

Formulation development of diclofenac sodium extended-release tablet using hydrophobic and hydrophilic matrix systems

Truc-ly Thi Duong¹✉, Duyen Thi My Huynh², Tu-Uyen Thi Nguyen^{3,4}, Quoc-Dung Tran Huynh⁵, Thuy-Tien Thi Phan^{5,6}, Thu-Thi Tran¹, Ha Van Nguyen⁷, Benni Iskandar⁸, Dang-Khoa Nguyen^{7*} 

¹Faculty of Traditional Medicine, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam.

²Faculty of Pharmacy, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam.

³Faculty of Pharmacy, Ton Duc Thang University, Ho Chi Minh City, Vietnam.

⁴Quality Assurance Department, Pymepharco Joint Stock Company, DakLak, Vietnam.

⁵Institute of Pharmaceutical Education and Research, Binh Duong University, Ho Chi Minh City, Vietnam.

⁶Graduate Institute of Biomedical Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan.

⁷School of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam.

⁸Department of Pharmaceutical Technology, Riau College of Pharmaceutical Sciences (STIFAR), Riau, Indonesia.

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ABSTRACT

This study aimed to develop diclofenac sodium sustained-release tablets using different matrix systems and to evaluate their physicochemical properties. Diclofenac sodium was characterized for solubility, flowability, and particle size. Solubility in water and phosphate buffer (pH 7.5) was determined by UV-Vis spectrophotometry, while flowability was assessed via angle of repose, Hausner ratio, and Carr's index. Product X SR 75 mg tablets were analyzed as a reference for uniformity, hardness, and dissolution. Two matrix approaches were explored: a hydrophobic system (carnauba wax and cetyl alcohol) via melt granulation and a hydrophilic system (Arabic gum) via direct compression. The research results indicate that diclofenac sodium exhibited slight solubility and poor flowability. Formulations based on both hydrophobic and hydrophilic systems were developed, meeting the physical, quantitative, and dissolution criteria of the United States Pharmacopeia (USP). The formulation exhibited a drug release profile in USP pH 7.5 medium equivalent to that of the reference product, Product X SR 75. The hydrophobic matrix formulations followed zero-order release kinetics, whereas the hydrophilic matrix formulations followed the Higuchi release model and showed stability over 3 months under accelerated and long-term aging conditions. Hydrophobic matrices provided a more sustained drug release compared to hydrophilic matrices. Both systems effectively modulated drug release, indicating their potential for once-daily extended-release diclofenac formulations.

1. INTRODUCTION

Since the 1970s, diclofenac sodium has been recognized as an effective anti-inflammatory, analgesic, and antipyretic agent with a high therapeutic index. Despite its therapeutic benefits, diclofenac sodium is associated with adverse effects,

including gastric ulceration and renal impairment. Additionally, its short plasma half-life of approximately 1–2 hours necessitates multiple daily doses when using conventional formulations. This frequent dosing regimen increases the likelihood of missed doses and reduces patient compliance, ultimately affecting therapeutic outcomes [1].

Extended-release (ER) formulations of diclofenac sodium, such as Dicloflex[®] 75 mg SR, Diclomax[®] Retard, and Voltaren[®] SR 75 mg, offer significant advantages over conventional formulations. These formulations allow for once-daily dosing, improving patient adherence and reducing the risk of missed doses. Furthermore, they enhance bioavailability,

*Corresponding Author

Dang-Khoa Nguyen, School of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam. E-mail: ndkhoa@ump.edu.vn

✉These authors contributed equally to this work.

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reduce systemic side effects associated with peak plasma concentrations, and lower the total drug dosage required for effective treatment. As a result, there is increasing interest in developing ER formulations to optimize the therapeutic efficacy of diclofenac sodium while minimizing its adverse effects [2,3].

Two matrix systems were explored in this research. The first is an erodible hydrophobic matrix, which utilizes waxes and fatty excipients to regulate drug release through erosion or slow diffusion. This matrix is typically prepared using hot-melt granulation techniques. The second system is a soluble hydrophilic matrix, comprising high molecular weight hydrophilic polymers that swell and form gels to modulate drug release. These matrices are generally prepared using direct compression or wet granulation methods [4,5]. Previous studies have demonstrated the potential of waxes such as carnauba wax and hydrophilic polymers like Arabic gum for achieving controlled drug release. However, there is a lack of comparative investigations directly evaluating hydrophobic matrix systems (cetyl alcohol and carnauba wax) versus hydrophilic matrix systems (Arabic gum) for the same active pharmaceutical ingredient (diclofenac sodium) under standardized experimental conditions. Moreover, the influence of excipient ratios on drug release performance and the underlying kinetic mechanisms remains poorly understood.

This study builds upon existing research to formulate and ensure the quality of extended-release diclofenac sodium tablets, with an emphasis on scalability and clinical applicability. The objective is to develop matrix-based systems capable of controlling drug release, elucidating the underlying release kinetics, and ultimately improving patient outcomes.

2. MATERIALS AND METHODS

2.1. Materials

Diclofenac sodium ($\geq 98\%$ purity) was used as the active pharmaceutical ingredient (API), sourced from a certified supplier and tested for purity. To achieve extended release, both hydrophilic and hydrophobic matrix systems were used. Cetyl alcohol, carnauba wax, and Arabic gum ensured controlled release. Microcrystalline cellulose (MCC) provided structural integrity, polyvinylpyrrolidone (PVP K30) acted as a binder, talc improved powder flow, and magnesium stearate (0.5%–1%) reduced friction during compression. Ethanol and water were used for wet granulation. A rotary tablet press was used for compression, and dissolution testing followed the United States Pharmacopeia (USP) Type II. All materials were pharmaceutical grade.

2.2. Characterization of API and reference product

2.2.1. Solubility, flowability, and particle size of API

Solubility in water; a stock solution of diclofenac sodium (1,000 $\mu\text{g/ml}$) was prepared by dissolving 25 mg of API in 15 ml of 96% ethanol, sonicating for 20 minutes, cooling, and diluting to 25 ml with ethanol. A standard solution (20 $\mu\text{g/ml}$) was obtained by diluting 1 ml of stock to 50 ml with distilled water. For solubility testing, ~ 0.5 g of diclofenac sodium was added to 15 ml of distilled water at $25^\circ\text{C} \pm 2^\circ\text{C}$, stirred intermittently over

30 minutes, then filtered through a 0.45 μm PTFE membrane. The filtrate was diluted with water to match the absorbance of the standard solution. The maximum absorbance wavelength was determined by scanning 200–400 nm using UV-Vis spectrophotometry with distilled water as a blank. Absorbance measurements of the standard and test solutions were used to calculate the saturation solubility and the volume of water required to dissolve 1 g of diclofenac sodium [6].

