

TAILORING OF SOLUBILITY OF IBUPROFEN IN THE PRESENCE OF HYDROPHILIC EXCIPIENTS IN WATER-ETHANOL MIXTURES BY CRYSTALLIZATION METHOD

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Received: 11 Dec 2021, Revised and Accepted: 07 Feb 2022

ABSTRACT

Objective: The objective of this study was to determine the effect of some commonly used pharmaceutical excipients on the solubility of Ibuprofen (Ibu) in a co-solvent consisting of water (W) and ethanol (E).

Methods: The Ibu solubility studies were carried out by dissolving the drug to equilibrium into aqueous ethanol solvents at a fixed temperature. The temperature of the water bath was kept constant (± 0.1 °C of the desired temperatures 10, 25 and 40 °C). The solubility of Ibu was measured by using UV spectrophotometry.

Results: The low solubility (~ 50 ppm) of Ibu without excipients in water (zero ethanol) was observed. However, Ibu solubility was increased near exponentially with excipient containing co-solvent system. The maximum solubility of Ibu (1726 ppm) was occurred in a co-solvent containing 1.52% leucine, 5.22% mannitol, 0.25% HPMC, 1.55% Pl F127 and 10.75% w/w ethanol. The phase separation between 34% and 63% w/w E/(E+W) was observed at 40 °C. The individual effect of Pl F127 on enhancing the Ibu solubility was significant.

Conclusion: The individual addition of leucine, mannitol and HPMC has limited impact on the solubility of Ibu. However, the effect of combining these excipients together on Ibu solubility is significantly high.

Keywords: Ibuprofen, Solubility, Aqueous ethanol, Crystallization, Excipients, UV spectrophotometry

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DOI: <https://dx.doi.org/10.22159/ijap.2022v14i2.43871>. Journal homepage: <https://innovareacademics.in/journals/index.php/ijap>

INTRODUCTION

Racemic Ibuprofen, which contains equal quantities of R(-)Ibuprofen and S(+)Ibuprofen, has been used as an anti-inflammatory and analgesic agent for over 30 y [1]. Racemic ibuprofen is known as Ibuprofen (Ibu) is a water insoluble non-steroidal anti-inflammatory drug commonly used in the treatment of arthritis, fever, and analgesia. Owing to high permeability but poor aqueous solubility, it has been scheduled as class II drugs under the Biopharmaceutical Classification System (BCS) [2, 3]. To overcome the solubility problem of Ibu in aqueous solvent, a number of researchers investigated the application of various excipients to enhance its solubility in different combinations of solvents, excipients and temperature. Recently, Rashid *et al.* [4] reviewed the data for the Ibu solubility in high ethanol (E/(E+W)) >50% w/w aqueous ethanolic solutions (E = ethanol, W = water). Information on Ibuprofen solubility in aqueous solvents (especially at low ethanol aqueous) is not abundant or in those available, not in good agreement [5-7]. Additionally, there is considerable variability between the different data collected from different references.

Different approaches have been exploited to increase Ibu solubility. For example, Lipid-based nanostructured carriers containing Ibuprofen [8]. Moreover, co-crystallization and other techniques with aim of increasing bioavailability of ibuprofen when administered orally [9]. In addition, a solid dispersion system prepared by a spray drying technique with water, HPMC and poloxamer increased Ibu solubility approximately four-fold where the weight ratio of Ibu/HPMC/Poloxamer was 10:3:2 [10]. However, due to the elevated temperatures used in this process a potential concern is chemical degradation of the drug which could outweigh the solubility enhancement effect. Using hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP) with polyethylene glycol (PEG-300) and water as the cosolvents, the correlation of particle size and solubility of Ibu in solutions of various stabilizers was established in [11, 12]. The HPMC, minimally affecting the aqueous solubility of Ibu, resulted in lower mean

particle size compared to Pl F127 that significantly increased Ibu solubility [12]. The generation of small crystals (nanocrystals) by crash nucleation of Ibu has been proposed by Khan *et al.* [13]. They used Pluronic F127 and HPMC (hydroxypropyl methylcellulose) to restrict crystal growth and prevent agglomeration. Khan determined the Ibu solubility in ethanol and aqueous solution of HPMC and Pl F127 at four temperatures (15, 25, 35 and 45 °C) for controlled precipitation crystallization [13]. Recently, Afrina *et al.* prepared and characterized the Ibu microparticles with some excipients (Pluronic F127, HPMC, D-mannitol and L-leucine) by a controlled crystallization technique with improved dissolution performance [14]. In current study, we explored the effect of some pharmaceutical excipients such as HPMC, Pl F127, mannitol and leucine on Ibu solubility in water ethanol co-solvents. The novelty of this study was to find out the minimum concentrations of excipients and low percentage of ethanol content in developing Ibu crystals with extremely enhanced solubility. In general, this finding could contribute to precise and predictive control of producing engineered crystals of extremely poorly water soluble active pharmaceutical ingredients (API) for the development of different formulation with significantly improved solubility.

