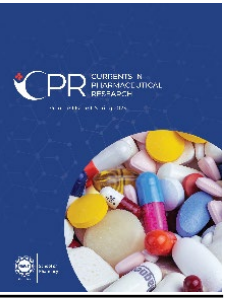
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Design and Evaluation of Bilayer Diclofenac Sodium Tablets Combining Orodispersible and Sustained-Release Systems

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ABSTRACT

Diclofenac sodium is a popular Non- Steroidal Anti-Inflammatory Drug (NSAID), and an analgesic medication. However, its classic dosage preparations do not ensure the rapid effect and a long-term therapeutic response. The objective of the current study was the creation and testing of a bilayer tablet with an orodispersible immediate-release layer and a sustained-release core of diclofenac sodium. The sustained-release core was made by wet granulation. Whereas, the orodispersible outer coating was made by direct compression using super disintegrants, that is, primogel (Sodium starch glycolate) and crospovidone. The pre-compression and post-compression properties of the powder blends and tablets were determined based on pharmacopeias standards. The physicochemical characteristics of the tablets, such as consistent weight, hardness, and friability were acceptable. The orodispersible layer dissolved within less than 30 seconds, with diclofenac sodium being released as a loading dose. The sustained-release core-maintained drug release over the 10-h study period. This demonstrated prolonged drug release consistent with the intended sustained-release behavior of the formulation. Crospovidone proved to be the best among the tested super disintegrants in terms of wetting, water absorption, and disintegration. The optimized bilayer tablet was able to attain a dual-release profile, providing a rapid and long-lasting therapeutic effect. The proposed formulation strategy offered an encouraging method to improve therapeutic efficacy, decrease the dosing frequency, and increase patient compliance in the treatment of inflammatory conditions.

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Keywords: bilayer tablet, direct compression, diclofenac sodium, orodispersible, sustained release, wet granulation

1 INTRODUCTION

Diclofenac sodium is 2-[(2,6-dichlorophenyl) amino] phenyl acetate and is sparingly soluble in water. It is a Non- Steroidal Anti-Inflammatory Drug (NSAID) with analgesic and antipyretic activity. It prevents Prostaglandin synthesis and inhibits both COX-1 and COX-2 isoenzymes, with preferential inhibition of COX-2 inhibitor. Furthermore, it is well-absorbed orally, and is 99% protein bound, metabolized and excreted 65% via urine and 35% via bile [1, 2]. Diclofenac sodium is a slightly yellow-white to light-beige, somewhat hygroscopic crystalline powder. It is freely soluble in methanol and sparingly soluble in non-polar solvents [3].

Physical separation between Active Pharmaceutical Ingredients (APIs) can be achieved with the help of bilayer tablets to prevent chemical incompatibilities and to improve different drug release profiles. Bilayer tablet can be used for successive release of two drugs together, keeping apart two incompatible substances and sustained release tablet where one coating is immediate release as loading dose and other coating is maintenance dose. Immediate release of bilayer tablet has been used as the loading dose and sustained release has ensured therapeutic plasma drug concentration over a longer period of time. The benefits of using this dosage form cover:

- Dose precision and less content variability
- Cheaper compared to all other types of oral dosage forms
- Light and compact
- Simple and cheap to pack and strip
- Easy to be swallowed
- Taste and odor masking
- Suitable for large scale production [4]

The clinical need to fulfill two conflicting pharmaceutical objectives at the same time, that is, rapid onset of action for relief of acute pain and sustained therapeutic drug levels to reduce the frequency of dosing and side effects associated with peak plasma concentrations[5], necessitates the

design of a bilayer tablet. Conventional single-layer formulations cannot provide both immediate and long-term release in a single dosage unit. This requires the development of a bilayer system that physically separates the immediate-release and sustained-release components [6].

A primary functional consideration in the administration of this bilayer tablet is the sequential drug delivery pathway. Upon placement of the tablet in the oral cavity, the orodispersible outer layer ruptures rapidly upon contact with saliva. This releases the loading dose of diclofenac sodium for buccal and sublingual absorption [7]. This route provides rapid systemic uptake, bypassing first-pass hepatic metabolism and allowing prompt onset of analgesia. The remaining sustained-release core is designed to be physically intact and unaffected by salivary enzymes and is naturally swallowed along with the saliva after complete disintegration of the outer layer. Once in the gastrointestinal tract, the matrix core based on HPMC hydrates and forms a viscous gel layer that controls diffusion of the drug, providing sustained release over 10 h [8].

