Research Article

Development and Characterization Of Solid Dispersion-Based Immediate-Release Meloxicam Pellets Prepared By Extrusion-Spheronization For Enhanced Solubility and Dissolution

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Abstract

Meloxicam is a BCS Class II non-steroidal anti-inflammatory drug (NSAID) that has high permeability and lower aqueous solubility, resulting in slow dissolution and delayed onset of action; this is not ideal for the treatment of acute pain. The objective of this study was to develop and characterise immediate-release Meloxicam pellets using the solid dispersion technology along with extrusion-spheronization to improve the release characteristics of the drug in terms of solubility and dissolution to increase its oral bioavailability. Physicochemical properties and BCS classification of the drug were confirmed by preformulation studies. Eight solid dispersions (MSD1–8) were prepared with polyvinylpyrrolidone K30 (PVP K30) in different drug-to-polymer ratios and processed into immediate-release pellets (MF1–8) using the extrusion-spheronization technique, with the inclusion of the functional excipients microcrystalline cellulose, lactose, sodium lauryl sulfate, and croscarmellose sodium. FTIR and DSC analysis confirmed that, compared to pure Meloxicam, the solid dispersions exhibited significantly higher aqueous solubility (3–4 times higher) with statistically significant results ($t = 5.39$, $p = 0.001$), which was ascribed to the reduced crystallinity. The resultant pellets were found to have good flow properties, uniform drug content (98.77-101.50 %), narrow particle size distribution and spherical morphology. Dissolution studies demonstrated a very fast release of the drug; more than 90% of Meloxicam was released from MF3 and MF8 formulations in 30 minutes. The results show that co-processing solid dispersion with EX-SPONIZATION is an effective and reproducible approach to tackle the solubility constriction of Meloxicam, in which MF3 is the optimized IR formulation.

Keywords: Meloxicam, Solid Dispersion, Extrusion–Spheronization, Immediate-Release Pellets, Solubility Enhancement, Dissolution Rate, BCS Class II Drug, PVP K30.

1. Introduction

1.1 NSAIDs and Management of Pain/Inflammation

Non-steroidal anti-inflammatory drugs (NSAIDs) are a broad group of compounds that are routinely used as primary drugs in the treatment of pain, inflammation and fever. The therapeutic mechanism is by inhibiting cyclooxygenase (COX) enzymes, thereby preventing the increased production of pro-inflammatory prostaglandins (Sohani et al. 2023). Inhibition of COX-2 is thought to be beneficial in terms of analgesia and anti-inflammatory effects, whereas inhibition of COX-1 is linked to gastrointestinal irritability and renal toxicity (Vishwakarma et al. 2020). COX-2 inhibitors were developed to increase gastric safety, but there are some concerns about cardiovascular risk. Nevertheless, despite these drawbacks, NSAIDs remain an important part of the treatment of musculoskeletal disorders, arthritis, postoperative pain and other inflammatory conditions (Stiller et al. 2022).

1.2 Pharmacological Profile of Meloxicam

Meloxicam is an enolic acid-derived non-steroidal anti-inflammatory drug (NSAID) with preferential inhibition of cyclooxygenase-2 (COX-2) over COX-1, and thus demonstrates effective anti-inflammatory and analgesic activity with a lower incidence of gastrointestinal adverse effects than non-selective NSAIDs (Bekker et al. 2018). It is indicated for the treatment of musculoskeletal pain disorders such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Oral meloxicam is highly bioavailable (~89%) and has a long elimination half-life of ~20 hours, on which basis it is administered once daily (Venut et al. 2018). Unfortunately, it is poorly soluble in water and slow to dissolve, which makes it unsuitable for acute pain and underscores the necessity of formulation approaches to improve its solubility and dissolution rate.

1.3 Biopharmaceutical Challenges of Meloxicam

Meloxicam, a non-steroidal anti-inflammatory drug (NSAID) of the benzothiazine class, has a broad spectrum of therapeutic uses, such as arthritis, and has potential applications in cancer and neurodegenerative diseases. It has broad pharmacological activity but has a poor aqueous solubility that leads to a slow dissolution rate and delayed onset of activity after oral administration (Reetu et al. 2022). Meloxicam is a BCS Class II drug with high

permeability and low solubility, and its dissolution is the rate-limiting step for its absorption. These biopharmaceutical limitations require formulation concepts that are more sophisticated, such as solid dispersion and pellet formulations, to increase the solubility, dissolution and oral bioavailability of the drug (Maggi et al. 2024).

1.4 Effect of Low Solubility on Oral Bioavailability and Onset of Action of Meloxicam

Meloxicam has a low aqueous solubility and a high permeability and is therefore a BCS Class II drug, with dissolution in gastrointestinal fluids being the rate-limiting step for its oral absorption. Meloxicam has an oral bioavailability of about 89% upon dissolution; however, its low solubility slows the dissolution of the drug (Muhammed and Kinani 2023). The maximum plasma level (T_{max}) is usually reached 3-7 hours after the oral suspension and 5-6 hours after the tablet. This means it does not work as well if you need to take it for quick pain relief. Thus, by optimizing the dissolution rate of these compounds by using advanced formulation techniques, such as nanocrystals or solid dispersions, intestinal absorption can be increased, bioavailable and faster therapeutic effects can be attained (Kumari et al. 2023).

1.5 Strategies to Improve Solubility and Dissolution of Poorly Water-Soluble Drugs

Many therapeutic agents, especially those of BCS Class II and IV, which have dissolution rate as the rate-limiting step for oral absorption, have poor aqueous solubility. The water solubility of about 40% of marketed drugs and nearly 90% of drug candidates is poor, which often leads to low oral bioavailability and therapeutic efficacy. In order to address these problems, many different formulation strategies have been developed to improve the solubility and dissolution of the drug (Bhalani et al. 2022). The conventional methods are particle size reduction (micronization and nanonization), salt formation, change in pH, co-solvency, solubilisation with surfactant and micellar, cyclodextrin complexation and prodrug formation (Bakrey et al. 2025). The use of advanced techniques such as solid dispersions, crystal engineering, nanocrystals, lipid-based drug delivery systems, polymeric micelles, solid lipid nanoparticles, self-emulsifying drug delivery systems (SEDDS), microemulsions and colloidal carrier systems has been shown to enhance dissolution rate, oral bioavailability and therapeutic performance (Narmada 2023). Choosing an appropriate solubility enhancement strategy is dependent on the physicochemical properties of the drug, dosage form requirements and the route of administration.

1.6 Solid Dispersion Technology

Solid dispersion is a useful technique to improve the solubility and dissolution of poorly soluble drugs in a hydrophilic carrier. It enhances wettability and decreases crystallinity, and can even cause the transformation of the drug into the amorphous form, which leads to enhanced dissolution and therefore to better oral bioavailability (Tekade et al. 2020). Solid dispersion is considered a widely adopted method for enhancing the performance of BCS class II drugs, with common preparation methods being solvent evaporation, hot-melt extrusion, spray drying and fusion (Malkawi et al. 2022).

1.6.1 Types of solid dispersions

Solid dispersions can be generally classified according to the type of carrier and the arrangement of the drug molecules in the carrier matrix. They are classified into four generations based on the carrier: 1st generation – crystalline carrier, 2nd generation – amorphous polymeric carrier, 3rd generation – carriers containing surfactant or surface-active agents, and 4th generation – controlled release solid dispersions (Cid et al. 2019). Solid dispersions are made up of eutectic mixtures, solid solutions, glass solutions, glass suspensions and amorphous precipitations in a crystalline carrier, each of which involves the drug in a different physical state and in a different distribution, affecting solubility and stability (Hallouard et al. 2016).

1.7 Pelletization as a Multiparticulate Drug Delivery System

Pelletization is a multiparticulate drug delivery system that aims to convert fine powder or granules into small, free-flowing and spherical pellets. Pellet dosage systems offer improved gastrointestinal distribution of the drug in comparison with conventional dosage systems based on single units, resulting in lower concentration in the gastrointestinal tract and less dose dumping and gastrointestinal irritation (Yadav and Verma 2016). They possess good flow characteristics, have a narrow particle size distribution, and are easily coated and formulated for immediate, delayed and controlled release. Moreover, pellets can be encapsulated or compressed into tablets, which results in better bioavailability, controlled drug release and better compliance by the patient (Zaman et al. 2016).

1.8 Extrusion–Spheronization for Enhanced Solubility and Dissolution

Extrusion–spheronization is a powerful and widely accepted pelletization method to obtain spherical pellets, having high drug loading capacity, narrow particle size distribution and excellent mechanical strength. The process starts by massing, then it is extruded, spheronized, dried and sized to produce uniform and suitable pellets for oral drug delivery (Agrawal et al. 2022). Extrusion–spheronization technology, when used alongside solid dispersion and/or amorphous drug systems, promotes rapid wetting, improved drug dispersion and more rapid drug dissolution, particularly for poorly water-soluble drugs (Baek and Jin 2025). Moreover, the spherical

pellets are well flowable, with reproducible drug release, uniform coating, and are easily scalable up to industrial production, making this method very attractive for immediate-release formulation development (Nikolakakis and Partheniadis 2017).