Solubility in phosphate buffer; phosphate buffer (0.05 M, pH 7.5) was prepared by mixing 85 ml of 11.93% disodium hydrogen phosphate and 15 ml of 4.54% potassium dihydrogen phosphate solutions, adjusting pH as needed, and diluting to 660 ml with distilled water. A standard solution (20 $\mu\text{g/ml}$) was prepared by diluting 1 ml of diclofenac sodium stock solution (1,000 $\mu\text{g/ml}$) to 50 ml with buffer. For testing, ~ 0.5 g of API was added to 15 ml of buffer at $25^\circ\text{C} \pm 2^\circ\text{C}$, agitated periodically, filtered, and diluted to match the standard's absorbance. Saturation solubility and the volume of buffer required to dissolve 1 g of API were determined by UV-Vis spectrophotometry at the maximum absorbance wavelength [6].

The saturation concentration of diclofenac sodium was calculated using the formula:

$$C_s = \frac{A_t}{A_{\text{stand.}}} \times C_{\text{stand.}} \times n$$

where:

C_s : saturation concentration of diclofenac sodium ($\mu\text{g/ml}$)

$C_{\text{stand.}}$: concentration of the standard solution ($\mu\text{g/ml}$)

A_t : absorbance of the test solution

$A_{\text{stand.}}$: absorbance of the standard solution

n : dilution factor

Solubility results were interpreted based on the classification system of the United States Pharmacopeia [7].

Flowability Assessment of Powder Materials, the flowability of the powder materials was evaluated using three key parameters: the angle of repose (θ), the Hausner ratio (HR), and Carr's index (CI). These indices provide insights into the cohesiveness, compressibility, and overall flow characteristics of the powder [8].

The angle of repose was determined using the fixed funnel method. The powder was allowed to freely flow through a funnel onto a flat surface until a stable conical pile was formed. The angle of repose (θ) was calculated using the following equation:

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

where:

h is the height of the powder cone (cm),

r is the radius of the base of the cone (cm).

An angle of repose below 30° generally indicates good flowability, while values above 40° suggest poor flowability.

The Hausner ratio was calculated as an indicator of powder cohesiveness and potential for densification. The ratio was determined using bulk and tapped density measurements:

$$HR = \frac{\rho_t}{\rho_b}$$

where:

ρ_t is the tapped density (g/cm³),

ρ_b is the bulk density (g/cm³).

A Hausner ratio close to 1.00 indicates excellent flowability, while values above 1.25 suggest high cohesiveness and poor flow properties.

Carr's index, also known as the compressibility index, was used to assess the powder's ability to pack under pressure. It was calculated as follows:

$$CI = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

where:

ρ_t is the tapped density (g/cm³),

ρ_b is the bulk density (g/cm³).

Carr's index values below 10% indicate excellent flowability, while values above 25% suggest poor flow properties. Each test was performed in triplicate, and the results were expressed as mean $\pm$ standard deviation.

2.2.2. Reference drug testing

Product X SR 75 mg tablets contain 75 mg of diclofenac sodium and excipients including carnauba wax, cetyl alcohol, cellulose derivatives, sucrose, magnesium stearate, povidone, talc, hypromellose, colloidal silicon dioxide, titanium dioxide, polysorbate 80, and iron oxide. The product was manufactured in December 2018, with an expiration date of November 2021 (Batch No. TW487). It is packaged in a box of 10 blisters, each containing 10 tablets. The manufacturer is Novartis Farmaceutica, S.A., Switzerland.

Evaluation was conducted on the Product X SR 75 mg film-coated tablets to evaluate appearance, mass uniformity, hardness, and dissolution. The tablets were visually inspected for size and thickness, and the mass uniformity was assessed by weighing 20 tablets. Hardness was measured for 20 tablets [9].

2.3. Development of tablet formulations

2.3.1. Erodible hydrophobic matrix system development

Tablets were formulated using carnauba wax and cetyl alcohol as matrix-forming agents through melt granulation. The process involved mixing diclofenac sodium, carnauba wax, and cetyl alcohol at high temperatures to create a uniform granulate, followed by compression into tablets. The detailed process was illustrated in Figure 1. The optimized formulation was evaluated for weight uniformity, hardness, friability, and dissolution.

2.3.2. Soluble hydrophilic matrix system development

Tablets were prepared using Arabic gum as matrix-forming excipients by direct compression. The detailed process was illustrated in Figure 2. Each formulation was assessed for physical properties, including weight uniformity and friability. The Arabic gum formulation exhibited dissolution variability across batches due to uneven distribution of excipients, while

the HPMC-based formulation achieved consistent friability at 15% concentration but required further optimization for dissolution control.

2.4. Quality control of intermediate products

2.4.1. Quality control of finished granules, semi-finished product

The flowability of the finished granules was evaluated based on parameters such as the angle of repose, Hausner ratio, and Carr's index. If the granules demonstrated excellent/good/average flowability and compressibility, tablet compression was performed. If the granules showed poor flowability and compressibility, the formulation was improved.

The quality control of the semi-finished product was carried out by evaluating various parameters. Sensory inspection was performed using visual observation and measuring the tablet diameter. The uniformity of mass was assessed by weighing 20 randomly selected tablets, and the average mass was determined. Hardness was measured for 20 randomly selected tablets, and the results were recorded.

Friability was tested by weighing 20 tablets before and after friability testing, and the change in weight was calculated using the formula [10]:

$$\text{Friability (\%)} = (m_b - m_a) / m_b \times 100,$$

where m_b is the mass of the tablet before testing, and m_a is the mass after testing.

