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COMPARATIVE STUDY ON THE SOLUBILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUGS USING SOLID DISPERSION TECHNIQUES

Chaitali S. Raut*, Shreyash Gosatwar, Sejal Khadse, Rupali Chavan

Pataldhamal Wadhawani College of Pharmacy, Yavatmal.

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***Corresponding Author**
Chaitali S. Raut
Pataldhamal Wadhawani College of Pharmacy, Yavatmal.

1. INTRODUCTION

The solubility of a drug significantly influences its bioavailability, therapeutic efficacy, and overall success as a pharmaceutical agent. Approximately 40% of new chemical entities (NCEs) identified through drug discovery programs exhibit poor water solubility, posing substantial challenges in drug development and delivery (Kalepu & Nekkanti, 2015). Poorly water-soluble drugs often demonstrate low dissolution rates in the gastrointestinal tract, leading to inadequate absorption and suboptimal therapeutic outcomes (Savjani et al., 2012).

To address these challenges, various formulation strategies have been developed to enhance the solubility and dissolution rates of hydrophobic drugs. Among these, solid dispersion techniques have emerged as a promising approach. Solid dispersions involve dispersing poorly soluble drugs within a hydrophilic carrier matrix, resulting in improved wettability, reduced particle size, and, in some cases, transformation of the drug into an amorphous state, thereby enhancing solubility and dissolution rates (Vasconcelos et al., 2007).

Several methods exist for preparing solid dispersions, including melting (fusion), solvent evaporation, and hot-melt extrusion. The melting method involves heating a physical mixture of the drug and carrier until it melts, followed by cooling to form a solid mass, which is then milled into powder (Dhirendra et al., 2009). The solvent evaporation method dissolves both the drug and carrier in a common solvent, which is then evaporated to yield a solid dispersion (Leuner & Dressman, 2000). Hot-melt extrusion, a more recent technique, involves the

application of heat and pressure to mix the drug and carrier, forming a homogeneous solid dispersion (Maniruzzaman et al., 2012).

The choice of carrier in solid dispersion systems is crucial for achieving the desired solubility enhancement. Hydrophilic polymers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), and hydroxypropyl methylcellulose (HPMC) are commonly used due to their ability to improve wettability and stabilize the amorphous form of the drug (Sekiguchi & Obi, 1961). Cyclodextrins, a class of cyclic oligosaccharides, have also been employed as carriers owing to their capability to form inclusion complexes with hydrophobic drugs, thereby enhancing solubility (Loftsson & Brewster, 1996).

Despite the advancements in solid dispersion technology, challenges such as physical and chemical instability, scale-up difficulties, and reproducibility issues persist. Physical instability, particularly the recrystallization of the amorphous drug to its more stable crystalline form, can negate the solubility advantages gained through solid dispersion (Hancock & Zografi, 1997). Additionally, the selection of an appropriate preparation method and carrier is critical, as these factors significantly influence the stability and performance of the solid dispersion (Bikiaris, 2011).

This study aims to conduct a comparative analysis of different solid dispersion techniques and carriers to enhance the solubility of poorly water-soluble drugs. By systematically evaluating various methods and materials, the research seeks to identify optimal strategies for solubility enhancement, thereby contributing to the development of more effective pharmaceutical formulations.

1.1 Background of the Study

The solubility of a drug is a fundamental physicochemical property that influences its absorption, distribution, metabolism, and excretion (ADME) profile. Drugs with poor water solubility often exhibit erratic absorption patterns, leading to variable bioavailability and therapeutic responses (Lipinski et al., 1997). This issue has become more pronounced with the advent of high-throughput screening techniques in drug discovery, which frequently yield compounds with high molecular weights and lipophilicity, characteristics associated with poor solubility (Di et al., 2009).

Several formulation strategies have been explored to address the solubility limitations of hydrophobic drugs, including particle size reduction, salt formation, complexation, and the use of surfactants (Kawabata et al., 2011). Among these approaches, solid dispersion has gained significant attention due to its versatility and effectiveness. The concept of solid dispersion was first introduced by Sekiguchi and Obi in 1961, who demonstrated that the eutectic mixture of sulfathiazole and urea exhibited enhanced dissolution rates compared to the pure drug (Sekiguchi & Obi, 1961). Since then, extensive research has been conducted to refine solid dispersion techniques and expand their applicability.

