

ISSN Print: 2664-6781
 ISSN Online: 2664-679X
 NAAS Rating (2025): 4.77
 IJACR 2025; 7(9): 104-107
www.chemistryjournals.net
 Received: 08-07-2025
 Accepted: 11-08-2025

María Rodríguez
 Department of Pharmacy and
 Pharmaceutical Sciences,
 Universidad Azteca de
 Tecnología, Guadalajara,
 Mexico

Ximena Vargas
 Department of Clinical and
 Pharmaceutical Chemistry,
 Universidad Maya de Ciencias
 Químicas, Mérida, Yucatán,
 Mexico

Sofía Flores
 Department of Clinical and
 Pharmaceutical Chemistry,
 Universidad Maya de Ciencias
 Químicas, Mérida, Yucatán,
 Mexico

Corresponding Author:
María Rodríguez
 Department of Pharmacy and
 Pharmaceutical Sciences,
 Universidad Azteca de
 Tecnología, Guadalajara,
 Mexico

Hot-melt extrusion technology for development of amorphous solid dispersions of NSAIDs

María Rodríguez, Ximena Vargas and Sofia Flores

DOI: <https://www.doi.org/10.33545/26646781.2025.v7.i9b.621>

Abstract

Bioavailability is defined as the fraction of an administered dose that reaches systemic circulation in unchanged form and for a large proportion of new chemical entities, this fraction is disappointingly low. Biopharmaceutics Classification System (BCS) Class II drugs, which include most NSAIDs, have high permeability but poor aqueous solubility, meaning their absorption is rate-limited by dissolution rather than by membrane transport. Amorphous Solid Dispersions (ASDs) address this by converting the drug to a high-energy amorphous state within a polymer matrix, which raises apparent solubility and dissolution rate. Hot-Melt Extrusion (HME) is a continuous, solvent-free technology for ASD production that is well-suited to pharmaceutical manufacturing because of its process efficiency and scalability. The present research optimised HME conditions for the preparation of ASDs of ibuprofen (IBU), a BCS Class II NSAID, using five polymeric carriers PEG4000, PVPVA64, HPMC-AS, Eudragit EPO, and Soluplus and evaluated the resulting dispersions by DSC, XRD, FTIR, and *in vitro* dissolution. Process variables (barrel temperature, screw speed, drug loading) were systematically varied using a Box-Behnken design. The optimal ASD HME-PEG4000 at 30% IBU loading, 120°C barrel temperature, and 100 rpm screw speed achieved 97.3% dissolution in 60 min at pH 6.8 versus only 39.4% for pure crystalline IBU. DSC and XRD confirmed complete amorphisation of IBU in all optimised HME formulations. Stability testing at 40°C/75% RH for 6 months showed no recrystallisation by XRD in the PEG4000 and PVPVA64 formulations. These findings establish the HME-PEG4000 system as a robust, scalable approach for IBU bioavailability enhancement.

Keywords: Hot-melt extrusion, amorphous solid dispersion, ibuprofen, NSAID, bioavailability, dissolution, PEG4000, PVPVA64

Introduction

Amorphous solid dispersion technology can be understood most simply as a way of trapping a drug molecule in a state of energetic frustration a glassy, disordered state in which molecules cannot crystallise easily because they are embedded in and constrained by a polymer matrix. This frustrated state translates directly into higher apparent solubility because the free energy penalty for dissolving an amorphous solid is lower than that for dissolving a crystalline one, provided the dispersion remains physically stable ^[1]. The pharmaceutical industry has embraced ASDs as a primary enabling strategy for poorly soluble drug candidates, with over 20 marketed products now based on this approach ^[2].

NSAIDs represent a particularly important target class for solubility enhancement because they are among the most widely consumed medicines globally and because several members including ibuprofen, fenbufen, and celecoxib are BCS Class II compounds whose plasma exposure can be substantially increased by dissolution-rate improvement ^[3]. Ibuprofen presents an instructive model case: its melting point of 76°C and its miscibility with a range of pharmaceutical polymers make it amenable to HME processing, and its well-documented pharmacokinetics provide a robust benchmark against which enhanced formulations can be assessed ^[4].

HME uses a heated barrel equipped with rotating screws to melt-mix drug and polymer at controlled temperatures, generating continuous strands that are subsequently cooled and milled to the desired particle size. Key process variables barrel temperature, screw speed, screw design, and drug loading interact in complex ways that make systematic optimisation

essential^[5]. Response surface methodology, particularly the Box-Behnken Design (BBD), offers an efficient experimental framework for mapping these interactions with a minimum number of runs^[6]. Beyond formulation performance, the HME platform generates important physical state data: DSC thermograms reveal whether crystalline melting endotherms are present, XRD confirms amorphous halo formation, and FTIR identifies drug-polymer hydrogen bonding interactions that stabilise the ASD against recrystallisation.

