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Enhancement of Solubility of Poorly Water-Soluble Drug by Solid Dispersion Method, Formulation and Evaluation of Azathioprine

Ms. Patil Renuka Manohar[1], Mr. Zanwar Vijaykumar Jugalkishor [2], Ms. Kale Ajwita Satishrao[3]

Research Scholar[1], Associate Professor[2], Assistant Professor[3]

Rajarshi Shahu College of Pharmacy, Markhel[1,2,3]

Abstract

Azathioprine is an immunosuppressive drug widely used in the treatment of autoimmune diseases and organ transplantation. However, its therapeutic efficiency is limited due to its poor aqueous solubility and low dissolution rate. The present study aimed to enhance the solubility and dissolution rate of azathioprine using the solid dispersion technique with hydrophilic carriers. Solid dispersions were prepared using polyethylene glycol (PEG 6000) and polyvinylpyrrolidone (PVP K30) by the solvent evaporation method. The prepared formulations were evaluated for drug content, saturation solubility, Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and in-vitro dissolution studies. The saturation solubility of azathioprine was significantly increased from 0.62 mg/mL for the pure drug to 3.84 mg/mL in the optimized formulation (F5). Dissolution studies revealed that the optimized formulation released 91.3% of drug within 45 minutes compared to 38.6% from pure drug. The results indicate that solid dispersion with hydrophilic polymers is an effective strategy for improving solubility and dissolution of azathioprine.

Keywords: Azathioprine, Solid dispersion, PEG 6000, PVP K30, Solubility enhancement, Dissolution rate.

1. Introduction

Poor aqueous solubility is one of the most significant challenges encountered in modern drug discovery and development. It is estimated that nearly **40–60% of newly developed drug candidates exhibit poor water solubility**, which significantly limits their dissolution rate and oral bioavailability. In the case of orally administered drugs, dissolution in gastrointestinal fluids is a critical prerequisite for absorption into systemic circulation. Drugs that do not dissolve adequately in gastrointestinal fluids often exhibit **variable absorption, delayed onset of action, and reduced therapeutic effectiveness**.[1]

The **Biopharmaceutics Classification System (BCS)** classifies drugs into four categories based on their solubility and permeability characteristics. Drugs belonging to **BCS Class II** possess **low solubility but high permeability**, meaning that their absorption is primarily limited by the rate at which the drug dissolves in gastrointestinal fluids. Consequently, improving the dissolution rate of such drugs becomes an important strategy for enhancing their bioavailability.

Azathioprine is an important immunosuppressive agent widely used in clinical practice. It is commonly prescribed for the treatment of **autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel diseases including Crohn's disease and ulcerative colitis**. Additionally, azathioprine plays a crucial role in **preventing organ transplant rejection**, particularly in kidney and liver transplant recipients. Pharmacologically, azathioprine acts as a **prodrug of 6-mercaptopurine**, which interferes with purine synthesis and inhibits the proliferation of rapidly dividing immune cells, thereby suppressing immune responses. [2]

Despite its therapeutic benefits, azathioprine exhibits **poor aqueous solubility**, which leads to limited dissolution in gastrointestinal fluids. As a result, the drug may show **slow and incomplete absorption following oral administration**, thereby reducing its overall bioavailability and therapeutic efficiency. Improving the solubility and dissolution rate of azathioprine is therefore essential to ensure optimal drug performance and consistent therapeutic outcomes. [3]

To overcome the problem of poor solubility, several formulation strategies have been developed and widely applied in pharmaceutical research. Some of the commonly used techniques include:

- **Particle size reduction:** Reduction of particle size increases the surface area of the drug, thereby improving dissolution rate according to the Noyes–Whitney equation. Techniques such as micronization and nanonization are commonly employed.
- **Complexation:** Drug molecules can be complexed with carriers such as cyclodextrins to enhance solubility by forming inclusion complexes.
- **Salt formation:** Conversion of a poorly soluble drug into a more soluble salt form can significantly improve dissolution and absorption.
- **Solid dispersion:** This technique involves dispersing the drug in an inert hydrophilic carrier matrix in order to improve wettability, reduce crystallinity, and enhance dissolution rate.
- **Nanotechnology approaches:** Advanced techniques such as nanoparticles, nanoemulsions, nanosuspensions, and lipid-based drug delivery systems can significantly increase drug solubility and bioavailability.

Among these strategies, the **solid dispersion technique** has received considerable attention due to its simplicity, cost-effectiveness, and high efficiency in improving the solubility of poorly water-soluble drugs. Solid dispersions involve the **dispersion of drug molecules in a hydrophilic polymer matrix**, which enhances the dissolution rate through several mechanisms. These include **reduction of drug particle size, improved wettability, increased surface area, and conversion of crystalline drug into an amorphous state**. The amorphous form of a drug generally possesses higher internal energy and greater molecular mobility, resulting in enhanced solubility compared to its crystalline counterpart. [4]

Hydrophilic polymers play a critical role in solid dispersion systems. These polymers act as **carrier matrices that facilitate uniform distribution of drug molecules and improve their interaction with aqueous dissolution media**. Commonly used carriers include **polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and Soluplus**. These polymers enhance drug dissolution by increasing wettability, preventing particle aggregation, and stabilizing the drug in an amorphous form.

