Enhancement of docetaxel solubility using binary and ternary solid dispersion systems

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Abstract

Context: Poor biopharmaceutical properties and toxicities associated with the intravenous formulation of docetaxel (DTX) necessitate the exploration of an alternate oral route of delivery. 
Objective: This study aims at enhancing the solubility of poorly soluble drug, DTX with the help of solid dispersion (SD) technique.
Method: DTX SDs were formulated with selected solubilizers, including Kollidon 12PF, Lutrol F68, Soluplus and Hydroxypropyl-β-cyclodextrin in different weight ratios. Freeze-drying method was used to prepare the binary and ternary SDs. Kinetic solubility of the SDs was evaluated in order to select best DTX-solubilizer combination. Best performing combination was then characterized using differential scanning calorimeter (DSC), powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM).
Results and Discussion: Among all SDs tested, Soluplus outperformed all the excipients at equivalent weight ratio. Binary SD of DTX and Soluplus (1:10) resulted in the highest improvement in solubility (362.93 ± 11.01 μg/mL). This is approximately a 93-fold increment as compared to the solubility of crystalline DTX (3.9 ± 0.2 μg/mL). This exceptional performance can be attributed to solid-state transformation as well as micellization.
Conclusion: Among all the excipients tested, Soluplus dispersion is the most promising candidate for oral formulation development.

Keywords
Anti-cancer, apparent solubility, freeze-drying, solubility parameter, Soluplus

Introduction

The rate and extent of drug absorption from solid oral dosage form mainly depend on the solubility and dissolution rate of the active pharmaceutical ingredient. In case of poorly soluble drugs, the solubility and dissolution rate often act as a rate-limiting step in absorption. Enhancements of these properties are a major challenge for pharmaceutical industry. Several techniques have been explored to enhance the aqueous solubility including, complexation, micronization, micro-emulsions, particle size reduction, self-emulsifying micro and nano disperse systems, preparation of SDs, salt and prodrugs.

Docetaxel (DTX) belongs to family of taxane and is widely prescribed chemotherapy drug for the treatment of breast, non-small cell lung, prostate, gastric, head and neck cancer. It acts by halting the cell cycle at G2/M phase via binding and subsequent stabilization of tubulin, leading to cell death. DTX is classified under Class IV drug of the Biopharmaceutics Classification System (BCS) having poor solubility and permeability. The low bioavailability of DTX (<10%) is mainly due to poor solubility in water and its affinity to the multi-drug efflux pump P-glycoprotein (P-gp) and extensive metabolism by CYP 3A4 in gut wall and liver. The poor bioavailability of DTX has made solubility an essential aspect to be augmented during product development.

Currently, DTX is available in single-dose vials with polysorbate 80 for the intravenous (IV) infusion. However, oral dosage form will offer obvious inherent benefits. Oral dosage form is generally cost effective, easier to use, and most importantly reduces the risk of severe hypersensitivity reaction that are related to IV administration of polysorbate 80. Certainly, an oral dosage formulation will increase patient compliance as well as improve the therapeutic outcome.

Among the various solubility enhancement techniques, SD preparation is considered simple, economical and amenable to scale up. SD is defined as the dispersion of one or more API in an inert carrier in the solid form. This technique has been effective in increasing the drug solubility, dissolution rate and bioavailability compared to pure drug and physical mixtures. Studies on drug SDs that have been shown to improve solubility include Carbendazin, Cilostazol, Danazol, Ibuprofen, Carbamazepin, Nimodipine, Ritonavir and Tacrolimus. It is understood that the solubility enhancement mechanisms could be attributed to the ability of SD in reducing the particle size of the
drug at molecular level and increase in the saturation solubility and/or transforming the drug from crystalline state to amorphous state\(^{10}\). Common methods for preparation of SDs include solvent evaporation, freeze-drying (FD), hot melt extrusion, fusion and spray drying. Spray drying and hot melt extrusion are industrially scalable\(^1\) but are of little value for small-scale discovery settings. Methods involving heating are limited due to drug stability. FD is one of the widely used techniques for milligram quantities and has good efficiency in terms of yield\(^1\).