The classification of solid dispersions has evolved over time, encompassing various types based on the molecular arrangement of the drug and carrier. These include simple eutectic mixtures, solid solutions, glass solutions, and amorphous precipitations in crystalline carriers (Chiou & Riegelman, 1971). The amorphous form of a drug, characterized by higher free energy and molecular mobility, generally exhibits superior solubility and dissolution rates compared to its crystalline counterpart (Yu, 2001). However, the amorphous state is thermodynamically unstable, necessitating the use of suitable carriers to inhibit recrystallization and maintain the enhanced solubility (Hancock & Parks, 2000).

The selection of an appropriate carrier is pivotal in the design of solid dispersions. Hydrophilic polymers such as PEG, PVP, and HPMC have been extensively utilized due to their ability to improve drug wettability, inhibit crystallization, and enhance dissolution rates (Leuner & Dressman, 2000). Cyclodextrins, particularly β-cyclodextrin and its derivatives, have also been employed as carriers owing to their unique capability to form inclusion complexes with hydrophobic drugs, thereby enhancing solubility and stability (Loftsson & Duchêne, 2007).

Various methods have been developed for the preparation of solid dispersions, each with its advantages and limitations. The melting method, also known as the fusion method, involves heating a physical mixture of the drug and carrier until it melts, followed by cooling to form a solid mass, which is then milled into powder (Dhirendra et al., 2009). This method is simple and economical but may not be suitable for thermolabile drugs. The solvent evaporation method, on the other hand, dissolves both the drug and carrier in a common solvent, which is subsequently evaporated under controlled conditions to yield a solid dispersion (Leuner & Dressman, 2000). This method is particularly advantageous for thermolabile drugs but poses challenges related to solvent selection, residual solvent content, and scalability. Another

advanced method, hot-melt extrusion, involves the application of heat and shear forces to mix the drug and carrier in an extruder, followed by extrusion and cooling to obtain a solid dispersion (Maniruzzaman et al., 2012). This technique offers better control over processing parameters and is more suitable for large-scale production but requires specialized equipment and high capital investment.

The effectiveness of solid dispersions in enhancing drug solubility and bioavailability has been demonstrated in numerous studies. For instance, Vasconcelos et al. (2007) reported that solid dispersions of itraconazole with HPMC and PEG significantly improved the drug's dissolution rate and bioavailability. Similarly, Chaudhary et al. (2012) observed that solid dispersions of celecoxib with PVP K30 enhanced the drug's solubility and dissolution rate compared to the pure drug.

Despite these advancements, the development of solid dispersion systems remains a complex and multifaceted process, requiring careful consideration of drug properties, carrier selection, preparation method, and stability issues. The present study aims to conduct a comprehensive comparative analysis of different solid dispersion techniques and carriers to optimize the solubility enhancement of poorly water-soluble drugs, thereby contributing to the development of more effective pharmaceutical formulations.

1.2 Need of the Study

The increasing prevalence of poorly water-soluble drugs in pharmaceutical pipelines highlights the urgent need for effective solubility enhancement strategies. The bioavailability of such drugs is often limited by their low dissolution rates, resulting in suboptimal therapeutic outcomes and increased variability in drug response. Solid dispersion techniques have emerged as one of the most promising approaches to address these challenges, offering significant improvements in drug solubility and bioavailability. However, the selection of an appropriate carrier and preparation method is critical to achieving the desired solubility enhancement and stability. This study aims to systematically evaluate different solid dispersion techniques and carriers to identify optimal strategies for solubility enhancement, thereby contributing to the development of more effective pharmaceutical formulations and improving patient outcomes.

1.3 Research Statement

Poorly water-soluble drugs present significant challenges in pharmaceutical development due to their low dissolution rates and bioavailability. Solid dispersion techniques have shown great

promise in enhancing drug solubility and bioavailability, but the choice of carrier and preparation method plays a crucial role in determining their efficacy. This study aims to conduct a comparative analysis of different solid dispersion techniques and carriers to optimize the solubility enhancement of poorly water-soluble drugs. By systematically evaluating various methods and materials, the research seeks to identify the most effective strategies for solubility enhancement, thereby contributing to the development of more effective pharmaceutical formulations and improving therapeutic outcomes.

1.4 Research Objectives

- To evaluate the solubility enhancement of poorly water-soluble drugs using different solid dispersion techniques.
- To compare the effectiveness of various hydrophilic carriers in solid dispersion systems.
- To investigate the impact of different preparation methods on the stability and dissolution rate of solid dispersions.
- To identify the optimal carrier and preparation method for enhancing the solubility and bioavailability of poorly water-soluble drugs.
- To provide insights into the practical applications of solid dispersion techniques in pharmaceutical formulation development.

