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# Solubility And Dissolution Rate Enhancement Of Fenoprofen By Binary And Ternary Phase Solid Dispersions.

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**ABSTRACT**
The purpose of this research was to increase the dissolution rate of Fenoprofen (FPN) by making solid dispersion systems (both binary and ternary) with different weight ratios of the active pharmaceutical ingredient (API), carrier, and surfactant. The binary and ternary solid dispersions were prepared by solvent and fusion methods. s. Binary solid dispersions of FPN were formed using polyethylene glycol 4000 (PEG 4000), and poloxamer 407. Tween 60 was added to create a ternary solid dispersion system. The optimal API-polymer weight ratio was determined to be 1:2. The addition of Tween 60 to the formulations prepared using the solvent method further improved the dissolution rate. Both binary and ternary solid dispersion systems demonstrated a significant enhancement in the dissolution of FPN. Solid dispersions containing poloxamer 407 exhibited higher solubility and faster dissolution profile, with the 1:2 API-polymer weight ratio identified as optimal.

**Keywords:** solid dispersion, Fenoprofen, polyethylene glycol, poloxamer, tween 60.

## INTRODUCTION

The oral route is the most commonly used and preferred method of drug administration. However, some orally administered active pharmaceutical ingredients (APIs) have low bioavailability due to their poor water solubility. According to the Biopharmaceutical Classification System (BCS), APIs with low solubility and high membrane permeability are classified as Class II . To improve the solubility issue, oral drug delivery systems focus on formulation strategies such as modifying solvent composition, using carrier systems, and making chemical and physical modifications. One promising strategy to improve solubility is the use of solid dispersion of the API in a water-soluble polymer [1].

PEG 4000 and Poloxamer are hydrophilic polymers commonly utilized in the formulation of solid dispersion systems. PEG 4000 is known for its chemical stability, low viscosity in the molten state (melting point of 58-60°C), and suitability as a carrier for solid dispersion preparation via fusion method. It aids in enhancing solubility by addressing issues such as particle aggregation, , wettability, dispersibility, and surface properties of API particles. Similarly, Poloxamer, another hydrophilic polymer, has been effectively employed in the creation of solid dispersion systems [2].

To prepare solid dispersions, the solvent or fusion method is typically utilized. Each approach presents distinct advantages and limitations. The fusion method ensures the formation of a solid solution, with the possibility of maintaining molecular dispersion depending on the API's solubility in the carrier. This method is particularly beneficial when a common solvent is unavailable. Conversely, the solvent method is suitable for thermolabile APIs as it requires minimal heat, resulting in amorphous solid dispersions that enhance solubility [3].

Fenoprofen is a nonsteroidal anti-inflammatory API (NSAID) used to treat Rheumatic diseases, Migraines, Sore throats, and Primary dysmenorrhea. Fenoprofen (calcium salt hydrate) is soluble in organic solvents such as DMSO and dimethyl formamide, which should be purged with an inert gas. The solubility of fenoprofen (calcium salt hydrate) in these solvents is approximately 33 mg/ml. Fenoprofen (calcium salt hydrate) is sparingly soluble in aqueous buffers. Fenoprofen is poorly soluble and highly permeable (BCS class II) which makes it a suitable candidate for solid dispersion formulation [4].

The current investigation involved the preparation of solid dispersions of FPN using both fusion and solvent methods. Polyethylene glycol 4000 (PEG 4000) and poloxamer, were used to create binary solid dispersion systems. These systems were prepared with API to carrier ratios of 1:1, 1:2, and 1:3, as previous studies have shown that these excipient ratios have a significant impact on enhancing the dissolution of various APIs. Additionally, Tween 60, a non-ionic surfactant, was included as a third component to create ternary solid dispersion system to further improve the dissolution rate of FPN.

## MATERIALS AND METHODS

### Materials

Fenoprofen was Obtained from Suven Pharmaceuticals Ltd, India. The polymers and surfactant (Poloxamer, PEG 4000 and Tween 60) were purchased from Sigma-Aldrich, India. All other materials and reagents were of analytical grade.

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**Preparation of solid dispersions**
Solid dispersions of Fenoprofen (FPN) were prepared using both the solvent evaporation method and fusion method. For the binary system, FPN, PEG 4000, or poloxamer 407 were combined in three different API-polymer weight ratios (1:1, 1:2, and 1:3). In the ternary system, Tween 60 (T60) was added to all 1:2 formulations to achieve an API-polymer-surfactant weight ratio of 1:2:1. The specific composition of each formulation can be found in Table 1.

**Table 1**: Formulation table for the solid dispersions

| Solid dispersion method | Components | Ratio's |
|---|---|---|
| Solvent method | FPN-PEG | 1:1 |
| | FPN-PEG | 1:2 |
| | FPN-PEG | 1:3 |
| | FPN-PEG-Tween 60 | 1:2:1 |
| | FPN-Poloxamer | 1:1 |
| | FPN-Poloxamer | 1:2 |
| | FPN-Poloxamer | 1:3 |
| | FPN-Poloxamer-Tween 60 | 1:2:1 |
| Fusion method | FPN-PEG | 1:1 |
| | FPN-PEG | 1:2 |
| | FPN-PEG | 1:3 |
| | FPN-PEG-Tween 60 | 1:2:1 |
| | FPN-Poloxamer | 1:1 |
| | FPN-Poloxamer | 1:2 |
| | FPN-Poloxamer | 1:3 |
| | FPN-Poloxamer-Tween 60 | 1:2:1 |

**Fusion Method**
The fusion method involved melting the appropriate amount of polymer at a temperature of 80 ± 1°C. FPN was added to the molten polymer and stirred constantly for 15 minutes, then quickly cooled in an ice bath for 2 hours. The mixture was then refrigerated at 2-8°C for 3 days to solidify. The solid dispersions were scraped, pulverized in a mortar, and passed through a 40-mesh sieve. The obtained dispersion was n stored in amber glass vials and placed in a desiccator at 25±3°C for further analysis.

**Solvent Method**
The solvent method involved using a minimal amount of methanol to dissolve FPN and the polymers through continuous stirring with a magnetic stirrer at room temperature for an hour. To ensure complete dissolution of PEG 4000, the samples were heated to 40°C. Methanol was then removed under reduced pressure using a rotary evaporator set at 40°C until all the solvent had evaporated. The resulting solid dispersions were further dried in an oven at 40°C for 24 hours. The solid dispersions were scraped, pulverised in a mortar, and sieved through a 40-mesh sieve. Subsequently, all solid dispersions were stored in amber glass vials and placed in a dessicator at 25 ±3°C until further analysis.

**Dissolution Studies**
In this study, solid dispersions equivalent to 50 mg of FPN were added to 900 mL of Purified water and maintained at a temperature of 37°C with a variation of ± 0.5°C. Paddles were rotated at a speed of 50 RPM. At intervals of 5, 10, 15, 30, 45, and 60. 5 mL aliquots were taken and filtered through 0.45 µm pore size filters. The filtered samples were replaced with an equal volume of fresh dissolution medium also kept at 37°C. HPLC analysis with UV detection at 270 nm was performed on each sample. Each dissolution test was conducted in triplicate.

**RESULTS**
**Dissolution**
Dissolution data was evaluated based on cumulative percentage API release, which was plotted against time.

**Fusion Method**
Figure 1 illustrates the dissolution profiles of FPN and FPN solid dispersions in PEG 4000, which were prepared using the fusion method. The solid dispersions, formulated with varying ratios of PEG 4000, demonstrated enhanced API release compared to the pure FPN sample. As the concentration of PEG 4000 increased, the dissolution rate also increased.
Notably, the FPN solid dispersion in PEG 4000 prepared in a 1:1 ratio exhibited a slightly lower API release compared to formulations with higher ratios of PEG 4000. Moreover, the addition of Tween 60 to the solid dispersion formulation containing PEG 4000 resulted in a slightly faster release profile compared to formulations without Tween 80 [5].

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Similar trends were observed in solid dispersions prepared with an equal combination of PEG and Poloxamer, as shown in Figure 2. The solid dispersion containing Poloxamer exhibited a faster dissolution rate compared to the formulation with PEG 4000.

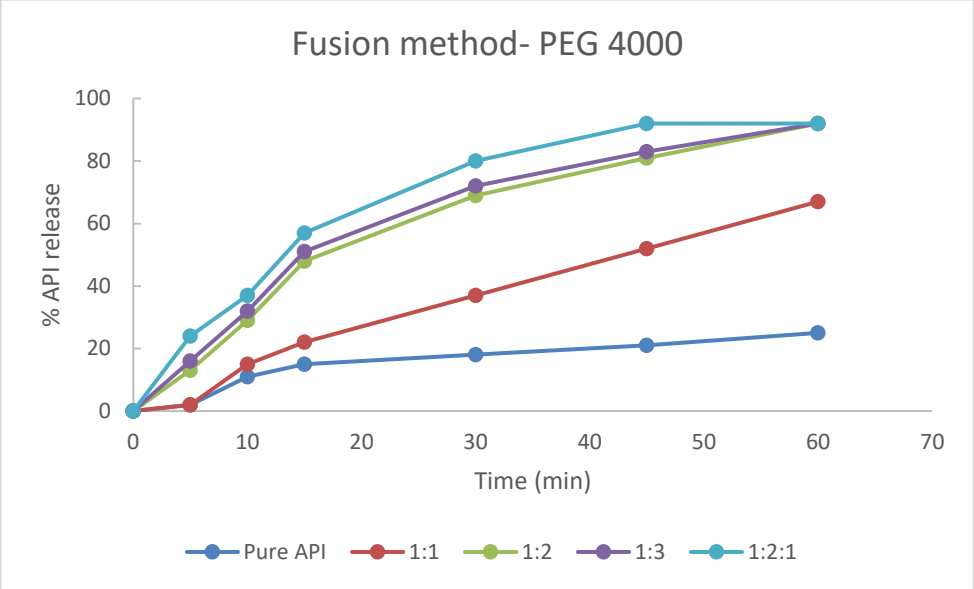


**Figure 1.** Dissolution profiles of FPN dispersion prepared by Fusion method using PEG4000- Tween 60 in different ratios

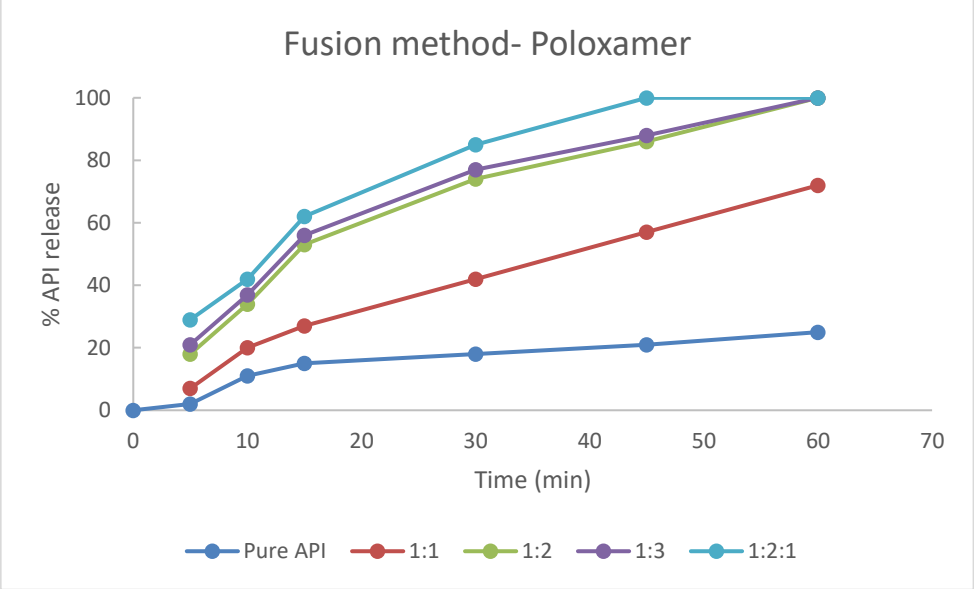


**Figure 2.** Dissolution profiles of FPN dispersion prepared by Fusion method using Poloxamer- Tween 60 in different ratios

