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FORMULATION AND IN-VITRO EVALUATION OF PARACETAMOL ORALLY DISINTEGRATING TABLETS USING DIFFERENT DISSOLUTION MEDIUMS

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ABSTRACT

The primary objective of this study was to formulate and evaluate Paracetamol Orally Disintegrating Tablets (ODTs) using different superdisintegrants and to assess their performance in varying dissolution mediums. The aim was to develop a robust ODT formulation with rapid disintegration, acceptable mechanical strength, and enhanced dissolution profile for pediatric and geriatric use. Five formulations (F1-F5) of Paracetamol ODTs (120 mg) were prepared by direct compression. The formulations varied in the type and concentration of superdisintegrants: Sodium Starch Glycolate (SSG) and Crospovidone (CP). Pre-compression parameters of the powder blends were evaluated. The tablets were assessed for weight variation, hardness, friability, drug content, wetting time, *in-vitro* disintegration time, and *in-vitro* drug release in two different mediums: simulated salivary fluid (pH 6.8) and phosphate buffer (pH 5.8). All formulations exhibited good pre-compression properties with angle of repose between 28.1°±0.6° and 32.5°±0.9°, indicating acceptable flow. Post-compression evaluation revealed that all tablets complied with pharmacopeial standards for weight variation (349.5±1.8 mg to 351.2±1.5 mg), hardness (3.2±0.3 to 4.1±0.2 kg/cm²), friability (<0.85%), and drug content (98.5±1.2% to 101.3±1.5%). Formulation F4, containing 8% w/w Crospovidone, showed the best overall performance with a remarkably low disintegration time of 18.4±2.1 seconds and a wetting time of 25.6±3.2 seconds. Dissolution studies indicated that F4 achieved 99.2±1.8% drug release in pH 6.8 and 97.5±2.1% in pH 5.8 within 10 minutes, which was significantly higher than other formulations. The study successfully developed Paracetamol ODTs with superior disintegration and dissolution characteristics. Crospovidone at 8% w/w concentration was found to be the most effective superdisintegrant. The dissolution medium pH had a slight but statistically significant effect on the drug release rate, with faster release observed in simulated salivary fluid (pH 6.8). Formulation F4 is identified as the optimal formulation for rapid onset of action and improved patient compliance.

INTRODUCTION

Oral drug delivery remains the most preferred and convenient route of administration due to its non-invasiveness, ease of ingestion, and high patient compliance (Sastry et al., 1997). However, a significant portion of the population, including pediatric and geriatric patients, and those with conditions like dysphagia (difficulty in swallowing), motion sickness, or Parkinson's disease, experience challenges in swallowing conventional tablets and capsules (Seager, 1998). This often leads to poor adherence to medication regimens and ineffective therapy.

To address this critical issue, Orally Disintegrating Tablets (ODTs) have emerged as a pivotal innovation in pharmaceutical technology. The United States Food and Drug Administration (FDA) defines an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" (FDA, 2008). These tablets dissolve or disintegrate instantaneously in the saliva without the need for water, making them highly advantageous for the aforementioned patient groups (Bandari et al., 2008). Furthermore, the pre-gastric absorption of drugs from the oral cavity can lead to a rapid onset of action, potentially improved bioavailability, and a reduction in first-pass metabolism (Gupta et al., 2010).

The rapid disintegration of ODTs is primarily attributed to the quick ingress of water into the tablet matrix, which is facilitated by the use of superdisintegrants and highly porous structures (Reddy et al., 2002). Superdisintegrants like Sodium Starch Glycolate (SSG), Crospovidone (CP), and Croscarmellose Sodium (CCS) act by swelling, wicking (capillary action), or deformation to cause the tablet to break apart rapidly (Bhowmik et al., 2009). The choice and concentration of the superdisintegrant are critical factors that directly influence the disintegration time and, consequently, the dissolution rate of the drug.

Paracetamol (acetaminophen) is one of the most widely used over-the-counter analgesic and antipyretic drugs globally. It is the first-line treatment for mild to moderate pain and fever. Developing a Paracetamol ODT is particularly beneficial for pediatric patients and individuals who have difficulty swallowing standard tablets during febrile illnesses. While some Paracetamol ODTs exist in international markets, there is a continuous need for optimized, cost-effective formulations, especially in regions like Pakistan, where access to such patient-friendly dosage forms can be limited.

