Quality by Design Driven Development and Optimization of Hot Melt Extruded Amorphous Solid Dispersions for Enhanced Dissolution of a Poorly Soluble BCS Class IV Drug

Richa Sharma[1], Monika Targhotra[2], Deepti Seth[3], Aparajita Pundeer[4], Aashi Tyagi[5], Anuj Pathak[6*]

[1,2,3,4,5,6*]KIET School of Pharmacy, Krishna Institute of Engineering & Technology (KIET), Ghaziabad – 201206, Delhi-NCR, Uttar Pradesh, India

***Corresponding author: Dr. Anuj Pathak, Associate Professor, KIET School of Pharmacy, Krishna Institute of Engineering & Technology (KIET), Ghaziabad, Delhi NCR, Uttar Pradesh, India, 201206**

Email: anuj.pathak1@gmail.com

Received: 25th May, 2026; **Revised:** 6th June, 2026; **Accepted:** 8th June, 2026; **Available Online:** 21st June, 2026

ABSTRACT

Low solubility and membrane permeability in the aqueous environment are the primary impediments to the oral bioavailability of BCS Class IV drug candidates. Poor dissolution and variable absorption have been the challenges. The intent of the current study was to optimize the formulation of amorphous solid dispersions (ASDs) of a poorly soluble BCS Class IV drug using HME technology to augment dissolution performance. The saturation solubility studies showed very low solubility of the drug in aqueous and several dissolution media, thus indicating the need for a suitable formulation approach. Various hydrophilic polymers, including Kollidon® VA64, Soluplus®, Kollidon® 30 and PEG 6000, were investigated using solvent evaporation and hot melt extrusion methods. Of all the investigated carriers, Kollidon® VA64 exhibited the highest solubility enhancement, particularly in HME formulations. To optimize the polymer concentration, a QbD-based approach using a full factorial experimental design was employed, and the optimized formulation was evaluated and compared with the other formulations. This formulation exhibited a considerably improved drug release than the pure drug, and the dissolution profile was found to be comparable with the marketed formulation (F2 = 74.47). The effect of polymer concentration on enhancement of dissolution was well modelled (R^2 = 0.98294), and the model was statistically meaningful (p = 0.0010). Solid state characterization was performed using DSC and X-Ray Diffraction (XRD). The DSC thermograms depicted an absence of the characteristic melting endotherm of the drug and the XRD patterns depicted a decrease in the diffraction peaks of the crystalline form suggesting that the crystalline form of the drug was converted to amorphous form due to the molecular dispersion of the drug into the polymeric matrix during hot melt extrusion processing. Conclusively, the results of this study suggest that HME-based ASD technology, when supported by QbD optimization, is a viable and scalable approach to improve dissolution behaviour for poorly soluble BCS Class IV drugs.

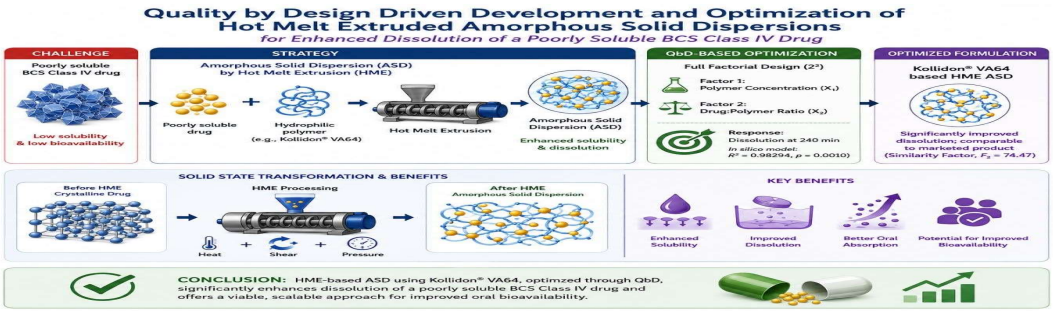
Keywords: amorphous solid dispersion, hot melt extrusion, quality by design, dissolution enhancement, solubility enhancement.

How to cite this article: Sharma R, Targhotra M, Seth D, Pundeer A, Tyagi A, Pathak A. Quality by Design Driven Development and Optimization of Hot Melt Extruded Amorphous Solid Dispersions for Enhanced Dissolution of a Poorly Soluble BCS Class IV Drug. Int J Drug Deliv Technol. 2026;16(62s): 1160-1177. DOI: 10.25258/ijddt.16.62s.125

Source of support: Nil.

Conflict of interest: None.

Graphical Abstract



1. Introduction

The oral route for drug delivery remains the predominant and preferred route. The non-intrusive, simple and convenient way of oral drug administration results in better patient compliance than the parenteral route [1]. It is the most preferred route for the local and systemic delivery of drugs. However, while the GI tract presents physiological and physicochemical barriers to oral drug absorption and targeted drug delivery to the systemic circulation [2], oral therapeutics have greater than 90% patient acceptability, and as a consequence, oral dosage forms constitute an overwhelming majority of the pharmaceutical products on the market [3]. As evidenced by their clinical success and commercial availability, oral dosage forms such as tablets or capsules, also referred to as solid oral dosage forms, have become an integral part of pharmacotherapy.

Good solubility of the active pharmaceutical ingredient (API) in aqueous solution is key for oral dosage forms but solubility is one of the most common drug development issues today [4]. Up to 40% of marketed drug products and 70-90% of drug candidates in preclinical development and clinical trials are poorly soluble with poor bioavailability, concentration-dependent adverse effects and high doses [5]. The high prevalence of poorly soluble compounds in drug discovery has been a major roadblock to successful clinical translation of new chemical entities (NCEs) from the drug discovery phase to the clinic. Almost 40% of new drug candidates have suboptimal aqueous solubility, which limits the absorption of many drugs administered via the oral route [6]. Low concentrations of drug in the plasma due to poor solubility lead to ineffective pharmacotherapy and require costly and time-consuming reformulation of the drugs to achieve complete bioavailability [7].

The Biopharmaceutics Classification System (BCS) was developed as a scientific method for classifying drugs into four classes based on the estimated solubility and permeability in the gastrointestinal tract, to solve biopharmaceutical issues of drug candidates in a systematic and practical manner [8]. BCS captures the two most meaningful factors controlling the oral absorption of drugs (i.e., solubility and intestinal permeability). BCS has been considered a widely accepted, practically useful, and scientifically justified starting point for drug product development and regulatory decision-making [9]. The Biopharmaceutical Classification System separates drugs into one of four classes. Class I drugs (high solubility/high permeability) are the most favourable for oral delivery to the body, Class II drugs (low solubility/high permeability), Class III drugs (high solubility/low permeability) and Class IV (low solubility/low permeability) are the least [10] .

Class IV drugs are generally characterized by a combination of low solubility and permeability of the biological barrier. This generally makes drugs in Class IV poor candidates for oral drug delivery due to their intrinsically poor solubility and permeability, both of which adversely affect oral bioavailability[11, 12]. Additionally, several BCS Class IV drugs are substrates of CYP3A4 and/or P-glycoprotein (P-gp) and also display a high variability (inter- as well as intra-subject variability) [13]. The most relevant BCS Class IV drugs in clinical use are furosemide, ritonavir, paclitaxel, cyclosporine and itraconazole. The drugs are valuable, but low bioavailability presents meaningful clinical challenges [14].

Class IV drugs are both poorly soluble and poorly permeable, and usually have very low oral bioavailability and high inter- and intra-subject variability. Therefore, Class IV drugs are poor oral drug candidates, unless the dose is very low [15]. Solubility and poor permeability prevent bioavailability improvement via the common formulation strategies, which usually require overcoming one of these barriers [16]. BCS Class IV drugs require simultaneous enhancement of solubility and permeability to achieve improved bioavailability. Simply improving solubility and/or dissolution rate will not improve bioavailability since both permeability and solubility are needed to be improved. This means that technologies that can overcome both solubility-related and permeability-related barriers must be developed [17, 18].

