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Title: Development of deep eutectic solvent systems and their formulation: Assessment of solubilization potential on poorly water-soluble drugs.

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Abstract

Modern strategies to deliver drugs efficiently via less toxic non-aqueous carriers like deep eutectic solvents (DES) has grown tremendously. Herein, we develop several synthetic and natural DES to improve solubility of poorly soluble drug, docetaxel (DTX). Menthol:Thymol-based natural DES showed 1500-folds higher solubility for DTX than that in water. FTIR-spectroscopy confirmed reduced crystallinity and stable encapsulation of DTX in DES through formation of hydrogen-bond. DTX-DES was developed further into self-emulsified formulation that upon dilution formed nano-sized globules (<200 nm) and released 20-folds higher DTX than pure drug thereby highlighting the potential of DES for designing formulations of poorly soluble drugs.

Key words: Deep eutectic solvent, poorly water-soluble drug, self-emulsified delivery system.

Introduction

The biggest challenge preventing novel chemical therapeutic candidates with high therapeutic potential, which is almost 50% of the entire drugs developed, is poor solubility. As a result, developing an effective formulation with higher bioavailability would demand employing novel techniques like polymeric and lipid-based nano formulations, amorphous solid dispersions, complexation, and lipid dispersions etc. These approaches enhance the solubility of drugs in the gastrointestinal fluid, alter first-pass metabolism, thus leading to improved absorption. Lipid-based formulations have been used widely to tackle aforesaid challenges.[1,2] Amongst, self-emulsifying drug delivery system (SEDDS) remains most popular, promising, and unique formulation approach for poorly water-soluble drugs (PWD) due to ease of reproducibility, scalability, and commercial availability.[3,4] Furthermore, SEDDS are highly stable formulation because they do not contain aqueous part, instead, they emulsify (micro or nano emulsion) upon contact with the gastric fluid.[3] In general, SEDDS formulation contain completely soluble drug in a single or blend of lipids with or without surfactants and cosolvents. Like SEDDS, as an alternative to non-aqueous delivery systems, the application of ionic liquids and its counterpart deep-eutectic solvent (DES) has shown tremendous growth in the last five years for improving solubility of PWD.[5-7] DES are formed when a hydrogen-bond donor (HBD) and a hydrogen-bond acceptor (HBA) interact strongly in specific molar ratios under mild to moderate stirring with or without heating, resulting in decrease in the melting temperature to a level where the final eutectic mixture retains its liquid state at room temperature.[8] DES falls under green solvents and is reported to be safer and less toxic system over ionic liquids.[5,7] Besides regular DES, there are natural DES being explored in biomedical and pharmaceutical research meticulously due to their inert and non-toxic nature.[5] In few cases, a pure drug can act either as HBD or HBA and this way, very high solubility of PWD can be achieved. The key mechanism by which DES improves solubilization of PWD is attributed to disrupting the intermolecular forces of the drug that holds the drug in a solid state. Once hydrogen bonds form between HBA and HBD, disruption weakens the internal lattice energy- within the drug, leading to its solubilization in the eutectic mixture. Although hydrogen bonding is a primary mechanism, other factors such as the polarity, viscosity, and overall structure of the DES also contribute to its solubilizing capabilities. Detailed reports on the thermodynamics of DES, therapeutic applications and regulatory insights etc. have been published by

Abdelquader et al. and Maan Hayyan.[9,10] Several reports have been published for topical, transdermal, and intravenous applications wherein DES-based approach is used to deliver PWD.[7,11]

Docetaxel (DTX), a widely used anti-cancer drug, is a known PWD and commercially available only as intravenous formulations. Several lipid-based formulations (SEDDS, liposomes, lipid nanoparticles etc.) have been published showing improved absorption for DTX.[12] However, till date, DES-based approach for DTX has not been reported. DTX being class IV drug, aqueous solubility of the DTX is <0.2 µg/mL and is very poorly permeable therefore, chosen as a model drug in this study. In such a condition, based on the published outcomes of DES, it seems to be an ideal candidate to investigate PWD (DTX) for improving solubility and bioavailability by exploring DES-based formulation for DTX (DTX-DES). Furthermore, developed DTX-DES can be considered as a primary component of the SEDDS formulation and using that DTX-DES based SEDDS (DDS) formulation can be developed.

In this direction, the aim of the present study was to develop a natural DES based SEDDS formulation for DTX. We developed a series of DES systems and evaluated DTX solubility. By using the optimum DES having highest solubility for the DTX, DDS was developed. We characterized developed formulations (DTX-DES and DDS) for interaction studies, dilution performances, globule size, comparative two-step dissolution and short-term stability. To the best of our knowledge, this preliminary study is the first report stating development of DES based SEDDS formulation of PWD. Future work will involve studying release profile in tissue and animal models.