Literature Review

- Solid dispersion techniques have long been employed to overcome the poor aqueous solubility of many pharmacologically active drugs, thus enhancing their bioavailability. Chiou and Riegelman (1971) pioneered the use of solid dispersions by incorporating drugs into hydrophilic carriers to achieve improved dissolution profiles. Since then, researchers have extensively explored a variety of carriers and preparation methods.

- Craig (2002) emphasized that the transformation of crystalline drugs into amorphous states within hydrophilic matrices like PVP K30 and PEG 4000 contributes significantly to solubility enhancement. Serajuddin (1999) discussed the role of drugpolymer miscibility and molecular dispersion in solubility improvements, suggesting that solvent methods often produce more homogenous systems compared to fusion techniques.

- In a study by Vasconcelos et al. (2007), the comparison of preparation methods such as kneading, solvent evaporation, and melting revealed that the solvent evaporation

technique yielded solid dispersions with greater dissolution enhancement due to better dispersion at the molecular level. Leuner and Dressman (2000) outlined how secondgeneration solid dispersions, containing amorphous drugs in polymeric matrices, provided superior solubility profiles and were more stable than their first- generation counterparts.

- Ahuja et al. (2015) studied the impact of different polymers on the solubility of poorly soluble drugs like itraconazole and showed that PVP-based solid dispersions improved aqueous solubility more than PEG-based ones. A study by Sharma et al. (2013) on naproxen demonstrated that solvent-evaporated solid dispersions with HPMC had the highest dissolution rate due to enhanced wettability and reduced crystallinity.

- Patel et al. (2011) investigated curcumin solid dispersions and reported a five-fold increase in solubility using PVP K30 through the solvent evaporation method. Similarly, Kiran et al. (2014) reported enhanced dissolution of ibuprofen when formulated with PEG 6000 via fusion and solvent evaporation methods, with the latter being more efficient due to uniform drug-polymer mixing.

- In work by Chauhan et al. (2019), the fusion technique was applied to prepare solid dispersions of poorly soluble drugs with PEG and PVP, and although both techniques improved solubility, solvent evaporation consistently outperformed the fusion method in dissolution tests. Tran et al. (2020) discussed novel carriers such as poloxamers and Soluplus, which offered higher drug loading and better dispersion efficiency in solid dispersion systems.

- Sinha and Saha (2011) carried out a comparative study of solid dispersions of lornoxicam using various techniques, demonstrating that solvent evaporation provided the highest drug release in acidic pH, suggesting the method's utility in oral drug delivery systems. Mahapatra et al. (2013) applied the fusion method for telmisartan and confirmed that PEG 4000 at a 1:2 ratio showed the greatest improvement in solubility, though minor drug degradation was observed at high temperatures.

- Shah et al. (2018) formulated solid dispersions of olmesartan medoxomil using solvent evaporation and found increased solubility and bioavailability compared to physical mixtures. A detailed study by Verma et al. (2017) revealed that solid dispersions using

PVP and Soluplus could maintain the drug in a supersaturated state, effectively preventing precipitation and leading to sustained drug release.

- Rajput et al. (2021) explored the use of natural polymers such as guar gum and xanthan gum in solid dispersions and found comparable results to synthetic polymers, suggesting their application in green formulations. In a more recent study, Mehta et al. (2023) evaluated various solid dispersion methods for aprepitant, concluding that spray drying and solvent evaporation led to higher dissolution rates than traditional melting methods, especially when using modern carriers like HPMCAS.

AIM AND OBJECTIVES

AIM

To formulate and evaluate solid dispersions of a poorly water-soluble drug using various techniques and carriers, with the ultimate goal of enhancing its solubility and dissolution rate, thereby improving its oral bioavailability.

OBJECTIVES

1. **Drug and Carrier Selection**

- To select a model poorly water-soluble drug (e.g., Ibuprofen, Ketoconazole, Griseofulvin, etc.) belonging to BCS Class II or IV.

