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Formulation and *in vitro* assessment of indomethacin submitted to solid dispersion for the purpose of enhancing its dissolution

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ABSTRACT

Indomethacin (IND), a nonsteroidal anti-inflammatory drug, is widely employed in the pharmaceutical sector for its analgesic, anti-inflammatory, and antipyretic properties. However, IND exhibits poor dissolution in gastrointestinal tract fluids, leading to limited bioavailability. Solid dispersion (SD) is a well-established and widely adopted strategy for enhancing drug dissolution. This study aimed to formulate and evaluate, *in vitro*, the SD technique for improving IND dissolution. IND-based SDs were prepared using the solvent evaporation method and three distinct polymers: Soluplus®, polyvinylpyrrolidone K30 (PVP K30), and hydroxypropyl methylcellulose E5 (HPMC E5). The resulting SDs were assessed for *in vitro* drug release and subjected to solid-state characterization. Among the formulations, the Soluplus®-based SD demonstrated superior performance, achieving 100% drug release within 2 h, compared to 74.75% and 53.00% release from PVP K30 and HPMC E5-based SDs, respectively. Solid-state analyses confirmed complete amorphization of IND within the SD matrix, with no evidence of physicochemical incompatibility. In conclusion, the Soluplus®-based SD prepared *via* solvent evaporation represents an effective approach for enhancing the dissolution profile of IND.

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1. Introduction

Poor aqueous solubility is widely recognized as a major challenge for formulation scientists during the early stages of modern drug development[1]. This limitation is directly associated with reduced oral bioavailability and suboptimal therapeutic outcomes[1].

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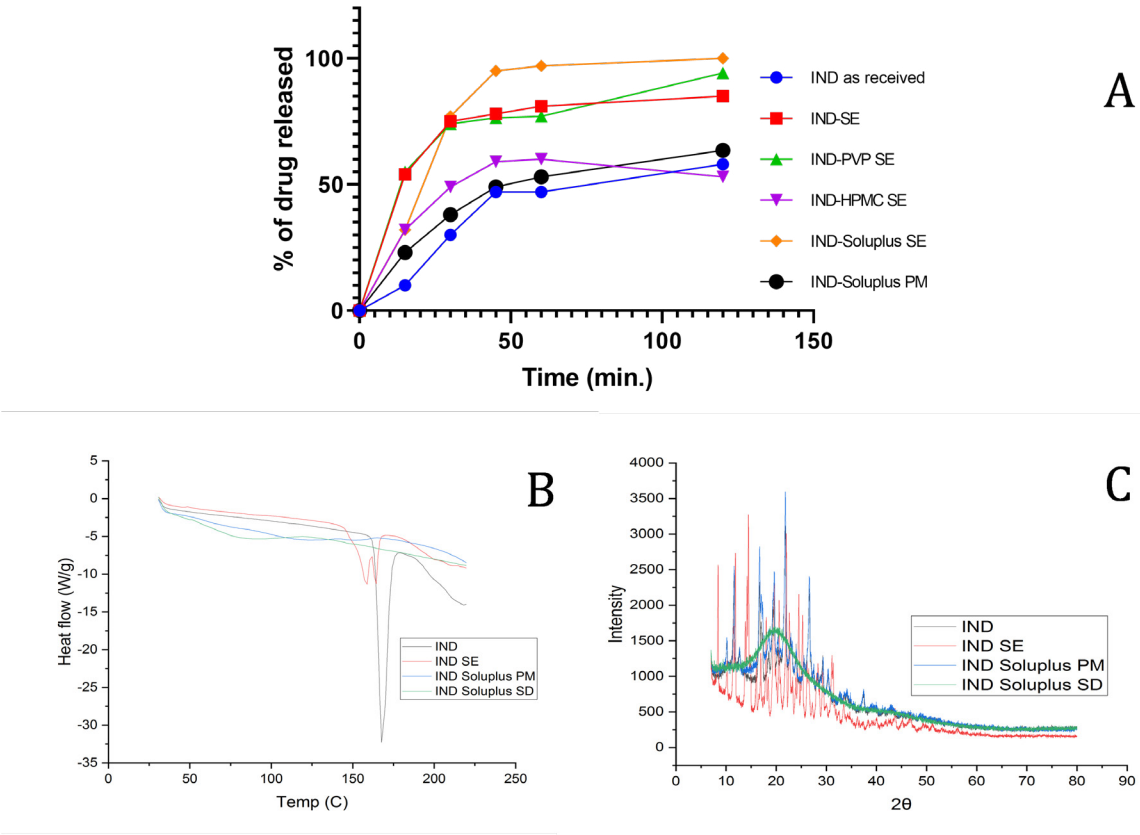

Figure 1. *In vitro characterization of indomethacin (IND) solid dispersion (SD) formulations: dissolution profiling (A); differential scanning calorimetry (B); powder X-ray diffraction (C).*

Solid dispersion (SD) is a widely adopted technique for enhancing drug dissolution[2]. SDs are formed by dispersing hydrophobic active pharmaceutical ingredients within a hydrophilic polymeric matrix in the solid state[3]. The mechanism underlying dissolution enhancement in SD formulations involves several key factors, including improved wettability, reduced particle size, prevention of aggregation, and conversion of the drug from a crystalline to an amorphous phase[2,4].