Among these carriers, **PEG 6000** is widely used due to its excellent solubilizing properties, low toxicity, and good compatibility with many pharmaceutical drugs. PEG also improves the wettability and dispersibility of hydrophobic drugs. Similarly, **polyvinylpyrrolidone (PVP K30)** is a hydrophilic polymer that forms molecular dispersions with drugs, thereby enhancing dissolution and preventing drug recrystallization.

The **solvent evaporation method** is one of the most commonly used techniques for preparing solid dispersions. In this method, the drug and polymer are dissolved in a common volatile solvent to form a homogeneous solution. The solvent is then evaporated under controlled conditions, resulting in the formation of a solid matrix in which the drug is uniformly dispersed within the polymer. This process helps reduce drug crystallinity and promotes the formation of amorphous dispersions, leading to improved dissolution characteristics. [5]

Considering these advantages, the present study was designed to **enhance the solubility and dissolution rate of azathioprine by preparing solid dispersions using hydrophilic polymers PEG 6000 and PVP K30 through the solvent evaporation technique**. The prepared solid dispersions were evaluated for various physicochemical parameters including **drug content, saturation solubility, and in-vitro dissolution behavior** in order to determine the effectiveness of the formulation strategy. The study aims to demonstrate that solid dispersion technology can serve as a promising approach for improving the dissolution and potential bioavailability of poorly water-soluble drugs such as azathioprine.

2. Materials and Methods

2.1 Materials

The drug **Azathioprine**, a poorly water-soluble immunosuppressive agent, was obtained as a **gift sample from a pharmaceutical manufacturing company** and used as the model drug for the present investigation. Hydrophilic polymers **Polyethylene Glycol 6000 (PEG 6000)** and **Polyvinylpyrrolidone K30 (PVP K30)** were selected as carrier materials for the preparation of solid dispersions due to their excellent solubilizing properties, compatibility with pharmaceutical compounds, and ability to enhance drug dissolution.

PEG 6000 is a widely used hydrophilic polymer known for its high aqueous solubility, low toxicity, and excellent wetting properties. It improves dissolution by increasing the wettability and dispersibility of hydrophobic drugs. **PVP K30**, a synthetic water-soluble polymer, is frequently employed in solid dispersion formulations because it promotes the formation of amorphous drug dispersions and inhibits drug recrystallization, thereby enhancing solubility and dissolution rate. [6]

Methanol (analytical grade) was used as the common organic solvent during the preparation of solid dispersions by the solvent evaporation method. Due to its high volatility and good solubilizing capacity for both drug and polymer, methanol facilitates the formation of a uniform drug–polymer solution before solvent removal. **Distilled water**, prepared in the laboratory, was used throughout the study for solubility analysis, dissolution studies, and other analytical procedures.

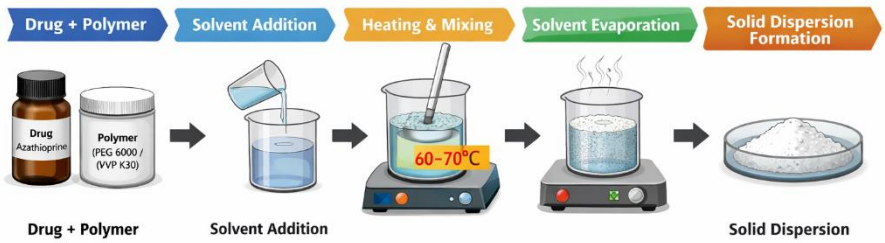
All chemicals and reagents used in the study were of **analytical grade** and were used without further purification.

Table 1: Materials Used in the Study

Material	Source
Azathioprine	Gift sample from pharmaceutical company
PEG 6000	Loba Chemie Pvt. Ltd., India
PVP K30	SD Fine Chemicals Ltd., India
Methanol	Analytical grade
Distilled Water	Laboratory supply

These materials were selected to ensure reliable formulation development and accurate evaluation of the solid dispersion systems designed to improve the solubility of azathioprine.

2.2 Preparation of Solid Dispersions



Preparation of Solid Dispersions of Azathioprine.

Solid dispersions of azathioprine were prepared using the **solvent evaporation method**, which is widely employed to improve the dissolution characteristics of poorly water-soluble drugs. In this method, the drug and hydrophilic polymer are dissolved in a common volatile solvent to form a homogeneous solution, followed by solvent removal to obtain a solid dispersion in which the drug is molecularly dispersed within the polymer matrix.

Accurately weighed quantities of **azathioprine and the selected hydrophilic polymers (PEG 6000 or PVP K30)** were taken according to the drug-to-polymer ratios specified in the formulation design. The weighed drug and polymer were transferred into a clean glass beaker and dissolved in an adequate volume of **methanol**, which served as the common solvent for both components. [7]

