RESEARCH PAPER

# Melt Solid Dispersion-Based Pelletization of Etodolac Using PVP K30 and Functional Excipients: A Scalable, Solvent-Free Strategy for Immediate-Release Drug Delivery

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***ABSTRACT***

Etodolac's low aqueous solubility constrains dissolution rate-limited absorption. This study developed melt solid dispersions of etodolac with PVP K30 and converted them into immediate-release pellets via extrusion-spheronization. Eight solid dispersions (ESD1-ESD8) were formulated and incorporated into eight pellet batches (EF1-EF8) containing MCC, lactose, SLS, and croscarmellose sodium. Methods included shake-flask solubility, mixer torque rheometry (MTR) for wet mass end pointing, DSC, SEM, laser-diffraction particle sizing, flow indices (bulk/tapped density, Hausner ratio, and Carr's index), drug content assay, and USP dissolution in pH 1.2. Solid dispersions increased solubility from 299 µg/mL (pure drug) to 317-458 µg/mL (EF8 highest: 457.58 ± 1.93 µg/mL); enhancement versus pure drug was significant ($t = 5.39$, $p = 0.001$). MTR identified an optimal plasticity window at 20-25% binder. Pellets showed excellent manufacturability (Hausner 1.009-1.119; Carr's 0.85-10.64%), narrow size distributions (means 1034-1269 µm; spans 0.50-0.65), and uniform drug content (98.27-102.34%). Dissolution improved markedly over pure etodolac; EF8 achieved 99.99% release at 30 min and EF7 reached 89.32%. Data indicated that PVP K30 based solid dispersion, balanced wetting/disintegration, and controlled pellet microstructure synergize to deliver rapid, reproducible etodolac release using a scalable, solvent-free process.

**Keywords:** Etodolac; PVP K30; amorphous solid dispersion; extrusion-spheronization; mixer torque rheometer; immediate release; dissolution enhancement; pellets.

**How to cite this article:** Harishchandre SS, Patil DM. Melt Solid Dispersion-Based Pelletization of Etodolac Using PVP K30 and Functional Excipients: A Scalable, Solvent-Free Strategy for Immediate-Release Drug Delivery. Int J Drug Deliv Technol. 2026;16(5): 1617-1626. DOI: 10.25258/ijddt.16.5.147

**Source of support:** Nil.

**Conflict of interest:** None.

## Introduction

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) whose clinical performance is often limited by low aqueous solubility and dissolution-rate limited absorption, features that place it within Biopharmaceutics Classification System (BCS) class II. In such cases, increases in apparent solubility and dissolution rate can meaningfully improve exposure without altering permeability. Recent etodolac studies continue to underscore this challenge, reporting poor water solubility and variable oral absorption that motivate formulation-based solutions (Mustafa et al., 2024; Czajkowska-Kośnik et al., 2024; Ahirrao et al., 2022).

Amorphous solid dispersions (ASDs) represent a mature strategy to overcome dissolution constraints for BCS II drugs. Among hydrophilic carriers, polyvinylpyrrolidone (PVP) especially PVP K30, remains widely used due to its glass-forming ability, hydrogen-bonding interactions, and inhibition of drug recrystallization. Contemporary reviews detail how PVP- based ASDs, prepared by solvent evaporation or solvent-free routes such as melt quenching, enhance wettability and sustain supersaturation, thereby accelerating dissolution and bioavailability. For thermally stable actives, melt processing avoids residual solvents and can be readily scaled. This rationale directly supports the selection of PVP K30 and a fusion (melt) method for etodolac in the present work (Rusdin et al., 2024).

Multiparticulate pellet systems further complement ASD technology by providing robust flow, reduced dose-dumping risk, and flexible downstream operations (e.g., encapsulation or compression into multiple-unit tablets). Extrusion - spheronization is a proven pelletization route in which a wetted mass is extruded and rounded on a friction plate to yield narrow size distributions and smooth, mechanically resilient spheres. Benchmark literature highlights critical variables - liquid content, plasticity, spheronizer speed/time, and the central role of microcrystalline cellulose (MCC) as a plasticity aid enabling successful sphere formation and satisfactory mechanical properties. These attributes make extrusion - spheronization an attractive platform for immediate-release (IR) multiparticulates containing ASDs (Vervaet et al., 1995; Dukić-Ott et al., 2009; Tripurasundari & Prabhakar, 2012).

Achieving reproducible pellet quality requires tight control of wet-mass characteristics. Mixer torque rheometry (MTR) offers a quantitative process

analytical tool to identify the window of optimal cohesiveness and plasticity by monitoring the evolution of mean line torque during binder addition. Studies have shown that MTR correlates with granulation endpoints, predicts extrudability/spheronization behaviour, and can support scale-up decisions by mapping transitions from under-wet (brittle) to over-wet (sticky, agglomerating) regimes. Incorporating MTR into development thus reduces trial and error and strengthens process understanding for ASD containing pellet systems (Ibrahim et al., 2019; Kuhs et al., 2017; Sakr et al., 2011).