To overcome these barriers, various strategies have been studied, such as solid dispersion technology which has attracted much research interest in the academic and industrial sectors in recent years. Solid dispersions have received much attention as a successful strategy in improving the dissolution rate and bioavailability of a wide variety of poorly water-soluble drugs; water-soluble carriers, in particular, can result in an important enhancement of the dissolution profile [19, 20]. Solid dispersion (SD) technology has become a well-established methodology to achieve solubility and bioavailability increases of poorly water-soluble drugs by stabilizing the drugs in the amorphous state using polymeric carriers [21]. The present study is therefore focused on the development and characterization of solid dispersion based formulations as a rational approach to overcome

the biopharmaceutical limitations posed by poor solubility and low permeability with a view to observing clinically meaningful enhancements in oral bioavailability [22].

2. Materials and Method

The model drug and all the excipients namely – Kollidon VA64 (manufacturer BASF), Soluplus (manufacturer BASF), Kollidon 30 (manufacturer BASF), PEG 6000 (manufacturer Clariant) was obtained from Sun Pharmaceuticals, Gurugram. All the excipients were of analytical grade.

2.1. Solubility Study

The saturation solubility of model drug was determined under equilibrium conditions in various media. The results gave information about the pH and surfactant influence on the drug dissolution. The drug excess was added in 250 mL of the drug dissolution medium including: 0.1 N hydrochloric acid, phosphate buffer pH 6.8, phosphate buffer pH 4.5 and media with 0.4% w/v sodium lauryl sulfate (SLS). The suspensions were incubated in stoppered volumetric flasks by shaking on a calibrated laboratory bioshaker for 24 h at 120-150 rpm until equilibrium was attained [23]. At the end of the period of incubation, the samples were separated from undissolved drug particles by centrifugation at 1500 rpm and the clear supernatant was collected. The drug concentration in the supernatant was then determined using a UV-Visible spectrophotometric method. The experiment was carried out under controlled conditions to ensure reproducibility [24].

2.2. Screening of Polymers

Polymer screening was done by literature survey to select the suitable carrier for the dosage form. Screening was done in such a way that the drug's intrinsic release pattern is not modified by carrier. Ultimately, the melting point and calorimetry properties of the polymers indicated that those with low melting points were not stable during handling and extrusion and those with high melting points were not processable [25]. Hot-melt extrusion is a solvent-free process (no solvent is used), thus solvent compatibility was also taken into account during the screening process (i.e. polymers that would require the use of solvent, or those that gave poor interactions with solvents, were eliminated). Note that, to keep the integrity of the formulation, only solid polymers were used in the screening phase, which excluded liquid polymers or plasticizers (e.g. polysorbates) from the study [26]. Waxy materials were not considered, because they are not easily processed and are not readily miscible in the extrusion equipment. This systematic approach enables the selection of process-compatible polymers that also meet the desired immediate-release properties. Furthermore, the polymer with a relatively high Tg and good miscibility with the drug was another contributing factor that improved the overall dissolution performance of the ASDs in combination with the other physicochemical properties [27]. A Tg above room temperature generally decreases the spontaneous molecular mobility of the solid dispersion and therefore decreases the likelihood of recrystallization and improves physical stability. The molecular interaction between the drug and selected polymer might also have contributed to the wettability/dissolution improvement. These findings highlight the importance of the choice of polymer in improving the dissolution profile and the stability of the final amorphous formulations [28].

2.3. Preparation of Screening Batches through Solvent Evaporation

The API and polymer were weighed in a 1:1 ratio and dissolved in acetone while being stirred with a magnetic stirrer. After the solution became homogeneous, the temperature was raised to about 50°C to further remove the solvent in a controlled manner. The solid residue was vacuum dried in an oven at a controlled temperature to remove residual solvent, and then ground to a fine powder [29]. The powder was then placed through a sieve to obtain the desired grade and was packaged in the double polyethylene bag and air-tight trilaminate pouch to prevent moisture absorption. Table 1. represents the screening batches for solvent evaporation process.

Table 1. Screening Batches for Solvent Evaporation.

S. No.	Composition	Screening Batches (gm) Solvent Evaporation			
		F1	F2	F3	F4
1.	Model Drug	1	1	1	1
2.	Kollidon VA 64	1	-	-	-
3.	Soluplus	-	1	-	-
4.	Kollidon 30	-	-	1	-

5.	PEG 6000	-	-	-	1

2.4. Preparation of Screening Batches through Hot Melt Extrusion

The API and polymer were mixed in equal proportions by weight via geometric mixing, before being fed into a hot melt extruder, with multi-zone barrel extrusion used. The temperature of the zones of the barrel was varied according to the thermal properties of the polymer (25 to 160°C over zones) [30]. The speed at which the screw rotated (20 to 100 rpm) was controlled to ensure adequate mixing and residence time. Melted polymer obtained after processing was used to prepare the drug-containing matrix by dispersing the drug throughout the polymer at
molecular level. The extrudates obtained were cooled at room temperature, collected and ground to size [31]. Table 2 represents the screening batches for solvent evaporation process.

Sr. No.	Composition Screening Batches (gm)				
		Hot Melt Extrusion			
		F5	F6	F7	F8
1.	Model Drug	1	1	1	1
2.	Kollidon VA 64	1	-	-	-
3.	Soluplus	-	1	-	-

2.5. Evaof Screening Batches for Best Polymer Selection

Preparation of solid dispersion batches through solvent evaporation and hot melt extrusion techniques were prepared. The drug: polymer ratio was taken as 1:1. After the solid dispersion preparation through both the methods the solubility of the extrudes for each batch was analysed for the defined ratio. Through the solubility analysis the selection of polymer was done for optimization batches that were to be prepared. The best polymer and technique selection was done based on the solubility of the screening batches of both the techniques [32].

2.6. Optimization using QbD Approach

Optimization of formulation was done to improve the dissolution of the API. A Quality by Design (QbD) approach was adopted in the optimization study. A single-factor full factorial design was used to screen and evaluate the effect of varying polymer concentrations on the critical quality attribute of the formulation using the JMP software (18th edition 18.2.2). Polymer concentration was selected as the continuous independent variable. Percentage drug dissolution at 240 min. was selected as a dependent response variable. We also investigated the effect of varying polymer concentration, and a correlation between polymer concentration and dissolution behaviour was established [33, 34].
Experimental batches of the selected optimum formulation were prepared and processed under the mentioned conditions. The prepared extrudates were subjected to dissolution studies at different intervals. The data obtained were statistically analysed using the software JMP. The model adequacy and the region of optimum formulation were assessed by regression analysis,
analysis of variance (ANOVA), residuals analysis, prediction profiling, actual versus predicted response situated in the design space, and desirability optimization [35]. These analyses showed that polymer concentration has a meaningful effect on dissolution response and that it has an acceptable predictive ability in the design space region studied. This desirability function was then used to find an optimal polymer concentration with the maximum dissolution [36].

2.7. Evaluation of Formulations

The evaluation of the formulation was done based on different techniques.

2.7.1 In Vitro Dissolution Studies

Dissolution studies were performed in USP Type III (reciprocating cylinder) apparatus in a dissolution medium of (phosphate buffer, pH 6.8 with 0.4% SLS) at 37±0.5°C, and a paddle speed of 20 dpm. At predetermined time intervals, samples were withdrawn, filtered, and analysed for drug content. Sink conditions were maintained throughout all dissolution experiments, as verified by ensuring the drug concentration in the dissolution medium did not exceed 30% of its equilibrium solubility [37]. The optimized batch was analysed against the marketed formulation to check whether the optimized formulation behaved similar to the marketed. F2 was also calculated for the optimized batch.

