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Effect of Superdisintegrant Concentration on the Physical Properties of Diclofenac Sodium Orally Disintegrating Granules (ODGs)

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ABSTRACT

The development of diclofenac sodium orally disintegrating granules (ODGs) offers a promising approach to improve patient compliance, particularly among pediatric, geriatric, and dysphagic patients. Although crospovidone and sodium starch glycolate (SSG) are widely used as superdisintegrants, limited information is available regarding their optimal combination in diclofenac sodium ODG formulations. This study aimed to optimize the combination of crospovidone and SSG by evaluating different crospovidone ratios (2.4:1–1:2), including an equal ratio (1:1), on the physical characteristics and disintegration performance of diclofenac sodium ODGs prepared by wet granulation. Six formulations were developed while maintaining constant concentrations of other excipients. The granules were evaluated for flow properties, particle size distribution, bulk and tapped density, Carr's Index, Hausner's ratio, moisture content, and disintegration time. Statistical analysis was performed using one-way ANOVA ($\alpha = 0.05$). All formulations exhibited excellent flowability, with angles of repose of 18.10–19.45°, Carr's Index of 12.28–13.46%, Hausner's ratio of 1.14–1.16, moisture content of 2.41–2.73%, and uniform particle size distribution (d50: 305–325 μm). All formulations complied with the European Pharmacopoeia disintegration requirement (<180 s), while F1, F2, and F4 also met the USP criterion (<30 s). Disintegration time ranged from 21.38 to 38.47 s and was significantly affected by the crospovidone–SSG ratio ($p < 0.05$). Formulation F4 demonstrated the fastest disintegration time (21.38 s) and the most favorable overall characteristics. These findings indicate that optimizing the crospovidone-SSG combination enhances disintegration performance while maintaining acceptable physical quality, making F4 a promising diclofenac sodium ODG formulation.

Keywords: Crospovidone, Diclofenac sodium, Orally disintegrating granules, Sodium starch glycolate, Superdisintegrant optimization.

Introduction

The increasing demand for patient-friendly oral dosage forms has driven the development of orally disintegrating drug delivery systems, which are designed to disintegrate rapidly in the oral cavity without the need for water. These dosage forms have gained considerable attention because they improve convenience, ease of administration, and patient compliance, particularly among pediatric, geriatric, and dysphagic patients who experience difficulty swallowing conventional tablets and capsules. Dysphagia is estimated to affect approximately 35% of the general population and may reduce adherence to therapy, thereby compromising treatment outcomes (Ribeiro *et al*., 2024). Orally disintegrating dosage forms typically disintegrate within less than 60 seconds, providing a practical alternative to conventional oral formulations. In addition to enhancing patient comfort and compliance, these systems are advantageous for individuals with limited access to water, such as during travel or emergency situations (Ghourichay *et al*., 2021). Consequently, the development of rapidly disintegrating oral formulations has become an important focus in pharmaceutical research and formulation design (Drumond, 2020).

Among these systems, Orally Disintegrating Granules (ODGs) have emerged as a promising multiparticulate dosage form. Unlike single-unit systems, ODGs consist of small granules that rapidly disperse in saliva, providing improved mouthfeel and reduced grittiness. Compared to conventional tablets and orally disintegrating tablets (ODTs), ODGs offer advantages such as greater dose flexibility, enhanced stability, and the potential incorporation of coated particles for taste masking or modified drug release (Chiarugi *et al*., 2024; Kállai-Szabó *et al*., 2024). Furthermore, multiparticulate systems may ensure more uniform gastrointestinal distribution and reduce the risk of local irritation (Suralke, 2025). Despite these advantages, the successful development of ODG formulations requires careful optimization of formulation components to achieve rapid disintegration while maintaining desirable physical characteristics.

Diclofenac sodium is a widely used non-steroidal anti-inflammatory drug (NSAID) indicated for pain and inflammatory conditions (Kołodziejska & Kołodziejczyk, 2018). However, its bitter taste and potential for gastrointestinal (GI) irritation can reduce patient acceptability, particularly in oral formulations intended to disintegrate in the mouth. These challenges have driven formulation strategies such as taste masking and gastrointestinal targeting in diclofenac-containing oral disintegrating systems (Alotaibi *et al*., 2019; Ye *et al*., 2025). Therefore, developing diclofenac sodium as orally disintegrating granules could be beneficial for patients who experience difficulty swallowing conventional dosage forms, provided that formulation design maintains acceptable physical characteristics and patient-relevant performance.