Given this background, our study had four simple goals. First, we made etodolac - PVP K30 solid dispersions by melting the drug with the polymer at several drug-to-polymer ratios. Second, we turned these into fast-release pellets using extrusion - spheronization with MCC, lactose, SLS, and croscarmellose sodium. Third, we used a mixer torque rheometer to find the right amount of binder for a workable wet mass. Fourth, we checked how recipe and process choices affected key qualities - flow, particle size and span, content uniformity, pellet shape, and dissolution in pH 1.2. By combining the solubility boost from the solid dispersion with careful control of pellet structure and data - driven wet-massing, we offer a scalable, solvent- free way to achieve rapid etodolac release. This integrated, standards - aligned approach is still rarely reported for etodolac. The same strategy can help other BCS II drugs where dissolution limits absorption: the polymer promotes brief supersaturation and better wetting, while the pellet design supports easy manufacturing and flexible dosing. Clear, transparent methods make this a practical template for future immediate-release products.

## 1. Materials and Methods

### 1.1. Materials

The active pharmaceutical ingredient, Etodolac, was obtained as a gift sample from Alpine Laboratories, Baddi, Himachal Pradesh, India. Polyvinylpyrrolidone K30 (PVP K30), selected as the hydrophilic carrier for solid dispersions, was procured from Himedia Laboratories Pvt. Ltd., Mumbai, India. Microcrystalline cellulose (MCC), used as the plasticity aid and filler, was purchased from Loba Chemie Pvt. Ltd., Mumbai, India, while lactose monohydrate (used as a water-soluble filler and porosity enhancer) was supplied by Himedia Laboratories. Sodium lauryl sulfate (SLS), acting as a surfactant and wetting agent, was obtained from Loba Chemie Pvt. Ltd., and croscarmellose sodium (CCS), the chosen superdisintegrant, was sourced from Sigma-Aldrich, USA. Purified water, prepared in the laboratory using a Milli-Q water purification system, was used as the granulating fluid. All other chemicals and solvents employed in the study were of analytical grade to ensure reliability and reproducibility. The following instruments were used in the study: Mixer Torque Rheometer (MTR-3, Caleva, Dorset, UK) for wet-massing analysis, Turbula mixer (Erweka S27, Germany) for powder blending, extruder with die and spheronizer with friction plate (Caleva, UK) for pelletization, and hot-air oven/fluidized-bed dryer (Himedia Instruments, India) for drying. For characterization, a UV-Vis spectrophotometer (Shimadzu UV-1800, Japan; $\lambda$ = 276 nm) was used for solubility and drug-content analysis, differential scanning calorimeter (DSC-60, Shimadzu, Japan) for thermal studies, a scanning electron microscope (JSM-1600, Jeol, Tokyo, Japan) for morphological evaluation, and a laser diffraction particle-size analyzer (Mastersizer Scirocco 2000, Malvern Instruments, UK) for particle-size analysis. USP dissolution apparatus II (paddle type, Electrolab, India) was employed for in vitro dissolution studies.

### 1.2. Preparation of solid dispersions (melt method)

Pre-weighed etodolac and PVP K30 were blended in predetermined ratios and heated slightly above the melting point of etodolac, ensuring the polymer did not degrade. The melt was stirred to homogeneity, then rapidly cooled on a stainless-steel plate or by ice-bath immersion to solidify. The mass was pulverized and sieved to a uniform particle size suitable for downstream processing. Compositions are shown in Table 1.

**Table 1.** Solid Dispersion Composition

| Formulation Code | Etodolac (mg) | PVP K30 (mg) | Etodolac:PVP K30 Ratio | Preparation Method |
|---|---|---|---|---|
| ESD1 | 400 | 50 | 8:1 | Melt method |
| ESD2 | 400 | 70 | 5.7:1 | Melt method |
| ESD3 | 400 | 100 | 4:1 | Melt method |
| ESD4 | 400 | 60 | 6.7:1 | Melt method |
| ESD5 | 400 | 80 | 5:1 | Melt method |
| ESD6 | 400 | 90 | 4.4:1 | Melt method |
| ESD7 | 400 | 50 | 8:1 | Melt method |
| ESD8 | 400 | 75 | 5.3:1 | Melt method |

### 1.3. Pelletization by extrusion - spheronization

Pulverized solid dispersions were dry blended with MCC, lactose, SLS, and CCS in a planetary mixer to achieve uniform distribution. Purified water was

gradually introduced as granulating fluid with kneading to form a cohesive, plastic wet mass. The mass was extruded through a die to produce cylindrical extrudates, which were then spheronized at controlled speed/time to form smooth, spherical pellets. Pellets were dried at 40 - 50 °C to target moisture content, then sieved to the desired size fraction. Formulations are summarized in Table 2.

**Table 2.** Immediate-Release Pellet Formulation

| Code | Solid Dispersion (mg) | MCC (mg) | Lactose (mg) | SLS (mg) | CCS (mg) | Purified Water |
|---|---|---|---|---|---|---|
| EF1 | 450 (ESD1) | 250 | 250 | 20 | 30 | q.s. |
| EF2 | 470 (ESD2) | 230 | 250 | 15 | 35 | q.s. |
| EF3 | 500 (ESD3) | 200 | 230 | 10 | 60 | q.s. |
| EF4 | 460 (ESD4) | 240 | 240 | 20 | 40 | q.s. |
| EF5 | 480 (ESD5) | 220 | 230 | 15 | 55 | q.s. |
| EF6 | 490 (ESD6) | 210 | 220 | 10 | 70 | q.s. |
| EF7 | 450 (ESD7) | 260 | 240 | 20 | 30 | q.s. |
| EF8 | 475 (ESD8) | 225 | 250 | 15 | 35 | q.s. |

### 1.4. Shake - flask solubility studies

Equilibrium solubility of etodolac (pure) and of each solid-dispersion-derived formulation was measured in water using a standard shake-flask protocol at ambient temperature. Suspensions were agitated to equilibrium, filtered, and analyzed spectrophotometrically at 276 nm against a validated calibration curve. Results are reported as mean ± SD ($n \geq 3$). Statistical comparison between pure drug and the solid-dispersion group used an independent-samples t-test ($\alpha = 0.05$).

