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Research Article

Enhancement of Solubility and Dissolution Rate of BCS Class 2 Drug

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ABSTRACT

The present study focuses on the enhancement of solubility and dissolution rate of a BCS Class II drug, Diclofenac Sodium, which exhibits low aqueous solubility and high permeability. Poor solubility limits its bioavailability and therapeutic effectiveness. To overcome this limitation, a co-grinding technique using Hydroxypropyl Methylcellulose (HPMC) as a hydrophilic carrier was employed. Physical mixtures and co-ground formulations were prepared in different ratios and evaluated for solubility and dissolution characteristics. The prepared batches were subjected to saturation solubility studies and in-vitro dissolution testing using a USP Type II (paddle) apparatus. The results indicated a significant improvement in drug release from co-ground formulations compared to the pure drug and physical mixtures. Among all batches, the optimized formulation showed maximum dissolution, confirming the effectiveness of the co-grinding method. The enhancement in solubility is attributed to reduced particle size, improved wettability, and transformation of the drug from crystalline to amorphous form. Thus, the study demonstrates that co-grinding with HPMC is a simple and effective approach for improving the solubility and dissolution rate of poorly water-soluble drugs.

INTRODUCTION

Solubility refers to maximum quantity of solute that can be dissolved in given amount of solvent. It can be defined by both a quantitative and a qualitative definition. Quantitatively it is defined as the concentration of the solute in a saturated solution under a specified temperature. Qualitatively it can be defined as the spontaneous interaction of at least two substances, in which the solute forms a homogenous molecular dispersion with the solvent. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug can be expressed based on its various concentrations such as molarity, parts, percentage, molality, volume. The compendial books use the parts of solvents required to dissolve one part of solute (Table 1)[1,2,3]

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Guidelines for the Biopharmaceutical Classification System1 (BCS) were made available by the US Food and Drug Administration (FDA), to help improve the efficiency of drug product development process. According to which drugs are classified into four major classes based on their solubility and permeability. [4,5].

Table 1: Solubility Expressions

Definition	Parts of solvent required for 1 part of solute
Very soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly soluble	100 – 1000
Very slightly soluble	1000 – 10,000
Insoluble	> 10,000

BCS CLASSIFICATION[6]

The Biopharmaceutical Classification System (BCS) is a scientific framework used to classify drugs based on their solubility and intestinal permeability. It was introduced by the US FDA to simplify drug development and regulatory decisions. BCS helps in predicting the absorption and bioavailability of oral drugs. Drugs in Class I are well absorbed and usually do not require complex formulation strategies, while Class II drugs need solubility enhancement techniques. Class III drugs face permeability limitations, and Class IV drugs show poor solubility and permeability, making them the most challenging for formulation and development.

This system is widely used for biowaivers, reducing the need for in vivo bioequivalence studies in certain cases.

Table 2: Biopharmaceutical Classification System

BCS Class	Solubility	Permeability	Description	Examples
Class I	High	High	Well absorbed; no major limitations	Propranolol, Metoprolol, Diltiazem, Verapamil
Class II	Low	High	Absorption limited by solubility	Ketoconazole, Mefenamic acid, Nifedipine, Nicardipine, Felodipine, Piroxicam
Class III	High	Low	Absorption limited by permeability	Acyclovir, Neomycin B, Captopril, Enalaprilate, Alendronate
Class IV	Low	Low	Poor absorption; major formulation challenges	Chlorthiazide, Furosemide, Tobramycin

Solubility Enhancement Techniques [7]

Solubility enhancement is a key concept in pharmaceutics, especially for poorly water-soluble drugs (common in BCS Class II and IV). Improving solubility helps increase bioavailability, dissolution rate, and therapeutic effectiveness.

Table 3: Classification of Solubility Enhancement Techniques[15]

Category	Technique	Principle	Examples / Notes
Physical Methods	Particle Size Reduction	Increases surface area → faster dissolution	Micronization, nanosuspension
	Solid Dispersion	Drug dispersed in carrier → improved wettability	PEG, PVP
	Hot Melt Extrusion	Forms amorphous solid → better solubility	Drug + polymer melt
	Crystal Engineering	Modifies crystal form	Polymorphs, hydrates

Chemical Methods	Salt Formation	Converts drug into more soluble salt	Diclofenac sodium
	Prodrug Approach	Chemical modification improves solubility	Converts back in body
	pH Adjustment	Increases ionization of drug	Used in liquid dosage forms
Surfactant-Based Methods	Micellar Solubilization	Surfactants form micelles	Tween, SDS
	Co-solvency	Addition of water-miscible solvents	Ethanol, PEG, propylene glycol
Complexation Techniques	Cyclodextrin Complexation	Forms inclusion complex	β-cyclodextrin
	Ion Pairing	Forms ion pairs with oppositely charged ions	Improves permeability
Novel Drug Delivery Systems	Liposomes	Lipid vesicles entrap drug	Improves bioavailability
	Nanoparticles	Very small size increases dissolution	Nanoformulations
	SEDDS	Forms emulsion in GI tract	Self-emulsifying systems
	Solid Lipid Nanoparticles	Lipid-based carriers	SLN
Miscellaneous Methods	Hydrotropy	Uses hydrotropic agents	Urea, sodium benzoate
	Supercritical Fluid Technology	Uses supercritical CO_2	Particle size reduction

MATERIAL AND METHODOLOGY

Materials

Diclofenac Sodium was used as the active pharmaceutical ingredient (API) in this study. It is a BCS Class II drug with low solubility and high permeability, appearing as a white crystalline powder. It is poorly soluble in acidic media, but its solubility increases with pH ($pK_a \approx 4.0$). The drug was selected to enhance its solubility and dissolution rate.