SDs increase the apparent solubility of the compound by achieving supersaturation. The phenomenon of supersaturation can be explained by ‘spring and parachute’ concept proposed for the dissolution of drug\(^{13,14}\). When thermodynamically stable form of a drug is dissolved into the medium, the concentration of drug increases until it reaches an equilibrium solubility (path A, Figure 1). When a high-energy form (‘spring’) comes in contact with a medium, the solubility reaches a highest point, \(S_{\text{max}}\) corresponding to a time \(T_{\text{precipitation}}\), after which the solubility start to decline and reaches a point where the solution of a drug is in equilibrium with its thermodynamically most stable solid form (path B, Figure 1); the solubility corresponding to this point is the \(S_{\text{equilibrium}}\) (Figure 1). When the thermodynamically unstable, high-energy form (‘spring’, e.g. an amorphous dispersion) of the same drug is subjected to the dissolution, it follows path C. Wherein, it achieves higher maximum solubility value by supersaturation (\(S_{\text{ss}}\)), and maintain it for a certain time before entering into decline phase. The time corresponding to this maintenance phase is the hang time provided by the excipients which act as a ‘parachute’. However, the high-energy form of drug molecules club together and eventually precipitate as the most stable form over the period to give a solubility value equivalent to \(S_{\text{equilibrium}}\). As compared to dissolution experiments, in solubility studies non-sink conditions are maintained. But, the ‘spring and parachute’ concept can be extended to kinetic solubility measurements for rank ordering different SDs given that the initial amount used for the solubility measurements is kept constant.

The present study was undertaken to improve the therapeutic performance of DTX through solubility enhancement using SD formulated using Lutrol F68 (L), Kollidon 12PF (P), Hydroxypropyl-beta cyclodextrin (HP-\(\beta\)-CD) and Soluplus(S).

Lutrol F68 is a non-ionic poly (ethylene oxide) (PEO)–poly (propylene oxide) (PPO) co-polymer that is commonly used as solubilizing agent, surface active, emulsifying and dispersing agent. Kollidon 12PF is a member of the low-molecular polyvinyl pyrrolidones (PVP) and is used as solubilizing agent, dispersant or crystallization inhibitor. HP-\(\beta\)-CD is a cyclic oligosaccharide, derived from starch. HP-\(\beta\)-CD improves the aqueous solubility by providing the hydrophobic cavity for the lipophilic guest drug molecules. Soluplus is a graft co-polymer of poly-vinyl acetate and poly-vinyl caprolactam on a polyethylene glycol backbone. It is known to solubilize the poorly soluble drugs and serve as the matrix polymer for the solid solutions. It exhibits an excellent solubilizing property for the drugs from the BCS Class II and IV\(^{15,16}\).

In this study, SDs were prepared to compare the performance of excipients either alone or in combination. Comparison of Kollidon 12PF and Lutrol F68 combination would be of special importance as chemically this combination represents the copolymer composition of Soluplus (i.e. vinyl derivative and polyethylene glycol). Excipients were selected on the basis of solubility parameter (SP) approach. SD samples were prepared using FD, characterized and evaluated for various physic–chemical parameters.

**Materials and methods**

DTX anhydrous was purchased from Shanghai Jinhe Biotechnology Co., Ltd, Shanghai, China. HP-\(\beta\)-CD and Lutrol F68 were purchased from Sigma-Aldrich, Petaling Jaya, Selangor, Malaysia. Kollidon 12PF and Soluplus were gifted from BASF Australia Ltd (Melbourne, Australia). All other materials and reagents were of analytical grade.

**Solubility parameter analysis**

SP was used as a selection criterion for the polymeric excipients. SP is a measure of cohesive energy density of a substance. Cohesive energy is related to the molar heat of vaporization and can be calculated from the heat of vaporization for low-molecular weight substances. In studying polymers, indirect methods are preferred which include comparative swelling and solubility in a solvent of known cohesive energy. One of the mathematical
approaches for determining the SP is the Hansen solubility parameter (HSP) calculation. It defines a compound on the basis of dispersion ($\delta_d$), polarity ($\delta_p$) and hydrogen bonding ($\delta_h$) properties\(^{17}\). Each of these parameters accounts for the atomic, molecular and electronic level interactions. SP approach has been successfully used as a measure of miscibility of the drugs in the polymeric excipients for the preparation of SDs\(^{18,19}\). Greater the miscibility, lesser is the chance of recrystallization, hence literature value of DTX was compared with the polymer to select the polymeric carriers.