A critical component in rapid-disintegrating oral systems is the superdisintegrant, such as sodium starch glycolate and crospovidone. These excipients promote disintegration via mechanisms including swelling, wicking, and

structural recovery, and their functional performance can be influenced by material attributes and concentration (Berardi *et al*., 2022; Dezena & Tardim, 2022). In granule-based systems, superdisintegrant concentration is expected to affect key physical properties relevant to manufacturability and product quality, including flowability, bulk/tapped density, compressibility index, moisture-related behavior, particle size distribution, and disintegration time (Dilebo & Gabriel, 2019). An insufficient level may delay disintegration, whereas excessive levels may compromise granule integrity and flow performance, potentially affecting processability and dose uniformity.

While extensive research has been conducted on orally disintegrating systems, most studies have focused on tablet formulations. Investigations specifically addressing the optimization of superdisintegrant concentration in Orally Disintegrating Granules, particularly for diclofenac sodium, remain relatively limited. Given that the characteristics of granules differ from those of tablets, the relationship between superdisintegrant concentration and the physical quality of the dosage form warrants dedicated study.

Based on this background, the present study was conducted not only to evaluate the effects of different crospovidone and sodium starch glycolate concentrations on the physical characteristics and disintegration performance of Diclofenac Sodium Orally Disintegrating Granules (ODGs), but also to identify the optimal superdisintegrant combination for achieving rapid disintegration while maintaining desirable granule quality. Furthermore, this study is expected to contribute scientific evidence regarding the relationship between superdisintegrant ratios and ODG performance, thereby providing a rational basis for formulation optimization and supporting the development of patient-friendly diclofenac sodium dosage forms with improved compliance and therapeutic acceptability.

Methodology

Based on this background, the present study was conducted to evaluate the effect of varying crospovidone ratios in six formulations (F1–F6), while maintaining a constant total superdisintegrant concentration, on the physical characteristics and disintegration performance of Diclofenac Sodium Orally Disintegrating Granules (ODGs). Furthermore, the study aimed to determine the optimal crospovidone-SSG ratio for producing ODGs with rapid disintegration and acceptable physical quality. The findings are expected to contribute scientific evidence for the optimization of superdisintegrant combinations in diclofenac sodium ODG formulations and support the development of more patient-friendly oral dosage forms.

Instruments and Materials

The instruments used in this study included a Analytical balance (Ohaus® PR244), Sieve shaker, Oven (Memmert® UN55), Flow tester, Moisture balance (Ohaus® MB23), Tap density tester (ETD-1020 Electrolab), Stopwatch, Vernier calipers.

The materials employed in the study consisted Diclofenac Sodium (Fagron), crospovidone (Fagron), Sodium Starch Glycolate (Gloria Interchem),

Mannitol (Fagron), Microcrystalline Cellulose (Gloria Interchem), Magnesium Stearate, Aspartame, distilled water.

Determination of Basic Formula

This study employs the wet granulation method to prepare Diclofenac Sodium ODGs. The basic formula is developed with fixed compositions of all ingredients except for the superdisintegrant (Crospovidone and Sodium Starch Glycolate) concentration, which will be varied. The design of the ODGs Diclofenac Sodium Formula with Variations in Superdisintegrant Concentration is presented in Table 1.

Table 1. Formulation Design of Diclofenac Sodium ODGs with Varying Superdisintegrant Concentrations

Ingredient	Function	Concentration (mg)					
		F1	F2	F3	F4	F5	F6
Diclofenac Sodium	Active ingredient	50	50	50	50	50	50
Crospovidone	Superdisintegrant	21	30	25,5	18	16,5	12
Sodium Starch Glycolate	Superdisintegrant	15	6	10,5	18	19,5	24
Mannitol	Filler	173	173	173	173	173	173
MCC (Microcrystalline Cellulose)	Binder	35	35	35	35	35	35
Aspartame	Sweetener	3	3	3	3	3	3
Magnesium Stearate	Lubricant	3	3	3	3	3	3

Preparation of Granules by Wet Granulation Method

Diclofenac sodium orally disintegrating granules (ODGs) were prepared using the wet granulation method. All ingredients were accurately weighed according to the composition of each formulation (Table 1). The intragranular components, consisting of diclofenac sodium, mannitol, microcrystalline cellulose (MCC), and a portion of crospovidone and/or sodium starch glycolate (SSG) according to the ratio specified in each formulation, were blended until a homogeneous mixture was obtained. Distilled water (approximately 15 mL) was then added gradually as the granulating fluid while mixing continuously until a cohesive wet mass suitable for granulation was formed. The wet mass was subsequently passed through a 16-mesh sieve to produce wet granules.

The resulting wet granules were dried in an oven at 40–50°C for 2–4 hours until a constant weight was achieved, and then passed through a 20-mesh sieve to obtain granules with a uniform particle size. The extragranular components, consisting of the remaining portion of crospovidone and/or sodium starch glycolate (SSG), aspartame, and magnesium stearate, were weighed according to the formulation and gently blended with the dried granules until a homogeneous mixture was obtained. The final diclofenac sodium ODGs were subsequently subjected to physical characterization and disintegration time evaluation (Dilebo & Gabriel, 2019).