MATERIALS AND METHODS

Materials

USP grade untreated Ibuprofen (CAS Registry Number 15687-27-1) was purchased from Professional Compounding Chemists of Australia Pty Ltd (PCCA, Matraville, NSW 2036), as a high purity racemate of (R)/(S)-(±)-[2-(4-isobutyl-phenyl) propionic acid] with the empirical formula $C_{13}H_{18}O_2$ and molecular weight 206.27. Pluronic F127 (Pl F127; CAS Registry Number 9003-11-6), Poloxamer 407 NF) was purchased from PCCA (Matraville, NSW). Hydroxypropyl methyl cellulose (HPMC) (CAS Registry Number 9004-65-3), was purchased from Sigma-Aldrich. D-mannitol ($C_6H_{12}O_6$) (CAS Registry Number 69-65-8) was purchased from Sigma-Aldrich. L-Leucine ($C_6H_{13}NO_2$) (Bioultra® 99.5%), an

amphiphilic surfactant used as a dispersive adjuvant was purchased from Sigma-Aldrich (CAS Registry Number 61-90-5). Analytical grade ethanol was purchased from Sigma-Aldrich and deionised/Millipore water was available in the laboratory.

Solubility studies

The Ibu solubility studies were carried out by dissolving the drug to equilibrium into aqueous ethanol solvents at a fixed temperature. The temperature of the water bath was kept constant (± 0.1 °C of the desired temperatures 10, 25 and 40 °C). In this study, an excess amount of Ibu was added to ~ 20 g of aqueous ethanol solvents of different compositions (0-50% w/w E/(E+W)). Fig. 1 shows the approach to equilibrium for several experiments. Equilibrium was reached within a few h; however, the bottles containing the Ibu solution were stirred with magnetic stirrers for at least 6 h. The long duration was used to ensure the equilibrium condition. After leaving the bottles for 24 h to settle in the bath, the supernatant from each bottle was filtered using preheated/pre-cooled syringes with 0.22 μ m pores polymer membranes. The equilibrium point for Ibu concentration was investigated in three different solvent compositions i.e., 0.1% excipients 10% Ethanol (red curve), 0.0005% excipients 5% Ethanol (green curve), and 0.25% excipients and 10% ethanol (blue curve) by crystallization method (fig. 1). The green curve shows Ibu concentration in 0.0005% excipients and 5% ethanol solvent composition at 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 40, 50 and 60 min intervals. Among the obtained concentration values the only outlier found at 2 min time point, otherwise, the concentration values remained steady (within 72.8 ± 1.9 ppm) throughout the experiment. The obtained results indicated that the equilibrium was achieved within 1 min of the crystallization process. The samples were drawn for Ibu concentration determination in 0.1% excipients 10% ethanol solvent system (Red curve) at five seconds interval up to one min and the final sample was drawn after 60 min. The initial concentration of Ibu at 5 seconds and 1 min were 372.72 ppm and 640.23 ppm, respectively. The maximum concentration was at 1 min

and the terminal concentration at 60 min was 483.83 ppm. The outcome of this investigation showed that the Ibu concentration did not change significantly after 60 min of the crystallization process. Considering the 1 min time point concentration as an outlier, remaining average concentration values from five seconds to 60 min was 423.06 ± 36.9 ppm, which indicated that the equilibrium achieved in first few seconds of the crystallization process. The blue curve represents the Ibu concentration in 0.25% excipients and 10% ethanol solvent system and samples withdrawn at different time intervals from five seconds to 62 h. The Ibu concentration in the first min was 3339.45 ± 237.11 ppm, which indicated that the solubility of Ibu drastically increased with increasing concentrations of excipients. Later on, the Ibu concentration values were decreased to 822 ppm after one hour. The equilibrium was not achieved in this investigation due to the presence of a high concentration of excipients which changed the Ibu solubility with time. However, the concentration was not more than 2 %, which was maintained in the crystallization process during this experiment. The crystallization equilibrium studies gave us an idea of the duration of the experiments to be maintained which was 6 h for solubility studies to ensure that the solution reached at the supersaturation state, which was used to determine the actual solubility of Ibu.

