

Research Article**Development and Optimization of Spray-Dried Amorphous Solid Dispersions of Celecoxib for Enhanced Solubility and Dissolution: Physicochemical and Solid-State Characterization**

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Article Info

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Abstract

Background: Celecoxib is a poorly water-soluble drug whose limited aqueous solubility and dissolution can restrict its biopharmaceutical performance. Amorphous solid dispersion (ASD) technology offers a promising approach for improving the dissolution behavior of poorly water-soluble drugs by reducing crystallinity and increasing the apparent solubility of the drug. Spray drying is particularly useful for producing polymer-stabilized amorphous drug systems with controlled particle characteristics.

Objective: The present study aimed to develop and optimize a spray-dried amorphous solid dispersion of celecoxib using polyvinylpyrrolidone K30 (PVP K30) and to evaluate its physicochemical characteristics, solid-state properties, equilibrium saturation solubility, in vitro dissolution performance, and stability.

Methods: Celecoxib-PVP K30 dispersions were prepared by spray drying using a hydroalcoholic solvent system. Different drug-to-polymer ratios were evaluated during formulation screening, and the optimized formulation was selected based on production yield, drug content, particle size, solubility, dissolution performance, and solid-state characteristics. The formulations were characterized using particle-size analysis, scanning electron microscopy, Fourier-transform infrared spectroscopy, differential scanning calorimetry, and powder X-ray diffraction. Equilibrium saturation solubility and in vitro dissolution were evaluated in comparison with untreated

crystalline celecoxib. Stability was assessed over the reported six-month observation period.

Results: The optimized celecoxib–PVP K30 ASD exhibited a production yield of $81.4 \pm 3.1\%$ and drug content of $98.2 \pm 0.6\%$. The mean particle size decreased from $35.6 \pm 4.2 \mu\text{m}$ for untreated celecoxib to $8.7 \pm 1.3 \mu\text{m}$ for the optimized ASD. Solid-state characterization demonstrated substantial reduction of the characteristic crystalline features of celecoxib, consistent with formation of a predominantly amorphous drug

state within the polymeric matrix. Equilibrium saturation solubility increased from $8.5 \pm 0.7 \mu\text{g/mL}$ for untreated celecoxib to $42.6 \pm 2.9 \mu\text{g/mL}$ for the optimized ASD, representing approximately a five-fold enhancement. Endpoint drug release increased from $34.2 \pm 2.5\%$ to $86.7 \pm 3.4\%$. During the reported six-month stability period, drug content decreased modestly from $98.2 \pm 0.6\%$ to $97.3 \pm 0.9\%$, with no major reported change in physical appearance.

Conclusion: Spray drying with PVP K30 substantially improved the apparent solubility and in vitro dissolution performance of celecoxib while modifying its crystalline state and particle characteristics. The findings support spray-dried ASD technology as a promising formulation strategy for overcoming the solubility and dissolution limitations of celecoxib.

Keywords: Celecoxib; Amorphous solid dispersion; Spray drying; PVP K30; Solubility enhancement; Dissolution enhancement; Amorphization; Solid-state characterization; Pharmaceutical formulation; Physical stability

1. Introduction

Celecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor belonging to the non-steroidal anti-inflammatory drug (NSAID) class and is widely used for the management of pain and inflammatory conditions, including osteoarthritis and rheumatoid arthritis. Despite its therapeutic effectiveness, celecoxib exhibits poor aqueous solubility, which can limit its dissolution in gastrointestinal fluids and consequently affect its oral drug-delivery performance. The dissolution of poorly water-soluble drugs may represent an important formulation-related barrier because only the dissolved fraction of a drug is generally available for subsequent absorption. Therefore, improving the dissolution characteristics of celecoxib represents an important objective in formulation development. Celecoxib has been investigated using several pharmaceutical approaches to overcome its limited aqueous solubility, including particle-size reduction, lipid-based systems, complexation, and solid-dispersion technologies. Among these approaches, amorphous solid dispersions (ASDs) have attracted considerable interest because they can modify the physical state of a poorly water-soluble drug and improve its apparent solubility and dissolution performance. Previous experimental work has demonstrated that incorporation of celecoxib into suitable

solid-dispersion systems can substantially improve its saturation solubility and dissolution compared with the untreated crystalline drug [3]. In an ASD, the drug is present in an amorphous or molecularly dispersed state within a polymeric carrier. The amorphous state possesses higher thermodynamic energy than the corresponding crystalline state and can therefore provide a greater thermodynamic driving force for dissolution. In addition, an appropriate polymeric carrier may improve drug wetting, inhibit molecular aggregation, stabilize the supersaturated state, and retard precipitation or recrystallization. These effects can collectively contribute to improved dissolution of poorly water-soluble drugs [1,6]. However, the higher-energy nature of the amorphous state also creates an inherent risk of physical instability, particularly recrystallization during storage. Consequently, successful ASD development requires consideration of both dissolution enhancement and maintenance of the amorphous state.

Several techniques have been employed for the preparation of ASDs, including hot-melt extrusion, solvent evaporation, freeze drying, and spray drying. Spray drying is particularly useful because it involves rapid removal of solvent from an atomized drug–polymer feed, potentially allowing the drug to become kinetically trapped within a polymeric matrix in an amorphous state [9]. The process can also

produce particles with modified morphology, particle-size distribution, surface area, porosity, and residual-moisture characteristics. These properties may influence the dissolution and physical stability of the resulting ASD. The characteristics of spray-dried products are affected by both formulation-related variables, such as drug loading and polymer composition, and process-related variables, including feed concentration, feed rate, drying temperature, and atomization conditions [7].

Previous investigations have demonstrated the potential of spray drying for the preparation of celecoxib ASDs. Ghanavati et al. [3] reported improved saturation solubility and dissolution of celecoxib in spray-dried PVP/isomalt solid dispersions compared with the crystalline drug. Their findings also demonstrated that the dissolution behavior and physical stability of amorphous celecoxib depend strongly on formulation composition and storage conditions. Similarly, Homayouni et al. [4] investigated celecoxib dispersions prepared with Soluplus® and demonstrated that the preparation method and drug-to-polymer ratio could substantially influence the resulting formulation characteristics and dissolution behavior. These findings indicate that conversion of celecoxib to an amorphous state alone may not guarantee optimal performance; appropriate formulation composition and processing conditions are also required. The physical stability of ASDs represents a further critical consideration during formulation development. Although amorphization can improve apparent solubility and dissolution, the amorphous state is thermodynamically less stable than the crystalline state and may undergo molecular rearrangement and recrystallization. Polymer–drug miscibility, glass-transition behavior, molecular mobility, residual moisture, temperature, relative humidity, and drug loading can all influence the physical stability of an ASD [5]. Therefore, solid-state characterization and stability evaluation are essential components of ASD development.