Hydroxypropyl Methylcellulose (HPMC) was used as the carrier. It is a hydrophilic, semi-synthetic polymer with good film-forming properties and stability over a wide pH range. HPMC improves drug wettability and prevents aggregation, thereby enhancing solubility and dissolution.

Table 4: Materials and Reagents Used

Category	Material/ Reagent	Description	Role in Study
Active Pharmaceutical Ingredient (API)	**Diclofenac Sodium**	BCS Class II drug with low solubility and high permeability	Model drug selected for solubility enhancement
Hydrophilic Carrier (Polymer)	HPMC (Hydroxypropyl Methylcellulose)	Water-soluble polymer (Grades: E5, E15, K4M)	Enhances wettability, stabilizes amorphous form
Chemicals & Solvents	Distilled/Deionized Water	Purified water free from impurities	Used for solubility and dissolution studies

Methodology: Manual Co-Grinding Method (Steps)[8,9]

1. **Preparation**

- Pass **Diclofenac Sodium** and HPMC through a #60 mesh sieve.
- Accurately weigh drug and polymer in required ratios (e.g., 1:1, 1:2).

2. **Geometric Dilution (Mixing)**

- Place the drug in a mortar.
- Add HPMC gradually in equal portions and mix to obtain uniform blending.

3. **Grinding (Co-Grinding Process)**

- Grind the mixture using a pestle with uniform pressure in circular motion.
- Continue grinding for 30–60 minutes.
- Scrape the sides at regular intervals to ensure uniform grinding.

4. **Sieving and Storage**

- Pass the final mixture through a #100 mesh sieve.
- Store in an airtight container or desiccator to prevent moisture absorption

Evaluation & Characterization[10-12]

To prove that the co-grinding method worked, the following tests are performed:

Table 5: Evaluation and Characterization of Co-Ground Solid Dispersion

Test	Method/Procedure	Conditions	Purpose/Outcome
Saturation Solubility Study	Excess co-ground sample added to 10 mL distilled water or phosphate buffer (pH 6.8), shaken for 24–48 hrs, filtered and analyzed by UV spectrophotometer at 276 nm	37 ± 0.5°C, rotary shaker, 0.45 µm filter	Determines improvement in solubility of Diclofenac Sodium
In-vitro Dissolution Test	Sample equivalent to 50 mg drug added to dissolution medium; samples withdrawn at intervals and analyzed	USP Type II (Paddle), 900 mL medium, 50 RPM, time points: 5–60 min	Evaluates drug release rate and dissolution enhancement
FTIR Spectroscopy	Analysis of functional group peaks	Standard FTIR conditions	Detects drug–polymer interactions (e.g., hydrogen bonding)
DSC (Differential Scanning Calorimetry)	Thermal analysis of sample	Heating profile applied	Confirms amorphous nature by disappearance of melting peak (~284°C)

Experimental Work [13,14]

The experimental work was carried out using Diclofenac Sodium as the active pharmaceutical ingredient, a BCS Class II drug with poor solubility, and HPMC as a hydrophilic carrier to enhance dissolution. Initially, physical mixtures of drug and polymer were prepared in different ratios to serve as control samples. The co-grinding process was then performed using a ball mill, where mechanical forces such as impact and attrition converted the crystalline drug into an amorphous form, improving its solubility. The prepared formulations were sieved and stored in a

desiccator to prevent moisture-induced recrystallization. Evaluation was carried out through saturation solubility and in-vitro dissolution studies using phosphate buffer (pH 6.8), with drug concentration analyzed by UV spectrophotometry at 276 nm to confirm enhancement in solubility and drug release.