The effect of excipients on Ibu solubility was investigated at 25 °C as the solubility study at 40 °C caused phase separation (discussed in section 3.5). The concentration ranges of excipients used were 0 to 2% w/w HPMC/(E+W), 0 to 1.85% w/w PI F127/(E+W), 0 to 1.5% w/w leucine/(E+W), 0-9% mannitol/(E+W) in 0 to 20% w/w E/(E+W) aqueous-ethanol solvents. The samples were diluted as required and analysed using a UV spectrophotometer at a wavelength of 264 nm [12, 15, 16]. Each experiment was done in triplicate. Drug concentrations were determined in triplicate under each condition and the results were reported as the average with estimated 95% level of uncertainties. The values for 10% E, 0.1% of each excipient have been multiplied by a factor of 6 to expand the scale for comparison.

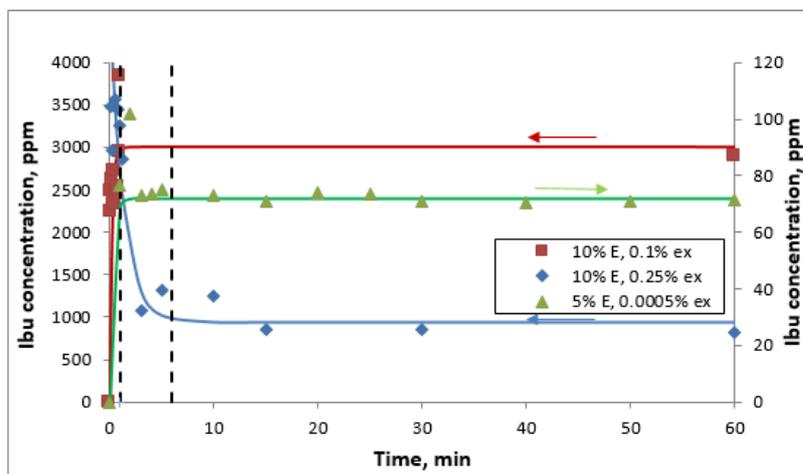


Fig. 1: Studies of Ibu equilibrium attainment for two dissolutions and one crystallization (falling curve) in aqueous ethanol with excipients

Calibration of UV spectrophotometry

In aqueous ethanol solvent system, the concentration range of the Ibu was 50 to 1500 ppm by wt. Prior to the spectrophotometric analysis, the spectrophotometer was calibrated against weighed solutions of ethanol, water and Ibuprofen. The calibration curves, illustrated in fig. S1, showed the linearity. It is worthwhile to note that the slope of the linear lines varies with the ethanol content and this indicates the interaction of the added ethanol with the structure of Ibu.

Preparation of HPMC solutions

5% w/w HPMC solutions were prepared by adding HPMC powder to a required weight of water that was used to make up to one tenth of the final weight. The aggregates of powder were dissolved in the

solvent by vigorous agitation. The solutions were refrigerated for 24 h at 4 °C to allow polymer hydration and stored for 72 h prior to use [17]. The final solvents of the excipients with the required concentrations were prepared by dissolving the weighed amounts of excipients (PI F127, leucine and mannitol) powder water/aqueous ethanol system.

Phase separation studies

In aqueous ethanol solution, Ibu showed two liquid phases >35% E/(E+W) concentration at 40 °C [18]. This outcome was confirmed by using NIR. Excess amount of Ibu was added in 40 and 50% E/(E+W) solutions with continuously stirred for 24 h and allowed to stand for 72 h at 40 °C temperature in a controlled bath. Samples were collected from each layer, diluted (if required) and the Ibu

concentration was determined by a UV spectrophotometer. The ethanol content for each layer was determined by subtracting the measured Ibu and water content.

Statistical analysis

Data analysis for deriving best fit correlations was done using table Curve2D software (Systat Software, Inc, CA 95131, USA).

RESULTS AND DISCUSSION

Solubility of Ibu in aqueous ethanol without excipients

The solubility measurements of Ibu in various compositions of solvent at 10, 25 and 40 °C are summarised in table 1, where maximum Ibu solubility (67450 ppm) was obtained in 50.19% w/w ethanol at 25 °C. Similar solvent ethanolic solvent (49.67%w/w) showed Ibu solubility of 20410 ppm at 10 °C. At 40 °C, maximum Ibu solubility (6525 ppm) was observed in 29.9% ethanol and no experiments were conducted at

above 30% aqueous ethanol solvent as phase separation occurred above this concentration (fig. 2). Therefore, in this study, all solubility experiments were carried out at 25 °C. The obtained data are presented in fig. 3, which showed consistency with the prior data of [18]) who studied at higher ethanol contents.

The results on fig. 2 and 3 have been fitted by the sigmoid relation as presented in eq. 1.

$$\log_{10}(\text{sol}) = a + (b + e^{t-25})(1 + \exp[-X_e - c + f(t-25)]/d) \dots \dots \dots [1]$$

Where sol = Ibuprofen solubility as $I^*/(E+W)$ in ppm, t = temperature in °C and $X_e = E/(E+W)$ as mass fraction. The four parameters of the sigmoid (a-d) were taken to be linear functions of temperature but only the two showed as functions of temperature were significant. Values determined for a to f in this correlation are shown in table 2. This equation is useful to predict Ibu solubility at known temperature and fraction of ethanol in water co-solvents.