- To select suitable hydrophilic polymeric carriers such as:
  - Polyethylene Glycol (PEG 4000/6000)
  - Polyvinylpyrrolidone (PVP K30)
  - Hydroxypropyl Methylcellulose (HPMC)
  - Poloxamer 188 or 407

2. **Preparation of Solid Dispersions**

- To prepare solid dispersions using the following techniques:
  - Fusion method (Melting technique)
  - Solvent evaporation method o Kneading method
  - (Optional) Spray drying or supercritical fluid method if facilities are available

3. **Optimization of Drug-Carrier Ratio**

- To prepare different formulations with varying drug-to-carrier ratios (e.g., 1:1, 1:2, 1:4)

for comparative evaluation.

4. Preformulation Studies

- To conduct preliminary studies including:
  - Drug-excipient compatibility (e.g., FTIR)
  - Solubility profile of the pure drug
  - Melting point determination

5. Evaluation of Solid Dispersion Formulations

- Solubility studies in water and different pH media.
- Drug content uniformity.
- Saturation solubility analysis.
- In vitro dissolution studies to assess drug release profiles.
- Dissolution efficiency (DE), T50%, T90% calculations.

6. Physicochemical Characterization

- To perform advanced characterization to understand physical and chemical behavior:
  - FTIR Spectroscopy – to assess drug-polymer interactions.
  - Differential Scanning Calorimetry (DSC) – to determine thermal behavior and crystalline/amorphous transition.
  - X-ray Diffraction (XRD) – to assess the crystallinity of drug before and after dispersion.
  - Scanning Electron Microscopy (SEM) – for surface morphology (if facilities permit).

7. Comparative Study

- To compare all the solid dispersion techniques based on:
  - Solubility enhancement
  - Dissolution rate

8. Statistical Analysis

- To apply suitable statistical tools (e.g., ANOVA) to validate significant differences in dissolution rates among formulations.

9. Stability Studies

- To conduct short-term stability testing of the optimized solid dispersion formulation under ICH guidelines.

10. Conclusion and Recommendations

- To draw a conclusion regarding the most effective solid dispersion technique and carrier.
- To suggest possible improvements or further studies for scale-up or commercial application.

PLAN OF WORK

The proposed research work will be systematically carried out in the following phases to ensure thorough execution and scientific integrity:

1. Literature Survey

A comprehensive review of published research articles, scientific journals, and reference books will be conducted to understand the challenges related to the solubility of poorly water-soluble drugs. The focus will be on various solubility enhancement strategies, particularly solid dispersion techniques, and the polymers/carriers commonly used in these approaches.

2. Selection of Drug and Polymers

Based on the literature findings, a poorly water-soluble model drug will be selected (e.g., Ibuprofen, BCS Class II). Suitable hydrophilic carriers like PEG 4000, PVP K30, or HPMC will be chosen based on their physicochemical properties, safety profile, and reported efficacy in improving drug solubility.

3. Procurement of Materials

All required chemicals, reagents, excipients, and analytical-grade solvents will be procured from certified suppliers. Analytical instruments such as UV-Visible spectrophotometer, FTIR, and dissolution apparatus will be prepared for experimental use.

4. Preformulation Studies

Physicochemical characterization of the selected drug will be performed, including melting point determination, UV λmax identification, solubility profile, and drug– polymer compatibility analysis using FTIR spectroscopy. These studies will help ensure formulation feasibility.

5. Preparation of Solid Dispersions

Solid dispersions of the drug with selected polymers will be prepared in various drugto-polymer ratios (1:1, 1:2, 1:3 w/w) using the following three techniques:

- Physical Mixing Method

- Solvent Evaporation Method
- Melting (Fusion) Method

Each method will be carefully executed under controlled conditions to ensure reproducibility.

6. Evaluation of Solid Dispersions

The prepared solid dispersions will be evaluated for:

- Drug content analysis
- Saturation solubility studies
- In vitro dissolution studies

Dissolution tests will be conducted in appropriate media (e.g., 0.1 N HCl or phosphate buffer pH 6.8), and samples will be analyzed using a UV-Visible spectrophotometer.

7. Comparative Analysis

The results obtained from all three methods will be compared in terms of solubility enhancement and dissolution rate. Graphical representations such as cumulative % drug release vs. time curves will be plotted and interpreted.

8. Advanced Characterization (If Available)

Selected formulations, especially the most effective one, will be further characterized using: o FTIR Spectroscopy – to check chemical interactions

- DSC (Differential Scanning Calorimetry) – to evaluate thermal behavior
- PXRD (Powder X-Ray Diffraction) – to study crystallinity changes
- SEM (Scanning Electron Microscopy) – for surface morphology analysis These techniques will provide a better understanding of the physical state of the drug within the dispersion.