2.7.2 Differential Scanning Calorimetry (DSC) Analysis

Differential Scanning Calorimetry (DSC) studies were carried out on the solid dispersions, polymers, physical blends and pure drug in order to check into any drug polymer interaction and to determine whether the drug in the formulation was

in crystalline or amorphous form. The samples, with a range of approximately 3-5 mg, were weighed and put in closed aluminium pans, along with an empty pan for reference, in the Differential Scanning Calorimeter (DSC) instrument, and both sample and reference pans were scanned. The samples were heated at a constant rate from 25 °C to 300 °C. The DSC thermograms were examined for typical endo- (glass transition temperature (Tg), melting point, etc.) and exothermic (recrystallization, etc.) transitions [38, 39].

The melting peak of the drug was lost or shifted once it had been formulated into a solid dispersion with the polymer, indicating the loss of crystallinity and formation of an amorphous solid dispersion. In order to study the interactions between the drug and polymer, thermal behaviour of the samples was also studied. DSC of both crude drug as well as optimized

formulation was analysed to determine the melting point and to check the conversion of drug from crystalline to amorphous form [40, 41].

2.7.3. X-Ray Diffraction Analysis

The solid state of the optimized solid dispersion was confirmed by X-ray diffraction (XRD) analysis to determine the crystalline or amorphous property of the solid dispersion. The X-ray diffractometer should be equipped with Cu-Kα radiation, an appropriate 2θ range (usually 5° to 50°), and an appropriate scanning speed under a standard condition. Crystalline drugs are typcally characterized by sharp peaks in the diffraction pattern, while amorphous polymers are characterized by broad halos [42, 43]. Loss of peak intensity, peak broadening, or peak disappearance of the crystalline drug is indicative of a possible drug-to-amorphous phase transition, or formation of a solid solution of the crystalline drug with the polymeric carrier in the solid dispersions. Since the solubility affects dissolution behaviour, the preparation of an amorphous form is important [44, 45]. A commonly used method to evaluate the dispersion quality is comparing diffraction patterns, which also provide information about drug-polymer interactions and system stability. XRD of both the crude drug and the optimized formulation was analysed to check whether the drug has converted to amorphous form or not from the crystalline form [46].

3. Results and Discussion

The results of the above flow of methods used for preparation of final optimized drug product or formulation is described in this section.

3.1. Saturation Solubility of Model Drug

The saturation solubility of the drug was analysed in different media which helped to gain a clarity of the drug solubility. The media that shows the highest solubility will be used as a dissolution medium to check the release profile of the prepared batches. The solubility of the drug in different media is provided in Table 3.

Table 3. Solubility of Model Drug in various media.

S. No.	Media	Solubility (mg/mL)
1.	0.1N HCL	0.043
2.	0.1 HCL + 0.4% SLS	0.055
3.	pH 4.5	0.028
4.	pH 4.5 + 0.4% SLS	0.032
5.	Ph 6.8	0.048
6.	pH 6.8 + 0.4% SLS	0.061

The comparative solubility of the model drug in different medias is represented in Figure 1.

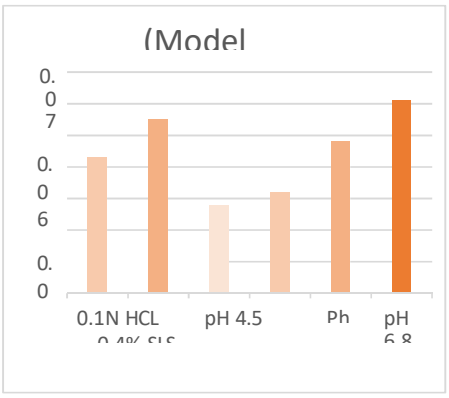


Figure 1 Solubility of model drug in different media.

From the solubility analysis results the solubility of the model drug was seen highest in pH 6.8+0.4% SLS. Hence for the dissolution Ph 6.8+0.4% SLS will be used.

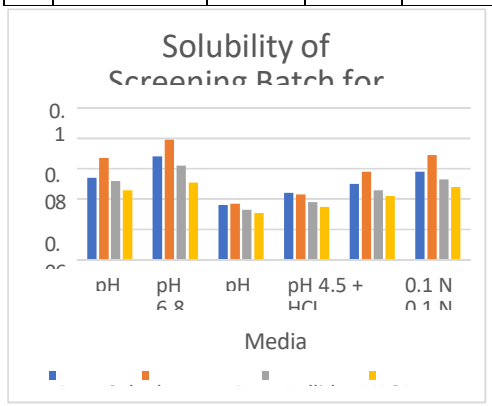
3.2. Polymer Screening

The polymers to be used for screening batches were selected after a proper screening for their

melting point and Tg. This screening is done to check if the polymer is suitable for the process of solid dispersion and will not get degrade during the process and affect the formulation. Table 4. represents different polymers along with their melting point and Tg and their solubility in the solvent as for the solvent evaporation process.

Table 4. Melting point, Tg and solubility of polymers.

S. No.	Polymer	Melting Point	Tg	Solubility solvent
1.	Kollidon 30	170	131	Soluble
2.	Kollidon VA 64	140	-	Soluble
3.	Soluplus	-	70	Soluble
4.	PEG 6000	~60	-	Soluble
5.	Kollidon 17	140	-	Insoluble
6.	HPMC AS	~120	-	Insoluble



From the polymer analysis we found that Kollidon 30, Kollidon VA64, Soluplus and PEG 6000 are suitable polymers for preparing screening batches of the drug.

3.3. Solubility of Screening Batches of Solvent Evaporation and Hot Melt Extrusion

The screening batches prepared using drug: polymer ratio as 1:1 for solvent evaporation and hot melt extrusion were analysed for saturation solubility in different medias to check the increase in drug solubility after prepa
ration of solid dispersion. Table 5. describes the solubility of the screening batches in various media after processing the drug with polymer through solvent evaporation and Table 6. describes the solubility of the screening batches in various media after processing the drug with polymer through hot melt extrusion. The comparative solubility of screening batches for solvent evaporation is represented in Figure 2. and the comparative solubility of screening batches for hot melt extrusion is represented in Figure 3.

Table 5. Solubility of Screening batches in different media for Solvent Evaporation.

S. No.	**Screening Batches (1:1)**	**Solubility (mg/mL)**					
		pH 6.8	**pH 6.8 + 0.4 % SLS**	**pH 4.5**	**pH 4.5 + 0.4 % SLS**	**0.1**	**0.1 SLS**
1.	Drug:Soluplus	0.054	0.068	0.036	0.044	0.050	0.058
2.	Drug:Kollidon VA64	0.067	0.079	0.037	0.043	0.058	0.069
3.	Drug:Kollidon 30	0.052	0.062	0.033	0.038	0.046	0.053
4.	Drug:PEG6000	0.046	0.051	0.031	0.035	0.042	0.048

Figure 2 Comparative solubility analysis of screening batches for Solvent Evaporation.

Table 6. Solubility of Screening batches in different media for HME.

S. No.	**Screening Batches (1:1)**	**Solubility (mg/mL)**					
		pH 6.8	**pH 6.8 + 0.4 % SLS**	**pH 4.5**	**pH 4.5 + 0.4 % SLS**	**0.1**	**0.1 SLS**
1.	Drug:Soluplus	0.068	0.092	0.042	0.058	0.063	0.074
2.	Drug:Kollidon VA64	0.082	0.126	0.048	0.064	0.072	0.086

3.	Drug:Kollidon 30	0.066	0.079	0.036	0.043	0.052	0.061
4.	Drug:PEG6000	0.057	0.072	0.031	0.039	0.051	0.059

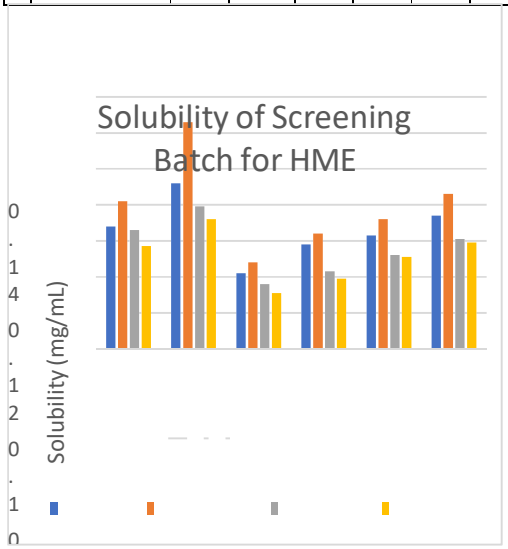


Figure 3 Comparative Solubility of screening batches of HME.