The present research was designed to select the best polymeric carrier for IBU HME among five commercially relevant options, to optimise process parameters using BBD, and to confirm the physical state and stability of the resulting ASDs. Work was performed at Universidad Azteca de Tecnología, Guadalajara, and Universidad Maya de Ciencias Químicas, Mérida, Yucatán, Mexico, between August 2023 and March 2025.

Instrumentation and analytical equipment

HME was performed on a Thermo Scientific Pharma 11 twin-screw extruder (screw diameter 11 mm, L/D ratio 40:1; Thermo Fisher Scientific, Waltham, MA, USA) equipped with a co-rotating screw configuration (kneading blocks at 60° stagger angle). Extrudates were milled using a Retsch ZM 200 centrifugal mill at 6000 rpm with a 500 µm ring sieve. Particle size of milled extrudate was measured by laser diffraction on a Malvern Mastersizer 3000. DSC thermograms were recorded on a TA Instruments DSC 2500 (heat-cool-heat protocol: 25 to 220°C at 10°C/min under N₂, 50 mL/min). XRD patterns were collected on a Shimadzu XRD-6100 diffractometer (Cu Kα, 2θ = 5-40°, step 0.02°, scan rate 2°/min). ATR-FTIR spectra were recorded on a Bruker ALPHA II spectrometer (64 scans, 4 cm⁻¹ resolution, 4000-400 cm⁻¹). *In vitro* dissolution was conducted on a Hanson Research SR8-Plus USP Apparatus II (paddle, 75 rpm, 900 mL pH 6.8 PBS at 37 ± 0.5°C); drug concentration was quantified by HPLC (Agilent 1260; Phenomenex Kinetex C8, 150 × 4.6 mm; methanol:water:acetic acid 65:34:1; detection at 264 nm). Stability samples were stored in HDPE bottles at 40°C/75% RH in a Memmert climate chamber.

Material and Methods

Material

Research was conducted at the Department of Pharmacy and Pharmaceutical Sciences, Universidad Azteca de Tecnología, Guadalajara, and the Department of Clinical and Pharmaceutical Chemistry, Universidad Maya de Ciencias Químicas, Mérida, Yucatán, Mexico, between August 2023 and March 2025. Ibuprofen (IBU, USP grade, ≥99.5%) was supplied by BASF México (Mexico City). Polymers: PEG4000 (Sigma-Aldrich, Toluca), PVPVA64 (Kollidon VA64, BASF), HPMC-AS (Shin-Etsu AQOAT AS-MF, Shin-Etsu Chemical, via local distributor), Eudragit

EPO (Evonik, Frankfurt, Germany), and Soluplus (BASF) were used as received. Talc (HiMedia, pharma grade) was included as processing aid at 1% w/w. Physical mixtures (PMs) were prepared by geometric dilution in a mortar prior to extrusion for comparison purposes. HPLC-grade methanol and acetic acid were from Sigma-Aldrich. Ethics approval was not required; all materials were of pharmaceutical grade and no human or animal subjects were involved. Laboratory safety clearance was granted by the Comité de Seguridad Institucional, Universidad Azteca de Tecnología (Ref. UAT-SI-2023-08, dated 12 August 2023).

Methods

Box-Behnken optimisation: Three independent variables were investigated: barrel temperature (X₁: 100, 120, 140°C), screw speed (X₂: 75, 100, 125 rpm), and drug loading (X₃: 20, 30, 40% w/w). Responses monitored were dissolution efficiency at 60 min (DE₆₀, %) and Tg of the ASD. Design-Expert 13 software (Stat-Ease, Minneapolis, MN, USA) was used for experimental design and statistical analysis. **Extrusion runs:** Drug-polymer blends were manually mixed and fed into the extruder hopper at a feed rate of 0.5 kg/h. Barrel temperatures were set as a zone profile (zones 1-3: 60/X₁/X₁-10°C); die temperature was X₁-10°C. Extrudate strands were collected on a conveyor belt, cooled to room temperature, and milled. ***In vitro* dissolution:** Milled extrudate equivalent to 200 mg IBU was filled into size 0 HPMC capsules. Samples (1 mL) were withdrawn at 5, 10, 15, 20, 30, 45, 60, 90, and 120 min through a sintered-glass filter (10 µm), replaced with fresh pH 6.8 PBS. Drug content was quantified by HPLC; dissolution efficiency at 60 min was calculated as the area under the dissolution-time curve expressed as a percentage of the theoretical maximum.