Experimental method

Materials

Docetaxel (DTX) was purchased from the LC laboratories (Woburn, MA). Acetonitrile and methanol HPLC grade were purchased from Spectrum chemicals Ltd. (New Brunswick, NJ). Hydrochloric acid, sodium hydroxide, choline chloride, ethylene glycol, propane diol, tween 80, tween 20, urea, menthol, thymol, camphor and glycerol were purchased from Sigma Aldrich (Boston, MA). UPLC Luna omega C18 column was purchased from Phenomenex (Torrance, CA).

UPLC method development

UPLC method was developed to quantify DTX in the final formulation and in release samples. Luna omega C18 column (150 × 2.1 mm, 1.6 µm particle size, Phenomenex, CA, USA) was used as a stationary phase while mobile phase consisted of 0.02M ammonium format and 0.1% formic acid in acetonitrile (40:60 v/v) at the flowrate of 0.3 mL/min. The column temperature was kept at 30.0 °C. DTX primary stock solution and standard samples were prepared in the methanol. The injection volume was 3 µL and the detection wavelength was 228 nm. Acquity UPLC I-class system from Waters (Milford, MA) was used for this purpose.

Formation of DES system

DES systems, synthetic and natural, were prepared by simple mixing of HBA and HBD on stirrer at room temperature or under mild heating (40.0 ± 2.0 °C). Under synthetic DES, Tween 20 and choline chloride (CHCL) were selected as HBA while urea, ethylene glycol (EG), propane diol (PD), and glycerol (Gly) were HBD, respectively. Under natural DES, menthol was HBA and HBD were thymol and camphor, respectively. In general, HBA and HBD at a selected molar ratio were weighed in a glass vial and allowed to stir until clear mixture forms.

Solubility of DTX in DES system

To select an optimal DES system, solubility of DTX was determined in several DES systems and few individual liquid components (Tween 20, EG, Gly, PD, and purified water). Briefly, in a 4 mL glass vial, 2 mL of DES or individual components were added and on top, DTX was added. This mixture was allowed to stir at slow speed (to avoid vortex formation) at room temperature. Once clear mixture forms, additional DTX is added. DTX was added until super saturation takes place. DTX was allowed to mix overnight and the next day, samples were transferred to the centrifuge tubes. Samples were centrifuged at 12000 rpm for 20 min to settle the undissolved DTX. Supernatant was taken in a separate tube and diluted with methanol. Absorbances were taken on UV spectrophotometer at 228 nm. Plain methanol and inert components mixed with methanol were used as control to nullify their absorbances affecting DTX responses. The presence of DTX in DES system and individual components was plotted only when DTX solubility is more than 10 mg/mL.

Preparation of optimized DTX-DES loaded formulation

To formulate optimized DTX-DES, DES system showing highest solubility for the DTX was selected. To this DES system, DTX was added and allowed to stir for 30 min to get clear mixture. Once clear mixture forms, DTX-DES was stored aside and was used as a lipid phase to formulate DTX-DES based SEDDS (DDS). To formulate DDS, in a glass vial, DTX-DES was vortexed at 3000 rpm with surfactant (Tween 80) and cosolvent (EG) at 1:2:2, respectively for 2 min. Furthermore, glass vial was sonicated for 5 min to make homogenous DDS. In similar way, as a control, blank DDS was prepared using blank DES system.

Characterization of formulation

Dilution studies and particle size measurements: Considering an oral application, to evaluate the self-emulsification potential, DDS was diluted (100 times) individually with simulated gastric fluid (SGF), 0.1N HCl pH 1.2, and simulated intestinal fluid (SIF), PBS pH 6.4 maintained at 37 °C. Similarly, blank DDS was diluted to serve as a control. Diluted samples were observed visually for phase separation, if any. Globule size and polydispersity index (PDI) of the diluted samples were measured by particle size analyzer (Litesizer 100, Anton Paar, VA).

Drug content: DDS formulation equivalent to 5 mg of DTX was taken and diluted in methanol. Samples were transferred into centrifuge tubes and vortexed. After centrifugation (10 min, 4000 rpm), supernatant was collected and diluted further with methanol to make it suitable in terms of concentration for UPLC analysis. Samples were filtered through 0.22 µ PVDF syringe filter (Corning, Inc.) and after discarding initial 2 mL sample, final samples were injected onto UPLC to analyze DTX content at 228 nm.

Interaction studies: To determine the chemical interaction between drug and the DES system, FTIR analysis was performed for DTX, blank DES, DTX-DES physical mixture, and DTX-DES using FTIR spectrophotometer. DTX-DES physical mixture was prepared by roughly grinding the DTX, menthol, and thymol to make a fine or coarse powder like sample. Samples were placed on the stage and scanned in the range of 4000 cm^{-1} to 500 cm^{-1}. IR spectra in the infrared region were compared to investigate the interaction between DTX and DES system. FTIR spectra were corrected against the ambient air as background.