### 1.5. Drug and excipient compatibility studies using FTIR and DSC

Drug - excipient compatibility was assessed using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). FTIR spectra of pure etodolac, individual excipients (PVP K30, MCC, lactose monohydrate, SLS, and CCS), physical mixtures (drug + excipient), and optimized solid dispersions were recorded using an FTIR spectrophotometer (Bruker ALPHA II, Germany). Samples (2–5 mg) were blended with potassium bromide (Himedia, India) and compressed into transparent pellets; spectra were collected in the 4000-400 $cm^{-1}$ range to identify possible shifts in characteristic drug peaks indicating interactions. DSC analysis was carried out on a DSC-60 instrument (Shimadzu, Japan) using 3-5 mg of sample (pure drug, excipients, physical mixtures, and solid dispersions). Samples were sealed in aluminum pans and heated from 25-250 °C at a constant rate of 10 °C/min under nitrogen purge (30 mL/min), with indium used for calibration. FTIR provided information on functional group stability and hydrogen bonding, while DSC thermograms revealed thermal events such as melting, crystallization, or enthalpic changes, enabling evaluation of potential incompatibilities or amorphization within the solid dispersions.

### 1.6. Wet massing behaviour by mixer torque rheometer (MTR)

A 15 g sample of the standardized dry blend was processed in the MTR-3 at 50 rpm. Granulating fluid (5 mL total) was added in seven increments; each increment consisted of 1 min mixing followed by a 20 s data-collection period. Mean line torque (Nm) was recorded at each binder level to identify transitions from under-wet (brittle), through plastic/optimal, to over-wet (sticky/agglomerating) regimes.

### 1.7. Flow property measurements

The flowability and packing characteristics of the prepared pellet formulations were evaluated by determining bulk density and tapped density using a graduated cylinder method, performed in triplicate for accuracy. For each batch, a fixed weight of pellets was carefully poured into a 10 mL graduated cylinder without compacting, and the initial volume was recorded as bulk volume. The cylinder was then tapped mechanically (100 taps) until a constant volume was obtained, which was noted as the tapped volume. Bulk density (g/mL) was calculated by dividing the weight of pellets by the bulk volume, and tapped density was calculated similarly using the tapped volume. From these values, the Hausner ratio (tapped density / bulk density) and Carr's compressibility index (tapped - bulk) / tapped × 100 were derived. The Hausner ratio was interpreted as an index of interparticle friction, while Carr's index reflected the compressibility of the powder bed. According to USP-1174, values of Hausner ratio close to 1.00 and Carr's index <10% indicate excellent flow properties, whereas higher values suggest reduced flowability. This evaluation provided essential insight into the handling, processability, and downstream capsule/tablet filling potential of the formulated pellets.

### 1.8. Drug content uniformity

Drug content uniformity was determined to ensure homogeneous distribution of etodolac within the pellet formulations. For each batch, approximately 25 mg of pellets was accurately weighed and finely powdered

using a porcelain mortar and pestle. The powdered sample was dispersed in 20 mL of distilled water, followed by sonication for 5 minutes to ensure complete drug extraction. The resulting mixture was filtered through a Whatman filter paper (No. 1), and the clear filtrate was analyzed spectrophotometrically at λmax 276 nm using a UV-Visible spectrophotometer (Shimadzu UV-1800, Japan). Drug content was calculated with reference to a previously established calibration curve, and results were expressed as mean ± standard deviation (SD) for three independent determinations (n = 3). This method ensured quantitative estimation of etodolac content and provided evidence of formulation uniformity and reproducibility.

### 1.9. Particle-size distribution

The particle size distribution of the prepared pellets was determined using a dry dispersion laser diffraction technique (Mastersizer Scirocco 2000, Malvern Instruments, UK). Approximately 300 mg of pellets from each batch was introduced into the sample feeder, and five replicate measurements were performed for each formulation to ensure precision. The parameters recorded included d (0.1), d (0.5), and d (0.9), representing the particle diameters at which 10%, 50%, and 90% of the total volume of particles were smaller, respectively. The mean particle size was calculated as the arithmetic average of these three values. Uniformity of size distribution was further evaluated by calculating the span value using the equation:

$$\text{Span} = d(0.9) - d(0.1) / d(0.5)$$

A smaller span value indicated a narrower distribution and greater uniformity, which is essential for consistent flow, packing, and dissolution performance of the pellets.