Table 1: Ibu solubility data in 0-50% aqueous ethanol solvents at 10, 25 and 40 °C

10 °C		25 °C		40 °C	
E/(E+W) % w/w	I*/(E+W) ppm w/w	E/(E+W) % w/w	I*/(E+W) ppm w/w	E/(E+W) % w/w	I*/(E+W) ppm w/w
0	41.1 (±1.1)	0	45.5(±0.9)	0	88.4(±2.0)
10.18	65.1 (±1.3)	5.16	71.0(±1.1)	10.44	216.7(±6.0)
20.16	124.4 (±4.0)	10.07	102.4(±2.0)	20.57	1029(±16.0)
29.36	403 (±4.9)	15.28	159.8(±2.9)	29.92	6525(±29.0)
39.94	2165 (±20.1)	19.94	284.7(±3.8)		
49.67	20410 (±35.2)	20.85	367.3(±8.0)		
		30.1	1852(±21.0)		
		39.65	12470(±15.0)		
		50.19	67849.4 (±78.0)		

Each observation is an average of three experiments (n=3)±SD

For low ethanol contents (<50%), the data presented in fig. 3 approximately follow a straight line. Therefore, the effect of ethanol content on the Ibu solubility is near exponential, i.e. the solubility doubles for each ~ 3% increase in ethanol content. As demonstrated by Rashid *et al.*[18], aqueous Ibu solubility with low to higher (0-50%) ethanol solvent increases with a sigmoidal relationship (fig. 3). A clear

phase separation (three phases) occurred for a range of solution concentrations at 40 °C. The phase separation occurred due to the density differences between two layers. The drug used in this study is hydrophobic and contains-COOH group available for hydrogen bonding with water molecule at a higher temperature like 40 °C. The lower density upper layer contains higher concentration of Ibu in ethanol [18].

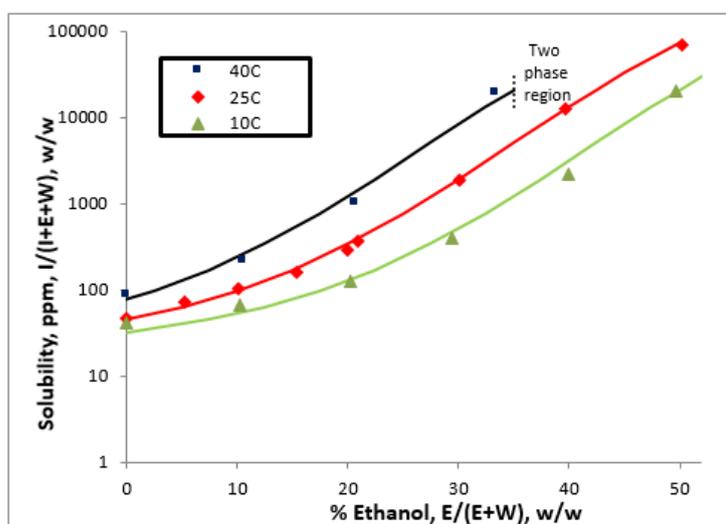


Fig. 2: Study on the solubility of Ibu in aqueous ethanol

Solubility with excipients

The Ibu solubility in different excipient solvents with/without additional ethanol (0-20% w/w) has been summarized in table 3. The solubility of Ibu without excipients in water was very low (47 ppm);

however, increased (up to 1860 ppm with 20% ethanol) near exponentially with other excipients and increasing ethanol content. The maximum solubility of Ibu (1726 ppm) in table 3 was observed in a solvent containing all excipients i.e., 1.52% leucine, 5.22% mannitol, 0.25% HPMC, 1.55% Pl F127 and 10.75% w/w ethanol.

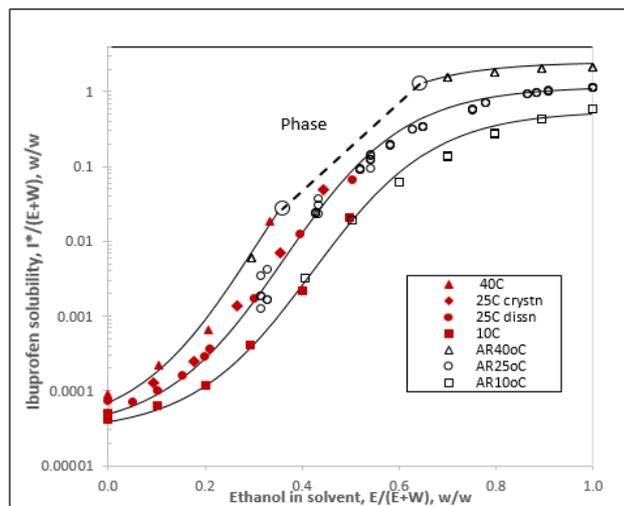


Fig. 3: Studies of Ibu solubility in aqueous ethanol (filled symbols), compared with the results of Rashid et al. [18] (unfilled symbols)