**Solvent Method**

**In Figure 3**, the dissolution of FPN and solid dispersions of FPN in PEG 4000, prepared using the solvent method, is presented. All solid dispersion systems exhibited a quicker release of FPN compared to a pure FPN sample. The addition of Tween 80 to PEG 4000, prepared using the solvent method, resulted in further enhancements in dissolution parameters. Similarly, Figure 4 illustrates a similar release pattern with solid dispersions in Poloxamer, prepared through the solvent method. It was observed that solid dispersions prepared using the solvent method displayed a faster dissolution rate in comparison to those prepared using the Fusion method.

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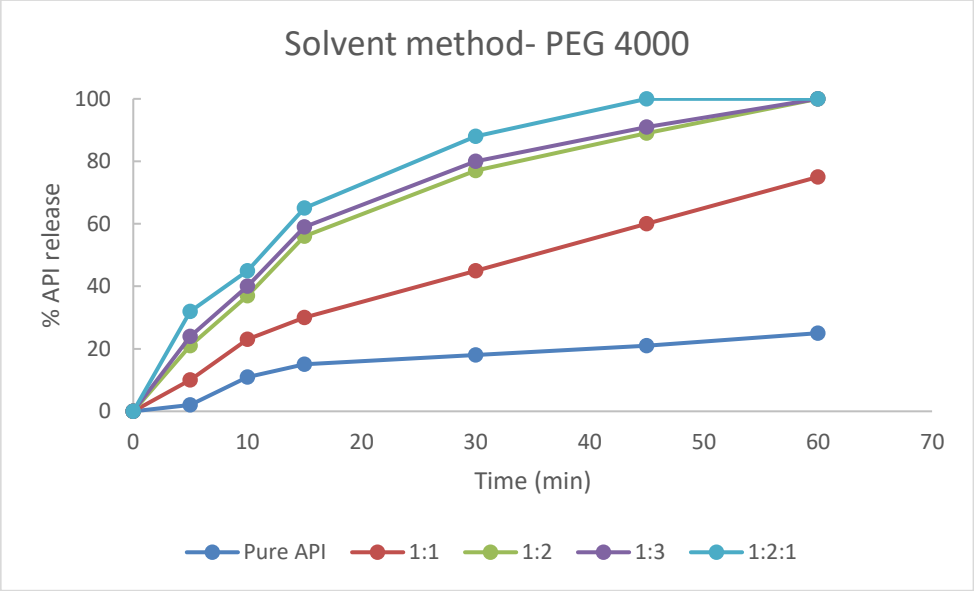


**Figure 3.** Dissolution profiles of FPN dispersion prepared by Solvent method using PEG4000- Tween 60 in different ratios