1.9 Immediate-Release Pellet Formulations

Immediate release (IR) pellet formulations are multiparticulate dosage forms that disintegrate quickly and release the drug from the dosage form after oral administration. The spherical geometry is very small and offers high surface area, which leads to rapid wetting, dissolution and absorption of the drug, even for poorly water-soluble drugs (Seiler 2018). Incorporation of super disintegrants and appropriate pelletizing agents also increases the rate of disintegration, leading to better dissolution and increased oral bioavailability. IR pellets have superior gastrointestinal distribution properties, lower dose dumping potential, better flow properties and increased formulation flexibility when compared to conventional tablets, which makes them an effective platform to further enhance the therapeutic performance of poorly soluble drugs (Xia et al. 2018).

1.10Combining Solid Dispersion with Pelletization

The solid dispersion and pelletization technology overcomes the drawbacks of solid dispersions and combines their solubility-enhancing effect with the manufacturing and biopharmaceutical benefits of multiparticulate pellets (Abolelela). Solid dispersion can increase drug wettability, decrease crystallinity and promote dissolution; whereas pelletization can achieve excellent drug flowability, uniform drug distribution, coating and ease of gastrointestinal transit (Jia et al. 2026). The use of solid dispersions in pellets has the advantage of avoiding the flowability and handling difficulties which are common with conventional solid dispersion powders, does not require extensive milling and results in a stable dosage form that offers improved dissolution and oral bioavailability (Tambosi et al. 2018). This approach has significant advantages in formulation performance and scalability to industrial production for BCS Class II drugs.

1.11 Advantages of integrating both technologies (Xiang et al. 2021)

- Improves the wettability and dissolution of poorly water-soluble drugs by enhancing their solubility and reducing crystallinity.
- Enhances oral absorption of the drug by promoting faster drug dissolution and absorption.
- Excellent content uniformity and mechanical strength of pellets that result in uniform, free-flowing pellets.
- Provides even release in the gut and minimises dose dumping and gut irritation.

While both Meloxicam solid dispersions and extrusion–spheronization have been examined, most of the studies examining solid dispersions have been performed as powders or compressed into conventional or fast disintegrating tablets; however, the extrusion–spheronization process of Meloxicam has been based on coating the drug over a pre-formed inert core rather than directly incorporating the solid dispersion into the extrudate. However, in the national literature, the study of solid dispersion formulations of Meloxicam is mainly focused on tablet formulation, and a direct single-step combination of solid dispersion and extrusion–spheronization for Meloxicam formulation is not widely investigated.

Meloxicam has favourable pharmacokinetic properties, such as high oral bioavailability (around 89%), a long half-life and can be administered as a single daily dose; however, the dissolution process is the rate-limiting step in the absorption due to the poor aqueous solubility, which leads to a delayed Tmax of 3-7 hours, limiting use in diseases that require rapid onset of anti-inflammatory or analgesic effects. Solid dispersion technology is recognized as an effective, economic approach to enhance the solubility of BCS Class II drugs via de-crystallization and wettability and extrusion-spheronization is a solid multiparticulate technology providing good, uniform gastrointestinal distribution and lower risk of dose dumping. It was therefore considered a logical move to combine these two technologies to solve both Meloxicam's solubility problem and provide the desired delivery in a convenient, industry-scale immediate release delivery system.

Thus, the aim of the present study was to formulate and characterize immediate-release Meloxicam pellets using a combination of solid dispersion technology with extrusion-spheronization. The specific aims were (i) to prepare and evaluate solid dispersion of Meloxicam with PVP K30; evaluate the effect of PVP K30 on the aqueous solubility, crystallinity and drug-excipient compatibility; (ii) to formulate the optimized solid dispersion into immediate-release pellets by extrusion-spheronization technique and evaluate the micromeritic properties, drug content uniformity of the developed pellet formulations; and (iii) to assess the in vitro release profile and release kinetics of the developed pellet formulations to identify the optimum immediate-release formulation.

2. Materials and Methods

2. 1 Materials

The model poorly water-soluble active pharmaceutical ingredient (API) Meloxicam was obtained as a gift sample from a reputable pharmaceutical manufacturer. Polyvinylpyrrolidone K30 (PVP K30), which has the ability of solubilization and compatibility with poorly water-soluble drugs, was chosen as the hydrophilic carrier polymer for the preparation of solid dispersions. The pelletization aid and spheronization enhancing agent was the microcrystalline cellulose (Avicel PH-101) and the filler was lactose monohydrate, which was used to increase the hardness of the pellets and its processability. Sodium lauryl sulfate (SLS) was added as a surfactant to facilitate the wetting of the drug and its dissolution, while croscarmellose sodium was added as a superdisintegrant to aid the drug to absorb water rapidly and release the drug. For granulating, the extrusion-spheronization was processed using purified water.

2. 2 Instruments

Solid dispersions were prepared by a thermostatically controlled water bath while pellets were prepared by a laboratory scale extruder and spheroniser followed by drying in a hot-air oven. UV-visible spectrophotometric method was used to quantify the drugs with calibration curve created for each analysis. The drug-excipient compatibility was assessed by Fourier Transform Infrared spectroscopy (FTIR) and thermal and crystalline behavior of Meloxicam before and after formulation was analyzed using Differential Scanning Calorimetry (DSC). Throughout the study, standard laboratory equipment was used such as an analytical balance, pH meter, magnetic stirrer, a mortar and pestle, sieve set, volumetric glassware and dissolution accessories.

2. 3 Experimental Design

The purpose of this study was to formulate immediate release pellets of Meloxicam by a solid dispersion method along with extrusion-spheronization technique. In order to determine the physicochemical properties of Meloxicam such as aqueous solubility, partition coefficient, calibration curve and the compatibility of excipients, preformulation studies were conducted first. The solid dispersions were then prepared at different Meloxicam:PVP K30 ratio by the melt method and then were extruded-spheronized to produce eight different immediate-release pellets (MF1–MF8). Solubility enhancement, thermal behaviour, flow properties and drug content were evaluated for all formulations to find the optimum formulation.

2. 4 Preformulation Studies

2.4.1 Determination of Physicochemical Properties

Meloxicam physical characteristics, colour, odor and solubility were studied. Solubility was compared to that in aqueous solution, ethanol, chloroform, acetone, dimethyl sulfoxide, ethyl acetate, and n-hexane. The value of the partition coefficient (log P) was obtained using the n-octanol/water partitioning method, and compared with literature to confirm the Biopharmaceutical Classification System (BCS) category of the drug.

2.4.2 Preparation of Calibration Curve

The stock solution of Meloxicam was prepared and then serially diluted and absorbance measurements of each dilution were recorded at the determined λmax using UV-visible spectrophotometry. A calibration graph Absorbance versus concentration was plotted and the regression equation and correlation coefficient was computed to establish linearity of the method.

2.4.3 Drug-Excipient Compatibility Study

Compatibility between Meloxicam and PVP K30 was assessed by FTIR spectroscopy. Spectra of the pure drug, PVP K30, and their physical mixture were compared over the appropriate spectral range to detect peak shifts, disappearance of characteristic bands, or the appearance of new peaks indicative of chemical interaction.

2.4.4 Selection of Excipients

The excipients were chosen based on their intended purpose in the formulation. The solubilizing carrier polymer used was PVP K30, the main pelletization aid was microcrystalline cellulose due to its plastic extrusion-spheronization property, the drug was dispersed in lactose monohydrate, which increased pellet strength, sodium lauryl sulfate was used as a wetting and dissolution aide, and croscarmellose sodium was used as a rapid disintegrating aide to promote the immediate release of the drug.

2. 5 Preparation of Solid Dispersions

2.5.1 Preparation of Physical Mixtures

Selected drug-to-polymer ratios were blended together in a gentle manner to ensure a homogeneous mixture without altering the drug crystallinity; this was achieved by blending together drug and PVP K30 in a mortar for

10–15 min. The mixtures were sieved through 60-mesh sieve and were kept in sealed containers for further characterization by Fourier Transform Infrared (FTIR) and Differential Scanning Calorimeter (DSC).

2.5.2 Preparation of Solid Dispersions by Melt Method

Solid dispersions were prepared by the melt method with the use of PVP K30 as a hydrophilic carrier. The weighed amounts of Meloxicam and PVP K30 (Table 1) were mixed and melted in a thermostatically controlled water bath under continuous stirring at 80-90 °C to ensure complete melting and uniform dispersion of the drug. The molten mass was cast on a surface covered with aluminium foil and allowed to solidify at room temperature and then crushed and screened through 60 mesh. This procedure was used to prepare eight solid dispersion formulations (MSD1–MSD8) with different ratios of Meloxicam/PVP K30, which were then stored in air-tight desiccators until further use.