### Preparation of the binary and ternary solid dispersions

All the SDs were prepared by FD method for two reasons: (1) DTX is an expensive drug and (2) FD allows small quantities to be processed with 100% yield. DTX stock solution (10 mg/mL) was prepared in absolute ethanol. HP-$\beta$-CD, Soluplus and Kollidon 12PF were dissolved in purified water at 10 mg/mL concentration. One milliliter of DTX solution was mixed with an appropriate amount of polymer solution to make different ratios of binary and ternary dispersions (Table 1). The final volume was adjusted with water so that ethanol did not exceed 10% v/v in the solution used for the FD. For 1:1 HP-$\beta$-CD inclusion complex preparation\(^{20}\), DTX solution was added to the HP-$\beta$-CD solution and stirred at room temperature for 2 h. Solution was filtered through 0.45-μm syringe filter (PVDF). Before FD, solutions were frozen at −80°C for at least 6 h and then subjected to lyophilization in Novalyphe-NL 500 (Savant Instruments Corp., Holbrook, NY) lyophilizer for at least 24 h at −45°C and 7 × 10⁻³ mbar pressure. The SDs were then stored in the desiccator for further analysis. Best performing binary ratios were further combined to make ternary dispersions. Table 1 shows the different combinations and ratios used for preparing dispersions. Amorphous DTX was prepared using solvent evaporation method\(^{21}\) using Buchi Rotavap II instrument. 50 mg of DTX was dissolved in 5–7 mL of acetone, then the mixture was dried at 55–60°C under vacuum (500–600 mbar). The product was collected and stored in desiccator before analysis.

### Kinetic solubility test

The dispersion equivalent to about 1 mg of DTX was weighed and kept for solubility study in 2.5 mL of 0.1 M, pH 6.8 phosphate buffer at ambient temperature. The samples were continuously rotated using a mechanical shaker (Axyos Technologies, Brisbane, Australia) throughout the test. Solubility samples were collected at the predetermined time interval and filtered through 0.45-μm PVDF syringe filter. Subsequently, the filtrates were diluted using acetonitrile. The analysis of the samples was performed on an HPLC (Shimadzu, Kyoto, Japan) system equipped with a UV–VIS detector [SPD-20 A], DGU-20A3 online degasser, CBM-20 A system controller, SIL-20AHT autosampler and a LC solution Chrompack data processor. Zorbax Eclipse XDB-C$_18$ (4.6 × 150 mm, 3.5 μm) analytical column was used. The mobile phase used was acetonitrile and ammonium acetate pH 5 (0.02 M) at the ratio of 57:43. The injection volume was 20 μL with a flow rate of 1 mL/min, and detection was performed at 230 nm\(^{22,23}\).

### Scanning electron microscopy (SEM)

Samples were platinum coated using Quorumtech K757X sputter coater to get 10-nm thick deposits. SEM CamScan MX2500 (Ottawa, Canada) was used to study the morphology of DTX and the SD samples. It was operated in secondary electron mode at an accelerating voltage of 15 kV.

### Fourier transform infrared spectroscopy

FTIR patterns were recorded between 800 and 4000 cm⁻¹ at 2 cm⁻¹ scan rate using Shimadzu Fourier Transform Infra-Red Spectrophotometer 8400S (Tokyo, Japan). Conventional, potassium bromide (KBr) pallet method was used for the sample preparation.

### Differential scanning calorimetry

Thermal analysis was performed using differential scanning calorimeter (DSC) (TA Q3 Model 2920, New Castle, DE). Hermetically sealed samples were heated at 10°C/min from ambient to 220°C under nitrogen purge (50 mL/min).

### Powder X-ray diffractometry

X-ray diffraction patterns were obtained from a Rigaku MiniFlex 600 bench top XRD (Rigaku Corporation, Tokyo, Japan). Radiations were generated from Cu source (Kα, $\lambda = 1.54$ Å) operating at 30 kV and 20 mA. Samples were scanned at a step size of 0.02° between 3–40° 2θ.

### Statistical analysis

All experiments were performed in triplicate and the values are reported as mean ± standard deviation. The analysis of variance (ANOVA) and Tukey HSD post-hoc test was performed using the IBM SPSS software (Armonk, NY). A probability level of $p < 0.05$ was considered statistically significant.