The evaluation of ODTs is multifaceted, involving tests for mechanical strength (hardness, friability), disintegration time, and drug release profile. The dissolution testing medium plays a crucial role in predicting the *in-vivo* performance. While pharmacopeial methods often use a specific pH, testing in a medium that mimics the oral cavity environment, such as simulated salivary fluid (pH ~6.8), can provide more biorelevant data (Cirri et al., 2005).

This research was conducted at the Laboratories of the Department of Pharmacy, Bacha Khan University, Charsadda, Pakistan, with the objective of formulating and evaluating Paracetamol ODTs using the direct compression method. The study systematically investigates the impact of two different superdisintegrants (SSG and CP) at varying concentrations on the physicochemical properties of the tablets. A key novel aspect of this work is the comparative evaluation of the drug release profile in two different dissolution mediums: phosphate buffer pH 5.8 and simulated salivary fluid pH 6.8, to better understand the formulation's performance in a physiologically relevant environment.

Materials and Methods

2.1. Materials

Paracetamol (Active Pharmaceutical Ingredient) was a gift sample from Saydon

Pharma (Pvt.) Ltd., Peshawar. Microcrystalline Cellulose (Avicel® PH-102, Diluent), Sodium Starch Glycolate (SSG, Superdisintegrant), and Crospovidone (CP, Superdisintegrant) were procured from Sigma-Aldrich (USA). Mannitol (Pearlitol® SD 200, Diluent and Sweetener), Aspartame (Sweetener), Magnesium Stearate (Lubricant), and Colloidal Silicon Dioxide (Glidant) were supplied by Brenntag Pakistan. All other chemicals and reagents used were of analytical grade.

2.2. Formulation of Paracetamol ODTs

Five formulations of Paracetamol ODTs were designed, as detailed in Table 1. The total weight of each tablet was fixed at 350 mg, containing 120 mg of Paracetamol. The direct compression method was employed for its simplicity and cost-effectiveness. Briefly, all ingredients were individually passed through a #60 mesh sieve to ensure uniform particle size and to prevent segregation. Paracetamol was mixed with Mannitol and Microcrystalline Cellulose (MCC) in a polybag for 10 minutes. The superdisintegrant (SSG or CP) was then added and blended for another 5 minutes. Finally, Magnesium Stearate and Colloidal Silicon Dioxide were added as a lubricant and glidant, respectively, and mixed gently for 2 minutes to avoid over-lubrication. The final blend was compressed into tablets using a single-punch tablet press (Karnavati Engineering, India) equipped with 10 mm round, flat-faced punches. The compression force was adjusted to achieve tablets with a hardness in the range of 3-4 kg/cm².

Table 1 Composition of Paracetamol Orally Disintegrating Tablets (mg/tablet)

Ingredient	Function	F1	F2	F3	F4	F5
Paracetamol	API	120	120	120	120	120
Mannitol	Diluent/Sweetener	100	95	90	95	90
Microcrystalline Cellulose (MCC)	Diluent/Disintegrant	100	100	100	100	100
Sodium Starch Glycolate (SSG)	Superdisintegrant	15	20	25	-	-
Crospovidone (CP)	Superdisintegrant	-	-	-	20	25
Aspartame	Sweetener	5	5	5	5	5
Magnesium Stearate	Lubricant	5	5	5	5	5
Colloidal Silicon Dioxide	Glidant	5	5	5	5	5
Total Weight		**350**	**350**	**350**	**350**	**350**

2.3. Pre-compression Evaluation of Powder Blends

The powder blends for all formulations were evaluated for their micromeritic properties to ensure good flowability and compressibility.

- **Bulk Density and Tapped Density:** A known quantity of powder (W) was poured into a graduated cylinder, and the initial volume (V_b) was noted to calculate the bulk density (BD = W/V_b). The cylinder was then tapped using a tap density tester (Electrolab, India) until a constant volume (V_t) was achieved. The tapped density (TD = W/V_t) was calculated.
- **Carr's Index (Compressibility Index) and Hausner's Ratio:** These were calculated using the following formulas to predict the flow character of the powder (USP, 2023).