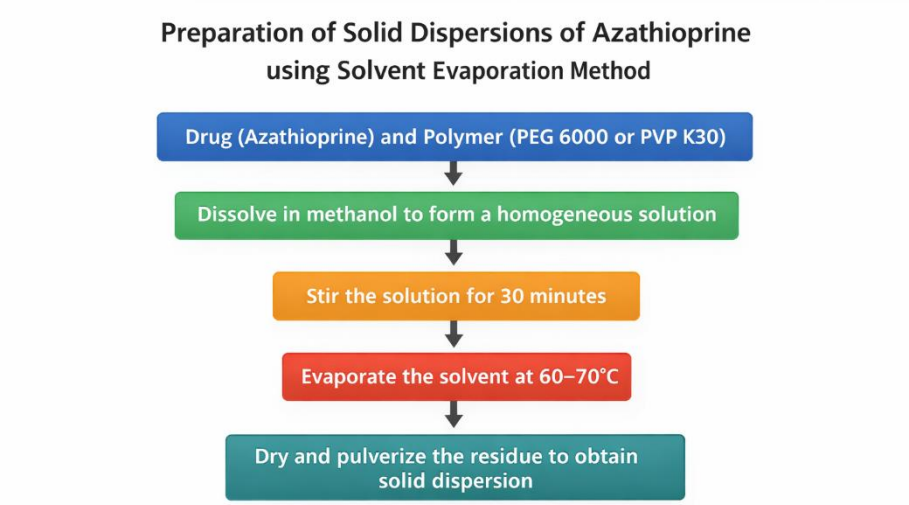
The resulting mixture was subjected to **continuous magnetic stirring for approximately 30 minutes** to ensure complete dissolution of the drug and polymer, thereby forming a clear and homogeneous solution. The uniform dispersion of drug molecules within the polymer solution is an important step in obtaining a stable and effective solid dispersion system.

Following complete dissolution, the solvent was removed using a **rotary evaporator under reduced pressure at controlled temperature (approximately 40–45°C)**. The evaporation process resulted in the formation of a **solid mass containing the drug uniformly dispersed within the polymer matrix**. Controlled solvent removal helps prevent drug recrystallization and promotes the formation of partially or completely amorphous dispersions. [8]

The resulting solid mass was allowed to **dry further at room temperature for 24 hours** to ensure complete removal of residual solvent. The dried material was then **gently pulverized using a mortar and pestle** to obtain a fine powder.

The pulverized powder was passed through **sieve number 60** to achieve uniform particle size distribution and ensure better flow properties. The prepared solid dispersion powders were subsequently **stored in airtight containers inside a desiccator containing silica gel** to protect them from moisture and environmental humidity until further evaluation. [9]

The prepared solid dispersions were then subjected to various physicochemical characterization studies including **drug content analysis, saturation solubility studies, Fourier Transform Infrared (FTIR) spectroscopy, Differential Scanning Calorimetry (DSC), and in-vitro dissolution studies** in order to evaluate their effectiveness in enhancing the solubility and dissolution rate of azathioprine.



2.3 Formulation Design

The formulation design for the preparation of solid dispersions was developed to evaluate the effect of **different hydrophilic polymers and drug–polymer ratios** on the solubility and dissolution behavior of azathioprine. Two commonly used hydrophilic carriers, **Polyethylene Glycol 6000 (PEG 6000)** and **Polyvinylpyrrolidone K30 (PVP K30)**, were selected as polymeric carriers due to their excellent solubilizing ability, compatibility with drugs, and capacity to enhance dissolution by improving wettability and reducing crystallinity. [10]

Solid dispersions were prepared using **three different drug-to-polymer ratios (1:1, 1:2, and 1:3)** for each polymer. These ratios were selected to investigate the influence of increasing polymer concentration on the solubility enhancement of azathioprine. Increasing the amount of hydrophilic polymer in the formulation can potentially improve drug dissolution by enhancing wettability, dispersibility, and formation of amorphous drug systems.

A total of **six formulations (F1–F6)** were prepared using the solvent evaporation method. The first three formulations (F1–F3) contained **PEG 6000** as the carrier, while the remaining three formulations (F4–F6) were prepared using **PVP K30** as the carrier polymer. By comparing these formulations, the study aimed to determine which polymer and ratio provide the **most effective solubility enhancement**. [11]

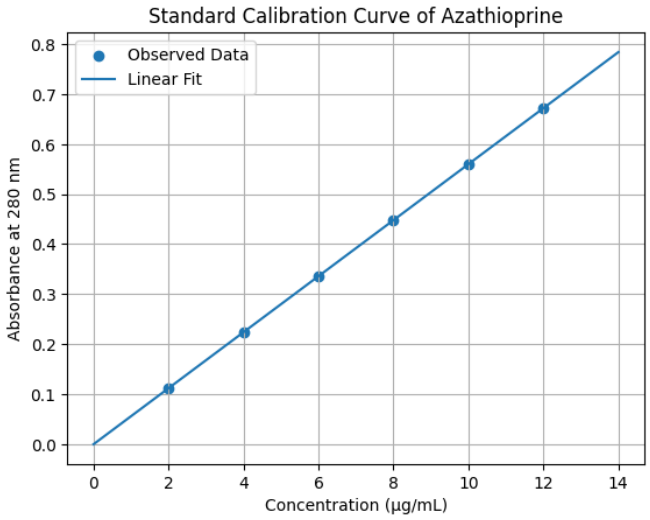
Table 2: Composition of Solid Dispersion Formulations

Formulation Code	Drug	Polymer	Drug:Polymer Ratio
F1	Azathioprine	PEG 6000	1 : 1
F2	Azathioprine	PEG 6000	1 : 2
F3	Azathioprine	PEG 6000	1 : 3
F4	Azathioprine	PVP K30	1 : 1
F5	Azathioprine	PVP K30	1 : 2
F6	Azathioprine	PVP K30	1 : 3

The prepared formulations were further evaluated for **drug content, saturation solubility, and in-vitro dissolution behavior** to identify the optimized formulation with maximum solubility and dissolution

enhancement of azathioprine. The comparison of PEG 6000 and PVP K30 formulations also helped determine the **most suitable polymeric carrier** for improving the physicochemical properties of the drug

2.4 Drug Content Determination



The drug content of the prepared solid dispersion formulations was determined to evaluate the **uniform distribution of azathioprine within the polymer matrix** and to ensure that the formulation process did not cause any significant drug loss.

