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NOVEL MICROWAVE-ASSISTED SOLID DISPERSION TECHNOLOGY ENHANCES PIROXICAM DISSOLUTION AND THERAPEUTIC EFFICACY: AN IN VITRO AND IN VIVO STUDY

Charit Kumar, Arun Nanda*

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ABSTRACT

Background: Piroxicam (PRX), a nonsteroidal anti-inflammatory drug, exhibits poor aqueous solubility, limiting its therapeutic efficacy. Enhancing solubility can directly improve bioavailability and therapeutic effectiveness. This study explores the development of a new solid dispersion (SD) system of PRX using polyvinylpyrrolidone (PVP K30) as a carrier by MW-assisted method. **Methods**: The involvement of microwave (MW) in the solvent evaporation method is a newer concept aimed at enhancing the solubility and in vivo bioavailability of PRX. Various ratios of PRX: PVPK30 (1:5, 1:7, 1:9, and 1:11 w/w) were evaluated using conventional and MW-assisted solvent evaporation methods and conducted in vitro dissolution studies. **Results**: The optimized MW-assisted formulation (1:7 w/w) exhibited 94.69±0.24% drug release in 15 minutes, showing a 5.37-fold increase compared to pure PRX (17.63%) and surpassing the marketed drug release (90.82±0.39%). Fourier Transform Infrared, Differential Scanning Calorimetry, Thermogravimetric analysis, Scanning Electron Microscopy, and powdered X-ray diffraction authenticated the OF. In vivo studies demonstrated significant enhancements ($p<0.0001$) compared to control. The anti-inflammatory activity showed increased paw oedema inhibition (44.4±0.4%) compared to control and pure PRX (35.37±0.3%). The analgesic activity of OF demonstrated improved pain response time (10.6±0.8 seconds) compared to control (4.2±0.5 seconds) and pure PRX (8.1±0.7 seconds). **Conclusion**: The SD developed via the MW-assisted drug formulation technique significantly enhances the solubility, bioavailability, and therapeutic efficacy of PRX, offering a potential strategy to improve clinical outcomes for similar drugs with solubility challenges.

INTRODUCTION

Numerous new compounds are discovered annually with the advent of combinatorial chemistry and efficient screening processes in drug discovery. However, over 40% of Active Pharmaceutical Ingredients (APIs) show poor aqueous solubility and insufficient *in vivo* oral bioavailability [1]. The amorphous form of drugs offers higher solubility and faster dissolution than crystalline forms, making solid dispersion (SD) systems an efficient approach for drug amorphization [2, 3]. Therefore, SD systems are reported as a highly efficient method for converting crystalline to amorphous forms of drugs. The solvent evaporation method, a conventional approach for developing

*Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak 124001, India

***For Correspondence:** **an_mdu@rediffmail.com**

SDs, involves dissolving the drug and polymer in a common solvent followed by solvent removal [4, 5]. However, this conventional method relies on conduction, convection, and radiation for heat transfer, which can lead to phase separation or drug recrystallization. To address this problem, a rapid solidification process was desirable to improve the physical stability of the formulation [5]. Microwave (MW) irradiation has gained remarkable attention as an innovative approach to developing polymer-based carrier systems for enhanced drug delivery performance. MW energy penetrates substances uniformly, causing molecular vibration through dielectric heating, which generates heat at any point within the sample. This process offers several advantages, such as improved drug dispersibility within carriers, limited drug recrystallization, enhanced physical stability of formulations, and superior molecular-level interactions between API and polymer matrix. Furthermore, when integrated with the solvent evaporation method, MW irradiation enables rapid solvent removal and effectively transforms crystalline drugs into amorphous solid dispersions (SDs) through uniform electromagnetic energy distribution [6-9].

PRX, a potent oxicam NSAID, treats osteoarthritis, acute pain, rheumatoid arthritis, and musculoskeletal disorders due to its analgesic properties. It falls under BCS class II, characterized by low solubility and high permeability, challenging its dissolution rate and solubility at physiological pH. Its aqueous solubility and half-life are 0.023 mg/mL and 55 hours, respectively [10]. This low solubility can lead to side effects like gastrointestinal bleeding or irritation in the gastric mucosa [11]. Therefore, PRX is considered an ideal candidate for formulation into SD to enhance its therapeutic efficacy and patient compliance. A suitable carrier must be chosen to design the formulation and enhance the stability and dissolution profile of PRX. Previous studies have demonstrated the role of water-soluble carriers like PVP K30 in SD formulation due to its efficiency in molecularly dispersing the drug within its polymer matrix and its ability to maintain the drug in amorphous form, thereby ensuring improved drug solubility and bioavailability [12-14]. Additionally, it offers various advantages, such as thermal stability, efficient drying, and drug-polymer compatibility, which are crucial for formulation development using the MW-assisted solvent evaporation method. It also can maintain the drug in amorphous form and ensure improved drug solubility and bioavailability [15, 16].

Therefore, this study addresses several critical gaps in current research, such as the limited exploration of MW-assisted SD for enhancing PRX bioavailability, the lack of comparative studies between conventional and MW-assisted methods for PRX formulation, and the absence of comprehensive in vivo evaluation of MW-assisted PRX solid dispersions. By combining MW-assisted solvent evaporation with PVP K30 as a carrier, this work presents a novel approach to enhance the therapeutic efficacy of PRX. The study provides an in vivo evaluation of both anti-inflammatory and analgesic activities of MW-assisted PRX solid dispersions, offering valuable insights for similar poorly soluble drugs.

MATERIALS AND METHODS

Materials

PRX was received as a gift sample from Ravenbhel Healthcare Pvt. Ltd., located in Bari-Brahmana-18133, Jammu. PVP K30 was purchased from Loba Chemie Pvt. Ltd. Solvents such as methanol (HPLC grade) and hydrochloric acid were acquired from Thermo Fisher Scientific India Pvt. Ltd. Carrageenan was sourced from Sigma-Aldrich, St. Louis, USA.

