M. M. A International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 18, Issue 3, 2026

Original Article

COPOVIDONE-BASED HOT-MELT EXTRUDED INDOMETHACIN CAPSULES: OPTIMIZED AMORPHOUS FORMULATION ACHIEVING ENHANCED DISSOLUTION AND IMPROVED ORAL BIOAVAILABILITY

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Received: 05 Dec 2025, Revised and Accepted: 21 Feb 2026

ABSTRACT

Objective: Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) classified asa biopharmaceutics classification system (BCS) Class II drug, characterized by low aqueous solubility and high permeability. Its poor solubility results in dissolution rate-limited and variable oral absorption. To overcome this limitation, the present study aimed to develop and optimize a copovidone-based capsule formulation using hot-melt extrusion (HME) to enhance dissolution and oral absorption.

Methods: Copovidone was selected as the polymer of choice following an initial screening. A two-factorial experimental design was employed to optimize the critical HME process parameters. The prepared extrudates were characterized using powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and Fourier-transform infrared spectroscopy (FTIR) to assess the solid-state characteristics of indomethacin and potential drug–polymer interactions. The optimized extrudate was filled into capsules and evaluated for mechanical strength, *in vitro* dissolution performance, and accelerated stability (40±2 °C and 75±5% relative humidity for 3 mo) in accordance with International Council for Harmonization (ICH) guidelines. Pharmacokinetic studies were conducted in male Sprague–Dawley (SD) rats, and plasma drug concentrations were quantified using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method.

Results: The optimized formulation demonstrated a significant improvement in aqueous solubility and a faster dissolution rate compared to the pure drug and marketed tablet ($p<0.05$). PXRD and DSC analyses confirmed the complete conversion of indomethacin into an amorphous form within the copovidone matrix, whereas FTIR analysis indicated the absence of detrimental drug–polymer interactions. Pharmacokinetic evaluation revealed a faster absorption rate, characterized by a 1.16-fold increase in maximum plasma concentration (C_{max}) and a markedly reduced time to reach (T_{max}), indicating rapid early systemic exposure. Stability studies confirmed the maintenance of the amorphous state and dissolution performance throughout the storage period.

Conclusion: The findings demonstrate that copovidone-based hot-melt extrusion is an effective strategy for improving solubility, dissolution, and the rate of oral absorption of poorly water-soluble indomethacin, leading to enhanced early systemic exposure. The optimized amorphous capsule formulation shows strong potential for further pharmaceutical development and commercialization in the future.

Keywords: Hot-melt extrusion, Copovidone, Indomethacin, Amorphous solid dispersion, Capsule formulation, Solubility enhancement

DOI: https://dx.doi.org/10.22159/ijap.2026v18i3.57709 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Hot-melt extrusion (HME) is a robust, scalable, and solvent-free manufacturing technique widely used in the pharmaceutical industry to improve the solubility and oral performance of poorly water-soluble drugs. The process enables intimate molecular mixing of active pharmaceutical ingredients (APIs) with polymeric carriers under controlled thermal and mechanical conditions, resulting in uniform extrudates with improved physical stability and dissolution characteristics [1–3]. The use of co-rotating twin-screw extruders further enhances mixing efficiency, process reproducibility, and suitability for continuous large-scale manufacturing, making HME particularly effective for addressing dissolution-limited bioavailability in biopharmaceutical classification system (BCS) Class II drugs [4].

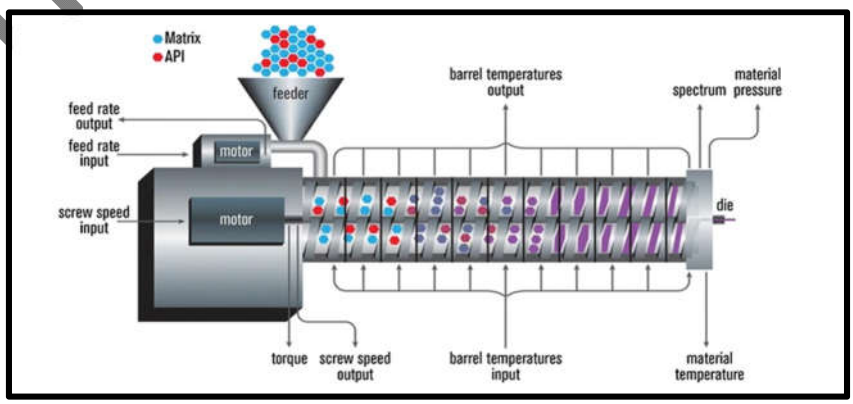

Fig. 1: Schematic representation of the twin-screw hot-melt extrusion (HME) process [5]

BCS Class II drugs exhibit high membrane permeability but poor aqueous solubility, with dissolution being the primary rate-limiting step for oral absorption. Insufficient dissolution often leads to delayed therapeutic onset, variable plasma drug concentrations, and reduced bioavailability. Although formulation approaches such as particle size reduction, solid dispersions, and nanotechnology-based systems have been explored to overcome these limitations, challenges related to scalability, process reproducibility, and long-term stability remain [6].

Indomethacin is a widely used BCS Class II nonsteroidal anti-inflammatory drug (NSAID) for the treatment of pain and inflammatory disorders. However, its low aqueous solubility and slow dissolution rate restrict gastrointestinal absorption, resulting in variable oral bioavailability and fluctuating systemic exposure [7, 8]. Conventional strategies such as micronization and salt formation have demonstrated limited success, necessitating the development of more advanced formulation approaches.

HME facilitates the development of amorphous solid dispersions (ASDs), wherein the drug is molecularly dispersed within a polymer matrix, leading to enhanced dissolution and improved oral bioavailability [9–11]. Among the polymers employed for HME, copovidone (polyvinylpyrrolidone–vinyl acetate copolymer) is particularly advantageous due to its relatively low glass transition temperature, good miscibility with poorly water-soluble drugs, and ability to stabilize the amorphous state by inhibiting recrystallization [12].

Despite extensive research on HME-based amorphous solid dispersions of indomethacin using polymers such as polyethylene glycol, Soluplus®, and HPMCAS, systematic studies focusing on copovidone-based hot-melt extruded indomethacin formulations—especially in capsule dosage forms with integrated process optimization and *in vivo* pharmacokinetic validation-remain limited [13].

Therefore, the present study aims to develop and optimize a copovidone-based hot-melt extruded formulation of indomethacin to enhance its dissolution and oral bioavailability. A factorial design approach was employed to optimize extrusion parameters, and the optimized extrudates were characterized using PXRD, DSC, and FTIR to confirm amorphization and drug–polymer compatibility. Furthermore, the formulation was evaluated for dissolution performance, stability under International Council for Harmonization (ICH) conditions, and *in vivo* pharmacokinetics in male Sprague–Dawley rats using a validated LC–MS/MS method.

MATERIALS AND METHODS

Chemicals and reagents

Indomethacin (USP grade) was procured from Yarrow Chemicals Pvt. Ltd., Mumbai, India, and used as the model Biopharmaceutics Classification System (BCS) Class II drug. Hydroxypropyl cellulose (HPC EXF) was obtained from Ashland Inc., Lexington, USA. Soluplus® (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer) and copovidone (Kollidon® VA 64) were supplied by BASF SE (Ludwigsh Polyethylene oxide (Polyox WSR-N) was procured from BASF SE (Ludwigshafen, Germany). Analytical-grade solvents, including methanol and chloroform, were purchased from Merck Life Science Pvt. Ltd., Mumbai, India. Milli-Q water was prepared in-house and used for the entire study.

Instrumentation

Hot-melt extrusion was performed using a co-rotating twin-screw extruder (Omicron 10P; Steer Life India Pvt. Ltd., Bengaluru, India). Differential scanning calorimetry (DSC) analysis was performed using a DSC instrument (Shimadzu, Kyoto, Japan). Fourier-transform infrared (FTIR) spectroscopy was performed using an FTIR spectrophotometer (Shimadzu, Kyoto). Powder X-ray diffraction (PXRD) analysis was conducted using an X-ray diffractometer (Proto Manufacturing Ltd., Ontario, Canada). Tablet evaluation parameters were assessed using a disintegration tester, friability tester (Electrolab, Mumbai, India), hardness tester (Erweka GmbH, Langen, Germany), and analytical balance (Ohaus Corporation, Parsippany, USA).

Methods

Drug-polymer composition

Physical mixtures of indomethacin with distinct polymers (Soluplus®, Copovidone, and Poly-oxy ethylene) were prepared at 1:1, 1:2, 1:3, and 1:4 (w/w) ratios using a fixed batch size of 10 g. The extrudates were initially evaluated visually for clarity, surface homogeneity, and the absence of phase separation as a preliminary screening step. Formulations exhibiting translucent and smooth extrudates were selected for further evaluations. Quantitative confirmation of drug–polymer miscibility and solid-state behavior was subsequently performed using DSC and PXRD analyses, as described in Section 2.3.4 of this manuscript [13].

Hot melt extrusion processing

Hot-melt extrusion was performed using a co-rotating twin-screw extruder (Omicron 10P, Steer Life, Bengaluru, India). The drug–polymer blend was fed at 2 g/min with a screw speed of 300–400 rpm. The barrel temperature was maintained at 30, 80, 160, and 160 °C across successive zones to enable controlled melting and uniform mixing. The initial low-temperature zones (30–80 °C) facilitated the gradual softening of copovidone and stable feeding of the blend, while the higher-temperature zones (160 °C) exceeded the glass transition temperature of copovidone (~106 °C) and approached the melting point of indomethacin (~162 °C), thereby promoting complete drug melting, molecular dispersion, and formation of an amorphous solid dispersion without inducing thermal degradation. Stable processing conditions were defined by a torque range of approximately 20–50%, within which smooth and continuous extrudates were obtained without evidence of overloading or process instability. Only smooth and homogeneous extrudates with acceptable torque values were selected for further milling and characterization (fig. 2) [14, 15].

Fig. 2: Steer omicron 10P hot-melt extruder used for processing indomethacin–copovidone formulations. The image is provided for illustrative purposes; the actual extrusion performance and product characteristics may vary depending on the screw configuration, processing parameters, and specific equipment setup. Adapted with permission from steer engineering Pvt. Ltd

Process optimization using design of experiments (DoE)

A 3^2 full factorial design was employed to optimize the most promising drug–polymer combination and evaluate the influence of critical processing variables on extrusion performance and formulation quality. Screw speed (300, 400, and 500 rpm) and barrel temperature (160, 180, and 190 °C) were selected as independent variables and systematically varied (table 1). The optimized processing conditions (180 °C and 400 rpm) were selected based on the highest experimentally observed aqueous solubility in combination with stable torque and power consumption values. Torque (%), power consumption (kWh), and aqueous solubility (mg/ml) were selected as dependent variables, representing indicators of process stability, energy utilization, and formulation performance, respectively.