### 1.10. Scanning electron microscopy (SEM)

The morphology of the prepared pellets was examined using scanning electron microscopy (SEM) to assess surface texture, sphericity, and structural integrity. Representative samples were mounted on aluminum stubs with double sided conductive adhesive tape. To enhance conductivity, the pellets were sputter-coated with a thin layer of gold–palladium alloy under vacuum using a sputter coater (Jeol JFC-1600, Japan). Imaging was performed on a SEM instrument (Jeol JSM-1600, Tokyo, Japan) at an accelerating voltage of 15 kV, and micrographs were captured at different magnifications. This analysis provided detailed visualization of pellet surface smoothness, porosity, and the degree of spheronization achieved, which are critical factors influencing flow behaviour, packing, and dissolution performance.

### 1.11. In vitro dissolution testing

The in vitro dissolution profile of etodolac from the pellet formulations was evaluated using a USP Type II dissolution apparatus (paddle method, Electrolab TDT-08L, India). The test medium consisted of simulated gastric fluid (SGF, pH 1.2, 900 mL) maintained at 37 ± 0.5 °C. The paddle speed was set at 50 rpm, ensuring adequate mixing while minimizing mechanical stress on the pellets. At predetermined intervals of 5, 10, 15, 20, 25, and 30 minutes, 5 mL aliquots were withdrawn, filtered through a 0.45 µm membrane filter, and immediately replaced with fresh medium to maintain sink conditions. The samples were analyzed spectrophotometrically at λmax 276 nm using a UV-Vis spectrophotometer (Shimadzu UV- 1900, Japan). Dissolution efficiency and cumulative drug release (%) were calculated. The
choice of acidic media and test conditions aligns with USP 1092 recommendations for immediate-release formulations and allows biopredictive assessment of drug release under gastric conditions.

### 1.12. Statistical Analysis

All experiments were done in triplicate, and results were reported as mean ± standard deviation (SD). Data were checked for normal distribution and equal variances. Differences between two groups (e.g., pure drug vs. solid dispersions) were tested using the unpaired Student's t-test, while comparisons among multiple formulations (e.g., EF1–EF8 dissolution data) were analyzed using one-way ANOVA with Tukey's post hoc test. A p-value less than 0.05 was considered statistically significant. Statistical analyses were carried out using GraphPad Prism version 9.0 (GraphPad Software, USA) and IBM SPSS Statistics version 25.0 (IBM Corp., USA). Microsoft Excel 2019 was used for basic calculations and plotting graphs.

## 2. Results

### 2.1. Solubility enhancement

The intrinsic solubility of pure etodolac in water was 299 µg/mL, consistent with its hydrophobic, BCS II character. All solid-dispersion-derived formulations increased apparent solubility to 317–458 µg/mL, with EF8 showing the highest value (457.58 ± 1.93 µg/mL). The difference between the pure drug and the solid-dispersion group was statistically significant ($t = 5.39$; $p = 0.001$).

**Table 3.** Solubility of Etodolac from Solid-Dispersion-Based Formulations (Shake-Flask, µg/mL)

| Code | Solubility (µg/mL) |
|---|---|
| EF1 | 360.54 ± 1.33 |
| EF2 | 416.59 ± 1.39 |
| EF3 | 441.33 ± 1.64 |
| EF4 | 374.21 ± 1.84 |

| | |
|---|---|
| EF5 | 317.17 ± 1.78 |
| EF6 | 354.82 ± 1.92 |
| EF7 | 440.75 ± 1.92 |
| EF8 | 457.58 ± 1.93 |

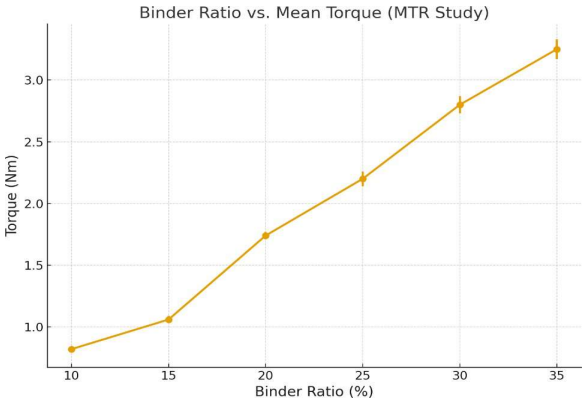


**Figure 1.** Solubility of Etodolac from Solid-Dispersion-Based Formulations (Shake-Flask, µg/mL)

## 2.2. Drug and excipient compatibility studies using DSC

The DSC thermograms provided clear evidence of drug excipient compatibility and the transformation of etodolac in solid dispersions. Pure etodolac displayed a sharp endothermic melting peak at around 147-150 °C, confirming its crystalline nature. PVP K30 showed no distinct melting transition but rather a broad endotherm due to its amorphous character, while MCC, lactose, SLS, and CCS exhibited minor thermal events mainly related to moisture loss or decomposition. In the physical mixtures, the melting peak of etodolac was still visible,
although slightly broadened and reduced in enthalpy, suggesting weak physical interactions such as hydrogen bonding but no chemical incompatibility. In contrast, the solid dispersion thermograms revealed a marked suppression or complete disappearance of the drug's melting peak, demonstrating conversion into an amorphous state and homogeneous distribution within the polymeric matrix. These results indicate that PVP K30 successfully stabilized etodolac in its amorphous form, providing a molecularly dispersed system that directly supports the enhanced solubility and dissolution profiles observed in the optimized pellet formulations.