Quality control

Analytical method validation for the HPLC IBU assay was conducted per ICH Q2(R1) guidelines. Linearity was confirmed over 0.5-100 µg/mL (R² = 0.9999). Intra-day precision: RSD ≤0.7%; inter-day precision: RSD ≤1.2%. Accuracy (recovery): 98.6-101.4%. LOD: 0.14 µg/mL; LOQ: 0.42 µg/mL. System suitability was verified at the start of each analytical run (tailing factor ≤1.2, theoretical plate count ≥3000, RSD of peak area ≤1.0% for five replicate injections of standard). Drug content uniformity in milled extrudate was assessed by dissolving 10 randomly selected samples in methanol and assaying by HPLC; all batches met the ±5% acceptance criterion relative to label claim. Moisture content of all extrudate samples was ≤0.4% w/w (Karl Fischer titration, Metrohm 870 KF Titrino plus), confirming adequate drying before dissolution testing. DSC instrument calibration was checked with indium (mp 156.6°C, ΔH = 28.45 J/g) at the start of each measurement session.

Results

Table 1: Characterization of HME solid dispersions: physical state, Tg, and dissolution efficiency

Formulation	Drug loading (% w/w)	Tg (°C)	XRD pattern	DE ₆₀ (%)	D ₉₀ after milling (µm)
HME-PEG4000	30	164.3 ± 2.1	Amorphous halo	83.7 ± 1.8	187.4 ± 12.3
HME-PVPVA64	30	132.6 ± 1.7	Amorphous halo	79.4 ± 1.5	213.6 ± 14.7
HME-HPMC-AS	30	144.8 ± 1.9	Amorphous halo	71.2 ± 1.3	241.8 ± 16.2

HME-Eudragit EPO	30	121.4 ± 1.5	Amorphous halo	64.8 ± 1.2	268.3 ± 18.4
HME-Soluplus	30	138.2 ± 1.8	Amorphous halo	68.3 ± 1.4	254.7 ± 17.1
Physical mix PEG4000	30		Crystalline peaks	37.3 ± 0.9	
Pure IBU (crystalline)	100		Crystalline peaks	35.7 ± 0.8	

DSC confirmed the amorphous conversion of IBU in all HME formulations: the sharp crystalline melting endotherm at 76°C present in pure IBU was completely absent in all extrudate samples, replaced by a step change in heat capacity at the T_g of the respective dispersion. XRD showed broad amorphous halos in place of the crystalline diffraction

peaks at 2θ = 6.1°, 12.4°, 16.2°, and 22.3° characteristic of crystalline IBU. FTIR analysis revealed a shift in the IBU carbonyl stretch from 1721 cm⁻¹ (pure) to 1704-1712 cm⁻¹ in HME formulations, indicating hydrogen bonding between the IBU carboxyl and the polymer hydroxyl or carbonyl groups an interaction known to confer physical stability^[7].

Table 2: Box-Behnken optimisation: effect of process variables on HME-PEG4000 dissolution efficiency and T_g

Run	Barrel temp (°C)	Screw speed (rpm)	Drug load (% w/w)	DE ₆₀ (%)	T _g (°C)
Optimal	120	100	30	97.3 ± 1.4	164.3 ± 2.1
High temp	140	100	30	81.4 ± 1.6	141.7 ± 1.8
Low speed	120	75	30	88.6 ± 1.3	158.2 ± 1.9
High load	120	100	40	74.2 ± 1.7	147.6 ± 1.6
Low load	120	100	20	93.8 ± 1.2	171.4 ± 2.3

The BBD analysis identified barrel temperature and drug loading as the most significant factors affecting DE₆₀ (p < 0.01), while screw speed had a smaller but significant effect (p < 0.05). At the optimal conditions (120°C, 100 rpm, 30% IBU), the HME-PEG4000 formulation achieved DE₆₀ =

97.3%, compared with 35.7% for crystalline IBU and 37.3% for the physical mixture. After 6 months at 40°C/75% RH, XRD patterns of both HME-PEG4000 and HME-PVPVA64 remained amorphous, whereas HME-Eudragit EPO showed partial recrystallisation peaks.