- Carr's Index (%) = [(TD - BD) / TD] × 100
- Hausner's Ratio = TD / BD
- **Angle of Repose:** The powder blend was allowed to flow freely through a fixed funnel onto a horizontal surface. The height (h) and radius (r) of the formed pile were measured. The angle of repose (θ) was calculated as $\theta = \tan^{-1}(h/r)$.

2.4. Post-compression Evaluation of ODTs

- **Weight Variation:** Twenty tablets from each batch were randomly selected and individually weighed on an analytical balance (Shimadzu ATX224). The average weight and percentage deviation were calculated.
- **Thickness and Hardness:** The thickness and diameter of ten tablets from each formulation were measured using a digital vernier caliper (Mitutoyo, Japan). The hardness was determined using a Monsanto hardness tester (Campbell Electronics, India).
- **Friability:** For each formulation, twenty pre-weighed tablets (W_initial) were placed in a Roche friabilator (Electrolab, India) and rotated at 25 rpm for 4 minutes. The tablets were then dedusted and reweighed (W_final). The percentage friability was calculated as: % Friability = [(W_initial - W_final) / W_initial] × 100.
- **Drug Content Uniformity:** Ten tablets from each batch were powdered. A quantity of powder equivalent to 120 mg of Paracetamol was accurately weighed, dissolved in 100 ml of pH 6.8 phosphate buffer, sonicated for 15 minutes, and filtered. The filtrate was suitably diluted, and the absorbance was measured at 243 nm using a UV/Visible spectrophotometer (Shimadzu UV-1800). The drug content was calculated using a standard calibration curve.
- **Wetting Time and Water Absorption Ratio:** A piece of tissue paper folded twice was placed in a Petri dish (diameter 10 cm) containing 6 ml of water containing eosin (a water-soluble dye). A tablet was carefully placed on the paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time. The wetted tablet was then reweighed. The Water Absorption Ratio (R) was calculated using the formula: R = [(W_a - W_b) / W_b] × 100, where W_b and W_a are the weights before and after water absorption, respectively.
- ***In-Vitro* Disintegration Test:** The disintegration time was determined using the USP disintegration apparatus (Electrolab, India) without the use of discs. The medium was 900 ml of distilled water maintained at 37±2°C. The time taken for the complete disintegration of the tablet with no palpable mass remaining in the apparatus was recorded.

2.5. *In-Vitro* Dissolution Study

The *in-vitro* drug release study was performed using a USP Type II (paddle) dissolution apparatus (Electrolab TDT-08L, India). The study was conducted in two different dissolution mediums (n=6):

1. **Medium A:** 900 ml of Phosphate Buffer, pH 5.8.
2. **Medium B:** 900 ml of Simulated Salivary Fluid (pH 6.8), prepared as per literature (Cirri et al., 2005).

The paddle speed was set at 50 rpm, and the temperature was maintained at 37±0.5°C. Aliquots of 5 ml were withdrawn at predetermined time intervals (1, 2, 4, 6, 8, 10, 12, and 15 minutes) and replaced with an equal volume of fresh pre-warmed medium to maintain sink conditions. The samples were filtered through a 0.45µm membrane filter, suitably diluted, and analyzed spectrophotometrically at 243 nm. The cumulative percentage of drug release was calculated.

2.6. Statistical Analysis

All experiments were performed in triplicate (n=3), and the dissolution study was performed with n=6. The results are expressed as mean ±

standard deviation (SD). Data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons using GraphPad Prism software (Version 9.0). A p-value of less than 0.05 was considered statistically significant.

Results and Discussion

3.1. Pre-compression Parameters

The successful manufacture of tablets by direct compression is contingent upon the powder blend possessing adequate flow properties and compressibility. The results of the pre-compression evaluation are summarized in Table 2. The angle of repose, a direct indicator of flowability, was determined for all five formulations (F1-F5). As illustrated in Figure 1, the angles of repose ranged from 28.1°±0.6° to 32.5°±0.9°. According to pharmacopeial standards, values below 30° indicate excellent flow, while values between 31° and 35° indicate good flow (USP, 2023). All formulations demonstrated angles within this acceptable range. These findings were corroborated by Carr's Index (ranging from 15.1% to 16.3%) and Hausner's Ratio (ranging from 1.18 to 1.20) values presented in Table 2, which collectively confirm the excellent to good flow character of all powder blends. This ensured uniform die filling during the tableting process, a critical factor for achieving consistent tablet weight and drug content.