Differential scanning calorimetry (DSC) analysis: DSC analysis of pure DTX, physical mixture of DTX-DES and DTX-DES was performed using DSC Q20 (TA instruments, USA). Briefly, samples (3–5 mg) were hermetically sealed in standard aluminum pans and analysis was performed at heating rate of 10 °C/min from 25 to 250 °C under a nitrogen atmosphere with a flow rate of 50 ml/min. An empty sealed aluminum pan was used as a reference. The endothermic, exothermic transitions and melting events of the samples were captured and overlaid to interpret the interaction between DTX and DES. For DTX-DES physical mixture sample, menthol and thymol were grounded roughly at 1:1 ratio and to that pure DTX was sprinkled. DSC thermograms were interpreted through universal analysis-TA advantage V4.5A software.

Dissolution study: Dissolution of DDS and controls (Pure DTX and DTX-DES) was performed in SGF and SIF as a two-step dissolution over 4 h. Briefly, DDS, pure DTX powder and DTX-DES equivalent to 20 mg of DTX were placed in a glass vessel containing 50 mL of SGF under stirring at 100 rpm at 37 °C for 2 h. At 0.5, 1, 1.5 and 2 h, 0.5 mL of samples were withdrawn. After 2 h, 48 mL of SIF was added, and pH was adjusted to 6.8 by adding 6.0 mL of 1.0 N NaOH. Stirring was continued for the next 2 h and samples were withdrawn at 2.5, 3, 3.5 and 4 h. All the samples were centrifuged at 4000 rpm for 10 min to settle down undissolved particulates, if any. Supernatants were collected and filtered through 0.22 µ PVDF syringe filter. After suitable dilutions with methanol, samples were injected on UPLC to determine the concentration of DTX as per aforesaid UPLC method. Experiments were performed in triplicate. In a similar manner, dissolution for DDS without DTX was performed to serve as a control.

Short-term stability of the formulation: To demonstrate the behavior and/or stability of DTX in the DDS formulation, DDS was stored at room temperature (25±2 °C) for two months. At the end of one month and two month, short-terms stability of the DDS was evaluated in terms of precipitation, drug content, and globule size.

Results and discussion

Analytical method of DTX by UPLC and UV spectrophotometer

Standard solution of DTX in methanol (100 µg/mL) was scanned under UV spectrophotometer and spectra showed maximum absorbance at the wavelength of 228 nm. To measure DTX concentration for solubility in different components and DES system, interferences of excipients were nullified by preparing placebo samples in methanol and were scanned at 228 nm against plain methanol as a reference solution. The standard curve for DTX in UPLC and UV spectroscopy in the concentration range of 0.5-25 µg/mL and 10-100 µg/mL, respectively was found to be linear (R^2 = 1.0). For UPLC method, DTX retention time was found to be 4.0 min and at that time point, there was no interference from any components. Overall, DTX peak was found to be sharp and UPLC method seem to be specific, system suitable and no carryover effects were observed.

Solubility of DTX in DES system

Solubility of DTX was performed in several synthetic DES system (CHCL:Urea, CHCL:PD, CHCL:Gly, CHCL:EG, Tween20:PD, Tween20:EG, Tween20:CH:EG, and Tween20:CH:PD), natural DES system (Menthol:Camphor, Menthol:Thymol, and Menthol:Tween20:Camphor), and individual liquid components (Purified water, PD, Gly, EG, and Tween 20). Amongst them, the highest solubility for DTX was observed in the menthol: thymol (1:1), natural DES system (150 mg/mL). As per figure 1, the second highest solubility for DTX was observed in the DES system

made up of Tween20:EG (57.81 mg/mL). This could be ascribed to the individual solubility of DTX, 30.45 mg/mL, in Tween20 which in combination with EG resulted in almost two times higher solubility. However, the natural DES system showed improved solubility for DTX against synthetic DES system (Figure 1). Menthol has been widely used in several drug delivery systems for different routes as a natural and biologically inert pharmaceutical excipient.[13] Reports have suggested that for several hydrophobic drugs, the solubility and permeation was improved when menthol was used as a part of formulation.[13] Menthol, being HBA, when interacts with the HBD at an optimized molar ratio, forms eutectic mixture and depresses the melting point of drug and increases the hydrogen bonding, resulting in higher solubility.[14] Testosterone when processed with menthol, the melting point of the drug was lowered from 155 °C to 40 °C.[15] Additionally, the terpenes present in the menthol are reported to enhance the penetration of pharmaceuticals. Similar findings have been reported for thymol when formulated with meloxicam[16] and ibuprofen[17], resulting in enhanced absorption due to increased solubility of an individual drug. In this study, natural DES system of menthol: thymol (1:1) lowered the melting of DTX to a level that nearly 150 mg/mL of DTX was easily solubilized into DES while solubility of DTX in purified water was less than 0.1 mg/mL. In other words, DTX solubility was 1500-fold higher in DES than that in water. Plausibly, at equimolar ratio, strong interaction between menthol and thymol results in the formation of a newer eutectic composition with a very low melting point. At this ratio, overall molar free volume of the system decreases, and formation of new hydrogen bonds occurs therefore both components do not undergo molecular rearrangements necessary for further crystallization.[14]