### Results

### Solubility parameter analysis

It has been observed that less than 7 MPa$^{1/2}$ difference in the SP leads to favorable interactions between drug and polymer, resulting in mutual miscibility\(^{18,24}\). Although this value has been proposed on the basis of specific drug–polymer combination, it can serve as a criterion for the excipient selection. SP value for DTX is 26.6 MPa$^{1/2}$. It was compared with the polymeric excipients as shown in Table 2\(^{25,26}\). Using above value as a guideline, it can be predicted that the excipients having value between 19.6 and 33.6 MPa$^{1/2}$ should be miscible with DTX, whereas an excipient with SP value less than 19.6 or greater than

| Dispersion type | Combination | Code     | Weight ratio |
|-----------------|-------------|----------|--------------|
| Binary dispersion | DTX and HP-$\beta$-CD | DH:1:1 MC | 1:1          |
|                 | DTX and Soluplus     | DS       | 1:2, 1:5, 1:10 |
|                 | DTX and Kollidon 12PF | DP       | 1:2, 1:5, 1:10 |
| Ternary dispersion | (DTX:HP-P-CD) + Soluplus | (DH):S   | 1:2, 1:5, 1:10 |
|                 | (DTX:Kollidon 12PF) + Lutrol F 68 | (DP):L   | 1:2, 1:5, 1:10 |

MC, molecular complex.
33.6 MPa\(^{1/2}\) is likely to be less soluble. Difference between DTX and Lutrol F68 is 6.3, while the difference of Soluplus and Kollidon 12PF is same, i.e. 7.2. Hence, Soluplus and Kollidon 12PF can be expected to moderately solubilize DTX due to the SP difference >7.2. In addition to above polymers, HP-β-CD was also selected, as cyclodextrins have been reported to form 1:1 molecular complex with DTX thereby increasing the solubility\(^{27,28}\).

**Kinetic solubility test**

Prepared SDs were subjected to kinetic solubility analysis. Figure 2 shows the 24 h solubility values for DTX, binary and ternary dispersions. From here on, the solubility at 24 h will be referred as equilibrium solubility.

Crystalline and amorphous forms of DTX show nearly the same equilibrium solubility of about \(\sim3.9\,\mu g/mL\), which is in close agreement with the previously published data\(^{2,29}\). Though both forms show 5 min of\(\text{T}_{\text{precipitation}}\) value, but the amorphous forms show slightly higher\(\text{S}_{\text{max}}\) value, 14.23 \(\mu g/mL\) as compared to crystalline form (Table 3).

For all the combinations of SDs, the equilibrium solubility is greater than any of the DTX forms. Equimolar complex of DTX with HP-β-CD showed an equilibrium solubility of \(\sim5\,\mu g/mL\) and \(\text{S}_{\text{eq}}\) of about \(\sim6\,\mu g/mL\) at 10 min. \(\text{S}_{\text{equilibrium}}\) was 1.3-folds higher than the crystalline form.

All the binary combinations of DTX and Kollidon 12PF show polymer concentration dependent improvement in the \(\text{S}_{\text{equilibrium}}\) value ranging from 5.4 to 10 \(\mu g/mL\). Improvements were also seen in the hang time, as shown in Table 3. Binary dispersions of Soluplus at all the ratios showed significant improvement in the solubility value ranging from 53.4 to 363 \(\mu g/mL\). These are 24 h solubility numbers, as no\(\text{T}_{\text{precipitation}}\) was observed.

**Table 2. Solubility parameters of DTX and solubilizers.**

| Component         | \(\delta_d\) MPa\(^{1/2}\) | \(\delta_p\) MPa\(^{1/2}\) | \(\delta_h\) MPa\(^{1/2}\) | HSP MPa\(^{1/2}\) | \(\Delta\text{HSP}\) MPa\(^{1/2}\) |
|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| DTX\(^{26}\)      | 21.19           | 3.51            | 15.63           | 26.60           | 0.0             |
| Lutrol F68\(^{25}\) | 17.80           | 1.00            | 9.8             | 20.30           | 6.3             |
| Soluplus\(^{25}\) | 17.40           | 0.30            | 8.60            | 19.40           | 7.2             |
| Kollidon 12PF\(^{25}\) | 17.30           | 2.40            | 8.50            | 19.40           | 7.2             |