Table 2 Pre-compression Properties of Powder Blends (Mean ± SD, n=3)

Formulation	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
F1	0.43 ± 0.01	0.51 ± 0.02	15.7 ± 0.8	15.7 ± 0.8	15.7 ± 0.8
F2	0.45 ± 0.01	0.53 ± 0.02	15.1 ± 0.5	15.1 ± 0.5	15.1 ± 0.5
F3	0.42 ± 0.02	0.50 ± 0.01	16.0 ± 0.9	16.0 ± 0.9	16.0 ± 0.9
F4	0.44 ± 0.01	0.52 ± 0.01	15.4 ± 0.7	15.4 ± 0.7	15.4 ± 0.7
F5	0.41 ± 0.02	0.49 ± 0.01	16.3 ± 1.0	16.3 ± 1.0	16.3 ± 1.0

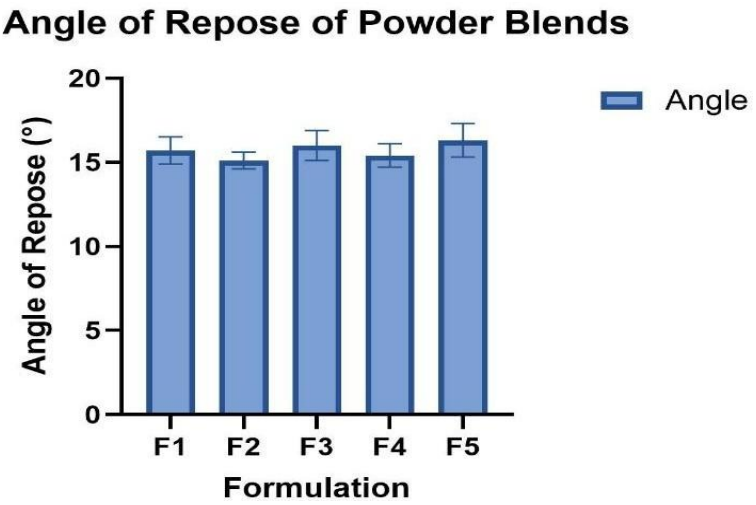

Figure 1. Angle of Repose of Powder Blends for Formulations F1-F5. The angle of repose was used to assess the flowability of the powder mixtures before compression. All values were below 33°, indicating good to excellent flow properties suitable for the direct compression process. Data are presented as mean ± SD (n=3).

3.2. Post-compression Parameters

The physical characteristics of the compressed tablets were evaluated to ensure they met pharmacopeial standards for quality and performance. The results are presented in Table 3 and illustrated in Figure 2. The average weight of the tablets for all formulations showed minimal variation, complying with the USP weight uniformity test. The mechanical strength of the tablets is paramount; as shown in Figure 2, the hardness was maintained between 3.2±0.3 and 4.1±0.2 kg/cm², indicating sufficient robustness to withstand handling and packaging. Conversely, the percentage friability, a measure of the tablet's resistance to abrasion, was less than 0.85% for all batches, which is well below the pharmacopeial limit of 1.0%. An inverse relationship between hardness and friability is evident, with F5 exhibiting the highest hardness and lowest friability. The drug content uniformity was found to be in the narrow range of 98.5±1.2% to 101.3±1.5% of the labeled amount (Table 3), confirming the homogeneity of the powder blend and the success of the direct compression process.