Table 1: Composition of Meloxicam solid dispersions

Formulation Code	Meloxicam (mg)	PVP K30 (mg)	Drug:Polymer Ratio	Preparation Method
MSD1	20	2.5	8:1	Melt Method
MSD2	20	3.5	5.7:1	Melt Method
MSD3	20	5.0	4:1	Melt Method
MSD4	20	3.0	6.7:1	Melt Method
MSD5	20	4.0	5:1	Melt Method
MSD6	20	4.5	4.4:1	Melt Method
MSD7	20	2.5	8:1	Melt Method
MSD8	20	3.75	5.3:1	Melt Method

Interpretation: Meloxicam was encapsulated in eight solid dispersion formulations containing fixed concentration of Meloxicam (20 mg) and different concentrations of PVP K30 prepared by melt method. These different drug to polymer ratios were used to determine the effect on polymer concentration on the solubility enhancement and also to find the best one for further pellet preparation.

2. 6 Preparation of Immediate-Release Pellets by Extrusion-Spheronization

The prepared solid dispersions were used as the source material in the preparation of pellet formulations. The compositions of each solid dispersion (20 mg Meloxicam) were composed with microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate and croscarmellose sodium as described in Table 2. Dry ingredients were mixed for about 15 min the purified water was gradually added until a wet mass that can be extruded was obtained. Wet mass was extruded from a laboratory-scale screw extruder equipped with a proper screen and the extrudates were spheronized to form spherical pellets. The pellets were dried in a hot-air oven to constant weight at 40 °C and stored in airtight containers. This procedure was used to prepare eight pellet formulations (MF1 - MF8), which are related to the respective solid dispersions.

Table2: Composition of immediate-release pellet formulations

Formulation Code	Solid Dispersion (mg)	MCC (mg)	Lactose Monohydrate (mg)	SLS (mg)	Croscarmellose Sodium (mg)	Purified Water
MF1	22.50 (MSD1)	12.50	12.50	1.00	1.50	q.s.
MF2	23.50 (MSD2)	11.50	12.50	0.75	1.75	q.s.
MF3	25.00 (MSD3)	10.00	11.50	0.50	3.00	q.s.
MF4	23.00 (MSD4)	12.00	12.00	1.00	2.00	q.s.
MF5	24.00 (MSD5)	11.00	11.50	0.75	2.75	q.s.
MF6	24.50 (MSD6)	10.50	11.00	0.50	3.50	q.s.
MF7	22.50 (MSD7)	13.00	12.00	1.00	1.50	q.s.
MF8	23.75 (MSD8)	11.25	12.50	0.75	1.75	q.s.

Interpretation: Eight immediate release pellet formulations (MF1-MF8) were prepared by extrusion-spheronization technique, with the aid of the corresponding meloxicam solid dispersions (MSD1–MSD8). Systematic variations in the concentrations of MCC, lactose monohydrate, SLS and croscarmellose sodium were performed for optimum pellet formation and immediate drug release. The formulation design allowed the assessment of the impact of excipients composition on the physical properties and dissolution of the pellets in order to select the optimized formulation.

2. 7 Evaluation of Solid Dispersions

The solubility, crystallinity, and thermal behaviour were assessed for the solid dispersions as compared to pure Meloxicam and as compared to the physical mixtures to evaluate the effect of PVP K30. The shake-flask method, FTIR spectroscopy and DSC were used for evaluation.

2.7.1 Determination of Solubility by Shake-Flask Method

Excessive amounts of either pure Meloxicam or solid dispersion (about 20 mg of Meloxicam) were placed in 10 mL of distilled water in screw-capped vials and shaken for 24 h at 37 ± 0.5 °C and 100 rpm. The samples were then aged for 1 h, centrifuged at 5000 rpm for 10 min and subsequently filtered with a 0.45 µm membrane. The samples were diluted and assayed spectrophotometrically at the determined λmax, with the use of the calibration curve. All measurements were made in triplicates (mean ± SD) and the solubility enhancement compared to the pure drug with an independent Student's t-test ($p < 0.05$).

2.7.2 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of the pure Meloxicam, PVP K30, physical mixture of both and optimized solid dispersion were obtained by making KBr discs (1–2 mg sample) under a hydraulic press and scanning the spectra in the range of 4000-400 cm^{-1}. Drug-excipient compatibility was assessed by comparing the spectra for peak shifting, disappearance of peaks, or formation of new peaks.

2.7.3 Differential Scanning Calorimetry (DSC)

Samples of pure Meloxicam and optimized solid dispersion (2–5 mg) were placed in aluminium pans and scanned against an empty reference pan in a temperature range of 30–300 °C at a heating rate of 10 °C/min under nitrogen atmosphere (40 mL/min). Thermograms were examined for melting endotherms changes and the presence of any disappearance of the Meloxicam melting peak was considered as a reduction in the crystallinity or amorphization of the drug.

2. 8 Evaluation of Immediate-Release Pellets

2.8.1 Evaluation of Flow Properties

Standard pharmacopoeial procedure was used to determine bulk density, tapped density, Hausner ratio and Carr's compressibility index.

The mass of the pellets and the volume of the graduated cylinder in which they were initially placed (bulk volume) were used to calculate bulk density,

$$\text{Bulk Density} = \frac{\text{Mass of pellets}}{\text{Bulk volume}}$$

Tapped density was determined after mechanical tapping to constant volume,

$$\text{Tapped Density} = \frac{\text{Mass of pellets}}{\text{Tapped volume}}$$

Hausner ratio was calculated as tapped density divided by bulk density,

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

and **Carr's index was calculated as**,

$$\text{Carr's Index (\%)} = \frac{\text{Tapped Density-Bulk Density}}{\text{Tapped Density}} \times 100$$

2.8.2 Drug Content Analysis

The 20 mg equivalent of Meloxicam were dissolved in an appropriate amount of dissolution medium by sonication, diluted, filtered through a 0.45 µm membrane and analyzed by UV-visible spectrophotometry by using the pre-determined λmax and the calibration curve. The percentage drug drug content was calculated for three samples of each formulation (mean ± SD).

2. 9 Statistical Analysis

Each experiment was repeated three times, and the mean ± standard deviation (SD) is reported. GraphPad Prism software (Version 9.0, GraphPad Software, San Diego, CA, USA) was used for statistical analysis. An independent Student's t-test was conducted to compare the pure Meloxicam and solid dispersion formulations with the value of $p < 0.05$ set as statistically significant.

3. Results and Discussion

3.1 Preformulation Studies

Preformulation studies were conducted to determine the physicochemical properties of Meloxicam and its suitability to formulate in the form of immediate release pellet. The investigations involved in this were the evaluation of the physicochemical properties of the drug, analytical calibration and compatibility studies with the excipients selected. The results showed that a solubility enhancement technique is required for Meloxicam and helped to choose the carrier polymer PVP K30.

3.1.1 Physicochemical Properties of Meloxicam

Meloxicam was purchased as a yellow, crystalline powder which had no odour. The drug was poorly soluble in water, but more soluble in polar organic solvents as expected for a hydrophobic compound. The experimentally determined log P value of approximately 2.67 indicated moderate lipophilicity and it was classified as a BCS Class II drug, in which dissolution is the rate determining step in the oral absorption process. The properties made them suitable for the application of solid dispersion technology for enhancing the dissolution behaviour and bioavailability of Meloxicam.

3.1.2 Calibration Curve of Meloxicam

A good linear range was obtained for Meloxicam's UV spectrophotometric calibration curve with a correlation coefficient (R^2) close to 1 over the selected concentration range. The method used was found to be in compliance with Beer-Lambert's law and showed good accuracy and reproducibility in the quantitative estimation of the drug in the solubility studies and during the drug content analysis.