Preparation of PRX SDs

The PRX SDs were prepared by combining PRX with PVP K30 in various ratios (1:5, 1:7, 1:9, and 1:11 w/w) using conventional and novel MW-assisted solvent evaporation methods. The PRX: PVP K30 ratios were selected based on preliminary optimization studies and a literature review. The preformulation study showed that lower ratios (<1:5) showed insufficient drug solubilization and stabilization, while higher ratios (>1:11) did not provide significant additional benefits in terms of drug release and stability. This range was chosen to ensure adequate polymer concentration for complete drug amorphization and provide cost-effective formulation development. In the conventional method, drug-polymer mixtures were dissolved in methanol and stirred at 200 rpm with a magnetic stirrer to ensure homogeneous mixing. The solvent evaporated at 45°C to ensure complete removal [17]. In the MW-assisted method, each mixture was placed in a silica crucible and exposed to microwave radiation using a domestic microwave oven (LG Model MG-555F) at 900 W for 3 minutes with 5 seconds on/off cycles until complete solvent evaporation. The processing parameters were systematically optimized through experimental evaluation. First, power optimization studies demonstrated that 600 W resulted in insufficient heating and incomplete solvent removal, while 1200 W led to excessive heating and potential drug degradation. The

900 W power level provided optimal heating conditions for solvent evaporation. Secondly, the cycle duration was critical for process efficiency. Continuous heating resulted in localized overheating, 3-second cycles provided insufficient cooling intervals, and 7-second cycles unnecessarily extended the processing time. The 5-second on/off cycle was selected as it achieved optimal balance between the heating and cooling phases. Finally, total processing time was evaluated systematically. 2 minutes resulted in incomplete solvent removal, while 4 minutes showed no additional benefits compared to 3 minutes. The optimized parameters (900 W, 3 minutes, 5-second cycles) achieved complete solvent removal while maintaining drug stability and ensuring uniform heating throughout the sample.

The uniform heating of samples was ensured by processing one crucible at a time and placed above a polypropylene watch glass. For both methods, the resulting solid products were crushed using a glass mortar, passed through a 100-mesh sieve, and then collected on a 200-mesh sieve. This process ensures uniform particle size distribution of solid dispersion. The sieve material was then stored in a desiccator for future analysis at room temperature [18]. The physical mixtures (PM) were prepared in ratios of 1:5 and 1:11 w/w, based on representing the extreme ends of the polymer concentration range studied. They were gently mixed in a glass mortar and pestle for 5 minutes at ambient temperature and stored in a desiccator for 24 hours.

In-vitro dissolution study

The developed SD formulation was evaluated for *in vitro* dissolution study using USP apparatus type II to determine the drug release rate. The tests were performed for SDs prepared by MW-assisted (MSD1-MSD4) and conventional solvent evaporation method (SD1-SD4), pure PRX as well as physical mixtures (PM1, PM2) in the medium containing 900 mL of 0.1 N methanolic hydrochloric acid solution (10% methanol), paddle speed 100 rpm and maintained at 37±0.5°C (Lab India Instruments, Mumbai, India). Additionally, the in vitro dissolution study was performed under sink conditions as it is also a crucial parameter for evaluating the effect of sink index (SI) on the solubility profile of solid samples. To maintain a perfect sink condition, the volume of the dissolution medium should be 3 times the volume required to attain the saturated solution of the drug [19]. SI was calculated using the results obtained from the dissolution study at the clinical dose of PRX. A 5 mL supernatant was collected at specific intervals (5, 10, 15, 30, 45, and 60 min) and subjected to UV spectrophotometry at a wavelength of 334 nm [20]. After each withdrawal, an equal volume of methanolic hydrochloric acid was replaced. All experiments were conducted in triplicate [21]. The percentage cumulative drug release (%CDR) was plotted against the time interval.

An independent mathematical model proposed by Moore and Flanner was used to identify the best OF to calculate the similarity factor (f2) among the two best drug release formulations [22]. A value between 50 and 100 indicated that dissolution profiles were similar, while a value smaller than 50 suggested that the drug release profiles were dissimilar.

$$f2 = 50 \times log\left\{\left[1 + (1/n)\sum_{k=1}^{n} n(Rt - Tt)^2\right]^{-0.5} \times 100\right\}$$

Drug Release Kinetics

The drug release data was analyzed to compare the drug release kinetics of the OF using kinetic models including zero order, first order, Higuchi, and Korsmeyer Peppas. These kinetic models are used to evaluate the drug release mechanism from the polymer matrix. The best-fitting model was selected based on the highest coefficient of variation (R^2) values [23, 24].

Characterization of prepared SD Formulation

FT-IR Spectrophotometric Analysis

FT-IR spectroscopy was utilized to evaluate the bonding interaction between PRX and PVP K30 using OPUS software version 8.0 (Model: Alpha Laser Class 1, Bruker, Germany). The IR spectra of PRX, PVP K30, and OF were recorded in reflectance mode with a resolution of 4 cm^{-1}, averaging 32 scans for each spectrum. Before each measurement, a background spectrum of atmospheric air was obtained. A total of 4 scans were set, and the resulting spectrum was recorded in the range of 400-4000cm^{-1} [25]. For comparative evaluation and assessment of formulation homogeneity, optimized solid dispersion was characterized using PM containing drug and polymer in ratios identical to the optimized formulation (OF).

Thermal analysis (DSC and TGA)

DSC helps analyze the various exothermic and endothermic changes during SD formulation. Pure PRX, PVP K30, PM, and OF thermal analysis were evaluated using Pyris 6 software in the DSC (Perkin Elmer, USA). This instrument was equipped with

a hermetically sealed aluminium pan containing 8–10 mg of pure PRX, PM, PVP K30 and OF. To ensure complete removal of water or any residual solvent, the OF was subjected to a heating-cooling-heating cycle where OF was heated to 100°C, followed by cooling to 25°C and then re-heating back to 250°C at 10°C/min. Additionally, the glass transition temperature (Tg) of OF was also determined. Ultrapure nitrogen (50 mL/min flow) was continuously purged in the chamber throughout the experiment [20]. TGA was performed to determine the residual solvent content and thermal stability of API in the OF using TGA 5500 (TA Instruments – Waters LLC, USA). Approximately 16.283 mg of sample was placed in a platinum pan and heated from 30°C to 1000°C at a rate of 10°C/min under nitrogen atmosphere (flow rate: 35 mL/min). The weight loss (%) was plotted as a function of temperature to generate the thermogram.