Table 3: The solubility of Ibu in aqueous-ethanolic solvents containing different concentrations of various excipients

Solvent composition					IBU solubility, ppm
Leucine, L/(E+W), w/w,%	Mannitol, M/(E+W), w/w,%	HPMC, HP/(E+W),w/w,%	PI F127, PI/(E+W),w/w,%	Ethanol, E/(E+W), w/w,%	
Intrinsic solubility (water)					45.55±0.05
0.51	5.32	0.42	1.43	11.15	1496.17±0.05
1.02	5.20	0.43	1.41	11.12	1599.04±0.08
1.52	5.22	0.42	1.55	10.75	1725.76±0.04
0.11	0.00	0.00	0.00	11.21	164.34±0.07
0.52	0.00	0.00	0.00	11.21	185.32±0.05
1.02	0.00	0.00	0.00	11.21	221.62±0.10
1.54	0.00	0.00	0.00	11.21	243.19±0.12
0.13	0.00	0.00	0.00	0.00	74.52±0.11
0.67	0.00	0.00	0.00	0.00	112.99±0.04
1.03	0.00	0.00	0.00	0.00	129.56±0.02
1.60	0.00	0.00	0.00	0.00	155.19±0.06
0.98	0.98	0.39	1.37	0.00	1007.21±0.05
0.98	5.04	0.39	1.37	0.00	1173.15±0.03
1.00	11.04	0.40	1.40	0.00	1124.01±0.02
0.00	1.08	0.00	0.00	10.02	59.65±0.08
0.00	5.51	0.00	0.00	10.02	127.95±0.08
0.00	10.14	0.00	0.00	10.02	166.54±0.06
0.00	13.95	0.00	0.00	10.02	88.47±0.03
0.00	1.30	0.00	0.00	0.00	55.32±0.11
0.00	5.44	0.00	0.00	0.00	65.81±0.04
0.00	12.66	0.00	0.00	0.00	60.69±0.06
0.00	17.82	0.00	0.00	0.00	58.40±0.06
0.49	0.51	0.00	0.00	0	330.46±0.01
0.46	0.45	0.00	0.00	9.40	562.42±0.06
0.39	0.42	0.00	0.00	20.23	1195.52±0.04
0.22	0.26	0.00	0.00	0	161.32±0.01
0.22	0.23	0.00	0.00	9.95	321.42±0.03
0.21	0.21	0.00	0.00	17.84	658.23±0.07
0.96	0.99	0.00	0.00	0	663.80±0.04
0.85	0.92	0.00	0.00	10.11	1260.58±0.04
0.77	0.80	0.00	0.00	19.85	1859.76±0.01
0.00	0.00	0.00	1.03	0	680.58±0.05
0.00	0.00	0.00	0.93	10.06	857.49±0.06
0.00	0.00	0.00	0.82	20.07	1662.20±0.01
0.00	0.00	0.00	2.02	0	1152.19±0.01
0.00	0.00	0.00	1.85	10.06	1534.14±0.07
0.00	0.00	0.00	1.68	19.6	2847.70±0.06
0.00	0.00	0.99	0.00	0	55.09±0.06
0.00	0.00	0.88	0.00	9.17	112.37±0.02
0.00	0.00	0.81	0.00	19.66	355.96±0.05
0.00	0.00	1.99	0.00	0	92.66±0.07
0.00	0.00	1.78	0.00	10.52	119.48±0.01
0.00	0.00	1.60	0.00	19.82	362.58±0.03

Each observation is an average of three experiments (n=3)±SD

Effect of Pluronic F127 (PI F127)

The effect of surfactant PI F127 on Ibu growth rate inhibition is well established [11-12,13]. However, here in this study, PI F127 was chosen as the additive for producing fine Ibu crystals to investigate the effect of the additive on Ibu solubility at low ethanol aqueous solvents. The fig. 4 showed the Ibu solubility was increased linearly with the PI F127 at each of the three concentrations of ethanol contents. The slopes of the lines are 560 (± 4) for 0% E; 785 (± 5) for

10% E and 1520 (± 3) for 20% E. A correlation for the effect of PI F127 on the solubility may be given as:

$$\text{Sol} = \text{Sol}_0 + (562 - 3.09 \times E + 2.54 \times [E]^2) \text{PI F127} \dots \dots \dots [2]$$

where, Sol is the solubility of Ibu (as $1/(E+W)$ in ppm) in the presence of excipients, Sol_0 is the solubility in the absence of excipients (as given by equation 1) and [E] and [PI F127] are the concentrations of ethanol and PI F127 (as % g/g solvent), respectively.