Through the solubility analysis of screening batches of both solvent evaporation and hot melt extrusion procedure - Kollidon VA64 shows the highest solubility enhancement as compared to the crude drug solubility. Hence, Kollidon VA 64 was taken as factor affecting the solubility and dissolution and Hot Melt Extrusion process was selected for preparing DOE batches.

3.4. Optimization batches using DOE

The full factorial design with one factor and four levels and with one centre point was used to generate trial runs for estimating the required response. The trial batches provided by DOE were prepared and the dissolution of each batch was conducted to match with the desired results of the marketed tablets. Table 7. represents the trail batches provided by the JMP software on one factor that is polymer concentration (X1) of Kollidon VA64 for the response (Y) that is the dissolution rate.

Table 7. Trail batches of DOE

Sr. No.	Pattern	Kollidon VA 64 Concentration (mg)	Dissolution
1.	1	300	95
2.	2	500	100
3.	0	600	103
4.	4	900	109
5.	3	700	106

After these trial batches were run the following prediction was done for these batches.

3.4.1. Dissolution Profile of the prepared DOE batches

The DOE batches were formulated according to the given concentrations of Kollidon VA 64. After successful preparation of different solid dispersions, tablets were formed and the dissolution of each formulation was conducted. Table 8. provides the formula for optimized batched by DOE for tablet compression.

Table 8. Formula for Optimized DOE batches

Sr. No.	Composition (mg)	F9	F10	F11	F12	F13
1.	Drug	100	100	100	100	100
2.	Kollidon VA 64	300	500	600	700	900
3.	Colloidal Silicon Dioxide	10	10	10	10	10
4.	Sodium Stearyl Fumarate	5	5	5	5	5

After the compression of the tablets through the above formula the dissolution was conducted in the OGD media that is pH 6.8 + 0.4% SLS. Table 9. represents the dissolution profile of the optimized DOE batches at different time points.

Table 9. Dissolution Profile of DOE batches.

Sr. No.	Time Point (in min.)	% Drug Release				
		F9	F10	F11	F12	F13
1.	15	11	9	14	23	18
2.	30	21	17	25	41	33

3.	45	29	24	38	56	46
4.	60	39	31	54	69	59
5.	90	51	46	71	87	79
6.	120	60	58	98	100	97
7.	180	81	80	101	106	108
8.	240	95	100	103	106	109

The comparative % dissolution release profile of the DOE batches was plotted against the time (in min.). Figure 4. represents the % Drug release of the DOE batches.

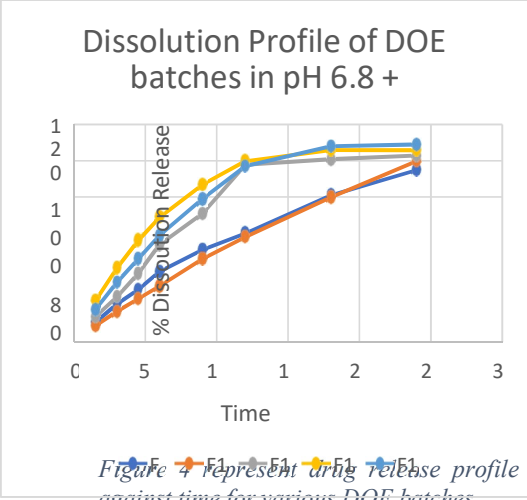


Figure 4 represent drug release profile against time for various DOE batches

3.4.2. Linear Regression Plot

The effect of increasing the concentration of Kollidon VA 64 on the dissolution profile of the formulation can be seen in the linear regression plot. The data points represent the dissolution profile of the formulation carried out in different concentrations of polymer, and the red line is the fitted linear regression line. Figure 5. Linear regression of the dissolution for the Kollidon VA 64 data.

Figure 5 shows the linear regression plot of Kollidon VA 64 v/s Dissolution

The graph shows the influence of Kollidon VA 64 concentration on the formulation's dissolution. As the concentration of the polymer is increased from the low to the high concentration, the dissolution response is improved. These findings suggest that Kollidon VA 64 is the primary polymer responsible for improving drug wettability and solubilization in the formulation matrix. There was a good correlation between the fitted regression line and the experimental data points, as the data points were relatively close to the fitted regression line predicted by the model. This indicates the DOE model applied in this study was satisfactory and that the chosen factor had meaningful effects on dissolution.

3.4.3. Actual By Predicted Plot

The relationship between the experimentally observed dissolution values ("Actual") and the statistically predicted dissolution values ("Predicted") generated by the DOE model can be seen in actual by predicted plot.
The red diagonal regression line represents the ideal agreement between predicted and observed responses, while the surrounding confidence bands indicate the prediction variability of the model. Figure 6. represents actual by predicted plot.

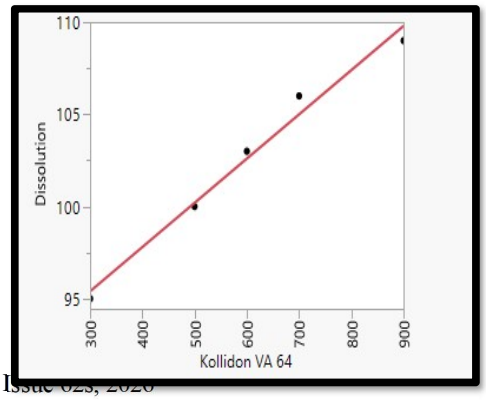


Figure 6 shows the actual by predicted plot

As depicted in the Actual vs Predicted plot, there is a very good correlation between the experimental dissolution values and the predicted values obtained from DOE statistical model. The experimental values were very close to the regression line, which shows the predictability of the DOE model developed. The model had a high coefficient of determination (R^2) = 0.98294.

A coefficient of determination (R2) value of 0.98294 showed that 98.29% of the variability in the dissolution response variable could be explained by the formulation factor chosen; thus, polymer concentration had a considerably high degree of influence on the dissolution behaviour and fit the model.

The low Root Mean Square Error (RMSE) of 0.8165 indicates that the actual and predicted values were close to each other, meaning the model made accurate predictions.

RMSE=0.8165

The model was statistically important (P-value of 0.0010) , implying that the effect of polymer concentration on the dissolution response was important and not due to chance experimental variation.

p=0.0010

Conversely, narrow confidence bands around the regression line can indicate a model that is stable, reproducible in the examined design space, whereas the absence of large outliers and large deviations away from the fitting line can indicate an acceptable experimental reproducibility and robustness of the formulation process.

3.4.4. Residual v/s Predicted Plot

The distribution of residual values against the predicted dissolution responses generated by the DOE model can be seen in residual v/s predicted plot. Residuals represent the difference between experimentally observed values and model-predicted values.

The horizontal reference line at zero indicates the ideal condition where no prediction error exists. Figure 7. Represents the residual v/s predicted plot for the experimental runs.