SEM

The surface morphology of pure PRX, PVP K30, PM and OF was analyzed using SEM (JEOI-Japan Model JSM-IT500). The samples were secured onto double-sided carbon tapes and coated with a thin layer of gold to enhance conductivity and ensure proper visualization of the image under the electron beam [26].

PXRD Analysis

The powder XRD analysis was conducted using a Rigaku MiniFlex 600 tabletop X-ray diffractometer with Cu Kα radiation and an automatic divergence slit to evaluate the change in the crystalline nature of pure PRX during the preparation of SD. Sharp diffraction peaks indicate the crystalline nature of the material. Samples were prepared by spreading finely ground material onto a microscope cover glass mounted on a zero-background aluminum wafer to minimize background noise and enhance the quality of the diffraction pattern. This setup was then scanned at a rate of 1°/min over a range of 2θ angles [14].

In vivo evaluation of SD

Based on the maximum drug release profile and physiochemical characterization, SD prepared by the MW-assisted method in a ratio 1:7 (OF) was selected for further *in vivo* anti-inflammatory and analgesic studies to compare its therapeutic effect with pure PRX (API) and PM. For this purpose, 24 Wistar rats with an average weight (125 ± 50 g) and 20 albino mice weighing (30 ± 5 g) of mixed genders were obtained from Central Animal House at Maharshi Dayanand University, Rohtak (Reg. No. 1767 GO/RE/S/14/CPCSEA: Dated 18/07/2014 Renewed on Dated 06/10/2022). All procedures adhered to current standards for treating laboratory animals and ethical protocols. The animals were given free access to water and food; however, Wistar rats fasted for twelve hours, whereas albino mice for six hours but had unrestricted access to water before the experiments to prevent undue stress and adverse health effects, which can compromise their well-being and the validity of the research outcomes. The OF was evaluated for anti-inflammatory activity in rats through the carrageenan-induced paw oedema method and for analgesic activity in mice through the tail flick method. The results were then compared with the pure PRX.

Anti-inflammatory activity

The development of oedema in the right hind paw of the rat was induced by injecting 0.2 mL of carrageenan (1% (w/v)) into the planter side subcutaneously using saline. All the Wistar rats were split into four groups (n = 6) and their respective samples were administered by oral route. Group A (the control group) received normal saline (10 mL/kg), while Group B received API (PRX). Group C was treated with PM that was prepared in the same ratio as OF, while Group D received an OF, providing a dose based on animal body weight (4.11 mg/kg) in each group (n = 6). Before the carrageenan injection, a digital calliper was used to measure the diameter of the paw from its ventral to dorsal surfaces. Subsequent measurements were taken every half hour up to four times [27]. The mean oedema for six rats was calculated. The inhibition (%) of oedema was calculated with respect to control using the following formula:

$$Inhibition(\%)\ of\ edema = \frac{MEIC\ -\ MEIT}{MEIC}\ X\ 100$$

MEIC – Mean edema increase in the control group;
MEIT – Mean edema increase in the test group

Analgesic Activity

The tail flick method assessed the thermal responsiveness of twenty Swiss albino mice, randomly divided into four groups (Control, pure PRX, PM, OF) with five animals each. Pain sensitivity was evaluated by measuring the tail-flick reflex or pain reaction time, achieved by immersing the tail of mice approximately 1-2 cm into a water bath maintained at 50±1°C. The duration until the mouse flicked or pulled its tail from the water was recorded, with a maximum cut-off time of 15 seconds to prevent potential harm to the tail tissue. Before tail immersion, the mice were pretreated for 1 hour with their respective

treatments. Group A (Control) received a normal saline solution (10 mL/kg), Group B received a standard dose of pure PRX (4.11 mg/kg), Group C received PM (4.11 mg/kg), and Group D received the OF (4.11 mg/kg) via the oral route. Subsequently, they were placed in suitable restraints with their tails extended. The response time was determined by averaging the subsequent two readings after discarding the initial reading. The tail-flick reflex was measured at 0, 30, 60, and 90 minutes post-drug administration [27].

Statistical Analysis

GraphPad Prism Version 9.5.1 (San Diego, California, USA) was used for statistical analysis and graphical representation. The data were analyzed using a two-way ANOVA followed by Dunnett's multiple comparisons tests. The results were expressed as mean ± standard deviation, and a p-value less than 0.05 was considered statistically significant.

RESULTS

***In vitro* Dissolution study**

Dissolution represents a rate-limiting step during drug absorption, where sink conditions require that drug concentrations in the GIT do not approach saturation levels [28]. In this study, the dissolution characteristics of PRX were evaluated using a dissolution medium volume of 900 mL, with a measured saturated solubility (Cs) of 47 µg/mL. The SI is a critical parameter for assessing dissolution conditions, was calculated using the equation:

$$SI = \frac{C_s \times V}{Dose}$$

where V represents the volume of dissolution medium (900 mL). The calculated SI value of 4.23 exceeded the minimum threshold of 3, confirming adequate sink conditions for the dissolution testing. This indicates that the selected volume of dissolution medium effectively maintains sink conditions throughout the dissolution process, ensuring a reliable assessment of piroxicam dissolution behaviour [19].

Afterwards, the best OF was identified based on dissolution profiles of PRX-PVPK30 SDs compared with pure PRX and the marketed drug, as shown in **Figure 1**. The immediate drug release SD prepared by conventional solvent evaporation for SSD1, SSD2, SSD3, SSD4, PM1, and PM2 was 62.01%, 56.27%, 57.05%, 69.63%, 57.86%, and 36.10%, respectively, at 5 min, while compared with the pure PRX (7.12%). Considering more on this, the dissolution rate of SSD1 to SSD4, PM1, and PM2 at 15 min was 77.27%, 72.05%, 69.18%, 70.37%, 72.74%, and 53.58%, respectively, by comparing the drug release of pure PRX, which was 17.63%. Following 60 minutes, the drug release of pure PRX was 37.03%, while formulation SSD1, SSD2, SSD3, and SSD4 were 78.56%, 81.34%, 74.09%, and 71.42% respectively. Among all these four formulations, SD prepared by conventional solvent evaporation followed a better approach to drug release when compared with pure PRX. The dissolution profiles of all SD batches lay between 56.27% and 81.34%. Further, the enhanced dissolution in the case of PM compared to pure PRX can be attributed to higher wettability and dispersibility caused by the hydrophilic nature of PVP K30 (**Figure 1)**.