9. Optimization and Selection of Best Formulation

Based on solubility, dissolution profile, and characterization data, the best method and optimal drug–polymer ratio will be selected.

10. Short-Term Stability Study

The optimized formulation will be subjected to a short-term stability study under accelerated conditions (as per ICH guidelines) to observe any changes in physical appearance, drug content, and dissolution behavior over time.

11. Statistical Analysis

All experimental data will be subjected to statistical analysis (e.g., mean, standard deviation, t-test or ANOVA) to determine the significance of the results and ensure data reliability.

12. Conclusion and Report Compilation

A summary of all findings will be compiled. Conclusions will be drawn regarding the most effective method and formulation for solubility enhancement. The final project report will be written, incorporating the entire methodology, data, results, discussion, and references.

MATERIAL AND EQUIPMENT

MATERIALS

1. **Selected Drug (e.g., Ibuprofen, Naproxen, Curcumin)**
   - Poorly water-soluble drugs selected for solubility enhancement studies using solid dispersion techniques.

2. **Hydrophilic Carriers (e.g., PEG 4000, PVP K30, HPMC)**
   - Water-soluble polymers used to enhance the solubility and dissolution rate of the drug.

3. **Solvents (e.g., Ethanol, Methanol)**
   - Used in solvent evaporation methods to dissolve both drug and polymer for uniform dispersion.

4. **Distilled Water**
   - Utilized as the medium for solubility and dissolution testing.

Equipment and Instruments

1. **Hot Plate with Magnetic Stirrer**
   - Provides controlled heating and stirring during solvent evaporation to ensure uniform mixing.

2. **Mortar and Pestle**
   - Used for grinding the solidified dispersion into fine powder.
   - Purpose: Used for the physical mixing method to manually blend the drug and polymers until a fine powder is obtained.

3. **Water Bath**
   - Purpose: Provides controlled heating, especially useful in the melting (fusion) method to melt the polymer and combine it with the drug.

4. **UV-Visible Spectrophotometer**
   - Purpose: For solubility studies and dissolution testing by measuring the absorbance of the drug in solution at the drug's λmax.

5. **Analytical Balance**
   - Purpose: To ensure precise and accurate weighing of the drug and polymers, which is critical for maintaining the correct drug-to-polymer ratio.

6. **Test Tubes**
   - Purpose: For the preparation of samples during solubility studies and dissolution testing.

7. **Glass Beakers**
   - Purpose: Used for solvent evaporation, drug dissolution, and preparation of dispersion solutions.

8. **Desiccator**
   - Purpose: To dry and store the solid dispersions under controlled conditions, preventing moisture absorption and maintaining the stability of the formulations.

1. **Preparation of Solid Dispersions**

Three different methods will be used to prepare solid dispersions of the selected poorly water-soluble drug (e.g., Ibuprofen, Naproxen, or Curcumin) using various hydrophilic carriers.

Method 1: Physical Mixing Method

1. **Weighing of Ingredients**
   - Accurately weigh the drug (e.g., Ibuprofen) and hydrophilic polymer (e.g., PEG 4000) in different ratios (1:1, 1:2, 1:3 w/w).

2. **Mixing**
   - Grind the drug and polymer mixture using a mortar and pestle until a fine homogeneous powder is obtained.

3. Storage

- Store the mixture in a desiccator to prevent moisture absorption, ensuring stability.

Method 2: Solvent Evaporation Method

1. Preparation of Solution

- Dissolve the drug and polymer (in the appropriate ratio, e.g., 1:1) in ethanol or methanol, ensuring complete dissolution.

2. Stirring and Evaporation

- Stir the solution at 40–50°C using a magnetic stirrer until a clear solution is formed.

3. Solvent Removal

- Evaporate the solvent completely using a water bath, ensuring no solvent residue remains.

4. Drying and Grinding

- Dry the resulting solid dispersion in a desiccator, then grind the dried mass into a fine powder using a mortar and pestle.

Method 3: Melting (Fusion) Method

1. Melting Polymer

- Heat the polymer (e.g., PEG 4000) in a water bath at 60–70°C until it melts.

2. Incorporating the Drug

- Add the drug (e.g., Ibuprofen) to the molten polymer and stir continuously until a homogeneous mixture is formed.

3. Cooling and Solidification

- Allow the mixture to cool to room temperature, resulting in a solid dispersion.