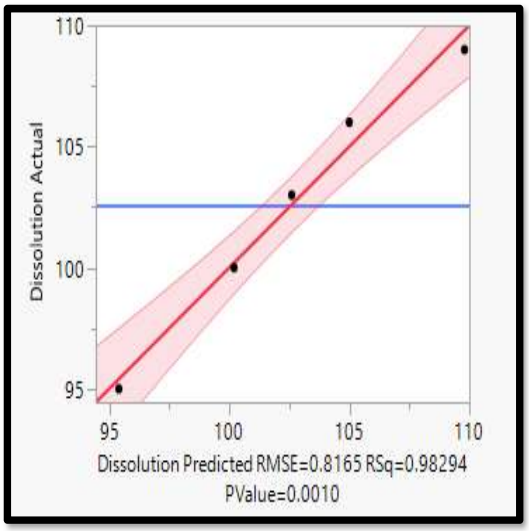
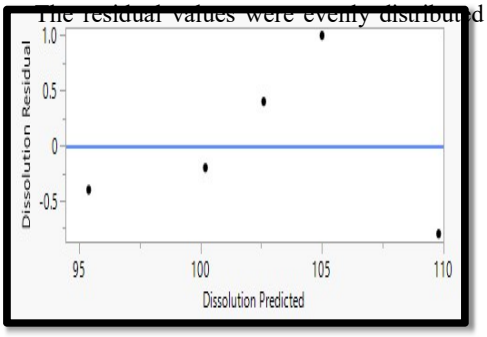


Figure 7 shows the residual v/s predicted plot

In the Residual vs. Predicted plot, the residual value is randomly scattered around the zero-reference line. This observation shows good agreement of the experimental observations to those predicted by the statistical function. Furthermore, the low and randomly scattered values of the differences throughout the entire effective dissolution range indicate that no important systematic error is introduced by the developed function. This indicates that the DOE model chosen was adequate to describe the relationship between the polymer concentration and the dissolution response. The residual values were evenly distributed



with no pattern, funnel shape or curvature trend, evidence of a homogeneity of variance and an adequate model fit throughout the design build. The random pattern of residuals also indicates that the model development assumptions are met. The positive and negative values of the residuals around the zero line further indicate that the prediction behaviour of the model is balanced and that the model is not underpredicting or overpredicting dissolution responses. There was some variation in the size of the residuals in the intermediate predicted dissolution range, but it was within an acceptable range and was generally stable, indicating that the model fit the data well. The absence of extremely high or low values of the residual values is an indicator of a good reproducibility of the experiments and good reliability of the formulation experimental data. The Residual vs Predicted plot also shows the fitness, robustness, and predictability of the designed factorial design model for polymer concentration optimization, with regard to dissolution enhancement.

3.4.5. Prediction Profiler with Desirability Function Plot

A prediction profiler from the DOE model and the desirability function for optimization of polymer concentration are shown in the figure. The prediction profiler depicts the effect of Kollidon VA 64 concentration on the dissolution profile of a formulation and the desirability function curve shows the best formulation domain that corresponds to the most desirable response. Figure 8. Prediction profiler with the desirability function plot.

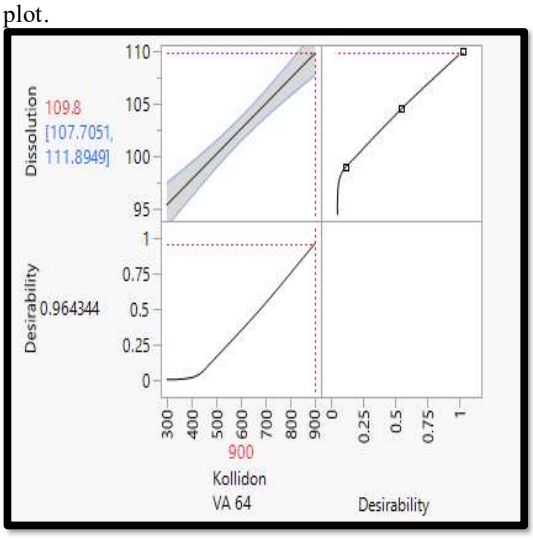


Figure 8 shows the prediction profiler with desirability function

The Prediction Profiler corroborated the effect of Kollidon VA 64 concentration on the dissolution response of the formulation as earlier discussed, with an increasing polymer concentration giving a higher dissolution response across the presented experimental region.

Based on data from profiler plot, it was found that an increase in the Kollidon VA 64 concentration in the formulation resulted in improved profiles, probably due to improved wettability, the drug being more finely dispersed in the polymeric carrier, and a reduction in the drug's degree of crystallinity, leading to an improved dissolution profile.

The optimization study demonstrated that the maximum predicted dissolution response was 109.8% for Kollidon VA 64 concentration of approximately 900 mg (0.964344 showing high potential of optimization) . A desirability value close to 1 indicated that the optimum was well defined and that the cost function was optimized; the concentration choice for the polymer was the optimum of the formulation involved.

Desirability=0.964344

The width of the confidence interval bands around the prediction line is relatively small, indicating that the statistical model is a good fit. The steep upward slope indicates that polymer concentration has a large and statistically important effect on the performance of the dissolution
rate. The desirability function profile also suggested that the desirability of the target dissolution response increased with increasing polymer concentration, suggesting that higher Kollidon VA 64 concentrations were more desirable. In addition, no decrease in desirability was observed in the profile within its concentration range, which indicated that the upper concentration limit was consistent with the optimal region.

Both the results from overall profiler and the desirability analysis suggested that Kollidon VA 64 was indeed an effective dissolution enhancer, and at the best polymer concentration derived from the DOE approach.

3.4.6. Analysis of Variance (ANOVA) for the Effect of Kollidon VA64

Concentration on Dissolution Response

The ANOVA table tests the effect of Kollidon VA64 concentration on the dissolution response with the applied factorial design model (Table 10) . represents the analysis of variance for the effect of Kollidon VA 64 concentration on the dissolution response. Table 10. Analysis of variance for the effect of Kollidon VA 64 concentration on dissolution.

Source	Nparm	DF	Sum Squares	F Ratio	Prob > F
Kollidon 64 (300,900)	1	1	115.20000	172.8000	0.0010*

ANOVA indicates that the concentration of Kollidon VA64 has a statistically meaningful effect on the dissolution profile of the formulation. The high F-ratio of the model (172.80) indicates that the variation in dissolution response explained by the model is much greater than the unexplained variation in the experiment. $F = 172.80$

The model generated a p-value of 0.0010 ($p<0.05$), showing that the rise in dissolution was highly associated with the change in polymer concentration and was not a random variation in the experimental results.

$$p = 0.0010$$

The high value of the Sum of Squares for the Kollidon VA64 suggests that the formulation factor has considerably contributed towards the total dissolution response and that polymer concentration has been an important factor contributing to the drug's release profile.
In a statistically meaningful model, the increase of Kollidon VA64 concentration provides an improvement of the dissolution characteristics over the researched experimental range. The results of the study also illustrate the adequacy of the selected DOE approach for polymer concentration optimization in the formulation.

In most cases, ANOVA analysis revealed that the factorial design model developed is reliable, valid and statistically meaningful in predicting the dissolution behavior.

3.4.7. Regression Model Equation for Dissolution Response

Using a linear regression equation as described in the factorial design, the dependent variable (the dissolution response) regressed on the independent variable (the content of Kollidon VA64) , with the regression equation statistically meaningful at $p < 0.01$. Therefore, an increase in the content of Kollidon VA64 provided an improvement to the drug release profile.

$$Y = 88.2 + 0.024X$$

where Y is the predicted dissolution response and X is the concentration of Kollidon VA64.