Considering these results, four new formulations were prepared using an MW-assisted solvent evaporation method with the same ratios previously described to enhance drug release. For this reason, the initial dissolution rate at 15 minutes for MSD1 to MSD4 was examined. The results indicated the solubility enhancement of 3.87 times (68.38%), 5.37 times (94.69%), 5.47 times (96.46%), and 5.42 times (95.70%) compared with pure PRX (**Figure 1**). The order of efficiencies of drug release from SD based on PRX was MSD3> MSD4> MSD2> PM1> SSD2> SSD1> SSD3> SSD4> MSD1> PM2> PRX. The results showed that MW-assisted SD formulations (1:7, 1:9, and 1:11) have better drug release than SDs prepared by conventional method, PM, and pure PRX, which also shows the role of polymers and methods of preparation in enhancing solubility. It signifies that the improved wettability and dissolution of PRX in OF may be due to the hydrophilic properties of PVPK30 and the molecular dispersibility of PRX in PVPK30 [16]. Moreover, the *in vitro* dissolution profile shows that MSD2, MSD3, and MSD4 were better than MSD1 at each sampling point throughout the 60 minutes when compared with each other. The MSD3 exhibited a maximum dissolution rate (97.81±0.4%). However, MSD2, MSD3, and MSD4 produce almost similar results in terms of drug release profile. So, to identify the best OF, among these formulations, the similarity indices (f2) factor was applied. The value within the range of 50-100 indicates a similar drug release profile. From the results obtained using the f2 factor formula, it was found that the value of f2 was 90 and 97 to MSD2, indicating similarity between the dissolution profile of formulation. Thus, MSD3 and MSD4 can be used interchangeably with MSD2. Based on this, MSD2 was selected by considering the formulation with the least polymer ratio. Later, the drug release rate of MSD2 was compared with the

marketed formulation of PRX (Pirox DT^{TM}, 20 mg, Cipla Ltd, India Batch No. B680661), which showed a release time of 90.82% at the 15-minute time point. At the same time, MSD2 exhibited a higher drug release rate, i.e., 94.69% (**Figure 1**).

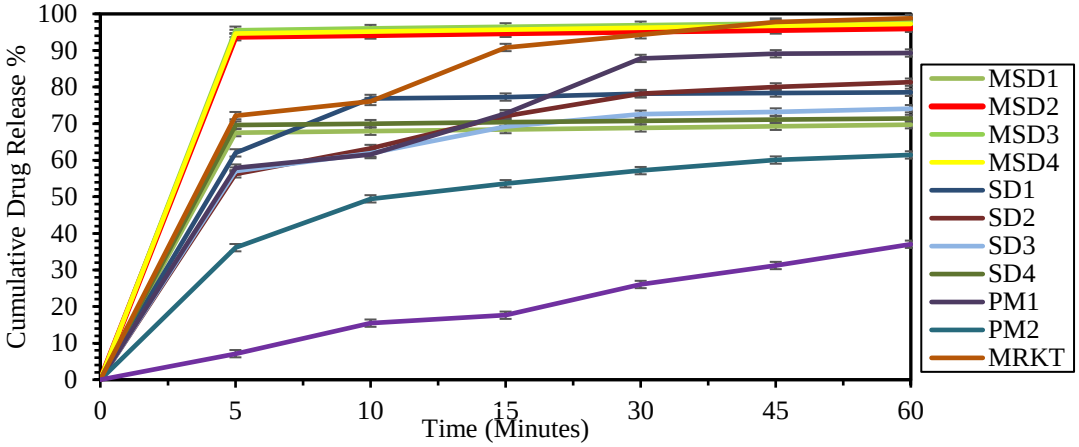

Figure 1: The Dissolution profile of pure piroxicam, marketed formulation, physical mixture, microwave-assisted solid dispersion (MSD), and Simple solid dispersion (SSD) in different ratios. All values are represented in mean ±SD (n=3)

So, MSD2 (1:7) was selected as OF and subjected to further physiochemical characterization (FTIR, SEM, DSC, and PXRD) and *in vivo* bioavailability studies (anti-inflammatory and analgesic activity) in comparison with pure PRX, PVP K30, and PM.

Drug Release Kinetics

Drug release kinetics were evaluated using four models: zero-order, first-order, Higuchi, and Korsmeyer-Peppas. The R^2 for each model was as follows: zero-order (0.9426), first-order (0.9297), Higuchi (0.9387), and Korsmeyer-Peppas (0.9614). The Korsmeyer-Peppas exhibited the highest linearity (R^2 = 0.9614), suggesting the best fit mathematical model for drug release kinetics of SD formulation. The calculated 'n' value was 0.75, corresponding to non-fickian transport, implying that the drug release mechanism involves a combination of matrix diffusion and erosion.

FTIR Spectroscopy

FTIR spectroscopy helps in identifying the intermolecular interaction and chemical bonds within the molecule by producing an infrared absorption spectrum. The IR spectra of PRX, PVP K30, PM, and OF were analyzed to identify the interaction between PRX and PVPK30, as given in **Figure 2**. The spectrum of PRX displayed prominent peaks at 3391 cm^{-1} and 3386 cm^{-1}, which signifies the presence of N-H or O-H stretching vibrations and was considered crucial for the H-bonding interaction between the pyrrolidinone moiety of PVP K30 and N-H group of PRX. PVPK30 exhibited prominent peaks at 1649 cm^{-1} for C=O stretching and 1283 cm^{-1} for C-N stretching [29]. The FTIR spectra of the PM showed spectral peaks of both PRX and PVP K30, indicating no intermolecular interaction between them. In contrast, the OF demonstrated notable spectral modifications, specifically a significant broadening and bathochromic shift of the PRX N-H stretching band to 3338 cm^{-1} and modification of the PVP K30 C=O stretching vibration at 1660 cm^{-1}, characterized by peak broadening and shifting. These spectral changes suggest the formation of hydrogen bonds between the N-H group of PRX and the C=O group of the pyrrolidone ring in PVP K30, indicating molecular-level mixing of the components. The observed spectral modifications in OF, while confirming intermolecular hydrogen bonding, maintained the fundamental structural integrity of both components, supporting the physical stability of the formulation [30].