2.4.2. Dissolution and drug release kinetics analysis

Dissolution was evaluated by constructing a standard curve for diclofenac sodium in 0.05 M phosphate buffer at pH 7.5. The dissolution test used a paddle-type apparatus with 900 ml of dissolution medium, and absorbance was measured at 276 nm. Samples were taken at 1, 2, 4, 6, 8, and 10 hours, filtered, and diluted for UV-Vis spectrophotometry. The release of the active ingredient was calculated based on the standard curve, and a dissolution profile was plotted to select the optimal formulation [9].

Cumulative drug release (%) was calculated from the calibration curve, corrected for sample withdrawal, and plotted against time. The mean dissolution profile was fitted to zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models using linear regression. Model fit was evaluated by correlation coefficient (R^2), and the best-fitting model was selected. For Korsmeyer-Peppas, the release exponent (n) was used to interpret the release mechanism [11].

2.4.3. Assay analysis

A standard solution (10 μ g/ml) was prepared by dissolving 50 mg of diclofenac sodium in 100 ml of distilled water, followed by sonication for 20 minutes. After cooling, the solution was filtered through a 0.45 μ m PTFE membrane and diluted as necessary. Similarly, the sample was prepared by grinding 20 tablets (removing any coating) and accurately weighing 50 mg of the powdered tablet. The solution was prepared and processed in the same manner as the standard. Absorbance was measured at 282 nm, with 96% ethanol as a

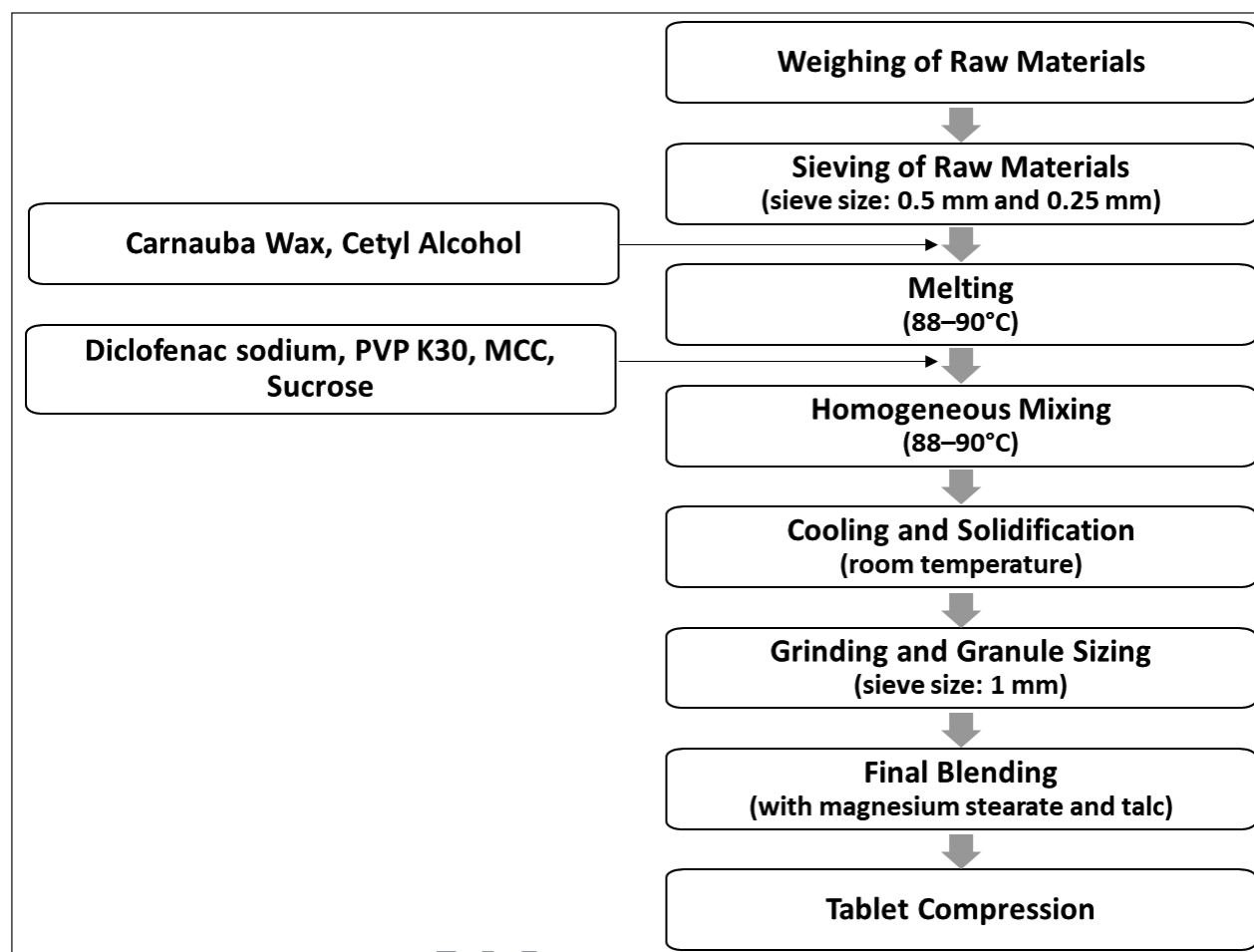


Figure 1. Diclofenac sodium tablet manufacturing - erodible hydrophobic matrix system.

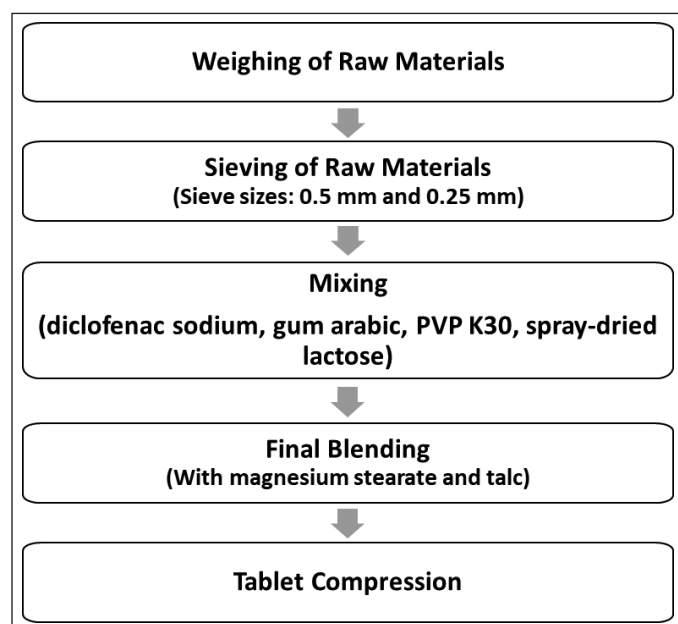


Figure 2. Diclofenac sodium tablet manufacturing - soluble hydrophilic matrix system.