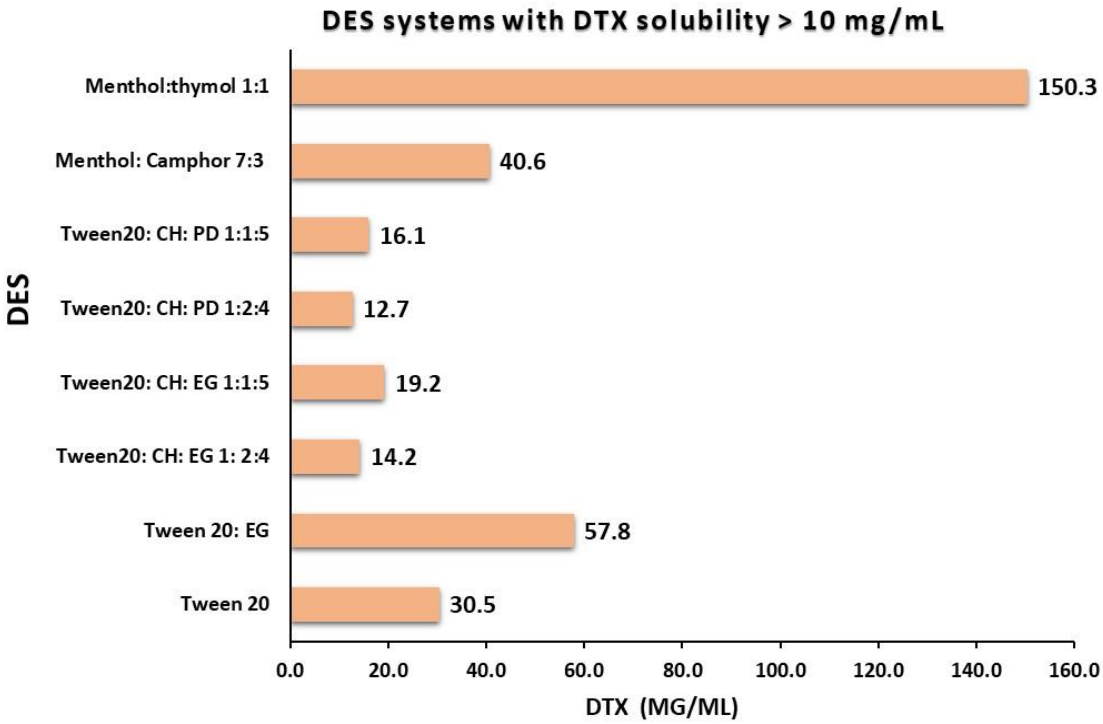


Figure 1. Solubility study representing amount (mg) of DTX per mL of natural and synthetic DES system, and individual components.

Preparation of optimized DTX-DES loaded formulation

The type of formulation or carrier into which the drug is loaded or entrapped plays a key role in the delivery of drug across the site of absorption. As per figure 1, solubility of DTX was highest in menthol: thymol (1:1) DES system. Therefore, DTX was dissolved in this DES to formulate DTX-DES containing 150 mg/mL DTX. To improve solubilization, and stability of DTX in the formulation and considering oral application, DTX-DES system was further designed into SEDDS formulation (DDS). Upon oral delivery, SEDDS formulation when encounters the gastrointestinal fluid, self-emulsification takes place and forms a colloidal suspension with nano sized globules, which could further increase the solubility of the drug. Thus, in this study, utilizing DTX-DES as a lipid phase, DDS was prepared by adding tween 80 and EG at 1:2:2, respectively. Prior to optimization for DDS, blank DES, tween 80, and EG were mixed at 1:2:2, respectively to optimize the formulation without DTX. Phase behavior and dilution potential of the blank formulation (blank DDS) was found to be promising. DTX did not show any visual precipitation in the DDS formulation. Tween 80, a widely used GRAS (generally recognized as safe) nonionic surfactant with HLB (hydrophilic lipophilic balance) value of 15.0 is reported to enhance the solubility and permeability of the poorly absorbed drugs. On the other side, cosolvent with low HLB value (< 5), when mixed with a surfactant having high HLB, offers stable emulsification and superior solubilization.[18] This is because cosolvents tend to accumulate around the interfacial layer, decreases the blending stress and increases the fluidity by penetrating the surfactant monolayer.[18] Herein, tween 80 and EG as a surfactant-cosolvent mixture when mixed with DTX-DES (lipid phase), DTX could not precipitate, instead, stable DDS formulation was obtained.