The selected temperature levels were determined based on preliminary extrusion trials and thermal considerations to ensure processing above the glass transition temperature of copovidone (~106 °C) and near or slightly above the melting point of indomethacin (~162 °C), thereby facilitating complete drug amorphization while minimizing the risk of thermal degradation. Similarly, the selected screw speed range (300–500 rpm) was chosen to provide adequate shear and distributive mixing while maintaining a stable extrusion and acceptable torque levels.

The drug–polymer ratio of indomethacin to copovidone (1:3, w/w), identified as optimal during preliminary screening studies, was maintained as a constant throughout the experimental design and was not included as a variable factor.

To monitor the process stability and mechanical energy input, the torque and power consumption were continuously recorded during each experimental run. The power consumption ranged from 0.4 to 0.65 kWh, whereas the torque values ranged from 20 to 50%, indicating consistent and stable extrusion across the investigated design space. Based on the experimental outcomes, a barrel temperature of 180 °C and a screw speed of 400 rpm were selected as optimal, as they provided the highest observed aqueous solubility along with stable torque and power consumption values, demonstrating efficient and robust extrusion performance [16].

Table 1: Design of experiment (DoE) layout for optimizing hot-melt extrusion parameters for indomethacin–copovidone extrudates

Factors (Independent variables)	Level			Machine responses (Dependent variables)	Range
	-1	0	+1		
Temperature (°C) (F1)	160	180	190	Torque (%)	20%-50%
Screw speed(rpm)(F2)	300	400	500	Power consumption (kWh)	0.4-0.65kWh
				Aqueous solubility (mg/ml)	Observed experimentally

Independent variables (factors) were coded as –1 (low), 0 (medium), and+1 (high). Dependent variables (torque %, power consumption in kWh, and aqueous solubility in mg/ml) were measured experimentally during hot-melt extrusion runs

Characterization and evaluation

Particle size reduction and sizing

Optimized extrudates were initially crushed through a 1.5 mm mesh and then sieved through #100 to produce a fine, consistent powder that could be used for solubility testing and tablet formulation.

Saturation solubility studies

The saturation solubility was determined using the shake-flask method. An excess amount of sample (approximately 1 g) was added to 10 ml of distilled water in tightly stoppered vials and shaken in an orbital shaker at 25±1 °C for 24 h to ensure that equilibrium was reached. After equilibration, the suspensions were centrifuged, and the supernatant was filtered through a 0.45 µm membrane filter. A fixed volume of 1 ml of the clear supernatant was withdrawn and diluted with chloroform prior to analysis. The drug concentration was determined using a previously established calibration curve. All measurements were performed in triplicate, and the results are expressed as the mean±SD [17].

Solid-state profiling

Fourier transform infrared spectroscopy (FTIR)

A Shimadzu 8400S spectrophotometer (Japan) was used to record the FTIR spectra to evaluate possible drug–polymer interactions. The samples were made into KBr pellets and scanned between 4000 and 400 cm^{-1}. The emergence, shift, or disappearance of distinctive peaks suggestive of intermolecular interactions was assessed in the spectra [18].

Differential scanning calorimetry (DSC)

A Shimadzu DSC-60 calorimeter was used to investigate the thermal behavior of the materials. A nitrogen purge (20 ml/min) was used to heat 2–3 mg of each sample from 30 °C to 300 °C at a rate of 10 °C/min after it had been precisely weighed and sealed in aluminum pans. The samples were hermetically sealed inaluminum pans to prevent moisture loss and oxidative effects during thermal analysis. Thermograms were evaluated for crystallinity-related transitions and melting endotherms [19].

Powder X-ray diffraction (PXRD)

To assess the crystalline characteristics of the pure drugs and extrudates, X-ray diffraction patterns were acquired using a Proto diffractometer (USA). The samples were scanned over a 2θ range of 10–60 °at a scan rate of 6°/min with a step size of 0.02 °while operating at 40 kV and 30 mA. The reduction or absence of crystalline peaks was evaluated by comparing the diffractograms [20]. Prior to analysis, the samples were gently ground using an agate mortar and pestle to obtain a uniform particle size and minimize preferred orientation effects.

Flowability evaluation of milled extrudates

Flow properties

Powder flowability was assessed by determining the tapped density, bulk density, Hausner's ratio, Carr's index, and angle of repose using an ElectroLab ETD 1020 tap density tester. Carr's Index values<15% and Hausner's ratio<1.25 were interpreted as indicative of good flow properties [21]. Flow property classifications were assigned based on pharmacopeial guidelines and published USP-based criteria for the Carr index, Hausner ratio, and angle of repose.

Particle size distribution

The particle size distribution of the milled extrudates was determined by sieve analysis using an Electro Lab sieve shaker with standard sieves. The results were expressed as the percentage of material retained on each sieve fraction [22].

Formulation of indomethacin conventional capsule

Conventional indomethacin capsules were prepared by blending the optimized granules with the capsule premix, as shown in table 2. The milled granules of the indomethacin formulation were accurately weighed according to the formulation table and co-sifted through a #40 mesh sieve to ensure uniformity. The required quantity of capsule premix excipients was passed through a #40 sieve and then transferred to a container containing indomethacin granules. The mixture was then blended for 10 min to obtain a uniform powder blend. Finally, the prepared blend was filled into size 5 hard gelatine capsules to produce a conventional capsule formulation.

Table 2: Composition of the optimized indomethacin capsule formulation prepared from copovidone-based solid dispersions

Ingredient	Quantity per capsule (mg)
Optimized solid dispersed indomethacin	Optimized solid dispersion of indomethacin (25 mg indomethacin+75 mg Copovidone)
Polyplasdone™ xl Copovidone	2
AEROSIL® colloidal silicon dioxide	1
Magnesium stearate	1
Total	104 Mg

All quantities are expressed per capsule. The optimized solid dispersed indomethacin consists of 25 mg of indomethacin incorporated in 75 mg of Copovidone.

Post-processing characteristics of indomethacin capsules

In accordance with compendial standards and regulatory guidelines for unit dosage capsule products, the filled Indomethacin capsules were subjected to a series of quality control tests, such as weight variation, drug potency, dissolution, and moisture content, to ensure batch uniformity, integrity, and compliance.

***In vitro* dissolution studies**

In vitro dissolution studies were conducted using a USP type II (paddle) dissolution apparatus. The dissolution medium consisted of 900 ml of ammonium buffer of pH 9.5 maintained at 37±0.5 °C, representing the sink conditions for indomethacin. The paddle rotation speed was set to 50 rpm. Capsules equivalent to 25 mg indomethacin was placed in each dissolution vessel. At predetermined time intervals (5, 10, 15, 30, 45, and 60 min), 5 ml samples were withdrawn manually and immediately replaced with an equal volume of fresh dissolution medium, which was maintained at the same temperature. The withdrawn samples were filtered through a 0.45 µm membrane filter, diluted, and analyzed spectrophotometrically. Dissolution studies were performed in triplicate, and the results are expressed as the mean±SD.

Bioanalytical methodology for pharmacokinetic evaluation

Chromatographic and mass spectrometric conditions

Indomethacin levels in plasma were measured using a Shimadzu LC-20AD system linked to an AB Sciex 4000 QTRAP mass-spectrometer. Chromatographic separation was achieved using a Chromasol ONYX Phenyl Hexyl column (5 µm, 4.6 × 50 mm) with a mobile phase of 0.1% formic acid and acetonitrile (30:70, v/v), delivered at a flow rate of 0.8 ml/min. The injection volume was 5 µl**, and the total runtime was 2.5 min. Detection was performed in positive electrospray ionization (ESI) mode using multiple reaction monitoring (MRM), monitoring the transition of m/z 240.2 → 196.1 for indomethacin. Plasma samples were prepared by protein precipitation using acetonitrile as an organic solvent. Briefly, 100

µl** of rat plasma was mixed with 300 µl** of acetonitrile containing the internal standard, vortex-mixed for 2 min, and centrifuged at 12,000 rpm for 10 min at 4 °C. The clear supernatant was transferred to auto sampler vials, and 2 µl** was injected into the LC–MS/MS system for analysis [23].

Bioanalytical method validation

The LC–MS/MS method was validated for linearity accordingtothe regulatory bioanalytical method validation guidelines. Calibration curves were prepared using spiked plasma samples over the concentration range of 250–80,000 ng/ml, and linearity was evaluated using least-squares regression analysis [24].

Pharmacokinetic study

Male Sprague Dawley rats (180–220 g; n = 3) were procured from the CPCSEA-registered animal breeding facility of Skanda Life Sciences, Bidadi, Ramanagara, Bengaluru, India, and used for pharmacokinetic evaluation. Animals were housed under standard controlled conditions (22±2 °C, 55±5% RH, 12 h light/dark cycle) with free access to pellet diet and water. All procedures were approved by the Institutional Animal Ethics Committee (IAEC), Skanda Life Sciences, and conducted in accordance with CPCSEA guidelines (Approval No.: IAEC-SLS-2024-116).

The rats were randomly divided into two groups (n = 3 per group). Group I received a suspension of pure indomethacin, whereas Group II received the optimized hot-melt extruded indomethacin capsules. A single oral dose of indomethacin (10 mg/kg) was administered to each animal via oral gavage. Blood samples were collected from the retro-orbital plexus under light anesthesia induced using isoflurane (2–3% v/v in oxygen). The collected blood samples were centrifuged to separate the plasma, which was then stored at –20 °C until analysis [25].

Statistical analysis

All pharmacokinetic parameters were expressed as mean±standard deviation (SD) for each group (n = 3). Statistical comparisons between the conventional suspension (G1) and the optimized HME formulation (G2) were performed using an unpaired two-tailed Student's t-test for C_{max} and $AUC_{0-\infty}$, and a Mann–Whitney U test for T_{max}, as time data were non-parametric. Statistical significance was set at $p<0.05$. Statistical analyses and graphical plots were generated using GraphPad Prism (version 10.0; GraphPad Software Inc., USA). Non-compartmental pharmacokinetic analysis was performed using the Phoenix® WinNonlin® software (Certara, USA).

Stability study

The stability of the optimized Indomethacin HME capsules prepared by hot-melt extrusion was evaluated under accelerated conditions in accordance with the ICH Q1A (R2) guidelines. The samples were placed in tightly closed HDPE containers containing a desiccant and stored in a stability chamber (Thermo Lab, India) set at 40±2 °C/75±5 % RH for 3 mo. Samples were removed at regular intervals (0, 1, 2, and 3 mo) and examined for their physical appearance, drug content, *in vitro* dissolution, and solid-state properties using PXRD and DSC. The data obtained were compared with the initial values to evaluate any alterations in crystallinity, degradation, or dissolution behavior, and hence the physical and chemical stability of the optimized formulation [26].

RESULTS

Drug–polymer screening for hot-melt extrusion of indomethacin

Extrudates corresponding to formulations I1–I8 were visually examined for clarity, surface appearance, and presence of particulates, and their initial aqueous solubility outcomes are summarized in table 3. Based on these findings, I3 and I7 were selected for optimization. The preliminary visual observations were further supported by solid-state characterization, where DSC and PXRD analyses confirmed amorphization and the absence of crystalline drug, indicating good drug–polymer miscibility in the selected formulations.