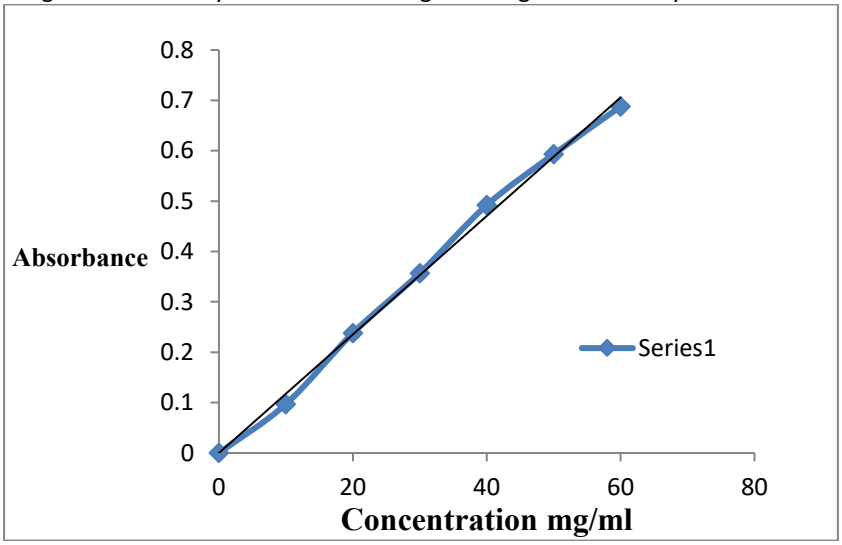

Figure1: Calibration curve of Meloxicam

3.1.3 Drug-Excipient Compatibility Study

FTIR spectroscopy was then used to check the compatibility of Meloxicam with PVP K30. Meloxicam characteristic absorptions were present in the spectra of all the formulations with no additional peaks or significant peak shift, suggesting no chemical interaction between the drug and polymer. These results showed that PVP K30 was suitable as carrier in solid dispersion preparation and no chemical change was observed in Meloxicam during formulation process.

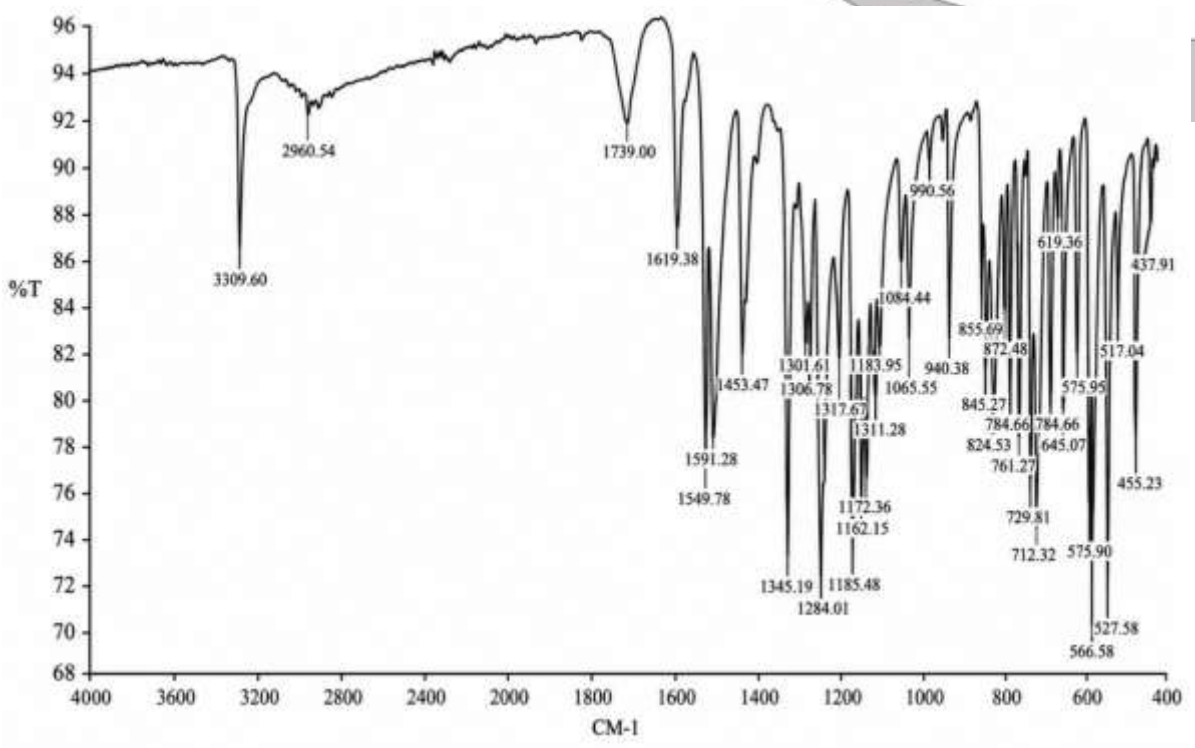

Figure2: FTIR spectrum of pure Meloxicam

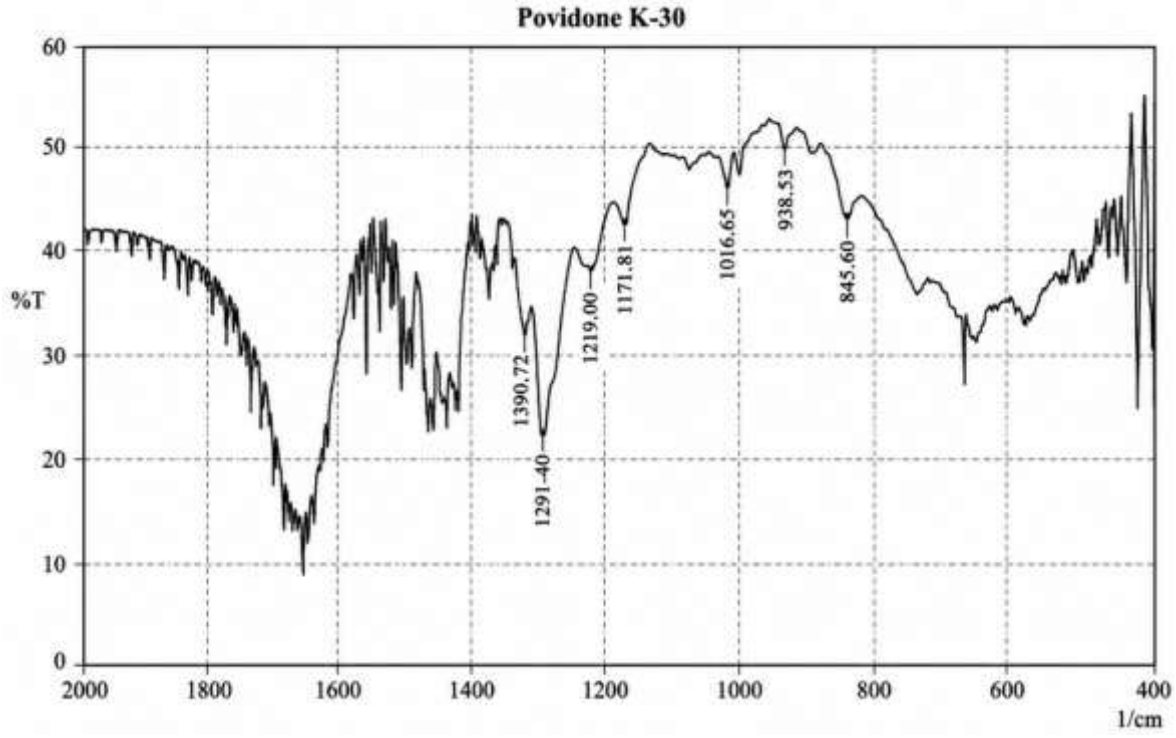

Figure3: FTIR spectrum of PVP K30

The ability shown by FTIR is found to be compatible and supports the suitability of PVP K30 as carrier polymer for the preparation of solid dispersion aimed to improve the dissolution characteristic of Meloxicam.

3.2 Development and Characterization of Solid Dispersions

Using PVP K30 as the hydrophilic carrier, eight solid dispersion formulations (MSD1–MSD8) were successfully prepared by the melt method. The successful incorporation of Meloxicam into the polymer matrix has been confirmed as all the formulations were found to be free flowing pale yellow in the form of powder without any agglomeration or recrystallisation.

3.3 Solubility Study of Solid Dispersions

The aqueous solubility of pure Meloxicam was low (8.80-12.70 µg/mL) and all solid dispersion formulations exhibited significant improvement in their aqueous solubility 3-4 fold (28.4-45.1 µg/mL). MF3 exhibited the highest solubility (45.1 ± 0.80 µg/mL), followed by MF8 and MF6 while comparatively lower, but still appreciable, solubility was seen in MF1 and MF7. The improvement is due to increased wettability, drug molecular dispersion in polymer matrix and decrease in crystallinity, which proves the effectiveness of the polymer to enhance the dissolution behaviour of Meloxicam.

Table3: Solubility of pure Meloxicam and solid dispersion formulations

Formulation	Pure Drug (µg/mL)	Solid Dispersion (µg/mL)
MF1	10.00 ± 0.04	28.4 ± 0.62
MF2	11.57 ± 0.04	36.9 ± 0.74
MF3	12.25 ± 0.05	45.1 ± 0.80
MF4	10.30 ± 0.05	31.6 ± 0.70
MF5	8.80 ± 0.05	39.4 ± 0.75
MF6	9.84 ± 0.05	42.8 ± 0.79
MF7	12.23 ± 0.05	28.5 ± 0.62
MF8	12.70 ± 0.05	44.7 ± 0.81

(Values expressed as mean ± SD, n = 3.)