**Figure 2.** DSC thermograms indicating drug and excipient compatibility studies

## 2.3. Wet massing behaviour (MTR)

Binder addition increased mean line torque from 0.82 ± 0.02 Nm at 10% (dry/brittle) to 3.25 ± 0.08 Nm at 35% (over-wet/agglomerating). A broad plateau of optimal plasticity was observed at 20-25% binder, consistent with cohesive, extrudable masses and efficient spheronization. **Table 4.** MTR-Based Wet Massing Profile

| Binder Ratio (%) | Torque (Nm), Mean ± SD | Observation |
|---|---|---|
| 10 | 0.82 ± 0.02 | Dry, brittle, insufficient cohesion |
| 15 | 1.06 ± 0.03 | Partially cohesive; some cracking |
| 20 | 1.74 ± 0.03 | Cohesive, good plasticity; extrudable |
| 25 | 2.20 ± 0.06 | Highly cohesive/plastic; optimal for spheronization |
| 30 | 2.80 ± 0.07 | Over-wet, sticky; flow reduced |
| 35 | 3.25 ± 0.08 | Excessively wet; agglomerates form |

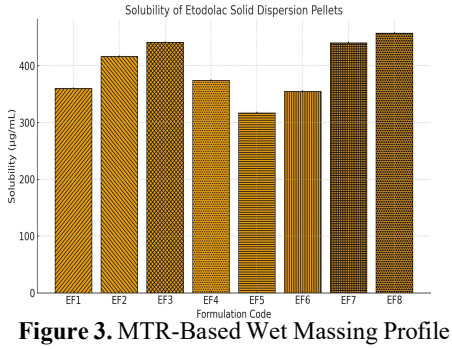


**Figure 3.** MTR-Based Wet Massing Profile

## 2.4. Flow properties of pellets

Flow and packing indices were generally excellent to good across EF1-EF8 (Table 5). EF2 showed the best flow (Hausner 1.009; Carr's 0.85%), while EF7 displayed relatively higher compressibility (Hausner 1.119; Carr's 10.64%) yet remained within acceptable handling limits.

**Table 5.** Flow Property Metrics

| Code | Bulk (g/mL) | Tapped (g/mL) | Hausner Ratio | Carr's (%) |
|---|---|---|---|---|
| EF1 | 0.701 ± 0.0099 | 0.714 ± 0.0009 | 1.019 | 1.82 |
| EF2 | 0.696 ± 0.0009 | 0.702 ± 0.0019 | 1.009 | 0.85 |
| EF3 | 0.664 ± 0.0069 | 0.696 ± 0.0019 | 1.048 | 4.60 |
| EF4 | 0.681 ± 0.0069 | 0.709 ± 0.0009 | 1.041 | 3.95 |
| EF5 | 0.654 ± 0.0019 | 0.698 ± 0.0019 | 1.067 | 6.30 |
| EF6 | 0.609 ± 0.0009 | 0.635 ± 0.0009 | 1.043 | 4.09 |
| EF7 | 0.622 ± 0.0019 | 0.696 ± 0.0009 | 1.119 | 10.64 |
| EF8 | 0.655 ± 0.0009 | 0.704 ± 0.0069 | 1.075 | 6.82 |

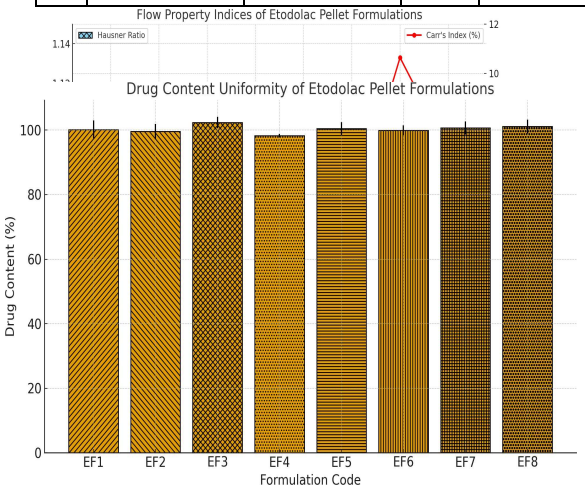


**Figure 4A.** Bulk Density (g/mL) and Tapped Density (g/mL)

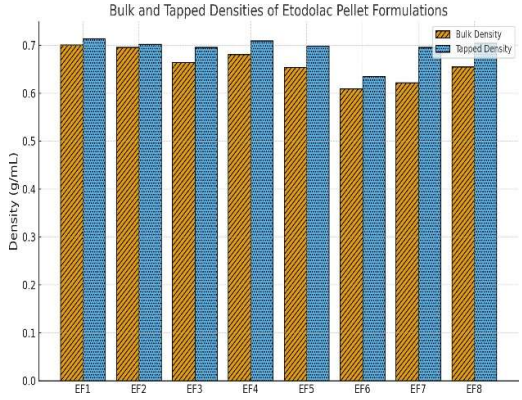


**Figure 4B.** Flow Property Indices (Hausner Ratio and Carr's Index) of Etodolac Pellet Formulations

## 2.5. Drug content

Drug content was uniform across batches (98.27-102.34%), supporting adequate blend uniformity and minimal loss during processing.