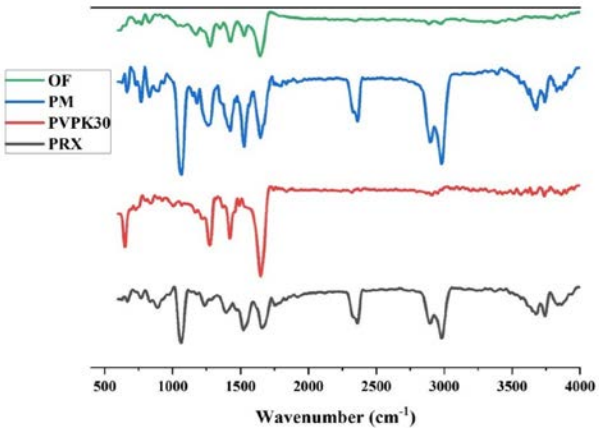

Figure 2: FTIR Spectra of Piroxicam, PVPK30, PM and Optimised formulation (OF, MSD2)

Thermal analysis (DSC and TGA)

The OF (MSD2) DSC thermogram analysis was compared to PRX, PVPK30, and PM to identify PRX crystallinity and its miscibility in the polymer **(Figure 3a)**. The thermal analysis of PRX exhibited a characteristic sharp endothermic peak at 201.4°C, corresponding to its melting point, indicating its crystalline nature. The DSC thermogram of PVPK30 demonstrated a broad endothermic peak between 82.57°C to 116.87°C, attributed to water loss due to the hygroscopic nature of the polymer. Additionally, the Tg observed at 160°C confirmed the amorphous nature of PVP K30. The PM thermogram revealed a broadened endothermic range with reduced peak intensity at 198.85°C, indicating partial drug-polymer interaction while maintaining drug crystallinity. In the OF thermogram, the absence of the characteristic endothermic peak of PRX at 201.4°C indicated drug-polymer miscibility. The Tg of OF was determined after the first heating cycle up to 100°C, with 82°C obtained from the second heating cycle, as shown in **Figure 3a**. A single Tg in OF and the absence of PRX recrystallization exotherm demonstrated uniform drug distribution and amorphization of PRX within the polymer matrix. TGA was conducted to quantify the residual volatile solvent content and evaluate the thermal degradation profile of the OF at elevated temperatures. The TGA thermogram (**Figure 3b**) exhibited a multi-stage decomposition profile. The initial weight loss of approximately 0.24% observed up to 65°C corresponded to the volatilization of residual methanol (boiling point: 64.7°C). According to ICH Q3C guidelines, methanol is classified as a Class II solvent with potential neurotoxicity, necessitating its limitation to 3000 ppm in pharmaceutical formulations. The observed methanol content in OF was within this specified regulatory limit.

The thermal decomposition and drug-polymer miscibility were further evaluated as a function of temperature. A weight loss of 2.73% was observed up to 100°C, attributable to the elimination of absorbed moisture. The minimal weight loss during these initial stages confirmed efficient solvent removal during the microwave-assisted preparation process. The formulation exhibited good thermal stability, evidenced by gradual weight loss up to 250°C, which is crucial for solid dispersion formulations. A significant weight loss observed in the temperature range of 250-500°C indicated the thermal decomposition of the drug-polymer system. Analysis of the residual mass above 500°C confirmed complete decomposition of OF.

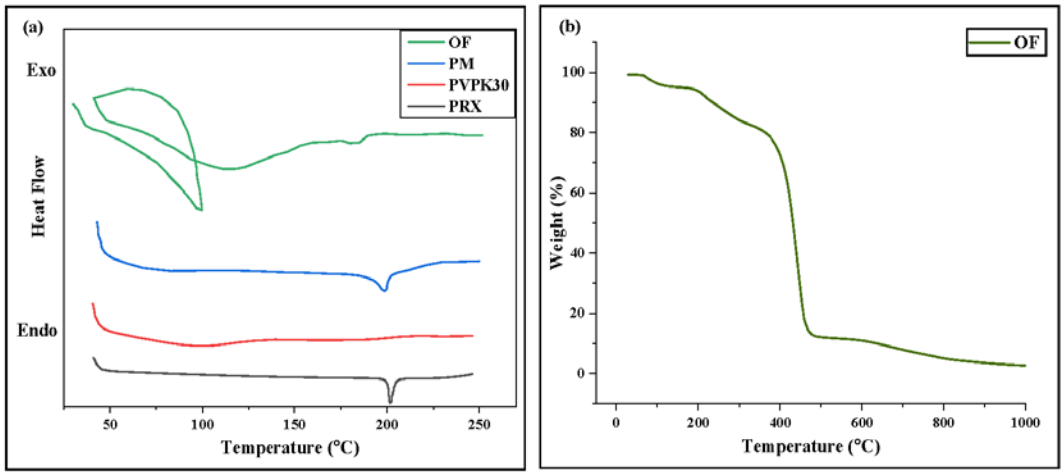

Figure 3: (a) DSC curves of PRX, PVPK30, PM & Optimised formulation (MSD2) (b) TGA of Optimised formulation (MSD2)

SEM analysis

The surface morphologies of PRX, PVP K30, PM, and OF were evaluated using Scanning Electron Microscopy (SEM) at different magnifications. The SEM images revealed that PRX appeared as cubic-shaped particles of various sizes (**Figure 4a**). In contrast, PVP K30 exhibited a smooth and round surface (**Figure 4b**). The SEM analysis of the PM showed distinct PRX particles alongside PVP K30 particles, with the latter displaying irregular shapes (**Figure 4c**). However, the OF showed no visible cubic particles of PRX, and the smooth surface of PVP K30 was predominant (**Figure 4d**). This altered morphology may be due to enhanced water retention, suggesting adequate mixing of PRX with the PVP K30 carrier, promoting its transition to an amorphous state and significantly enhancing the dissolution rate of PRX.

