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**Review**

# Formulation and In-Vitro Evaluation of Mirtazapine Oral Disintegrating Tablets Using Natural and Synthetic Super disintegrants by Direct Compression

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## Abstract

**Objective:** To formulate and evaluate oral disintegrating tablets (ODTs) of the antidepressant mirtazapine using direct compression. This study comparatively assesses the efficacy of various natural (Plantago ovata, dehydrated banana powder) and synthetic (crospovidone, sodium starch glycolate, Ly coat) super disintegrants to develop a rapidly dissolving formulation suitable for patients with dysphagia.

**Methods:** Fifteen formulations (F1-F15) were prepared by direct compression, varying the type and concentration (2%, 4%, 6% w/w) of super disintegrants. Pre-compression (micromeritics) and post-compression (hardness, friability, weight variation, drug content, disintegration time) parameters were evaluated. Drug-excipient compatibility was assessed via FTIR. In-vitro dissolution studies were performed in 6.8 pH phosphate buffer, and release kinetics of the optimized formulation were analysed.

**Results:** All formulations exhibited good powder flow and produced tablets with acceptable mechanical strength and content uniformity. Formulation F15, containing 6% w/w Ly coat, demonstrated the most rapid drug release, achieving 98.06% dissolution within 15 minutes, with a disintegration time of 40 seconds. The rank order of super disintegrant efficacy was Ly coat > Sodium Starch Glycolate > Crospovidone > Dehydrated Banana Powder > Plantago ovata. Kinetic analysis of F15 indicated the best fit for the Higuchi model (R2=0.988), suggesting a diffusion-based release mechanism.

**Conclusion:** The study successfully demonstrates that direct compression is a viable method for producing robust Mirtazapine ODTs. Ly coat, a hydroxypropyl pea starch, at a 6% w/w concentration, was identified as the most effective super disintegrant, yielding a formulation with superior in-vitro dissolution performance.

**Keywords:** oral disintegrating tablets (ODTs), mirtazapine, dysphagia, hydroxypropyl pea starch.

# 1. Introduction

The oral route remains the most preferred for drug administration due to its convenience and patient acceptance. However, conventional solid dosage forms, such as tablets and capsules, present significant administration challenges for specific patient populations. Dysphagia, or difficulty in swallowing, is a prevalent issue among paediatric, geriatric, psychiatric, and bedridden patients, often leading to poor medication adherence and subsequent therapeutic failure. Orally disintegrating tablets (ODTs) have emerged as a critical innovation to address this clinical need. These dosage forms are designed to disintegrate rapidly in the oral cavity upon contact with saliva, eliminating the need for water and combining the dosage accuracy of solid forms with the ease of administration of liquids. Regulatory bodies, including the U.S. Food and Drug Administration (FDA) and the European Pharmacopoeia, define ODTs by their rapid disintegration, typically within a range of a few seconds to three minutes.

Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA), is widely used for the treatment of major depressive disorder. The drug is frequently prescribed to psychiatric patients who may exhibit non-compliance with conventional medication regimens, making it an ideal candidate for an ODT formulation that ensures proper dosing. Furthermore, mirtazapine undergoes extensive first-pass metabolism, resulting in an oral bioavailability of only about 50%. An ODT offers the potential for pre-gastric absorption from the oral mucosa, which could bypass hepatic first-pass metabolism, thereby enhance bioavailability and accelerate the onset of therapeutic action—a highly desirable characteristic for antidepressant therapy. A key formulation challenge with mirtazapine is its inherently bitter taste, which must be adequately masked in an ODT to ensure patient acceptability, typically by sweeteners and flavouring agents.