RESULT:

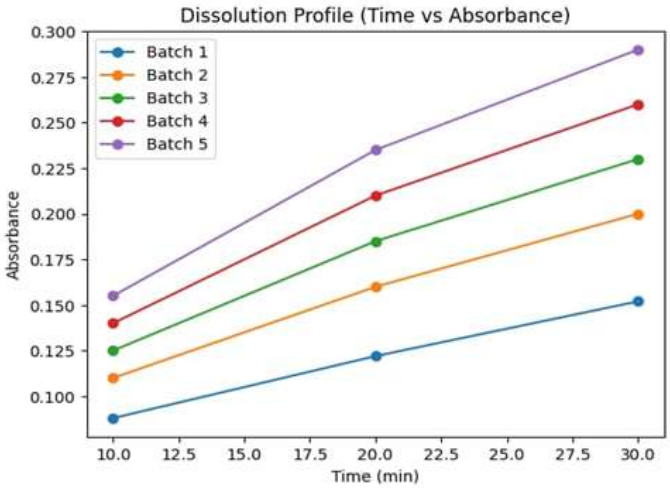
Absorbance Data Analysis

The absorbance of each sample containing **Diclofenac Sodium** was measured at 276 nm using a UV-Visible spectrophotometer. The absorbance values correspond to the concentration of drug released into the dissolution medium at different time intervals, indicating the rate of drug dissolution.

Table 6: Absorbance Readings of Diclofenac Sodium at 276 nm

Sample	10 min	20 min	30 min
Pure Drug	0.048	0.229	0.256
Batch 1	0.088	0.122	0.152
Batch 2	0.110	0.160	0.200
Batch 3	0.125	0.185	0.230
Batch 4	0.140	0.210	0.260
Batch 5	0.155	0.235	0.290
Batch 6	0.165	0.260	0.315

The in-vitro dissolution profile of Diclofenac Sodium showed that co-ground batches released the drug faster than the pure drug and physical mixtures. This indicates improved solubility and dissolution due to amorphization and better wettability.



The percentage drug dissolution analysis

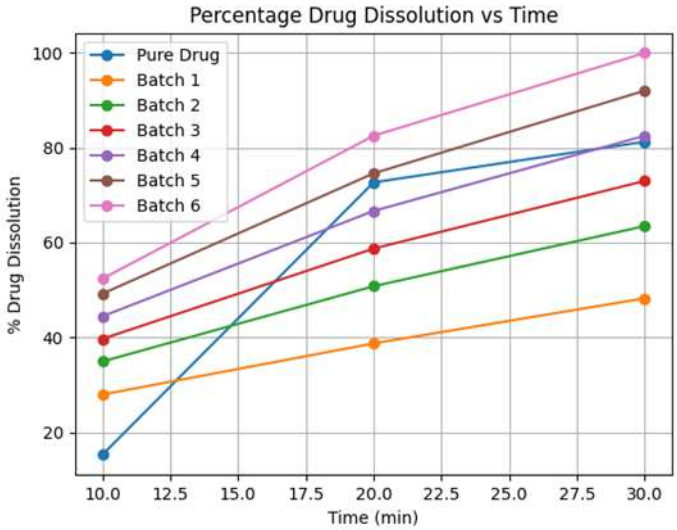
The % cumulative drug release (%CDR) increases with time for all formulations. Among all batches, Batch 6 shows the highest drug release (100% at 30 min), indicating maximum enhancement in solubility and dissolution compared to the pure drug. This confirms the effectiveness of the co-grinding method with HPMC.

Table 7: Cumulative % Drug Dissolution of Diclofenac Sodium Formulations

Sample	10 min (%CDR)	20 min (%CDR)	30 min (%CDR)	Final Absorbance
Pure Drug	15.24%	72.70%	81.27%	0.256
Batch 1	27.94%	38.37%	63.49%	0.200
Batch 2	34.92%	50.79%	48.25%	0.152
Batch 3	39.68%	58.73%	73.02%	0.230
Batch 4	44.44%	66.67%	82.52%	0.260

Batch 5	49.21%	74.60%	92.06%	0.290
Batch 6	52.38%	82.54%	100%	0.315

The percentage drug dissolution study serves as a critical in-vitro indicator of drug release kinetics. For BCS Class II drugs like Diclofenac Sodium, the dissolution rate is the rate-limiting step for systemic absorption; therefore, monitoring the cumulative percentage release over time is essential to evaluate the success of the solubility enhancement process.



CONCLUSION

The study successfully evaluated the in-vitro dissolution profiles of seven distinct formulations of Diclofenac Sodium. The results clearly demonstrate that Batch 6 is the most effective formulation, achieving a complete 100% drug release within 30 minutes. This is a significant improvement over the other experimental groups and confirms that the specific parameters used for Batch 6 likely the optimal co-grinding time or drug-to-carrier ratio successfully overcame the inherent solubility limitations of the drug.The significant upward shift in the dissolution curve for Batch 6 (starting at ~53% at 10 minutes and ending at 100% at 30 minutes) validates the hypothesis that reducing particle size and increasing the amorphous nature of Diclofenac Sodium through co-grinding directly translates to enhanced dissolution. By reaching the 100% threshold so rapidly, this formulation ensures faster onset of action and potentially higher bioavailability in a clinical setting. In conclusion, Batch 6 is identified as the optimized formulation for Diclofenac Sodium. It not only meets but exceeds the pharmacopoeial requirements for dissolution, proving that the co-grinding method is a viable and efficient strategy for enhancing the performance of BCS Class II drugs. This research provides a solid foundation for further in-vivo studies to confirm the therapeutic benefits of the optimized Batch 6 formulation.

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