Additionally, the current study was aimed at overcoming the low aqueous solubility and enhancing the therapeutic efficacy through providing rapid pain relief at low toxicity. The ratios of drug polymer varied since primogel and crospovidone were used as super disintegrating agents. Moreover, HPMC was used as a polymer to modify the release of diclofenac sodium through formulation. This dual-release form is also meant to decrease the dosing frequency and increase patient compliance. This is because it offers a convenient and an effective dosage form.

2 METHODS

2.1 Materials

Diclofenac sodium (purity ≥ 98.5%) was obtained from Sigma-Aldrich (St. Louis, MO, USA). Hydroxypropyl methylcellulose (HPMC K15, viscosity 15,000 cP for 2% aqueous solution) was procured from Colorcon Asia Pvt. Ltd. (Mumbai, India). Lactose monohydrate (FlowLac® 100) and microcrystalline cellulose (Avicel® PH-200) were purchased from Merck KGaA (Darmstadt, Germany). Magnesium stearate (vegetable grade) was obtained from Merck KGaA (Darmstadt, Germany). Crospovidone (Polyplasdone® XL, cross-linked polyvinylpyrrolidone) was sourced from ISP Technologies Inc. (Wayne, NJ, USA). Primogel (Primogel®) was procured from DFE Pharma (Goch, Germany). Talcum powder (Pharma

Grade) was purchased from Luzenac Group (Toulouse, France). Amaranth dye (for wetting studies) was obtained from a local market in Pakistan. All other reagents and solvents used were of analytical grade and used without further purification. Deionized water was used throughout the study.

2.2 Preparation Method of Matrix Tablet

All ingredients, that is, diclofenac sodium + lactose + appropriate quantity of HPMC K-15 were blended using a horizontal mixer following sieved through a No. 60 mesh. Water was slowly added until a slightly moist aggregate was formed (wet mass). The wet mass was transferred into stainless steel trays and dried in a hot air oven at 60°C. The moist material was then sieved through a No. 30 mesh to obtain granules. Magnesium stearate was added to the remaining uncombined HPMC K-15 and mixed thoroughly after sieving through a No. 60 mesh. The granules were mixed with the lubricating agents and blended for approximately five minutes. The resulting blend was then compressed into tablets using a ZPW rotary tablet press. The composition of sustained release core is shown in Table 1 [9].

Table 1. Composition of Sustained Release Core

Sr. No.	Ingredients (mg)	F1	F2
1	Diclofenac sodium	50.0	50.0
2	HPMC K15	13.5	17.5
3	Lactose	38.5	36.5
4	Magnesium stearate	3.0	1.0
Total weight		105	105

Table 2. Composition of Extended Release Orodispersible Layer

Sr. No.	Ingredients (mg)	F1	F2
1	Diclofenac sodium	50.0	50.0
2	Avicel	301.5	301.5
3	Primogel	28.5	—
4	Crospovidone	—	28.5
5	Lactose	10.5	10.5
6	Magnesium stearate	2.3	2.3
7	Talcum	2.3	2.3
Total weight		395	395

2.3 Preparation of Orodispersible Layer

Diclofenac sodium, crospovidone, avicel, and primogel were sieved through No. 60 mesh and blended together for 15 mins to yield a uniform mixture. After this blending time, magnesium stearate was added to the blend and then blended for 5 min. After lubricating (using talc) the finished tablets, the tablets were compressed so that the first and third feeds contained the powder mixture and the second feed contained diclofenac sodium. Table 2 shows the orodispersible extended release tablets layer [9].

2.4 Physicochemical Properties of Granules and Powder

2.4.1 Angle of Repose. Angle of repose was determined using the funnel technique. The powder blend was allowed to flow through a funnel onto a surface until a conical heap of maximum height (h) was formed. The radius of this heap was then measured, and the angle of repose (θ) was calculated using the appropriate equation.:

$\theta = \tan^{-1} h/r$

where θ is the angle of repose, h is the height of your pile, and r is the radius of your pile [10].

2.4.2 Bulk Density. To determine the bulk density, an amount of powdered material was measured and added to a graduated measuring cylinder. Afterwards, the volume of the powder was measured. The bulk density was calculated with the formula given below:

Bulk Density = Mass of the powder/ bulk volume

2.4.3 Tapped Density. To calculate the tap density, a certain quantity of the powder was weighed and placed in a graduated cylinder and tapped for a constant volume to be achieved. Tapped density was calculated using the following formula [11].