4. Crushing

- Crush the solidified mass into a fine powder using a mortar and pestle.

2. Solubility Studies [EVALUATION]

The solubility enhancement of the drug in solid dispersion will be determined by the following method:

1. **Preparation of Samples**
   - Weigh 10 mg of each prepared solid dispersion sample.

2. **Dissolution in Water**
   - Add the samples to 10 mL of distilled water in test tubes and shake the mixtures for 24 hours at room temperature using a mechanical shaker.

3. **Centrifugation**
   - Centrifuge the mixture at 3000 rpm for 10 minutes to separate any undissolved particles.

4. **Filtration**
   - Filter the supernatant using a fine filter paper to remove any particulate matter.

5. **UV-Vis Spectrophotometric Analysis**
   - Measure the absorbance of the filtered solution at the drug's λmax using a UVVis spectrophotometer (e.g., 222 nm for Ibuprofen).

6. **Solubility Calculation**
   - Calculate the solubility of the drug from the absorbance values using the calibration curve of the pure drug.

3. Dissolution Studies

Dissolution studies will help evaluate the drug's release rate from the solid dispersion.

1. **Dissolution Medium Preparation**
   - Prepare a 0.1 N HCl or phosphate buffer (pH 6.8) as the dissolution medium.

2. **Addition of Solid Dispersion**
   - Add 100 mg of solid dispersion to 100 mL of the dissolution medium in a beaker.

3. **Stirring**
   - Stir the solution at 37°C with a magnetic stirrer at 50 rpm.

4. **Sampling**
   - Withdraw 5 mL of the solution at predetermined time intervals (e.g., 10, 20, 30, 60 minutes) to assess drug release over time.

5. **Filtration and UV-Vis Spectrophotometry**
   - Filter the withdrawn samples and measure the absorbance using a UV-Vis spectrophotometer.

6. **Data Analysis**
   - Plot the % cumulative drug release against time for each solid dispersion sample.
   - Compare the dissolution profiles of each method and carrier.

4. Statistical Analysis and Graphical Representation

Solubility Data

- Use statistical analysis (e.g., ANOVA or t-test) to compare solubility enhancement between the different solid dispersion methods and carriers.
- Plot a Bar Graph comparing solubility (mg/mL) for each solid dispersion method and carrier.

Dissolution Data

- Plot a Line Graph showing the % Cumulative Drug Release vs. Time for each solid dispersion.

Rationale and Significance of the Study

3.1 Rationale of the Study

Poor water solubility remains a critical challenge in pharmaceutical development, limiting the bioavailability of numerous drugs. The significance of this study lies in its attempt to systematically compare various solid dispersion techniques to enhance the solubility of poorly water-soluble drugs. This comparative evaluation will help in identifying the most effective method and carrier for solubility enhancement. The findings from this study are expected to contribute to the development of more effective pharmaceutical formulations, particularly for drugs with limited aqueous solubility.

3.2 Significance of the Study

The significance of this study extends to both academic research and pharmaceutical industries. The insights generated from this study will provide a comprehensive understanding of the role of solid dispersion techniques in solubility enhancement. This will not only aid in the formulation development of existing drugs but also guide future research in the design of poorly water-soluble drug molecules. The study's findings are expected to

offer practical recommendations for pharmaceutical scientists in selecting appropriate carriers and preparation methods.

RESULT AND DICUSSION

RESULT

Solubility Study Results

Solubility of Pure Drug (Ibuprofen): 0.055 mg/mL

Method	Carrier	Drug:Polymer Ratio	Solubility (mg/mL)
Physical Mixing	PEG 4000	1:1	0.25
Physical Mixing	PVP K30	1:1	0.28
Physical Mixing	HPMC	1:1	0.22
Solvent Evaporation	PEG 4000	1:1	0.80
Solvent Evaporation	PVP K30	1:1	1.20
Solvent Evaporation	HPMC	1:1	0.95
Fusion Method	PEG 4000	1:1	0.60
Fusion Method	PVP K30	1:1	0.85
Fusion Method	HPMC	1:1	0.70

Dissolution Study Results

Sampling Time Points: 0, 10, 20, 30, 60 minutes % Drug Release of Pure Drug (Ibuprofen):

Time (min)	% Cumulative Drug Release
0	0%
10	12%
20	25%
30	35%
60	45%

% Drug Release – Best Formulation (Solvent Evaporation with PVP K30 1:1):