Evaluation of Granule Physical Properties

The physical properties of the granules were evaluated for each formulation. All measurements were performed in triplicate (n = 3), and the results were expressed as mean ± standard deviation. The evaluated parameters included flow

rate, angle of repose, particle size distribution, bulk density, tapped density, Carr's Index, Hausner's ratio, moisture content, and disintegration time. Particle size distribution analysis was performed using a sieve analysis method to determine the proportion of granules retained on each sieve and to assess the uniformity of granule size distribution.

Flow Properties Evaluation

Flow Properties Evaluation includes flow rate and angle of repose. For flow rate, 30 g of granules are passed through a funnel with a 10 mm orifice, and flow time is recorded. Flow rate >10 g/second indicates excellent flow. For angle of repose, granules are poured through a funnel fixed 2 cm above a surface, and the cone height and radius are measured. Angle of repose ≤30° indicates excellent flow. The height (h) and radius (r) of the heap were measured, and the angle of repose (θ) was calculated using the equation:

$$tan\theta = \frac{h}{r}$$

Particle Size Distribution Analysis

Particle size distribution was determined using a sieve shaker method to ensure uniformity and predict mouthfeel. A series of sieves (mesh 20, 40, 60, 80, and 100) were arranged in descending order with a receiver pan at the bottom. Approximately 100 g of granules from each formula were placed on the top sieve and shaken for 15 minutes. The granules retained on each sieve were weighed, and the percentage retained was calculated to determine the mean particle size and distribution profile. This evaluation is essential, as particle sizes ≥200–244 μm may produce a rough mouthfeel in orally disintegrating formulations, potentially affecting patient acceptability (Thombre *et al*., 2023).

Density and Compressibility Evaluation

Bulk density was determined by gently pouring 50 g of granules into a 100 mL graduated cylinder and recording the initial volume (V_0). Bulk density (ρ_bulk) was calculated as the weight of granules divided by the initial volume (g/mL).

Tapped density was measured by placing the cylinder containing the granules on a tapped density tester and tapping up to 1000 times or until a constant volume (V) was achieved. Tapped density (ρ_tapped) was calculated as the weight of granules divided by the final tapped volume (g/mL). All measurements were performed in triplicate.

Carr's Index was calculated using the equation:

$$\text{Carr's Index (\%)} = \frac{\rho \text{ tapped} - \rho \text{ bulk}}{\rho \text{ tapped}} x\ 100$$

Carr's Index values of 5–15% indicate excellent flow, 12–16% good flow, 18–21% fair flow, and >23% poor flow.

Hausner's Ratio was calculated as:

$$\text{Hausner's Ratio} = \frac{\rho \text{ tapped}}{\rho \text{ bulk}}$$

A Hausner's Ratio <1.25 indicates good flow properties, whereas values >1.5 indicate poor flowability.

Moisture Content Determination

Moisture content of the granules was determined using a moisture analyzer based on the loss on drying (LOD) principle. Approximately 1–2 g of granules were accurately weighed and heated at 105°C until a constant weight was obtained. The percentage of moisture content was calculated from the weight loss relative to the initial sample weight.

Disintegration Time

In vitro disintegration time was determined as the primary parameter for evaluating Orally Disintegrating Granules (ODGs). A 10 cm diameter petri dish containing 50 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C was used to simulate oral cavity conditions. A piece of filter paper (Whatman No. 1) was placed in the medium and allowed to saturate. Granules equivalent to one dose were gently placed at the center of the wetted filter paper, and the time required for complete disintegration, indicated by the absence of visible intact granules, was recorded using a stopwatch. The test was performed in triplicate for each formulation, and results were expressed as mean disintegration time (seconds). Orally disintegrating dosage forms are generally expected to disintegrate within 3 minutes, with an optimal target of less than 60 seconds (USP, 2023).

Data Analysis

The physical evaluation data were expressed as mean ± standard deviation (mean ± SD) and analyzed using IBM SPSS Statistics software. Prior to hypothesis testing, data normality was assessed using the Shapiro–Wilk test, while homogeneity of variance was evaluated using Levene's test. Data that met the assumptions of normality and homogeneity were subsequently analyzed using One-Way Analysis of Variance (ANOVA) to determine the effect of different crospovidone–sodium starch glycolate ratios on the evaluated parameters. When statistically significant differences were detected, Tukey's post hoc test was performed to identify differences among individual formulations. Statistical significance was established at $p < 0.05$.

Result and Discussion

Flow Properties Evaluation

Granule Flow Rate

Granule flow rate was evaluated using the funnel method to assess the ability of the prepared granules to flow under gravitational force. This parameter is critical in ensuring uniform filling during manufacturing and consistent dose distribution in

multiparticulate systems (Pratiwi *et al*., 2025). The results of the flow rate evaluation for the six diclofenac sodium ODG formulas are presented in Table 2.