Interpretation: The saturation solubility study showed that meloxicam obtained as solid dispersion has significant improvement of aqueous solubility level. The pure drug had low solubility (8.80–12.70 µg/mL) while the solid dispersions had significantly high solubility (28.4 – 45.1 µg/mL). From the formulations, MF3 showed the highest solubility (45.1 ± 0.80 µg/mL) followed by MF8 and MF6, suggesting that solid dispersion approach has proved beneficial in enhancing the solubility of meloxicam and this formulation is likely to enhance its dissolution and oral bioavailability.

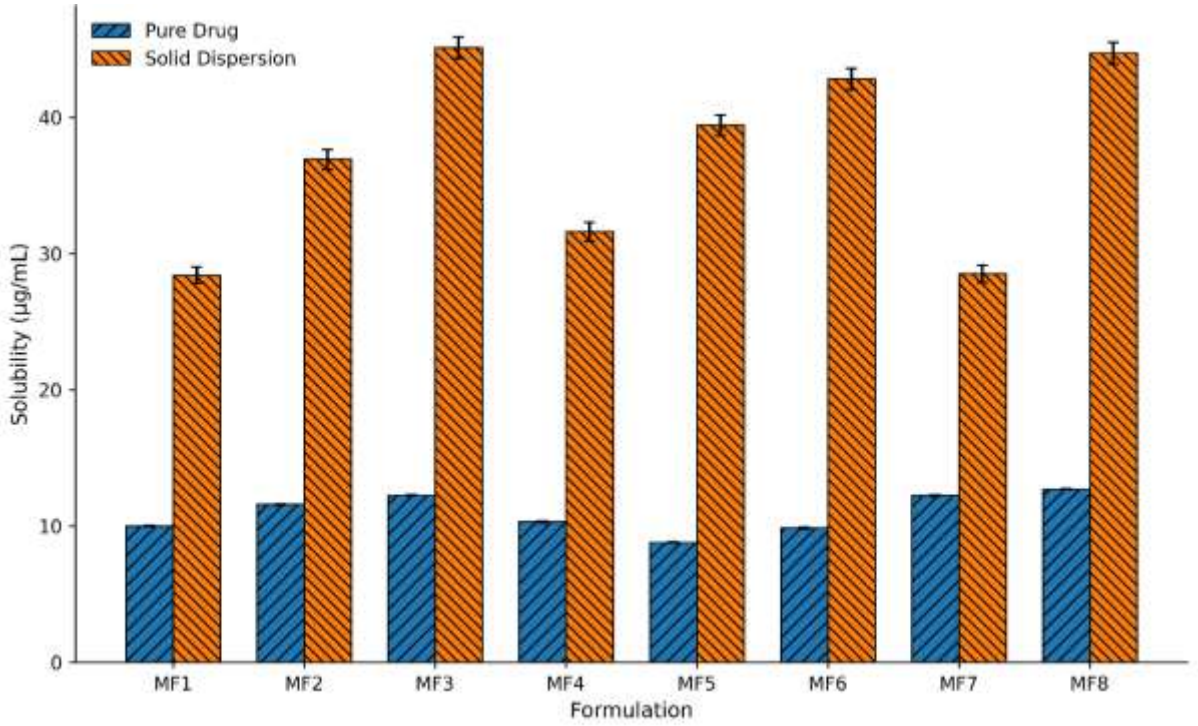

Figure4: Comparison of aqueous solubility of pure Meloxicam and solid dispersion formulations

3.3.1 Statistical Analysis of Solubility Enhancement

The t value obtained after independent Student's t test for statistical comparison of pure Meloxicam and solid dispersion formulations was 5.39 and p value was 0.001. The p value obtained was less than 0.05, indicating that the enhancement of the aqueous solubility was statistically significant, and that the improvement is due to the solid dispersion approach, and not due to experimental variation.

3.3.2 Differential Scanning Calorimetry (DSC)

The DSC thermogram of pure Meloxicam exhibited a distinct endothermic peak of melting which is typical of crystalline substance. The solid dispersion formulations showed a significant decrease in the peak or its total elimination, suggesting the partial transformation of the drug to an amorphous or molecularly dispersed form in the PVP K30 matrix. No other thermal events were detected, indicating that there was no incompatibility or degradation during processing. The decrease in crystallinity of the formulations was found to be in accordance with the increase in their aqueous solubility.