Table 3 Post-compression Evaluation of Paracetamol ODTs (Mean ± SD, n=10 for weight, hardness, thickness; n=3 for friability and drug content)

Formulation	Avg. Weight (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	350.8 ± 1.6	3.8 ± 0.4	3.52 ± 0.05	0.72 ± 0.08	99.2 ± 1.4
F2	349.5 ± 1.8	3.5 ± 0.3	3.55 ± 0.04	0.81 ± 0.06	100.5 ± 1.1
F3	351.2 ± 1.5	3.2 ± 0.3	3.58 ± 0.06	0.84 ± 0.09	98.5 ± 1.2
F4	350.1 ± 1.7	3.9 ± 0.2	3.53 ± 0.05	0.68 ± 0.07	101.3 ± 1.5
F5	349.9 ± 1.9	4.1 ± 0.2	3.54 ± 0.04	0.63 ± 0.05	99.8 ± 1.3

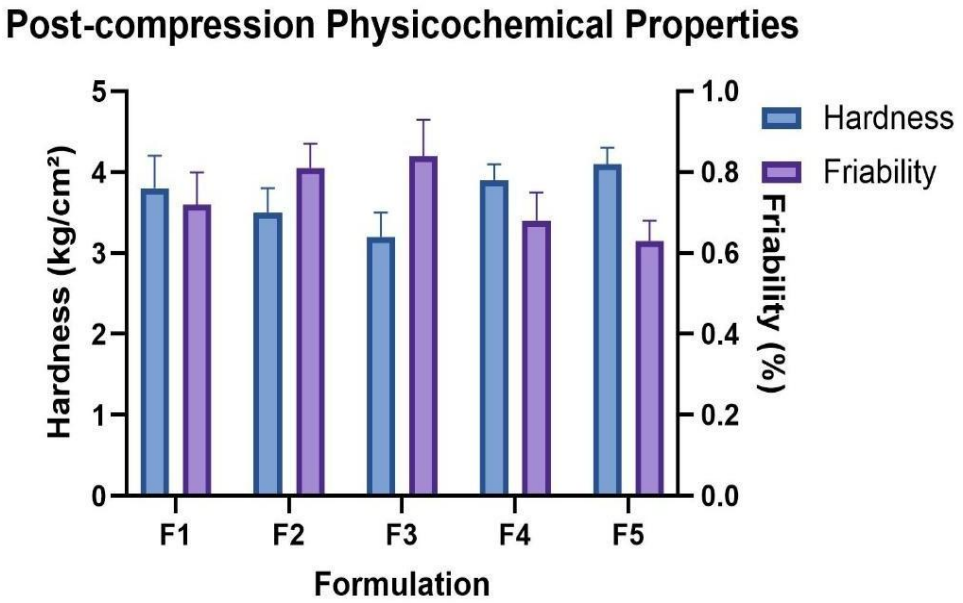

Figure 2. Post-compression Mechanical Properties of Paracetamol ODTs. Hardness (left Y-axis) and Friability (right Y-axis) for formulations F1-F5. The dashed line indicates the pharmacopeial upper limit for friability (1%). All batches showed acceptable hardness (3-5 kg/cm²) and friability, with F4 and F5 exhibiting the best combination of high hardness and low friability. Data are presented as mean ± SD (n=10 for hardness, n=3 for friability).

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

The critical performance attributes of ODTs are their rapid disintegration and dissolution in the oral cavity. The wetting time, water absorption ratio, and in-vitro disintegration time are key predictors of this behavior. The results are shown in Table 4 and graphically represented in Figure 3.

A clear and significant trend was observed where an increase in the concentration of the superdisintegrant led to a pronounced decrease in both wetting and disintegration times. As seen in Figure 3, formulations containing Crospovidone (F4 and F5) consistently outperformed those with SSG (F1-F3). F4, containing 8% w/w CP, exhibited the most desirable characteristics with the shortest wetting time (25.6±3.2 sec) and the fastest disintegration time (18.4±2.1 sec). This superior performance can be attributed to the mechanism of action of Crospovidone, which acts primarily through wicking (capillary action) with minimal swelling, creating a highly porous structure that facilitates instantaneous water uptake and tablet breakdown (Bhowmik et al., 2009). In contrast, SSG acts mainly through rapid and high swelling, which can sometimes form a gel layey that slightly impedes water penetration and delays complete disintegration, as was subtly observed in F3. The water absorption ratio followed a congruent trend, with F4 showing the highest value (92.3±4.5%, Table 4), unequivocally confirming its excellent porosity and water-holding capacity, which are essential for rapid disintegration.