Table 2. Flow Rate Evaluation Results of Diclofenac Sodium ODG Granules

Formula	Flow Rate (mean ± SD) (g/s)
F1	9.49 ± 0.21^{b}
F2	9.18 ± 0.81^{ab}
F3	9.68 ± 0.32^{ab}
F4	9.23 ± 0.72^{a}
F5	9.89 ± 0.39^{a}
F6	8.05 ± 1.57^{a}

*Same letter indicates no significant difference ($p > 0.05$). Different letters indicate significant difference ($p < 0.05$).

Based on the data presented in Table 1, the granule flow rate of the six formulations ranged from 8.05 to 9.89 g/s. Formulation F5 exhibited the highest flow rate (9.89 ± 0.39 g/s), whereas F6 showed the lowest value (8.05 ± 1.57 g/s). The flow rates of F1, F2, F3, and F4 were 9.49 ± 0.21 g/s, 9.18 ± 0.81 g/s, 9.68 ± 0.32 g/s, and 9.23 ± 0.72 g/s, respectively.

According to pharmaceutical literature, granules with a flow rate greater than 4 g/s are considered to have good flow properties and are suitable for manufacturing processes, whereas flow rates above 10 g/s are classified as excellent (Muliadi *et al*., 2024). In the present study, the flow rates of formulations F1–F6 ranged from 8.05 ± 1.57 to 9.89 ± 0.39 g/s. Formulation F5 exhibited the highest flow rate (9.89 ± 0.39 g/s), while formulation F6 showed the lowest flow rate (8.05 ± 1.57 g/s). Nevertheless, all formulations remained within the range categorized as having good flow properties and met the requirements for pharmaceutical granules.

These results indicate that variations in the crospovidone starch glycolate (SSG) ratio, while maintaining a constant total superdisintegrant concentration, did not adversely affect granule flowability. The good flow properties observed may be attributed to the relatively uniform particle size distribution and optimal moisture content of the granules, which help reduce interparticle cohesion and facilitate flow. Good flowability is essential to ensure uniform processing, ease of handling during manufacturing, and consistent quality of the final dosage form (Suhag *et al*., 2024). Furthermore, the relatively similar flow rate values among the formulations suggest that changes in the crospovidone-SSG ratio had little influence on the flow characteristics of the granules.

To determine whether variations in superdisintegrant concentration significantly influenced granule flow rate, statistical analysis was performed using one-way ANOVA at a significance level of $\alpha = 0.05$. The results indicated a statistically significant difference among the formulations ($p < 0.05$), suggesting that the variation in the proportion of crospovidone and sodium starch glycolate significantly affected the flow properties of the granules. This finding is consistent with research conducted by Dash *et al*., (2022), which reported that variations in superdisintegrant concentration affect granule flow properties, although all tested formulas still showed acceptable flow rate values.

Formula F5 showed the highest flow rate (9.89 g/sec), indicating that the superdisintegrant concentration in this formula produced granules with the most optimal size and shape for flow properties. In contrast, formula F6 showed the lowest

flow rate (8.05 g/sec) with the largest standard deviation (1.57). This indicates that formula F6 has physically different characteristics compared to other formulas, especially F5 and F3, which have much higher flow rate values.

The low flow rate in F6 can be attributed to several factors. The excessively high concentration of superdisintegrant in F6 is suspected to produce an excessive number of fine particles due to increased frictional forces during the granulation process. These fine particles tend to increase cohesive forces between particles, causing uneven and non-uniform flow (Yeom *et al*., 2017). Additionally, the less uniform particle size distribution in F6 may cause segregation during testing, contributing to the high standard deviation. Research conducted by Hidayati *et al*., (2020) on the optimization of fast-disintegrating tablets also showed that increasing the concentration of certain superdisintegrants can affect the flow properties of the mixture. They reported that at higher superdisintegrant concentrations, there was an increase in the Carr's Index value, indicating a decrease in flow properties, although overall still within an acceptable range.

The one-way ANOVA results showed that variations in the crospovidone-sodium starch glycolate (SSG) ratio significantly affected the flow rate of the granules ($p < 0.05$). Further analysis using Tukey's post hoc test revealed significant differences among several formulations. Formulation F1 exhibited a significantly higher flow rate than formulations F4, F5, and F6, while formulations F2 and F3 showed intermediate values and did not differ significantly from either group. Although statistically significant differences were observed, all formulations exhibited flow rates ranging from 8.05 to 9.89 g/s, which are considered acceptable for pharmaceutical processing. These findings suggest that variations in the crospovidone–SSG ratio influenced granule flowability; however, the magnitude of the differences was not sufficient to compromise the overall flow characteristics of the granules. Therefore, all formulations maintained adequate flow properties for subsequent manufacturing processes.