blank. The average diclofenac sodium content in the tablets was calculated using the formula:

$$\text{Average content (\%)} = \left(\frac{A_t}{A_c} \right) \times \left(\frac{m_c}{m_t} \right) \times \left(\frac{m_{\text{aver.}}}{m_{\text{label}}} \right) \times 100$$

where A_t is the absorbance of the sample, A_c is the absorbance of the standard, m_c is the mass of the standard, m_t is the mass of the sample powder, $m_{\text{aver.}}$ is the average mass of 20 tablets, and m_{label} is the labeled diclofenac content (75 mg).

Dissolution testing was performed similarly to the Product X SR 75 mg film-coated tablets. Samples were considered to meet the standard if the dissolution profile met the criteria outlined in USP, with further testing performed if the results did not meet the required specifications.

2.4.4. Evaluation of stability under long-term and accelerated conditions

Formulations that comply with the initial quality requirements will be subjected to stability monitoring under accelerated conditions ($40^\circ\text{C} \pm 2^\circ\text{C}$ / 75% RH $\pm$ 5%) and long-term conditions ($30^\circ\text{C} \pm 2^\circ\text{C}$ / 75% RH $\pm$ 5%) in Vietnam, which is classified as Climatic Zone IVb according to the

WHO stability testing guidelines (TRS 953—Annex 2) [12]. Appearance, dissolution, and drug content are used to assess the product quality at various time points during the stability monitoring process. The aim is to provide initial scientific data to ensure that the product maintains its quality, efficacy, and safety.

2.5. Statistical analysis

The statistical analysis of diclofenac sodium tablets involved evaluating quality control parameters such as mass uniformity, hardness, friability, and dissolution profiles. Descriptive statistics (mean, standard deviation, and range) were calculated to assess consistency and variability. For dissolution testing, the percentage of active ingredient released at various time points was compared to the established criteria. Regression analysis was used to determine the relationship between time and active ingredient release, with the R^2 calculated to assess data fit. Deviations from the expected profile were noted, and adjustments to the formulation or process were considered. For content quantification, the absorbance values of the samples were compared to the standard, and the average content was calculated as a percentage of the labeled content (75 mg). This approach ensured the tablets met the required standards for potency and dissolution.

3. RESULTS AND DISCUSSIONS

3.1. Active pharmaceutical ingredient properties

3.1.1. Solubility in water, phosphate buffer pH 7.5

UV-Vis spectroscopic analysis revealed that the standard solutions of diclofenac sodium in water and in 0.05 M phosphate buffer (pH 7.5) exhibited maximum absorbance peaks at 275.80 nm and 275.82 nm, respectively. Consequently, a wavelength of 276 nm was selected for solubility determination in both media. The solubility results are summarized in Table 1.

Diclofenac sodium demonstrated a solubility of 20.6 mg/ml in water, consistent with the value reported by Žilnik *et al.* [13] (20.4 mg/ml). For extended-release systems, drugs with solubility classified between slightly soluble and sparingly soluble are generally preferred to balance release control and bioavailability [14,15]. Thus, the solubility findings support

the suitability of diclofenac sodium for the development of extended-release formulations.

3.1.2. Flowability and particle size distribution (PSD)

The flowability of diclofenac sodium is summarized in Table 3. The percentage of diclofenac sodium retained on each sieve size is shown in Figure 3. Flowability is a critical factor in the formulation design of tablets; the flowability of powders is assessed by determining the Hausner Ratio and Carr's Index [8,16]. The particle size distribution analysis shows that the majority of the sample (70.37%) consists of particles smaller than 90 μm , indicating a predominantly fine powder, which may enhance the homogeneity of powder blends but could potentially affect flowability during processing [17]. The flowability assessment of diclofenac sodium indicates relatively poor flow properties. The angle of repose was measured at 43.26°, which is categorized as poor flowability according to standard classifications. The Hausner ratio of 1.38 and Carr's index of 27.42% further support this observation, as values above 1.25% and 25%, respectively, typically indicate poor powder flow. These results suggest that diclofenac sodium may present challenges during direct compression tablet manufacturing and may require flow-improving strategies, such as granulation or the use of suitable flow enhancers [18–20].

3.2. Results of reference drugs

3.2.1. Appearance evaluation, mass uniformity, and hardness

The appearance of Product X SR 75 mg film-coated tablets is shown in Figure 4. The tablets are pink, triangular with two convex sides, marked “ID” on one side and “CG” on the other. Each tablet measures approximately 9 mm in length and 2 mm in thickness. Mass uniformity and hardness results are summarized in Table 4. Characterizing the morphology and physical properties of the reference product provides guidance for tablet design to achieve the desired release profile [21].

3.2.2. Dissolution analysis

The absorbance data and linear regression curve for diclofenac sodium in 0.05 M phosphate buffer (pH 7.5) are shown in Figure 5. Statistical analysis using MS Excel indicated that $F = 7165.50 > F_{0.05} = 7.71$, confirming the model's

Table 1. Solubility of diclofenac sodium in water and 0.05 M phosphate buffer at pH 7.5.

Buffer	No.	A _{stand.}	C _{stand.} (µg/ml)	A _{test}	n	C _{saturation} (µg/ml)	V (ml) dissolved 1 g	
Water	1	0.646	20.096	0.655	1,000	20,375.83	49.08	
	2	0.644	20.216	0.652		20,488.20	48.81	
	3	0.633	19.984	0.662		20,899.02	47.87	
	Average value					20.6 mg/ml	48.59	
	Evaluation						Slightly soluble	
Phosphate buffer pH 7.5	1	0.648	20.128	0.686	500	10,654.17	93.86	
	2	0.655	20.256	0.679		10,493.95	95.29	
	3	0.625	19.952	0.682		10,874.69	91.96	
	Average value					10.7 mg/ml	93.70	
	Evaluation						Slightly soluble	

compatibility. The intercept was not significant ($|t_0| = 2.07 < t_{0.05} = 2.78$), while the slope was highly significant ($|t_1| = 84.65 > t_{0.05} = 2.78$). The resulting regression equation, $y = 0.0326x$

Table 2. The ratio of ingredients of diclofenac sodium tablet formulas.