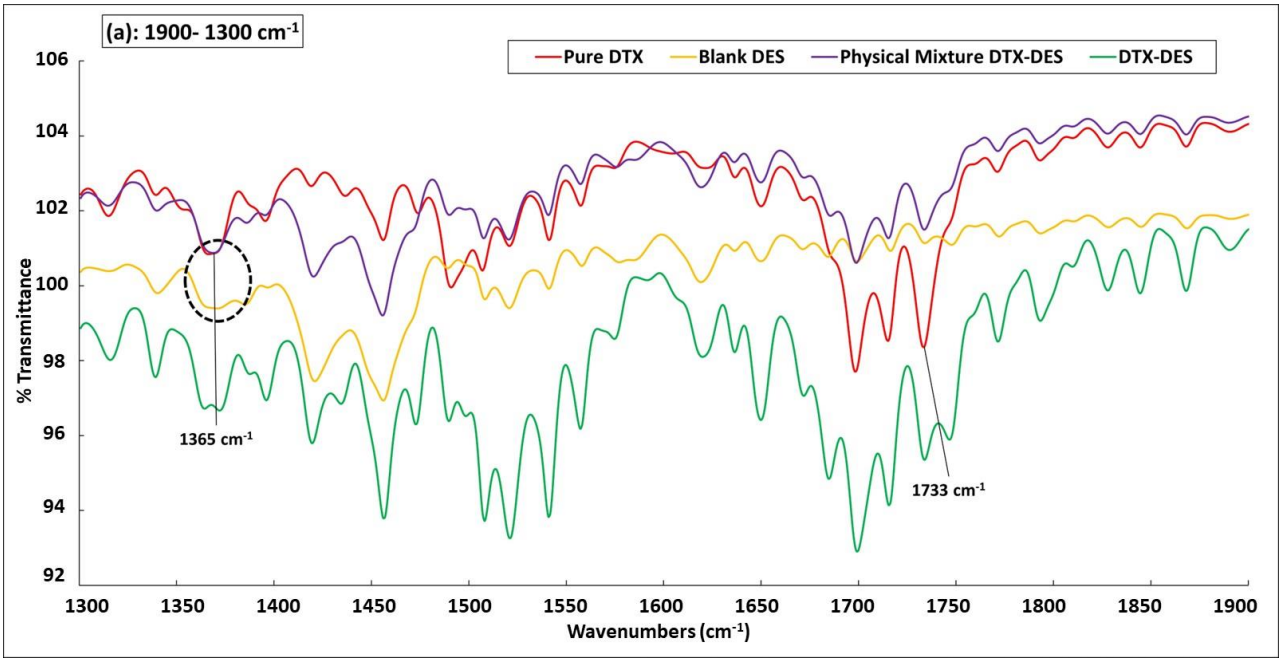
Characterization of formulation

The prepared DDS and blank formulation were diluted 100 times with SGF and SIF and in both the cases, slightly milky emulsion formation was observed. After 4 h of observation, no phase separation was seen which indicates the stability of the formulation against dilution. Further, the globule size of all the formulations were within 130-150 nm, conforming the formation of nanosized emulsion globules from DDS. Probably, DTX-DES globules remained dispersed into continuous dilution phase and the thin layer of tween 80-EG accumulated surrounding those globules thus forming stable emulsification and avoid aggregation of DTX-DES globules. As a result, PDI was below 0.2, suggesting uniform and narrow size distribution within the entire population of the diluted sample. Overall, it can be assumed that upon oral delivery of DDS, self-emulsification in the gastrointestinal fluid would take place and the nano sized globules of DTX-DES would release the DTX which shall be absorbed from the upper intestinal region, most likely via lymphatic transport. This suggests DES can be incorporated into polymeric or lipidic nanocarriers, to further enhance drug solubility and improve delivery to target sites.

Drug content was found to be 98.2 ± 0.5% indicating higher amount of DTX was entrapped in the final formulation. Additionally, the UPLC results confirmed that the DTX in DES and in final formulation was stable as the DTX peak shape, and pattern was identical with the DTX standard peak and was not interfering with any of the formulation components as confirmed by the placebo samples.

To identify structural or functional shifts within the composition against individual component, FTIR is a useful technique. To understand the intermolecular interaction between DTX and DES components, FTIR spectra for pure DTX, blank DES, physical mixture of DTX-DES and DTX-DES were overlayed as shown in Figure 2 and

observed for change in the peak intensity, widening or shifts. As per Figure 2a (1900-1300 cm^{-1}), FTIR spectrum for DTX showed a sharp peak at 1733 cm^{-1} for C=O stretching vibration and wide peak at 1365 cm^{-1} for O-H bending vibration of carboxylic group. As per Figure 2b (1300-700 cm^{-1}), DTX peaks at 1245 cm^{-1} attributed to C-N stretching, 1055 cm^{-1} corresponds to the C-N bending vibration of amide group, and 883 cm^{-1} corresponds to the C=C bending vibration of alkane group in the DTX.[19] Sharp peak at 753 cm^{-1} ascribed strong C-H bending. Amongst these DTX events, a few peaks were significantly different in the final DTX-DES (highlighted with black circle), suggesting obvious interactions between DTX and DES. The noticeable differences were observed at 1365 cm^{-1} that corresponds to the elongation vibrations of hydroxyl groups, while major change in the peak intensity for DTX at 1245 cm^{-1} in DTX-DES compared to pure DTX and DTX in physical mixture is indicative of DTX interaction with DES. This also confirms the crystallinity of DTX is reduced in DTX-DES compared to those samples and thus showed improved solubility in DES. At 1055 cm^{-1} region, corresponding to the amide bending vibration of DTX, showed shift and enlargement in DTX-DES spectra which confirms formation of hydrogen bond between them, and similar trend was observed at 975 cm^{-1}. Peak at 753 cm^{-1} in pure DTX overlapped in DTX-DES peak (733 cm^{-1}) and showed widening compared to the same peak in blank DES. Overall, based on aforesaid events, it was indicative that DTX was entrapped or interacted with DES chemically via hydrogen bonding and as per solubility data, significantly higher solubility in DES was due to decreased crystallinity of the DTX.