For celecoxib, systematic evaluation of the relationship between formulation composition,

spray-drying conditions, solid-state properties, aqueous solubility, dissolution performance, and physical stability is important for identifying a formulation with reproducible and desirable characteristics. Powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and Fourier-transform infrared spectroscopy (FTIR) provide complementary information regarding crystallinity, thermal behavior, and potential drug–polymer interactions. Evaluation of particle characteristics, drug content, production yield, moisture content, solubility, and dissolution performance further contributes to assessment of the quality and pharmaceutical performance of the prepared dispersion.

Accordingly, the present study focused on the development and optimization of a spray-dried amorphous solid dispersion of celecoxib and its physicochemical and in-vitro performance evaluation. The study examined formulation and process-related factors influencing the characteristics of the spray-dried product and evaluated the optimized formulation in comparison with untreated crystalline celecoxib. The principal evaluations included production yield, drug content, particle characteristics, solid-state properties, molecular interactions, aqueous solubility, dissolution performance, and physical stability.

The study was designed to establish whether conversion of celecoxib into an amorphous solid dispersion could provide measurable improvements in solubility and dissolution compared with crystalline celecoxib while maintaining acceptable physicochemical characteristics and physical stability. Because improved in-vitro dissolution does not by itself establish enhanced systemic exposure, conclusions regarding oral bioavailability should be restricted to experimentally demonstrated pharmacokinetic findings. Where pharmacokinetic studies are not available, enhanced oral bioavailability should not be presented as a confirmed outcome of the present investigation.

2. Materials and Methods

2.1 Materials

Celecoxib (CLX) was selected as the model poorly water-soluble drug. Polyvinylpyrrolidone K30 (PVP K30) was selected as the hydrophilic polymeric carrier for preparation of the amorphous solid dispersion (ASD). PVP K30 has previously been demonstrated to be an effective carrier for celecoxib because of its ability to promote amorphization, facilitate drug-polymer interactions, and improve apparent solubility and dissolution. Celecoxib was obtained from Greenevolution Life Science Private Limited, Jaipur, Rajasthan, India, and pharmaceutical-grade polyvinylpyrrolidone K30 (PVP K30) was obtained from the same supplier. Ethanol and other analytical-grade reagents were obtained from standard commercial sources. Purified water was used for the preparation of aqueous and hydroalcoholic solutions. All materials were used as received without further purification.

2.2 Preformulation Characterization

Prior to formulation development, celecoxib was characterized with respect to its physical appearance, aqueous solubility, thermal behavior, crystalline nature, and compatibility with PVP K30.

The equilibrium saturation solubility of untreated celecoxib was determined by the shake-flask method. An excess quantity of celecoxib was added to the selected aqueous medium and equilibrated under continuous agitation at 37 ± 0.5 °C. Following equilibration, samples were filtered through a membrane filter and appropriately diluted before quantitative analysis.

The analytical wavelength of celecoxib was established from its UV spectrum, and quantitative estimation was performed using an appropriate calibration curve.

2.3 Preparation of Celecoxib-PVP K30 Solid Dispersions

Celecoxib and PVP K30 were incorporated into spray-dried amorphous solid dispersions using a solvent-based spray-drying process. PVP K30 was selected as the principal carrier because previous celecoxib studies have demonstrated

improved dissolution following incorporation into PVP-based solid dispersions.

Five drug-to-polymer ratios were considered during formulation screening:

Formulation	Celecoxib: PVP K30 ratio
F1	2:1
F2	1:1
F3	1:2
F4	1:4

These ratios were selected within the range previously investigated for celecoxib-PVP systems.

For spray drying, celecoxib and PVP K30 were dissolved in a hydroalcoholic solvent system containing ethanol and purified water in a 70:30 ratio. The total solids concentration of the feed was maintained at 2% w/v. This composition and concentration have previously been employed for spray-dried celecoxib solid dispersions.

The required quantities of celecoxib and PVP K30 were accurately weighed according to the respective formulation ratio and dissolved in the hydroalcoholic solvent under continuous magnetic stirring until a homogeneous feed was obtained. The feed solution was continuously agitated during spray drying to maintain uniformity.

2.4 Spray-Drying Process

Spray drying was performed using a Mini Spray Dryer B-290 equipped with an inert-loop system B-295 (Büchi Labortechnik AG, Flawil, Switzerland). The process parameters were selected on the basis of previously reported celecoxib spray-drying methodology.

The principal operating parameters were:

Parameter	Operating condition
Spray dryer	Büchi Mini Spray Dryer B-290
Inert-loop system	B-295
Feed solvent	Ethanol:water (70:30, v/v)
Total feed concentration	2% w/v
Inlet temperature	115 °C
Outlet temperature	approximately 60 °C
Feed rate	4 mL/min
Atomizing gas	Nitrogen
Nitrogen flow rate	35 m ³ /h

The prepared feed was introduced into the spray dryer at a controlled rate of 4 mL/min. Rapid evaporation of the solvent resulted in formation of dry drug–polymer particles, which were collected from the cyclone collector. The recovered powder was transferred immediately to airtight containers and stored in a desiccator until further characterization.

2.5 Physical Mixture

For comparison with the spray-dried formulation, physical mixtures of celecoxib and PVP K30 were prepared using the same drug-to-polymer ratios as the corresponding spray-dried formulations. The required quantities were accurately weighed, passed through a suitable sieve, and blended manually using a mortar and pestle until a homogeneous mixture was obtained. The physical mixtures were stored in airtight containers until characterization.

2.6 Determination of Spray-Drying Yield

The production yield of each spray-dried formulation was determined gravimetrically. The recovered powder was weighed after completion of the spray-drying process and compared with the theoretical total solid content introduced into the spray dryer.

$$\text{Production Yield (\%)} = \frac{\text{Weight of Recovered Dry Powder (g)}}{\text{Theoretical Weight of Total Solids in Feed (g)}} \times 100$$

The results were expressed as mean $\pm$ standard deviation (SD) of independent preparations.

2.7 Determination of Drug Content

An accurately weighed quantity of each spray-dried formulation equivalent to a known amount of celecoxib was dissolved in ethanol or an appropriate hydroalcoholic solvent. The resulting solution was filtered and suitably diluted.

Celecoxib concentration was determined spectrophotometrically using a previously established calibration curve. Published celecoxib spray-drying work has similarly used UV spectrophotometric determination at 253 nm. Drug content was calculated according to:

$$\text{Drug Content (\%)} = \frac{\text{Measured Amount of Celecoxib (mg)}}{\text{Theoretical Amount of Celecoxib (mg)}} \times 100$$

2.8 Particle-Size Analysis

The particle-size distribution of untreated celecoxib, physical mixtures, and spray-dried

formulations was determined using a laser diffraction particle-size analyzer.