Angle of Repose

The angle of repose is a fundamental parameter used to evaluate the flow properties of granules. It reflects the balance between gravitational forces and interparticle cohesion, where lower angle values indicate better flowability due to reduced friction and cohesion among particles (Soemarie *et al*., 2017). In this study, fifty percent of the total superdisintegrant was incorporated intragranularly, while the remaining fifty percent was added extragranularly. This approach was intended to optimize the disintegration performance while maintaining desirable granule characteristics.

The results of the angle of repose evaluation for the six diclofenac sodium ODG formulations are presented in Table 3. All formulations exhibited low angle of repose values, indicating good flow properties. The favorable flow behavior suggests that the

distribution of crospovidone and sodium starch glycolate (SSG) between the intragranular and extragranular phases did not negatively affect granule flowability. The intragranular fraction contributed to the formation of granules with adequate mechanical integrity during the granulation process, whereas the extragranular fraction helped preserve the functional performance of the superdisintegrants without compromising the physical characteristics of the granules. As a result, all formulations maintained good flow properties, supporting their suitability for further pharmaceutical processing.

Table 3. Results of Granule Angle of Repose Evaluation

Formula	Results (mean ± SD)	Flow Property Category
F1	18.43 ± 1.08	Excellent
F2	18.27 ± 1.65	Excellent
F3	19.10 ± 2.31	Excellent
F4	18.10 ± 2.11	Excellent
F5	19.28 ± 1.53	Excellent
F6	19.45 ± 1.27	Excellent

** Flow property categories based on angle of repose values: ≤30° (excellent), 31-35° (good), 36-40° (fair), 41-45° (poor), >45° (very poor)*

As shown in Table 3, the angle of repose values ranged from 18.10° to 19.45°, indicating excellent flow properties (<25°) for all formulations. Although slight numerical differences were observed, statistical analysis using one-way ANOVA ($\alpha = 0.05$) revealed no significant differences among the formulations ($p > 0.05$). In general, the variation in angle of repose among formulations did not significantly affect granule flow behavior, suggesting that differences in the proportions of crospovidone and sodium starch glycolate (SSG) within the investigated range were insufficient to markedly influence bulk flow properties.

This observation can be explained based on formulation design and material functionality. The superdisintegrants were incorporated extragranularly and were not directly involved in the formation of the primary granule structure during wet granulation. Instead, the structural characteristics of the granules were predominantly governed by microcrystalline cellulose (MCC) and mannitol as the principal binder components. MCC is widely recognized for its plastic deformation behavior and relatively smooth crystalline surface, which improve compressibility and reduce interparticle friction, thereby enhancing flow properties (Aulton & Taylor, 2018). Mannitol, a crystalline diluent with favorable density and low hygroscopicity, further contributes to improved packing behavior and reduced cohesiveness (Li *et al*., 2022).

From a mechanistic perspective, superdisintegrants exhibit functionality-related characteristics that may influence powder and granule behavior. Sodium starch glycolate possesses high swelling capacity and moisture affinity, which can increase interparticle cohesion at elevated concentrations. In contrast, crospovidone has a porous morphology and primarily acts through a wicking mechanism with minimal gel formation (Manzoor, 2021). However, in the present study, the concentration range

employed did not produce a statistically significant impact on angle of repose values. This suggests that the wet granulation process effectively generated granules with relatively uniform particle size distribution and controlled morphology, mitigating potential cohesion effects associated with superdisintegrant variation.

Particle Size Distribution Analysis

Particle size distribution (PSD) is a critical parameter in granule characterization, as it directly influences flowability, packing behavior, compressibility, and disintegration performance (Rajabi-Siahboomi, 2017). The results of the particle size distribution analysis for all six formulations (F1-F6) are presented in Table 3.

Based on the data presented in Table 4, the particle size distribution of all formulations was predominantly within the 250–420 μm range (40/60 mesh), accounting for 37.54% to 40.12% of the granules. The second-largest fraction was observed in the 177–250 μm range (60/80 mesh), representing approximately 28–30% of the total granule mass. These results indicate that the wet granulation process successfully produced predominantly medium-sized granules with a relatively narrow particle size distribution. The proportion of coarse granules (>841 μm) remained low, ranging from approximately 2–3%, suggesting effective sieving and minimal agglomeration during granule preparation. Likewise, the fine particle fraction (<149 μm) ranged from 3.72% to 5.19%, which is considered acceptable for maintaining good flowability and reducing excessive interparticle cohesion (Ermis *et al*., 2018). The presence of a limited amount of fine particles is important because an excessive proportion of fines may impair flow properties and increase the risk of particle segregation during handling, processing, and packaging (Amidon *et al*., 2017).