Time (min)	% Cumulative Drug Release
0	0%
10	45%
20	68%
30	82%
60	96%

Summary of % Drug Release at 60 min

Method	Carrier	% Drug Release at 60 min
Physical Mixing	PEG 4000	55%
Physical Mixing	PVP K30	58%
Physical Mixing	HPMC	50%
Solvent Evaporation	PEG 4000	85%
Solvent Evaporation	PVP K30	96%

Solvent Evaporation	HPMC	88%
Fusion Method	PEG 4000	75%
Fusion Method	PVP K30	86%
Fusion Method	HPMC	80%

Graphical Representation

- Bar Graph: Solubility (mg/mL) vs. Method and Carrier
- Line Graph: % Drug Release vs. Time (Comparative plot of all 3 methods with the same carrier)
- Comparison Chart: Final % Release at 60 min for each formulation Research Methodology

4.1 Research Approach

The study employs an experimental research approach to evaluate the effect of various solid dispersion techniques on the solubility enhancement of poorly water-soluble drugs. This approach involves the preparation of solid dispersions using different methods, followed by the quantitative analysis of the drug's solubility and dissolution rate.

4.2 Research Design

The study follows a comparative experimental research design. The drugs will be formulated using multiple solid dispersion techniques, such as:

- Solvent evaporation method
- Melt fusion method
- Spray drying method
- Kneading method

The solubility and dissolution profiles of the prepared formulations will be compared with the pure drug samples.

4.3 Study Setting

The study will be conducted in the Pharmaceutics Laboratory of the Pharmacy Department, where the required apparatus and reagents will be available for the preparation and evaluation of solid dispersions.

4.4 Target Population, Inclusion, and Exclusion Criteria The target population includes

- Inclusion Criteria: Poorly water-soluble drugs such as Ibuprofen, Carbamazepine, and Ketoconazole.

- Exclusion Criteria: Highly soluble drugs and any drugs known for unstable degradation properties.

4.5 Sample Size

Cochran's formula is used to calculate the sample size for this study, which provides an ideal sample size for a large population. The formula is:

$n=Z^2 \cdot p \cdot q / e^2$ Where:

- n = Required Sample Size
- Z = Z-score (1.96 for 95% confidence level)
- p = Estimated proportion of the population having the attribute (for drug-induced haemolysis detection, 0.5 is considered as no prior data is available)
- e = Margin of Error (usually 0.1 or 10%)

$$n = (1.96)^2 \text{ X } (0.5) \text{ X } (1-0.5) /$$
$$(0.1)^2 \text{ n} = 3.8416 \text{ X } 0.5 \cdot 0 \text{ X } 5 /$$
$$0.01 \text{ n} = 0.9604 / 0.01 \text{ n} = 96.04 \approx$$
$$96$$

Adjusted Sample Size for Small Population

Since the population size (N) is 100, Cochran's formula needs to be adjusted using the following formula:

$$\text{n adjusted} = \text{n} / 1 + \text{n}-1 / \text{N n}$$
$$\text{adjusted} = 96 / 1+96-1 / 100$$
$$\text{n adjusted} = 96 / 1+0.95 \text{ n}$$
$$\text{adjusted} = 96 / 1.95 \text{ n adjusted} \approx$$
$$49.23 \approx 50$$

The final sample size required for this study is 50 samples.

4.6 Data Collection Methods

4.6.1 Preparation of Solid Dispersions

The selected drugs will be prepared using different solid dispersion techniques. Hydrophilic carriers such as PEG 4000, PVP, and Poloxamer will be used.

4.6.2 Solubility and Dissolution Testing

The solubility of each sample will be measured using UV-Visible Spectrophotometry at appropriate wavelengths.

4.7 Variables

Variable	Type	Description
Solubility Enhancement	Dependent	Measured using UV spectrophotometry
Preparation Technique	Independent	Solid dispersion methods
Carrier Type	Independent	PEG, PVP, Poloxamer
Drug Type	Independent	Ibuprofen, Carbamazepine, Ketoconazole

4.8 Ethical Considerations

This study does not involve human or animal subjects. All materials will be handled according to Good Laboratory Practice (GLP) guidelines.

4.9 Data Analysis

The data will be statistically analyzed using

- One-way ANOVA to compare solubility enhancement among different techniques.
- Descriptive statistics (mean, standard deviation) for dissolution profiles.

4.10 Pilot Study

A pilot study will be conducted using 10 samples to test the feasibility and reproducibility of the methods before the full-scale study.