Tapped density = Mass of the powder/Tapped volume

2.4.4 Carr's Compressibility Index. Compressibility, which indicates how easily the material would flow, provides the simplest means of measuring powder's ability to flow freely. The compressibility index can be determined by calculating Carr's compression index using the following formula [12],

$C = 100(1 - B/T)$

2.4.5 Hausner's Ratio. Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula:

Hausner's Ratio= ρt/ ρo

where ρt is tapped density and ρo is bulk density [13].

2.5 Post-compression Properties of Tablets

2.5.1 Weight Variation. Each formulation was randomly picked to select 20 tablets and weighed separately using an electronic balance. Average weight of the tablets was calculated. Weight of the tablets was individually compared with weight average. Percentage deviation for each tablet was calculated by using the following formula [14]:

Percentage Deviation= (Wavg)- (Winitial)/ (Wavg) × 100

2.5.2 Hardness. Monsanto hardness tester was used to measure the hardness of the formulated tablets. The fracture force was measured and the zero force was subtracted. It is stated in kg/cm^2 [15].

2.5.3 Friability. Friability was measured by the help of Roche friabilator. The mass of 10 tablets was measured and put in plastic chamber that rotates at 25 rpm in 4 minutes. Tablets were re-weighed following removal of fines (de-dusted). The friability was determined by the following formula [16]:

Friability = weight loss × 100 / Initial weight

2.5.4 Thickness. Tablet thickness depends on diameter of dye, quantity of fill allowed to get into dye, and compression or pressure applied to compress. For this purpose, vernier caliper was used. The tablet was placed between the jaws vertically and then horizontally and the reading was noted to measure thickness and diameter of tablet [17].

2.5.5 Wetting Time. This test was performed to determine how long each tablet formulation takes to become fully wetted. A small Petri dish containing 6 mL of water with amaranth (a water-soluble dye) was prepared, and a piece of tissue paper folded twice was placed inside it. A tablet was then positioned on the paper, and the time taken for the liquid to reach the upper surface of the tablet was recorded as the wetting time [18].

2.5.6 Water Absorption Ratio. A small Petri dish containing 6 mL of water with amaranth dye (a water-soluble marker) was covered with a piece

of tissue paper folded twice. A tablet was placed on the prepared surface, and the time required for complete wetting was recorded. Afterwards, the wetted tablet was reweighed. The water absorption ratio (R) was determined using the following equation:

$R = 10 (W_a / W_b)$

where Wb represents the tablet weight before water uptake and W_a corresponds to the weight after absorption [19].

2.5.7 *In vitro* Dispersion Time. Two tablets were added to a 100 mL beaker with 37 ℃ phosphate buffer solution pH 6.8 and time taken to disperse the tablet completely was recorded [19].

2.5.8 *In vitro* Disintegration Time. Disintegration refers to the breaking down of a solid dosage form (tablet) into smaller particles in preparation for the dissolution of the drug in the dosage form. A disc was placed on each of the 6 tubes in the apparatus with a single tablet. It was run in a phosphate buffer (pH 6.8) at 37˚C and was raised/lowered 30 times per minute. The machine was used to measure and record the duration that the tablets fully disintegrated and left no residue. Tablets should be able to disintegrate fully in 3 minutes [20]. All measurements were performed in triplicate and data was presented as mean ± *SD* (*n*=3)**.**

2.6 *In Vitro* Dissolution Studies

An in vitro experiment was performed on drug release with a USP type-II apparatus. Dissolution of the orodispersible layer was performed in 900 mL of phosphate buffer (pH 6.8) for a duration of 2 minutes in each vessel of the dissolution apparatus. The testing was performed at a temperature of 37˚C +/- 0.5 and had one tablet in each vessel and operated at 50 rpm. At specified time intervals, 3ml of testing solution was taken and subjected to UV-visible spectrophotometer. The diclofenac sodium sustained-release tablets were subjected to a similar test which was first dissolved in 0.1N HCl in the solution and allowed to test for 2 hours and then 8 hours in phosphate buffer of pH 6.8. The samples were all measured in the testing solution at constant time intervals and re-measured in a UV-visible spectrophotometer at 276nm to determine the diclofenac content in them. After each withdrawal from the testing solution, 5ml of a newly-prepared and pre-warmed testing solution was returned back into the respective dissolution vessel to keep the volume same. Each of the tested formulations showed the percentage of drug released [21]. All measurements were

performed in triplicate and data was presented as mean ± *SD* (*n*=3).