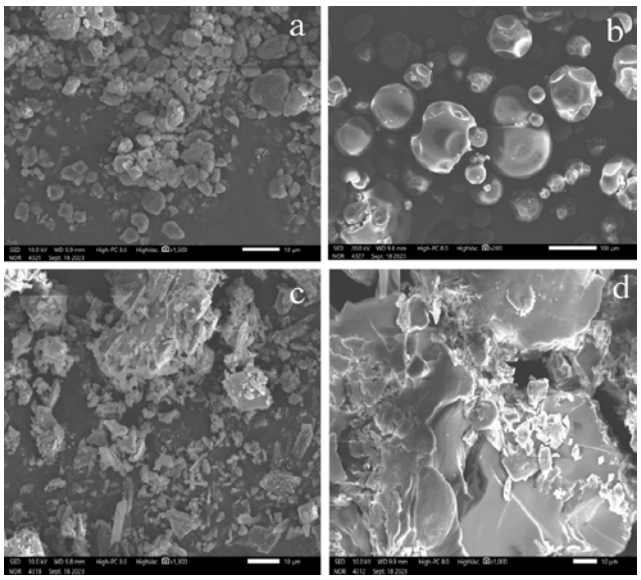

Figure 4: The SEM images of (a) Piroxicam; (b) PVPK30; (c) Physical Mixture; (d) Optimised formulation.

Powder XRD study

The degree of crystallinity was assessed using powder XRD technology. The diffraction patterns of PRX, PVP K30, PM, and OF are presented in **Figure 5**. The powder XRD analysis of PRX demonstrated firm diffraction peaks at 2θ angles of 15.2°, 17.5°, 22.9°, and 27.3°, with secondary peaks at 19.8°, 23.6°, and 28.4°, confirming its crystalline structure. In contrast, PVP K30 exhibited no intense peaks, confirming its amorphous nature. The diffraction peaks of the PM displayed a combination of PVP K30 and PRX patterns with a reduced intensity of the PRX peaks, indicating no change in the crystalline nature of the drug. Additionally, the OF exhibited diffused and halo diffraction patterns of PRX, indicating the transition of PRX from crystalline to amorphous form. Further, no new peaks were observed in OF, suggesting the absence of any interaction between PRX and PVPK 30. As evidenced by the FTIR analysis, DSC thermograms, SEM analysis, and PXRD patterns, the crystalline structure of PRX in the OF was successfully transformed into an amorphous state due to the inclusion of the PVP K30 carrier.

***In vivo* evaluation of SD**

In vivo anti-inflammatory activity

The study used a carrageenan-induced paw oedema animal experiment to investigate how well OF worked as an anti-inflammatory agent compared to PRX (API), Physical Mixture (PM), and a control group, as shown in **Figure 6a**. It was observed with the findings that after administering the OF, there was a gradual decrease in paw volume from 30 min to 120 min with percent inhibition of 13.4%, 31%, 38.4%, and 44.4%, respectively, which was higher than API and PM. Moreover, it was also found from statistical analysis using a two-way ANOVA with Dunnett's multiple comparisons test revealed that OF showed significant results ($p<0.0001$) and reduced inflammation with time increased compared with the control group.

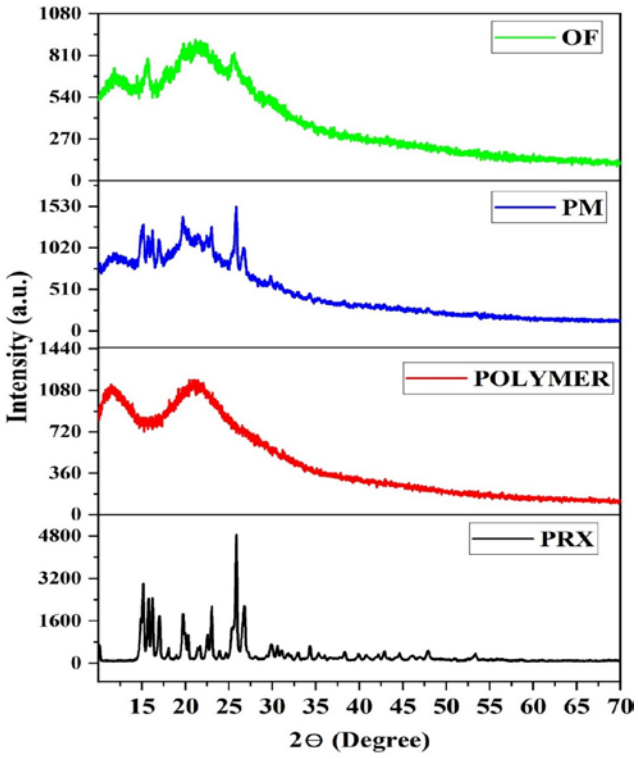

Figure 5: The Powder X-ray diffraction patterns of pure PRX, PVPK30, PM and Optimised formulation (OF, MSD2)

In vivo analgesic activity

To evaluate the OF's analgesic activity, the tail immersion method was used in albino mice compared with the control, pure PRX (API), and PM. From the results obtained, the reaction time of OF efficiently increased as time passed when compared with control, API, and PM. As the study revealed, the OF showed a continuous increment of response from 30 min to 120 min, which is higher than that produced by PRX and PM. The lapse time of OF was not observed during the study, while PM and API were found to be 6.6 ± 0.8 s and 9.6 ± 0.8 s, respectively, after 90 min. Moreover, it was also observed from statistical analysis using a two-way ANOVA followed by Dunnett's multiple comparisons test that OF showed significant results ($p<0.0001$) when compared with control and the increase in latency of pain reaction time, as given in **Figure 6b**.