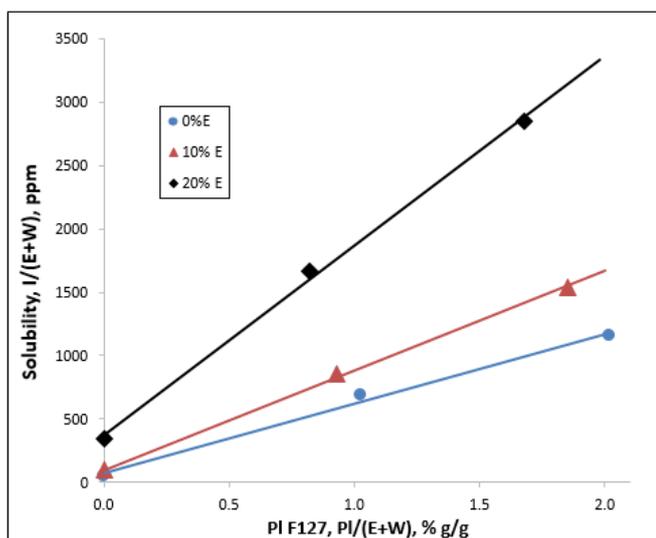


Fig. 4: Studies on the effect of PI F127 on Ibu solubility in aqueous ethanol at 25 °C

Although actual mechanism is unclear, the possible explanation for the observed trend might be due to the effect of the ethylene oxide (EO) and propylene oxide (PO) blocks in PI F127. It is suggested that the hydrophobic core (PO) block acts a reservoir for the drug and the hydrophilic portion (EO) serves as interface between the aqueous medium and the drug [19]. The surfactant PI F127 is nonionic and may form monomolecular micelles with the drug at a low concentration. These monomolecular micelles form aggregate with each other at higher concentration (above the critical micelle concentration, typically $\sim 0.7\%$ (PI F127) [19]. Therefore, in this study, it was necessary to identify the optimum concentration of Pluronic F127 prior to use it in precipitating Ibu.

The solubility increases in presence of ethanol but the relative effect of PI F127 on the solubility of Ibu insignificantly falls. The actual mechanism behind this is not clear; however, it could be due to the proximate attraction of ethanol towards hydrophobic Ibu suppresses the effect of PI F127 on enhancing the solubility. Verma *et al.* [11], determined Ibu solubility in 0.5% PI F127 and the outcome was in agreement with this study (fig. S2). Very recently, the hydrophilic PI F127 found to closely associate with Ibu particle and strongly promoted Ibu wettability by reducing the surface tension [14]. Thus, the outcome of this study suggests that PI F127 caused to increase the Ibu solubility linearly with its concentration in water and aqueous ethanol solvents.

Effect of HPMC

The HPMC did not produce remarkable Ibu solubility in the absence of PI F127. The data looked to be linear with the concentration of excipient (fig. S3). The slope of the line is ~ 17 (± 4) ppm/HPMC (% g/g of solvent) at all ethanol contents. This effect is very low (approx. one fiftieth) compared with the effect of PI F127. The additive HPMCs are the substituted cellulosic polymers, which are used as the most effective stabilizers for preparing the Ibu suspensions [13]. This excipient adsorbs onto the surface of the Ibu particles through the interaction of the hydrophobic methoxymethyl groups and hydrophilic hydroxypropyl groups present in the polymeric chain and stabilise the suspension [11]. Furthermore, it has been demonstrated that the

intermolecular hydrogen bonding between Ibu and HPMC plays a key role in prolonging supersaturation through nucleation inhibition, resulting in stabilizing the amorphous Ibu particles in the suspensions [20]. Therefore, HPMC is required as a stabilizer to keep the fine Ibu crystals non-aggregated in suspension.

As a first approximation, it could be assumed the effect of both PI F127 and HPMC is the sum of the single effects, i.e.

$$\text{Sol} = \text{Solo} + (562 - 3.09 \times [E] + 2.54 \times [E]^2 \times [\text{PI F127}] + 17 \times \text{HPMC} \dots \dots [3]$$

Where, Sol is the Ibu solubility (as $1/(E+W)$ in ppm) in the presence of excipients, Sol_0 is that in the absence of excipients (as given by equation 3) and [E], [PI F127] and [HPMC] are the concentrations of ethanol, PI F127 and HPMC, respectively as % g/g to solvent.