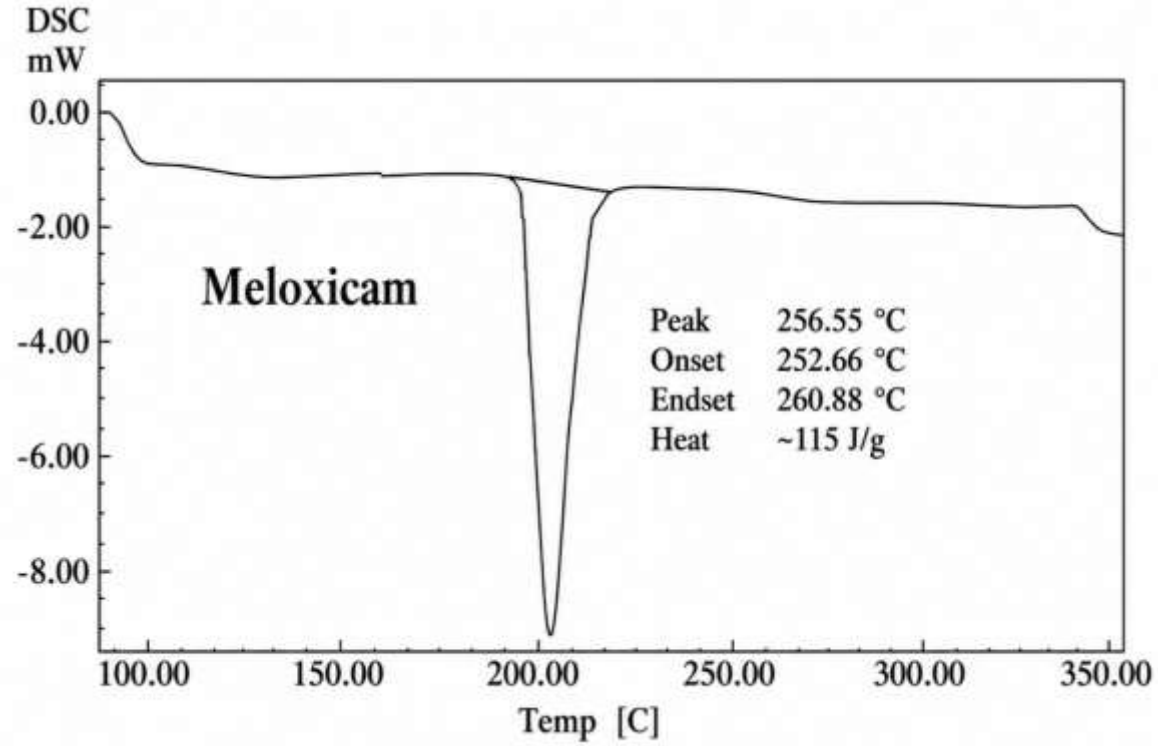

Figure5: DSC thermogram of pure Meloxicam

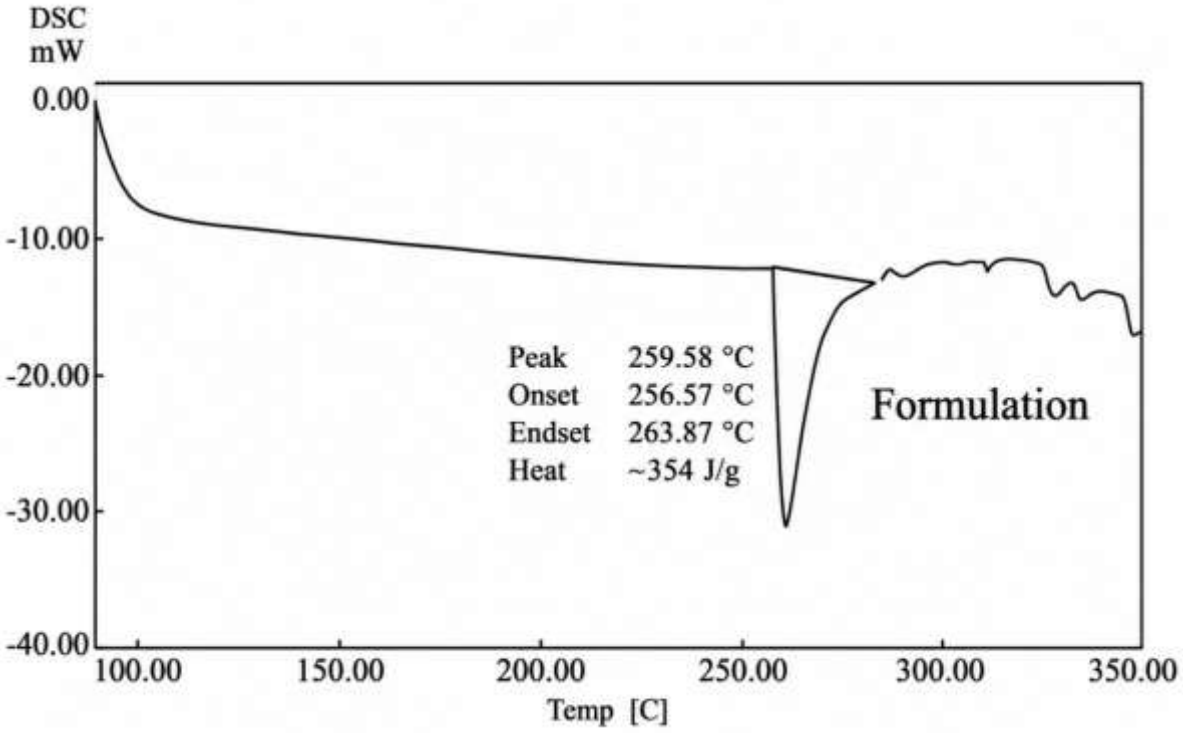

Figure6: DSC thermogram of optimized solid dispersion

3.3.3 Selection of the Optimized Solid Dispersion

Optimized formulation selection was done by considering solubility enhancement and thermal characteristics. The aqueous solubility of the eight formulations was found to be greatest for MSD3 (corresponding to MF3), while a marked decrease in crystallinity was seen, suggesting good molecular dispersion of Meloxicam in the polymer matrix. The characteristics made MF3 the best formulation to be evaluated in pellets.

3.4 Characterization of Immediate-Release Pellet Formulations

The optimized solid dispersions were formulated in the immediate-release pellet dosage form and characterized by flow properties and drug content assessment for suitability in pharmaceutical processing and dosage uniformity. The outcomes exhibited that all formulations had acceptable physical properties demanded for extrusion-spheronisation and capsule filling.

3.4.1 Flow Properties

Good packing was seen in formulations by bulk density (0.46 – 0.655 g/mL) and tapped density (0.50 – 0.704 g/mL). The Hausner ratio (1.075–1.15) and the Carr's index (6.82–13.21%) indicated good to excellent flowability, where MF8 demonstrated the best flow (lowest Hausner ratio and Carr's index), which might be attributed to its spherical shape and pelletisation efficiency.

Table4: Flow properties of immediate-release pellet formulations

Formulation	Bulk Density (g/mL)	Tapped Density (g/mL)	Hausner Ratio	Carr's Index (%)
MF1	0.60	0.68	1.13	11.76
MF2	0.49	0.56	1.14	12.50
MF3	0.46	0.53	1.15	13.21
MF4	0.46	0.50	1.09	8.00
MF5	0.57	0.65	1.14	12.31
MF6	0.47	0.54	1.15	12.96
MF7	0.50	0.57	1.14	12.28
MF8	0.655	0.704	1.075	6.82

Interpretation: The flowability and compressibility of all the formulations were acceptable, with the values of Hausner ratio between 1.075 and 1.15 and Carr's Index ranging between 6.82% and 13.21%. The best flow properties were obtained by MF8 while MF3 and MF6 exhibited relatively higher compressibility. However, the pharmacopoeial limits were still within acceptable limits for all formulations, demonstrating that they had good handling characteristics and uniform pellet quality. These results demonstrate the appropriateness of the formulations for the subsequent pellet processing, capsule filling and industrial production.

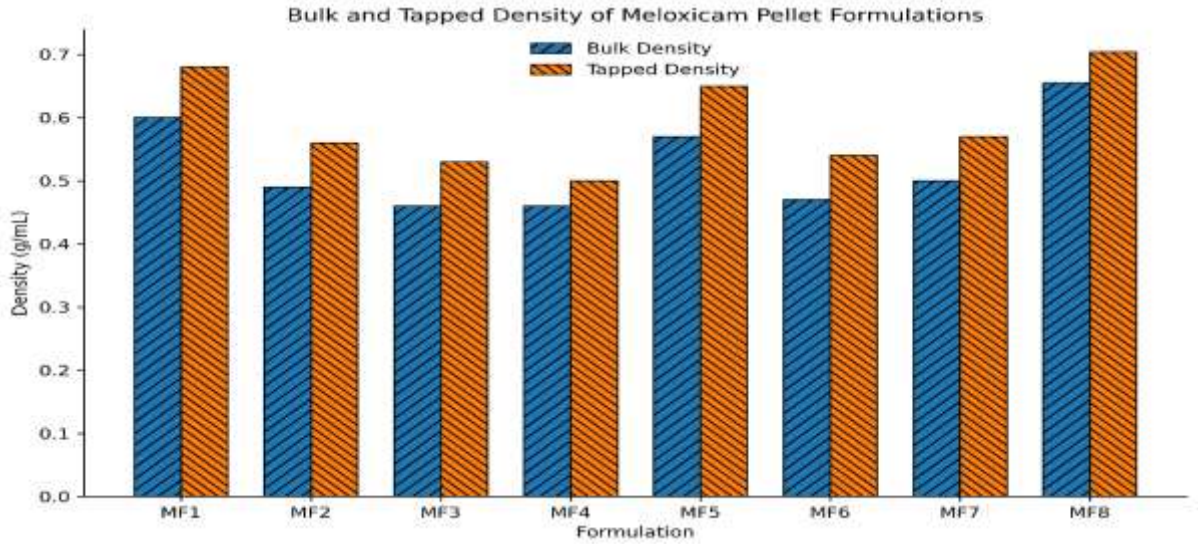

Figure7: Comparison of flow properties of Meloxicam pellet formulations

3.4.2 Drug Content Analysis

The uniformity of distribution of Meloxicam was found to be good across all the pellet formulations by drug content analysis (Table 5). All the formulations were within the acceptable limits of the pharmacopeia with drug

content ranging from 98.77 ± 2.25% to 101.50 ± 1.98%. The optimized formulation (MF3) had the highest value of drug content (101.50 ± 1.98%) while MF2 had the lowest drug content (98.77 ± 2.25%). The low standard deviation values show good reproducibility of the extrusion-spheronisation process, while the low differences between the formulations also suggest good uniformity of the incorporation of the solid dispersion into the formulations and effective blending of the excipients. The results indicate that the formulation process provided drug uniformity and did not affect drug stability or processing yield.

Table 5: Drug content of immediate-release pellet formulations

Formulation	Drug Content (%)
MF1	101.10 ± 2.67
MF2	98.77 ± 2.25
MF3	101.50 ± 1.98
MF4	99.89 ± 1.65
MF5	99.99 ± 2.56
MF6	100.55 ± 2.39
MF7	101.25 ± 2.29
MF8	99.98 ± 2.57

(Values are expressed as mean ± SD, n = 3.)

Interpretation:

The drug content uniformity of all the pellet formulations was excellent and the percentage of drug contents ranged from 98.77 ± 2.25% to 101.50 ± 1.98% within acceptable pharmacopeial limits. The drug content of MF3 was the highest, indicating efficient incorporation of the drug, whereas the small differences in drug content between the different formulations confirmed the uniformity of blending, reproducible production of pellets and uniform dose content in the formulations.

3.5 Morphological Analysis of Pellet Formulations

To analyze the shape and surface characteristics of the pellets, the surface morphology of the optimized pellet formulations (MF3 and MF8) was examined by scanning electron microscopy (SEM). SEM micrographs showed that both formulations were predominantly spherical with smooth and compact surfaces, which were obtained by using the extrusion-spheronisation process to make pellets. There were no visible cracks, surface erosion or aggregation observed, which is the good mechanical integrity of the pellets. A few small irregularities were observed on the surface of the pellets, which is expected during the drying process and are not expected to affect the product performance. In addition, no visible drug crystals were seen on the surface of the pellet, further indicating good uniformity of the incorporation of the solid dispersion into the pellet matrix observed during the drug content uniformity evaluation. In conclusion, SEM analysis confirmed the prepared pellets had good morphological features which are suitable for immediate release multi-particulate drug delivery.