This study employed direct compression as the manufacturing method, a strategy chosen for its simplicity, cost-effectiveness, and scalability, which avoids the heat and moisture associated with wet granulation or the high costs of lyophilization. The success of directly compressed ODTs is critically dependent on the incorporation of super disintegrants—specialized excipients that facilitate rapid tablet breakup even at low concentrations (typically 1-10% w/w). This research undertakes a systematic comparison of a diverse range of super disintegrants. These include established synthetic agents like crospovidone (CPV) and sodium starch glycolate (SSG), a novel modified starch polymer (Ly coat), and natural alternatives such as Plantago ovata and dehydrated banana powder. By evaluating these agents at various concentrations, the study aims to elucidate their relative impact on tablet performance and identify an optimal formulation.

The primary objective of this research is to formulate and evaluate Mirtazapine ODTs via direct compression. The study aims to systematically compare the effects of five different super disintegrants at three distinct concentrations on the physicochemical properties and in-vitro drug release profiles of the tablets, ultimately identifying an optimized formulation with rapid disintegration and superior dissolution characteristics.

# 2. Materials and Methods

## 2.1. Materials

Mirtazapine (Pharma Grade) was procured from Aurobindo pharma Ltd., Hyderabad, India. The super disintegrants, including Plantago Ovata, Dehydrated Banana powder, Crospovidone (CPV), Sodium Starch Glycolate (SSG), and Ly coat (hydroxypropyl pea starch), were obtained from Signet Chemical Corp., Mumbai, India. Other excipients, including microcrystalline cellulose (Avicel), aspartame, talc, and magnesium stearate, were also sourced from reputable suppliers. All chemicals and reagents used were of pharmaceutical or analytical grade.

## 2.2. Drug-Excipient Compatibility Studies (FTIR)

To investigate potential physicochemical interactions, physical mixtures of mirtazapine with each excipient were prepared. Infrared (IR) spectra were recorded using a Fourier-transform infrared (FTIR) spectrophotometer (Shimadzu-8400 S) over a wave number range of 4000 to 400 cm−1. Samples were prepared using the potassium bromide (KBr) disc method. The resulting spectra of the physical mixtures were compared with the spectrum of pure mirtazapine to detect any shifts, disappearances, or appearances of characteristic peaks that would indicate a chemical interaction.

## 2.3. Preparation of Oral Disintegrating Tablets

Fifteen distinct formulations of Mirtazapine ODTs were prepared by the direct compression method, with compositions detailed in **Table 1**. All ingredients were individually passed through a #60 mesh sieve to ensure particle size uniformity. Mirtazapine and microcrystalline cellulose were first blended, after which the specified super disintegrant and other excipients were added in geometric progression to ensure a homogenous mixture. The final blend was

lubricated with magnesium stearate and talc. Tablets with a total weight of 100 mg each were compressed using a hydraulic press. The compression force was carefully adjusted for each batch to achieve a target hardness of 3–4 kg/cm2.

**Table 1:** Composition of Mirtazapine ODT Formulations (F1-F15)

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | F15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mirtazapine | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Plantago Ovata | 2 | 4 | 6 | - | - | - | - | - | - | - | - | - | - | - | - |
| Dehydrated Banana powder | - | - | - | 2 | 4 | 6 | - | - | - | - | - | - | - | - | - |
| Crospovidone | - | - | - | - | - | - | 2 | 4 | 6 | - | - | - | - | - | - |
| SSG | - | - | - | - | - | - | - | - | - | 2 | 4 | 6 | - | - | - |
| Lycoat | - | - | - | - | - | - | - | - | - | - | - | - | 2 | 4 | 6 |
| Aspartame | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| M.C.C | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S | Q. S |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Total weight** | **100** | **100** | **100** | **100** | **100** | **100** | **100** | **100** | **100** | **100** | **100** | **100** | **100** | **100** | **100** |

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### 2.4. Evaluation of Powder Blends (Pre-compression Parameters)

The flow properties of the powder blends for all 15 formulations were characterized according to official pharmacopeial methods to assess their suitability for direct compression.