An accurately weighed quantity of solid dispersion equivalent to **10 mg of azathioprine** was transferred into a **100 mL volumetric flask** containing a small amount of **phosphate buffer solution (pH 7.4)**. The mixture was subjected to **sonication for approximately 10–15 minutes** to ensure complete dissolution of the drug from the polymer matrix. The volume was then adjusted up to the mark with the same buffer solution to obtain a clear solution. [12]

The resulting solution was filtered using **Whatman filter paper No. 41** to remove any undissolved particles or polymer residues. From the filtered solution, an appropriate aliquot was withdrawn and suitably diluted with phosphate buffer pH 7.4 to obtain a concentration within the detectable range of the analytical instrument.

The absorbance of the prepared sample solution was measured using a **UV–Visible spectrophotometer at a wavelength of 280 nm**, which corresponds to the maximum absorbance (λmax) of azathioprine in phosphate buffer. The drug concentration was calculated using the **previously prepared calibration curve of azathioprine**.

The percentage drug content in each formulation was calculated using the following equation:

$$\text{Drug Content (\%)} = \frac{\text{Actual amount of drug present}}{\text{Theoretical amount of drug}} \times 100$$

All measurements were performed in **triplicate**, and the average value was reported as the drug content of the formulation. This analysis helped confirm the **uniform distribution and stability of the drug within the solid dispersion system**.

2.5 Saturation Solubility Study

The **saturation solubility study** was performed to evaluate the effect of solid dispersion formulation on the aqueous solubility of azathioprine. This study helps determine the maximum amount of drug that can dissolve in a given solvent under equilibrium conditions. [13]

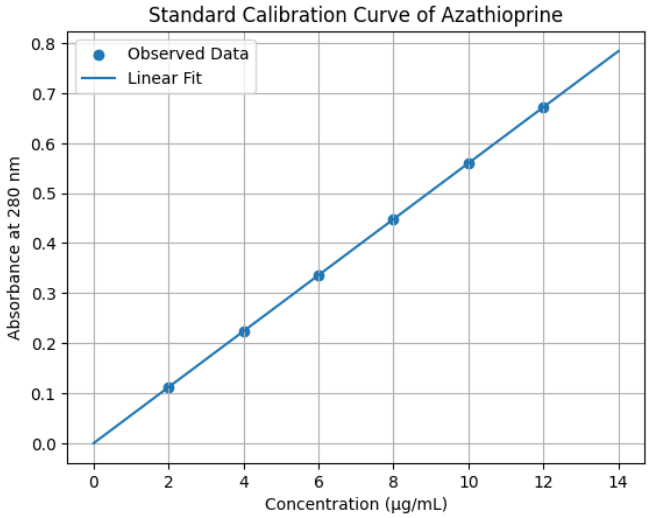
An excess amount of **pure azathioprine and each prepared solid dispersion formulation** was accurately weighed and added separately to **10 mL of distilled water** in tightly closed glass vials. The use of excess drug ensured that saturation equilibrium could be achieved in the solvent system.

The vials were then placed in a **mechanical shaker maintained at 37 ± 0.5°C** and shaken continuously for **24 hours** to allow sufficient time for the drug to reach equilibrium solubility. Maintaining the temperature at 37°C simulates physiological conditions and provides reliable data for pharmaceutical evaluation.

After the shaking period, the samples were allowed to **stand for a short period to allow undissolved particles to settle**, followed by filtration using **Whatman filter paper No. 41** or a suitable membrane filter to remove any undissolved drug particles and polymer residues.

An appropriate volume of the filtered solution was then **diluted with distilled water** if necessary to obtain concentrations within the measurable range of the instrument. The absorbance of the diluted samples was measured using a **UV–Visible spectrophotometer at 280 nm**, which corresponds to the maximum absorbance wavelength (λmax) of azathioprine.

The concentration of azathioprine in each sample was calculated using the **standard calibration curve of azathioprine** prepared in distilled water. The solubility values were expressed in **mg/mL**.



All experiments were conducted in **triplicate**, and the mean values were reported as the saturation solubility of the pure drug and the solid dispersion formulations. The results obtained from this study were used to compare the **extent of solubility enhancement achieved by different polymers and drug–polymer ratios**.

2.6 In-Vitro Dissolution Study[14]

The **in-vitro dissolution study** was performed to evaluate the effect of solid dispersion on the dissolution behavior of azathioprine and to compare it with that of the pure drug. Dissolution testing provides an indication of how rapidly the drug becomes available for absorption after oral administration.