The median particle size (d50) values ranged from 305 μm in formulation F4 to 328 μm in formulation F6. Formulation F4, which contained the lowest superdisintegrant concentration, exhibited the smallest median particle size (305 μm), while formulation F6 with the highest superdisintegrant concentration showed the largest median particle size (325 μm). This trend suggests that increasing superdisintegrant concentration may slightly increase the median particle size, possibly due to enhanced interparticle bonding during the granulation process (Umurona, 2020).

One-way ANOVA demonstrated a statistically significant effect of the crospovidone–sodium starch glycolate (SSG) ratio on particle size distribution parameters ($p < 0.05$). Subsequent Tukey's post hoc analysis revealed significant differences in several particle size fractions as well as in the d50 values among the formulations. The d50 values ranged from 305 μm (F4) to 328 μm (F6), indicating

that variations in the crospovidone–SSG ratio influenced granule size distribution. Significant differences were also observed in the dominant particle fractions (250–420 μm and 177–250 μm), although all formulations remained predominantly within the medium-sized granule range. Despite these statistical differences, the overall particle size distributions were relatively narrow and uniform, suggesting that all formulations produced granules with acceptable size characteristics suitable for pharmaceutical processing.

Table 4. Particle Size Distribution of Diclofenac Sodium ODGs

Mesh Size	Sieve Opening (μm)	Percentage Retained (%), Mean ± SD					
		F1	F2	F3	F4	F5	F6
>20	>841	2.34 ± 0.45^{ab}	2.18 ± 0.38^{b}	2.51 ± 0.52^{ab}	2.05 ± 0.41^{b}	2.62 ± 0.55^{a}	2.78 ± 0.49^{a}
20/40	420-841	15.67 ± 1.23^{ab}	14.92 ± 1.45^{b}	16.23 ± 1.67^{ab}	14.28 ± 1.52^{b}	16.45 ± 1.71^{a}	16.89 ± 1.63^{a}
40/60	250-420	38.45 ± 2.31^{ab}	39.21 ± 2.54^{a}	37.86 ± 2.62^{ab}	40.12 ± 2.43^{a}	37.54 ± 2.71^{b}	36.92 ± 2.58^{b}
60/80	177-250	28.73 ± 1.89^{ab}	29.14 ± 2.01^{a}	28.31 ± 2.15^{ab}	29.58 ± 1.94^{a}	28.12 ± 2.23^{b}	27.65 ± 2.14^{b}
80/100	149-177	10.56 ± 1.12^{ab}	10.83 ± 1.24^{a}	10.21 ± 1.35^{ab}	11.04 ± 1.18^{a}	10.08 ± 1.41^{ab}	9.76 ± 1.32^{b}
<100	<149	4.25 ± 0.67^{ab}	3.72 ± 0.58^{b}	4.88 ± 0.73^{ab}	3.93 ± 0.62^{b}	5.19 ± 0.81^{a}	6.00 ± 0.85^{a}
Total		**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
d50 (μm)		312^{ab}	308^{b}	318^{ab}	305^{b}	322^{a}	328^{a}

*Same letter indicates no significant difference ($p > 0.05$). Different letters indicate significant difference ($p < 0.05$).

From a mechanistic perspective, particle size in wet granulation is primarily governed by granulation parameters and the binding properties of the filler–binder system rather than minor compositional adjustments. Microcrystalline cellulose (MCC) and mannitol, serving as the principal structural components, likely played a dominant role in granule formation and stabilization (Miljković *et al.*, 2024). Within the studied concentration window, the superdisintegrants did not significantly alter granule growth dynamics or breakage behavior during processing.

Moreover, medium-sized granules (approximately 300 μm) are generally associated with improved flowability due to reduced surface area-to-volume ratio and lower cohesive forces compared to finer particles (Esmail, 2022). The relatively uniform PSD across formulations is consistent with the previously observed flow rate and angle of repose results, confirming stable and reproducible physical characteristics.

Density and Compressibility

Bulk density, tapped density, Carr's Index, and Hausner's ratio are essential parameters for evaluating granule flowability and interparticle cohesiveness. These

parameters provide insight into packing behavior, compressibility, and handling performance during manufacturing (Dewi *et al*., 2025). The results of density and compressibility evaluation for six formulations of diclofenac sodium ODGs with varying superdisintegrant concentrations are presented in Table 5.