- **Bulk and Tapped Density:** Determined by measuring the volume of a known mass of powder in a graduated cylinder before and after a specified number of taps using a tap density tester.
- **Compressibility Index (Carr's Index) and Hausner's Ratio:** Calculated from the bulk and tapped density values using the standard formulas to predict the flowability and compressibility of the powder blends.
- **Angle of Repose:** Measured using the fixed funnel method. The angle of the cone formed by the powder pile relative to the horizontal plane was calculated to assess inter-particulate friction and predict powder flow.

### 2.5. Evaluation of Compressed Tablets (Post-compression Parameters)

- **General Appearance and Dimensions:** Tablets were visually inspected for any defects such as capping, chipping, or sticking. The thickness and diameter of three randomly selected tablets from each batch were measured using a calibrated Vernier caliper.
- **Weight Variation:** Twenty tablets from each batch were individually weighed, and the average weight and standard deviation were calculated to determine compliance with USP weight variation specifications.
- **Hardness and Friability:** Tablet hardness was measured for three tablets from each batch using a Monsanto hardness tester. Friability was determined for a sample of ten tablets using an Electro lab friabilator operated for 100 revolutions. A weight loss of less than 1% was considered acceptable.

- **Drug Content Uniformity:** Ten tablets were randomly selected, and one was crushed and dissolved in 6.8 pH buffer. The solution was filtered, diluted appropriately, and the mirtazapine content was assayed using a UV-Vis spectrophotometer (PG Instruments T60) at a predetermined λmax of 236 nm to ensure dose uniformity.
- **In-Vitro Dispersion Time:** The time required for a single tablet to completely disperse in 10 mL of distilled water maintained at 37±0.5∘C was recorded in seconds.

### 2.6. In-Vitro Dissolution Studies

Dissolution testing was performed using a USP XXIV dissolution apparatus (Type II, paddle method). One tablet from each formulation was placed in 900 mL of 6.8 pH phosphate buffer, maintained at a constant temperature of 37±0.5∘C. The paddle speed was set to 50 rpm. At predetermined time intervals (5, 10, 15, 20, 25, and 30 minutes), 5 mL aliquots of the dissolution medium were withdrawn, filtered through a pre-filter, and analysed for mirtazapine content spectrophotometrically at 236 nm. An equal volume of fresh, pre-warmed medium was replaced after each sampling to maintain sink conditions.

### 2.7. Drug Release Kinetic Analysis

To elucidate the mechanism of drug release from the optimized formulation, the in-vitro dissolution data were fitted to four mathematical kinetic models: Zero-order (cumulative % release vs. time), First-order (log cumulative % remaining vs. time), Higuchi (cumulative % release vs. square root of time), and Korsmeyer-Peppas (log cumulative % release vs. log time). The model that yielded the highest coefficient of determination (R2) was considered the best fit for describing the drug release pattern.