2.7 Drug Release Kinetics

All the experimental data was expressed as mean ± standard deviation (n = 3). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by post hoc Tukey's test to determine significant differences between formulations. A p-value of less than 0.05 ($p < 0.05$) was considered statistically significant.

3 RESULTS

3.1 Pre-compression Properties

For both formulations, the angle of repose was below 30° (F1: 29.93°, F2: 29.30° for core; F1: 26.38°, F2: 25.56° for orodispersible layer). This indicated good flow properties essential for consistent die filling during compression [22]. The Hausner ratios (1.18–1.19 for core; 1.33 for orodispersible layer) and Carr's indices (15.15–18.16% for core; 24.99–26.30% for orodispersible layer) suggested fair to good flow characteristics. According to the widely accepted scale for powder flowability, materials with Carr's index below 15% exhibited excellent flow, 16–20% indicated good flow, and 21–25% suggested fair flow [23]. The sustained-release core granule properties are shown in Table 3. These properties demonstrated good to excellent flow, which is essential to achieve uniform die filling during high-speed compression. The slight improvement in F2 flow properties (Carr's index 15.15%) compared to F1 (18.16%) may be attributed to the lower lubricant concentration in F2, which reduces interparticulate friction and enhances powder movement [24]. Additionally, the wet granulation process employed for the core improved particle size distribution and reduced fines, contributing to better flow characteristics. The orodispersible layer exhibited higher Carr's index values (24.99–26.30%) compared to the sustained-release core. This can be explained by the cohesive nature of super disintegrants, particularly microcrystalline cellulose, which increases powder bed cohesiveness through hydrogen bonding and mechanical interlocking [25]. Despite these higher values, the powder blend properties are shown in Table 4. This demonstrated acceptable flow for direct compression, as Hausner ratios remained below 1.35, which is considered the threshold for acceptable flow in tableting operations [26]**.** The slightly better flow properties of F2 (Carr's index 24.99%) compared to F1 (26.30%) may be attributed to the more porous

and spherical nature of crospovidone particles. These facilitate better particle rearrangement and reduce interparticulate friction. These findings align with previous reports emphasizing the influence of excipient selection and particle size distribution on powder flow and compressibility [23]. The improved flow properties observed in both formulations remained significant. This is because they ensured consistent tablet weight and drug content uniformity, which are critical to maintain therapeutic efficacy and minimize batch-to-batch variability.

Table 3. Pre-compression Properties of Sustained-Release Core Granules (mean ± *SD*, *n*=3)

Sr. No.	Parameter	F1 (Mean ± *SD*)	F2 (Mean ± *SD*)
1	Angle of repose (°)	29.93 ± 0.18	29.30 ± 0.18
2	Bulk density (g/mL)	0.713 ± 0.04	0.758 ± 0.04
3	Tapped density (g/mL)	0.850 ± 0.006	0.879 ± 0.002
4	Carr's index (%)	18.16 ± 0.06	15.15 ± 0.06
5	Hausner ratio	1.19 ± 0.02	1.18 ± 0.03

Table 4. Pre-compression Properties of Orodispersible Powder Blends (mean ± *SD*, *n*=3)

Sr. No.	Parameter	F1 (Mean ± *SD*)	F2 (Mean ± *SD*)
1	Angle of repose (°)	26.38 ± 0.12	25.56 ± 0.18
2	Bulk density (g/mL)	0.383 ± 0.03	0.403 ± 0.04
3	Tapped density (g/mL)	0.523 ± 0.001	0.538 ± 0.006
4	Carr's index (%)	26.30 ± 0.01	24.99 ± 0.06
5	Hausner ratio	1.338 ± 0.03	1.333 ± 0.01

3.2 Post-Compressional Properties of Tablets

All formulations exhibited consistent weight (within ±5% of average) and low friability (<1%), confirming adequate mechanical strength for handling, packaging, and transportation [27]. The low friability values (<0.2% for core tablets and <0.75% for bilayer tablets) were particularly noteworthy. This is because they indicated excellent resistance to mechanical stress during manufacturing and distribution. Friability is a critical quality attribute. This is because excessive powder loss during handling can lead to dose inaccuracy and patient dissatisfaction [28]. The sustained-release core tablets shown in Table 5 have acceptable hardness (3.02–3.50 kg/cm²). F2 core tablets displayed significantly higher hardness