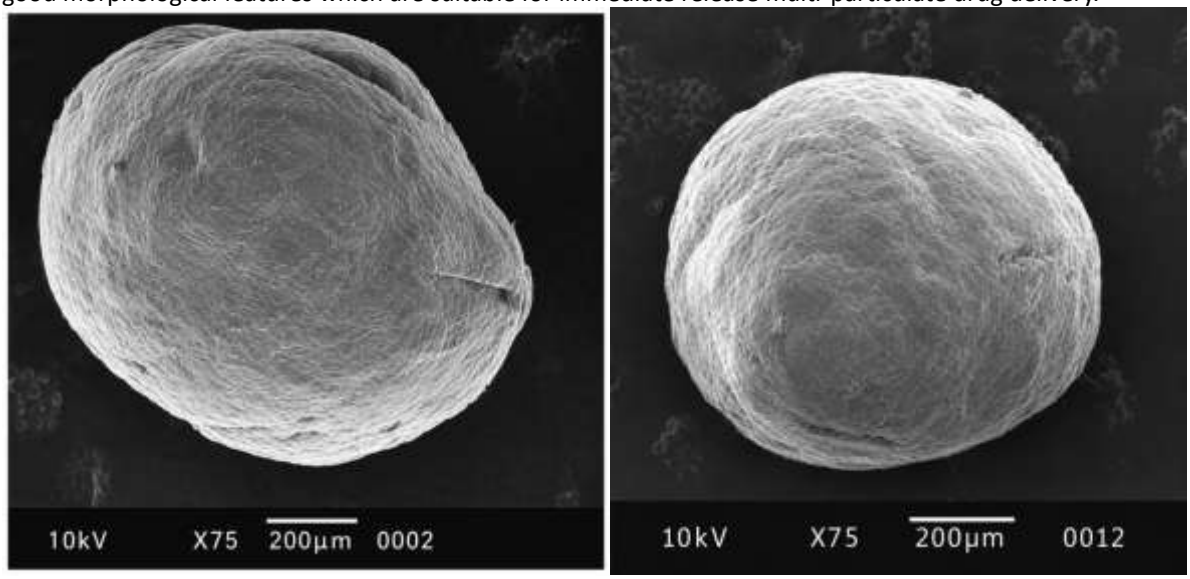

Figure8: Scanning electron micrographs of optimized Meloxicam pellet formulations (MF3 and MF8)

3.5.1 Particle Size Analysis

The particle size analysis showed that all the pellet formulations were extruded in a well controlled and pharmaceutically acceptable size range of about 690 µm – 750 µm which confirmed the reproducibility of the extrusion-spheronisation process. Formulations MF3, MF6 and MF8 were comparatively smaller and more uniform in particle size which was due to good rounding of the pellet and lesser size variation. The size distribution in MF8 was the widest, indicating good spheronisation efficiency and mechanical stability. Formulations MF1 and MF7 resulted in slightly bigger pellets as it may have been related to the relatively higher amounts of microcrystalline cellulose in the formulations, which enhanced the cohesiveness of wet mass during extrusion. However, all formulations were within acceptable limits for multiparticulate dosage forms of immediate release type. The small particle size distribution of each batch is likely to lead to good drug content uniformity, good flowability, reproducibility in dissolution and gastrointestinal distribution.

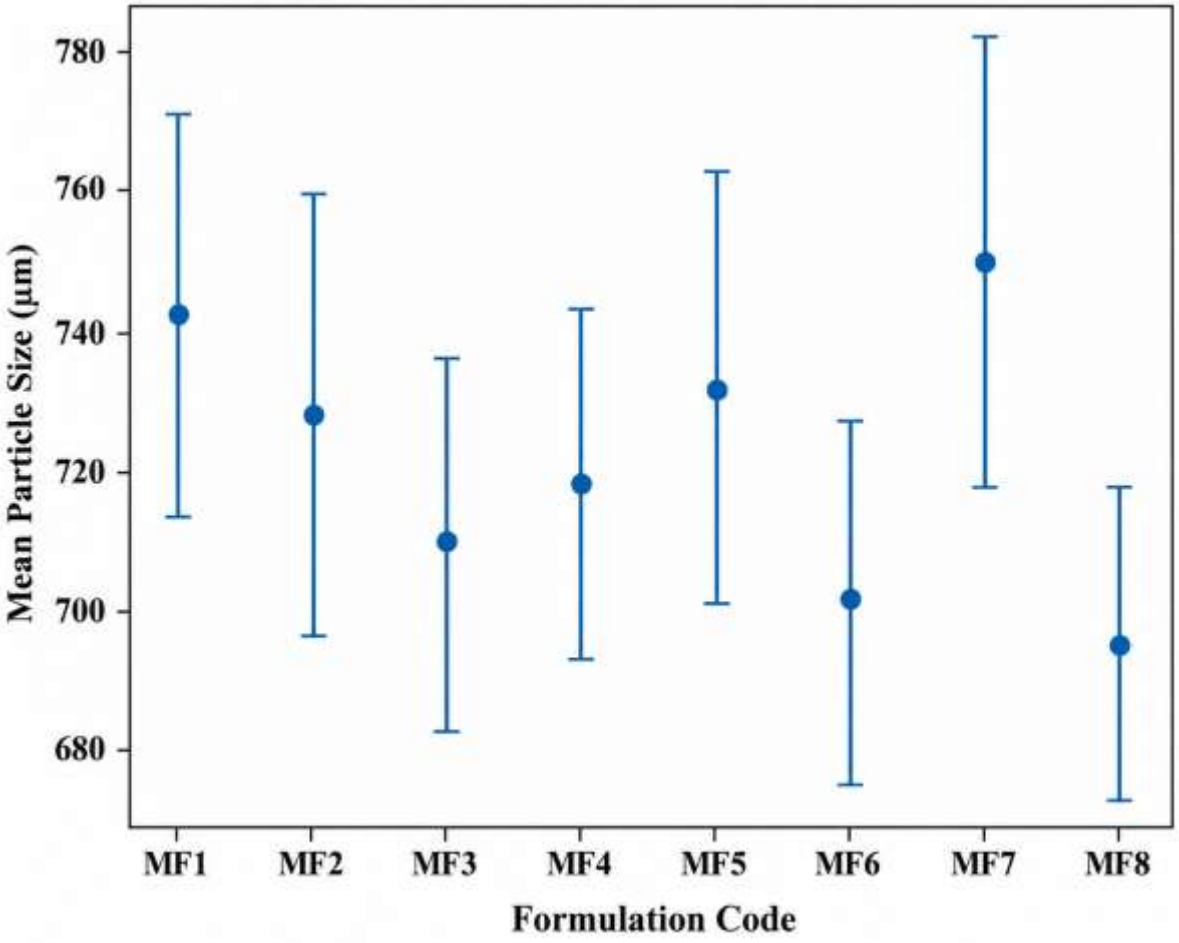

Figure9: Particle size distribution of Meloxicam immediate-release pellet formulations.

3.6 In Vitro Drug Release Studies

In vitro dissolution study showed that the drug release was found to be rapid for all the three formulations of pellets which confirms them to be suitable as immediate release multiparticulate systems. The dissolution profiles exhibited rapid release of the drug in comparison with the gradual release of the drug during the study period. The most effective dissolution of the investigated formulations was obtained by MF3 and MF8 where it was observed that over 90% of Meloxicam was dissolved in 30 min and more than 80% of the drug was dissolved in 45–60 min. This improved dissolution was likely caused by the use of solid dispersion technology, decreased crystallinity of the drug, increased wettability by PVP K30, accelerated pellet disintegration due to croscarmellose sodium, and increased solubilisation due to sodium lauryl sulfate. The release profiles of formulations MF5 and MF6 were also found satisfactory while formulations MF1 and MF7 exhibited comparatively slow dissolution which might be due to their lower polymer content and denser pellet matrix. Overall, both MF3 and MF8 were found to have good immediate release properties and the formulation with MF3 was optimized for dissolution.

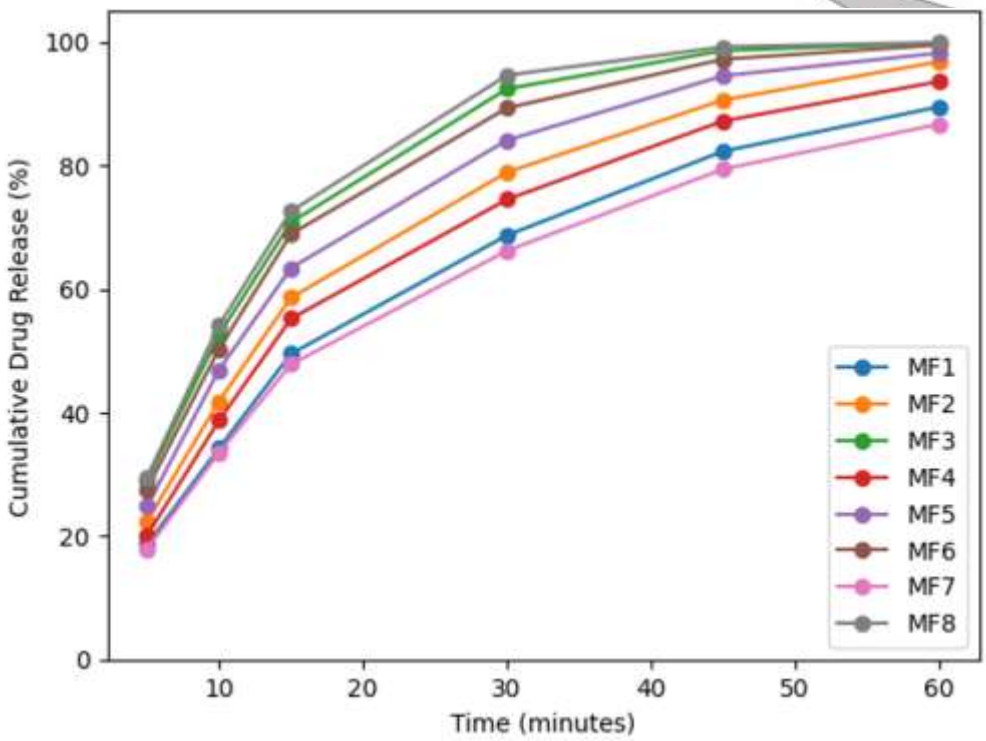

Figure10: Comparative dissolution profiles of Meloxicam immediate-release pellet formulations

