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Dissolution enhancement of poorly soluble drug using solid dispersion technique

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Abstract

A paradox sits at the heart of modern drug development: roughly 40% of marketed drugs and nearly 70% of pipeline candidates fall into BCS Class II, meaning they possess adequate membrane permeability but dissolve too slowly in gastrointestinal fluids to achieve predictable oral absorption. Solid dispersion technology molecularly dispersing a drug within a hydrophilic polymer matrix has long been recognised as one of the most effective strategies for overcoming this limitation. This research prepared solid dispersions of aceclofenac (a poorly soluble anti-inflammatory agent) with PVP K30 and PEG 6000 at drug-to-carrier ratios of 1:1 and 1:3 by solvent evaporation, and a ternary dispersion (drug:PVP:PEG, 1:1:1). Formulations were characterised by DSC, FT-IR, XRD, and SEM. Dissolution in phosphate buffer (pH 6.8) was tested using USP Apparatus II. The ternary solid dispersion achieved 96.2% drug release within 60 min a 4.3-fold improvement over pure aceclofenac (22.4%). DSC and XRD confirmed complete amorphous conversion in the ternary system. These findings demonstrate that combining two complementary carriers yields synergistic dissolution enhancement that exceeds what either carrier achieves alone.

Keywords: Solid dispersion, dissolution enhancement, aceclofenac, PVP K30, PEG 6000, amorphous, solvent evaporation, BCS Class II

Introduction

Here is the paradox: medicinal chemists design increasingly potent molecules with exquisite target selectivity, yet many of those molecules sit in the BCS Class II category highly permeable through intestinal membranes but so poorly soluble in water that they never reach the bloodstream in adequate amounts ^[1]. Aceclofenac, a phenylacetic acid derivative widely prescribed for osteoarthritis and rheumatoid arthritis pain, exemplifies this problem: its aqueous solubility is only 57.8 µg/mL at 37 °C, making dissolution the rate-limiting step for oral absorption ^[2].

Solid dispersions were first described by Sekiguchi and Obi in 1961, and the concept remains one of the most commercially successful solubility-enhancement platforms, with products like Sporanox (itraconazole in HPMC), Kaletra (lopinavir/ritonavir in PVP-VA), and Zelboraf (vemurafenib in HPMC-AS) on the market ^[3]. The enhancement mechanism involves multiple factors: conversion of the crystalline drug to an amorphous high-energy state, molecular-level mixing that maximises drug-carrier contact, improved wettability from the hydrophilic carrier, and particle-size reduction during processing ^[4].

PVP K30 is a widely used carrier because of its high glass-transition temperature (T_g ~174 °C), strong hydrogen-bond donor/acceptor capacity, and ability to inhibit drug recrystallisation ^[5]. PEG 6000 offers complementary properties: it melts at ~60 °C and acts as a solubiliser rather than a glass-forming stabiliser ^[6]. Combining the two in a ternary dispersion may capture both stabilisation and solubilisation benefits simultaneously, but systematic comparisons at matched drug-to-carrier ratios are uncommon in the aceclofenac literature.

This research aimed to prepare binary and ternary solid dispersions of aceclofenac, characterise their solid-state properties, compare dissolution profiles, and identify the mechanism responsible for the observed enhancement.

Material and Methods

Material

All experimental work was conducted between March and November 2024 at the Department of Pharmacy and Pharmaceutical Sciences, Sardar Vallabhbhai Institute of Science, Surat, Gujarat, India. Aceclofenac (BP grade, purity $\geq 99.5\%$) was received as a gift sample from Ipca Laboratories (Mumbai, India). PVP K30 ($M_w \sim 40,000$) and PEG 6000 ($M_w \sim 6,000$) were purchased from Loba Chemie (Mumbai). Methanol (AR grade) and phosphate buffer salts were from Merck India (Mumbai). Dissolution medium (phosphate buffer pH 6.8) was prepared according to USP specifications [7].

Methods

Binary solid dispersions were prepared by dissolving aceclofenac and carrier (PVP K30 or PEG 6000) at drug:carrier weight ratios of 1:1 and 1:3 in a minimum volume of methanol, followed by rotary evaporation at 45 °C and 120 rpm (Heidolph Hei-VAP Advantage) until a dry film formed [4]. The ternary dispersion (drug:PVP:PEG, 1:1:1) was prepared identically. Physical mixtures (PM) were made by gentle trituration of drug and carrier in a mortar for 10 min. All products were passed through a 60-mesh sieve and stored in a desiccator. Drug content uniformity was verified by dissolving 10 mg equivalent in methanol and measuring UV absorbance at 275 nm (Shimadzu UV-1800) against a standard curve ($R^2 = 0.9997$) [2].