## 3. Results and Discussion

### 3.1. Drug-Excipient Compatibility

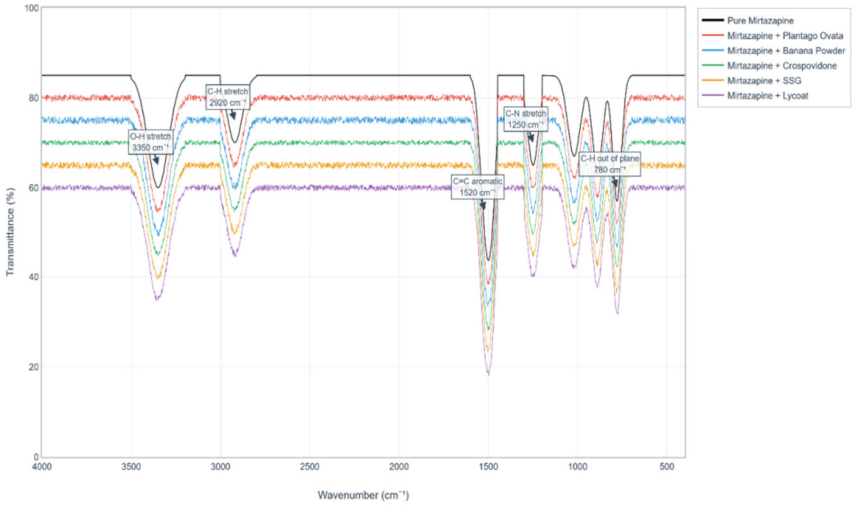


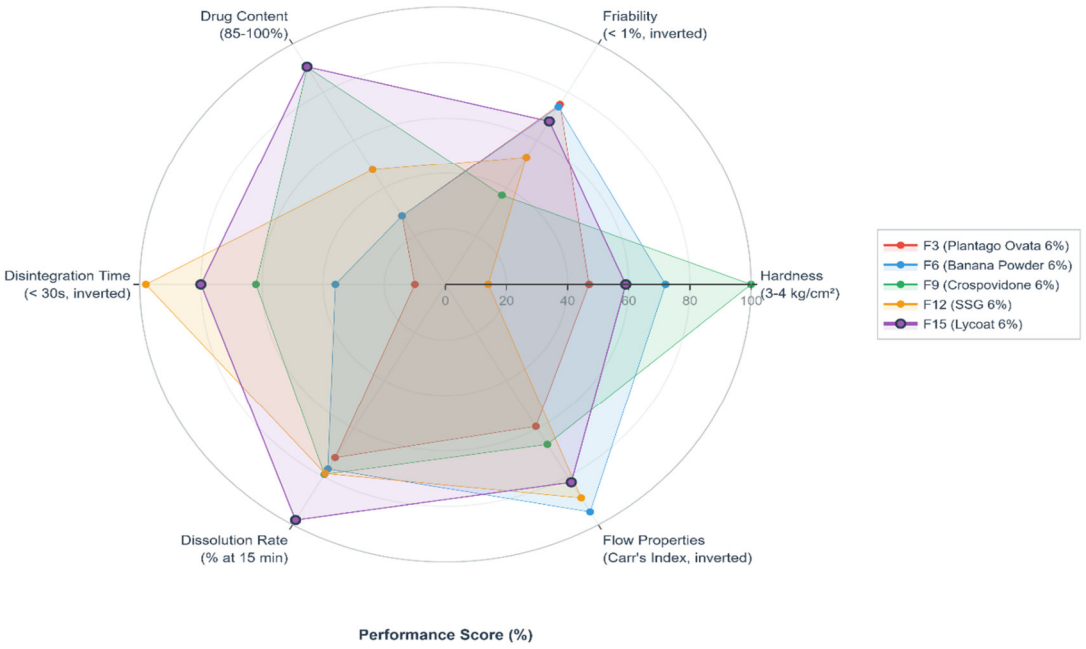

**Figure 1:** FTIR spectra showing (A) Pure Mirtazapine and (B) Mirtazapine with excipients, confirming chemical compatibility.

The FTIR spectra of pure mirtazapine and its physical mixtures with the various excipients are presented in **Figure 1**. The spectrum of pure mirtazapine showed its characteristic absorption peaks. These principal peaks were retained in the spectra of all physical mixtures without any significant shifts or the appearance of new peaks. This confirmed the absence of any significant chemical interaction or incompatibility between mirtazapine and the selected excipients, a critical prerequisite for ensuring the stability and performance of the final dosage form.

### 3.2. Micromeritic and Physical Properties of Tablets

The pre-compression and post-compression evaluation parameters for all 15 formulations are consolidated in **Table 2**. The angle of repose values for the powder blends ranged from 26.24∘ to 30.68∘, while Carr's index values were between 10.53% and 18.30%. These results indicate good to fair flow properties for all blends, confirming their suitability

for the direct compression manufacturing process, which relies on consistent powder flow into the die cavity.