**Table 6.** Drug Content Uniformity

| Code | Drug Content (%), Mean ± SD |
|---|---|
| EF1 | 100.21 ± 2.83 |
| EF2 | 99.56 ± 2.35 |
| EF3 | 102.34 ± 1.79 |
| EF4 | 98.27 ± 0.56 |
| EF5 | 100.47 ± 2.02 |
| EF6 | 99.96 ± 1.55 |
| EF7 | 100.68 ± 2.04 |
| EF8 | 101.11 ± 2.12 |

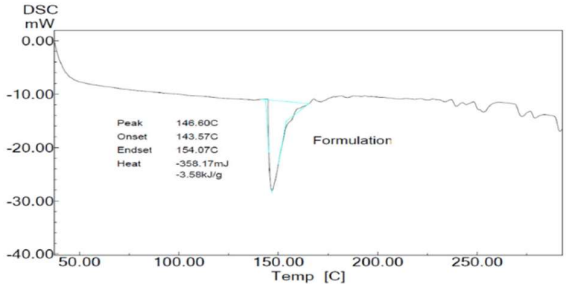


**Figure 5.** Drug Content Uniformity of Etodolac Pellet Formulations

## 2.6. Particle-size distribution

Pellets exhibited mean diameters of 1034-1269 µm with narrow spans (0.50-0.65), indicating tight distributions favourable for reproducible filling and dissolution.

**Table 7.** Laser Diffraction Particle Size Metrics

| Code | Mean (µm) | d (0.1) (µm) | d (0.5) (µm) | d (0.9) (µm) | Span |
|---|---|---|---|---|---|
| EF1 | 1034.40 | 755.85 | 1010.56 | 1417.23 | 0.65 |
| EF2 | 1195.15 | 833.06 | 1098.48 | 1512.98 | 0.59 |
| EF3 | 1269.62 | 817.84 | 1174.66 | 1427.87 | 0.52 |
| EF4 | 1171.67 | 824.90 | 1178.95 | 1422.78 | 0.50 |

| | | | | | |
|---|---|---|---|---|---|
| EF5 | 1127.37 | 897.14 | 1191.50 | 1421.95 | 0.55 |
| EF6 | 1158.21 | 868.65 | 1135.42 | 1523.76 | 0.57 |
| EF7 | 1087.95 | 843.17 | 1102.67 | 1407.81 | 0.61 |
| EF8 | 1223.48 | 815.94 | 1168.85 | 1502.34 | 0.53 |

**Figure 6A.** Particle Size Distribution of Etodolac Pellet Formulations

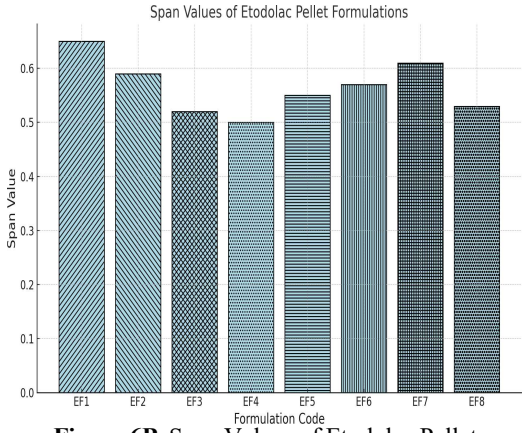


**Figure 6B.** Span Values of Etodolac Pellet Formulations

## 2.7. Morphology (SEM)

Scanning electron microscopy revealed that the prepared pellets were nearly spherical in shape, with surfaces appearing smooth to slightly textured, which is characteristic of well-spheronized pellets. The uniformity in size and spherical geometry is an indication of successful extrusion- spheronization, where microcrystalline cellulose provided sufficient plasticity to support rounding and compaction during spheronization. The smooth surfaces also suggest low friability and good mechanical strength, which are desirable properties for downstream processing such as capsule filling or tablet compression. At the magnifications examined, no cracks, fissures, lamination, or gross defects were observed, confirming that the pellets had intact structural integrity. The slightly textured surfaces, likely due to lactose and disintegrant incorporation, may be advantageous for faster wetting and dissolution once in contact with the dissolution medium. In inference, the SEM micrographs support the view that the optimized formulations achieved both good mechanical stability and functional surface properties required for immediate-release performance.