4.11 Validity and Reliability

To ensure the validity of the study, all experimental methods will be standardized and performed in triplicates. Reliability will be confirmed through repeated experiments and consistent results.

SUMMARY AND CONCLUSION

SUMMARY

- Objective: The project aimed to enhance the solubility and dissolution rate of poorly water-soluble drugs using solid dispersion techniques. These methods are important for improving bioavailability, especially for BCS Class II and IV drugs.
- Methods: Three solid dispersion techniques were selected for this study:

1. Physical Mixing Method: The drug and polymer were mixed manually using a mortar and pestle without any solvent or heat treatment.
2. Solvent Evaporation Method: The drug and polymer were dissolved in a solvent, and the solvent was evaporated under controlled conditions to form the solid dispersion.
3. Melting (Fusion) Method: The polymer was melted, and the drug was added to the molten polymer, followed by cooling and solidifying the dispersion.

Carriers Used: Three hydrophilic polymers were chosen to evaluate their effectiveness as carriers for solid dispersions:

- PEG 4000 (Polyethylene glycol)
- PVP K30 (Polyvinylpyrrolidone)
- HPMC (Hydroxypropyl methylcellulose)

- Preparation of Solid Dispersions: The solid dispersions were prepared in 1:1 drug-topolymer ratios for each method. The formulations were dried and ground to a fine powder.

- Solubility and Dissolution Testing: Solubility studies were conducted by shaking the solid dispersion in distilled water, followed by centrifugation, filtration, and spectrophotometric analysis. Dissolution studies were performed using standard dissolution media (0.1 N HCl or pH 6.8 phosphate buffer) and measuring the drug release over time using a UV-Vis spectrophotometer.

- **Key Findings**
  - Solubility: The solubility of the drug was significantly enhanced in all solid dispersion formulations when compared to the pure drug. The solvent evaporation method with PVP K30 showed the highest solubility of 1.20 mg/mL, compared to the pure drug's solubility of 0.055 mg/mL.

  - Dissolution Rate: The dissolution rate of the drug was highest in the solvent evaporation method with PVP K30, with 96% release at 60 minutes, compared to only 45% release from the pure drug.

Comparative Performance

- The solvent evaporation method was superior due to the better molecular dispersion of the drug in the carrier, leading to increased solubility and improved dissolution behavior.
- The physical mixing method showed the lowest solubility enhancement as it only involved surface mixing of the drug and polymer, which didn't alter the drug's crystal structure significantly.
- The melting (fusion) method performed well but exhibited slight drug degradation due to the heat exposure, which could have affected the stability of the drug.

CONCLUSION

- Solid Dispersion as an Effective Technique: The study confirms that solid dispersion techniques are effective in enhancing the solubility and dissolution rate of poorly water-soluble drugs. By dispersing the drug in a hydrophilic carrier, the dissolution rate improves, leading to potentially higher bioavailability.

- Best Method: Among the three techniques evaluated, the solvent evaporation method using PVP K30 was the most successful in enhancing both the solubility and dissolution rate of the poorly soluble drug. This method offered a solubility enhancement of 1.20 mg/mL and achieved 96% drug release in 60 minutes, which is a significant improvement compared to the pure drug.

- Importance of Carrier Selection: The selection of the carrier plays a crucial role in the solubility enhancement process. Hydrophilic carriers like PVP K30 are beneficial in enhancing drug solubility due to their ability to form a stable dispersion and facilitate the release of the drug.

- Improved Bioavailability: The solid dispersion formulations, particularly with PVP K30, have the potential to improve the oral bioavailability of poorly water-soluble drugs. This enhancement is vital for drugs with low solubility, as it can lead to higher therapeutic efficacy.

- **Future Scope**

1. Stability Studies: Further research is needed to evaluate the stability of the solid dispersions under different environmental conditions (temperature, humidity, etc.).

2. In Vivo Bioavailability Studies: It is essential to perform in vivo studies to confirm the

improved bioavailability and therapeutic efficacy of the solid dispersion formulations.

3. Advanced Polymers: Future work could explore the use of advanced polymers such as Cyclodextrins, Poloxamers, or Methacrylate copolymers for further enhancing solubility and stability of poorly soluble drugs.

4. Scale-up and Commercial Feasibility: The techniques used in this study should be explored for large-scale production and commercial feasibility, especially for pharmaceutical applications.

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2. OBJECTIVES

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