Ingredients	F1 (%)	F2 (%)	F3 (%)	F4 (%)
Diclofenac sodium	25.00	25.00	25.00	25.00
Carnauba wax	11.67	11.67	11.67	11.67
Cetyl alcohol	5.00	5.00	10.00	15.00
PVP K30	15.00	10.00	10.00	10.00
MCC	21.66	21.66	21.66	21.66
Sucrose	20.00	25.00	20.00	15.00
Talc	1.00	1.00	1.00	1.00
Magnesium stearate	0.67	0.67	0.67	0.67
Tablet weight (mg)	300			

Table 3. The results of flowability for API and formulas F1, F2, F3, F4, FG1, FG2.

No.	Parameter	API	F1	F2	F3	F4	FG1	FG2
1	Angle of repose (°)	43.26°	26.95°	27.64°	25.92	26.73	27.34	27.12
2	Bulk density (g/ml)	0.45	0.49	0.46	0.48	0.49	0.39	0.42
3	Tapped density (g/ml)	0.62	0.54	0.52	0.54	0.53	0.45	0.48
4	Hausner ratio	1.38	1.10	1.13	1.13	1.08	1.15	1.14
5	Carr's index (%)	27.42	9.26	11.54	11.11	7.55	13.33	12.50

($R^2 = 0.9994$), demonstrated excellent linearity and accuracy for quantifying diclofenac sodium within the tested range.

The dissolution results and profile of Product X SR 75 mg tablets are presented in Table 5 and Figure 5. The reference product met USP dissolution criteria, providing a scientific foundation for developing formulations aimed at achieving *in vitro* dissolution equivalence, a critical requirement for bioequivalence studies [22].

3.3. Development of tablet formulations

3.3.1. Erodible hydrophobic matrix system development

Based on the composition of Product X SR 75 mg film-coated tablets, formulate diclofenac sodium extended-release tablets using the melt granulation method, incorporating a combination of carnauba wax and cetyl alcohol as matrix-forming excipients.

Development of formulation, the studies were conducted to evaluate the binder excipient ratio of PVP K30 (formula 1 – PVP K30: 15.00%; formula 2 – PVP K30: 10.00%), the ratio of cetyl alcohol (formula 3 – cetyl alcohol: 10.00%; formula 4 – cetyl alcohol: 15.00%). Tablets for F1, F2, F3, and F4 were formulated according to the composition and proportions shown in Table 2, with each formulation prepared in a batch size of 300 tablets.

Inspection of the finished granules and semi-finished products, the test results of the finished granules for formulations F1, F2, F3, and F4 are presented in Table 3. All formulations (F1–F4) showed improved flowability, with angle of repose values ranging from 25.92° to 27.64°. F3 exhibited the lowest angle (25.92°), indicating the best flow. Similarly, all formulations had low Hausner ratio values (1.08–1.13) and consistent Carr's index results, further confirming enhanced flow properties [8,16,23]. These excipients, in combination

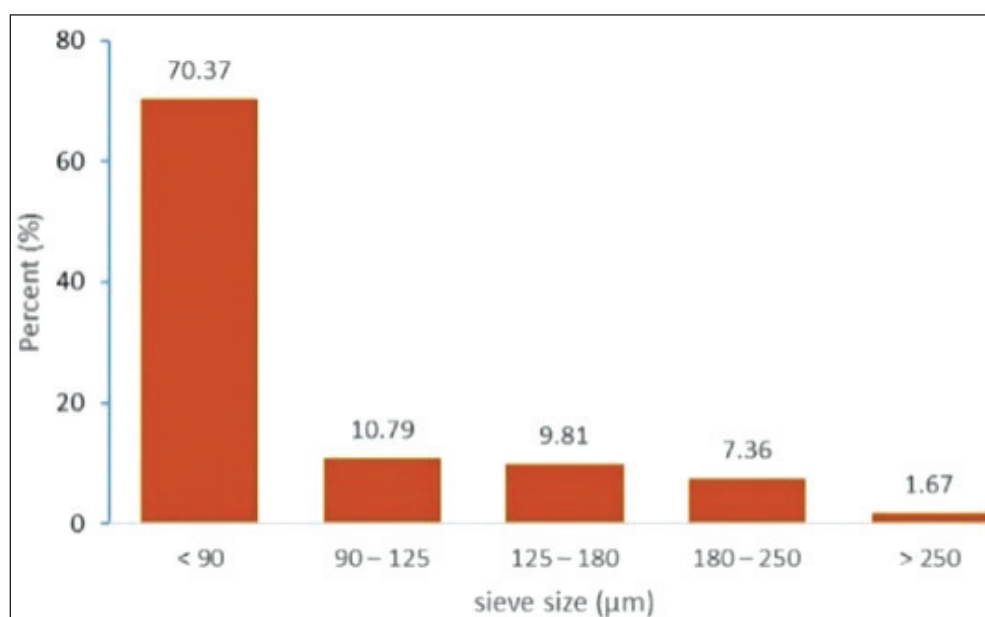


Figure 3. The PSD of diclofenac sodium ingredient.

with PVP K30 as a binder and other additives such as MCC and sucrose, were formulated into four different batches (F1, F2, F3, and F4) to evaluate the influence of excipient ratios on tablet properties and drug release characteristics. The variation in hardness and friability of the semi-finished tablets also remained within acceptable limits, ensuring tablet integrity during storage and handling [24]. Notably, the hardness values varied slightly, with formulation F1 showing the highest mean hardness (134.9 N) and F3 the lowest (125.6 N). These differences reflect the impact of excipient composition on the mechanical strength of the final tablets, which can affect the tablet's ability to withstand disintegration and erosion during dissolution [25,26].

The test results of the semi-finished products for formulations F1, F2, F3, and F4 are presented in Table 4. The weight variation analysis showed that the maximum and minimum values across all formulations remained within acceptable limits, with deviations of $\pm 4.27\%$ from the mean.