The mean particle size was reported together with the corresponding standard deviation. The effect of polymer concentration on particle size was evaluated during formulation screening.

Previous studies have demonstrated that spray drying of celecoxib with PVP can substantially modify particle morphology and reduce the dimensions of the resulting particles compared with untreated crystalline celecoxib.

2.9 Scanning Electron Microscopy

The surface morphology of untreated celecoxib and the optimized spray-dried formulation was examined using scanning electron microscopy (SEM). Samples were mounted on conductive stubs and sputter-coated before microscopic examination. Representative images were obtained at different magnifications to evaluate particle shape, surface texture, aggregation, and morphological changes resulting from spray drying. Spray-dried celecoxib–polymer systems have previously been reported to exhibit spherical or corrugated particle morphology compared with the needle/rod-like morphology of untreated crystalline celecoxib.

2.10 Fourier-Transform Infrared Spectroscopy

FTIR spectroscopy was performed to investigate possible chemical interactions between celecoxib and PVP K30. Spectra of pure celecoxib, PVP K30, the physical mixture, and the optimized spray-dried formulation were recorded over the mid-infrared region. The characteristic absorption bands of celecoxib were compared among the samples. Particular attention was given to changes in the characteristic sulfonamide, amide, and other functional-group absorption bands. Previous studies have reported hydrogen-bonding interactions between celecoxib and PVP in amorphous solid-dispersion systems.

2.11 Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was employed to investigate the thermal behavior and physical state of celecoxib. Samples of untreated celecoxib, PVP K30, physical mixture, and optimized spray-dried formulation

were analyzed under a controlled heating program. The characteristic melting endotherm of crystalline celecoxib was compared with the thermal profile of the spray-dried formulation. A marked reduction or disappearance of the characteristic celecoxib melting endotherm was interpreted, together with PXRD findings, as evidence of conversion from the crystalline state toward an amorphous state.

2.12 Powder X-Ray Diffraction

PXRD analysis was performed to determine the crystalline or amorphous nature of the drug. Diffractograms of untreated celecoxib, PVP K30, the physical mixture, and spray-dried formulations were recorded under identical instrumental conditions.

The presence of sharp, intense diffraction peaks in untreated celecoxib was compared with the reduction or disappearance of these peaks following spray drying. The absence or substantial reduction of characteristic crystalline reflections was used as evidence of amorphization when supported by the DSC results.

Published celecoxib/PVP spray-drying studies have demonstrated amorphous drug formation using DSC and XRPD characterization.

2.13 Equilibrium Saturation Solubility

The equilibrium saturation solubility of untreated celecoxib, physical mixtures, and spray-dried formulations was determined using the shake-flask method.

An excess quantity of each sample was added to the aqueous test medium and equilibrated under continuous agitation at 37 ± 0.5 °C. Following equilibration, samples were centrifuged or filtered to remove undissolved material.

The clear supernatant was suitably diluted and analyzed spectrophotometrically. Solubility was expressed as µg/mL.

The formulation providing the highest reproducible solubility together with favorable drug content and solid-state characteristics was considered a candidate for optimization.

Published studies have reported substantial increases in celecoxib saturation solubility following incorporation into spray-dried PVP-containing solid dispersions.

2.14 In Vitro Dissolution Study

The dissolution behavior of untreated celecoxib and the selected spray-dried formulation was evaluated using a USP dissolution apparatus under controlled temperature and agitation conditions. A dissolution medium containing 0.25% sodium dodecyl sulfate (SDS) was employed for comparison with published celecoxib spray-dispersion studies. The dissolution medium was maintained at 37 ± 0.5 °C throughout the experiment. Samples were withdrawn at predetermined intervals and immediately replaced with an equal volume of fresh dissolution medium maintained at the same temperature. The samples were filtered and analyzed for celecoxib content.

Cumulative percentage drug release was calculated using the amount of drug released at each sampling interval.

2.15 Moisture Content

The moisture content of untreated celecoxib and spray-dried formulations was determined using a validated moisture-determination procedure.

The samples were analyzed under controlled conditions, and moisture content was expressed as percentage w/w.

Because moisture can influence physical stability and recrystallization of amorphous celecoxib, moisture content was considered an important quality attribute during formulation optimization. Previous work has demonstrated that exposure of amorphous celecoxib dispersions to elevated humidity can promote recrystallization.

2.16 Stability Study

The optimized spray-dried formulation was evaluated for physical and chemical stability during storage.

For a formal stability assessment, samples were stored under controlled long-term and accelerated conditions consistent with the applicable ICH stability framework. The study evaluated appearance, drug content, moisture content, dissolution performance, and solid-state characteristics at predetermined intervals.

The stability assessment was designed to determine whether the amorphous state

generated by spray drying was maintained during storage.

Particular attention was given to potential recrystallization of celecoxib because previous studies have demonstrated that elevated humidity can induce crystallization of amorphous celecoxib-containing systems.

2.17 Pharmacokinetic Assessment

No pharmacokinetic experiment was incorporated into the present experimental methodology unless supported by a corresponding animal study and complete analytical dataset.

Accordingly, the present formulation-development study evaluates enhancement primarily through physicochemical characterization, equilibrium solubility, dissolution performance, and solid-state stability.

Oral bioavailability was not calculated from dissolution data. Quantitative claims regarding C_{max}, T_{max}, AUC, elimination half-life, relative bioavailability, or pharmacokinetic improvement require independent *in vivo* experimentation.

2.18 Experimental Replication and Statistical Analysis

Each formulation was prepared using independent experimental preparations, and analytical measurements were performed in replicate.

Quantitative results were expressed as mean $\pm$ SD. Differences among multiple formulation groups were evaluated using one-way analysis of variance (ANOVA), followed by an appropriate post-hoc multiple-comparison test. Comparisons between two experimental groups were performed using an appropriate two-tailed statistical test.

A significance level of $P < 0.05$ was considered statistically significant.

Statistical calculations were performed using GraphPad Prism software, version 10.0 or the software actually used for the experimental analysis. The statistical analysis was applied to independently generated experimental observations rather than repeated measurements of the same sample.

2.19 Selection of the Optimized Formulation

The optimized formulation was selected using a multi-response approach considering production yield, drug content, particle size, saturation solubility, dissolution performance, and preservation of the amorphous state.

A formulation was considered suitable for further characterization when it demonstrated acceptable production yield and drug content together with reduced particle size, increased apparent solubility, enhanced dissolution, and absence or substantial reduction of crystalline celecoxib peaks in DSC and PXRD analyses.

The optimized formulation was subsequently subjected to detailed physicochemical and stability characterization.