(3.50 kg/cm²) compared to F1 (3.02 kg/cm²), which can be attributed to the lower lubricant concentration in F2 (1.0 mg vs 3.0 mg). Magnesium stearate, while essential to prevent sticking during compression, may negatively impact tablet hardness by forming a hydrophobic film around particles that reduces interparticulate bonding [29]. The higher hardness of F2 suggests that reducing lubricant concentration to 1.0 mg provides an optimal balance between lubrication and mechanical strength. Hardness is significant because tablets must withstand handling without breaking while still achieving appropriate disintegration and dissolution profiles [30]. Bilayer tablets demonstrated in Table 6 slightly showed higher hardness values than the core tablets alone due to the compressible nature of the outer layer. Interestingly, F1 bilayer tablets exhibited greater hardness (3.70 kg/cm²) than F2 (3.30 kg/cm²). This finding may appear counterintuitive given that F1 core tablets were softer. However, it can be explained by the superior binding properties of primogel compared to crospovidone. Primogel has been shown to enhance tablet hardness through its cohesive properties and ability to form strong interparticulate bonds during compression. Crospovidone, with its highly porous structure, may slightly reduce bonding between particles, leading to marginally lower hardness [24]. However, the slight reduction in hardness for F2 tablets is acceptable (3.30 kg/cm²), and was compensated by superior disintegration performance. This trade-off between hardness and disintegration is well-documented in the literature, where super disintegrants that promote rapid disintegration often produce slightly softer tablets. Nevertheless, all formulations met the minimum hardness requirement for bilayer tablets (typically >2.5 kg/cm²) and exhibited acceptable friability (<1%). This confirmed their suitability for commercial manufacturing and patient use [31].

Table 5. Post-compression Properties of Sustained-Release Tablets (mean ± SD, n=3)

Sr. No.	Parameter	F1 (Mean ± *SD*)	F2 (Mean ± *SD*)
1	Average weight (mg)	106.0 ± 1.2	105.5 ± 1.0
2	Thickness (mm)	3.23 ± 0.05	3.30 ± 0.04
3	Hardness (kg/cm²)	3.02 ± 0.12	3.50 ± 0.10
4	Friability (%)	0.16 ± 0.02	0.15 ± 0.02

Table 6. Post-compression Properties of Bilayer Tablets (Mean ± *SD*, *n*=3)

Sr. No.	Parameter	F1 (Mean ± *SD*)	F2 (Mean ± *SD*)
1	Average weight (mg)	501.0 ± 2.5	502.2 ± 2.0
2	Thickness (mm)	5.70 ± 0.06	5.71 ± 0.05
3	Hardness (kg/cm²)	3.70 ± 0.08	3.30 ± 0.09
4	Friability (%)	0.71 ± 0.03	0.73 ± 0.04

3.3 Orodispersible Layer Evaluation

The break-up and diffusion of the orodispersible layer should be rapid to attain an immediate therapeutic effect. Table 7 provides the assessment of the wetting time, water absorption ratio, in vitro dispersion time, and disintegration time. F2, which had crospovidone as a super disintegrant, had the shortest wetting time (14.6 s) and in vitro disintegration time (23.6 s), in comparison to F1 that contained primogel (wetting time 23.4 s, disintegration time 26.8 s). F2 (29.5% vs 25% F1) had a greater ratio of water absorption and in vitro dispersion was faster (31.2 s vs 36.5 s). This can be attributed to high porosity and wicking capacity of crospovidone that quickly absorbs water in the tablet matrix, facilitating rapid swelling and disintegration. Conversely, primogel is mostly based on swelling, which leads to slower disintegration. Increased disintegration of F2 is desirable, since it guarantees timely release of diclofenac sodium loading dose, which is essential to timely analgesia and anti-inflammatory activity. This finding concurs with the literature in which crospovidone has been observed to be superior in super disintegrant characteristics relative to other disintegrants based on starch. All measurements were performed in triplicate and data was presented as mean ± *SD* (*n*=3).

Table 7. Orodispersible Properties of Bilayer Tablets (Mean ± *SD*, *n*=3)

Sr. No.	Parameters	F1 (Mean ± *SD*) (Primogel)	F2 (Mean ± *SD*) (Crospovidone)
1	Wetting time (sec)	23.4 ± 1.5	14.6 ± 1.2
2	Water absorption ratio (%)	25.0 ± 1.8	29.5 ± 1.5
3	In vitro dispersion time (sec)	36.5 ± 2.0	31.2 ± 1.8
4	In vitro disintegration time (sec)	26.8 ± 1.5	23.6 ± 1.3