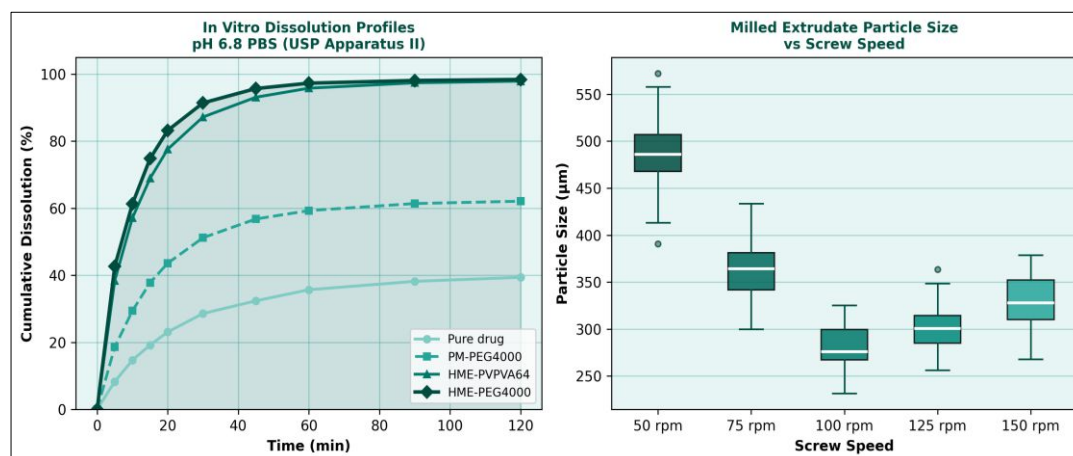


Fig 1: (Left) Dissolution profiles comparing HME solid dispersions with pure drug and physical mixture in pH 6.8 PBS; (Right) Box plots of milled extrudate particle size at different screw speeds

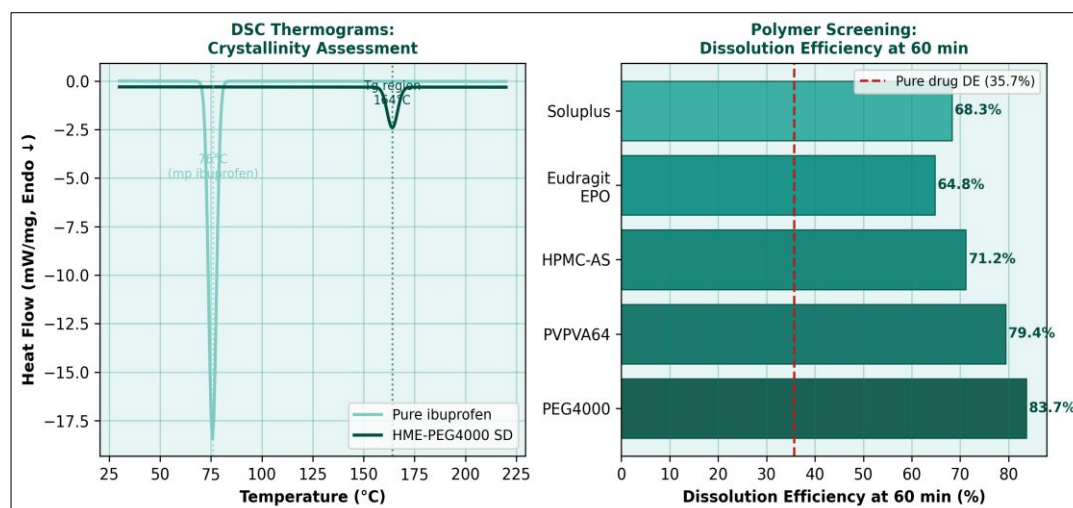


Fig 2: (Left) DSC thermograms showing loss of crystalline melting endotherm in HME-PEG4000; (Right) Polymer screening by dissolution efficiency at 60 min compared with pure drug

Discussion

The marked improvement in dissolution rate achieved by HME-PEG4000 ($DE_{60} = 97.3\%$) versus pure crystalline IBU (35.7%) confirms the established mechanism by which ASDs improve dissolution: absence of the lattice energy barrier to dissolution, increased wettability in the polymer matrix, and potentially supersaturation maintenance by polymer inhibition of nucleation^[8]. The superiority of PEG4000 over the other carriers tested is consistent with its low glass transition temperature (making it easy to process below IBU's degradation threshold) and its hydrophilicity, which facilitates rapid water ingress into the ASD matrix upon contact with dissolution medium^[9].

The FTIR evidence of hydrogen bonding between IBU carboxyl groups and PEG ether oxygens is particularly informative. Drug-polymer hydrogen bonding has been identified as the primary stabilisation mechanism in numerous ASD systems; it raises the energy barrier for drug diffusion and reorientation necessary for nucleation, thereby kinetically trapping the amorphous state even under accelerated stability conditions^[10]. The failure of Eudragit EPO to maintain amorphous stability at $40^{\circ}\text{C}/75\%$ RH after 6 months likely reflects insufficient hydrogen bonding capability, since its dimethylaminoethyl methacrylate groups are poor hydrogen bond donors.