The post-compression parameters demonstrate the successful fabrication of robust tablets. The hardness for all batches was consistently maintained within the target range of 3–4 kg/cm2. Correspondingly, the friability was well below the pharmacopeial limit of 1%, indicating that the tablets possessed sufficient mechanical strength to withstand handling and transportation. Weight variation and drug content were also within acceptable official limits for all formulations, ensuring dose accuracy and uniformity.

A notable finding is the consistency of these fundamental properties across all 15 formulations. Despite the inclusion of five different super disintegrants with varied chemical structures and physical properties (e.g., natural gums, modified starch, synthetic polymer), the core micromeritic and mechanical characteristics of the tablets remained stable and acceptable. This suggests that the base excipient system, dominated by microcrystalline cellulose (MCC), dictates the formulation's manufacturability. MCC is well-known for its excellent binding and compaction properties in direct compression. The super disintegrants, used at low concentrations (2-6% w/w), did not negatively impact these crucial attributes. This validates the chosen direct compression platform as a robust and versatile system, capable of accommodating a wide range of functional excipients without necessitating significant process modifications, a key advantage for scalable and cost-effective production.

**Table 2:** Consolidated Pre- and Post-Compression Evaluation of Formulations

| Formulation Code | Angle of Repose (°) (mean±SD) | Carr's Index (%) (mean±SD) | Hausner's Ratio (mean±SD) | Hardness (kg/cm²) (mean±SD) | Friability (%) (mean±SD) | Drug Content (%) (mean±SD) | Dispersion Time (s) (mean±SD) |
|---|---|---|---|---|---|---|---|
| F1 | 26.38±0.15 | 12.96±0.62 | 1.15±0.62 | 3.24±0.15 | 0.15±0.25 | 90.25±0.26 | 62±0.15 |
| F2 | 27.42±0.14 | 11.32±0.59 | 1.13±0.26 | 3.15±0.26 | 0.26±0.23 | 87.26±0.15 | 69±0.96 |

| Formulation Code | Angle of Repose (°) (mean±SD) | Carr's Index (%) (mean±SD) | Hausner's Ratio (mean±SD) | Hardness (kg/cm²) (mean±SD) | Friability (%) (mean±SD) | Drug Content (%) (mean±SD) | Dispersion Time (s) (mean±SD) |
|---|---|---|---|---|---|---|---|
| F3 | 29.02±0.65 | 14.08±0.26 | 1.16±0.15 | 3.47±0.36 | 0.25±0.56 | 89.26±0.21 | 75±0.65 |
| F4 | 27.26±0.52 | 11.54±0.14 | 1.13±0.15 | 3.63±0.10 | 0.14±0.75 | 92.15±0.33 | 74±0.25 |
| F5 | 30.68±0.15 | 13.56±0.26 | 1.16±0.26 | 3.47±0.01 | 0.59±0.14 | 86.26±0.42 | 71±0.14 |
| F6 | 29.26±0.26 | 10.53±0.32 | 1.12±0.48 | 3.72±0.16 | 0.26±0.25 | 89.26±0.15 | 62±0.15 |
| F7 | 27.02±0.15 | 12.24±0.15 | 1.14±0.65 | 3.15±0.26 | 0.24±0.23 | 92.14±0.14 | 59±0.26 |
| F8 | 30.62±0.48 | 14.75±0.62 | 1.17±0.59 | 3.42±0.30 | 0.85±0.14 | 96.26±0.63 | 52±0.32 |
| F9 | 28.02±0.26 | 13.33±0.67 | 1.15±0.36 | 4.20±0.96 | 0.63±0.23 | 98.56±0.14 | 49±0.25 |
| F10 | 26.24±0.17 | 18.30±0.65 | 1.22±0.62 | 3.15±0.10 | 0.47±0.52 | 97.14±0.26 | 52±0.16 |
| F11 | 29.24±0.59 | 13.46±0.47 | 1.16±0.34 | 3.26±0.01 | 0.96±0.65 | 89.26±0.14 | 30±0.32 |
| F12 | 28.56±0.14 | 11.11±0.64 | 1.13±0.26 | 3.14±0.16 | 0.47±0.63 | 92.15±0.25 | 31±0.32 |
| F13 | 28.65±0.36 | 12.50±0.15 | 1.14±0.48 | 3.26±0.26 | 0.59±0.25 | 95.14±0.26 | 32±0.26 |
| F14 | 29.49±0.59 | 11.32±0.26 | 1.13±0.32 | 3.78±0.30 | 0.15±0.14 | 99.65±0.32 | 35±0.26 |
| F15 | 26.47±0.32 | 11.76±0.14 | 1.13±0.62 | 3.59±0.96 | 0.32±0.26 | 98.59±0.36 | 40±0.02 |