The dissolution of the tablets for F1, F2, F3, and F4 was shown in Table 5. The key factors in formulating controlled-release tablets are the selection of excipients, the drug release mechanisms, and the ability to maintain consistent therapeutic plasma levels over an extended period [27]. Formulation F1 exhibited the fastest drug release, with approximately 70% release at 4 hours and over 90% at 6 hours, but failed to meet acceptance criteria due to overly rapid release. Formulation F2 demonstrated moderate release, passing at all time points, with a more controlled release than F1, but still faster than Product X, especially at 6, 8, and 10 hours. F2 and F3 released the drug

faster than Product X, but both remained within acceptable limits. F3, with a higher cetyl alcohol concentration, was more similar to Product X, particularly after 4 hours. F4 showed a slower release profile compared to Product X at most time points, making it the closest to a controlled-release behavior. F3 released 85.26% of diclofenac sodium by 8 hours, while F4, with the highest cetyl alcohol content (15%), demonstrated the slowest release, highlighting the significant role of cetyl alcohol in modulating drug release [28,29]. Higher concentrations of cetyl alcohol, as seen in F4, seem to slow down the release of diclofenac sodium, which could be advantageous for achieving a prolonged therapeutic effect. Formulation F4 was best described by the zero-order kinetic model ($R^2 = 0.9724$). Analysis using the Korsmeyer–Peppas model ($R^2 = 0.9710$, $n = 0.7436$) indicated an anomalous transport mechanism (a combination of diffusion and erosion), consistent with the release behavior observed for the reference product ($R^2 = 0.9945$). Cetyl alcohol and carnauba wax, as hydrophobic matrix formers, limited water penetration and preserved tablet integrity during dissolution. The wax–alcohol network created tortuous diffusion pathways, while gradual pore formation sustained a uniform release [30].

3.3.2. Soluble hydrophilic matrix system development

Diclofenac sodium extended-release tablets were developed using Arabic gum as a matrix-forming excipient, with two formulations (FG1 and FG2) as shown in Table 6. Each batch consisted of 300 tablets. The evaluation results for the finished granules and semi-finished tablets are presented in Tables 3 and 4, respectively. FG1 exhibited the highest weight variation, ranging from 333.21 mg (-4.27%) to 361.85 mg ($+3.96\%$). Arabic gum, known for its solubility and ability to form hydrophilic networks, was selected to create a soluble matrix system allowing gradual drug release [31]. FG1 and FG2 differed in the proportions of Arabic gum, PVP K30, spray-dried lactose, and talc. Both formulations demonstrated acceptable flowability and compressibility, as indicated by appropriate Hausner ratios and Carr's indices.

The dissolution profiles of FG1 and FG2, shown in Table 5 and Figure 5, revealed significant differences due to varying Arabic gum concentrations. FG1, containing 42.86% Arabic gum, released 93.07% of the drug at 8 hours and 79.58%

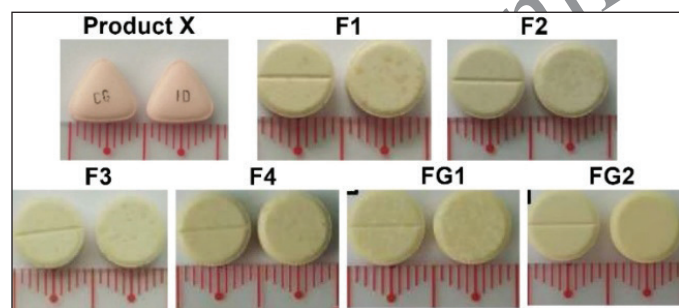


Figure 4. Appearances of Product X SR 75 mg tablet and formulas.

Table 4. Test results of refence drug and semi-finished tablets F1, F2, F3, F4, FG1, FG2.

Parameter		Product X	F1	F2	F3	F4	FG1	FG2
Average weight (mg)	Mean	231.68	303.74	302.32	302.93	300.78	348.07	355.34
	Max	233.09	310.28	308.45	305.52	306.13	361.85	358.69
		(+0.61%)	(+2.15%)	(+2.03%)	(+0.85%)	(+1.78%)	(+3.96%)	(+0.94%)
	Min	229.79	290.69	297.88	297.81	298.92	333.21	346.32
		(-0.82%)	(-2.98%)	(-1.47%)	(-1.69%)	(-0.61%)	(-4.27%)	(-2.53%)
Hardness (N)	Mean	126.4	134.9	132.5	125.6	130.4	153.2	177.1
	Max	141.4	145.8	140.6	139.8	139.2	189.6	182.9
	Min	117.2	123.6	117.3	109.2	117.5	106.2	143.5
Friability (%)		/	0.16	0.09	0.07	0.07	0.56	0.33
Assay (%)		/	/	/	/	97.60	/	98.71

Table 5. Dissolution results of product X, F1, F2, F3, F4, FG1 and FG2 tablets.