**Statistical analysis**

ANOVA was performed at T\(_{20}\) and T\(_{45}\) min solubility data for the best-performing formulations (Table 4) and it was found that there was significant difference at both time points. The kinetic solubility profiles and the details of the statistical tests can be found under Supplementary material (S1 and S2). The results of\(\text{post-hoc Tukey test}\) showed that at 20 min time point, formulations DH (\(p=0.98\)), DP 1:10 (\(p=0.91\)) and (DP)L 1:10 (\(p=0.60\)), did not differ significantly from the crystalline DTX. But the formulations containing Soluplus, i.e. DS 1:10 (\(p=0.00\)) and (DH)S 1:10 (\(p=0.00\)) were significantly different from the crystalline DTX. Similar observation was made at 45 min. The formulations DH (\(p=0.91\)), DP 1:10 (\(p=1.00\)) and (DP)L 1:10 (\(p=0.44\)) were statistically not different as compared to crystalline DTX, while Soluplus containing formulations differed significantly from the crystalline DTX. When the Soluplus containing formulations were compared at T\(_{20}\) and T\(_{45}\), it was found that at T\(_{20}\) there was significant difference in the solubility of DS 1:10 and (DH)S 1:10, but at T\(_{45}\) min there was no statistical difference between the two (\(p=0.43\)). Combination of Lutrol F68 with DP 1:10 SD did not improve the solubility significantly at T\(_{20}\) and T\(_{40}\) (\(p=0.99\) and \(p=0.72\), respectively). Addition of Soluplus to HP-β-CD complex significantly improved the solubility at both time points.

**Scanning electron microscopy (SEM)**

SEM analysis was performed to study the morphological feature of best combinations from each SD group. DTX shows needle-shaped acicular crystals (Figure 3A). Dispersion of DTX along with the Soluplus, HP-β-CD and Lutrol F68 combinations.
exhibited a typical sponge-like morphology (Figure 3B, C and D). No traces of crystalline DTX were observed.

**Fourier transform infrared spectroscopy**

Fourier transform infrared spectroscopy (FTIR) was performed on the best performing binary combination, i.e., DTX and Soluplus. The IR spectra are shown in Figure 4. Spectrum of DTX showed peaks corresponding to N–H and O–H stretching around 3460 cm\(^{-1}\). Aliphatic and aromatic C–H stretches were observed between 2820 and 3060 cm\(^{-1}\) and C = O stretching corresponding to the peak around 1720 cm\(^{-1}\). Soluplus showed peaks around 3450 cm\(^{-1}\) corresponding to O–H stretching, and carbonyl stretching at 1635 and 1740 cm\(^{-1}\). Peaks corresponding to C–H stretching were observed around 2930 cm\(^{-1}\). There were no peak shifts/appearance or disappearance of characteristic peaks in the SD of DTX and Soluplus (1:1) as compared to pure DTX and Soluplus. It indicated that there was no chemical incompatibility and the DTX is chemically intact in the Soluplus matrix.

**Differential scanning calorimetry**

DSC was performed on Soluplus dispersion to determine the solid-state changes in DTX dispersion preparation. In the thermogram of freeze-dried Soluplus, no thermal event was recorded (Figure 5A), indicating the amorphous nature of the polymeric carrier. Amorphous DTX do not show an event corresponding to the melting peak shown by the crystalline DTX at 169.13 °C (Figure 5C and D). In the case of DTX Soluplus dispersion (1:1) no endothermic event corresponding to melting of DTX was observed, indicating the amorphization of the DTX in the SD (Figure 5B).

**Powder X-ray diffraction**

Powder X-ray diffractometry (PXRD) was performed to confirm the solid-state characteristics of the Soluplus dispersion. Figure 6 shows the PXRD pattern for DTX Soluplus (1:1) dispersion, freeze-dried Soluplus, amorphous and crystalline DTX. As expected, crystalline form of DTX showed sharp characteristic diffraction peaks confirming the crystallinity of the initial form used for the preparation of SDs. In freeze dried Soluplus and amorphous DTX samples broad hallows were observed indicating the amorphous nature. The PXRD pattern of DTX Soluplus (1:1) dispersion did not exhibit crystallinity which corroborates the DSC results, where no thermal events were recorded corresponding to the melting of DTX.