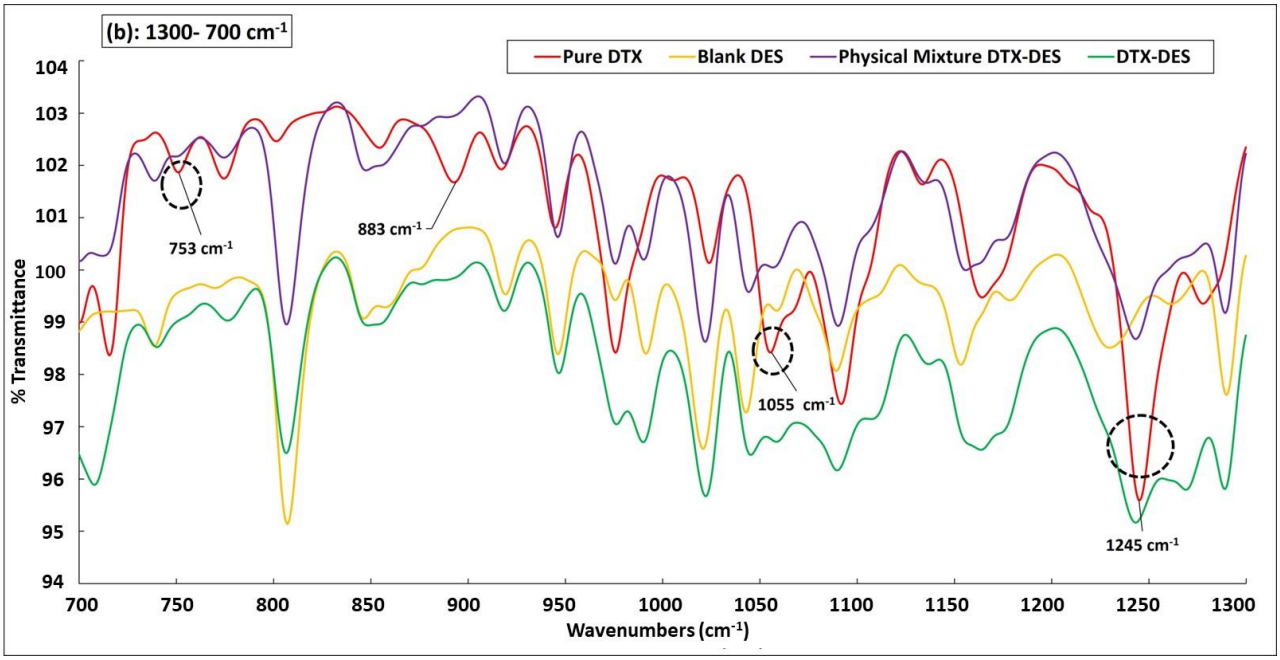


Figure 2. FTIR spectra overlay of DTX, blank DES, physical mixture of DTX-DES and DTX-DES system in infrared region representing stretching and bending vibration events. Major events confirming the formation of DTX-DES are highlighted with a black circle. (a) 1900-1300 cm^{-1}. (b) 1300-700 cm^{-1}.

DSC analysis was conducted to investigate and compare the crystallization behavior and melting events of the pure DTX with DES. Figure 3 represents an overlay of pure DTX, DTX-DES physical mixture and DTX-DES. DSC thermogram of pure DTX showed sharp endothermic melting peak at 231.88 °C indicating extremely crystalline nature of DTX. In the case of physical mixture, the melting event of DTX was shifted from 231.88 °C to 217.85 °C with a very broad peak suggesting the crystallinity of DTX was partially reduced in the presence of DES components. This depression in the meting point of DTX in physical mixture was attributed to presence of menthol: thymol blend which upon melting at 42.06 °C, produced partial solubilization effect on DTX resulting in broad peak compared to sharp melting peak of pure DTX. In contrast, the DSC thermogram of DTX-DES, a processed sample, did not show any events for DTX which represents DTX was completely converted to amorphous state in DTX-DES. As a result, high amount of DTX (≈ 150 mg) could get solubilized into 1 mL of DES. A very broad endothermic event in the DTX-DES sample before 100 °C could be ascribed to molecular transitions taking place into liquid sample due to distortion in the crystalline arrangements of DES components. Additionally, the sharp endothermic event observed in the DTX-DES physical mixture at 42.06 °C was absent in the final DTX-DES sample due to strong depression in the melting point, resulting in formation of less ordered crystalline DES structure thus favoring higher and stable encapsulation for DTX. This phenomenon highlights the potential of DES to maintain the drug in the soluble state up to a temperature lower than its melting point.