Formulas	No.	Diclofenac sodium released at each time point (%)					
		1 hour (≤ 28%)	2 hours (20%–40 %)	4 hours (35%–60 %)	6 hours (50%–80%)	8 hours (≥ 65%)	10 hours (≥ 65%)
Product X	Average	13.31	20.43	35.53	50.97	66.71	80.35
	Max	13.89	20.88	36.14	51.07	67.25	83.61
	Min	12.69	20.05	35.29	50.24	65.76	78.11
	RSD (%)	3.46	1.40	0.99	1.66	0.85	1.73
	Evaluation	Pass	Pass	Pass	Pass	Pass	Pass
F1	Average	24.39	39.70	70.21	92.15	98.80	No test
	Max	24.86	40.51	74.63	95.64	99.93	
	Min	23.89	39.13	65.43	89.15	97.41	
	RSD (%)	1.54	1.40	4.91	2.77	0.85	
	Evaluation	Pass	No pass	No pass	No pass	Pass	
F2	Average	20.79	30.87	51.33	74.75	86.13	No test
	Max	21.58	31.52	53.29	77.91	87.64	
	Min	19.44	30.03	48.79	72.80	84.67	
	RSD (%)	4.03	1.75	3.28	2.52	1.45	
	Evaluation	Pass	Pass	Pass	Pass	Pass	
F3	Average	20.19	29.17	49.17	65.98	85.26	No test
	Max	21.04	31.21	51.21	68.94	87.57	
	Min	19.59	27.62	47.17	62.27	81.41	
	RSD (%)	2.73	4.46	3.28	3.59	2.53	
	Evaluation	Pass	Pass	Pass	Pass	Pass	
F4	Average	17.65	26.17	43.28	54.69	76.61	85.72
	Max	19.31	27.23	44.56	56.74	79.94	89.52
	Min	16.70	24.83	41.38	51.52	72.82	82.54
	RSD (%)	5.27	3.48	3.27	4.33	3.57	2.20
	Evaluation	Pass	Pass	Pass	Pass	Pass	Pass
FG1	Average	23.00	37.10	58.29	79.58	93.07	No test
	Max	24.56	40.48	65.49	87.01	96.01	
	Min	21.07	33.83	55.21	71.55	91.07	
	RSD (%)	5.71	5.94	6.53	6.63	2.13	
	Evaluation	Pass	No pass	No pass	No pass	Pass	
FG2	Average	16.24	28.46	47.84	62.80	74.10	84.07
	Max	19.50	36.35	56.84	71.18	84.78	93.53
	Min	13.67	23.20	38.13	55.07	65.12	75.14
	RSD (%)	12.82	16.64	15.31	11.42	10.77	6.17
	Evaluation	Pass	Pass	Pass	Pass	Pass	Pass
NA: Not applicable							

at 6 hours but failed to meet dissolution acceptance criteria at 6 and 8 hours, making it unsuitable for extended-release use. In contrast, FG2, with a higher Arabic gum content (68.57%), exhibited a slower, more controlled release, reaching 84.07% and 74.10% at 10 and 8 hours, respectively, while meeting dissolution requirements at all time points, though with higher RSD values, indicating greater variability.

When compared to Product X, FG1 released diclofenac sodium significantly faster, whereas FG2 more closely resembled Product X's release profile, particularly during the early time points. FG2 demonstrated a release behavior more closely aligned with the target extended-release characteristics. The slower release observed in FG2 can be attributed to the higher concentration of Arabic gum,

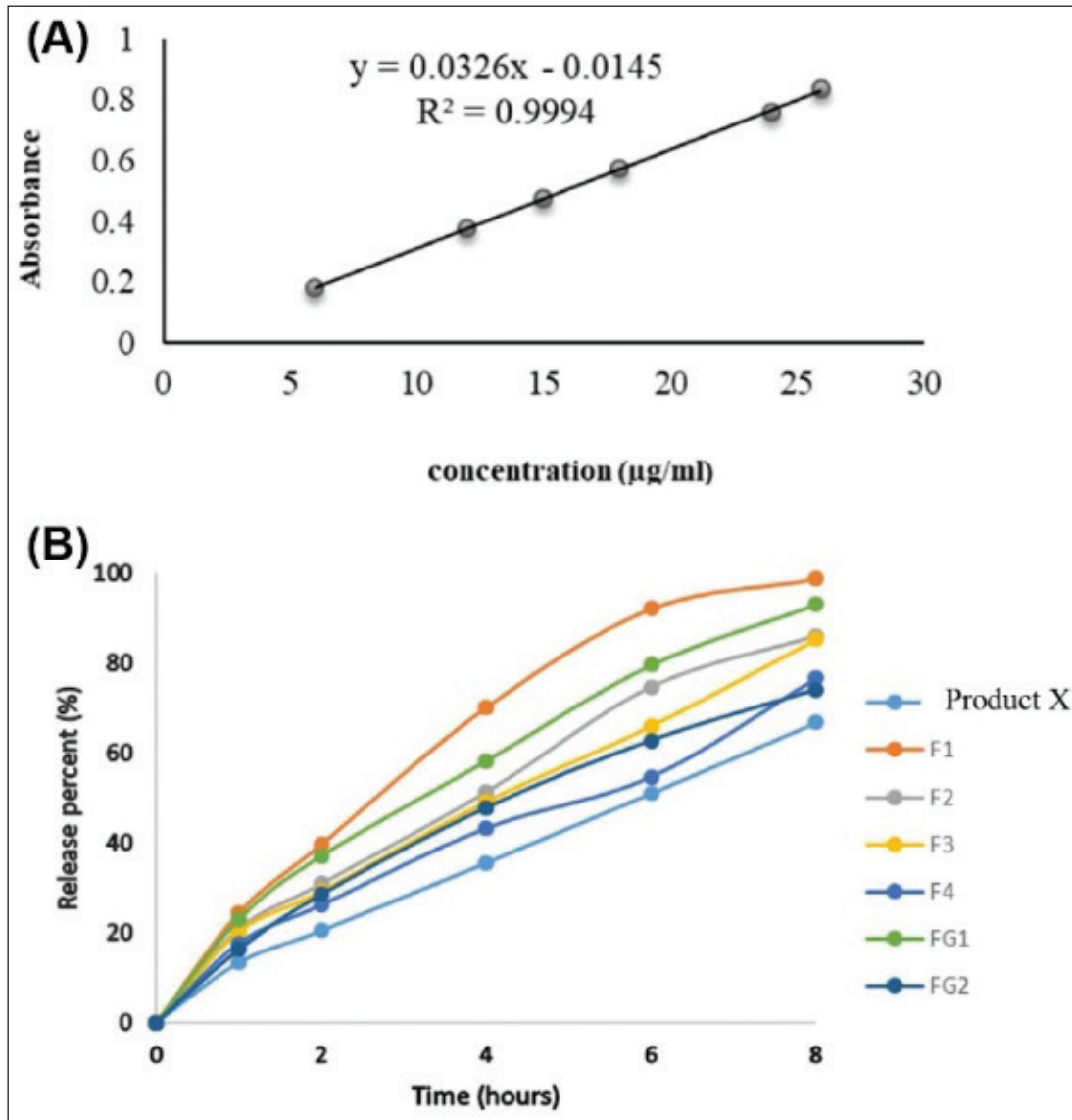


Figure 5. Linear regression curve of diclofenac sodium (A) and dissolution of formulas (B) at pH 7.5.

Table 6. Composition and proportions of formulations FG1 and FG2.