**Discussion**

Amorphous form of DTX was prepared successfully using the solvent evaporation method. Amorphization was confirmed using DSC and XRD analyses. Amorphous DTX showed kinetic advantage as compared to the crystalline form (\(S_{\text{max}}\) Crystalline DTX < \(S_{\text{max}}\) amorphous DTX). However, equilibrium solubility in both cases is nearly same. This suggests the conversion of amorphous to a crystalline form by the end of the solubility experiment. In this study, anhydrous crystalline DTX was used. It is known that the DTX trihydrate is the thermodynamically most stable form, hence both amorphous and the anhydrous crystalline form could have converted to a trihydrate form by the end of the study. Tatini et al. have reported the conversion of methanolates and ethanolates to trihydrate form in presence of 95% relative humidity. Hence, it is important to point here that, no attempt was made to analyze the solid form after the solubility analysis as it is imperative that all the DTX after solubility analysis would eventually convert to trihydrate form.

SP was used as a selection criterion for preparing the binary and ternary SDs of DTX. As predicted, Lutrol F68 yielded amorphous product. In the case of Soluplus and Kollidon 12PF, SDs were prepared successfully despite the moderate miscibility predicted by SP. It is worthwhile to highlight here that, SP takes into consideration the van der Waals-type interactions but specific directional interactions like hydrogen bonding are outside the limits of this concept. Similar deviation has been observed for other drug–polymer combination, and this appears to be the case

| Table 3. Kinetic solubility parameters of DTX and SDs. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Sample**                      | **Ratio**       | **\(S_{\text{max}}\) or \(S_{\text{ss}}\) (µg/mL)** | **\(T_{\text{precipitation}}\) (min)** | **\(S_{24h}\) (µg/mL)** | **Folds enhancement*** |
| Crystalline DTX                 | –               | 10.46 ± 2.6     | 5               | 3.90 ± 0.2       | –               |
| Amorphous DTX                   | –               | 14.23 ± 3.9     | 5               | 3.60 ± 0.4       | –               |
| DH                               | 1:1 MC          | 5.80 ± 0.8      | 10              | 4.90 ± 0.3       | 1.3             |
| DP                               | 1:2             | 7.30 ± 1.0      | 10              | 5.40 ± 0.1       | 1.4             |
|                                | 1:5             | 15.21 ± 0.9     | 20              | 7.70 ± 0.2       | 2               |
|                                | 1:10            | 12.70 ± 0.8     | 30              | 10.00 ± 0.9      | 2.6             |
| DS                               | 1:2             | –               | –               | –               | 13.7            |
|                                | 1:5             | –               | –               | –               | 34.4            |
|                                | 1:10            | –               | –               | –               | 93.1            |
| (DP)L                           | 1:2             | 22.32 ± 2.9     | 5               | 9.48 ± 1.2       | 2.4             |
|                                | 1:5             | 16.74 ± 1.8     | 5               | 12.81 ± 0.6      | 3.3             |
|                                | 1:10            | 16.72 ± 1.8     | 10              | 13.51 ± 0.9      | 3.5             |
| (DH)S                           | 1:2             | 63.29 ± 6.8     | 45              | 54.84 ± 3.4      | 14.1            |
|                                | 1:5             | 121.71 ± 6.4    | 30              | 90.74 ± 11.2     | 23.3            |
|                                | 1:10            | –               | –               | 279.05 ± 12.4    | 71.6            |

*Calculated from \(S_{24h}\) of sample/\(S_{24h}\) of crystalline DTX.
between DTX and Soluplus/Kollidon 12PF. From the \( \delta_h \) values, it can be interpreted that both Soluplus and Kollidon 12PF have nearly the same propensity for hydrogen bonding (8.6 versus 8.5 for Kollidon 12PF) but Kollidon 12PF has higher likelihood of polar bonding (2.4 versus 0.3 for Soluplus).

Kinetic solubility was used as a performance criterion for SDs. All the binary and ternary SDs prepared showed higher \( S_{ss} \) (except DH and DP 1:2) as compared to the \( S_{max} \) of crystalline DTX. In the case of binary dispersion of HP-\( \beta \)-CD and Kollidon 12PF at 1:2 ratio though \( S_{ss} \) was lower, \( S_{equilibrium} \) was higher than crystalline DTX. Besides, the hang time of 5 min was achieved (as compared to crystalline DTX), which means that the higher amount of solubilizer used in the above two cases acted in sustaining the solubilization for longer but at the same time shielded the DTX instant solubilization. From here on, results for each excipient with all combinations (binary/ternary) will be discussed one by one.