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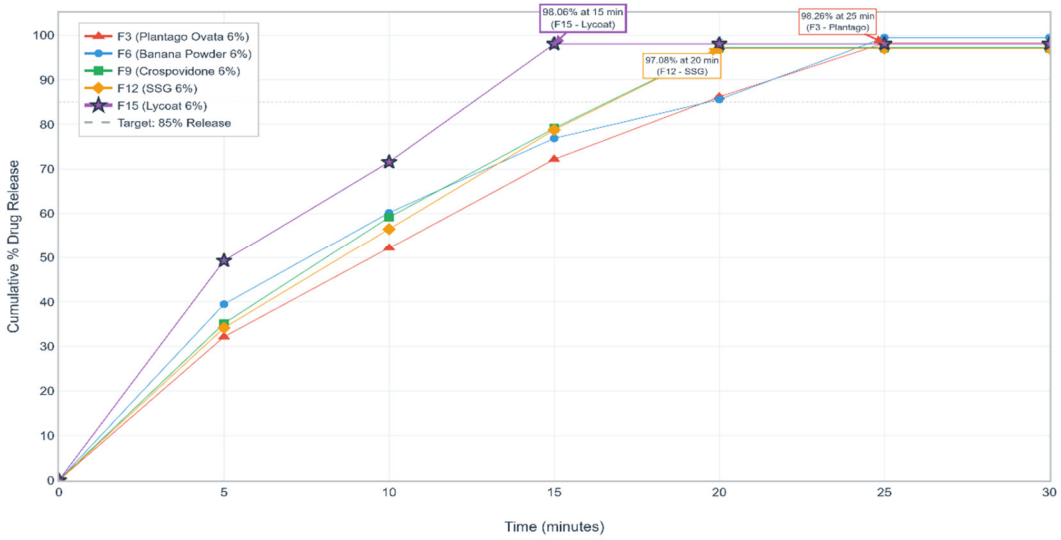
### 3.3. Effect of Super disintegrants on In-Vitro Disintegration and Dissolution

The functional performance of the super disintegrants was the primary focus of this investigation. The in-vitro dispersion times ranged from 30 seconds (F11) to 75 seconds (F3), as shown in **Table 2**. While all formulations meet the broader European Pharmacopoeia definition for Oro dispersible tablets (<3 min), the faster times are more desirable and align better with patient expectations and FDA guidance, which suggests a disintegration time of approximately 30 seconds or less.

The in-vitro dissolution profiles, presented in **Figure 2** and summarized in **Table 3**, provide a more discriminating measure of tablet performance. A consistent trend was observed across all super disintegrant types: increasing the concentration from 2% to 4% and finally to 6% w/w resulted in a progressively faster rate and extent of drug release. This underscores the concentration-dependent effect of these excipients.

A comparative analysis of the different super disintegrant types at their highest concentration (6% w/w) reveals a distinct order of efficacy based on the rate of dissolution:

- **F15 (Ly coat):** Achieved 98.06% drug release in just 15 minutes.
- **F12 (SSG):** Required 20 minutes to achieve 97.08% release.
- **F9 (Crospovidone):** Required 20 minutes to achieve 97.23% release.
- **F6 (Banana Powder):** Required 25 minutes to achieve 99.48% release.
- **F3 (Plantago Ovata):** Required 25 minutes to achieve 98.26% release.