The positive coefficient of Kollidon VA64 implies that overall, the polymer addition positively affected the dissolution enhancement in the concentration domain of interest, and when other variables are kept constant, there will be a corresponding increase in the dissolution response for every unit increase of polymer concentration. The improvement has often been attributed to better wettability, dispersion of the drug and decreased crystallinity leading to improved drug release behaviour.
The high value of coefficient of determination along with the statistical importance of ANOVA tests carried out as a part of DOE analysis justifies the high statistical importance of the regression model. The model showed good greement between the predicted and experimental values of the responses, thus, confirming model adequacy and predictability of formulation variables. The regression equation of the overall should be an appropriate reflection on the effect of Kollidon VA64 concentration on the dissolution performance and a reliable mathematical model to optimize the formula.
The QbD driven optimization thus helped us to understand the formulation behaviour, reduce the experimental variations and design a strong, reproducible formulation which showed improved drug release. Based on the QbD driven optimization, the optimized drug: polymer ratio was found to be 1:5 which showed the desired

dissolution and performance parameters. Because higher dissolution release profiles are toxic when administered to the body, the optimal drug: polymer ratio was determined to be 1:5 (F10).

3.5. Evaluation of Formulation

The evaluation of the optimized 1:5 drug: polymer HME batch was done through various tests against the crude drug.

3.5.1. Dissolution profile of the Optimized Batch v/s Marketed

The dissolution of the optimized HME batch and the marketed drug formulation was done to analyse the drug release behaviour is same or not and if the optimized batch is safe or will produce toxicity if faster dissolution as compared to the marketed. Table 11. represents the dissolution profile of both the optimized batch and the marketed formulation.

Table 11. Dissolution Profile of Optimized and Marketed Formulation.

Sr. No.	Time Points (in min.)	% Drug Release	
		Marketed Formulation	F10 (1:5) Formulation
1.	15	7	9
2.	30	14	17
3.	45	22	24
4.	60	28	31
5.	90	42	46
6.	120	55	58
7.	180	76	80
8.	240	97	100
F2			74.47

The F2 value shows a good similarity factor for the formulation.

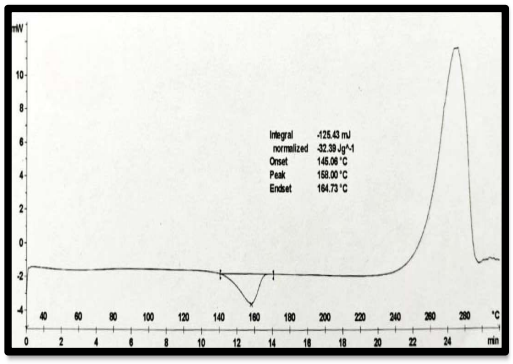


Figure 9. shows a comparative dissolution analysis of optimized and marketed formulation.

From the dissolution analysis we can see an increase in the solubility of the F10 (1:5) optimized formulation as compared to the marketed formulation.

3.5.2. Differential Scanning Calorimetry (DSC) Analysis

Melting and crystallization characteristics of the crude drug and the optimized formulation were studied using differential scanning calorimetry (DSC) and shown in figure 10. represents the DSC of the crude drug.

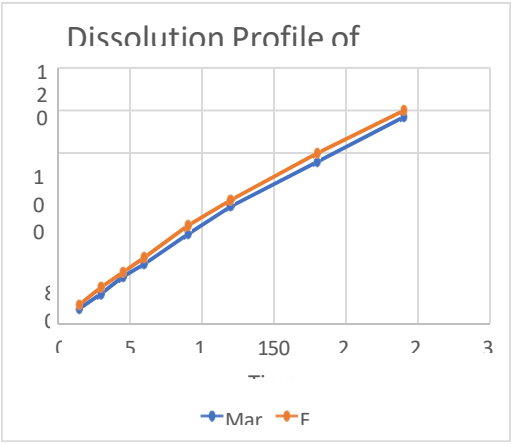


Figure 10 DSC of crude drug

On the basis of the change of the endothermic process, the onset, the melting endothermic peak temperature and the endset temperature of the drug were determined to be 148.00, 158.06 and 164.73 C respectively, and based on the sharp melting transition, the pure drug possesses a highly-ordered crystalline system.
Tpeak = 158.06°C

The sharp and narrow melting endotherm from the thermogram indicates that the drug material was of high purity and percentage crystallinity. The high level of crystallinity of the crystalline drugs provided a combination of strong intermolecular interactions and lattice arrangement leading to lower aqueous solubility and dissolution. These observations of the thermal profile appear to be consistent with the known poor solubility behaviour of the drug.
No further thermal transitions or decomposition peaks were found prior to the melting point acquisition. Thus, the drug was thermally stable throughout the evaluated temperature range. This shows that there are no polymorphic transitions or important impurities in the crude sample examined, since multiple endothermic or exothermic events would be observed otherwise.

Figure 11. represents the DSC of Optimized HME formulation.

The thermogram of the optimized formulation shows marked differences in thermal characteristics when compared to the DSC profile of the pure crystalline drug.
In the DSC thermogram of optimized HME formulation (figures 2 and 3) , melting endotherm peak of pure drug which shows in the range of 158°C was absent. The absence of melting endotherm peak indicates that drug crystallinity was considerably reduced due to conversion of the drug into an amorphous form or molecular dispersion of the drug within the polymeric carrier matrix during the hot melt extrusion processing step.

$T_{m,drug} \approx 158°C$

The lack of such a melting transition is also indicative of the proper deposition of the drug into the Kollidon VA64 polymeric carrier, which suggests that the drug at the molecular level was evenly distributed and recrystallization of the drug inside the carrier system did not occur during the thermal processing of the system.
The broadening of the thermal transition in the intermediate temperature range likely arises from the softening behaviour and thermal transitions of the polymeric carrier, including the glass transition. Additionally, the physical nature of the transition suggests that an amorphous solid dispersion is formed, rather than a crystalline drug phase.

3.5.3. X-Ray Diffraction Analysis

To evaluate the change in crystallinity and physical state of the crude drug and optimized formulation, XRD of the crude drug and the optimized formulation was done. The results are shown in Figure 12. represents the XRD of the crude drug.

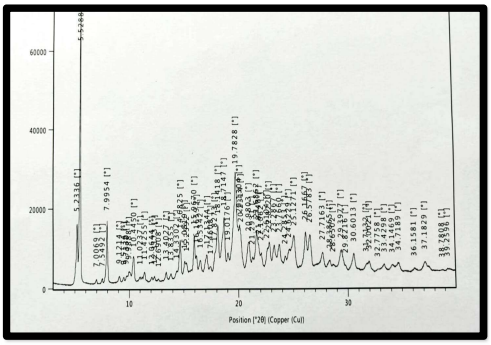


Figure 12 XRD of crude drug

The diffractogram of the crude drug recorded sharp and intense diffraction peaks at certain values of the diffraction angle (2θ) , indicating that the substance is highly crystalline in nature.
The presence of the drug was characterized by the presence of characteristic peaks in the XRD pattern at 2θ diffraction angles of 5.23°, 7.00°, 7.99°, 10.44°, 11.02°, 12.06°, 13.40°, 14.68°, 16.15°, 17.13°, 18.14°, 19.78°, 20.13°, 21.29°, 22.18°, 23.28°, 24.28°, 25.12°, 26.16°,
27.71°, 29.39°, 30.60°, 32.77°, 33.42°, 34.14°,

36.15°, and 37.18°, which indicates the high degree of crystallinity of the drug (well-defined sharp peaks with high intensity).
2θ = 5.23°, 7.99°, 10.44°, 19.78°

The presence of narrow and sharp diffraction peaks in this diffractogram indicates the long-range molecular organization of the crude drug material and confirms the high crystallinity of the drug material. High crystallinity of the drug material accounts for close packing of molecules, strong intermolecular interaction and as a result poor wettability, low aqueous solubility and slow dissolution.
The XRD pattern exhibited rather sharp peaks, which is consistent with the melting endotherm of the pure drug, as obtained from the DSC thermograms, and is characteristic of materials with crystalline structures. The DSC and XRD results indicate that the crude drug was in crystalline form before the processing steps required to formulate it.
There was no peak broadening or formation of an amorphous halo, suggesting that there was little presence of amorphous content in the untreated drug. The well-resolved diffraction peaks were proof of both the purity and overall crystalline integrity of the drug material.