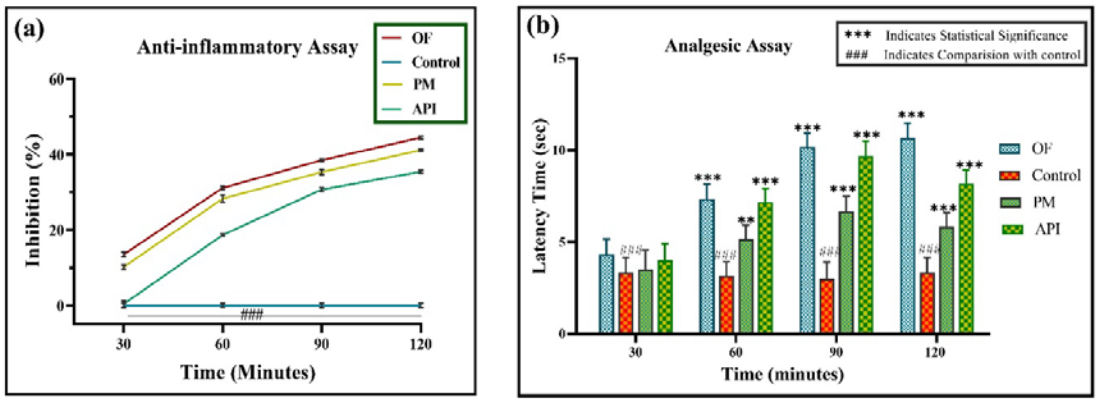

Figure 6: (a) Anti-inflammatory activity of optimized formulation (OF) with pure drug, Piroxicam (API) and Physical Mixture (PM) (b) Maximum Possible Analgesic activity of Optimised Formulation (OF) with pure drug, Piroxicam (API) and Physical Mixture by tail immersion method in mice. The data was represented as mean±SD. ***p<0.0001 and **p<0.001 refer to statistical significance from the control and ### indicates comparison with control

DISCUSSION

Low aqueous solubility and insufficient *in vivo* oral bioavailability are critical parameters in drug formulation, considerably influencing the therapeutic efficacy of drugs [5]. Addressing these challenges is essential for the successful development of effective pharmaceutical products. PRX, a potent NSAID, is clinically indicated for musculoskeletal disorders, rheumatoid arthritis and osteoarthritis due to its analgesic effects. However, as a BCS class II drug with low solubility and high permeability, PRX necessitates a high therapeutic dose at physiological pH. This regimen often leads to gastric mucosal irritation and an increased risk of gastrointestinal bleeding.

Previous research demonstrated that the SD approach effectively enhances the drug dissolution profiles. Solvent evaporation is a commonly employed technique for SD formulation. This method facilitates molecular-level drug dispersion within the polymer matrix, thereby promoting an amorphous state of the drug, associated with improved drug stability and solubility [31, 32]. However, this conventional method has limitations. A more rapid solidification process is needed to optimize drug delivery systems further. MW irradiation is a promising synergistic approach capable of accelerating solvent removal and potentially enhancing drug product attributes [7].

Extensive research has demonstrated the role of PVPK30 in enhancing the wettability, dispersibility and solubility of hydrophobic drugs through the formation of amorphous SD. Supporting this approach, Tantishaiyakul et al. (1996) reported that the SD of PRX with PVP K30 (1:4) showed a higher drug release than pure PRX, illustrating the potential of such a combination to improve therapeutic outcomes [33]. Madan et al. (2018) investigated both MW-assisted and conventional solvent evaporation methods to develop the SD of apremilast, finding that the developed SD by the MW-assisted method has a higher dissolution rate than the marketed formulation [9]. Therefore, in the present work, a novel MW-assisted solvent evaporation method was employed to develop SDs of PRX, thereby improving the solubility and in vivo bioavailability. Our research also focused on comparing the dissolution study of SDs prepared by conventional and MW-assisted methods using different carrier combinations that were not previously exploited.

Building upon these findings, our subsequent experiments focused on optimizing the PRX to PVP K30 ratios to maximize drug release. The selected ratios of PRX and PVP K30 (1:5, 1:7, 1:9, 1:11 w/w) were used to evaluate the SI and *in vitro* drug release of various formulations. The dissolution studies were conducted under sink conditions with a calculated SI of 4.23. this ensures that the dissolution rate was not limited by the saturation solubility of the drug in the dissolution medium, allowing for a more accurate comparison of the dissolution profiles between different formulations [19]. Moreover, the release profile of SD prepared by the conventional solvent evaporation method was in the range of 57.455% to 74.65%, while the release rate of MW-assisted SD was observed to be

considerably higher (67.55% to 97.81%) compared to the release from pure PRX (7.12% to 37.03%). The release rates of MSD2, MSD3, and MSD4 exhibited almost similar dissolution profiles. Therefore, based on similarity factor (f2) and least polymer ratio, MSD2 (1:7 w/w) was selected as the OF (**Figure 1)**. The optimized formulation (OF) exhibited a 94.69% drug release within 15 minutes, surpassing the 90.82% release rate of the marketed product. This result indicates a faster release profile for PRX from the PVP K30-based solid dispersion (**Figure 1**). The findings of our *in vitro* dissolution study highlight the synergistic effect of combining MW-assisted with solvent evaporation methods in enhancing PRX solubility and dissolution rates. The application of MW energy can ensure complete solvent evaporation and conversion of crystalline PRX to amorphous form. Moreover, the solubility enhancement of SD was also influenced by increased wettability, dispersibility, and particle size reduction [6].

Based on the aforementioned *in vitro* research, the OF was further investigated for physiochemical characterization with FTIR, DSC, TGA, SEM and PXRD. The FT-IR spectrum of MSD2 revealed a disappearance of prominent PRX peaks at 3391 cm^{-1} and 3386 cm^{-1}, along with a shift of other peaks towards lower wavenumbers (**Figure 2**). These observations suggest H-bonding formation between PRX and PVP K30, which can contribute to the physical stability of the formulation. The study revealed that H-bond formation has played a crucial role in drug-polymer interaction as the polymer can potentially reduce the recrystallization of drugs by promoting nucleation activation energy. Additionally, the spectrum showed no significant changes in other characteristic peaks of the drug, indicating good compatibility and minimal chemical interaction between them. This implies that the drug maintains its stability within the SD. Moreover, the finding was similar to the previous literature study where the formation of PRX-PVP K30 was explored using spectral techniques. The DSC thermogram of the OF (MSD2) showed no peak at 201.4°C, the expected melting point of PRX. Instead, showing Tg at 82°C found on second heating cycle. These thermal characterizations revealed two significant findings include a single Tg in the OF and the absence of PRX recrystallization exotherm. These observations conclusively demonstrate the achievement of uniform drug distribution and complete PRX amorphization within the polymer matrix system (**Figure 3a**). This suggests that the crystalline PRX has converted to an amorphous form or is molecularly dispersed within the polymer matrix. The TGA analysis provided crucial insights into the moisture content and residual solvent levels in the optimized formulation (**Figure 3b**). The subsequent weight loss of 0.23% around the boiling point of methanol (64.7°C) confirms minimal residual solvent content, well below the ICH Q3C guidelines limit for Class 2 solvents (<3000 ppm for methanol). This low residual solvent content is attributed to the efficient solvent removal capability of the microwave-assisted preparation method. The initial weight loss of 2.73% below 100°C indicates relatively low moisture content, which is essential for maintaining the physical stability of amorphous solid dispersions. Likewise, the SEM image of OF revealed a new (agglomerated) morphology distinct from the crystalline structure of pure PRX. This suggests good PRX and PVP K30 miscibility, with no evidence of phase separation (**Figure 4**). The observed morphology is likely to improve water retention and consequently, the dissolution rate of the drug. Consistent with the SEM results, the XRD spectrum of OF lacked the sharp peaks typically observed for crystalline PRX (**Figure 5**). This absence of peaks in OF indicates an amorphous state of PRX, characteristic of a well-dispersed drug in the polymeric matrix. Consequently, the outcomes supported by the earlier research analysis from FTIR, DSC, SEM and PXRD indicated that adding PVP K30 as a carrier successfully converted the crystalline PRX into an amorphous state within OF [34]. The findings demonstrated that the use of MW energy facilitates the rapid evaporation of solvent, thereby converting drugs into amorphous forms, which are more soluble than their crystalline counterparts.