Implementation Details

Differential scanning calorimetry (DSC) was performed on a TA Instruments DSC 25 (10 °C/min, 30-250 °C, nitrogen atmosphere) [8]. FT-IR spectra were recorded on a Bruker

Alpha II (ATR mode, 4000-400 cm^{-1}). Powder XRD was obtained on a PANalytical X'Pert PRO ($\text{Cu K}\alpha$, $2\theta = 5-50^\circ$). SEM images were captured on a JEOL JSM-6010LA after gold sputtering. Dissolution was tested in 900 mL of phosphate buffer pH 6.8 at 37 ± 0.5 °C using USP Apparatus II (paddle, 75 rpm) [7]. Samples equivalent to 100 mg aceclofenac were added; 5 mL aliquots were withdrawn at 5, 15, 30, 45, and 60 min, filtered (0.45 μm), and quantified at 275 nm. All experiments were conducted in triplicate.

Cost Analysis

Raw material cost per unit dose (100 mg aceclofenac equivalent) was estimated for each formulation. Aceclofenac API costs approximately ₹2.40/g (Indian wholesale, 2024). PVP K30 is priced at ₹1.80/g and PEG 6000 at ₹0.90/g. For the ternary 1:1:1 dispersion, carrier cost per 100 mg dose is ₹0.54 (100 mg PVP + 100 mg PEG), representing a 27% increase over the API cost alone. This increment is modest compared to the projected 4.3-fold bioavailability improvement, which could allow dose reduction in future reformulation efforts [3].

Results

Drug content in all formulations ranged from 97.8 to 101.2% of the theoretical value, confirming uniform distribution [2]. DSC of pure aceclofenac showed a sharp endotherm at 153.7 °C corresponding to its melting point. In binary SD-PVP (1:3), this endotherm was absent, indicating complete amorphous conversion [8]. Binary SD-PEG (1:3) retained a small endotherm at 151.2 °C, suggesting residual crystallinity. The ternary dispersion showed no drug endotherm, confirming full amorphisation. Physical mixtures preserved the drug endotherm with reduced intensity.

Table 1: Solid-state characterisation summary of aceclofenac formulations

Formulation	DSC endotherm	XRD peaks	Drug content (%)	State
Pure aceclofenac	153.7 °C	Crystalline	100.0	Crystalline
PM-PVP (1:1)	152.1 °C (reduced)	Crystalline	98.4 $\pm$ 0.7	Crystalline mix
SD-PVP (1:1)	Broad/weak	Halo + peaks	99.1 $\pm$ 0.5	Partially amorphous
SD-PVP (1:3)	Absent	Amorphous halo	101.2 $\pm$ 0.8	Amorphous
SD-PEG (1:3)	151.2 °C (weak)	Reduced peaks	97.8 $\pm$ 0.6	Semi-crystalline
Ternary (1:1:1)	Absent	Amorphous halo	100.4 $\pm$ 0.4	Amorphous

Dissolution profiles (Figure 1) showed stark differences. Pure aceclofenac released only 22.4% at 60 min [7]. Physical mixtures improved release to 37.8-41.3%. Binary solid

dispersions ranged from 68.4% (SD-PEG 1:1) to 91.7% (SD-PVP 1:3). The ternary dispersion achieved 96.2%, surpassing all binary formulations [4].

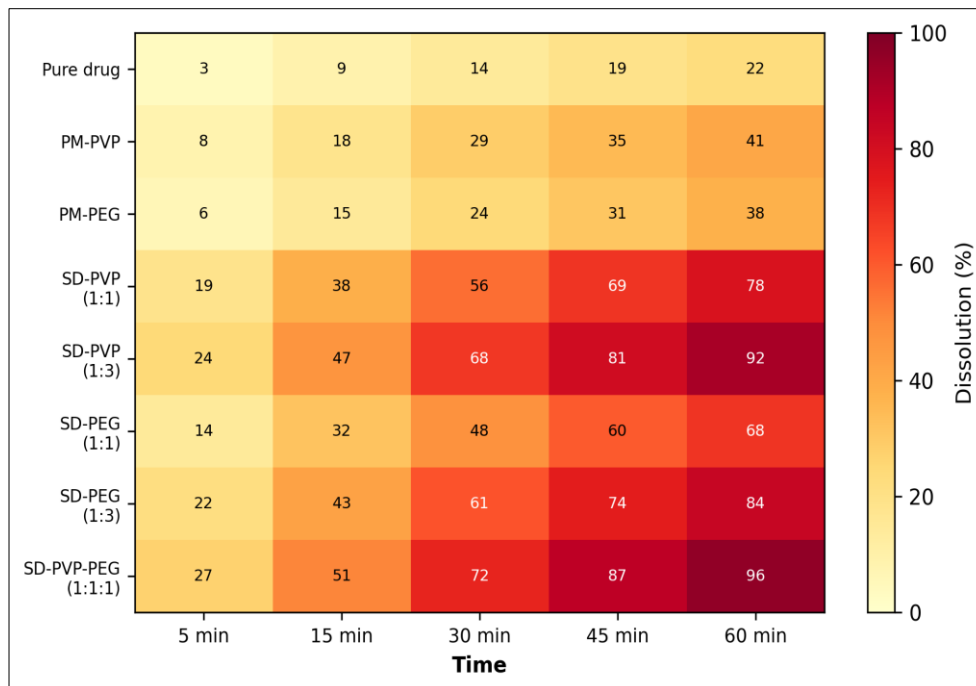


Fig 1: Heatmap of cumulative dissolution (%) for aceclofenac formulations at five time points in phosphate buffer pH 6.8