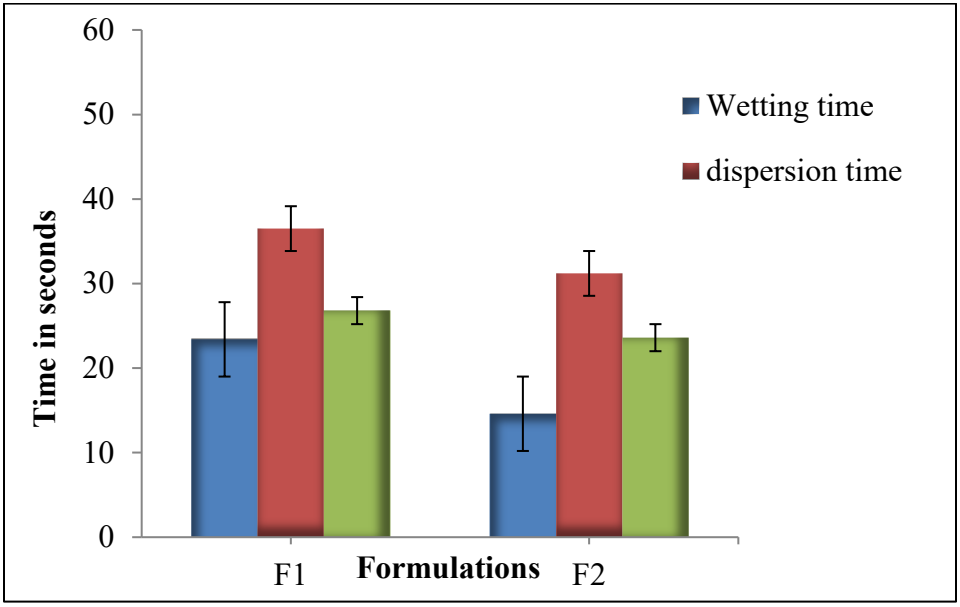


Figure 1. Comparative Evaluation of Wetting, Dispersion, and Disintegration Times for Formulations F1 and F2 (Mean ± *SD*, *n*=3; error bars indicate standard deviation)

F2 (containing crospovidone) demonstrated significantly faster wetting (14.6 s vs 23.4 s, $p < 0.05$), higher water absorption (29.5% vs 25.0%), and shorter disintegration time (23.6 s vs 26.8 s) compared to F1 (primogel). These differences are not merely statistically significant but also clinically meaningful, as faster disintegration translates to more rapid drug release and earlier therapeutic onset, which is critical for acute pain management. The superior performance of crospovidone can be attributed to its unique physicochemical properties. Crospovidone is a highly cross-linked polymer with a porous, sponge-like structure that facilitates rapid water uptake through capillary action. Unlike primogel, which relies primarily on swelling mechanisms, crospovidone exhibits both wicking (capillary) and swelling properties. This enables faster water penetration throughout the tablet matrix [32]. The wicking action of crospovidone is particularly efficient. This is because water is drawn into the tablet through numerous micropores and capillaries, creating a network of channels that rapidly conduct moisture to the interior of the tablet. This rapid water uptake generates significant swelling forces that effectively disrupt the tablet structure, leading to fast disintegration. In contrast, primogel primarily

functions through a swelling mechanism. Upon contact with water, the starch derivative rapidly absorbs water and swells to several times its original volume. This generates pressure within the tablet that causes rupture. While this mechanism is effective, it is comparatively slower than the combined wicking-swelling mechanism of crospovidone. Primogel also exhibits a tendency to form gel layers at the tablet surface, which can temporarily impede further water penetration and slightly delay complete disintegration [31]. The rapid disintegration of F2 within 30 seconds meets the pharmacopoeia requirement for orodispersible tablets. This typically specifies disintegration times of less than 3 minutes, with many commercial products disintegrating within 30–60 seconds [33]. The European Pharmacopoeia defines orodispersible tablets as those that disintegrate within 3 minutes. On the other hand, the FDA guidance suggests that rapid disintegration should occur within 30 seconds for optimal patient acceptability. Both formulations met this requirement. However, F2's superior performance positioned it as favorable for patients requiring rapid dissolution.