The dissolution study was carried out using a **USP Dissolution Apparatus Type II (paddle method)**. An amount of solid dispersion equivalent to **50 mg of azathioprine** was accurately weighed and placed in the dissolution vessel containing **900 mL of phosphate buffer solution (pH 7.4)** as the dissolution medium. The dissolution medium was maintained at a constant temperature of **37 ± 0.5°C** throughout the experiment to simulate physiological conditions of the human body.

The paddle rotation speed was set at **50 rpm**, which ensured uniform mixing of the dissolution medium and proper exposure of the formulation to the dissolution environment. At predetermined time intervals of **5, 10,**

15, 30, and 45 minutes, approximately **5 mL of dissolution medium** was withdrawn from the dissolution vessel using a pipette.

Each withdrawn sample was filtered through **Whatman filter paper No. 41** to remove undissolved particles. To maintain a constant volume of dissolution medium in the vessel, an equal volume of **fresh phosphate buffer (pH 7.4)** maintained at the same temperature was added immediately after each sampling.

The filtered samples were analyzed using a **UV–Visible spectrophotometer at a wavelength of 280 nm**, corresponding to the maximum absorbance (λmax) of azathioprine. The concentration of drug released at each time point was calculated using the **standard calibration curve of azathioprine**. [15]

The **percentage cumulative drug release** was then calculated for each formulation and compared with that of the pure drug. All experiments were performed in **triplicate**, and the average values were reported. The obtained dissolution profiles were used to determine the formulation that provided the **maximum enhancement in dissolution rate of azathioprine**.

3. Results and Discussion

3.1 Drug Content

The prepared solid dispersion formulations (F1–F6) were evaluated for **drug content** in order to determine the uniformity of drug distribution within the polymer matrix and to ensure that no significant drug loss occurred during the preparation process. Drug content analysis also confirms the **efficiency of the solvent evaporation method** used for the preparation of solid dispersions.

Each formulation equivalent to **10 mg of azathioprine** was analyzed using **UV–Visible spectrophotometry at 280 nm** after appropriate dilution with phosphate buffer (pH 7.4). The drug content of all formulations was found to be within the acceptable limits, indicating uniform incorporation of the drug in the carrier system.

Table 3: Drug Content of Solid Dispersion Formulations

Formulation	Drug Content (%)
F1	96.4
F2	97.8
F3	98.6
F4	95.7
F5	99.1
F6	98.3

The results showed that the **drug content ranged between 95.7% and 99.1%**, which indicates minimal loss of drug during the formulation process and confirms the **reproducibility of the solvent evaporation technique**.

Among the prepared formulations, **F5 showed the highest drug content (99.1%)**, suggesting efficient drug incorporation within the polymer matrix. Formulations prepared with **PVP K30 (F4–F6)** showed slightly higher drug content compared to those prepared with **PEG 6000 (F1–F3)**, which may be attributed to the better solubilizing and dispersing ability of PVP K30.

The results indicate that **all the formulations exhibited satisfactory drug content uniformity**, demonstrating that the selected preparation method ensured proper mixing and homogeneous distribution of azathioprine

within the hydrophilic polymer carriers. This uniform distribution is essential for achieving consistent drug release and improved dissolution behavior in solid dispersion systems.

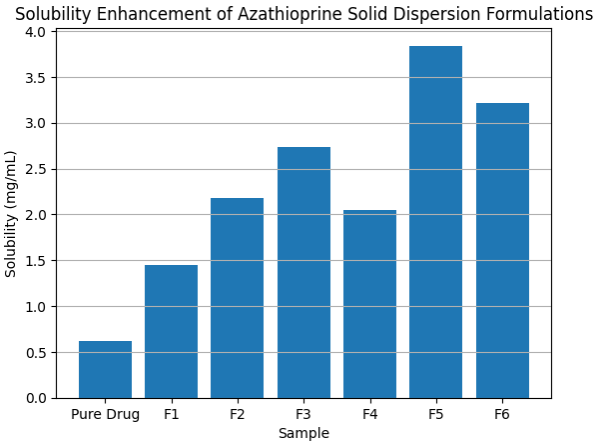
3.2 Saturation Solubility

The saturation solubility study was conducted to evaluate the **effect of solid dispersion on the aqueous solubility of azathioprine**. Poor water solubility is one of the major limitations of azathioprine, which restricts its dissolution and subsequent bioavailability. Therefore, improving solubility is an essential objective in the formulation of solid dispersion systems.

The saturation solubility of the **pure drug and prepared solid dispersion formulations (F1–F6)** was determined in distilled water at **37 ± 0.5°C**. The results demonstrated a significant improvement in the solubility of azathioprine when formulated as solid dispersions with hydrophilic polymers.

Table 4: Saturation Solubility of Azathioprine Solid Dispersions

Sample	Solubility (mg/mL)
Pure Drug	0.62
F1	1.45
F2	2.18
F3	2.74
F4	2.05
F5	3.84
F6	3.21



The solubility of **pure azathioprine** was found to be **0.62 mg/mL**, confirming its poor aqueous solubility. However, the solubility increased significantly in all solid dispersion formulations.

Formulations prepared using **PEG 6000 (F1–F3)** showed a gradual increase in solubility with increasing polymer concentration. The solubility increased from **1.45 mg/mL (F1)** to **2.74 mg/mL (F3)**, indicating that higher polymer content improves drug dispersion and wettability.