Figure 13. represents the XRD of Optimized HME formulation.

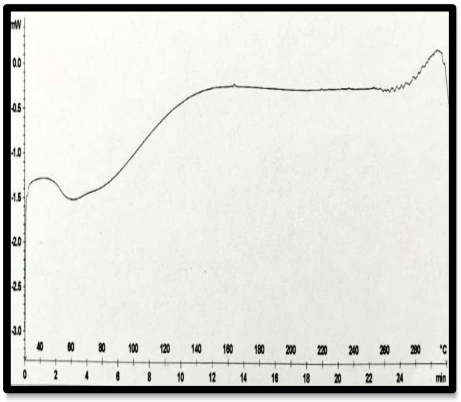


Figure 13 XRD of optimized formulation

The diffractogram of optimized formulation exhibited considerable change in diffraction pattern as compared to the XRD pattern of pure crystalline drug.
The sharp and intense peaks of the diffraction were observed in the diffractogram of the crude drug. These peaks were reduced in intensity in the optimized formulation. The diffractogram of the optimized formulation (F2) exhibited the broad diffuse halo pattern with few residual
peaks at 14.67°, 20.32°, 22.48° and 34.56° (2θ) with low intensity. The decrease in intensity and broadening of diffraction peaks indicated that there was an important loss of crystallinity, and a transformation to the amorphous form of the drug following the hot melt extrusion processing.
2θ= 14.67°, 20.32°, 22.48°, 34.56°

Broader diffraction pattern, as well as the loss of a number of sharp crystalline diffraction peaks compared with that of pure drug, suggests that regular crystal lattice structure was disrupted during extrusion so that the drug was completely dispersed molecularly within the Kollidon VA64 polymer and formed an amorphous solid dispersion system.
The broad halo in the diffractogram reflects the absence of molecular order in the optimized formulation, which is consistent with the presence of an amorphous system. The amorphization of poorly soluble drugs during hot melt extrusion is desirable, as the amorphous form is thermodynamically less stable than the crystalline form and possesses improved wettability and apparent solubility properties.
The characteristic low intensity peaks of the drug in the formulation may still be detected, albeit to a much lesser degree than the pure drug, indicating the presence of residual crystallinity or crystalline domains within the polymeric matrix. The important decrease in crystallinity is a good indication that the HME process is able to successfully alter the states of the drug.

4. Discussion and Conclusion

This study highlighted the potential of using amorphous solid dispersion technology to improve the dissolution performance of a poorly soluble BCS Class IV drug. Hot melt extrusion and solvent evaporation techniques were successfully employed to manufacture solid dispersions. Saturation solubility studies showed that the crude

drug is poorly water soluble, warranted formulation approaches to improve dissolution performance. Polymer screening studies revealed that Kollidon VA64 exhibited better solubility enhancement than Soluplus, Kollidon 30 and PEG 6000 with respect to SE and HME systems. HME exhibited better dissolution enhancement and formulation uniformity when compared to other methods of preparation due to the severe mixing conditions, the molecular dispersion of the drug in the polymeric matrix
and solvent-free continuous processing. The developed QbD based optimization technique with a single factor full factorial design was able to realize the influence of polymer concentration on the dissolution responses. It has been observed that the drug release behaviour was considerably improved when the concentration of Kollidon VA64 was increased. Regression modelling and ANOVA statistics, along with prediction profiling and desirability optimization, indicated a suitable fit and considerably determined the effect of concentration of polymer on dissolution behaviour, with a high coefficient of determination.

Improved dissolution was corroborated by a study of solid-state characterization. According to DSC results, the crude drug displayed a sharp, highly intense melting endotherm, suggesting the material was a highly crystalline solid. The absence of the characteristic melting peak in the HME of the optimized composition confirmed the successful reduction of crystallinity and conversion of the drug into amorphous state or molecular dispersion as a result of optimization. On the other hand, the pure drug exhibited multiple sharp diffraction peaks in the XRD pattern, confirming its crystalline nature. A broad halo with considerably reduced sharp diffraction peaks of the optimized formulation confirmed the amorphization of the substance through the extrusion process. The better dissolution behaviour was attributed to the reduction of crystallinity of the drug and its better wetting, molecular dispersion and better stabilization of the amorphous state by Kollidon VA64 in the polymer matrix. The hydrophilicity of the polymer also supports maintenance of supersaturation and inhibition of recrystallization during dissolution, thereby easing improved drug release behaviour.

Ultimately, based on the findings of the present study, hot melt extrusion in combination with a quality by design driven optimization approach represents an effective and scalable formulation strategy to improve the dissolution performance of poorly soluble BCS Class IV drugs. The dissolution behaviour of the optimized formulation was similar to the marketed product with a satisfactory statistical predictability, reproducibility and solid-state stability. Collectively, DSC and XRD results unequivocally indicate that the active pharmaceutical ingredient has been successfully amorphized and molecularly stabilized within the polymeric matrix. These results further suggest a strong potential for HME-based amorphous solid dispersions to substantially improve the oral bioavailability of poorly soluble drug candidates, and mark a clear path ahead towards formulation of stable and highly effective dosage forms.

References

[1] Shahiwala A. Formulation approaches in enhancement of patient compliance to oral drug therapy. Expert opinion on drug delivery. 2011 Nov 1;8(11):1521-9. https://doi.org/10.1517/17425247.2011.628311

[2] Ensign LM, Cone R, Hanes J. Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. Advanced drug delivery reviews. 2012 May 1;64(6):557-70. https://doi.org/10.1016/j.addr.2011.12.009

[3] Hauber B, Hand MV, Hancock BC, Zarrella J, Harding L, Ogden-Barker M, Antipas AS, Watt SJ. Patient acceptability and preferences for solid oral dosage form drug product attributes: a scoping review. Patient preference and adherence. 2024 Dec 31:1281-97. https://doi.org/10.2147/PPA.S443213

[4] Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. International journal of pharmaceutics. 2011 Nov 25;420(1):1-0. 10.1016/j.ijpharm.2011.08.032

[5] Kumari L, Choudhari Y, Patel P, Gupta GD, Singh D, Rosenholm JM, Bansal KK, Kurmi BD. Advancement in solubilization approaches: a step towards bioavailability enhancement of poorly soluble drugs. Life. 2023 Apr 27;13(5):1099. https://doi.org/10.3390/life13051099

[6] Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, Cho JM, Yun G, Lee J.

Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian journal of pharmaceutical sciences. 2014 Dec 1;9(6):304-16. https://doi.org/10.1016/j.ajps.2014.05.005

[7] Kakran M, Li L, Müller RH. Overcoming the challenge of poor drug solubility. Pharm. Eng. 2012 Jul;32(4):1-7. https://doi.org/10.1016/j.ddtec.2012.04.002

[8] Shah VP, Amidon GL. GL Amidon, H. Lennernas, VP Shah, and JR Crison. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability, Pharm Res 12, 413–420, 1995—Backstory of BCS. The AAPS journal. 2014 Sep;16(5):894-8. https://doi.org/10.1208/s12248-014-9620-9

[9] Benet LZ, Amidon GL, Barends DM, Lennernäs H, Polli JE, Shah VP, Stavchansky SA, Yu LX. The use of BDDCS in classifying the permeability of marketed drugs. Pharmaceutical research. 2008 Mar;25(3):483-8. https://doi.org/10.1007/s11095-007-9523-x

[10] Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. European Journal of Pharmaceutics and Biopharmaceutics. 2004 Sep 1;58(2):265-78. 10.1016/j.ejpb.2004.03.001

[11] Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL. A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan. Molecular pharmaceutics. 2006 Dec 4;3(6):631-43. https://doi.org/10.1021/mp0600182