Initial solubility evaluation of HME formulations

The impact of the polymer ratio and type on aqueous solubility was assessed for formulations I1–I8 (table 3). Soluplus®-containing formulations were most soluble at a 1:1 ratio, which decreased with increasing polymer ratios. However, copovidone-based formulations exhibited a concentration-dependent increase in solubility, with maximum solubility at a 1:3 ratio (I7: 0.000746 mg/ml). These findings indicate that copovidone compares favorably with soluplus® in increasing the solubility of indomethacin, especially at increased polymer concentrations.

Table 3: Aqueous solubility of indomethacin solid dispersions prepared with soluplus® and copovidone at different drug–polymer ratios (mean±SD, n = 3)

Drug: polymer	Trial no.	Ratio	Solubility (mg/ml, (mean ±SD (n = 3)
Indomethacin: soluplus	I1	1:1	0.00077±0.00004
	I2	1:2	0.00045±0.00003
	I3	1:3	0.00052±0.00002
	I4	1:4	0.00037±0.00003
Indomethacin: copovidone	I5	1:1	0.00203±0.00010
	I6	1:2	0.00514±0.00026
	I7	1:3	0.00746±0.00037
	I8	1:4	0.00377±0.00019

Solubility values are expressed as mean±standard deviation (SD); n = 3 for each drug–polymer ratio.

In light of its favorable performance, formulation I7 was selected for further process optimization. The concentration-dependent solubility enhancement observed with copovidone is consistent with its ability to form stable amorphous dispersions and sustain drug supersaturation through intermolecular interactions. Similar polymer-dependent solubility trends have been reported for copovidone-based amorphous systems of other BCS Class II drugs, supporting its suitability as a carrier for indomethacin.

Process optimization using design of experiments (DoE)

A 3^2 full factorial design was employed to optimize the hot-melt extrusion parameters for enhancing the solubility of indomethacin. Barrel temperature (160–190 °C) and screw speed (300–500 rpm) were selected as independent variables, whereas torque (%), power consumption (kWh), and aqueous solubility (mg/ml) were evaluated as responses to assess process stability and formulation performance (table 1).

Across all experimental runs, the torque values (25–48%) and power consumption (0.40–0.65 kWh) remained within acceptable ranges, indicating stable extrusion behavior throughout the design space. The aqueous solubility of the extrudates ranged from 0.0265 to 0.0454 mg/ml, with the highest solubility enhancement observed at a barrel temperature of 180 °C and a screw speed of 400 rpm (table 4). These processing conditions also exhibited moderate torque (45%) and acceptable power consumption (0.62 kWh), confirming efficient and reproducible extrusion performance. It should be noted that the selection of the 180 °C barrel temperature and 400 rpm screw speed was based on the highest experimentally observed aqueous solubility (0.0454 mg/ml, table 4), together with acceptable torque and power consumption values, rather than on model-derived statistical optimization.

Table 4: Experimental results from the DoE trials for optimizing indomethacin–copovidone solid dispersions

Run	Temperature (□)	Screw speed (rpm)	Torque (%)	Power consumption (kWh)	Solubility (mg/ml)
B1	160	300	47.5	0.65	0.0312
B2	160	500	45	0.6	0.0328
B3	160	400	37.5	0.55	0.0295
B4	180	300	25	0.4	0.0273
B5	180	400	45	0.6	0.0454
B6	180	500	35	0.51	0.0334
B7	190	400	45	0.62	0.0293
B8	190	300	45	0.63	0.0265
B9	190	500	45	0.6	0.0312

Torque (%) and power consumption (kWh) were recorded directly from the extruder during each DoE run. Solubility (mg/ml) represents the experimentally observed value for each run.

Analysis of variance (ANOVA)

ANOVA for torque (%)

As shown in table 5, The ANOVA results demonstrated that the model was not significant for torque, as indicated by the low F-ratio (0.0633) and high p-value (0.9770). This suggests that the selected formulation variables did not exert a measurable influence on the torque within the studied range. The high error variance relative to the model variance further indicates that most of the variability in the torque arose from experimental noise rather than the investigated factors.

Table 5: ANOVA summary for torque response in the indomethacin hot-melt extrusion DoE study

Source	Degree of freedom	Sum of squares	Mean square	F Ratio	p-value (Prob>F)
Model	3	15.60020	5.2001	0.0633	0.9770
Error	5	410.78869	82.1577	—	—
C. Total	8	426.38889	—	—	—

ANOVA was performed to evaluate the effect of independent variables on torque (%). DF = degrees of freedom; SS = sum of squares; MS = mean square; F ratio = test statistic; p-value indicates statistical significance.

ANOVA for power consumption (kWh)

As shown in table 6, The ANOVA results revealed that the model was not statistically significant for power consumption, with an F-ratio of 0.0318 and a corresponding p-value of 0.9914. This indicates that the formulation or process variables studied did not have any meaningful effect on the power consumption within the evaluated design space. The low model variance compared to the relatively higher error variance suggests that the observed variability in power consumption was largely due to experimental noise rather than the influence of the selected factors.

Table 6: ANOVA summary for power consumption in the indomethacin hot-melt extrusion DoE study

Source	Degree of freedom	Sum of squares	Mean square	F Ratio	p-value (Prob>F)
Model	3	0.00090000	0.000300	0.0318	0.9914
Error	5	0.04710000	0.009420	—	—
C. Total	8	0.04800000	—	—	—

ANOVA was performed to evaluate the effect of independent variables on power consumption. DF = degrees of freedom; SS = sum of squares; MS = mean square; F ratio = test statistic; p-value indicates statistical significance.

ANOVA for aqueous solubility (mg/ml)

As shown in table 7, the ANOVA evaluation indicated that the model was not statistically significant for aqueous solubility, as evidenced by the low F-ratio and high p-value (Prob>F = 0.9914). This result suggests that the selected process variables did not exert a systematic influence on the aqueous solubility within the investigated experimental range. The relatively low model variance compared to the residual error further indicates that the observed variability in solubility was primarily attributable to experimental variation rather than the independent variables studied.

The lack of statistical significance in aqueous solubility can be attributed to the formation of a fully amorphous solid dispersion across the evaluated processing window. Once complete amorphization is achieved, modest variations in the barrel temperature and screw speed are unlikely to produce meaningful changes in the equilibrium solubility. Therefore, the observed ANOVA outcome reflects the robustness of the extrusion process within the defined design space, rather than a limitation of the experimental design. This behavior is characteristic of a robust hot-melt extrusion process, where once complete amorphization is achieved, moderate variations in processing parameters have minimal impact on formulation performance, a phenomenon widely reported in the HME literature.

Table 7: ANOVA summary for aqueous solubility in the indomethacin–copovidone hot-melt extrusion DoE study

Source	Degree of freedom	Sum of squares	Mean square	F Ratio	p-value (Prob>F)
Model	3	0.00003045	0.000010	0.2321	0.8705
Error	5	0.00021865	0.000044	—	—
C. Total	8	0.00024910	—	—	—

ANOVA was performed to evaluate the effect of independent variables on aqueous solubility (mg/ml). DF = degrees of freedom; SS = sum of squares; MS = mean square; F ratio = test statistic; p-value indicates statistical significance.

Overall, the ANOVA results for torque, power consumption, and aqueous solubility demonstrated that none of the evaluated models were statistically significant within the experimental range studied. This outcome reflects the deliberate selection of a narrow and practically relevant processing window, within which variations in the barrel temperature and screw speed did not exert a measurable influence on the evaluated responses. Rather than indicating a limitation of the experimental design, these findings suggest a robust extrusion process that is relatively insensitive to minor process fluctuations, which is desirable for scalable pharmaceutical manufacturing applications.

Contour profiler

Contour profiler for torque (%)

The uniform pattern indicated a stable torque across all conditions, with no strong interactions or gradients. ANOVA results supported this and confirmed that there was no significant model effect. Therefore, the overall torque remained steady, demonstrating consistent process performance (fig. 3).

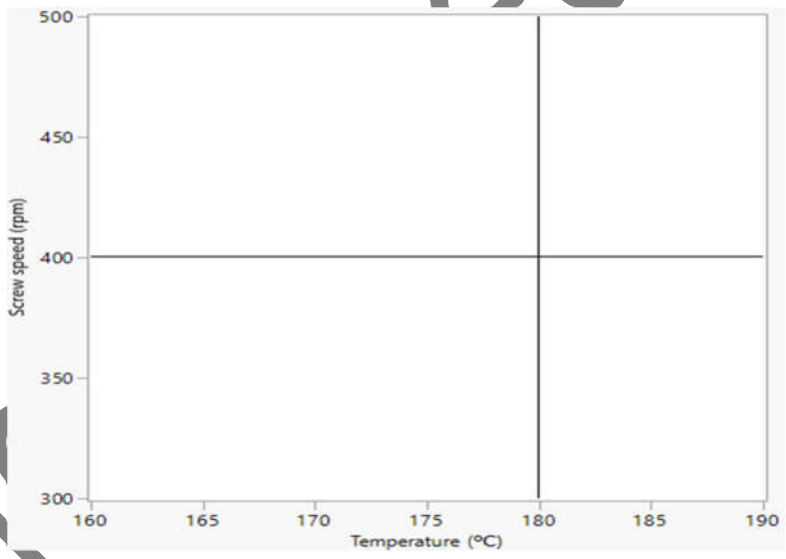

Fig. 3: Contour plot showing the effects of barrel temperature and screw speed on torque during hot-melt extrusion. The relatively flat response surface indicates minimal variation in torque across the studied design space, demonstrating robust and stable extrusion behaviour

Contour profiler for power consumption (kWh)

The plot shows a flat, uniform pattern, indicating that the temperature and screw speed had minimal impact. The power use remained consistent under all conditions, with no interactions. ANOVA results showed a stable energy demand throughout the extrusion process (fig. 4).

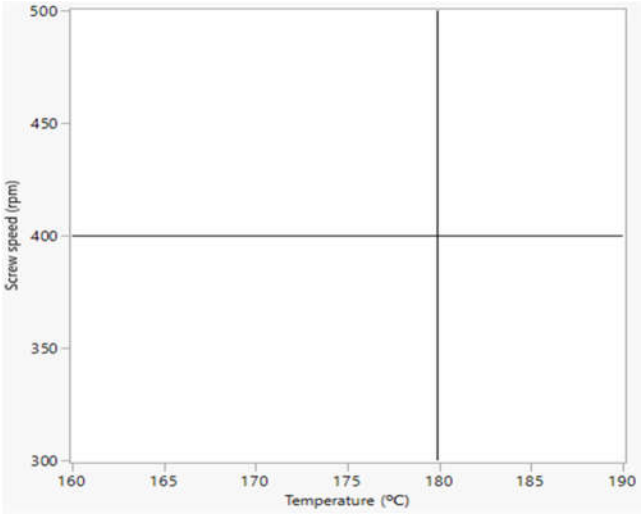

Fig. 4: Contour plot illustrating the influence of the barrel temperature and screw speed on the power consumption. The absence of steep gradients and the flat surface profile indicate that power consumption remains largely unaffected by moderate variations in processing parameters, supporting process robustness

Contour profiler for aqueous solubility (mg/ml)

The changes in temperature and screw speed did not result in any plausible changes in solubility. ANOVA results confirmed that the model was not significant for solubility, and the observed variability could influence the studied factors (fig. 5).