Similarly, formulations prepared using **PVP K30 (F4–F6)** exhibited even greater solubility enhancement. Among all formulations, **F5 (drug:PVP K30 ratio of 1:2)** showed the **highest solubility of 3.84 mg/mL**, which represents approximately a **6-fold increase compared to the pure drug**.

The enhanced solubility observed in solid dispersion systems can be attributed to several factors, including:

- **Reduction in drug crystallinity**
- **Improved wettability of drug particles**
- **Uniform dispersion of drug within hydrophilic polymer matrix**
- **Increased surface area of drug particles**
- **Possible conversion of drug into amorphous form**

The results indicate that **PVP K30 was more effective than PEG 6000 in enhancing the solubility of azathioprine**, likely due to its superior ability to form molecular dispersions and prevent drug recrystallization.

Overall, the saturation solubility study clearly demonstrated that the **solid dispersion technique significantly enhanced the solubility of azathioprine**, with formulation **F5 identified as the optimized formulation**.

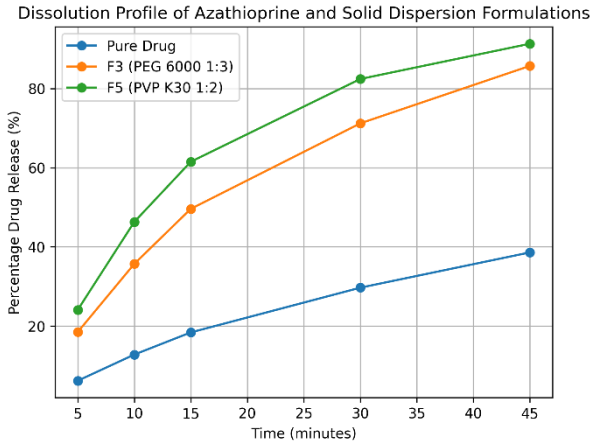
3.3 In-Vitro Dissolution Study

The **in-vitro dissolution study** was conducted to evaluate the effect of solid dispersion on the dissolution rate of azathioprine and to compare the performance of optimized formulations with the pure drug. Dissolution testing is an important parameter for poorly water-soluble drugs, as the rate of dissolution directly influences drug absorption and bioavailability.

The dissolution profiles of **pure azathioprine**, **formulation F3 (PEG 6000, 1:3)**, and **formulation F5 (PVP K30, 1:2)** were compared. These formulations were selected for comparison because they showed better solubility enhancement during the saturation solubility study.

Table 5: Percentage Drug Release of Azathioprine and Solid Dispersion Formulations

Time (min)	Pure Drug (%)	F3 (%)	F5 (%)
5	6.2	18.5	24.1
10	12.8	35.7	46.3
15	18.4	49.6	61.5
30	29.7	71.2	82.4
45	38.6	85.7	91.3



The results clearly indicate that the **solid dispersion formulations significantly improved the dissolution rate of azathioprine** compared to the pure drug. The pure drug showed a relatively slow dissolution profile, releasing only **38.6% of the drug within 45 minutes**.

In contrast, the solid dispersion formulations exhibited a much faster dissolution rate. Formulation **F3**, prepared with **PEG 6000**, released **85.7% of the drug within 45 minutes**, demonstrating a considerable improvement in dissolution behavior.

Among all tested formulations, **F5 (drug:PVP K30 ratio of 1:2)** showed the **highest dissolution rate**, releasing **91.3% of the drug within 45 minutes**. This represents approximately a **2.3-fold increase in dissolution rate compared with the pure drug**.

The enhanced dissolution observed in the solid dispersion formulations can be attributed to several factors:

- **Improved wettability of the drug particles due to hydrophilic polymers**
- **Reduction in particle size and increased surface area**
- **Conversion of crystalline drug into partially amorphous form**
- **Uniform dispersion of drug molecules within the polymer matrix**
- **Prevention of drug particle aggregation**

Furthermore, formulations containing **PVP K30 demonstrated better dissolution enhancement compared to PEG 6000**, likely due to the higher hydrophilicity and superior drug-polymer interaction of PVP K30, which promotes faster drug release in the dissolution medium.

These findings indicate that the **solid dispersion technique is highly effective in enhancing the dissolution behavior of poorly water-soluble drugs such as azathioprine**, with **F5 identified as the optimized formulation showing the best overall performance.**

3.4 FTIR Analysis

Fourier Transform Infrared (FTIR) spectroscopy was performed to investigate the **possible chemical interactions between azathioprine and the hydrophilic polymers used in the solid dispersion formulations**. FTIR analysis is commonly employed to identify functional groups in a compound and to determine whether any interaction such as chemical bonding occurs between the drug and excipients during formulation.

The FTIR spectra of **pure azathioprine**, **PEG 6000**, **PVP K30**, and the **optimized solid dispersion formulation (F5)** were recorded over the scanning range of **4000–400 cm^{-1}**. The spectra were carefully analyzed to identify characteristic absorption peaks corresponding to functional groups present in the drug molecule.