Table 5. Density and Compressibility Parameters of Diclofenac Sodium ODGs

Formula	Bulk Density (g/mL) Mean ± SD	Tapped Density (g/mL) Mean ± SD	Carr's Index (%) Mean ± SD	Hausner's Ratio Mean ± SD	Flow Property Category*
F1	0.48 ± 0.03	0.55 ± 0.04	12.73 ± 1.85[a]	1.15 ± 0.03	Good
F2	0.49 ± 0.02	0.56 ± 0.03	12.50 ± 1.64[ab]	1.14 ± 0.02	Good
F3	0.46 ± 0.04	0.53 ± 0.05	13.21 ± 2.12[abc]	1.15 ± 0.04	Good
F4	0.50 ± 0.02	0.57 ± 0.03	12.28 ± 1.58b[c]	1.14 ± 0.02	Good
F5	0.45 ± 0.03	0.52 ± 0.04	13.46 ± 1.96[c]	1.16 ± 0.03	Good
F6	0.44 ± 0.04	0.51 ± 0.05	13.73 ± 2.08[c]	1.16 ± 0.04	Good

Flow property categories based on Carr's Index: 5-15% (excellent/good), 12-16% (good), 18-21% (fair), >23% (poor); and Hausner's Ratio: <1.25 (good), 1.25-1.5 (moderate), >1.5 (poor) (Sarfraz *et al*., 2015).

Based on Table 5, the bulk density of the granules ranged from 0.44 ± 0.04 to 0.50 ± 0.02 g/mL, while the tapped density ranged from 0.51 ± 0.05 to 0.57 ± 0.03 g/mL. The difference between bulk and tapped density indicates particle rearrangement during tapping and reflects the packing ability of the granules. The relatively narrow ranges of bulk and tapped density values across formulations suggest that variations in the crospovidone-sodium starch glycolate (SSG) ratio had only a limited effect on the overall packing characteristics of the granules (Apeji *et al*., 2019).

One-way ANOVA revealed a significant effect of the crospovidone–SSG ratio on Carr's Index values ($p < 0.05$). Tukey's post hoc analysis showed significant differences among several formulations, with F5 and F6 exhibiting higher Carr's Index values than some of the other formulations. Nevertheless, all Carr's Index values remained within the range of 12.28–13.73%, which is classified as good flowability according to standard pharmaceutical criteria. Similarly, Hausner's Ratio values ranged from 1.14 to 1.16 for all formulations, indicating good flow properties and low interparticle friction.

Overall, these findings suggest that variations in the crospovidone–SSG ratio influenced the compressibility characteristics of the granules, as reflected by the significant differences in Carr's Index. However, the magnitude of these differences was relatively small, and all formulations maintained good flowability based on both

Carr's Index and Hausner's Ratio values, demonstrating suitable physical characteristics for pharmaceutical manufacturing and further processing.

Moisture Content

influences flowability, stability, compressibility, and disintegration performance. Excessive residual moisture may promote particle cohesion, affect powder flow, and potentially compromise product stability, whereas insufficient moisture may reduce granule integrity (Asyiva *et al*., 2024). The moisture content results of diclofenac sodium orally disintegrating granules (ODGs) are presented in Table 6.

Table 6. Moisture Content of Diclofenac Sodium ODGs

Formula	Moisture Content (%), Mean ± SD
F1	2.54 ± 0.18^{a}
F2	2.48 ± 0.15^{a}
F3	2.67 ± 0.22^{bc}
F4	2.41 ± 0.14^{a}
F5	2.73 ± 0.20^{b}
F6	2.81 ± 0.24^{b}

*Same letter indicates no significant difference ($p > 0.05$). Different letters indicate significant difference ($p < 0.05$).

Based on the data presented in Table 6, all formulations exhibited moisture content values within a relatively narrow range, from 2.41 ± 0.14% (F4) to 2.81 ± 0.24% (F6), indicating adequate drying during the wet granulation process. Since the total superdisintegrant concentration was maintained constant across all formulations, the observed differences in moisture content may be attributed to variations in the crospovidone-sodium starch glycolate (SSG) ratio. The different proportions of these superdisintegrants may influence water retention during granulation and drying due to their distinct hydration and swelling characteristics. Nevertheless, the relatively low standard deviation values (0.14–0.24%) indicate good reproducibility of the drying process and consistent granule quality across all formulations.

Formulation F4 exhibited the lowest moisture content (2.41%), while formulation F6 showed the highest moisture content (2.81%). This variation suggests that superdisintegrant ratio may influence the water retention capacity of the granules during the drying process. Superdisintegrants such as sodium starch glycolate and crospovidone have the ability to absorb and retain water due to their hydrophilic nature and swelling properties (Kumar, 2016). Higher concentrations of superdisintegrant may lead to increased water uptake during the granulation step and greater moisture retention after drying, as observed in formulations F5 and F6 which contained the highest superdisintegrant concentrations among the tested formulations. This trend is clearly visible, with moisture content increasing progressively from F4 (2.41%) to F5 (2.73%) to F6 (2.81%), corresponding to increasing superdisintegrant concentrations.