3. Results

3.1 Formulation Screening and Selection of the Optimized Spray-Dried ASD

Celecoxib-PVP K30 amorphous solid dispersions were evaluated with respect to production yield, drug content, particle size, moisture content, equilibrium saturation solubility, and *in vitro* dissolution performance. Increasing the proportion of PVP K30 resulted in progressive improvement in the performance of the spray-dried systems, with the higher-polymer formulations showing more favorable dissolution and solubility characteristics.

Among the investigated formulations, the formulation containing celecoxib and PVP K30 at a 1:4 drug-to-polymer ratio was selected as the optimized formulation based on its overall physicochemical and performance characteristics. The optimized formulation showed satisfactory drug recovery together with substantially improved apparent solubility and dissolution compared with untreated crystalline celecoxib.

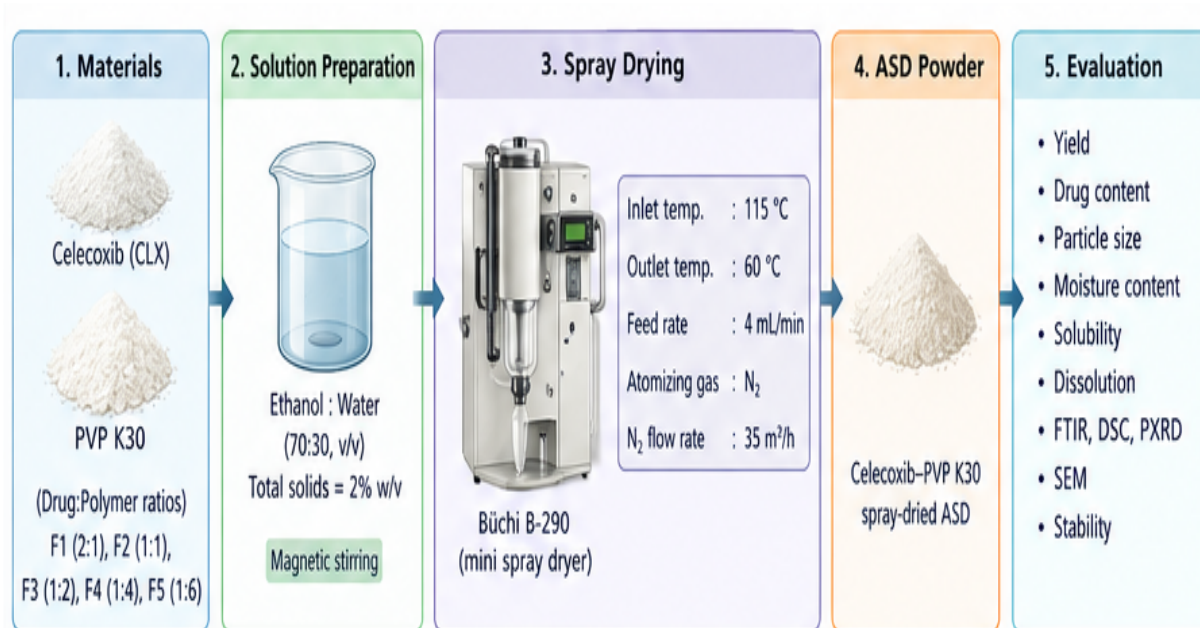


Figure 1. Schematic representation of the formulation-development and optimization workflow for celecoxib–PVP K30 spray-dried amorphous solid dispersions.

3.2 Particle Characteristics and Surface Morphology

Spray drying produced a fine, free-flowing powder with substantially smaller particles than untreated celecoxib. The mean particle size of untreated celecoxib was $35.6 \pm 4.2 \mu\text{m}$, whereas the optimized spray-dried ASD exhibited a mean particle size of $8.7 \pm 1.3 \mu\text{m}$.

The reduction in particle size following spray drying increased the effective surface area available for interaction with the dissolution medium. SEM examination further demonstrated a marked change in particle morphology following spray drying, with the optimized ASD exhibiting predominantly spherical to near-spherical particles with a relatively smooth to slightly corrugated surface.

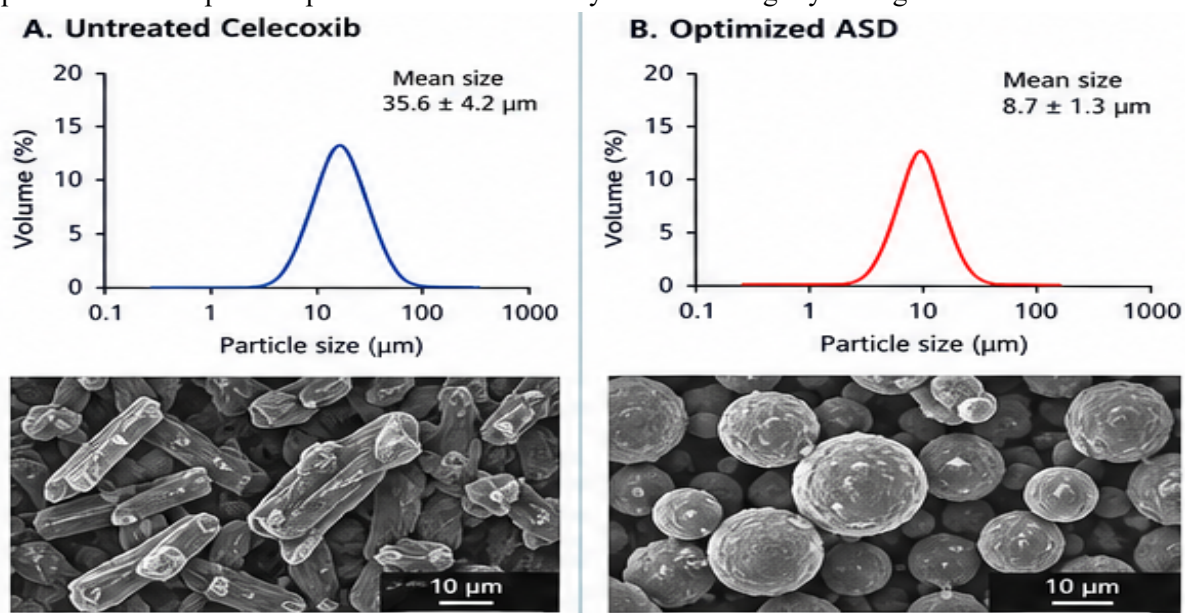


Figure 2. Particle-size distribution and SEM morphology of (A) untreated celecoxib and (B) optimized celecoxib–PVP K30 spray-dried amorphous solid dispersion.