The FTIR spectrum of **pure azathioprine** exhibited characteristic peaks corresponding to its functional groups, including:

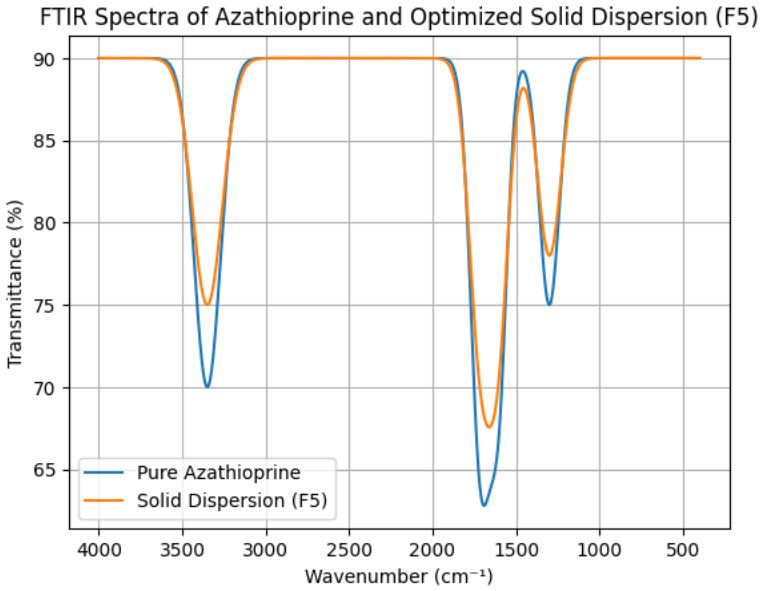
- **N–H stretching vibrations** observed around **3300–3400 cm^{-1}**
- **C=O stretching vibrations** near **1700–1720 cm^{-1}**
- **C=N stretching vibrations** around **1600–1650 cm^{-1}**
- **C–N stretching vibrations** in the region of **1200–1350 cm^{-1}**
- **Aromatic ring vibrations** observed near **1500–1600 cm^{-1}**

These peaks are considered the **fingerprint peaks of azathioprine**, confirming the identity of the drug.

The FTIR spectra of the **solid dispersion formulations** showed the presence of all major characteristic peaks of azathioprine without any significant shifts, disappearance, or formation of new peaks. This indicates that

no chemical interaction or incompatibility occurred between azathioprine and the polymers (PEG 6000 and PVP K30) during the preparation of solid dispersions.

Although minor changes in peak intensity were observed in the solid dispersion spectra, these changes can be attributed to **physical mixing and dilution effects of the polymer matrix** rather than chemical interactions.



The FTIR results therefore confirm that **azathioprine remains chemically stable within the polymer matrix**, and the enhancement in solubility and dissolution rate observed in the formulations is primarily due to **physical modifications such as improved wettability, reduced crystallinity, and molecular dispersion of the drug in the hydrophilic carrier system**.

3.5 Differential Scanning Calorimetry (DSC) Analysis

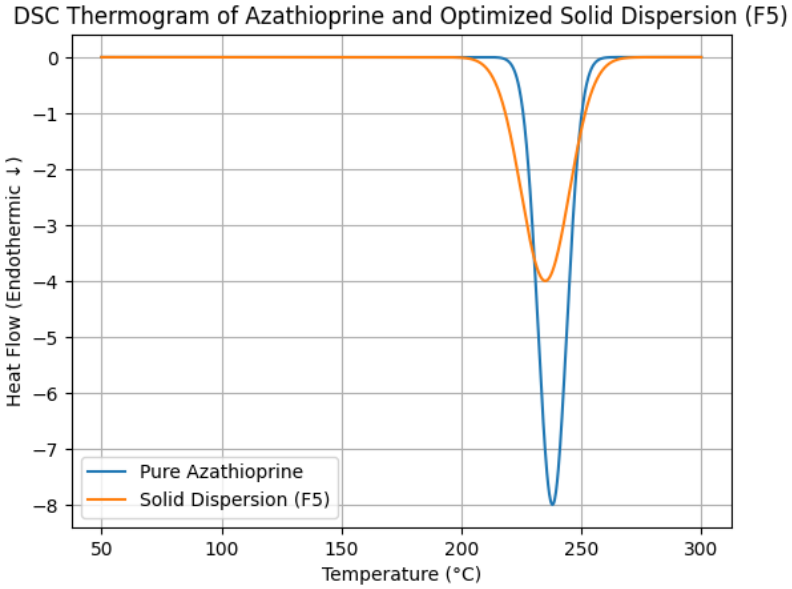
Differential Scanning Calorimetry (DSC) analysis was carried out to investigate the **thermal behavior and physical state of azathioprine in the solid dispersion formulations**. DSC is a valuable technique used to detect changes in crystallinity, melting point, and possible interactions between the drug and polymer.

The DSC thermogram of **pure azathioprine** exhibited a **sharp endothermic peak corresponding to its melting point**, which indicates the crystalline nature of the drug. The sharpness and intensity of this peak confirm that the drug exists in a well-defined crystalline form under normal conditions.

In contrast, the DSC thermograms of the **solid dispersion formulations**, particularly the optimized formulation **F5**, showed a **significant reduction in the intensity of the characteristic melting peak of azathioprine**. In some cases, the peak appeared broadened or slightly shifted towards a lower temperature.

This reduction or disappearance of the drug's melting peak suggests that the drug was **partially or completely converted from a crystalline state to an amorphous or molecularly dispersed state within the polymer matrix**. The amorphous form of a drug generally possesses higher free energy and increased molecular mobility compared to the crystalline form, which results in **improved solubility and faster dissolution rate**.