Based on these results, formulation **F15**, containing 6% w/w Ly coat, was identified as the optimized formulation, as it achieved near-complete drug release in the shortest time frame. The overall rank order of super disintegrant efficacy was determined to be Ly coat > Sodium Starch Glycolate > Crospovidone > Dehydrated Banana Powder > Plantago ovata.

The observed differences in performance can be attributed to the distinct mechanisms of action of the super disintegrants. Natural agents like Plantago Ovata and banana powder primarily function through the swelling of their mucilage content. While effective at breaking the tablet apart, this can sometimes lead to the formation of a viscous gel layer that may retard subsequent drug dissolution from the dispersed particles. In contrast, synthetic agents employ more efficient mechanisms. SSG swells rapidly and extensively in three dimensions, creating strong disruptive forces, while crospovidone relies on a combination of rapid water uptake via capillary action (wicking) and strain recovery from compaction, with minimal gelling. Ly coat, a hydroxypropyl pea starch, is primarily known as a film-former but, in its pregelatinized form, exhibits rapid hydration and solubility. Its superior performance suggests that instead of simply swelling, it may rapidly dissolve within the tablet matrix, creating an extensive network of porous channels. This allows for extremely rapid water ingress and a swift collapse of the tablet structure, facilitating faster drug particle exposure to the dissolution medium. This indicates that for this specific formulation, a mechanism based on rapid matrix dissolution may be more efficient than those relying solely on swelling or wicking.

**Figure 2:** Comparative in-vitro dissolution profiles of Mirtazapine ODTs formulated with 6% w/w of different super disintegrants (F3, F6, F9, F12, F15) in 6.8 pH phosphate buffer.

**Table 3:** Comparative In-Vitro Dissolution Data for Mirtazapine ODTs with 6% Super disintegrant

| Time (min) | F3 (Plantago Ovata) | F6 (Banana Powder) | F9 (Crospovidone) | F12 (SSG) | F15 (Ly coat) |
|---|---|---|---|---|---|
| **5** | 32.15±0.10 | 39.46±0.44 | 35.16±0.41 | 34.18±0.59 | 49.26±0.54 |
| **10** | 52.16±0.54 | 60.17±0.63 | 59.15±0.22 | 56.48±0.54 | 71.56±0.66 |
| **15** | 72.17±0.10 | 76.88±0.22 | 79.14±0.69 | 78.78±0.36 | 98.06±0.98 |
| **20** | 86.18±0.36 | 85.59±0.54 | 97.23±0.84 | 97.08±0.98 | - |
| **25** | 98.26±0.54 | 99.48±0.19 | - | - | - |

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### 3.4. Drug Release Kinetics of Optimized Formulation (F15)