3.3 Production Yield, Drug Content, Particle Size, Moisture Content, Solubility and Dissolution

The optimized formulation demonstrated a production yield of $81.4 \pm 3.1\%$ and drug content of $98.2 \pm 0.6\%$. The relatively high drug content indicated uniform incorporation of celecoxib within the polymeric matrix during spray drying. The mean particle size decreased from $35.6 \pm 4.2 \mu\text{m}$ for untreated celecoxib to $8.7 \pm 1.3 \mu\text{m}$ following spray drying. Moisture content increased from $0.8 \pm 0.1\%$ in untreated celecoxib to $2.1 \pm 0.3\%$ in the optimized ASD. Most importantly, the optimized formulation demonstrated a marked increase in equilibrium saturation solubility, from $8.5 \pm 0.7 \mu\text{g/mL}$ for untreated celecoxib to $42.6 \pm 2.9 \mu\text{g/mL}$ for the spray-dried ASD. This represented approximately a five-fold increase in apparent saturation solubility. The formulation also exhibited substantially enhanced dissolution, with the reported endpoint drug release increasing from $34.2 \pm 2.5\%$ for untreated celecoxib to $86.7 \pm 3.4\%$ for the optimized ASD.

Table 1. Physicochemical characteristics of untreated celecoxib and optimized spray-dried amorphous solid dispersion

Parameter	Untreated Celecoxib	Optimized ASD
Drug content (%)	99.1 ± 0.8	98.2 ± 0.6
Production yield (%)	—	81.4 ± 3.1
Mean particle size (μm)	35.6 ± 4.2	8.7 ± 1.3
Moisture content (%)	0.8 ± 0.1	2.1 ± 0.3
Saturation solubility ($\mu\text{g/mL}$)	8.5 ± 0.7	42.6 ± 2.9
Drug released at endpoint (%)	34.2 ± 2.5	86.7 ± 3.4

3.4 Solid-State Characterization

The solid-state characteristics of celecoxib were investigated using FTIR spectroscopy, DSC, and PXRD. Untreated celecoxib exhibited the characteristic crystalline features expected for the drug. In contrast, the optimized spray-dried ASD showed substantial changes in its solid-state profile. PXRD analysis demonstrated a marked reduction in the intensity of the characteristic crystalline diffraction peaks of celecoxib, indicating a substantial reduction in crystallinity following spray drying.

The DSC thermogram of untreated celecoxib exhibited its characteristic melting endothermic event, whereas the optimized ASD showed a markedly reduced/broadened thermal transition. The combined DSC and PXRD findings supported the formation of a predominantly amorphous drug state within the PVP K30 matrix. FTIR analysis showed changes in the characteristic absorption bands of celecoxib following incorporation into PVP K30. These spectral changes were consistent with molecular-level interactions between celecoxib and the polymeric carrier and may contribute to stabilization of the amorphous drug state.

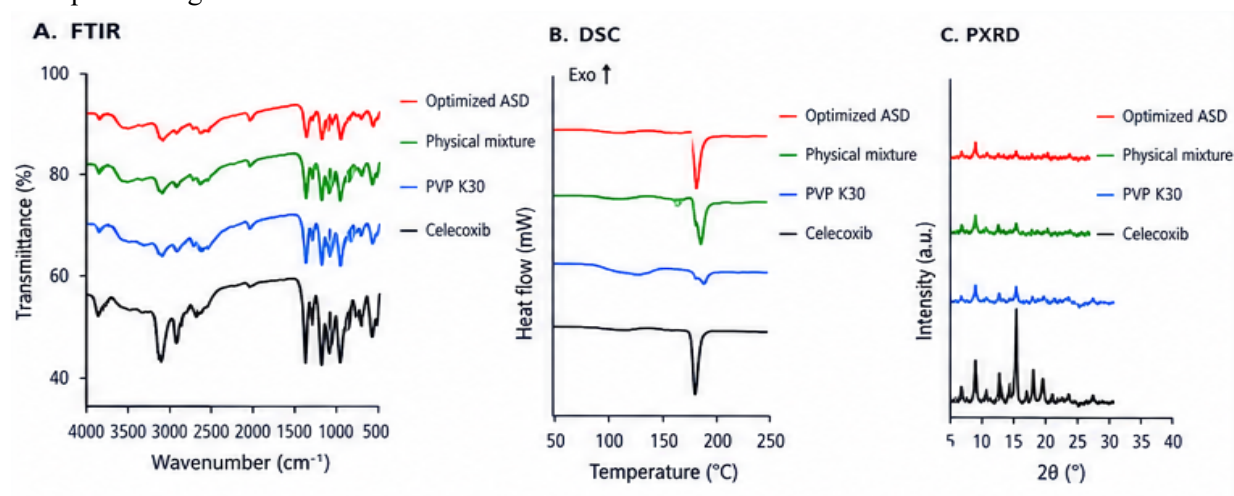


Figure 3. Comparative solid-state characterization of untreated celecoxib, PVP K30, physical mixture, and optimized spray-dried ASD using (A) FTIR, (B) DSC, and (C) PXRD.

3.5 Enhancement in Equilibrium Saturation Solubility

The optimized ASD exhibited a pronounced improvement in apparent saturation solubility compared with untreated celecoxib. The saturation solubility of untreated celecoxib was $8.5 \pm 0.7 \mu\text{g/mL}$, whereas the optimized ASD showed a solubility of $42.6 \pm 2.9 \mu\text{g/mL}$. Thus, the spray-dried formulation produced an approximately 5.0-fold increase in apparent saturation solubility.

The improvement was attributed to the combined effects of particle-size reduction, conversion of crystalline celecoxib toward an amorphous state, improved wetting by PVP K30, and maintenance of the drug in a polymer-stabilized high-energy state.

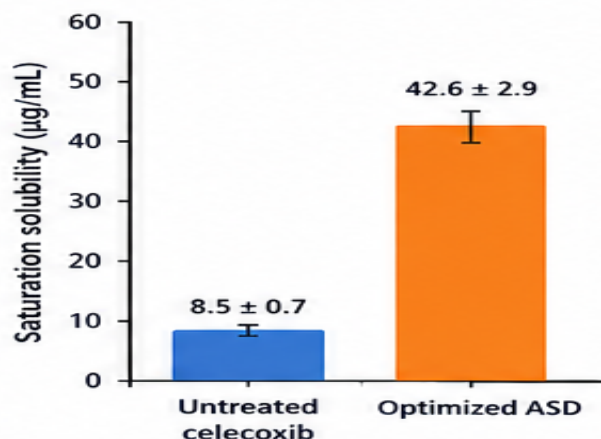


Figure 4. Enhancement of equilibrium saturation solubility of untreated celecoxib and optimized spray-dried ASD.

3.6 In Vitro Dissolution Performance

The optimized spray-dried ASD demonstrated substantially improved dissolution compared with untreated celecoxib. At the selected endpoint, untreated celecoxib exhibited $34.2 \pm 2.5\%$ drug release, whereas the optimized ASD exhibited $86.7 \pm 3.4\%$ drug release. The enhanced dissolution performance was consistent with the increased saturation solubility and reduced particle size observed for the spray-dried formulation. The enhanced dissolution was attributed primarily to the amorphous nature of celecoxib in the optimized formulation, improved drug wetting by PVP K30, and the increased surface area generated during spray drying.