Furthermore, to investigate the *in vivo* bioavailability of OF, Wistar rats and albino mice were used as animal models to evaluate anti-inflammatory and analgesic activity, respectively. It was suggested that mice and rats can have varying sensitivities to pain and inflammation. For instance, the tail flick method for analgesic activity is more sensitive in mice than in rats. Additionally, there was an established protocol for the carrageenan-induced paw oedema test, a widely used method for anti-inflammatory activity, which is well-defined for rats. Therefore, the anti-inflammatory activity of OF was explored using the carrageenan-induced paw oedema test [27]. The research indicated a progressive reduction in paw volume following the administration of OF observed from 30 min to 120 min, with percent inhibition of 13.4%, 31%, 38.4% and 44.4%, respectively, surpassing those of PRX and PM. The percentage

inhibition of OF showed significantly greater ($p<0.0001$) anti-inflammatory activity when compared to control and pure PRX (**Figure 6a**).

Conversely, for evaluating the analgesic activity of OF, the tail flick method was explored in albino mice, and the results were compared with those of the control, PRX, and PM. The results showed that the pain reaction time of OF significantly increased as time passed compared with control, PRX, and PM. The study also revealed that OF showed a continuous increment of response from 30 min to 120 min, higher than that produced by PRX and PM. The lapse time of OF was not observed during the study, while PM and PRX were found to be 6.6 ± 0.8 s and 9.6 ± 0.8 s, respectively, after 90 (**Figure 6b**) compared with the control group, all the results showed significant results ($p<0.0001$). The significantly increased analgesic activity of OF was due to the enhanced solubility of PRX caused by PVP K30, resulting in higher absorption of PRX in the GIT upon oral administration. Several studies have reported that using the MW-assisted method could increase the penetration efficiency of any substance, which may be the reason for the increased molecular dispersity of PRX in OF through MW and its higher analgesic effect.

The MW-assisted method demonstrates significant advantages over conventional techniques through its unique process-specific characteristics and superior outcomes. The volumetric heating mechanism of MW enables rapid and uniform heating at the molecular level, facilitating direct molecular activation and enhanced drug-polymer mixing. This efficient energy transfer results in accelerated solvent removal, reduced energy consumption, and better process control, evidenced by minimal residual solvent content (0.23%) and prevention of phase separation. The superiority is demonstrated in dissolution profiles, where MW-assisted solid dispersions achieved 67.55% to 97.81% release rates compared to 57.455% to 74.65% for conventional methods, with the optimized formulation (MSD2) exhibiting 94.69% drug release within 15 minutes. The uniform drug distribution and complete amorphization were confirmed through comprehensive analytical characterization (FTIR, DSC, TGA, SEM, PXRD). These process advantages translated into enhanced therapeutic outcomes demonstrated through improved in vivo anti-inflammatory and analgesic activities, better bioavailability, and consistent product quality. These findings collectively establish microwave-assisted solid dispersion as a more efficient and effective approach for pharmaceutical formulation development.

Hence, this study highlights the effectiveness of the MW-assisted method for PRX delivery, evidenced by enhanced in vitro dissolution profiles and significantly improved in vivo bioavailability compared to both control and pure PRX. The formulation optimization process investigated critical parameters, including polymer selection, carrier ratio optimization, drug amorphization, and wettability and dispersibility characteristics enhancement. The therapeutic efficacy of the OF was validated through in vivo analgesic and anti-inflammatory studies, establishing the microwave-assisted solid dispersion system as an effective delivery platform for PRX.

CONCLUSION

The developed SD of PRX successfully amorphized the crystalline PRX through the MW-assisted solvent evaporation method. The *in vitro* drug release profile demonstrated that the ratio PRX: PVP K30 (1:7 w/w) had a better drug release profile than pure PRX and the marketed formulation. Furthermore, the formulation was validated using various techniques, including FTIR, DSC, TGA, SEM, and PXRD. Additionally, an *in vivo* assessment of anti-inflammatory and analgesic activity showed significantly superior therapeutic efficacy of PRX in the SD compared to pure PRX. Based on the findings, it was determined that the SD prepared by the novel MW-assisted SD technology offers a promising approach for enhancing PRX systematic delivery in the long term, as it could avoid the associated side effects of pure PRX. While this study establishes a foundation for improving the bioavailability of poorly water-soluble drugs, several limitations warrant further investigation. Future research should address process optimization for industrial-scale production, including comprehensive scale-up feasibility studies. The findings from this research may apply to PRX and other Biopharmaceutics Classification System (BCS) Class II compounds.

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Human and animal rights CPCSEA guidelines (New Delhi) were strictly followed for animal experimental procedures. All reported methods aligned with these established standards.

FINANCIAL ASSISTANCE
NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
Charit Kumar contributed to the original draft's conceptualization, review, methodology, investigation, and writing. Arun Nanda contributed to methodology, writing, review and editing, and supervision resources. All authors have read and agreed to the published version of the manuscript.

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