In the case of binary HP-\( \beta \)-CD dispersion, improvement in \( S_{24h} \) and \( T_{precipitation} \) was observed with a decrease in the \( S_{ss} \) value. Previously, HP-\( \beta \)-CD has been shown to improve the
solubility of DTX to 7.43 mg/mL at 40% w/w concentration\textsuperscript{27}. It appears that a higher amount of HP-\(\beta\)-CD is required for a meaningful increment in the solubility value. Ternary dispersion of HP-\(\beta\)-CD with Soluplus clearly showed an increment in the S\textsubscript{ss}, T\textsubscript{precipitation} and S\textsubscript{24 h}. This appears to be primarily an effect of Soluplus, and it will be discussed at greater length in the later part of the discussion.

Kollidon 12PF binary SDs exhibited higher equilibrium solubility and longer T\textsubscript{precipitation} at all the ratios, with up to 2.6-fold increment. T\textsubscript{precipitation} of DP 1:10 reach up to 30 min. Viscosity increment has been considered as one of the factors for delayed precipitation\textsuperscript{34} when PVP K30 (MW \(\sim\) 40 K) is used\textsuperscript{8}. In this study, Kollidon 12PF was used which has lower molecular weight (MW 2–3 K) as compared to PVP K30. The viscosity of the medium does increase due to Kollidon 12PF but it is for sure, going to be lesser than the PVP K30 at the equivalent concentration. And also, there is a high potential of hydrogen-bonding interaction between PVP hydrogen bond acceptors\textsuperscript{35} and DTX hydrogen bond donors. So, it is not difficult to surmise that the overall increment could be a combined effect of viscosity\textsuperscript{34}, hydrogen-bonding interactions\textsuperscript{36} and shielding of DTX by PVP\textsuperscript{3}.

To further enhance the performance Kollidon 12PF, it was combined with Lutrol F68. When the binary dispersion of Kollidon 12PF is compared with a ternary dispersion containing Lutrol F68, there is a clear advantage in terms of S\textsubscript{ss} and S\textsubscript{24 h} due to surface activity of Lutrol F68. These ternary dispersions showed lesser T\textsubscript{precipitation} which means the rate of DTX release from the dispersion is higher as compared to binary dispersion with Kollidon 12PF alone. This infers that DTX dissociates faster from Kollidon 12PF in the presence of Lutrol F68.

Soluplus binary dispersion showed the best performance when equilibrium solubility is compared with all the other dispersions studied. Solid-state characterization, i.e. DSC and PXRD, clearly showed the successful amorphization of the DTX. No T\textsubscript{precipitation} was observed within the duration of experiment. This suggests that Soluplus acts as a precipitation inhibitor and keeps the supersaturated condition for more than 24 h. Shamma et al.\textsuperscript{16} have shown that an increase in the concentration of Soluplus in the SD can increase the drug solubility. The critical micelle concentration (CMC) of Soluplus was reported to be 0.0007% w/v at 37°C\textsuperscript{15}. Soluplus forms micelles by reorganizing the hydrophilic polyethylene glycol moiety into a micellar wall and the vinyl acetate and vinyl caprolactam side chains are buried inside the micelles. Again, there is a potential of hydrogen bonding interactions between the hydrogen acceptor groups in the vinyl acetate and vinyl caprolactam group\textsuperscript{10} with DTX. However, in solid state these interactions were not evident in the infrared spectroscopy.

**Figure 5.** DSC thermograms of (A) freeze-dried Soluplus, (B) DS 1:1, (C) amorphous DTX and (D) crystalline DTX.

**Figure 6.** PXRD patterns of (A) DS 1:1, (B) freeze-dried Soluplus, (C) amorphous DTX and (D) crystalline DTX.
possibly due to overlapping of the peaks. So it can be concluded that the kinetics of solubilization are positively influenced by both, formation of amorphous form ("Spring") as well as micelle in the solution ("Parachute").