The water absorption ratio of F2 (29.5%) was significantly higher than that of F1 (25.0%). This indicated that crospovidone has a greater capacity to take up water. The comparative evaluation is shown in Figure 1. This enhanced water uptake not only accelerates disintegration but also promotes drug dissolution by increasing the surface area of drug particles exposed to the dissolution medium. For a drug like diclofenac sodium with low aqueous solubility, this improved wettability is particularly beneficial as it can enhance drug dissolution and absorption. The faster dispersion and disintegration times observed with F2 are clinically significant. This is because they ensure prompt release of the diclofenac sodium loading dose, enabling rapid analgesic effect. This is particularly beneficial in acute pain management, where rapid onset of action is a key therapeutic objective. Furthermore, the excellent disintegration properties of crospovidone-containing tablets enhance patient acceptability, especially in populations with swallowing difficulties, as the tablets can be taken without water and disintegrate quickly in the oral cavity [34].

3.4 Comparative Analysis of Formulations

Among the developed formulations, F2 demonstrated overall superior performance compared to F1 across pre-compression, post-compression, disintegration, and dissolution evaluations. In pre-compression studies, F2

exhibited slightly improved flow properties and compressibility. This can be attributed to better powder uniformity and optimized excipient ratio. Post-compression evaluation further confirmed that F2 possessed improved mechanical strength and more consistent tablet quality, indicating enhanced formulation robustness. In the orodispersible layer assessment, F2 showed faster wetting time, higher water uptake capacity, and more rapid disintegration. This improvement is primarily attributed to the presence of crospovidone, which is known for its superior capillary action and wicking effect compared to other disintegrates. In dissolution studies, F2 demonstrated a more efficient initial burst release (loading dose) followed by a well-maintained sustained release profile. This indicated a successful balance between immediate and controlled release phases. These observations are consistent with the optimized concentration of HPMC in the sustained-release matrix, which effectively regulated drug diffusion and polymer hydration behavior as shown in Figure 2.

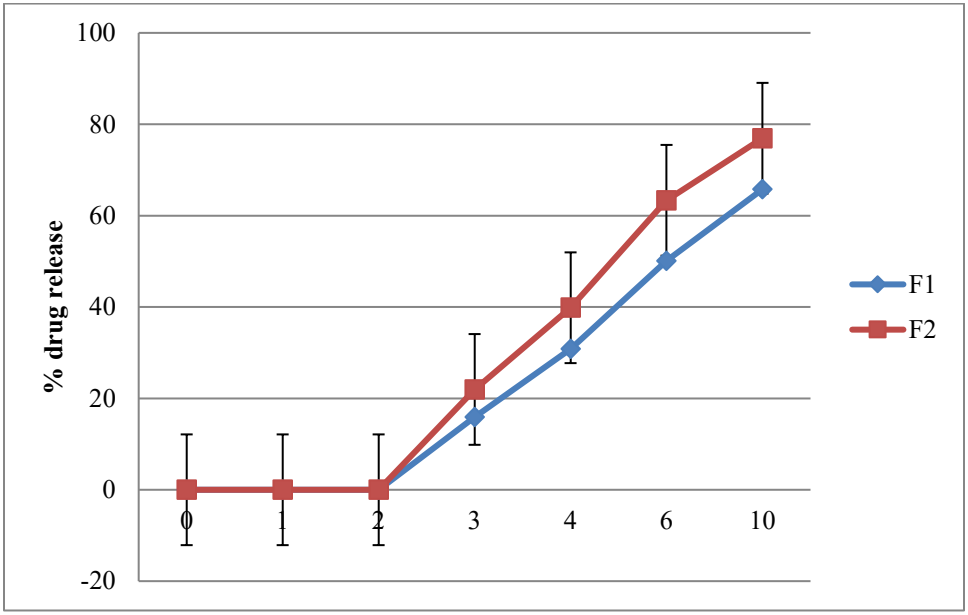


Figure 2. Cumulative Drug Release Profiles of F1, F2, and Marketed Formulation over 10 Hours (mean ± *SD, n*=3; error bars indicate standard deviation)

The recent literature also brings to the fore that the variances in the polymer grade and viscosity do not necessarily provide any significant differences in the release mechanism but can affect the release rate and

duration [35]. To illustrate this point, it has been shown that HPMC matrices can release drugs over a sustained period of up to 12 hours, although there are slight variations in viscosity grades, which would support the results of the current research [36]. Moreover, recent improvements in matrix tablet formulations have highlighted the importance of polymer swelling, water absorption, and matrix porosity as important factors in determining drug release responses. The release patterns in this study have been further confirmed by recent mechanistic investigations that collectively control diffusion and erosion processes in the matrix system [37]. Overall, the findings of the current study are in strong agreement with contemporary research. The findings confirmed that HPMC-based hydrophilic matrices provide a reliable and reproducible approach to achieve controlled and sustained drug release.