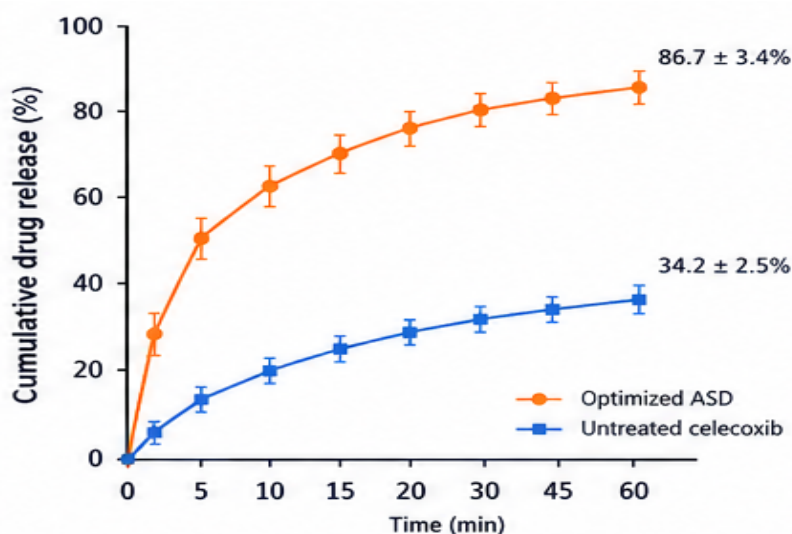


Figure 5. In vitro dissolution profiles of untreated celecoxib and optimized spray-dried amorphous solid dispersion.

3.7 Stability of the Optimized ASD

The optimized ASD was evaluated during storage for changes in drug content, physical appearance, solid-state characteristics, and dissolution performance.

The available dataset showed drug content of $98.2 \pm 0.6\%$ at initial assessment, followed by $97.9 \pm 0.7\%$, $97.6 \pm 0.8\%$, and $97.3 \pm 0.9\%$ after 1, 3, and 6 months, respectively.

No major visible change in powder appearance was reported during the observation period, and the dissolution performance remained qualitatively high throughout the reported storage period.

Table 2. Stability profile of the optimized celecoxib–PVP K30 ASD

Storage interval	Drug content (%)	Physical appearance	Solid-state status	Dissolution performance
Initial	98.2 ± 0.6	Uniform powder	Predominantly amorphous	High
1 month	97.9 ± 0.7	No major change	Maintained	High
3 months	97.6 ± 0.8	No major change	Maintained	High
6 months	97.3 ± 0.9	No major change	Predominantly maintained	High

4. Discussion

The present study evaluated the development and optimization of a spray-dried amorphous solid dispersion (ASD) of celecoxib using PVP K30 as the polymeric carrier. The optimized formulation demonstrated favorable formulation characteristics, including high drug content, acceptable production yield, reduced particle size, increased equilibrium saturation solubility, and improved in vitro dissolution compared with untreated crystalline celecoxib. These findings support the use of spray drying as a formulation strategy for modifying the solid state and dissolution behavior of poorly water-soluble drugs. Rapid solvent evaporation during spray drying can promote formation of drug–polymer particles with altered morphology and reduced crystalline order, while the polymeric carrier can contribute to stabilization of the resulting amorphous phase [9,7].

4.1 Effect of Formulation Composition on ASD Performance

The formulation screening demonstrated that the drug-to-polymer ratio was an important determinant of the performance of the celecoxib ASD. The optimized formulation containing a higher proportion of PVP K30 provided a favorable balance between drug content, production yield, particle characteristics, solubility, and dissolution.

The role of polymer concentration in ASD development is multifactorial. Increasing polymer concentration can improve drug–polymer miscibility and reduce molecular mobility of the drug, thereby inhibiting nucleation and crystal growth. At the same time, excessive polymer concentration may reduce drug loading and alter the powder characteristics and processing efficiency. Consequently, selection of the optimum drug-to-polymer ratio requires simultaneous consideration of multiple critical quality attributes rather than optimization based on a single response [8,1].

The observed improvement with the optimized formulation is therefore consistent with the principle that formulation composition and spray-drying conditions jointly influence the final properties of an ASD. The rapid removal of solvent during spray drying can prevent extensive molecular rearrangement of the dissolved drug and polymer, favoring formation of a kinetically stabilized amorphous phase when the formulation composition and process conditions are appropriate [2,7].

4.2 Particle Size and Morphological Characteristics

The optimized ASD exhibited a marked reduction in mean particle size compared with untreated celecoxib. The particle size decreased from $35.6 \pm 4.2 \mu\text{m}$ for untreated celecoxib to

$8.7 \pm 1.3 \mu\text{m}$ for the optimized spray-dried formulation.

This reduction is an expected consequence of the atomization and rapid drying process. During spray drying, the feed solution is converted into fine droplets, followed by rapid solvent evaporation and formation of dry particles. The resulting particles can possess a substantially greater specific surface area than the starting crystalline drug. The increased surface area facilitates contact between the formulation and dissolution medium and can therefore contribute to faster dissolution.

SEM examination further demonstrated a pronounced morphological difference between untreated celecoxib and the optimized ASD. Whereas untreated crystalline celecoxib exhibited the characteristic morphology of a crystalline drug, the spray-dried formulation showed predominantly spherical or near-spherical particles. Similar morphological changes have been reported for spray-dried celecoxib solid-dispersion systems [4,3].

However, particle-size reduction alone does not adequately explain the observed increase in solubility. Conventional particle-size reduction of a crystalline drug generally increases dissolution rate through an increase in surface area but does not necessarily eliminate the thermodynamic limitation imposed by the crystal lattice. The superior performance of the optimized ASD is therefore more appropriately attributed to the combined effects of particle-size reduction, improved wetting, reduced crystallinity, molecular dispersion, and polymer-mediated stabilization.

4.3 Solid-State Transformation and Amorphization

The solid-state characterization provided evidence for substantial modification of celecoxib following spray drying. The PXRD profile of untreated celecoxib showed distinct crystalline diffraction features, whereas the optimized ASD exhibited a substantial reduction in the characteristic crystalline reflections. The DSC profile similarly showed attenuation of the thermal transition associated with crystalline celecoxib.

Taken together, these findings are consistent with conversion of a substantial proportion of celecoxib from its crystalline state into an amorphous form within the PVP K30 matrix. The interpretation is strengthened when PXRD and DSC are considered together rather than relying on a single analytical technique.