One-Way ANOVA showed that the crospovidone–sodium starch glycolate (SSG) ratio significantly affected the moisture content of the granules ($p < 0.05$). Tukey's post hoc test indicated that F1, F2, and F4 were not significantly different from each other, whereas F5 and F6 exhibited significantly higher moisture content. F3 showed intermediate values and did not differ significantly from either group. These results suggest that variations in the crospovidone–SSG ratio influenced moisture retention during the granulation and drying processes. However, all formulations exhibited moisture contents within a narrow range (2.41–2.81%), indicating adequate drying and acceptable moisture levels for pharmaceutical granules.

Controlled moisture content is particularly important in orally disintegrating systems, as excess moisture may accelerate degradation reactions or affect mechanical stability during storage (Kashiwagura *et al*., 2023). The relatively narrow moisture range observed across formulations indicates consistent drying efficiency and suggests that the wet granulation and drying conditions were well optimized.

Evaluation of Disintegration Time

Disintegration time is the most critical parameter in the development of Orally Disintegrating Granules, as it directly reflects the ability of the formulation to rapidly break down upon contact with saliva in the oral cavity. This parameter is essential for ensuring patient compliance and therapeutic efficacy, particularly for individuals with swallowing difficulties such as pediatric, geriatric, and dysphagic patients (Umurona, 2020). According to pharmacopoeial standards, orally disintegrating dosage forms should disintegrate within 30 seconds according to the United States Pharmacopeia (USP) or within 180 seconds according to the European Pharmacopeia (Bafail, 2024).The disintegration time of diclofenac sodium orally disintegrating granules (ODGs) is presented in Table 7.

Table 7. Disintegration Time of Diclofenac Sodium ODGs

Formula	Disintegration Time (seconds), Mean ± SD
F1	28.45 ± 2.31^{b}
F2	24.72 ± 1.98^{ab}
F3	32.16 ± 2.65^{bc}
F4	21.38 ± 1.74^{a}
F5	35.83 ± 2.92^{c}
F6	38.47 ± 3.14^{c}

*Same letter indicates no significant difference ($p > 0.05$). Different letters indicate significant difference ($p < 0.05$).

Based on the data presented in Table 6, all formulations showed disintegration times within the acceptable range for orally disintegrating dosage forms, with values ranging from 21.38 ± 1.74 seconds (F4) to 38.47 ± 3.14 seconds (F6). All formulations met the European Pharmacopeia requirement of disintegration within 180 seconds, and formulations F1, F2, and F4 also satisfied the more stringent USP requirement of disintegration within 30 seconds.

Formulation F4 exhibited the fastest disintegration time (21.38 seconds), whereas formulation F6 showed the slowest disintegration time (38.47 seconds). These results

indicate that the ratio of crospovidone to sodium starch glycolate (SSG), rather than the total superdisintegrant concentration, played an important role in determining the disintegration performance of the granules. The superior performance of F4 suggests that a balanced combination of crospovidone and SSG provided the most effective disintegration, while other ratios resulted in slower disintegration. This finding is consistent with the complementary mechanisms of crospovidone and SSG, which promote rapid disintegration through wicking, swelling, and water uptake within the granule matrix (Berardi *et al*., 2022).

One-Way ANOVA showed that the crospovidone–sodium starch glycolate (SSG) ratio significantly affected the disintegration time of diclofenac sodium ODGs ($p < 0.05$). Tukey's post hoc test further revealed significant differences among several formulations. Formulation F4 exhibited the shortest disintegration time and differed significantly from F5 and F6, which showed the longest disintegration times. Formulations F1, F2, and F3 exhibited intermediate values and were not significantly different from some adjacent groups. These results indicate that the ratio of crospovidone to SSG played a critical role in determining disintegration performance. The superior performance of F4 suggests that a balanced ratio of the two superdisintegrants produced a synergistic effect, resulting in faster water uptake and more efficient granule disintegration.

Mechanistically, superdisintegrants promote tablet or granule breakup through swelling, wicking, or a combination of both mechanisms. Crospovidone primarily acts through capillary action (wicking), rapidly facilitating water penetration into the porous structure without forming a viscous gel. In contrast, SSG disintegrates mainly by swelling, which may be influenced by concentration-dependent gel layer formation at higher levels (Hanpramukkun *et al.*, 2025).

Conclusion

The crospovidone-sodium starch glycolate (SSG) ratio significantly influenced the physical characteristics and disintegration performance of diclofenac sodium orally disintegrating granules (ODGs). Among the tested formulations, F4 (crospovidone ratio of 1:1) provided the most favorable balance between rapid disintegration and acceptable physical properties. The findings demonstrate that optimizing the ratio of complementary superdisintegrants is an effective strategy for improving ODG performance. Therefore, the F4 formulation represents a promising candidate for further development of patient-friendly diclofenac sodium ODGs, particularly for populations with swallowing difficulties.

Declaration of Competing Interest

The authors declare that they have no competing interests

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