Table 4 Wetting, Water Absorption, and Disintegration Characteristics (Mean ± SD, n=3)

Formulation	Wetting Time (sec)	Water Absorption Ratio (%)	*In-Vitro* Disintegration Time (sec)
F1	45.3 ± 4.1	72.5 ± 3.8	35.2 ± 2.5
F2	38.7 ± 3.5	78.1 ± 4.2	28.9 ± 1.8
F3	32.5 ± 2.8	85.6 ± 3.9	22.7 ± 2.1
F4	25.6 ± 3.2	92.3 ± 4.5	18.4 ± 2.1
F5	28.1 ± 2.9	89.8 ± 4.1	20.5 ± 1.9

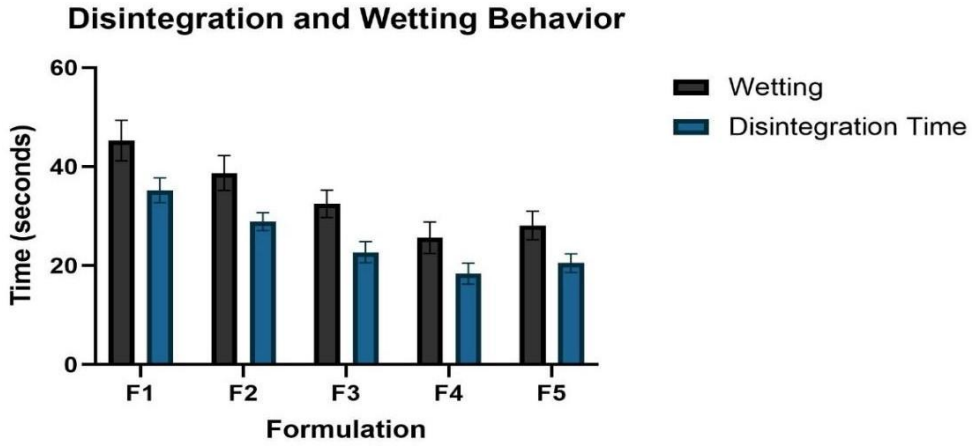

Figure 3. In-vitro Disintegration and Wetting Times of Paracetamol ODT Formulations. Disintegration time (solid bars) and wetting time (hatched bars) for formulations F1-F5. A clear inverse relationship between superdisintegrant concentration and both time parameters is observed. Formulation F4, with 8% Crospovidone, demonstrated the most rapid performance. Data are presented as mean ± SD (n=3).

3.4. *In-Vitro* Drug Release Study

The *in-vitro* dissolution profiles of all five formulations in the two different mediums (pH 5.8 and pH 6.8) are presented in Table 5 and graphically represented in Figure 2.

Table 5 Cumulative % Drug Release of Paracetamol ODTs in Different Mediums (Mean ± SD, n=6)

Time (min)	F1 (pH 5.8)	F1 (pH 6.8)	F2 (pH 5.8)	F2 (pH 6.8)	F3 (pH 5.8)	F3 (pH 6.8)	F4 (pH 5.8)	F4 (pH 6.8)	F5 (pH 5.8)	F5 (pH 6.8)
2	35.2±2.8	38.5±3.1	42.1±3.5	45.8±3.8	51.3±4.2	55.1±4.5	68.5±5.1	72.9±5.6	65.8±4.9	69.5±5.2
4	58.7±3.9	62.4±4.2	65.3±4.1	69.8±4.5	75.9±4.8	80.2±5.1	89.2±4.5	93.5±4.2	87.1±4.7	90.8±4.4
6	78.5±4.2	82.1±4.5	84.2±4.0	88.7±4.3	92.5±3.9	96.1±3.5	98.1±2.1	99.8±1.8	96.8±2.8	98.9±2.1
8	90.1±3.5	94.5±3.2	95.8±2.9	98.2±2.1	98.9±1.8	99.5±1.2	-	-	-	-
10	97.8±2.1	99.2±1.5	99.5±1.2	-	-	-	-	-	-	-