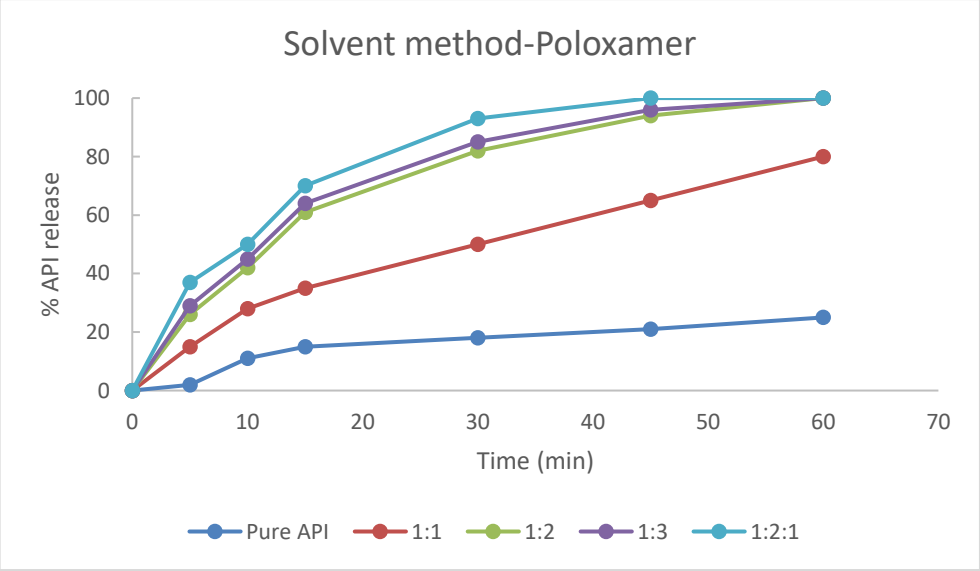


**Figure 2.** Dissolution profiles of FPN dispersion prepared by Solvent method using Poloxamer- Tween 60 in different ratios

**DISCUSSION**

In this research, dissolution tests were conducted using deionized water. Results revealed that only 25% of the drug was released at the end of dissolution (60min) from the pure FPN sample. Conversely, the dissolution rates of all solid dispersions showed significant improvement. This enhanced drug release from solid dispersions may be attributed to several factors, such as reduced API crystal size, prevention of API aggregation and agglomeration, inhibition of crystal growth, and increased wettability facilitated by the polymers. The polymer enhances wettability by forming a protective layer around the API, thereby decreasing the hydrophobic nature of FPN [6].

An increase in the polymer to API ratio resulted in improved API release compared to the pure FPN sample. This trend was consistent across all tested polymers. However, there was no significant difference in release rate between the 1:2 and 1:3 API-polymer ratios. Therefore, a 1:2 ratio was considered optimal. Carrier type also affected dissolution, with Poloxamer formulations demonstrating higher dissolution efficiency compared to solid dispersions with PEG 4000. This is attributed to the greater wetting and solubilizing effects of Poloxamer. The addition of Tween 60 further enhanced dissolution rate. When comparing techniques, solid dispersions using the solvent method exhibited a faster dissolution rate than other methods.

## CONCLUSION

The binary solid dispersions systems containing FPN with varying API-polymer weight ratios demonstrated enhanced drug release when compared to pure API. Higher polymer ratios resulted in increased dissolution rates. An API-polymer ratio of 1:2 was deemed optimal, as it required less excipient and additional increases in polymer amount yielded similar dissolution profiles. The addition of Tween 60 improved dissolution for solid dispersions created with PEG 4000 or Poloxamer through solvent methods. The overall conclusion is that the hydrophilic carriers such as PEG 4000, Poloxamer and Tween 60 are significantly increased the dissolution rate of the FPN by forming a binary or ternary solid dispersion systems.

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## DECLARATION OF INTEREST

The authors report no conflict of interest.

## REFERENCES

1. Sunil, S.A., Srikanth, M.V., Rao, N.S. et al. Investigation on in vitro dissolution rate enhancement of indomethacin by using a novel carrier sucrose fatty acid ester. DARU J Pharm Sci **20**, 4 (2012).
2. Singh J, Walia M, Harikumar S. Solubility enhancement by solid dispersion method: a review. Journal of Drug Delivery and Therapeutics .2013 3(5):148-55.
3. Sharma A, Jain CP. Preparation and characterization of solid dispersions of carvedilol with PVP K30. Res Pharm Sci. 2010 Jan;5(1):49-56.
4. Nash, J F et al. “Linear pharmacokinetics of orally administered fenoprofen calcium.” Journal of pharmaceutical sciences vol. 68,9 (1979): 1087-90.
5. Koh PT, Chuah JN, Talekar M, Gorajana A, Garg S. Formulation development and dissolution rate enhancement of efavirenz by solid dispersion systems. Indian J Pharm Sci. 2013 May;75(3):291-301.
6. MV Srikanth, GV Murali Mohan Babu, SA Sunil, N Sreenivasa Rao, K Praveen Kumar, KV Ramana Murthy. Studies on the Effect of Hydrophilic Carriers in the Dissolution Rate Enhancement of Poorly Soluble API, Bicalutamide. Research J. Pharm. and Tech. 3(2): April- June 2010; Page 592-595.