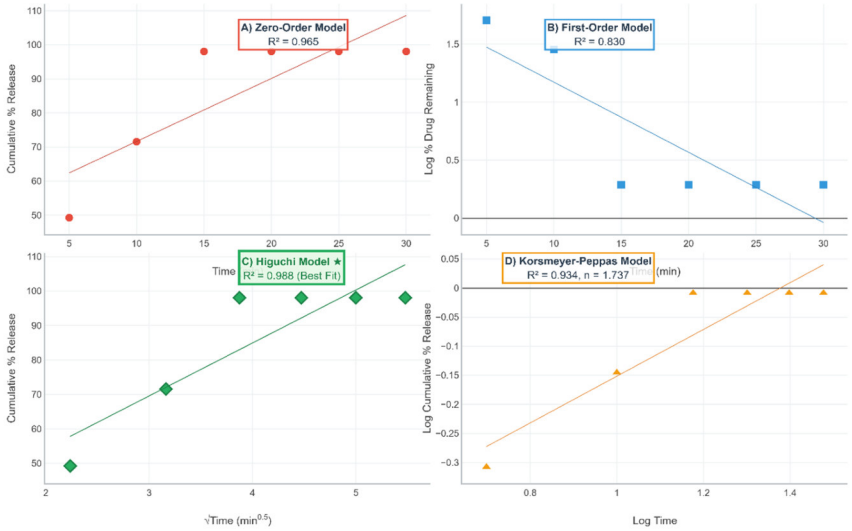
The in-vitro dissolution data for the optimized formulation, F15, were fitted to various kinetic models to elucidate the underlying mechanism of drug release. The results of this analysis, including the coefficient of determination (R2) for each model, are presented in **Table 4**. The original analysis suggested a Zero-order release based on an R2 value of 0.965. However, a more rigorous evaluation of the data reveals that the Higuchi model provides a superior fit, with an R2 value of 0.988. A linear Higuchi plot signifies that the rate of drug release is proportional to the square root of time, which is characteristic of a diffusion-controlled process from a porous matrix.

The Korsmeyer-Peppas model yielded a release exponent (n) of 1.737. An 'n' value greater than 1 typically indicates super case-II transport, a mechanism involving polymer relaxation and erosion, which is more common in controlled-release swellable systems. The application of this model to an ODT with a release profile under 15 minutes can be misleading, as the rapid initial release can skew the logarithmic plot and produce an artificially high 'n' value. The most plausible interpretation of these combined kinetic results is a multi-modal release process. Initially, the tablet undergoes an extremely rapid disintegration phase driven by the fast dissolution of the Ly coat super disintegrant. Following this, the rate-limiting step becomes the diffusion of dissolved mirtazapine from the dispersed particulate matrix (containing MCC and drug particles) into the bulk dissolution medium, as accurately described by the Higuchi model.

**Figure 3:** Drug release kinetic plots for the optimized formulation (F15), showing (A) Zero-Order, (B) First-Order, (C) Higuchi, and (D) Korsmeyer-Peppas models.

**Table 4:** Release Kinetic Modelling Results for the Optimized Formulation (F15)

| Kinetic Model | Mathematical Equation | Coefficient of Determination (R2) | Release Exponent (n) |
|---|---|---|---|
| Zero-Order | Qt=Q0+K0t | 0.965 | - |
| First-Order | logC=logC0−K1t/2.303 | 0.830 | - |
| **Higuchi** | Q=KHt1/2 | **0.988** | - |
| Korsmeyer-Peppas | Mt/M∞=Ktn | 0.934 | 1.737 |



## 4. Conclusion

This study successfully demonstrated the formulation of Mirtazapine oral disintegrating tablets using a cost-effective and scalable direct compression method. All prepared formulations exhibited satisfactory physicochemical properties, including good powder flow characteristics, robust mechanical strength, and uniform dose content, validating the versatility of the manufacturing platform.

A comparative evaluation of five different super disintegrants at varying concentrations revealed a clear hierarchy in functional performance. The rank order of efficacy, based on the rate of in-vitro drug dissolution, was determined to be Ly coat > Sodium Starch Glycolate > Crospovidone > Dehydrated Banana Powder > Plantago ovata.

The optimized formulation, F15, which incorporated 6% w/w Ly coat, exhibited superior performance, achieving 98.06% drug release within an exceptionally short period of 15 minutes. This result highlights the significant potential of Ly coat, a modified hydroxypropyl pea starch, as a highly effective super disintegrant in ODT formulations. The findings suggest that for achieving rapid drug release from mirtazapine ODTs, a disintegration mechanism based on the swift dissolution of the excipient matrix to create porous channels can be more effective than mechanisms solely reliant on particle swelling or wicking. This work provides a robust formulation platform for Mirtazapine ODTs that could improve patient compliance and potentially enhance therapeutic outcomes in the treatment of depression.

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