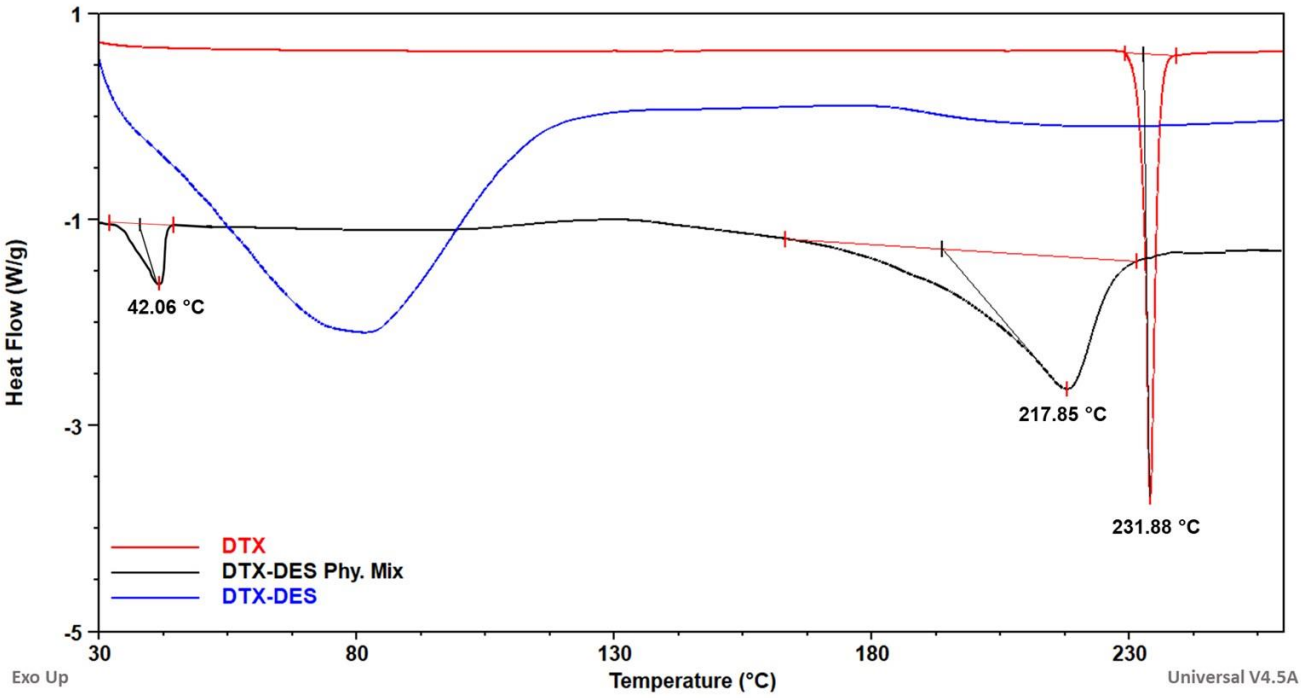


Figure 3. DSC thermograms overlay of DTX, DTX-DES physical mixture (DTX-DES Phy. Mix), and DTX-DES.