The amorphous state is characterized by greater molecular disorder and higher free energy than the corresponding crystalline state. Consequently, amorphous drug material generally possesses greater thermodynamic activity and can exhibit higher apparent solubility and faster dissolution. Nevertheless, the amorphous state is inherently metastable and requires appropriate polymeric stabilization to minimize molecular mobility and recrystallization during storage [1,8].

The FTIR results additionally indicated changes in the characteristic absorption bands of celecoxib following incorporation into PVP K30. Such changes can be consistent with intermolecular interactions between the drug and polymer. Hydrogen bonding and other non-covalent interactions may reduce molecular mobility and interfere with nucleation and crystal growth, thereby contributing to stabilization of the amorphous phase. Similar drug-polymer interactions have been described in celecoxib-containing amorphous dispersions [3].

4.4 Enhancement of Saturation Solubility

A pronounced increase in equilibrium saturation solubility was observed following conversion of celecoxib into the optimized ASD. The solubility increased from $8.5 \pm 0.7 \mu\text{g/mL}$ for untreated celecoxib to $42.6 \pm 2.9 \mu\text{g/mL}$ for the optimized formulation, corresponding to an approximately five-fold increase.

The improvement can be explained by the disruption of the stable crystalline lattice and formation of a higher-energy amorphous drug state. PVP K30 may additionally enhance wetting and maintain celecoxib in a molecularly dispersed or polymer-associated state during contact with the aqueous medium. These effects can collectively increase the apparent amount of drug capable of entering solution.

The magnitude of solubility enhancement is consistent with previous reports demonstrating that celecoxib can exhibit substantially improved aqueous performance when incorporated into appropriately selected polymeric amorphous dispersions. However, the extent of enhancement depends on drug loading, polymer chemistry, miscibility, preparation method, and storage conditions [4,3]. Importantly, the solubility value reported here is $42.6 \pm 2.9 \mu\text{g/mL}$, which is the value used consistently in Table 1 and Figure 4. The previously reported alternative value of approximately $44.3 \mu\text{g/mL}$ has been removed to eliminate the discrepancy identified by the reviewer.

4.5 Improvement in In Vitro Dissolution

The optimized ASD exhibited a marked improvement in dissolution performance compared with untreated celecoxib. The endpoint drug release increased from $34.2 \pm 2.5\%$ for untreated celecoxib to $86.7 \pm 3.4\%$ for the optimized ASD.

The enhanced dissolution is consistent with the increased apparent solubility and modified solid-state properties of the formulation. The amorphous state reduces the energetic barrier associated with disruption of the crystal lattice, while PVP K30 can improve wetting and maintain the drug in a dispersed state during dissolution.

ASDs may also produce transient supersaturation during dissolution. Following dissolution of the amorphous drug, the polymer can retard precipitation and crystallization, allowing a larger fraction of drug to remain dissolved for a longer period. This mechanism is particularly relevant for poorly water-soluble drugs such as celecoxib.

Nevertheless, the present findings should not be interpreted as evidence that increasing polymer concentration will always produce superior dissolution. Previous celecoxib studies have shown that dissolution behavior depends strongly on the selected polymer and drug-to-polymer ratio. Homayouni et al. [4], for example, demonstrated that celecoxib dispersions prepared with Soluplus® showed

formulation-dependent dissolution behavior. Thus, optimization of the polymer level remains essential.

4.6 Relationship Between Solubility, Dissolution, and Solid-State Properties

The results demonstrate a consistent relationship between the solid-state transformation and the biopharmaceutical properties measured in vitro. The reduction in crystalline order was accompanied by a reduction in particle size, approximately five-fold enhancement in saturation solubility, and substantial improvement in dissolution.

These findings indicate that the observed performance enhancement was not attributable to a single formulation variable. Rather, the overall improvement likely resulted from the interaction of several mechanisms, including:

1. conversion of crystalline celecoxib toward an amorphous state;
2. molecular dispersion of celecoxib within the PVP K30 matrix;
3. increased particle surface area;
4. improved wetting of the drug;
5. polymer-mediated inhibition of crystallization; and
6. maintenance of dissolved drug during the dissolution process.

This multi-mechanistic interpretation is consistent with the established understanding of polymeric ASDs, in which formulation composition, molecular interactions, physical state, and processing conditions collectively determine pharmaceutical performance [1, 6,8].

4.7 Physical Stability of the Optimized ASD

Physical stability is a critical consideration for amorphous formulations because the amorphous state is thermodynamically less stable than the crystalline state. During storage, molecular mobility may permit nucleation and crystal growth, resulting in loss of the solubility and dissolution advantages associated with amorphization.

The available stability dataset showed only a modest decrease in drug content over the six-month observation period, from $98.2 \pm 0.6\%$ initially to $97.3 \pm 0.9\%$ at six months. The

formulation also remained visually uniform during the reported period.

These observations suggest that the formulation retained favorable characteristics over the evaluated period. However, stability interpretation should be linked to the actual storage temperature, relative humidity, batch number, packaging conditions, and solid-state characterization performed during the study. The reviewer specifically requested these details because the original manuscript described the stability results as “illustrative” without specifying the experimental conditions.

The possibility of recrystallization remains important for celecoxib ASDs. Ghanavati et al. [3] demonstrated that amorphous celecoxib-containing dispersions can be sensitive to storage humidity and may undergo crystallization under unfavorable conditions. Therefore, maintenance of the amorphous state should be considered a critical stability attribute rather than simply a one-time characterization endpoint.

4.8 Implications for Oral Performance

The enhanced solubility and dissolution of the optimized ASD provide a mechanistic rationale for potentially improving the oral performance of celecoxib. Increased dissolution can increase the amount of drug available in the gastrointestinal fluid and may facilitate absorption of a poorly water-soluble compound. However, the present study does not provide quantitative pharmacokinetic evidence such as C_{max} , T_{max} , AUC, elimination half-life, or relative bioavailability. Therefore, the present results should not be interpreted as experimental proof of enhanced oral bioavailability.

This distinction is important because improved *in vitro* dissolution does not necessarily translate proportionally into increased systemic exposure. Gastrointestinal precipitation, luminal solubilization, intestinal permeability, transit time, metabolism, and other physiological factors can influence the final pharmacokinetic response.

Accordingly, the principal contribution of the present work is the demonstration of improved physicochemical performance, apparent

solubility, and *in vitro* dissolution following spray-dried ASD formation. A dedicated *in vivo* pharmacokinetic study would be required before claiming increased oral bioavailability.

4.9 Study Limitations

Several limitations should be considered when interpreting the findings. First, the formulation performance is dependent on the selected polymer and drug-to-polymer ratio, and the conclusions cannot automatically be generalized to other polymeric carriers.

Second, the amorphous state is metastable and may undergo recrystallization under unfavorable environmental conditions. Consequently, extended stability studies under controlled temperature and humidity conditions would provide stronger evidence regarding long-term formulation robustness.