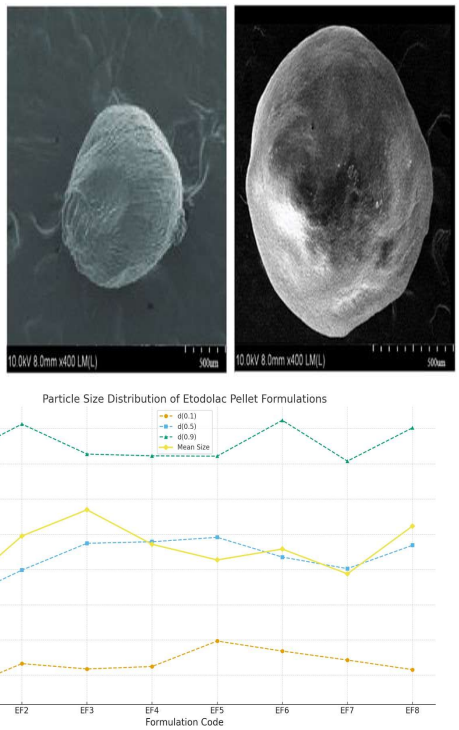


**Figure 7.** Scanning electron microscopy indicating the photomicrographs

## 2.8. *In vitro* dissolution

The in vitro dissolution study demonstrated that pure etodolac exhibited very slow release, with only 12.97 ± 0.60% drug release at 30 minutes, confirming its poor aqueous solubility. In contrast, all solid-dispersion pellet formulations (EF1-EF8) showed progressively higher dissolution, depending on the composition and ratio of excipients used. At the 30-minute mark, the release order was EF8 > EF7 > EF6 > EF5 > EF4 > EF3 > EF2 > EF1 ≫ pure drug, highlighting the formulation-dependent performance. Among these, EF8 achieved almost complete release (99.99 ± 0.31%), meeting the criteria for immediate-release dosage forms, while EF7 reached 89.32 ± 0.28%, also indicating rapid dissolution. Mid-range formulations such as EF5 and EF6 released 62-72% of the drug, whereas EF1-EF3 showed relatively lower release enhancement, with EF1 at only 16.54 ± 0.50%. The results confirm that combining PVP K30 as a solubility enhancer, SLS as a wetting agent, and croscarmellose sodium as a disintegrant significantly improved dissolution. The optimized EF8 formulation demonstrated that carefully balancing drug–polymer ratio and excipient selection can overcome etodolac's dissolution-limited absorption and provide a robust, scalable, and efficient immediate-release delivery system (Table 8).

**Table 8.** In Vitro Drug Release in pH 1.2 (%, Mean ± SD)

| Time (min) | Pure | EF1 | EF2 | EF3 | EF4 | EF5 | EF6 | EF7 | EF8 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 4.35 ± 0.31 | 6.41 ± 0.52 | 11.35 ± 0.56 | 31.21 ± 0.20 | 36.51 ± 0.29 | 44.45 ± 0.39 | 57.86 ± 0.21 | 67.83 ± 0.27 | 77.32 ± 0.57 |
| 10 | 5.11 ± 0.36 | 8.21 ± 0.32 | 13.36 ± 0.67 | 33.67 ± 0.24 | 38.41 ± 0.23 | 47.44 ± 0.31 | 61.94 ± 0.34 | 74.90 ± 1.39 | 81.47 ± 0.45 |
| 15 | 8.28 ± 0.62 | 10.34 ± 0.52 | 15.76 ± 0.20 | 35.64 ± 0.33 | 41.61 ± 0.24 | 51.42 ± 0.77 | 64.94 ± 0.28 | 77.94 ± 0.32 | 89.58 ± 0.23 |
| 20 | 9.47 ± 0.59 | 12.74 ± 0.63 | 17.40 ± 0.57 | 37.57 ± 0.21 | 43.61 ± 0.36 | 54.33 ± 0.30 | 68.85 ± 1.04 | 84.31 ± 0.48 | 93.32 ± 0.29 |
| 25 | 10.61 ± 0.44 | 14.41 ± 0.17 | 19.20 ± 0.25 | 38.76 ± 0.21 | 45.51 ± 0.27 | 58.31 ± 0.70 | 70.28 ± 0.29 | 87.57 ± 0.22 | 99.80 ± 0.21 |
| 30 | 12.97 ± 0.60 | 16.54 ± 0.50 | 21.35 ± 0.36 | 41.44 ± 0.24 | 46.11 ± 0.25 | 62.19 ± 0.97 | 72.38 ± 0.98 | 89.32 ± 0.28 | 99.99 ± 0.31 |

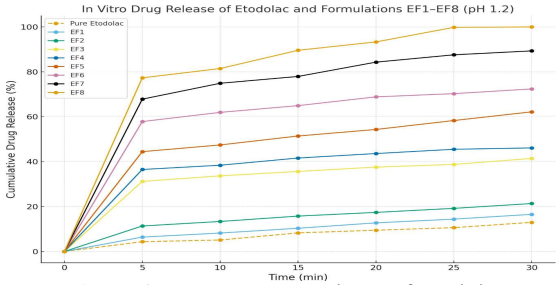


**Figure 8.** *In Vitro* Drug Release of Etodolac and Formulations EF1–EF8 (pH 1.2)

## 4. Discussion

The results of this work clearly show that etodolac, as a BCS Class II drug, is limited in its oral absorption by its low aqueous solubility and slow dissolution rate. Pure etodolac exhibited poor release characteristics, with only about 13% of the drug dissolving within 30 minutes in acidic medium, a finding that is consistent with its hydrophobic crystalline nature. Since dissolution is the rate-limiting step for such molecules, improving solubility and dissolution is central to enhancing therapeutic performance. Our findings confirm that PVP-based solid dispersions provided a marked increase in apparent solubility, and when further incorporated into pellet formulations via extrusion-spheronization, they led to a dramatic improvement in dissolution compared to the pure drug. This observation aligns well with the broader literature on polymer- stabilized amorphous dispersions, which enhance wettability, reduce crystallinity, and sustain supersaturation, thereby promoting rapid drug liberation in gastrointestinal fluids.