Indomethacin (IND), a nonsteroidal anti-inflammatory drug, is extensively used for its analgesic, anti-inflammatory, and antipyretic properties[5]. IND is a weakly acidic compound with a pKa ranging from 3.0 to 4.5. Upon oral administration, IND exhibits poor dissolution in gastrointestinal tract fluids, resulting in limited bioavailability. It is classified under the Biopharmaceutics Classification System[5]. The present study aims to evaluate the effectiveness of the SD technique in enhancing the dissolution of IND.

2. Methodology

IND and hydroxypropyl methylcellulose E6 (HPMC E6) were obtained from Macklin Co., Ltd. (China). Polyvinylpyrrolidone K30 (PVP K30) was purchased from HiMedia Laboratories (India) and Soluplus® from the BASF Pharmaceutical Industries (Germany).

IND-based SDs were prepared using the solvent evaporation method. A quantity of IND (25 mg) was mixed with 50 mg of each carrier polymer (PVP K30, HPMC E6, and Soluplus®) in a 1:2 ratio in a porcelain dish. Ethanol was used to dissolve the components, and the solvent was subsequently removed under reduced pressure for 90 min at 55°C using a rotary vacu-

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um evaporator. The resulting SDs were pulverized in a mortar, passed through a sieve, dried in an oven for 2 h, and stored in a desiccator containing silica gel in order to minimize moisture prior to characterization.

Samples including unprocessed IND, IND solvent evaporate (SE), IND SDs, and a physical mixture (PM) of IND with Soluplus® were subjected to *in vitro* dissolution testing (Figure 1.A). These experiments were conducted in parallel using a United States Pharmacopeia Type I dissolution apparatus. Each sample, equivalent to 25 mg of IND, was dissolved in 900 mL of phosphate buffer (pH 6.8) maintained at 37°C ± 0.5°C, with a paddle rotation speed of 75 revolutions per min. At predetermined intervals, 5-mL aliquots were withdrawn and replaced with fresh buffer. The filtered samples were analysed spectrophotometrically at 319.5 nm. All measurements were performed in triplicate[2].

Differential scanning calorimetry (DSC) was employed in order to determine the melting points of IND, IND SE, the PM, and the SD of IND with Soluplus® (Figure 1.B). Analyses were conducted using a Shimadzu DSC-60 (Japan). Approximately 3 mg of each sample was accurately weighed and sealed in aluminum pans (5–6-mg capacity). Thermal scans were performed from 35°C to 280°C at a heating rate of 10°C/min[6].

Powder X-ray diffraction (PXRD) analysis was conducted on IND, IND SE, the PM, and the SD of IND with Soluplus® using a diffractometer manufactured by Aires (Netherlands). Operational parameters included a current of 30 mA, voltage of 40 kV, scan rate of 1°/min, and a 2θ range of 10° to 90°[6].

Statistical analysis was performed using GraphPad Prism version 9. Data were expressed as mean ± standard deviation (SD). Statistical significance was assessed using one-way analysis of variance (ANOVA), followed by Tukey's or Dunnett's multiple comparison *post hoc* tests. A p-value <0.05 was considered statistically significant.

3. Results and Discussion

The dissolution profile of pure IND revealed limited solubility, with only 58% of the drug released after 2 h under the specified conditions. This poor performance is attributed to IND's hydrophobic nature, which causes it to float on the medium surface and hinder dissolution. In contrast, IND SE and SDs prepared with PVP K30 and Soluplus® exhibited significantly improved drug release compared to the unprocessed form (Figure 1.A). Enhanced solubility in SD systems is primarily due to particle size reduction and increased surface area[2]. The hydrophilic environment further promotes drug wettability and solubility[2,4]. Among the tested formulations, the Soluplus®-based SD demonstrated superior dissolution performance, supporting its selection for further evaluation. Previous studies have highlighted the efficacy of Soluplus® in improving the dissolution of poorly soluble drugs when used as a carrier in SD systems[7]. Soluplus® is an amorphous, amphiphilic copolymer composed of polyvinyl caprolactam, polyvinyl acetate, and polyethylene glycol. It forms micelles and serves as a polymeric matrix that enhances dissolution rates[8]. Additionally, Soluplus® prevents drug precipitation or recrystallization during dissolution, improves wettability, and stabilizes SDs during storage by forming hydrogen bonds with the drug[8]. Conversely, the SD of IND with HPMC E6 resulted in lower drug release after 2 h compared to the pure drug. Only the Soluplus®-based SD achieved significantly higher IND release than its SE counterpart (Figure 1.A).

The DSC analysis of pure IND revealed a sharp endothermic peak at 169.9°C, corresponding to its melting point (Figure 1.B). This observation aligns with previously published data and confirms the crystalline nature and purity of the drug[9]. The thermogram of the PM showed no distinct peak, likely due to dilution effects from mortar mixing. In the selected SD formulation, the absence of the endothermic peak indicates complete amorphization of IND (Figure 1.B)[3].

The PXRD analysis of pure IND displayed multiple sharp Bragg peaks at specific 2θ angles, confirming its crystalline structure (Figure 1.C). In contrast, the binary SD system of IND with Soluplus® exhibited a halo pattern with no sharp peaks, indicating a transition to the amorphous state (Figure 1.C)[10]. This transformation supports the successful formation of SD[3].

4. Conclusion

The Soluplus®-based SD of IND, prepared *via* the solvent evaporation method, proved to be an effective

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strategy for enhancing the drug's dissolution profile.

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Conflicts of interest

None exist.

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