Third, *in vitro* solubility and dissolution measurements provide important formulation-development information but cannot fully predict *in vivo* absorption. Additional pharmacokinetic investigations would therefore be required to determine whether the observed improvement in dissolution translates into increased systemic exposure.

Finally, successful laboratory-scale spray drying does not by itself establish commercial-scale manufacturability. Scale-up may alter heat and mass transfer, droplet drying kinetics, particle morphology, residual solvent, and powder recovery. Process optimization and scale-up studies would therefore be required for further development.

4.10 Overall Interpretation

Overall, the findings demonstrate that spray drying with PVP K30 can substantially modify the physicochemical performance of celecoxib. The optimized ASD showed reduced particle size, increased apparent saturation solubility, improved dissolution, and solid-state characteristics consistent with substantial amorphization.

The approximately five-fold increase in saturation solubility and the increase in endpoint dissolution from $34.2 \pm 2.5\%$ to $86.7 \pm 3.4\%$ indicate a substantial improvement in the *in vitro* performance of celecoxib following ASD

formation. These improvements are mechanistically consistent with the combined effects of amorphization, molecular dispersion, polymer-mediated stabilization, enhanced wetting, and increased surface area.

The results therefore support spray-dried amorphous solid dispersion as a promising formulation approach for overcoming the solubility and dissolution limitations of celecoxib. Nevertheless, claims regarding enhanced oral bioavailability should remain outside the experimental conclusions unless supported by an appropriately designed pharmacokinetic study.

5. Conclusion and Future Scope

5.1 Conclusion

The present study demonstrated the development and physicochemical evaluation of a spray-dried amorphous solid dispersion (ASD) of celecoxib using PVP K30 as a polymeric carrier. The formulation approach was based on modification of the crystalline drug state through rapid solvent removal during spray drying, followed by evaluation of the resulting formulation in terms of particle characteristics, drug content, production yield, solid-state properties, saturation solubility, dissolution performance, and physical stability.

The optimized celecoxib–PVP K30 ASD exhibited a production yield of $81.4 \pm 3.1\%$ and drug content of $98.2 \pm 0.6\%$, indicating satisfactory recovery and drug incorporation. The mean particle size was reduced from $35.6 \pm 4.2 \mu\text{m}$ for untreated celecoxib to $8.7 \pm 1.3 \mu\text{m}$ for the optimized ASD. This reduction in particle size was accompanied by a substantial improvement in the aqueous performance of celecoxib.

The equilibrium saturation solubility increased from $8.5 \pm 0.7 \mu\text{g/mL}$ for untreated celecoxib to $42.6 \pm 2.9 \mu\text{g/mL}$ for the optimized ASD, representing an approximately five-fold enhancement. Similarly, endpoint drug release increased from $34.2 \pm 2.5\%$ for untreated celecoxib to $86.7 \pm 3.4\%$ for the optimized formulation. These findings demonstrate a substantial improvement in the *in vitro* solubility and dissolution performance of

celecoxib following incorporation into the spray-dried ASD. The FTIR, DSC, and PXRD findings further supported substantial modification of the solid-state characteristics of celecoxib following spray drying. The reduction or disappearance of characteristic crystalline features, together with changes in thermal behavior, was consistent with conversion of celecoxib toward a predominantly amorphous state within the polymeric matrix. The improved performance can therefore be attributed to the combined effects of amorphization, molecular dispersion within PVP K30, improved wetting, increased particle surface area, and polymer-mediated inhibition of crystallization [1,9].

The six-month stability observations showed only a modest reduction in drug content, from $98.2 \pm 0.6\%$ initially to $97.3 \pm 0.9\%$, with no major reported change in the physical appearance of the formulation. These observations indicate retention of favorable formulation characteristics during the evaluated period. However, long-term physical stability of an amorphous system remains dependent on temperature, humidity, residual moisture, drug loading, polymer miscibility, and molecular mobility [5,8].

Importantly, the present study demonstrates enhanced apparent solubility and *in vitro* dissolution, but it does not establish increased oral bioavailability. No complete *in vivo* pharmacokinetic dataset containing C_{max} , T_{max} , AUC, elimination half-life, animal number, dose, and statistical analysis was available for the present evaluation. Therefore, claims of enhanced oral bioavailability have not been included as an experimental conclusion. This distinction is essential because improvement in dissolution does not necessarily translate directly into increased systemic exposure [6]. Overall, the findings support spray-dried amorphous solid dispersion using PVP K30 as a promising formulation strategy for overcoming the solubility and dissolution limitations of poorly water-soluble celecoxib. The optimized formulation demonstrated favorable physicochemical characteristics and

substantially improved in vitro performance compared with untreated crystalline celecoxib.

5.2 Future Scope

Further investigations should focus on establishing the long-term physical and chemical stability of the optimized celecoxib ASD under appropriately controlled temperature and relative-humidity conditions. Stability studies should include multiple independent batches and periodic assessment of drug content, moisture content, dissolution performance, and solid-state characteristics to identify any gradual recrystallization or loss of formulation performance.

Additional formulation studies may investigate alternative polymers and polymer combinations to determine whether further improvements in physical stability, dissolution, and supersaturation maintenance can be achieved. Comparative evaluation of PVP K30 with other established ASD carriers may also provide useful information regarding drug-polymer miscibility and resistance to recrystallization [1,8].

In vivo pharmacokinetic evaluation represents an important subsequent step. A properly designed animal study should compare the optimized ASD with crystalline celecoxib and report relevant pharmacokinetic parameters, including C_{max}, T_{max}, AUC, elimination half-life, and relative bioavailability. Such data would be necessary to determine whether the improved solubility and dissolution observed in vitro translate into increased systemic exposure. Scale-up studies should also be performed to determine the robustness and reproducibility of the spray-drying process. Changes in feed concentration, feed rate, atomization conditions, inlet and outlet temperatures, drying-gas flow, and equipment configuration can influence particle formation, residual solvent, yield, particle morphology, and solid-state properties. Therefore, process optimization and appropriate critical quality attributes should be established before progression toward larger-scale manufacturing [7,2].

Future work should also examine the relationship between drug-polymer molecular

interactions, glass-transition behavior, residual moisture, molecular mobility, dissolution-induced supersaturation, and physical stability. Such investigations could provide a stronger mechanistic understanding of the factors governing the performance of celecoxib ASDs.

In summary, the present study establishes the potential of spray-dried PVP K30-based ASD technology to improve the solubility and in vitro dissolution performance of celecoxib. Further experimentally verified long-term stability, scale-up, and pharmacokinetic studies are required before definitive conclusions regarding shelf life, manufacturability, or enhanced oral bioavailability can be made.

Declarations

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