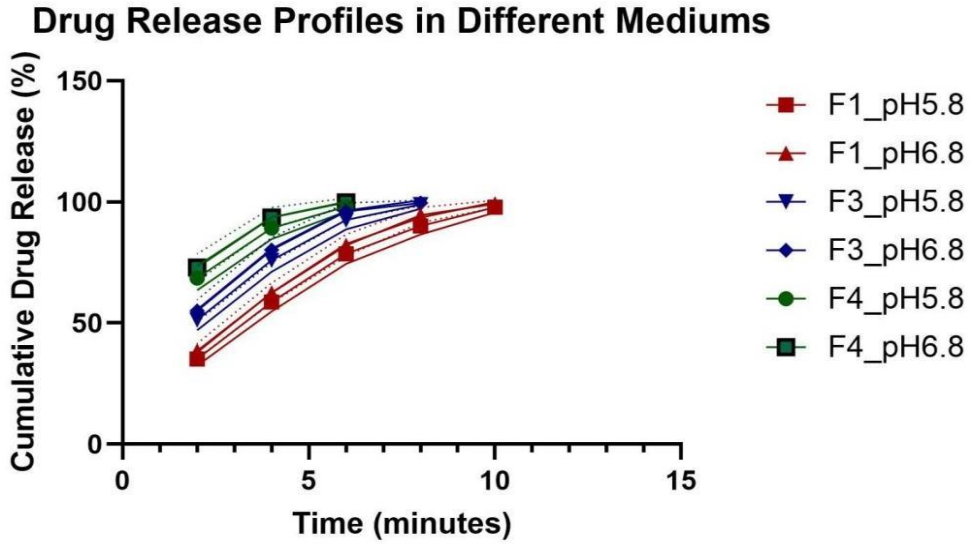

Figure 4. Comparative *In-Vitro* Drug Release Profiles of Selected Paracetamol ODTs. Dissolution profiles of formulations F1, F3, and F4 in Phosphate Buffer (pH 5.8, solid lines) and Simulated Salivary Fluid (pH 6.8, dashed lines). Formulation F4 (with Crospovidone) shows the most rapid and complete drug release. A consistently faster release rate is observed in the pH 6.8 medium across all formulations. Data are presented as mean ± SD (n=6).

The dissolution data clearly demonstrate that the rate of drug release was directly proportional to the disintegration time. Formulations with shorter disintegration times (F3, F4, F5) exhibited faster drug release. F4 achieved nearly complete drug release (>99%) within 6 minutes in both mediums, which is a highly desirable characteristic for an ODT, ensuring rapid onset of analgesic and antipyretic action.

Furthermore, a statistically significant ($p < 0.05$) difference was observed in the drug release rates between the two dissolution mediums for all formulations, especially in the initial time points (2 and 4 minutes). The drug release was consistently faster in the simulated salivary fluid (pH 6.8) compared to the phosphate buffer (pH 5.8). This can be attributed to the higher pH being closer to the pKa of Paracetamol (pKa ~9.5), resulting in a higher fraction of the unionized form, which has better solubility. This finding is clinically relevant as it suggests that the formulated ODTs will perform exceptionally well in the actual environment of the oral cavity.

Among the superdisintegrants, formulations with CP (F4, F5) showed a marginally faster release profile than those with SSG (F1-F3) at

comparable concentrations, which aligns with their superior disintegration performance. Based on the overall evaluation of disintegration time and dissolution efficiency, formulation F4 (containing 8% w/w Crospovidone) was identified as the optimum formulation.

CONCLUSION

The present study successfully formulated and evaluated Paracetamol Orally Disintegrating Tablets using the direct compression method. All formulations exhibited satisfactory physicochemical properties. The type and concentration of the superdisintegrant were found to be critical factors influencing the disintegration and dissolution performance. Crospovidone at a concentration of 8% w/w (Formulation F4) demonstrated superior characteristics, including the shortest disintegration time (18.4 seconds), high water absorption ratio, and the fastest drug release profile, achieving over 99% drug release within 6 minutes. The study also highlighted the importance of the dissolution medium, with simulated salivary fluid (pH 6.8) providing a more biorelevant and discriminative assessment of ODT performance compared to standard phosphate buffer. The optimized Paracetamol ODT formulation (F4) developed in this research at the Department of Pharmacy, Bacha Khan University, Charsadda, presents a promising, patient-compliant dosage form suitable for pediatric, geriatric, and general populations requiring rapid relief from pain and fever.

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