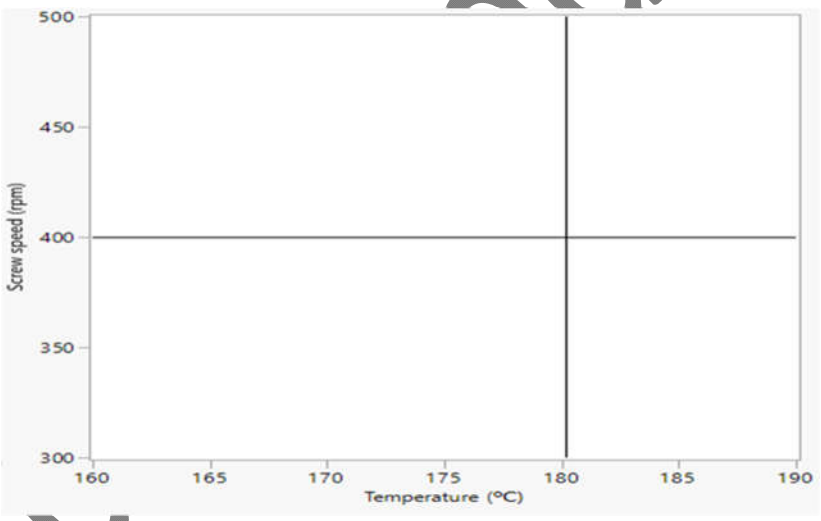

Fig. 5: Contour plot depicting the effect of barrel temperature and screw speed on the aqueous solubility of indomethacin solid dispersions. The minimal variation observed across the design space suggests that aqueous solubility is insensitive to small parameter changes once complete amorphization is achieved, confirming robustness of the optimized processing window

The contour plots for torque, power consumption, and aqueous solubility (fig. 4–6) exhibited relatively flat response surfaces across the investigated design space, indicating minimal variation in the responses with changes in the barrel temperature and screw speed. These visual trends are consistent with the ANOVA results and further support the robustness of the hot-melt extrusion process in the selected operating window.

Optimization of formulation using desirability function

The prediction profiler was used to analyze various factors, such as temperature, torque, screw speed and power consumption, solubility, and overall desirability, as depicted in fig. 6. The optimized settings (180.1 °C and 400 rpm) yielded predicted values that fell within acceptable ranges, resulting in a high overall desirability of 0.8605, demonstrating a suitable balance among all responses.

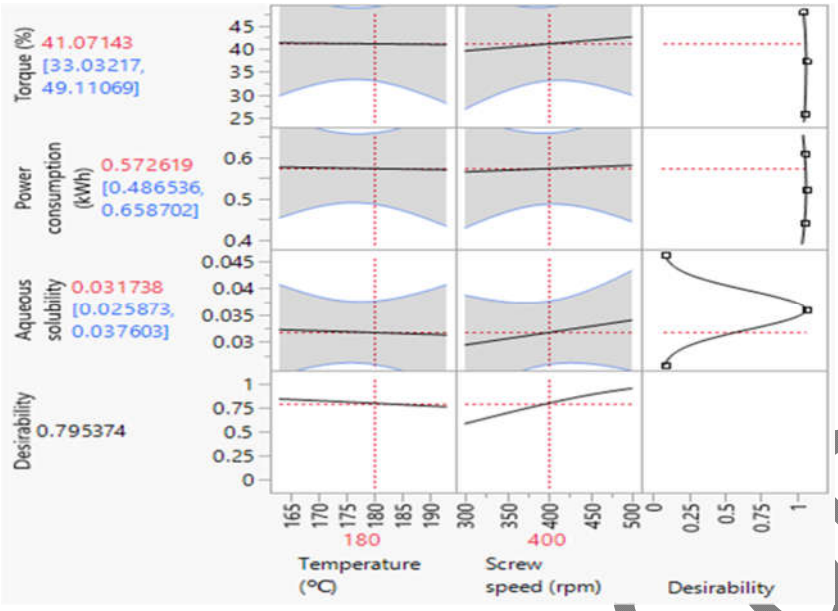

Fig. 6: Prediction profiler illustrating the combined effect of barrel temperature and screw speed on torque, power consumption, aqueous solubility, and overall desirability of the extrudate. The dashed vertical lines indicate the selected optimal processing conditions (approximately 180 °C and 400 rpm), corresponding to the highest observed solubility and stable processing performance

Characterization and evaluation

Particle size reduction and sizing

The processed extrudates, after milling and sieving, yielded a fine and even powder with a mean particle size of 116.4±6.7 µm. The percentage of particles less than 150 µm was more than 90%, suggesting its utility in tablet formulation and enhancement of dissolution performance.

Calibration curve of indomethacin

A UV–visible spectrophotometric calibration curve was obtained in chloroform in the concentration range of 20–100 µg/ml. The method exhibited excellent linearity (R^2 = 0.996), validating its suitability for quantification in solubility and dissolution studies (fig. 7).

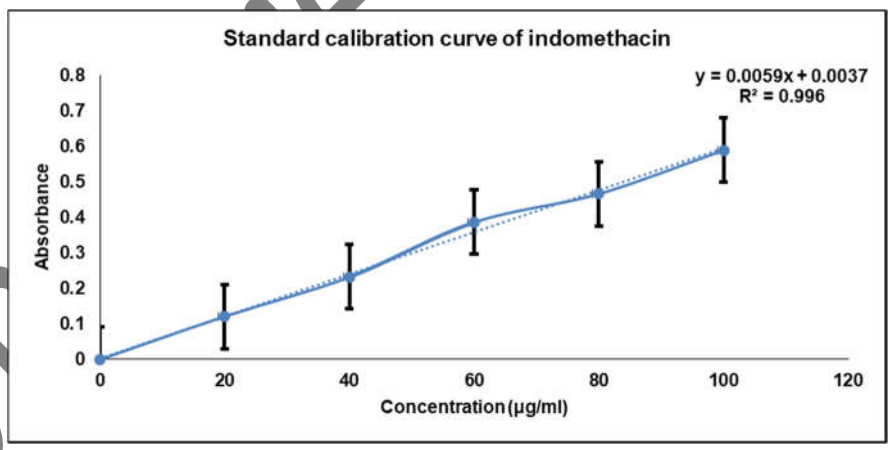

Fig. 7: Calibration curve of indomethacin obtained by UV–visible spectrophotometry in chloroform (20–100 µg/ml). The regression equation and coefficient of determination (R^2) are shown on the graph, demonstrating excellent linearity

Saturation solubility studies

The saturation solubility of pure indomethacin and hot-melt extruded optimized formulations (I3 and I7) was evaluated using the shake flask method at 25±1 °C in distilled water. The aqueous solubility of pure indomethacin was low (0.0042 mg/ml). Among the formulations, I7 (copovidone 1:3) exhibited the highest solubility (0.00746 mg/ml), corresponding to a 1.78-fold increase compared to the pure drug. In contrast, I3 (Soluplus® 1:3) showed lower solubility (0.0019 mg/ml), indicating reduced dissolution compared to that of the pure drug.

Solid state characterization

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrum of pure indomethacin exhibited characteristic peaks corresponding to O–H stretching at approximately 3400 cm^{-1} and C=O stretching vibrations near 1715 cm^{-1}. Copovidone showed prominent absorption bands associated with the C=O stretching of the lactam group at approximately 1660 cm^{-1}. In the optimized formulation (I7), minor shifts in the O–H stretching region, along with noticeable band broadening of the carbonyl stretching peaks, were observed. These spectral changes suggest the presence of intermolecular hydrogen bonding between indomethacin and copovidone, indicating molecular-level interactions rather than simple physical mixing (fig. 8).

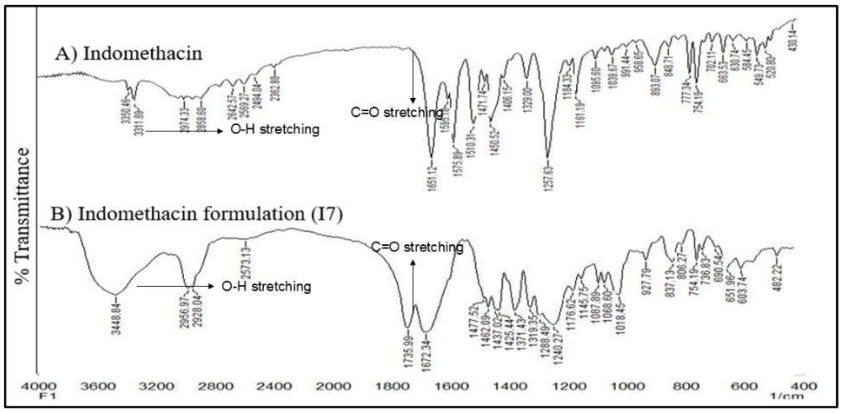

Fig. 8: FTIR spectra of pure indomethacin (A) and the optimized copovidone-based formulation I7 (B). The characteristic O–H (~3318 cm^{-1}) and C=O (~1715 cm^{-1}) stretching vibrations are labeled. Minor peak shifts and band broadening in the formulation indicate hydrogen bonding and molecular dispersion of indomethacin within the copovidone matrix

Differential scanning calorimetry (DSC)

The DSC thermogram of pure indomethacin shows a sharp endothermic peak at approximately 162 °C, corresponding to its crystalline melting point. This melting endotherm was completely absent in the optimized formulation (I7), providing strong evidence of drug amorphization after HME. The DSC trace of formulation I7 exhibited a thermal transition associated with the polymer matrix without a separate indomethacin melting event. The absence of a distinct drug melting peak and the presence of a polymer-dominated thermal transition suggest the good miscibility of indomethacin within the copovidone matrix (fig. 9)

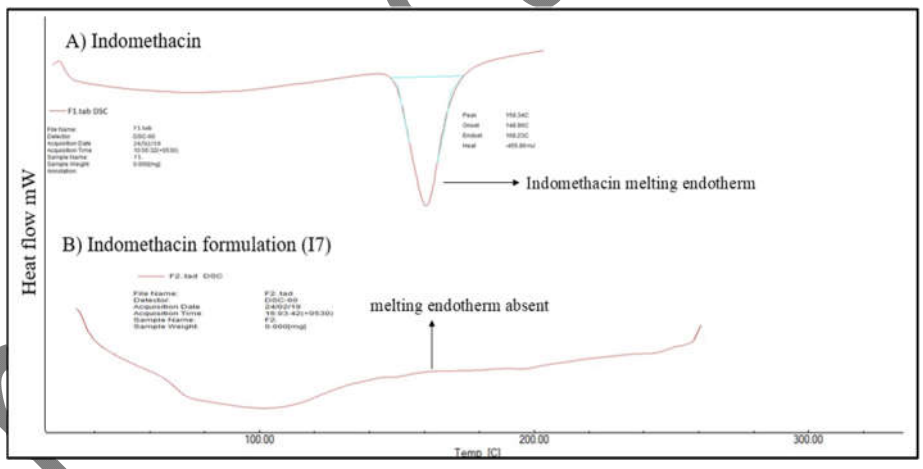

Fig. 9: DSC thermograms of pure indomethacin (A) and optimized formulation I7 (B). The sharp melting endotherm of indomethacin at approximately 162 °C is evident in the pure drug and absent in the formulation, confirming conversion to an amorphous state and indicating good miscibility within the Copovidone matrix

Powder X-ray diffraction (PXRD)

The PXRD pattern of pure indomethacin displayed multiple sharp diffraction peaks characteristic of its crystalline structure. In contrast, the optimized formulation I7 exhibited a diffuse halo pattern in the absence of distinct crystalline peaks, indicating a predominantly amorphous state. Although minor residual crystallinity below the detection limit of the technique cannot be entirely excluded, the PXRD results strongly support the effective amorphization of indomethacin within the copovidone matrix following hot-melt extrusion (fig. 10).