Ternary dispersion of Soluplus and HP-β-CD showed a decrease in equilibrium solubility and hang time when compared with the Soluplus binary dispersion, although it is an improvement when compared with a binary dispersion with HP-β-CD alone. It appears that the kinetics of solubilization is relatively suppressed in the case of ternary dispersion. In general, it has been observed that the presence of cyclodextrins increases the critical micellar concentration of the surfactant by binding with the hydrophobic part. This could explain the suppressed solubility and hang time observed when Soluplus is combined with HP-β-CD. From post-hoc analysis, binary Soluplus (1:10) and ternary dispersion with HP-β-CD (1:10) showed no significant difference at 45 min time point, but when overall profile was considered in terms of S_max T_premiscion/hang time and S_equilibrium, binary dispersion of Soluplus at 1:10 outperformed not only the ternary dispersion with HP-β-CD but all the other SDs studied.

It is worthwhile comparing the results of Kollidon 12PF/Lutrol F68 combinations with Soluplus alone due to similarity of the chemical composition. It was observed that the ternary complex of Kollidon 12PF and Lutrol F68 exhibited maximum T_premiscion of 10 min ([DP)L 1:10] and S_max of about 22.32 µg/mL ([DP)L 1:2] as opposed to the S_max of about 362.93 µg/mL (DS 1:10) without precipitation. These results can be explained from two perspectives, i.e. T_premiscion and S_max on the basis of molecular weight/dissociation and mechanism of solubility enhancement. Kollidon 12PF is a low-molecular weight polymer as compared to Soluplus (11.8 K); in addition, the presence of Lutrol F68 could have led to faster DTX dissociation. As for the solubility enhancement, Kollidon 12PF acts by amorphization alone as opposed to Soluplus whose action was supplemented by micellization.

As per the statistical analysis, Soluplus dispersions show higher solubility at T_20 and T_45 min which essentially points to the fact that DTX was converted to a metastable amorphous form ("Spring"), and the polymers used helped to maintain supersaturation for longer duration ("Parachute") relative to crystalline DTX. Though metastable forms present attractive avenue for increasing apparent solubility, form conversion during storage could lead to formulation instability. Hence, in solid dispersion (SD) approach a rigid polymer help in avoiding this tendency when compared with a binary dispersion with HP-β-CD alone. It appears that the kinetics of solubilization is relatively suppressed in the case of ternary dispersion. In general, it has been observed that the presence of cyclodextrins increases the critical micellar concentration of the surfactant by binding with the hydrophobic part. This could explain the suppressed solubility and hang time observed when Soluplus is combined with HP-β-CD. From post-hoc analysis, binary Soluplus (1:10) and ternary dispersion with HP-β-CD (1:10) showed no significant difference at 45 min time point, but when overall profile was considered in terms of S_max T_premiscion/hang time and S_equilibrium, binary dispersion of Soluplus at 1:10 outperformed not only the ternary dispersion with HP-β-CD but all the other SDs studied.

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Recently, a clinical study has reported encouraging results from a ternary SD of DTX with PVP K30 and SLS in 1:9:1 weight ratio. When combined with ritonavir, a CYP 3A4 inhibitor, no significant difference was observed in the DTX premix solution and the SD. In addition, inter-individual exposure variability was decreased in the SD group. This study reports a dissolution test which was performed in water for injection at 37 °C. The best performing combination (vide supra) afforded the S_max of ~210 µg/mL, T_premiscion of ~9 min and equilibrium solubility of ~20 µg/mL. If these results are compared with the kinetic solubility study performed in this study, it strongly suggests that the DTX and Soluplus combination could yield potentially higher bioavailability when combined with ritonavir.

**Conclusion**

SP approach can be a good guide for the polymer selection provided that no specific interactions are involved. SDs prepared with solubilizers using the FD method is a promising technique to enhance solubility of drugs. The results obtained shows that Soluplus, Kollidon 12PF, Lutrol F68 and HP-β-CD were effective in increasing solubility of the poorly soluble drug. The type of solubilizer and DTX-solubilizer ratio are critical in the selection of appropriate SD combination. Among all the SDs studied, Soluplus SD in 1:10 ratio exhibited the best performance in terms of equilibrium solubility and delayed precipitation. This article also demonstrates that the typical excipient combinations, i.e. polymer and a surfactant explored for SD preparations could be replaced with a graft copolymer Soluplus with greater efficiency at equivalent weight ratio. Thus, Soluplus is the best option for DTX SD preparation. However, further investigations dealing with stability and *in-vivo* behavior of this SD formulation is necessary to ensure therapeutic usefulness.

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**Declaration of interest**

The authors report no declarations of interest.

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Supplementary material available online
Supplementary materials (S1–S2)