[12] Dahan A, Beig A, Lindley D, Miller JM. The solubility–permeability interplay and oral drug formulation design: Two heads are better than one. Advanced drug delivery reviews. 2016 Jun 1;101:99-107. https://doi.org/10.1016/j.addr.2016.04.01 8

[13] Benet LZ. The role of BCS (biopharmaceutics classification system) and BDDCS (biopharmaceutics drug disposition classification system) in drug development. Journal of pharmaceutical sciences. 2013 Jan 1;102(1):34-42. https://doi.org/10.1002/jps.23359

[14] Chen ML, Amidon GL, Benet LZ, Lennernas H, Yu LX. The BCS, BDDCS, and regulatory guidances. Pharmaceutical research. 2011 Jul;28(7):1774-8. https://doi.org/10.1007/s11095-011-0438-1

[15] Michalek W, Semler JR, Kuo B. Impact of acid suppression on upper gastrointestinal pH and motility. Digestive diseases and sciences. 2011 Jun;56(6):1735-42. https://doi.org/10.1007/s10620-010-1479-8

[16] Sugano K. Biopharmaceutics modeling and simulations: theory, practice, methods, and applications. John Wiley & Sons; 2012 Aug 20. https://doi.org/10.1002/9781118354339

[17] Mahmood T, Sarfraz RM, Ismail A, Ali M, Khan AR. Pharmaceutical methods for enhancing the dissolution of poorly water-soluble drugs. ASSAY and Drug Development Technologies. 2023

[18] Xie B, Liu Y, Li X, Yang P, He W. Solubilization techniques used for poorly water-soluble drugs. Acta Pharmaceutica Sinica B. 2024 Nov 1;14(11):4683-716. https://doi.org/10.1016/j.apsb.2024.08.027

[19] Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. European journal of Pharmaceutics and Biopharmaceutics. 2000 Jul 3;50(1):47-60. 10.1016/S0939-6411(00)00076-X

[20] Bhatnagar P, Dhote V, Chandra Mahajan S, Kumar Mishra P, Kumar Mishra D. Solid dispersion in pharmaceutical drug development: from basics to clinical applications. Current drug delivery. 2014 Apr 1;11(2):155-71. https://doi.org/10.2174/15672018113109990044

[21] Vasconcelos T, Sarmento B,

Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water-soluble drugs. Drug discovery today. 2007 Dec 1;12(23-24):1068-75. 10.1016/j.drudis.2007.09.005

[22] Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. Biomedicines. 23;10(9):2055. https://doi.org/10.3390/biomedicines10092055

[23] Bergström CA, Avdeef A. Perspectives in solubility measurement and interpretation. ADMET and DMPK. 2019 Apr 5;7(2):88-105. https://doi.org/10.5599/admet.686

[24] Hiew TN, Heng PW. In Vitro Dissolution of Pharmaceutical Solids. Oral Bioavailability and Drug Delivery: From Basics to Advanced Concepts and Applications. 2023 Oct 10:31-46. https://doi.org/10.1002/9781119660699.ch3

[25] Repka MA, Shah S, Lu J, Maddineni S, Morott J, Patwardhan K, Mohammed NN. Melt extrusion: process to product. Expert opinion on drug delivery. 2012 Jan 1;9(1):105-25. https://doi.org/10.1517/17425247.2012.642365

[26] Verreck G, Six K, Van den Mooter G, Baert L, Peeters J, Brewster ME. Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion—part I. International journal of pharmaceutics. 2003 Jan 30;251(1-2):165-74. 10.1016/S0378-5173(02)00591-4

[27] Baghel S, Cathcart H, O'Reilly NJ. Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs. Journal of pharmaceutical sciences. 2016 Sep 1;105(9):2527-44. https://doi.org/10.1016/j.xphs.2015.10.008

[28] Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Kumar Battu S, McGinity JW, Martin C. Pharmaceutical applications of hot-melt extrusion: part I. Drug development and industrial pharmacy. 2007 Jan 1;33(9):909-26. https://doi.org/10.1080/03639040701498759

[29] Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor 2022 water-soluble drugs. Drug discovery Aug today. 2007 Dec 1;12(23-24):1068-75. 10.1016/j.drudis.2007.09.005

[30] Maniruzzaman M, Boateng JS, Snowden MJ, Douroumis D. A review of hot-melt extrusion: process technology to pharmaceutical products. International Scholarly Research Notices. 2012;2012(1):436763. https://doi.org/10.5402/2012/436763

[31] Breitenbach J. Melt extrusion: from process to drug delivery technology. European journal of pharmaceutics and biopharmaceutics. 2002 Sep 1;54(2):107-17. 10.1016/S0939-6411(02)00061-9

[32] Zhang X, Xing H, Zhao Y, Ma Z. Pharmaceutical dispersion techniques for dissolution and bioavailability enhancement of poorly water-soluble drugs. Pharmaceutics. 2018 Jun

[33] Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. Pharmaceutical research. 2008 Apr;25(4):781-91. https://doi.org/10.1007/s11095-007-9511-1

[34] Beg S, Rahman M, Kohli K. Quality-by-design approach as a systematic tool for the development of nanopharmaceutical products. Drug discovery today. 2019 Mar 1;24(3):717-25. 10.1016/j.drudis.2018.12.002

[35] Montgomery DC. Design and analysis of experiments. John wiley & sons; 2017. https://doi.org/10.1002/qre.458

[36] Singh B, Dahiya M, Saharan V, Ahuja N. Optimizing drug delivery systems using systematic" design of experiments." Part II: retrospect and prospects. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2005;22(3).

https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v22.i3.10

[37] Wang Y, Snee RD, Keyvan G, Muzzio FJ. Statistical comparison of dissolution profiles. Drug Development and Industrial Pharmacy. 2016 May 3;42(5):796-807. https://doi.org/10.3109/03639045.2015.1078349

[38] Craig DQ. The mechanisms of drug release from solid dispersions in water-soluble polymers. International journal of pharmaceutics. 2002 Jan 14;231(2):131-44. 10.1016/S0378-5173(01)00891-2

[39] Kawakami K. Current status of amorphous formulation and other special dosage forms as formulations for early clinical phases. Journal of pharmaceutical sciences. 2009 Sep 1;98(9):2875-85. https://doi.org/10.1002/jps.21816

[40] Baghel S, Cathcart H, O'Reilly NJ. Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs. Journal of pharmaceutical sciences. 2016 Sep 1;105(9):2527-44. https://doi.org/10.1016/j.xphs.2015.10.008

[41] Qian F, Huang J, Hussain MA. Drug–polymer solubility and miscibility: stability consideration and practical challenges in amorphous solid dispersion development. Journal of pharmaceutical sciences. 2010 Jul 1;99(7):2941-7. https://doi.org/10.1002/jps.22074

[42] Newman A, Engers D, Bates S, Ivanisevic I, Kelly RC, Zografi G. Characterization of amorphous API: polymer mixtures using X-ray powder diffraction. Journal of pharmaceutical sciences. 2008 Nov 1;97(11):4840-56. https://doi.org/10.1002/jps.21352

[43] Paudel A, Worku ZA, Meeus J, Guns S, Van den Mooter G. Manufacturing of solid dispersions of poorly water-soluble drugs by spray drying: formulation and process considerations. International journal of pharmaceutics. 2013 Aug 30;453(1):253-84. 10.1016/j.ijpharm.2012.07.015

[44] Janssens S, Van den Mooter G. Physical chemistry of solid dispersions. Journal of Pharmacy and Pharmacology. 2009 Dec;61(12):1571-86. https://doi.org/10.1211/jpp.61.12.0001

[45] Shinde SS, Shete A, Pranit A. Solid dispersions of poorly water-soluble drug using spray drying technique. International Journal of Drug Delivery. 2013 Jul 1;5(3):323. https://doi.org/10.1002/9781118444726.ch17

[46] Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water-soluble drugs. Drug discovery today. 2007 Dec 1;12(23-24):1068-75. 10.1016/j.drudis.2007.09.005