The dissolution data of formulations F1 and F2 was fitted into multiple kinetic models to determine the drug release mechanism. Among all models, the Korsmeyer–Peppas model exhibited the highest correlation coefficient ($R^2 \approx 0.993$–0.994), indicating it best describes the release behavior. The release exponent ($n > 0.85$) deduced a non-Fickian (anomalous) transport mechanism, involving both diffusion and polymer relaxation. The Higuchi model also showed strong linearity, indicating diffusion-controlled release. Whereas, the poor fit of the Hixson–Crowell model suggests that surface erosion is not a major mechanism in drug release. Moreover, the analysis of the release kinetics in Table 8 showed that the drug release was non-Fickian (anomalous) transport. This implies the combination of diffusion and polymer relaxation. This observation is consistent with recent studies on HPMC-based matrix tablets, in which the Korsmeyer Peppas model provided the most accurate description of drug release, which is an amalgamation of diffusion and erosion.

Table 8. Kinetic Modeling Parameters for Drug Release from Formulations F1 and F2

Model	Parameter	F1	R^2 (F1)	F2	R^2 (F2)
Zero Order	k_0	7.567	0.932	8.989	0.909
First Order	k_1	0.119	0.959	0.165	0.953
Higuchi	kH	34.23	0.954	40.62	0.939
Hixson–Crowell	kHC	0.461	0.700	0.485	0.714
Korsmeyer–Peppas	kP	1.940	0.993	2.155	0.994
	n (release exponent)	0.864	—	0.881	—

4 CONCLUSION

This study successfully developed and evaluated a bilayer tablet formulation of diclofenac sodium combining an orodispersible immediate-release layer with a sustained-release core. The optimized formulation (F2), containing crospovidone as the super disintegrant in the outer layer and HPMC K15 (17.5 mg) in the sustained-release core, demonstrated rapid disintegration within 24 seconds. This released a loading dose for prompt analgesic effect, followed by sustained drug release over 10 hours through a non-Fickian diffusion mechanism. The biphasic release profile of F2 showed a dissolution pattern comparable to that of the marketed formulation. However, in vivo pharmacokinetic studies are required to establish bioequivalence. The proposed bilayer tablet addresses critical clinical limitations of conventional diclofenac sodium therapy by providing rapid pain relief, maintaining therapeutic plasma concentrations with reduced dosing frequency, and improving patient compliance through water-free administration. The sequential administration pathway—orodispersible layer disintegration in the oral cavity followed by swallowing of the intact core—ensures both immediate and sustained drug delivery in a single dosage unit.

4.1. Future Research Studies

Future studies should include in vivo pharmacokinetic evaluation, long-term stability testing, and scale-up studies to facilitate clinical translation and confirm the therapeutic benefits of this novel drug delivery system.

4.2. Study Limitations

Despite the success of the current study in creating a bilayer diclofenac sodium tablet with both immediate and sustained-release properties, some weaknesses still need to be addressed. First, the analysis was mainly conducted using in vitro experiments, which might not reflect the actual in vivo pharmacokinetic profile of diclofenac sodium as gastrointestinal mechanisms. For instance, pH change, enzyme activity, and motility can play a significant role in drug release and absorption. Second, the research was primarily based on physical, mechanical, and dissolution properties without studying the stability over time in various storage conditions. Stability testing provides uniform drug release pattern, mechanical integrity, and shelf life of the formulation. Third, the study was confined to two super disintegrants (primogel and crospovidone) and desired

concentrations of HPMC, and optimal polymers or excipient combinations had not been investigated. To provide future insights, in vivo pharmacokinetics and bioavailability research should be conducted to verify therapeutic benefits of the created bilayer system. Additional investigation into other polymers, or additional super disintegrants or combination methods could improve short-term and long-term release properties. There is also a need to conduct scale-up and stability studies to facilitate industrial translation. Lastly, the bilayer design approach can be applied to other water-insoluble drugs, which need rapid absorption and extended effects, thus enhancing patient adherence and clinical efficacy.

Author Contribution:

Hira Javed: conceptualization. **Eesha Tariq Bhatty:** data curation. **Rabia Javaid:** formal analysis. **Aiman Mahmood:** investigation. **Omer Mahmood Mumtaz:** writing – review & editing. **Tayyaba Rana:** methodology. **Saleha Baber:** project administration. **Hadeeqa Khan:** resources. **Rizwana Raheel:** software.

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

Data Availability Statement

Data supporting the findings of this study will be made available by the corresponding author upon request.

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