges

Recent Advances

Natural–Synthetic Hybrid Superdisintegrant Systems: Beyond Isabgol–crospovidone, other natural-synthetic combinations have been explored including fenugreek mucilage + croscarmellose sodium (15-second disintegration; 100% release in 18 minutes), guar gum + sodium starch glycolate (cost-effective generic option), and xanthan gum + crospovidone. The common finding is that natural-synthetic binary combinations outperform either agent alone, confirming the generalizability of the binary superdisintegrant concept.

3D-Printed FDTs: FDTs fabricated by semi-solid extrusion or fused deposition modeling using Isabgol mucilage or HPMC as the printing matrix are under active investigation.

These allow personalized dosing (dose adjusted per patient), complex geometries for optimized surface area, and on-demand clinical manufacturing. Regulatory pathways for 3D-printed FDTs remain under development.

Challenges

Moisture sensitivity: Isabgol mucilage is hygroscopic; moisture uptake causes softening, premature disintegration during storage, and microbial growth requiring moisture-protective packaging and controlled-humidity manufacturing (<40% RH).

Batch-to-batch variability of natural excipients: Isabgol mucilage properties (swelling index 10–14 mL/g, viscosity) vary with botanical source, extraction method, and storage requiring stringent supplier qualification and in-house batch testing.

Taste and mouthfeel:

Rapid disintegration exposes drug and excipients to taste receptors; Isabgol may impart a slightly mucilaginous mouthfeel at concentrations >10 mg/tablet may require sweeteners, flavors, or cooling agents (menthol).

Manufacturing scalability: Over-lubrication during scale-up (lubricant blending time not tightly controlled) and blend segregation during large-scale transfer are common failure modes; process analytical technology (PAT) and continuous manufacturing approaches can mitigate these risks. [11]

Conclusion and Future Prospects

This review critically evaluated the rationale, formulation strategies, and evaluation of fast dissolving tablets employing the binary superdisintegrant system of Isabgol mucilage and crospovidone, with emphasis on cardiovascular drug applications and allied fast-dissolving technologies.

Key Conclusions:

1. **Isabgol mucilage alone** causes insufficient initial wetting in hydrophobic formulations; **crospovidone alone** may give incomplete disintegration in highly compressed matrices. Their binary combination at 1:1 to 2:1 (Isabgol:crospovidone) ratios achieves disintegration times of 7–11 seconds 30–50% faster than either agent alone.
2. **Optimized total superdisintegrant concentration of 6–12% w/w** provides the optimal balance between rapid disintegration and acceptable mechanical strength (hardness 4.0–5.5 kg/cm²; friability <1%).
3. **Sublimation using camphor (10% w/w)** combined with binary superdisintegrants creates porous matrices that further reduce disintegration time by 30–40% and achieve >97% drug release in 10 minutes — as demonstrated for amlodipine besylate FDTs.
4. **Magnesium stearate blending time (2–3 minutes maximum)** is a critical process parameter that must be validated to prevent over-lubrication-induced wetting retardation and dissolution failure.
5. **QbD-based factorial design** is the recommended optimization strategy for defining a robust formulation design space for Isabgol–crospovidone FDTs. [12]

Identified Research Gaps:

- Level A IVIVC for Isabgol–crospovidone FDT systems needs validation across multiple drugs and formulations
- In vivo pharmacokinetic and bioavailability studies in dysphagic patient populations (not only healthy volunteers) are lacking
- Long-term stability studies (24 months, ICH long-term conditions) are underreported for Isabgol-based FDTs
- Pharmacopoeial standardization of pharmaceutical-grade Isabgol mucilage (tighter specification for swelling index, viscosity, microbial limits) is urgently needed
- 3D-printed FDTs using Isabgol mucilage represent a promising future direction for individualized dosing in pediatric and geriatric patients

Rational excipient selection guided by QbD principles, combined with comprehensive pre- and post-compression evaluation, ICH-compliant stability testing, and moisture-protective packaging, will continue to drive development of robust, patient-compliant fast dissolving formulations for critical therapeutic areas including cardiovascular disease. [13]

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