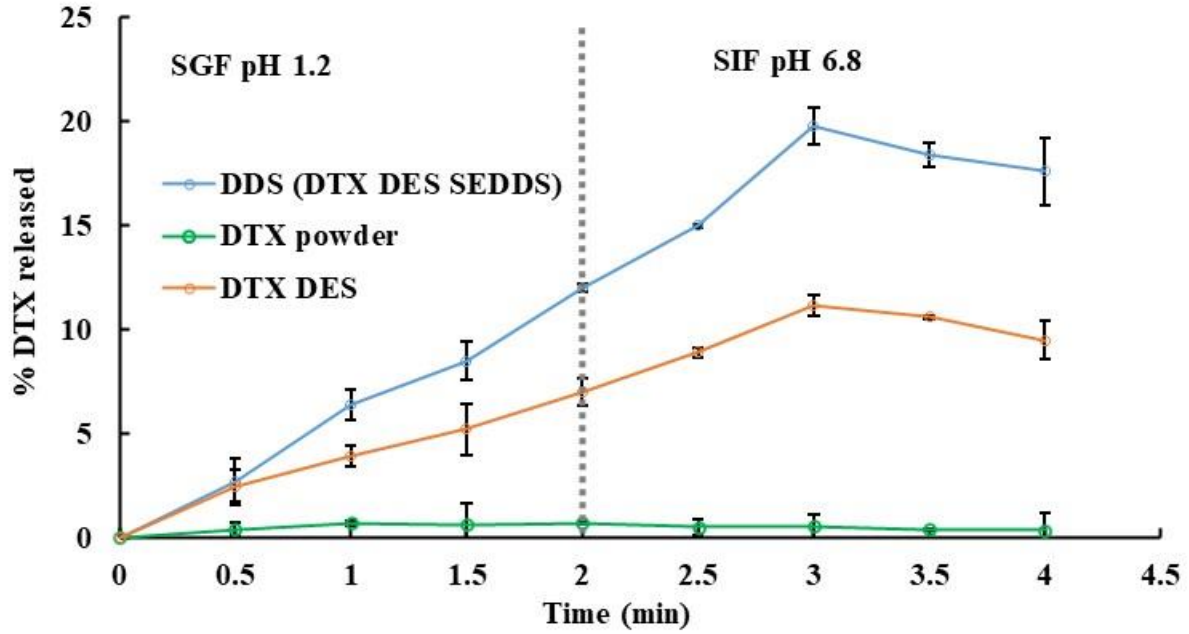


Figure 4. Dissolution profile of DTX-DES SEDDS (DSS), DTX-DES and DTX powder in SGF and SIF up to 4 h representing % DTX released against. After 2 h, SIF was added into SGF media and pH was adjusted to 6.8.

Two-step dissolution of DDS and control groups in SGF and SIF was performed over 4 h. In figure 4, the drug release profile was expressed as a cumulative percentage of drug against the time (h). From the studied groups, at all the time points, amount of DTX released (%) was highest from the DDS followed by DTX-DES and the lowest

(<1%) release was from pure DTX. This could be due to the very poor aqueous solubility of DTX which led to the precipitation of DTX in the release media. As per Figure 4, DTX-DES showed 7% and 11% release in SGF and SIF, respectively which was nearly 10 to 15 times higher compared to DTX powder. Higher DTX release from DTX-DES over DTX powder could be because of interaction of DTX with DES, that increased the amorphous nature of DTX and same was seen under FTIR as widening of stretching events. Overall, between DTX-DES and DTX powder, there was a significant difference ($p<0.05$) at all the time points. DDS showed 12% DTX release in SGF and nearly 20% DTX was released in SIF which declined to 18% at 4 h. DTX release in DDS compared to DTX-DES was 1.8 folds higher at 2 h and 3 h, respectively. The addition of tween80 and EG as a surfactant-cosolvent mixture improved the solubility of DTX in the release media. In other words, in the presence of DDS components, self-emulsification process in the release media formed nanosized globules, as seen in particle size measurement, into which DTX had higher solubility. Additionally, DTX particles in DES were protected through a layer of tween80-EG film which delayed the precipitation of DTX from DDS compared to DTX-DES. In general, interfacial film accumulated around the drug globules acted as a barrier between drug and release media until complete emulsification took place after which DTX precipitation begins. After 3 h, slight decline in the DTX release in case of DDS and DTX-DES could be ascribed to the supersaturation condition occurred in the release media. Overall, for poorly soluble drug like DTX, DES and DES based formulation approaches seem to be promising to improve the solubility of the drug.

Short-term stability of the DDS shows that the formulation remained stable over the period of two months at room temperature. Upon visual observation at the end of one and two months, no signs of instability such as phase separation or DTX precipitation were observed. In terms of globule size, PDI and drug content, at the end of one and two months, all the parameters were within 5% of initial characterization values, respectively suggesting that DTX remained intact with the menthol: thymol DES system and did not leach out. Perhaps, no change in the drug content values during the stability suggests chemical stability of DTX in the developed DES system.

Conclusion

In the present study, we demonstrated that natural DES system can significantly improve the solubility of the poorly soluble BCS IV drug, DTX. Menthol: Thymol based natural DES system offered 1500-folds higher solubility for DTX compared to its aqueous solubility. Such improvement in the solubility of a challenging anti-cancer drug, DTX, seems to be very promising and demonstrates therapeutic potential of DES for the formulation development of PWD. Additionally, current findings offer the opportunity to analyze and/or explore the commercial injection products of DTX wherein high amount of surfactant and alcohol-based solubilizer are present which may have severe side-effects. In contrast, menthol and thymol are natural components and as per FDA, they fall under generally recognized as safe (GRAS) excipients and therefore toxicity concerns are negligible. FTIR study proved interaction between DTX and DES via hydrogen bonding and thus DTX-DES could be utilized as a lipid phase to develop DES-based thermodynamically stable formulation, DDS. DSC analysis highlighted the potential of DES system to maintain DTX in the soluble state through a depression in the melting point of DES components and thus achieved higher DTX encapsulation. Dilution and dissolution studies suggested spontaneous emulsification potential of the DDS forming nano sized globules which released DTX 20 times higher than pure DTX powder. Collectively, natural DES systems can be a promising, non-toxic, cost reliable, and scalable approach to design formulation of poorly soluble drugs. Few

precise interaction studies such as thermogravimetry or x-ray diffraction are warranted to understand structural or functional changes between drug and DES. Future animal studies would shed more light on the in vivo pharmacokinetics/pharmacodynamics profile of this formulation. Given the potential of DES system, authors expect to investigate further novel DES systems to envisage the development of PWD into efficient therapeutics.

Data availability

The data can be made available on reasonable request.

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Author contributions

All authors contributed to the study conception. BS contributed to study design. BS and RO contributed to experimentation and analysis. BS contributed to writing original draft of the manuscript. SS contributed to supervision, review, and editing.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest.