

## SOLUBILITY ENHANCEMENT OF IBUPROFEN IN THE PRESENCE OF HYDROPHILIC POLYMER AND SURFACTANT

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**ABSTRACT:** Solid dispersions of ibuprofen (IBU) were prepared by solvent evaporation method using polyvinyl pyrrolidone (PVP) and/or sodium lauryl sulphate (SLS). Physicochemical properties of the various solid dispersion systems were determined by differential scanning calorimetry (DSC) and X-ray diffraction (XRD) analysis. The results from dissolution studies indicated that ternary solid dispersion systems were more efficacious than the corresponding binary ones. The increase in the dissolution rate of ibuprofen from its solid dispersions with the PVP and/or SLS used in this study could be attributed to several factors such as improved wettability, local solubilisation, and drug particle size reduction. The most effective solid dispersion was the 20:180:10 w/w IBU-PVP-SLS ternary system, which allowed dissolution of 85 % drug after only 9.15 minutes (in comparison with 94.61 minutes for drug alone and 17.92 minutes for the binary system).

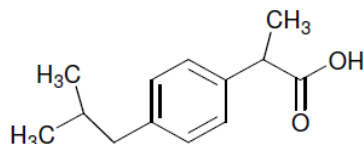
**KEYWORDS:** Ibuprofen, solid dispersion, phase solubility study, polyvinyl pyrrolidone, sodium lauryl sulphate, dissolution efficiency.

### INTRODUCTION

Compounds with poor aqueous solubility are increasingly posing challenges in the development of new drugs, since a large number of drugs coming directly from synthesis or from high throughput screening have a poor solubility (Ohara et al, 2005). It is well known that drug efficacy can be severely limited by poor aqueous solubility, leading to low dissolution rate and thus results in low absorption in the gastrointestinal tract following oral administration; hence, compromising oral bioavailability. Thus, enhancement of aqueous solubility is a valuable aid to increase the efficacy for certain drugs (Yalkowsky S, 1981).

The biopharmaceutical classification system divides drugs into four classes depending on in vitro solubility and in vivo permeability data (Amidon et al, 1995). It is obvious that for class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption than their ability to permeate through the intestinal epithelia. There are several pharmaceutical strategies available to improve the aqueous solubility of poorly soluble drug: solid dispersion (Sekiguchi and Obi, 1961; Sekiguchi et al, 1964; Goldberg et al, 1966a; Chiou and Riegelman, 1971;), reduction of particle size (Kubo et al, 1996), solubilisation in surfactant system (Martis et al, 1972; Rees and Collett, 1974), formation of water soluble complexes (Cassela et al, 1998) and use of prodrug (Trapani et al, 1998). However, among the various approaches to improve the dissolution of drugs the preparation of solid dispersion systems has often proven to be very successful.

Ibuprofen (Figure 1) is a non-steroidal anti-inflammatory drug (NSAID) that has been widely used in the treatment of mild to moderate pain. As its serum concentrations and analgesic effect are correlated, rapid absorption of ibuprofen could be a prerequisite for the quick onset of its action. However, the bioavailability of ibuprofen is relatively low after oral administration, since it is practically insoluble in water (Ghorab and Adeyeye, 1994; Glowka FK, 2000).



**Figure 1: Structure of ibuprofen**

Various reports are available for enhancing the solubility of ibuprofen in binary solid dispersion system (Mura et al, 1987; Najib et al, 1986; Newa et al, 2008). However, the solubilisation efficiency of binary solid dispersion system is frequently low and, thus relatively large amounts of carrier are needed to solubilise small amounts of a given drug. Therefore, this study was carried out to modify the solubility and dissolution characteristics of the drug using SLS as a third component in the ternary system.

## MATERIALS AND METHODS

### Materials

Pure drug sample of ibuprofen was procured from Dr.Reddy's Ltd., Hyderabad, India. Polyvinyl pyrrolidone and sodium lauryl sulphate (CDH (p) Ltd., New Delhi, India) and all other ingredients were obtained commercially and used as received.

### Preparation of solid dispersion

Solid dispersions of Ibuprofen with PVP, SLS, and with mixture of PVP and SLS were prepared by the solvent evaporation method. Accurately weighed quantities (Table 1) of Ibuprofen and the respective dispersion carrier(s) were transferred into a beaker. A sufficient quantity of solvent (ethanol 95%) was added to dissolve the ingredients. The mixture were then stirred and evaporated. The viscous residues thus obtained were allowed to solidify and were kept at room temperature for 48 hrs. The samples were further dried at 40°C for 1 hr, powdered, and passed through 100 screen.

### Phase solubility studies

Phase solubility studies of ibuprofen (Ibu) were carried out to evaluate the possible solubilising effect of the carrier by adding an excess of drug (50mg) to 10 ml of phosphate buffer pH 6.8 containing increasing concentrations of PVP (0-10% w/v) with or without the presence of 1.5% w/v of surfactant (SLS) in sealed glass containers and shaken at 25°C in a temperature controlled bath for 24 hrs. Drug concentration was spectrophotometrically determined at 222 nm.

### Differential scanning calorimetric study

Differential thermal analysis of the pure ingredient and solid dispersion were carried out using Perkin-Elmer instrument (Pyris Diamond TG/DTA, Singapore). Samples weighing approximately 5 mg were placed in the aluminium pans and heated at the scanning rate of 5°C/minute from 30°C to 210°C. Pure nitrogen gas, i.e., without water vapour was purged through the sample cell continuously.

### X-ray diffraction study

X-ray diffraction patterns of the pure ingredient and solid dispersion were recorded using X-ray powder diffractometer (Rigaku-ultima 3, Japan) with copper  $\alpha$  radiation, operated at 30 kV and 15 mA. The scanning rate was 1°/min over a 2 $\theta$  range of 5°C-60°C.

### In vitro release study

In vitro release of ibuprofen from the solid dispersion was studied in USP phosphate buffer solution (500ml, pH 6.8) using USP II dissolution test apparatus (model TDP-06P, Electrolab, Mumbai) at the paddle rotation speed of 50 rpm. The temperature of the medium was maintained at  $37 \pm 0.5^\circ\text{C}$ . At the specified times, 5ml samples were withdrawn, filtered and analyzed the content of ibuprofen spectrophotometrically (model UV-1800, Shimadzu, Japan) at 222 nm. Equivalent amount of fresh medium was replaced after each sampling.

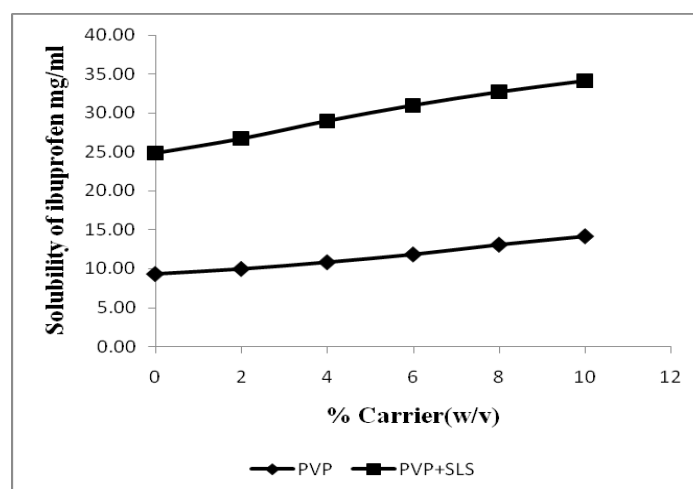
### RESULTS AND DISCUSSION

The solid dispersions of ibuprofen with PVP and/or SLS were prepared by solvent evaporation method. The compositions of the solid dispersions were shown in Table 1.

**Table 1: Compositions of solid dispersions**

Formulation	Ratio of Drug, PVP, and SLS	Ibuprofen(mg)	PVP(mg)	SLS(mg)
F <sub>1</sub>	20:40	200	400	-
F <sub>2</sub>	20:80	200	800	-
F <sub>3</sub>	20:180	200	1800	-
F <sub>4</sub>	20:40:10	200	400	100
F <sub>5</sub>	20:80:10	200	800	100
F <sub>6</sub>	20:180:10	200	1800	100

The resulting solid dispersions were subjected to phase solubility study, DSC and XRD analyses. The phase solubility diagram of ibuprofen containing carriers at  $37^\circ\text{C}$  in USP phosphate buffer solution (pH 6.8) are shown in Figure 2.



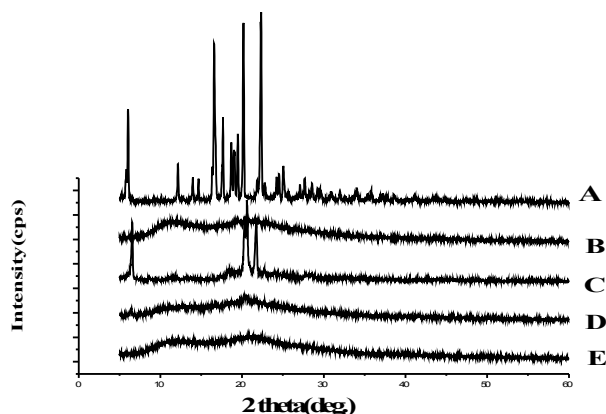
**Figure 2: Phase-solubility diagram of ibuprofen in USP phosphate buffer solution (pH 6.8) in the presence of PVP and PVP with 1.5% SLS.**

A gradual increase in solubility of ibuprofen was observed with an increasing concentration of dispersion carriers. At 10% (w/v) concentration of PVP and 10% (w/v) PVP with 1.5% (w/v) SLS, the solubility increased by 1.52 and 3.66 fold respectively. The ratio of the molar solubility of ibuprofen in carrier solution ( $S_s$ ) and the molar solubility of the drug in buffer solution ( $S_w$ ) can be considered as a partitioning ratio. Therefore, the Gibbs free energy of transfer ( $\Delta G_t^0$ ) from the buffer solution to the carrier solution can be calculated as:  $\Delta G_t^0 = -RT \ln (S_s/S_w)$ . Table 2 represents the thermodynamic parameters associated with the solubility of ibuprofen in the presence of different carriers.

**Table 2: The value of Gibbs free energy of transfer for the solubility process of ibuprofen in buffer-carrier system.**

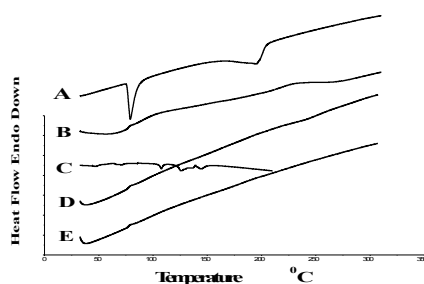
PVP(%w/v)	SLS(%w/v)	$\Delta G_r^0$
2	0	-171.89
4	0	-384.58
6	0	-612.39
8	0	-871.46
10	0	-1074.52
0	1.5	-2528.02
2	1.5	-2713.73
4	1.5	-2925.33
6	1.5	-3097.23
8	1.5	-3235.96
10	1.5	-3346.12

The Gibbs free energy values provide the information whether the reaction condition is favourable or unfavourable for drug solubilisation in the carrier solution. Negative Gibbs free energy values indicate favourable conditions. Gibbs free energy values (Table 2) were negative indicating the spontaneous nature of the drug solubilisation. The values decreased by increasing carrier concentration, demonstrating that the reaction more favourable as the concentration of carrier increased. The presence of surfactant markedly strengthened the solubilising power of PVP toward the drug.

**Figure 3: XRD patterns of ibuprofen and its solid dispersions.**

[A] = ibuprofen, [B] = polyvinyl pyrrolidone, [C] = sodium lauryl sulphate [D] = solid dispersion of ibuprofen: PVP=20:180, [E]= solid dispersion of ibuprofen: PVP: SLS=20:180:10

XRD patterns for ibuprofen drug substances and solid dispersion are shown in Figure 3. Pure ibuprofen showed numerous and strong diffraction peaks, which indicated that ibuprofen is present in a highly crystalline state. On the other hand binary and ternary solid dispersion showed no diffraction peaks. The complete disappearance of diffraction peaks of ibuprofen in solid dispersion system demonstrated that in solid dispersion ibuprofen had changed to an amorphous state.



**Figure 4: DSC patterns of ibuprofen and its solid dispersions.**

[A] = ibuprofen, [B] = polyvinyl pyrrolidone, [C] = sodium lauryl sulphate, [D] = solid dispersion of ibuprofen: PVP=20:180, [E] = solid dispersion of ibuprofen: PVP: SLS=20:180:10

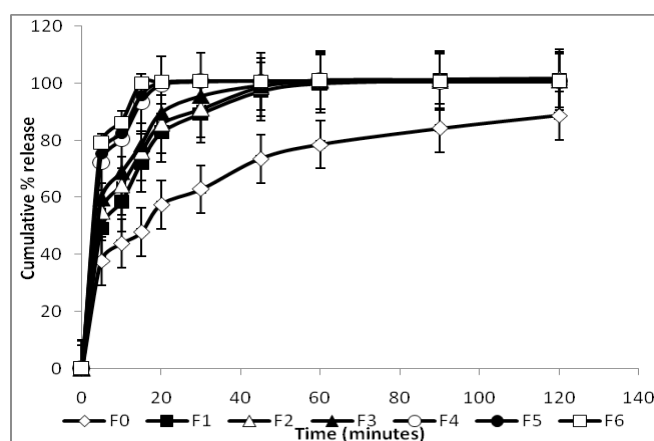
The differential scanning calorimetry curve of pure components and its solid dispersions are shown in Figure 4. The DSC thermogram of ibuprofen showed one sharp endothermic peak at 79°C which corresponds to the melting point of the drug. However, in binary and ternary solid dispersion systems the endothermic peak of ibuprofen was not observed. The findings indicated that ibuprofen in solid dispersion system had possibly changed to an amorphous state.

The results of dissolution tests in terms of dissolution efficiency and time to dissolve 85% drug ( $t_{85\%}$ ) are collected in Table 3, whereas the dissolution curves of ibuprofen and of binary and ternary systems with PVP and surfactant (SLS) are presented in Figure 5.

**Table 3: Characteristics of binary and ternary solid dispersions**

Formulation	F0	F1	F2	F3	F4	F5	F6
$t_{85\%,\text{minutes}}$	94.61 (2.63)	23.49 (0.68)	19.64 (0.20)	17.92 (0.07)	11.82 (0.17)	10.99 (0.07)	9.15 (0.15)
DE <sub>10 minutes</sub>	29.89 (0.37)	39.02 (0.15)	43.57 (0.27)	47 (0.22)	56.26 (0.37)	58.32 (0.19)	61.05 (0.17)

Figures in parentheses indicate  $\pm$ SD; n=3 for  $t_{50\%}$  and DE<sub>10 minutes</sub>



**Figure 5: Dissolution profiles of ibuprofen and its solid dispersion**

The DE is defined as the area under the dissolution curve up to a certain time,  $t$ , expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (Khan KA, 1975).

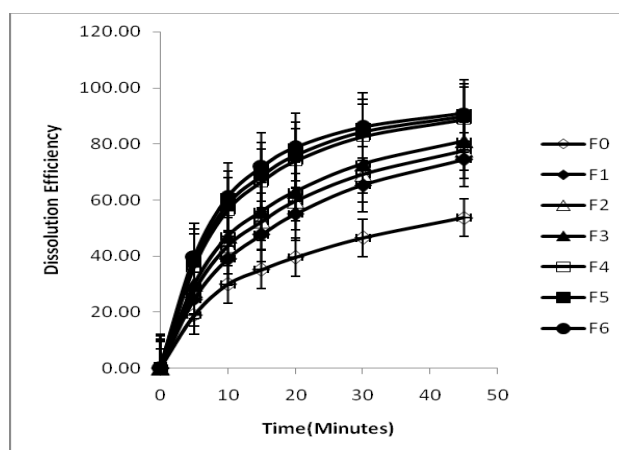
$$DE = \left[ \frac{\int_0^t y \cdot dt}{y_{100} \cdot t} \right] \times 100 \%$$

Where  $y$  is the drug percent dissolved in time  $t$ .