Ingredient	FG1 (%)	FG2 (%)
Diclofenac sodium	21.43	21.43
Arabic gum	42.86	68.57
PVP K30	8.57	8.57
Spray-dried lactose	25.71	-
Talc	0.86	0.86
Magnesium stearate	0.57	0.57
Tablet weight (mg)	350	

which forms a viscous gel matrix upon hydration, slowing drug diffusion. For formulation FG2, the Higuchi model exhibited the best fit to the drug release profile ($R^2 = 0.8129$), indicating a diffusion-controlled mechanism. This was further corroborated by the Korsmeyer–Peppas model ($R^2 =$

0.8101, $n = 0.6693$), suggesting anomalous transport with diffusion as the predominant release mechanism. The drug release kinetics of formulation FG2 are consistent with the characteristics of a hydrophilic matrix system. Arabic gum, serving as the matrix-forming excipient, rapidly hydrates upon contact with the dissolution medium, forming a viscous gel layer around the tablet. This gel layer functions as a diffusion barrier, controlling the rate at which the drug migrates into the surrounding medium [32].

3.3.3. Evaluation of stability results

After 3 months of stability evaluation under both accelerated and long-term storage conditions, the extended-release diclofenac sodium tablets complied with all quality specifications for appearance, dissolution, and assay (Table 7).

Both formulations (F4 and FG2) retained their physical integrity under accelerated (40°C/75% RH) and

Table 7. Stability study results under accelerated and long-term conditions.

Formula	Criteria	Initial	1 months		3 months	
			40°C/75% RH	30°C/75% RH	40°C/75% RH	30°C/75% RH
F4	Appearance	Round, light yellow tablets, one side plain, the other side scored	Equivalent to the initial state	Equivalent to the initial state	Equivalent to the initial state	Equivalent to the initial state
	Dissolution					
	- 1 hour ($\leq 28\%$)	17.65 $\pm$ 5.27	17.23 $\pm$ 5.87	16.23 $\pm$ 6.54	16.06 $\pm$ 5.59	17.02 $\pm$ 6.17
	- 2 hours (20%–40%)	26.17 $\pm$ 3.48	25.13 $\pm$ 4.51	26.65 $\pm$ 5.02	24.05 $\pm$ 3.05	25.38 $\pm$ 3.72
	- 4 hours (35%–60%)	43.28 $\pm$ 3.27	43.06 $\pm$ 4.81	42.18 $\pm$ 2.83	41.72 $\pm$ 4.18	41.92 $\pm$ 4.27
	- 6 h (50%–80%)	54.69 $\pm$ 4.33	52.42 $\pm$ 3.69	55.39 $\pm$ 3.01	51.59 $\pm$ 3.41	54.08 $\pm$ 3.97
	- 10 hours ($\geq 65\%$)	85.72 $\pm$ 2.20	82.25 $\pm$ 3.51	83.10 $\pm$ 4.73	80.15 $\pm$ 4.73	82.60 $\pm$ 3.12
	Assay (90%–110%)	97.60	96.94	97.30	96.14	97.03
	Appearance	Round, light yellow tablets, one side plain, the other side scored	Equivalent to the initial state	Equivalent to the initial state	Equivalent to the initial state	Equivalent to the initial state
	Dissolution					
FG2	- 1 hour ($\leq 28\%$)	16.24 $\pm$ 12.82	16.11 $\pm$ 10.54	17.83 $\pm$ 13.07	15.15 $\pm$ 13.64	15.98 $\pm$ 11.53
	- 2 hours (20%–40%)	28.46 $\pm$ 16.64	26.59 $\pm$ 9.12	27.05 $\pm$ 10.99	27.02 $\pm$ 12.72	27.02 $\pm$ 15.81
	- 4 hours (35%–60%)	47.84 $\pm$ 15.31	45.60 $\pm$ 13.54	48.15 $\pm$ 14.81	45.16 $\pm$ 9.95	47.85 $\pm$ 10.83
	- 6 hours (50%–80%)	62.80 $\pm$ 11.42	65.60 $\pm$ 9.54	63.05 $\pm$ 12.72	58.12 $\pm$ 10.47	60.47 $\pm$ 11.62
	- 10 hours ($\geq 65\%$)	84.07 $\pm$ 6.17	83.16 $\pm$ 7.92	85.06 $\pm$ 9.52	82.61 $\pm$ 12.73	83.06 $\pm$ 10.54
	Assay (90%–110%)		98.05	98.65	97.86	98.42
		98.71				

intermediate (30°C/75% RH) conditions for 3 months, with no changes in appearance. Dissolution profiles met all specifications throughout the study; F4 showed consistent results with no significant differences ($p > 0.05$), while FG2 exhibited greater variability at early time points, likely due to formulation matrix characteristics. Assay values remained within the pharmacopoeial range (90%–110%). These results indicate that both formulations possess satisfactory short-term stability under ICH-recommended stress conditions.

The development of controlled-release diclofenac sodium tablets is strongly influenced by the selection and ratio of excipients. While hydrophobic matrix systems combining carnauba wax, cetyl alcohol, and PVP K30 offer consistent release profiles, the hydrophilic matrix system using Arabic gum demonstrated promising results, particularly with FG2. Nonetheless, further studies are required to optimize excipient combinations and manufacturing processes to achieve better control over drug release for chronic pain management.

4. CONCLUSION

The extended-release diclofenac sodium tablets were successfully developed using both hydrophobic and hydrophilic matrix systems. The study demonstrated that the choice and proportion of excipients play a crucial role in controlling drug release profiles. Hydrophobic matrices (containing carnauba wax and cetyl alcohol) exhibited consistent drug release rates following zero-order kinetics, governed by erosion

and diffusion mechanisms, whereas hydrophilic matrices (containing Arabic gum) demonstrated promising sustained-release behavior, with drug release following the Higuchi model and controlled predominantly by diffusion. However, further optimization of formulation strategies is necessary to enhance release control and ensure prolonged therapeutic efficacy. These findings support the potential of matrix-based systems in the development of extended-release formulations for effective chronic pain management.

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6. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

7. CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

8. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

9. DATA AVAILABILITY

The authors declare that all the data supporting the findings of this study are available within the paper.

10. PUBLISHER'S NOTE

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11. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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