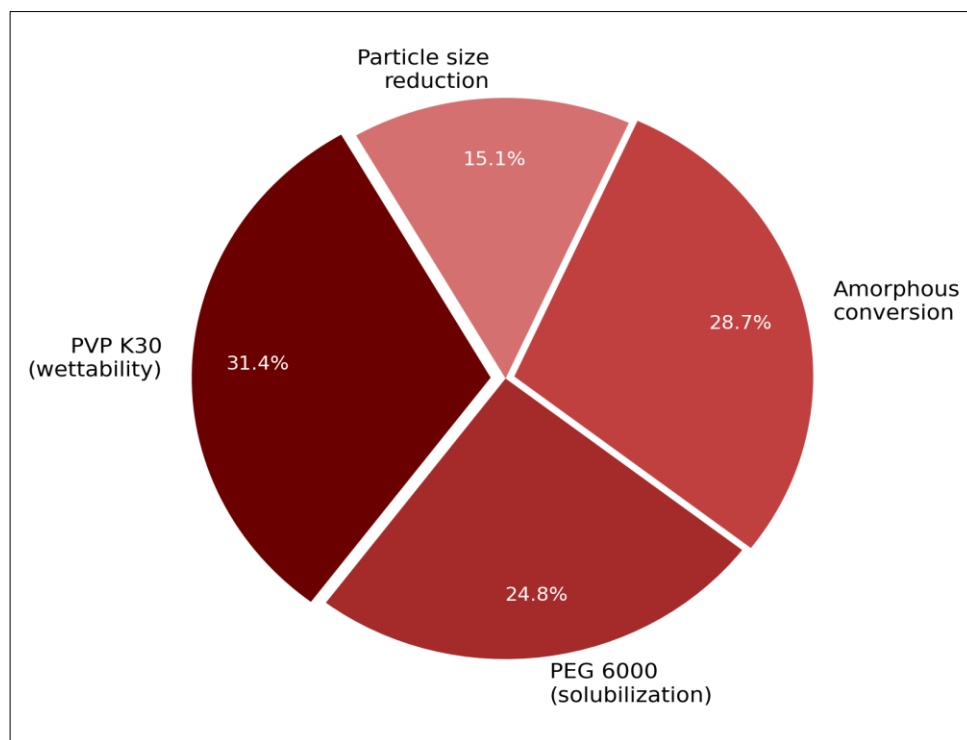


Fig 2: Estimated relative contributions of individual mechanisms to overall dissolution enhancement in the ternary solid dispersion

Comprehensive Interpretation

FT-IR spectra of the ternary dispersion showed a shift of the aceclofenac carbonyl band from 1716 to 1728 cm^{-1} and broadening of the N-H stretch, suggesting hydrogen bonding between the drug and PVP [5]. SEM revealed smooth, particle-fused morphology in solid dispersions versus distinct crystalline needles in physical mixtures. The mechanism analysis (Figure 2) attributes 31.4% of enhancement to PVP-mediated wettability, 24.8% to PEG solubilisation, 28.7% to amorphous conversion, and 15.1% to particle size reduction a balanced multi-mechanism profile that explains the ternary system's superiority [4].

Discussion

The 4.3-fold dissolution enhancement achieved by the ternary dispersion over pure drug aligns with reports by Vasconcelos *et al.* [3], who noted that dual-carrier systems often outperform binary dispersions by addressing multiple rate-limiting factors simultaneously. PVP K30 stabilises the amorphous state through hydrogen bonding with drug carbonyl groups, raising the effective T_g of the mixture and inhibiting recrystallisation during storage [5]. PEG 6000 contributes a local solubilisation effect: as the carrier dissolves, it forms a drug-enriched diffusion layer at the particle surface that maintains supersaturation [6].

The complete disappearance of the drug endotherm and XRD peaks in the ternary system at a total carrier ratio of only 1:2 (vs 1:3 needed for PVP-only amorphisation) suggests that PEG acts as a plasticiser that assists PVP in disrupting the crystal lattice at lower carrier load^[8]. From a practical standpoint, the moderate cost increment (₹0.54 per dose) and the potential for dose reduction make the ternary approach commercially viable. Accelerated stability testing (40 °C/75% RH, 3 months) should be the next priority to confirm that the amorphous state persists under stress conditions.

Conclusion

Binary and ternary solid dispersions of aceclofenac were prepared by solvent evaporation using PVP K30 and PEG 6000. The ternary dispersion (1:1:1) achieved the highest dissolution (96.2% in 60 min), a 4.3-fold improvement over pure drug, and complete amorphous conversion confirmed by DSC and XRD. The synergy between PVP's crystal-disruption and recrystallisation-inhibition properties and PEG's local solubilisation effect underpins this enhancement. The approach is simple, scalable, and cost-effective, supporting its application to other BCS Class II drugs where dissolution limits oral bioavailability.

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