The solubility data of Ibu against the concentration of PI F127 with ethanolic HPMC contents as parameters are presented in fig. 5. The lines show the values predicted by the correlation plot (Eqn. 3) for 0 and 2% HPMC. Although the amount of data is limited, the outcome is in reasonable agreement with the correlation plot. The correlation shows that Ibu solubility increases linearly as an effect of the excipients, though the effect of HPMC is negligible in comparison with PI F127.

The main purpose of using polymeric stabilizers was to ensure the stability of Ibu nanosuspensions on a short term storage and to achieve successful formation of nanocrystals during particle production and both the HPMC and the PI F127 serve these purposes effectively [10, 11, 13, 14]. In this study, the effect of the combined excipients on the Ibu solubility were investigated at three levels of aqueous ethanol (0, 10, 20% w/w, $E/(E+W)$) and the concentration of the excipients was varied up to 2%, w/w as [PI F127+HPMC]/ $(E+W)$. It has been reported that the polarity of the solvent decreases as the amount of organic solvent increases, which favors the solute-solvent interaction, and affects the function of nonionic polar excipients (HPMC and PI F127) on enhancing the Ibu solubility [10, 11, 13, 21]. It is interesting to note that, the effect of the combined excipients was found to increase the Ibu solubility by a factor of fourteen compared to the solubility of this drug determined in water-ethanol co-solvents alone.

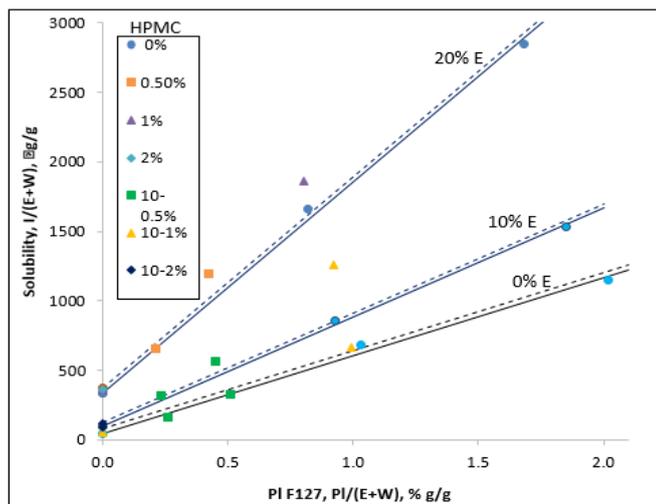


Fig. 5: The solubility of Ibu in the mixtures of solvent and excipients at 25 °C. The solid lines are the predictions without HPMC and the dotted lines are with 2% HPMC. Here, the first four entries in the legend are for 20% E and the last five entries are for the excipient HPMC and the solvent ethanol

Effect of L-Leucine

The effect of L-leucine, an amphiphilic amino acid on Ibu solubility was investigated at three concentrations (0.5, 1.0, and 1.5%) in the solvent, which was comprised of HPMC (0.4%), PI F127 (1.4%) and mannitol (5.2%) in 10% aqueous ethanol (all additive+0.1 E/(E+W)) (fig. S4; table 3). To understand the effect of leucine alone, the solubility of Ibu was determined at four different concentrations of L-leucine in water and 10% ethanol solutions (0.1 E/(E+W)). It was noticed that Ibu solubility with or without ethanol did not vary significantly. It could be due to the hydrophobic nature of both Ibu and leucine [22] causes competition for the solvent ethanol. As the leucine has both hydrophobic and hydrophilic components, the solubility of Ibu did not increase by the presence of leucine.

Effect of mannitol

The Ibu solubility was determined at four different concentrations of mannitol with aqueous and 10% ethanol solutions. The Ibu solubility trend in solvent containing mannitol as the only excipient was stable. For the 10% ethanol the Ibu solubility in 10% ethanol did not show specific trend; however, increased slightly due to the presence of semipolar ethanol. A similar effect was observed in the solvent of all excipients. Therefore, the increased concentration of mannitol in the solvent system showed no effect on the Ibu solubility in any solvent composition (fig. S5). A similar effect was also observed in the solubility behaviour of some water insoluble drugs (Ursodeoxycholic acid, rofecoxib) [23, 24]. Thus, this excipient did not cause any fundamental changes in the Ibu solubility.