Additionally, the DSC thermograms did not show any **new thermal events or additional peaks**, indicating the **absence of chemical interaction or incompatibility between azathioprine and the polymers (PEG 6000 and PVP K30)**.



The results obtained from DSC analysis therefore support the findings of the **solubility and dissolution studies**, confirming that the enhancement in solubility of azathioprine in the solid dispersion system can be attributed to:

- **Reduction in drug crystallinity**
- **Formation of amorphous drug dispersion**
- **Uniform molecular dispersion of drug within the hydrophilic polymer matrix**

Overall, the DSC study confirmed that the **solid dispersion technique successfully modified the physical state of azathioprine**, contributing significantly to the improved dissolution characteristics observed in the optimized formulation.

4. Conclusion

The present study successfully demonstrated the potential of the **solid dispersion technique** in enhancing the solubility and dissolution rate of the poorly water-soluble drug **azathioprine**. Poor aqueous solubility is a major limitation for many drugs belonging to **BCS Class II**, and improving their dissolution characteristics is essential for achieving better oral bioavailability.

In this study, solid dispersions of azathioprine were prepared using **hydrophilic polymers PEG 6000 and PVP K30** by the **solvent evaporation method**. The prepared formulations were evaluated for various physicochemical parameters including **drug content, saturation solubility, FTIR analysis, DSC analysis, and in-vitro dissolution studies**.

The results indicated that all prepared solid dispersion formulations exhibited **significant improvement in solubility and dissolution rate** compared with the pure drug. Drug content analysis confirmed the **uniform distribution of azathioprine within the polymer matrix**, with values ranging from **95% to 99%**, demonstrating the reliability and reproducibility of the preparation method.

Saturation solubility studies showed a considerable increase in drug solubility for all solid dispersion formulations. Among them, **formulation F5 (drug:PVP K30 ratio 1:2)** exhibited the **highest solubility (3.84 mg/mL)** compared to the pure drug (**0.62 mg/mL**), representing a significant enhancement.

Similarly, the **in-vitro dissolution studies** revealed a substantial improvement in drug release from the solid dispersion formulations. The optimized formulation **F5 released approximately 91.3% of the drug within**

45 minutes, whereas the pure drug released only **38.6%** under the same conditions. This corresponds to nearly a **2.3-fold increase in dissolution rate**.

FTIR analysis confirmed that there were **no significant chemical interactions between azathioprine and the polymers**, indicating compatibility between the drug and excipients. Furthermore, **DSC analysis suggested a reduction in drug crystallinity and partial conversion of the drug into an amorphous form**, which plays an important role in improving drug solubility and dissolution.

Overall, the results of this study demonstrate that **solid dispersion using hydrophilic polymers is an effective and promising strategy for enhancing the solubility and dissolution characteristics of poorly water-soluble drugs such as azathioprine**. Among the formulations developed, **F5 (Azathioprine:PVP K30 in a 1:2 ratio)** was identified as the optimized formulation.

This approach has the potential to **improve the oral bioavailability and therapeutic performance of azathioprine**, and the methodology may also be applied to other poorly soluble drugs in pharmaceutical formulation development. Future studies may include **stability studies, scale-up processes, and in-vivo bioavailability evaluation** to further validate the effectiveness of the developed formulation system.

5. Future Scope

Although the present study successfully demonstrated the enhancement of solubility and dissolution rate of azathioprine using the solid dispersion technique, further investigations are required to fully establish the practical applicability and long-term performance of the developed formulation. The following studies may be undertaken in the future:

1. Stability Studies

Stability studies should be conducted to evaluate the **physical and chemical stability of the optimized solid dispersion formulation during storage**. These studies can be performed according to **ICH stability guidelines** under different environmental conditions such as accelerated conditions (40°C ± 2°C / 75% ± 5% RH) and long-term conditions (25°C ± 2°C / 60% ± 5% RH). Stability testing will help determine whether the drug maintains its **amorphous state, solubility enhancement, and dissolution characteristics over time**, and whether any degradation or recrystallization occurs during storage.

2. Scale-Up Studies

The preparation method used in this study was carried out at a **laboratory scale**. For commercial pharmaceutical manufacturing, it is necessary to evaluate the feasibility of **scaling up the formulation process** using industrial equipment such as spray dryers, hot-melt extruders, or large-scale solvent evaporation systems. Scale-up studies would ensure that the **solid dispersion technique remains reproducible, efficient, and cost-effective during large-scale production** while maintaining consistent drug quality and performance.

3. In-Vivo Bioavailability Studies

Although the in-vitro studies demonstrated significant enhancement in solubility and dissolution rate, it is important to verify whether these improvements translate into **enhanced bioavailability in biological systems**. Therefore, **in-vivo pharmacokinetic studies** should be conducted using suitable animal models or clinical trials to evaluate parameters such as **maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), and area under the curve (AUC)**. These studies will confirm whether the optimized solid dispersion formulation leads to improved **oral absorption and therapeutic efficacy of azathioprine**.

Overall, these future investigations will help establish the **clinical relevance, stability, and industrial feasibility of the developed solid dispersion formulation**, thereby supporting its potential application in pharmaceutical drug delivery systems for poorly water-soluble drugs.

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