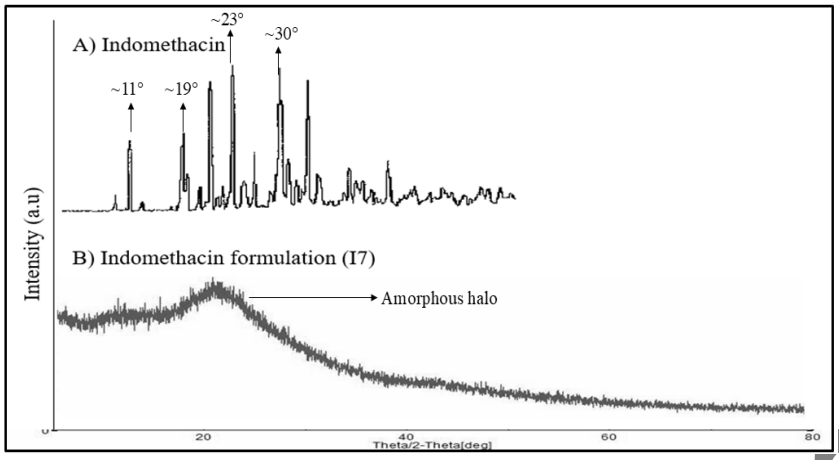

Fig. 10: PXRD patterns of pure indomethacin (A) and the optimized formulation I7 (B). Sharp crystalline reflections characteristic of indomethacin (marked by arrows) is present in the pure drug and absent in the formulation, which exhibits a broad halo pattern, confirming amorphization and molecular dispersion within the Copovidone matrix

Flowability and post-processing properties

The flow properties were measured using Carr's index, Hausner's ratio, bulk density, tapped density, and angle of repose (table 8). The initial HME blends and pure drug both demonstrated poor flow with Carr's index>25 and Hausner's ratio>1.35. Conversely, theoptimized capsule blendexhibited enhanced performance, with a Carr's index of 14%, Hausner's ratio of 1.16, and angle of repose of 8.42°, indicating fair to excellent flow properties suitable for direct compression.

Table 8: Powder flow properties of pure indomethacin, HME intermediates, and final capsule blend

S. No.	Material	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner ratio	The angle of repose (θ)
1	Pure indomethacin	0.471±0.003	0.776±0.004	39.30±0.25	1.647±0.02	30.75±0.21
2	HME Blend (pre-milling)	0.357±0.002	0.485±0.003	26.39±0.18	1.358±0.01	16.25±0.15
3	Milled HME extrudates	0.535±0.004	0.714±0.005	25.07±0.22	1.334±0.02	15.62±0.12
4	Final capsule blend	0.651±0.005	0.757±0.006	14.00±0.15	1.162±0.01	8.42±0.08

Data are presented as mean±standard deviation (SD) of three independent determinations (n = 3). Flowability classifications were assigned based on established criteria: Carr's index<15% (good), 15–25% (fair),>and>25% (poor); Hausner ratio<1.25 (good), 1.25–1.35 (fair),>and>1.35 (poor).

Post-processing characteristics of indomethacin capsules

Weight variation

The uniformity of the weight of 20 capsules was evaluated, and the results (table 9) complied with pharmacopeial limits, confirming the consistency and accuracy of the capsule-filling process.

Table 9: Weight variation results for indomethacin capsules

Tablet No.	Wt. of capsule (mg)	% Deviation	Tablet no.	Wt. of capsule (mg)	% Deviation
1	104.5	0.42%	11	103.8	−0.25%
2	103.9	−0.15%	12	103.5	−0.54%
3	103.5	−0.54%	13	104.2	+0.13%
4	104.8	+0.71%	14	104.4	+0.33%
5	102.6	−1.40%	15	104.0	−0.06%
6	103.2	−0.83%	16	104.7	+0.62%
7	104.2	+0.13%	17	104.3	+0.23%
8	104.7	+0.62%	18	103.4	−0.63%
9	104.0	−0.06%	19	105.1	+1.00%
10	103.9	−0.15%	20	104.5	+0.42%

Weight variation (%) was calculated as [(individual capsule weight – average capsule weight)/average capsule weight]×100. All weights are expressed in mg.

Drug potency

The drug potency of individual capsules ranged between 98.7% and 100.4%, with a batch mean of 99.6%, confirming a satisfactory potency within pharmacopeial specifications.

Table 10: Individual capsule potency values and batch mean for the indomethacin formulation

Capsule no.	Drug potency (%)
1	99.2
2	100.1
3	98.7
4	99.8
5	100.4
Mean±SD (n =5)	99.64±0.69

Drug potency (%) was determined for individual capsules. value are expressed as mean±standard deviation (SD) for n = 5 capsules.

Disintegration test

The disintegration time of the capsules ranged from 11 to 13 min, with a mean value of 12.2±0.7483 min (n = 5). These results indicate consistent performance across capsules, meeting the acceptable disintegration criteria for the formulation.

Table 11: Disintegration time of indomethacin capsules

Capsule no.	Disintegration time (min)
1	12
2	13
3	12
4	11
5	13
Mean±SD (n =5)	12.2±0.7483

Disintegration time (min) was measured for individual capsules. value are expressed as mean±standard deviation (SD) for n = 5 capsules.

Moisture content

The moisture content of the capsules ranged between 2.28% and 2.35%, with a batch mean of 2.31%±0.03%, indicating adequately low moisture levels suitable for maintaining formulation stability.

Table 12: Moisture content of indomethacin capsules

Capsule no.	Moisture content (%)
1	2.31%
2	2.28%
3	2.35%
4	2.29%
5	2.33%
Mean±SD(n=5)	2.31%±0.026%

Moisture content (%) was measured for individual capsules. value are expressed as mean±standard deviation (SD) for n = 5 capsules.

Dissolution studies of marketed and optimized indomethacin capsules formulation

The dissolution study demonstrated a markedly enhanced release profile for the optimized HME capsules compared to that of the marketed product. Within the first 5 min, the optimized formulation released 28.7% of the drug, compared to only 8.4% from the marketed capsules, indicating a rapid onset of dissolution. After 30 min, the optimized capsules achieved 88.3% drug release, nearly double that of the marketed product (41.7%). The overall faster and higher dissolution (98.9% at 60 min) confirms the effectiveness of hot-melt extrusion in improving the solubility and dissolution rate of the drug (fig. 11). The optimized HME formulation (I7) exhibited a markedly faster and higher dissolution rate than the marketed product, which can be attributed to drug amorphization and improved wettability within the copovidone matrix. Comparable dissolution acceleration has been reported for Copovidone-and HME-based amorphous indomethacin systems, where polymer-assisted molecular dispersion and reduced crystallinity govern rapid drug release.

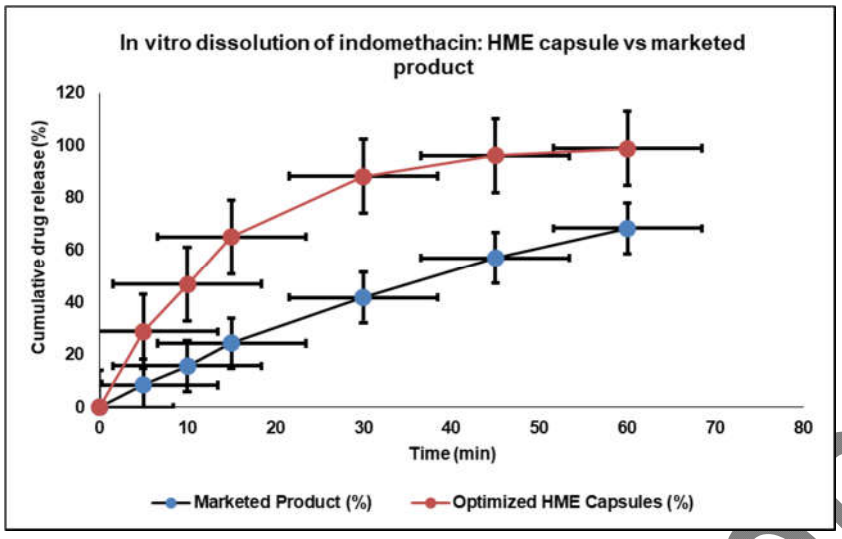

Fig. 11: Comparative *in vitro* dissolution profiles of marketed indomethacin capsules and optimized HME-based capsules in dissolution medium (specify medium, volume, pH). Data are presented as mean±SD (n = 3). The optimized HME formulation demonstrates a significantly faster and higher drug release compared to the marketed product

Release kinetics analysis

The release kinetics data summarized in table 13 indicate that the Korsmeyer–Peppas model provided the best fit for both the optimized HME formulation and the marketed product, as evidenced by the highest correlation coefficients. The release exponent (n) value of 0.62 obtained for the optimized HME formulation suggests anomalous (non-Fickian) transport, involving a combined mechanism of drug diffusion and polymer relaxation within the amorphous copovidone matrix. In contrast, the marketed formulation exhibited an n value of 0.45, which is characteristic of a predominantly Fickian diffusion-controlled drug release. These differences highlight the role of polymer–drug interactions and amorphous dispersion in governing the release behavior of HME-based formulations.

Table 13: Summary of drug release kinetic model fitting for optimized and marketed indomethacin capsules

Formulation	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsemeyer-Peppas (R^2)	n (exponent)
Optimizedindomethacin capsules	0.948	0.993	0.981	0.987	0.62
Marketedcompressindomethacin capsules	0.912	0.984	0.965	0.971	0.45

*Zero-order model: $Q_t = Q_0 + k_0 t$
*First-order model: $\log Q_t = \log Q_0 - \frac{k_1 t}{2.303}$
*Higuchi model: $Q_t = k_H t^{1/2}$
*Korsmeyer–Peppas model: $Q_t/Q_\infty = kt^n$

R^2 values represent the goodness of fit for different kinetic models. Q_t is the amount of drug released at time t, Q_0 is the initial drug amount, k_0, k_1, k_H, and k are the rate constants for zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, respectively. n is the release exponent in the Korsmeyer–Peppas model.

Bioanalytical methodology for pharmacokinetic evaluation

Chromatographic analysis

The developed LC–MS/MS method demonstrated high specificity and sensitivity for quantifying indomethacinin rat plasma. A sharp, well-resolved peak at the expected retention time confirmed the method reliability under the optimized chromatographic and mass spectrometric conditions.

Calibration and quality control

The method was linear over the range of 250–80000 ng/ml (r^2>0.99). The accuracy values for the calibration standards and quality control (QC) samples were within the acceptable bioanalytical limits (±15%), demonstrating the robustness of the method (table 14). The regression plot demonstrated strong linearity (r = 0.9812) over the full calibration range, confirming the suitability of the LC–MS/MS method for the accurate quantitative determination of indomethacin in plasma samples (fig. 12). Although most calibration standards and quality control samples met the recommended accuracy criteria, certain concentrations deviated beyond ±15%. These deviations are likely attributable to matrix effects and ion suppression at specific concentration levels, particularly at the lower and upper ends of the calibration ranges. Nevertheless, the overall method performance was considered suitable for exploratory pharmacokinetic evaluation, as indicated by the acceptable linearity, sensitivity, and reproducibility across the working range.

Table 14: Accuracy results for calibration standards and QC samples of indomethacin in plasma

S. No.	Sample name	Nominal concentration (ng/ml)	Measured concentration (ng/ml)	Accuracy (%)
1	CC1	250	272.41	108.96
2	CC2	500	457.19	91.44
3	CC3	1000	849.87	84.99
4	CC4	2500	2381.7	95.27
5	CC5	5000	4153.17	83.06
6	CC6	10000	10417.87	104.18
7	CC7	20000	23749.87	113.50
8	CC8	40000	41161.87	102.9
9	CC9	80000	88356.26	110.45
10	LQC	750	753.94	100.53
11	MQC	8000	9067.01	113.34
12	HQC	16000	17950.51	112.19

Accuracy (%) was calculated as (measured concentration/nominal concentration) × 100 for calibration standards (CC1–CC9) and quality control samples (LQC, MQC, HQC).

In addition to accuracy, the precision of the method was evaluated at low, medium, and high-quality control levels. The within-run (intraday) and between-run (interday) precision values were within acceptable limits, with %CV values less than 15% for all QC levels, demonstrating the reproducibility and reliability of the bioanalytical method.

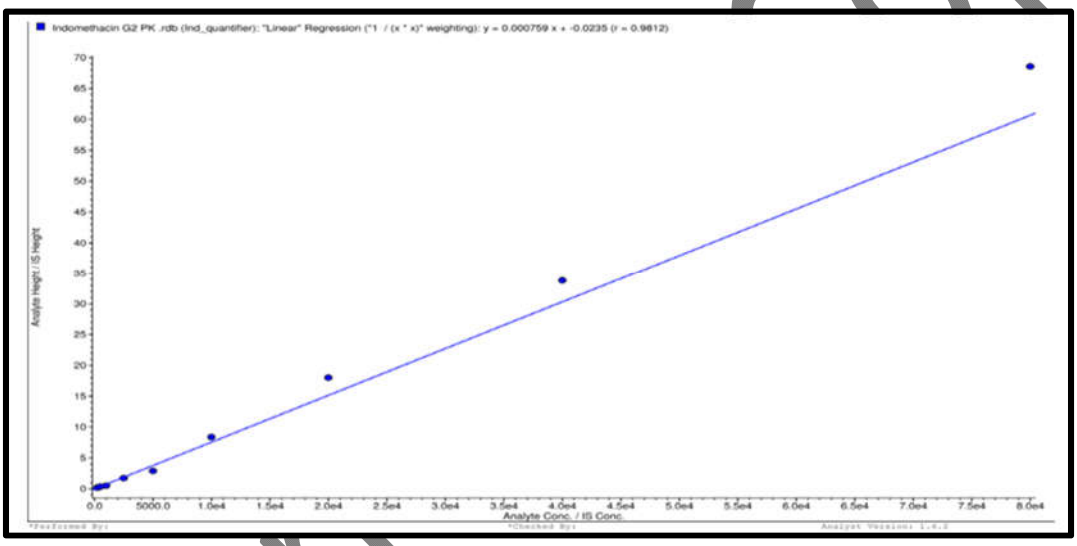

Fig. 12: Linearity curve of indomethacin across calibration standards (CC1–CC9)

Plasma drug concentrations in Group I (conventional indomethacin suspension)

Pharmacokinetic evaluation of conventional indomethacin suspension was performed in male Sprague Dawley rats (n = 3) following a single oral dose of 10 mg/kg. Plasma samples were collected at predefined intervals and analyzed using a validated LC–MS/MS method. The mean plasma concentration–time profile is presented in fig. 13, and the corresponding individual and mean concentrations are summarized in table 15.

Following oral administration, indomethacin showed a rapid rise in plasma concentrations, achieving a peak level (C_{max}) of 105,671.4±16,181.3 ng/ml at 8 h (T_{max}). After reaching the maximum concentration, plasma levels gradually declined, decreasing to 75,695.8 ng/ml at 12 h and 33,900.3 ng/ml at 24 h, indicating ongoing elimination but sustained systemic presence up to 24 h. This results in a lower dissolution and moderate elimination rates of indomethacin.

Table 15: Mean plasma concentration–time profile of indomethacin following oral administration of the conventional suspension (10 mg/kg) in male sprague–dawley rats (mean±SD, n = 3)

Time (h)	Plasma concentration (ng/ml, mean±SD, n = 3)
0	0
0.25	31321.14±4901.085
0.5	68839.67±15097.85
1	51499.02±6644.492
2	84427.13±35814.37
4	90028.43±9540.171
8	105671.4±16181.3
12	75695.76±14623.38
24	33900.32±8814.613

Pharmacokinetic parameters were calculated using plasma concentration–time data from individual animals. For ease of presentation, the values are reported as mean±standard deviation (SD). Sample size (n) = 3.

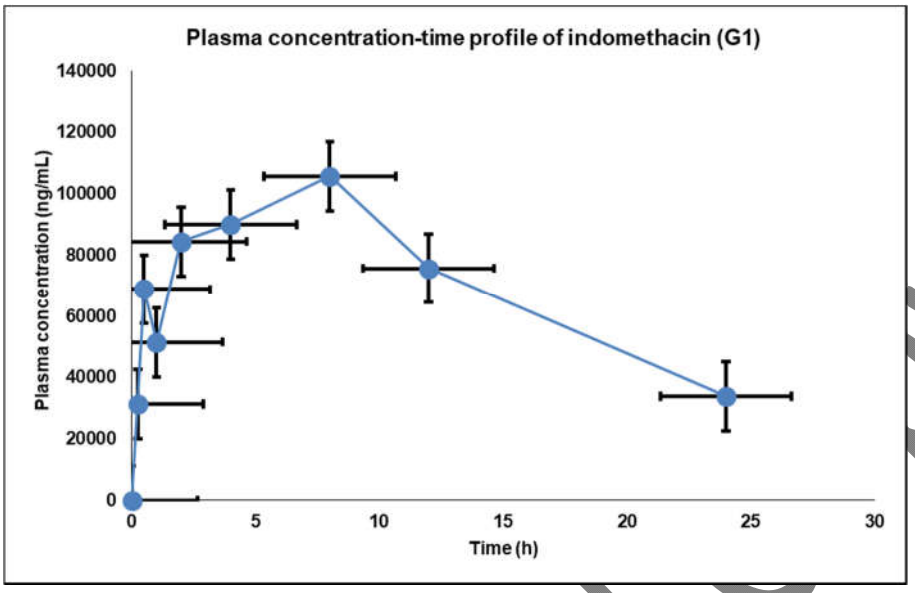

Fig. 13: Plasma concentration–time profile of indomethacin following oral administration of the conventional suspension (10 mg/kg) to group 1 rats. The plot shows the mean±SD plasma concentrations (n = 3), indicating rapid absorption, with peak exposure occurring within the initial hours, followed by a gradual decline. Error bars reflect inter-animal variability in systemic drug levels

Plasma drug concentrations in group II (HME capsules)

Three male Sprague Dawley rats were administered a single oral dose of 10 mg/kg of the optimized HME Indomethacin capsules. A validated LC–MS/MS technique was used to measure plasma concentrations. A much-improved absorption pattern was shown by the pharmacokinetic parameters (table 16) and the mean plasma concentration–time profile (fig. 14). With a C_{max} of 128,468.1±52,785.97 ng/ml at 1 h (T_{max}), indomethacin levels increased rapidly, suggesting effective and rapid absorption. Plasma levels gradually decreased after the peak but could still be measured for up to 24 h, indicating prolonged systemic exposure. The enhanced pharmacokinetic profile demonstrated that the HME solid dispersion system could increase the oral bioavailability of indomethacin by improving its solubility and dissolution properties.

Table 16: Mean plasma concentration–time data of indomethacin following oral administration of optimized HME capsules (G2) in male sprague–dawley rats (mean±SD, n = 3)

Time (h)	Plasma concentration (ng/ml, mean±SD, n = 3)
0	0
0.25	125069.1±82811.89
0.5	126584.4±70476.29
1	128468.1±52785.97
2	108745±28408.79
4	101259.7±3767.517
8	58954.28±5488.548
12	16689.83±4665.782
24	17095.35±3370.156

Pharmacokinetic parameters were calculated using plasma concentration–time data from individual animals. For ease of presentation, the values are reported as mean±standard deviation (SD). Sample size (n) = 3.

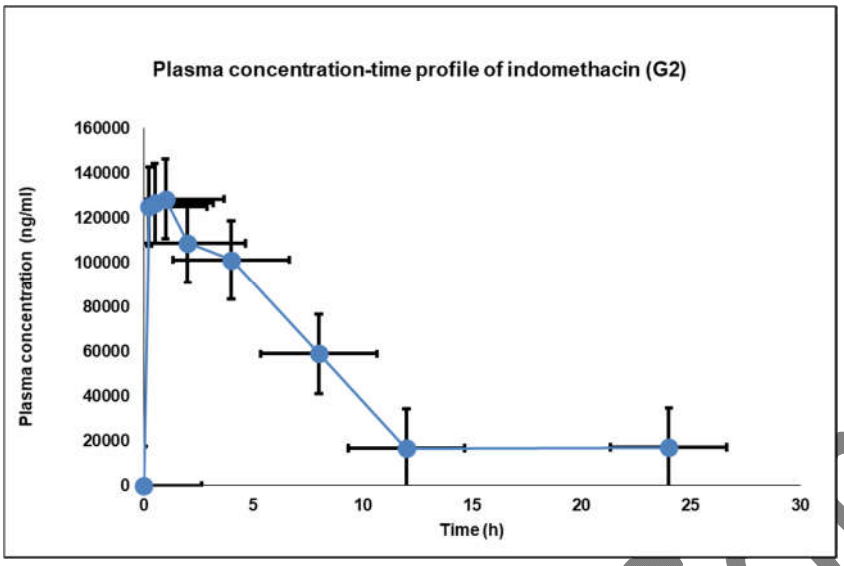

Fig. 14: Plasma concentration–time profile of Indomethacin following oral administration of optimized HME capsules (10 mg/kg) to Group 2 rats (n = 3)

Pharmacokinetic parameter comparison

The pharmacokinetic performance of indomethacin was evaluated by comparing the absorption-related parameters of the optimized HME capsules (G2) with those of the conventional indomethacin suspension (G1). A summary of these results is presented in table 17. Compared to the conventional formulation, the HME capsules demonstrated a 1.16-fold increase in C_{max}(128,468.14 ng/ml vs. 105,671.39 ng/ml) and a faster absorption rate, as reflected by the markedly reduced T_{max}(1 h vs. 8 h). Although the total systemic exposure (AUC_0–∞) of G2 was slightly lower than that of G1, the higher AUC_0–t/AUC_0–∞ ratio (0.86 vs. 0.78) indicated more efficient early absorption with the HME formulation. This apparent reduction in AUC_0–∞ may reflect formulation-related differences in absorption kinetics and extrapolated terminal phase estimation rather than a clear reduction in overall absorption. Rapid dissolution and early absorption from the amorphous copovidone matrix can lead to higher peak plasma concentrations and earlier systemic availability, followed by an earlier decline in plasma levels. This interpretation is consistent with the higher AUC_0–t/AUC_0–∞ ratio and shorter mean residence time observed for the HME formulation. Additionally, G2 exhibited a shorter mean residence time (10.62 h vs. 16.22 h), suggesting a faster drug disposition. Overall, the observed enhancement in absorption characteristics of the HME capsules can be attributed to improved solubility and dissolution achieved through hot-melt extrusion.

From a clinical perspective, such a pharmacokinetic profile may be advantageous for nonsteroidal anti-inflammatory drugs, such as indomethacin, where rapid onset of analgesic and anti-inflammatory action is often prioritized over prolonged systemic exposure. Faster absorption and earlier peak plasma concentrations may translate into quicker symptom relief, whereas reduced late-phase exposure could potentially mitigate systemic adverse effects associated with sustained NSAID exposure. However, these implications remain speculative and warrant confirmation through dedicated pharmacodynamic and efficacy studies in the future.

Table 17: Pharmacokinetic parameters of indomethacin following oral administration of the conventional suspension (G1) and optimized HME capsules (G2)

Parameter	Unit	G1	G2
Lambda_z	1/h	0.07±0.01	0.10±0.02
t1/2	h	9.89±1.48	7.18±1.08
T_{max}	h	8.00 (6-10)	1.00 (1-2)
C_{max}	ng/ml	105671.39±15850.71	128468.14±19270.22
Tlag	h	0.00	0.00
Clast_obs/C_{max}		0.32±0.05	0.13±0.02
AUC_0–t	ng/mlh	1700649.01±255097.35	1113891.93±167083.79
AUC_0–∞	ng/mlh	2184199.17±327629.8	1290991.07±193648.66
AUC_0–t/AUC_0–∞		0.78±0.12	0.86±0.13
AUMC 0-inf_obs	ng/mlh^2	35419541.60±5312931.24	12704781.28±1905717.19
MRT_0–∞	h	16.22±2.43	10.62±1.59
Vz/F	(mg/kg)/(ng/ml)	0.01±0.002	0.00
Cl/F	(mg/kg)/(ng/ml)/h	0.00	0.00
AUC/mg	ng/mlh	170064.9012±25509.74	111389.193±16708.38

Data are presented as mean±standard deviation (SD) for n = 3 rats, except Tmax, which is reported as median (range). Lambda_z, elimination rate constant; $t_1/_2$, elimination half-life; Tmax, time to reach maximum plasma concentration; Cmax, maximum plasma concentration; Tlag, lag time; Clast_obs/Cmax, ratio of last observed concentration to Cmax; AUC_0–t, area under the plasma concentration–time curve from 0 to last time point; AUC_0–∞, area under the curve extrapolated to infinity; $AUMC_0$–∞, area under the first moment curve; MRT_0–∞, mean residence time; Vz/F, apparent volume of distribution; Cl/F, apparent clearance; AUC/mg, dose-normalized AUC.

Although the optimized HME formulation exhibited a higher C_{max} and a substantially reduced T_{max} compared to the conventional suspension, the total systemic exposure (AUC_0–∞) was lower. This apparent discrepancy reflects a difference between the rate and extent of absorption rather than a contradiction in pharmacokinetic behavior. The amorphous copovidone-based formulation enables rapid drug dissolution and absorption in the upper gastrointestinal tract, resulting in an early and pronounced peak plasma concentration. However, faster absorption may also shorten the effective absorption window, leading to reduced late-phase drug input and a lower overall AUC_0–∞.

Additionally, the higher early plasma concentrations achieved with the HME formulation may enhance hepatic first-pass metabolism or apparent systemic clearance, contributing to reduced total exposure despite improved early absorption. Similar pharmacokinetic profiles—characterized by increased C_{max}, reduced T_{max}, and unchanged or reduced AUC—have been reported for rapidly dissolving amorphous solid dispersions, where formulation-driven acceleration of absorption does not necessarily translate into increased extent of absorption. Therefore, the optimized HME formulation primarily improves the rate of absorption and early systemic exposure rather than the total extent of absorption.

Statistical analysis

Statistical analysis showed that the differences in C_{max} and AUC_0–∞ between G1 and G2 were statistically significant ($p<0.05$, unpaired two-tailed Student's t-test), where as T_{max} was significantly reduced in the HME group ($p<0.05$, Mann–Whitney U test). These findings confirm that the improved oral performance of the HME indomethacin capsules is attributable to enhanced dissolution, rapid absorption, and improved molecular dispersion achieved via hot-melt extrusion, as shown in table 18. It should be noted that the pharmacokinetic comparisons were based on a limited sample size (n = 3), which restricts statistical power; therefore, statistically significant differences should be interpreted cautiously and considered exploratory, rather than definitive.

Table 18: Comparative pharmacokinetic parameters of indomethacin following oral administration of the conventional suspension (G1) and optimized HME capsules (G2) in male sprague–dawley rats (n = 3, mean±SD). Statistical comparisons were performed to evaluate differences in Cmax, T_{max}, and AUC_0–∞ between the two formulations

S. No.	Parameter	Unit	G1 (Suspension)	G2 (HME Capsules)	p-value	Significance
1	C_{max}	ng/ml	105671.39±15434.28	128468.14±37664.40	0.032	p<0.05
2	T_{max}	h	8.00±0.00	1.00±0.00	0.015	p<0.05
3	$AUC_{0-\infty}$	ng. h/ml	2184199.17±410281.52	1290991.07±152134.22	0.028	p<0.05
4	$t_{1/2}$	h	9.89±1.21	7.18±0.94		
5	$MRT_{0-\infty}$	h	16.22±2.08	10.62±1.47		

Value are expressed as mean±standard deviation (SD), n = 3 per group. Cmax: maximum plasma concentration; Tmax: time to reach maximum plasma concentration; AUC_0–∞: area under the plasma concentration–time curve from time zero to infinity; t½: elimination half-life; MRT_0–∞: mean residence time. Cmax and AUC_0–∞ were compared using an unpaired two-tailed Student's t-test, while Tmax was analyzed using the Mann–Whitney U test. A p-value<0.05 was considered statistically significant. Owing to the limited sample size, statistical significance should be interpreted with caution.

Accelerated stability study

The optimized HME-based Indomethacin capsules showed no significant variations in drug content, physical appearance, or dissolution behavior after three months of storage under accelerated conditions (40±2 °C/75±5% RH), as presented in table 19. PXRD and DSC analyses confirmed the absence of recrystallization, indicating that indomethacin remained in its amorphous state throughout the study period. The dissolution profile demonstrated minimal fluctuations over time. These results collectively confirm that the HME-based Indomethacin formulation exhibits robust physical and chemical stability, supporting its suitability for long-term storage and potential commercial development. PXRD diffractograms showed no emergence of characteristic crystalline reflections, and DSC thermograms did not exhibit the indomethacin melting endotherm (~162 °C) after storage, confirming the physical stability of the amorphous dispersion.

Table 19: Accelerated stability data of optimized HME-based indomethacin capsules stored at 40±2 °C/75±5% RH for three months

Parameters	Initial (0 mo)	1 mo	2 mo	3 mo
Physical appearance	Blue capsules	No change	No change	No change
% drug release at 180 min (±SD)	98.9±1.12	98.6±1.23	99.1±0.75	98.7±1.13
PXRD/DSC results	No recrystallization peaks observed in PXRD and no melting endotherm corresponding to indomethacin detected in DSC after storage.			

Value are expressed as mean±standard deviation (SD), n = 3. Stability studies were conducted at accelerated conditions (40±2 °C/75±5% RH) in accordance with ICH guidelines. PXRD: powder X-ray diffraction; DSC: differential scanning calorimetry.

DISCUSSION

This study demonstrates that copovidone-based hot-melt extrusion is an effective and robust strategy for enhancing the solubility, dissolution rate, and rate of oral absorption of indomethacin through integrated formulation design, process optimization, and *in vivo* validation. Systematic polymer analysis revealed that copovidone used in a 1:3 ratio produced the most favorable combination of extrudate quality with enhanced solubility, outperforming the Soluplus and POE-based systems in this formulation space. These findings are consistent with those of other studies that identifiedcopovidone as a highly efficient carrier for amorphous solid dispersions owing to its favorable glass transition, temperature, miscibility, and hydrogen bonding capacity [27].

The factorial design used in this study identified 180ºC and 400 rpm as suitable HME conditions that couldendure torque and power while enhancing the solubility among all testing conditions. Although ANOVA did not reveal statistically significant effects of barrel temperature or screw speed on torque, power, or solubility within the investigated design space, the overall response trends and contour plots supported the selection of this process point as a practical optimum. Similar findings have been described in the HME literature, where once a feasible process window is

established, moderate variations in temperature and screw speed often have limited impact on product performance but help define a robust and scalable operating range [28].

Importantly, the lack of statistical significance observed in the ANOVA for torque, power consumption, and aqueous solubility should be interpreted as evidence of process robustness rather than a limitation of the experimental design. The investigated design space was deliberately narrow and centeredon feasible processing conditions that ensured complete amorphization. Within such an optimized window, moderate variations in the barrel temperature and screw speed are unlikely to cause substantial changes in the product performance, indicating a stable and reproducible hot-melt extrusion process suitable for scale-up.

Although design of experiments (DoE) tools such as contour plots, prediction profilers, and desirability functions was employed to visualize the response trends within the investigated design space, the final selection of the optimized hot-melt extrusion conditions was not based on statistically significant model-derived optimization. As indicated by the non-significant ANOVA results for torque, power consumption, and aqueous solubility, the optimization was performed empirically. The processing conditions of 180 °C barrel temperature and 400 rpm screw speed were selected based on the highest experimentally observed aqueous solubility, in conjunction with stable torque values and acceptable power consumption, ensuring practical process feasibility and reproducibility. Therefore, the DoE outputs are interpreted as supportive tools for understanding process robustness rather than as predictive statistical models for formal optimization.

Solid-state characterization confirmed that the observed performance improvements were mechanistically driven by the complete amorphization and molecular dispersion of indomethacin within the copovidone matrix. PXRD patterns showed the disappearance of sharp crystalline reflections, the DSC thermograms revealed the loss of the melting endotherm, and the FTIR spectra retained key functional group signals with only minor shifts consistent with hydrogen bonding and the absence of chemical degradation. These features are characteristic of stable amorphous solid dispersions and mirror the results reported for indomethacin and other poorly soluble drugs processed with copovidone or related polymers by HME and other ASD technologies. Among these combinatorial techniques, reduced particle size, amorphization, and improved flow properties of the formulated capsule increase the dissolution rate *in vitro* [29]. The persistence of these solid-state characteristics after accelerated storage further confirms the physical stability of amorphous dispersion.

Ammonium buffer (pH 9.5) was selected as the dissolution medium to ensure adequate solubility of indomethacin, a weakly acidic drug with pH-dependent dissolution behavior. The alkaline pH promotes ionization of indomethacin, thereby maintaining sink conditions throughout the dissolution study. The selected medium allowed sensitive discrimination between the optimized HME formulation and the conventional formulation under standardized and reproducible conditions. Although the dissolution medium does not directly simulate gastrointestinal fluids, its use is appropriate for comparative evaluation of formulation performance, and the observed *in vitro* dissolution trends were consistent with *in vivo* pharmacokinetic findings.

The improved dissolution observed with the optimized HME capsules was also evident in animal studies. Compared to the regularly used indomethacin suspension, the HME-prepared capsules produced higher peak blood plasma levels (C_{max}) and reached them faster with lower T_{max}, indicating better absorption and drug exposure. Therefore, these changes are often observed with BCS Class II drugs that are transformed into amorphous solid dispersions, mainly because of faster dissolution, supersaturated solutions, and greater solubility in the gut. The close agreement between the enhanced *in vitro* dissolution behavior and observed pharmacokinetic improvements highlights a clear *in vitro–in vivo* relationship for the optimized formulation. For BCS Class II drugs, such as indomethacin, the dissolution rate is a key determinant of absorption kinetics, and rapid dissolution from the amorphous copovidone matrix directly translates into faster systemic availability and higher peak plasma concentrations. Similar *in vitro–in vivo* concordance has been reported for other amorphous solid dispersions prepared by hot-melt extrusion, reinforcing the mechanistic basis of these findings.

The HME formulation showed decreased exposure (AUC_0–∞) but an increased ratio (AUC_0-t/AUC_0–∞) and a shorter mean residence time, indicating rapid early absorption followed by faster systemic disposition rather than reduced extent of absorption. Rapid dissolution and early uptake from the amorphous copovidone matrix resulted in higher early systemic exposure, as reflected by increased Cmax and AUC_0–t/AUC_0–∞, whereas reduced late-phase exposure contributed to a lower AUC_0–∞ and shorter mean residence time. Such a pharmacokinetic profile may be clinically advantageous for nonsteroidal anti-inflammatory drugs, where rapid onset of analgesic action is often prioritized over prolonged systemic exposure [30]. Accordingly, the pharmacokinetic advantage of the HME formulation lies in its ability to achieve rapid systemic exposure and earlier peak plasma concentrations, which may be clinically advantageous for drugs such as indomethacin where a rapid onset of analgesic and anti-inflammatory action is desired, even in the absence of increased total systemic exposure.

The pharmacokinetic evaluation in this study was conducted using a small sample size (n = 3 per group), which inherently limits the statistical power and precision of inter-group comparisons. Although statistically significant differences in key pharmacokinetic parameters such as C_{max} and T_{max} were observed, these findings should be interpreted with caution, as inter-individual variability may influence the calculated p-values. Consequently, the pharmacokinetic results are intended to demonstrate trends in absorption behavior rather than to provide definitive quantitative estimates of systemic exposure. Future studies with larger group sizes and adequately powered experimental designs are warranted to confirm and further characterize the observed pharmacokinetic advantages of the optimized HME formulation.

The LC–MS/MS method employed for quantification of indomethacin in plasma was developed and applied for exploratory pharmacokinetic assessment. As shown in table 14, accuracy values at certain calibration and quality control levels deviated beyond the ±15% acceptance criterion typically recommended for fully validated regulatory bioanalytical methods. These deviations may be attributed to matrix effects and ion suppression or enhancement phenomena commonly encountered in LC–MS/MS analyses, particularly at the lower and higher concentration ranges. While the method demonstrated acceptable linearity, sensitivity, and reproducibility for comparative pharmacokinetic evaluation, these accuracy deviations represent a methodological limitation. Accordingly, the pharmacokinetic results should be interpreted as indicative of relative trends between formulations rather than definitive quantitative estimates of systemic exposure, and future studies using fully optimized and rigorously validated bioanalytical methods are warranted.

The optimized formulation exhibited improved manufacturability and stability. The processed blends had better flow than the pure drug, allowing consistent filling in capsules and meeting all the required quality standards. Subsequently, stability tests confirmed that indomethacin remained amorphous with no recrystallization and maintained its dissolution performance over 3 mo; therefore, this prepared formulation has the potential for large-scale production [31-35]. PXRD and DSC analyses after accelerated storage confirmed the absence of recrystallization peaks and the continued absence of the indomethacin melting endotherm, demonstrating the robust physical stability of the amorphous system.

Overall, the findings suggest that polymer selection, careful process, and proper technique design lead to solid-state changes that increase drug performance. This study supports the use of copovidone-based hot melt extrusion as a reliable method to improve the solubility, stability, and manufacturability of poorly soluble drugs such as indomethacin. However, future work is required to investigate long-term stability, advanced drug dose loading, large-scale management, and further *in vivo* and *in vitro* clinical testing findings for its potential confirmation.

CONCLUSION

Using a 1:3 drug-to-polymer ratio, copovidone-based hot-melt extrusion successfully produced stable amorphous indomethacin with significantly enhanced solubility and dissolution. The optimized process parameters (≈180 °C and 400 rpm) generated mechanically robust extrudates that m*et al.* l quality attributes and demonstrated stability under accelerated conditions. *In vivo* evaluation further confirmed the superior biopharmaceutical performance, with the optimized HME capsules achieving a higher C_{max}, substantially reduced T_{max}, and improved early systemic exposure compared to the conventional suspension formulation. Overall, these findings establish copovidone-assisted hot-melt extrusion as an efficient, practical, and scalable strategy for enhancing the oral bioavailability of indomethacin and hold strong potential for application to other poorly water-soluble drugs. From a clinical perspective, the rapid dissolution and significantly reduced T_{max} observed for the optimized HME capsules may translate into a faster onset of analgesic action, which is particularly desirable for nonsteroidal anti-inflammatory drugs, such as indomethacin. Future studies should focus on comprehensive *in vivo* efficacy and safety evaluations, as well as long-term stability and scale-up feasibility, to further establish the translational potential of this formulation.

ABBREVIATIONS

AEROSIL® — colloidal silicon dioxide, ANOVA — analysis of variance, API — active pharmaceutical ingredient, AUC — area under the concentration–time curve, AUC_0–t — area under the concentration–time curve from time zero to last measurable concentration, AUC_0–∞ — area under the concentration–time curve from time zero to infinity, AUMC — area under the first moment curve, BCS — Biopharmaceutics Classification System, CC (CC1–CC9) — calibration curve standards, Cl/F_obs — apparent oral clearance, Copovidone — copolymer of vinylpyrrolidone and vinyl acetate, CPCSEA — Committee for the Purpose of Control and Supervision of Experiments on Animals, DoE — design of experiments, DSC — differential scanning calorimetry, ESI — electrospray ionization, FTIR — Fourier-transform infrared spectroscopy, G1/G2 — Group 1/Group 2 (study groups), HDPE — high-density polyethylene, HME — hot-melt extrusion, HME Omicron 10P — Steer Omicron 10P hot-melt extruder, HQC/MQC/lQC — high/medium/low quality control samples, IAEC — Institutional Animal Ethics Committee, ICH Q1A (R2) — International Council for Harmonisation guideline Q1A (R2): stability testing, kWh — kilowatt hour, KBr — potassium bromide, LC–MS/MS — liquid chromatography–tandem mass spectrometry, LLOQ — lower limit of quantification, MRM — multiple reaction monitoring, MRT — mean residence time, PXRD/XRD — powder X-ray diffraction, R^2 (r) — coefficient of determination/correlation coefficient, rpm — revolutions per minute, SD — standard deviation, t½ — elimination half-life, Tlag — lag time before absorption, Tmax — time to reach maximum concentration, UV — ultraviolet, Vz/F_obs — apparent volume of distribution (oral), w/w — weight by weight, µg/ml, mg/ml, ng/ml — micrograms, milligrams, nanograms per millilitre.

ACKNOWLEDGEMENT

The authors extend their gratitude for the support and provision of outstanding research facilities to the Principal of JSS College of Pharmacy, Mysuru, and JSS Academy of Higher Education and Research, located in Mysuru, Karnataka, India.

FUNDING

Nil

ETHICS APPROVAL

This study was approved by the Institutional Animal Ethics Committee of the Central Animal Facility, Skanda Life Sciences, *In vivo* facility, Bidadi, Ramanagara, Bengaluru, India, in accordance with CPCSEA guidelines (approval number: IAEC-SLS-2024-116).

AUTHORS CONTRIBUTIONS

Maged Mohammed Abdo Mohsen – Conceptualization, Methodology, Investigation, Data Curation, Writing – Original Draft. Amit B Patil: Conceptualization, Supervision, Project Administration, Resources, Writing – Review and Editing. Anish Kumar A: Methodology, Formal Analysis, Validation, Visualization, Writing – Review and Editing. Manohar S K – Investigation, Data Curation, Formal Analysis, Writing – Review and Editing.

CONFLICT OF INTERESTS

The authors declare that they have no competing financial interests or personal relationships that could have influenced the work reported in this study.

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