3.7 Drug Release Kinetic Modelling

The dissolution data were fitted into the zero-order, first-order, Higuchi and Korsmeyer-Peppas models. The first order model is best fit for MF3, MF5, MF6 and MF8, suggesting that release is a concentration dependent process, characteristic of immediate release systems. The anomalous (non-Fickian) transport (diffusion and relaxation of the matrix) is best modeled as a combination of diffusion and relaxation of the matrix, which are the models used in MF1, MF2, MF4, and MF7. The overall dissolution rate of amorphous Meloxicam from the PVP K30 matrix was the predominant dissolution mechanism.

Table 6: Drug release kinetic modelling of Meloxicam pellet formulations

Formulation	Best Fit (by R^2)	Zero R^2	First R^2	Higuchi R^2	K-P R^2	Zero k_o (%/min)	First k_1 (1/min)	Higuchi kH (%/√min)	K-P kKP	K-P n
MF1	Korsmeyer–Peppas	0.9168	0.9978	0.9775	0.9999	1.234	0.0368	12.885	0.0443	0.8896
MF2	Korsmeyer–Peppas	0.8816	0.9943	0.9574	0.9996	1.267	0.0560	13.345	0.0547	0.8780
MF3	First-order	0.7836	0.9941	0.8891	—	1.174	0.1057	12.643	—	—
MF4	Korsmeyer–Peppas	0.8914	0.9979	0.9631	0.9996	1.256	0.0450	13.195	0.0457	0.9223
MF5	First-order	0.8466	0.9978	0.9348	—	1.234	0.0667	13.109	—	—
MF6	First-order	0.8071	0.9927	0.9064	—	1.196	0.0883	12.814	—	—
MF7	Korsmeyer–Peppas	0.9185	0.9961	0.9785	0.9999	1.192	0.0326	12.439	0.0425	0.8952
MF8	First-order	0.7609	0.9959	0.8714	—	1.156	0.1192	12.504	—	—

Interpretation

Drug release kinetic analysis showed that MF3, MF5, MF6, and MF8 best followed the first-order model, indicating concentration-dependent drug release typical of immediate-release formulations. In contrast, MF1, MF2, MF4, and MF7 followed the Korsmeyer–Peppas model**,** suggesting anomalous (non-Fickian) transport involving both diffusion and matrix relaxation. Overall, the results indicate that the amorphous solid dispersion of meloxicam in the PVP K30 matrix effectively promoted rapid drug release**.**

4. Discussion

The present study extends the work of (Emam et al. 2020) by an alternative formulation approach to enhance the solubility and dissolution of a BCS Class II drug, meloxicam. Emara et al. manufactured hot-melt extruded meloxicam pellets which were designed to have improved dissolution, stability and oral bioavailability by amorphizing the drug. The present study, on the other hand, uses solid dispersion technology in conjunction with the extrusion-spheronization technique in which meloxicam is first dispersed with PVP K30 and then processed into immediate release pellets.

In contrast to the previous study, the present work addresses the rapid release of the drugs by using croscarmellose sodium (CS) and sodium lauryl sulfate (SLS) the latter of which was considered to act as a softener and also the merits of multiparticulate pellets. The optimized formulation (MF3) exhibited a nearly four-fold improvement in its aqueous solubility and exhibited over 90% dissolution of meloxicam within 30 minutes, indicating the success of solid dispersion and extrusion–spheronization approach.

The study by (Ochi et al. 2016) focused on the Production of amorphous solid dispersions (ASDs) of meloxicam with PVP K30, HPC-SSL and Eudragit EPO to enhance the oral bioavailability with rapid dissolution. The Eudragit EPO-based ASD showed the best dissolution properties, good physical stability in the storage and a ratio of oral bioavailability, (2.4-fold) in rats, which was attributed to the high interaction between the drug and the polymer, preventing meloxicam recrystallization.

Likewise, the objective of the present study is to overcome the problem of poor aqueous solubility of meloxicam by using solid dispersion technology. Unlike Ochi et al. , the optimized solid dispersion, prepared using PVP K30, is also extruded–spheronized into immediate-release pellets, so as to achieve the benefits of a multiparticulate drug delivery system and solubility enhancement. This holistic approach not only increases the dissolution of drugs but also improves the flowability of the pellets, the uniformity of their content, the mechanical properties of the pellets and the suitability of the production process.

The study by (Chaturvedi et al. 2017) compared With the aim of increasing the solubility and dissolution of meloxicam, the surface solid dispersion (SSD) and conventional solid dispersion (SD) were compared and subsequently, orodispersible tablets (ODTs) were prepared. Compared with conventional SD, the optimized SSD prepared with crospovidone (1:8 drug-to-carrier ratio) by solvent evaporation showed better dissolution with 97% cumulative drug release, rapid tablet disintegration (11 s), and better wettability, indicating that SSD can be a better method of fast drug release than conventional SD formulation .

In a similar way, the objective of the present study is to enhance the dissolution of poorly soluble meloxicam by solid dispersion technique. The optimized solid dispersion containing PVP K30 was, however, not optimized for formulation in form of an orodispersible tablet but rather used in combination with the pharmaceutical benefits of multiparticulate pellet systems together with a high drug solubility to prepare immediate-release pellets by extrusion–spheronization. This method can improve flowability, ensure the uniformity of dosage form, have good mechanical strength, and can achieve reproducible release of drugs.

The reported study by (Shinde et al. ,2020) Employed the melt solidification technique to make an amorphous meloxicam formulation with the aim of improving the drug's solubility and dissolution by using Soluplus as the carrier. The formulation optimized (MS7, drug:polymer ratio 1:4) demonstrated a significant lower crystallinity (18.60%), 96.83% drug release and higher solubility, which was confirmed by FTIR, DSC and XRD analysis .

In a similar way, the present study uses solid dispersion technology as an approach to increase the solubility of meloxicam, but uses PVP K30 as the hydrophilic carrier and then incorporates the optimized solid dispersion into immediate release pellets by the extrusion–spheronization method. This is not only beneficial for drug solubility but also yields the benefits of multiparticulate pellet systems, such as optimized flowability, uniform drug distribution and suitability for industrial scale production. Finally, the optimized formulation (MF3) showed an increase in its aqueous solubility by around four-fold and showed drug release of over 90% within 30 minutes, which makes it an effective approach for developing immediate release meloxicam pellets by solid dispersion with extrusion–spheronization.

Overall, the present study has modified the concept of previous studies which proved the effectiveness of solid dispersion technologies for improving the solubility and dissolution of meloxicam, by combining solid dispersion with extrusion–spheronization to produce the immediate release pellets with better dissolution rate, better

pellet properties and better industrial applicability. In general, the previous studies have proved the effectivity of solid dispersion technologies to improve the solubility and dissolution of meloxicam, but in the present study, the solid dispersion technique was combined with the extrusion–spheronization technique to achieve immediate release pellets that have better dissolution, more excellent pellet properties, and a better industrial application.

5. Conclusion

The objective of this study was to overcome the poor solubility and slow dissolution of meloxicam by developing the pellets with its immediate release using solid dispersion technique based on extrusion–spheronization method. Formulation optimization led to a significant improvement of the aqueous solubility of the drugs (around 3-4 fold) by reducing the crystallinity and wettability of the drug in solid dispersions, with MSD3 (MF3) being the optimized solid dispersion. The resulting pellets had very good flow characteristics, a well-defined drug content, spherical morphology and a narrow particle size distribution, which suggested a well established and reproducible manufacturing process. The optimized formulations (MF3 and MF8) released more than 90% of the meloxicam within 30 minutes, thus being suitable for immediate release multiparticulate systems. These results suggest that solid dispersion combined with extrusion–spheronization is an effective and scalable method for improving the dissolution and solubility and hence the potential oral bioavailability of meloxicam, which is a suitable method for quick action pain medication.

The optimized formulation of the pellets could be further evaluated for its clinical and commercial potential in future studies through in vivo pharmacokinetic and bioavailability evaluation, ICH-guided stability studies, process scale-up and validation and comparative studies with marketed meloxicam formulations.

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