The results highlight the importance of the drug-to-polymer ratio and excipient balance in governing dissolution. EF8, prepared from a 5.3:1 etodolac:PVP dispersion with balanced MCC and lactose, moderate levels of SLS (15 mg), and CCS (35 mg), exhibited the highest solubility (457.6 µg/mL) and nearly complete release (99.99% at 30 minutes). EF7 also performed strongly with 89.32% release, while EF6, despite having the highest level of CCS (70 mg), achieved slower release than EF8. This finding indicates that excessive disintegrant alone cannot guarantee faster release. Instead, dissolution depends on a synergistic interplay of amorphization from PVP, surfactant-mediated wetting by SLS, porosity created by lactose, and the mechanical structure provided by MCC. The superior performance of EF8 supports the view that a hydrophilic polymer-rich microenvironment capable of stabilizing drug supersaturation, when combined with optimal wetting and microstructural porosity, is more impactful than maximizing any single excipient. These mechanistic insights mirror earlier reports describing the “spring–parachute” model of solid dispersions, where rapid supersaturation is generated and maintained long enough to accelerate absorption.

Pelletization played a crucial role in shaping release performance and manufacturability. The extrusion-spheronization method successfully yielded spherical pellets with smooth to slightly textured surfaces, as confirmed by SEM, with no gross defects or lamination. Particle-size analysis demonstrated narrow distributions with span values of 0.50–0.65, indicating good uniformity. The mean particle size of ~1.0–1.3 mm is ideal for multiparticulate dosage forms, ensuring predictable packing, uniform capsule or tablet filling, and consistent release behaviour. MCC proved indispensable as the spheronization aid due to its plastic deformation and water-retaining properties, while lactose enhanced porosity, further supporting rapid medium penetration and dissolution.

Process optimization using Mixer Torque Rheometry (MTR) provided valuable insights into wet-mass behavior. Torque profiles indicated that a binder range of 20–25% was optimal for
achieving plasticity and cohesiveness, producing

extrudates suitable for spheronization. Under- wet masses (<15%) were brittle and unsuitable, while over-wet masses (>30%) became sticky and formed agglomerates. These observations confirm earlier studies that quantitative torque signatures can be linked to wet mass quality, extrudability, and final pellet characteristics. Thus, MTR served as an efficient process-analytical tool to improve reproducibility and batch-to- batch consistency.

The prepared pellets also demonstrated favourable handling characteristics. Flow indices indicated excellent to acceptable flow, with Hausner ratios ranging from ~1.01 to 1.12 and Carr's indices between 0.9% and 10.6%, values considered suitable for industrial-scale processing. Content uniformity remained consistent across formulations (98–102%), confirming robust distribution of drug within the pellets and minimal risk of segregation or processing loss. Dissolution testing in simulated gastric fluid (pH 1.2) confirmed the strong discriminating ability of the method. While the pure drug released only 13% at 30 minutes, the best formulations achieved near-complete release within the same period, clearly demonstrating the enhancement afforded by solid dispersions and pellet design. The use of acidic medium was appropriate for initial screening of immediate-release dosage forms; however, future work should extend to pH-shift experiments (1.2 → 6.8) and biorelevant surfactant-containing media to confirm robustness of dissolution under varying gastrointestinal conditions and support in vitro-in vivo correlations. In inference, the combined findings establish that EF8 is the best performing formulation, with EF7 ranking second. EF8 consistently outperformed all other formulations in solubility, dissolution, particle size uniformity, and flowability, while EF7 offered strong performance with only slightly higher compressibility values. Both formulations demonstrated that carefully optimized PVP-based solid dispersions, when integrated into a pelletization workflow, provide rapid and complete release suitable for immediate-release dosage forms. From a translational perspective, this

Work illustrates the industrial relevance of combining solid dispersion technology with extrusion-spheronization. The approach is solvent-free, scalable, and regulatorily acceptable, employing excipients with long-standing precedence in pharmaceutical manufacturing. By addressing etodolac's BCS II limitation, the study provides a model strategy for enhancing dissolution of poorly soluble drugs. The integration of carrier-mediated supersaturation with pellet microstructural engineering represents a rational, reproducible, and versatile platform for improving the biopharmaceutical performance of a wide range of poorly soluble APIs.

## 5. Conclusion

This work demonstrates that melt solid dispersions of etodolac with PVP K30, further processed into pellets through extrusion-spheronization, markedly improved aqueous solubility and accelerated drug release compared with the crystalline form. Systematic characterization confirmed multiple advantages: an optimal binder range of 20-25% for wet mass plasticity defined by mixer torque rheometry, excellent flow indices and compressibility values suitable for industrial handling, tight particle size distributions with low span values, uniform drug content, and significant enhancement of dissolution in simulated gastric fluid (pH 1.2). Among the eight tested formulations, EF8 emerged as the lead candidate, achieving almost complete release (99.99% within 30 minutes) alongside the highest solubility enhancement, while EF7 ranked as the second-best formulation. These findings highlight the synergistic contribution of polymer ratio, surfactant-mediated wetting (SLS), superdisintegrant activity (CCS), and pellet microstructure (MCC/lactose) in driving rapid drug liberation. In conclusion, the study provides a scalable, solvent-free, and regulatorily acceptable strategy for developing immediate-release formulations of poorly soluble BCS II drugs. Future work should extend dissolution profiling to multiple pH conditions, assess the physical stability of the amorphous fraction, establish in vitro-in vivo correlations, and evaluate manufacturability at pilot and industrial scales to ensure clinical translation.

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