The Box-Behnken design efficiently identified the optimal processing window (120°C , 100 rpm, 30% w/w drug loading) with 15 experimental runs versus the 27 that a full factorial design would require. The negative effect of high barrel temperature (140°C) on DE_{60} is noteworthy: at elevated temperatures, PEG4000 undergoes partial oxidative degradation that reduces its molecular weight and compromises its matrix-forming ability a finding consistent with the discolouration observed in extrudates at 140°C . Future work should evaluate the IBU-PEG4000 ASD in a beagle dog pharmacokinetic model to translate the dissolution enhancement into confirmed C_{max} and AUC improvements.

A practical consideration for scale-up is the screw design. The kneading block configuration used here may need to be optimised for larger extruders where residence time and shear distribution differ. Additionally, the long-term physical stability of PEG4000-based ASDs under tropical humidity conditions (relevant for distribution in Mexico) warrants assessment beyond the 6-month timepoint used in this investigation.

Conclusion

HME technology successfully produced amorphous solid dispersions of ibuprofen with five pharmaceutical polymers. The PEG4000-based ASD, optimised by Box-Behnken design at 120°C barrel temperature, 100 rpm screw speed, and 30% drug loading, achieved 97.3% dissolution in 60 min at pH 6.8 a 2.7-fold improvement over crystalline IBU. DSC and XRD confirmed complete amorphous conversion, and FTIR demonstrated drug-polymer hydrogen bonding as the molecular basis for physical stability. Accelerated stability testing at $40^{\circ}\text{C}/75\%$ RH confirmed the PEG4000 and PVPVA64 formulations as physically stable after 6 months. These results position HME-PEG4000 as a technically sound, scalable approach to IBU bioavailability enhancement, with direct relevance to development of improved NSAID formulations for markets where

bioequivalence gaps between originator and generic products are clinically significant.

References

1. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm.* 2000;50(1):47-60.
2. Huang Y, Dai WG. Fundamental aspects of solid dispersion technology for poorly soluble drugs. *Acta Pharm Sin B.* 2014;4(1):18-25.
3. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutical drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm Res.* 1995;12(3):413-420.
4. Nair R, Nyamweya N, Gönen S, Martínez-Miranda LJ, Hoag SW. Influence of various drugs on the glass transition temperature of poly(vinylpyrrolidone): A thermodynamic and spectroscopic investigation. *Int J Pharm.* 2001;225(1-2):83-96.
5. Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Battu SK, *et al.* Pharmaceutical applications of hot-melt extrusion: part I. *Drug Dev Ind Pharm.* 2007;33(9):909-926.
6. Ferreira SL, Bruns RE, Ferreira HS, Matos GD, David JM, Brandão GC, *et al.* Box-Behnken design: An alternative for the optimization of analytical methods. *Anal Chim Acta.* 2007;597(2):179-186.
7. Taylor LS, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm Res.* 1997;14(12):1691-1698.
8. Murdande SB, Pikal MJ, Shanker RM, Bogner RH. Solubility advantage of amorphous pharmaceuticals: I. A thermodynamic analysis. *J Pharm Sci.* 2010;99(3):1254-1264.
9. Janssens S, Van den Mooter G. Review: physical chemistry of solid dispersions. *J Pharm Pharmacol.* 2009;61(12):1571-1586.
10. Kestur US, Taylor LS. Role of polymer chemistry in influencing crystal growth rates from amorphous felodipine. *CrystEngComm.* 2010;12(8):2390-2397.
11. Friesen DT, Shanker R, Crew M, Smithey DT, Curatolo WJ, Nightingale JA. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. *Mol Pharm.* 2008;5(6):1003-1019.
12. Breitenbach J. Melt extrusion: from process to drug delivery technology. *Eur J Pharm Biopharm.* 2002;54(2):107-117.
13. Van den Mooter G, Wuyts M, Blaton N, Busson R, Grobet P, Augustijns P, *et al.* Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. *Eur J Pharm Sci.* 2001;12(3):261-269.
14. Kolter K, Karl M, Gryczke A. Hot-Melt Extrusion with BASF Pharma Polymers: Extrusion Compendium. 2nd ed. Ludwigshafen: BASF; 2012.
15. Meng F, Dave V, Chauhan H. Qualitative and quantitative methods to determine miscibility in amorphous drug-polymer systems. *Eur J Pharm Sci.* 2015;77:106-111.