Based on the experimental data demonstrated (fig. S6-S9 and table 3, different compositions of excipients showed different trends of

solubility behaviour in various concentrations of aqueous ethanolic solvents. Although excipients solvents showed significantly increased solubility, the maximum solubility of Ibu (1726 ppm) in table 3 was observed in a solvent containing 1.52% leucine, 5.22% mannitol, 0.25% HPMC, 1.55% PI F127 and 10.75% w/w ethanol. The variation of solubility behaviours of these excipients in ethanol or the aqueous ethanol solvents played a significant role in Ibu solubility. We suggest that the presence of a significant amount of hydrophilic excipient (amphiphilic leucine and hydrophilic HPMC and D-mannitol) containing a large number of hydroxyl groups are responsible to impact on the drug-solvent interaction by hydrogen bonding network [14]. The presence of amphiphilic surfactant L-leucine (although it alone did not show significant role) in the complex solvent played a significant role in increasing the solubility of the Ibu possibly due to the orientation of hydroxyl groups towards the aqueous solvent, which increased the particle-solvent interactions by hydrogen bonding. Overall, the solubility studies of Ibu in aqueous ethanol systems with or without excipients developed in this investigation would be very useful for the pre-formulation studies of Ibu for the development of various dosage forms. The solubility enhancement of poorly water-soluble drugs in the presence of the excipients (especially PI F127) has the potential to overcome the limitations of the solubility issues in developing various formulations. The Ibu solubility in aqueous ethanol with these four excipients (PI F127, HPMC, L-leucine and D-mannitol) is the first novelty of our research. It is expected that the outcome of this study would contribute to advancing new technological possibilities in enhancing the solubility of poorly water-soluble drug's for developing any dosage forms.

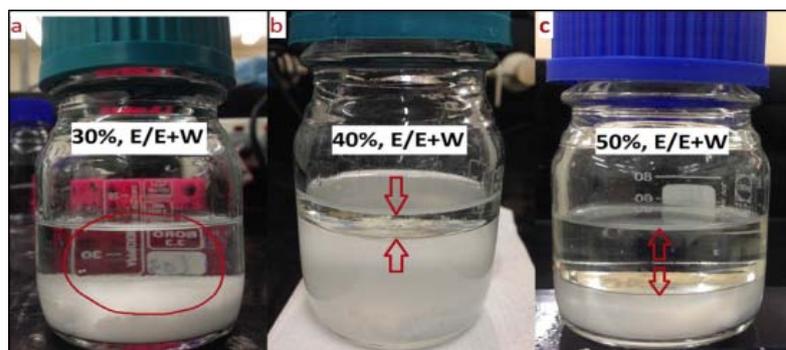


Fig. 6: Ibu in 30% E/(E+W) does not show phase separation (a); however, Ibu induced phase separation with 40% (b) and 50% E/(W+E) (c) solvents at 40 °C

Phase separation analysis at 40 °C

The phase separation of the Ibu solution has been presented in fig. 6, which shows two liquid layers. The 30% E/(W+E) (fig. 6 a) did not show any liquid phase separation but the other two (fig. 6 b and c) did. The interface between the two liquid layers (40 and 50% (E/E+W)) is clearly seen. Ibu crystals are the densest species and they sink to sit in the bottom liquid layer. At 40 °C, phase separation occurred above 34% aqueous ethanol solutions. At higher ethanol content it required excess IBU to saturate the solution caused density differences between aqueous and non-aqueous solvents and led to phase separation (fig. 6). As explained earlier the upper layer contains higher IBU in ethanol and the lower layer is the water with low IBU concentration. Below 34% aqueous ethanol solvent the IBU saturated solution remains at the same density and no liquid phase separation occurs. Phase separation of Ibu was initially demonstrated by Rashid *et al.* [18] at 40 °C when the ethanol in water used was above 34% and below 63%. This phenomenon was also reported by others [24-26]. A brief experiment was undertaken in this study to confirm these values, which are in agreement with the outcomes published by Rashid *et al.* [18].

CONCLUSION

The solubility of Ibu in aqueous ethanol solutions was determined at 10, 25 and 40 °C. The solubility of Ibu alone increased considerably with the increased ethanol contents and temperature. Phase separation at 40 °C limited the solubility observation to 35% E/(E+W); above this range phase separation with different phase ratios occurred. We established that the use of PI F127 alone had a significant effect on Ibu solubility compared to the use of HPMC alone. HPMC and PI F127 raise Ibu solubility with a factor of 14 but individually solubility enhancement effect of PI F127 is approximately 19 times higher than that of HPMC. Leucine and mannitol did not affect the Ibu solubility significantly; however, the combination of all excipients showed promising solubility. The maximum solubility of Ibu (1726 ppm) was observed in a solvent containing 1.52% leucine, 5.22% mannitol, 0.25% HPMC, 1.55% PI F127 and 10.75% w/w ethanol. Although the Ibu solubility alone increased considerably with increasing ethanol contents and temperature, the solubility effect of excipients is important in designing the crystallization technique for producing the Ibu crystals with enhanced solubility for the development of various drug delivery systems.

ACKNOWLEDGEMENT

The authors thank the Queensland University of Technology (QUT) for financial support of Afrina Afrose's PhD scholarship.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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