DE can have a range of values depending on the time interval chosen. However, while comparing a set of data a constant time interval should be selected. In the present study,  $DE_{10 \text{ minutes}}$  (dissolution efficiency up to 10 minutes) were calculated from the dissolution profile of ibuprofen and its solid dispersions and used for comparison.

From the dissolution profiles, it was observed that the dissolution rate of ibuprofen from all solid dispersion systems increased markedly corresponding to pure ibuprofen. In the present study binary solid dispersion of PVP and drug (40:20) released 85% of the drug in 23.49 minutes compared to 94.61 minutes from pure ibuprofen. When the ratio of PVP and drug in the solid dispersion was increased (80:20 and 180:20) the release of the drug were found to be faster (19.64 and 17.92 minutes respectively).

Dissolution efficiency curves of ibuprofen and of binary and ternary systems with PVP and SLS are presented in Figure 6. From the dissolution efficiency profiles, it was observed that the dissolution efficiency of ibuprofen from all solid dispersion systems increased markedly corresponding to pure ibuprofen.



**Figure 6: Dissolution efficiency profiles of ibuprofen and its solid dispersion**

It was found that in comparison to  $DE_{10 \text{ minutes}}$  obtained from pure drug, a 1.30, 1.45, and 1.57 fold increases in  $DE_{10 \text{ minutes}}$  were obtained from the binary solid dispersions. Various mechanisms (reduction of particle size of incorporated drug, partial transformation of the crystalline drug to the amorphous state, formation of solid solution and complexes, reduction of aggregation and agglomeration, improved wetting of drug and solubilisation of the drug by the carrier of the diffusion layer) are reported (Craig and Newton, 1985) responsible for improving aqueous solubility/dissolution properties of solid dispersions. Physicochemical state of the solid dispersion was studied using DSC and XRD. The results indicated the transformation of the crystalline drug to the amorphous state was noted. The amorphization together with improved wetting of the drug and solubilisation of the drug by the carrier could be responsible for improved solubility and consequent dissolution of the drug.

All ternary systems revealed better dissolution properties than the corresponding binary ones (Figure 5 and Figure 6). From the dissolution profiles, it was observed that the dissolution rate of ibuprofen from all ternary solid dispersion systems increased markedly corresponding binary ones. Similarly dissolution efficiency of ibuprofen from all solid dispersion systems increased markedly corresponding to binary ones. Micellar solubilisation phenomena can be excluded, because the final surfactant concentration in the dissolution medium (0.0002%w/v) was in all cases below their respective critical micelle concentration (Mukherjee and Mysels, 1971; Sjobqvist et al, 1991), which is, for example, between 0.1 and 0.2% w/v for SLS. Therefore, the observed effect can be attributed to the additive solubilising effect of the surfactant in the microenvironment surrounding the dissolving drug particles, together with its favourable influence on improving drug wettability and spreadability by decreasing the interfacial tension between drug particles and dissolution medium (Sheen et al, 1995).

## CONCLUSION

Binary solid dispersion of ibuprofen in PVP was effective in improving the drug dissolution properties. However, the addition of a surfactant when preparing the PVP-IBU solid dispersions improved ibuprofen dissolution properties in comparison with the simple binary product. The most effective system was the 20:180:10 w/w IBU-PVP-SLS ternary system, which allowed achievement of 85% dissolved drug after only 9.15 minutes (in comparison with 94.61 minutes for drug alone and 17.92 minutes for the binary system). Therefore, the IBU-PVP-SLS system appears to be the most suitable product for developing fast release formulations of the drug, which could be particularly useful in the treatment of clinical condition requiring quick pain relief.

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