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#### Review



## Solubilization Methods for Paclitaxel and Docetaxel: An Overview

Fariba Pourkarim<sup>1,20</sup>, Elaheh Rahimpour<sup>3,4</sup>, Sima Alvani-Alamdari<sup>5,6</sup>, Abolghasem Jouyban<sup>3,7\*</sup>

<sup>1</sup>Student Research Committee, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

<sup>2</sup>Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

<sup>3</sup>Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

<sup>4</sup>Food and Drug Safety Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

<sup>5</sup>Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

<sup>6</sup>Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

<sup>7</sup>Kimia Idea Pardaz Azarbayjan (KIPA) Science Based Company, Tabriz University of Medical Sciences, Tabriz, Iran.

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## Introduction

Abstract Cancer is s

Cancer is still a serious disease with high incidence over the past decades. Many anticancer drugs are discovered and used to treat cancer, among them, taxanes such as paclitaxel and docetaxel have high lipophilicity and low aqueous solubility which is further magnified considering the strong need for administering them by intravenous infusion. Currently, the poor water-solubility of taxanes is improved by prodrug formation, conjugation, inclusion complexation, micellar solubilization and liposome-based formulations. Recent achievements for solubilization of taxanes are reviewed and critically discussed regarding their pharmaceutical and chemical applications.

Cancer is a group of diseases characterized by uncontrolled growth, angiogenesis, the spread of abnormal cells and metastasis. The rate of cancer incidence has a significant increase in the past decades. Lung and breast cancers are the most common types of cancer and are the leading causes of the mortality in the world.<sup>1</sup> Chemotherapy are used in the treatment of cancer and an important class of systemic chemotherapeutic agents are taxanes. Taxanes are included paclitaxel (PTX) and docetaxel (DTX) (Figure 1), which are being utilized in chemotherapy of breast, head, neck, ovarian and non-small cell lung (NSCL) cancers.<sup>2-4</sup> These drugs inhibit mytosis by binding to the B-tubulin subunit of microtubules and induce apoptosis by preventing depolymerization of microtubules (Figure 2). Adverse effects of taxanes which are summarized in Figure 3.



\*Corresponding Author: Abolghasem Jouyban, E-mail: ajouyban@hotmail.com

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![](_page_1_Figure_1.jpeg)

![](_page_1_Figure_2.jpeg)

Figure 3. Common adverse effects of taxanes

PTX, a diterpene ester derived from the Pacific yew tree, was isolated for the first time in 1971 from *Taxus brevifolia*.<sup>5</sup> It found in the forests of North-West Canada and the USA. The solubility of PTX in water is about 0.0003 g.L<sup>-1</sup>. It belongs to biopharmaceutics classification system (BCS) class IV (low solubility, low permeability) and shows poor absorption and variable bioavailability after oral administration. PTX increased the area under the curve (AUC) of doxorubicin and its active metabolite. Therefore, it should be given 30 minutes before PTX. It is metabolized by the cytochrome P 3A4 enzyme system.<sup>6</sup>

DTX is a semi-synthetic and side-chain analog of taxol, which has been produced from 10-deacetylbaccatin III. It classified in BCS class II (low solubility, high permeability) and its absorption limited by dissolution rate. Other DTX derivatives include 10-deacetylbaccatin III, 10-deacetyltaxol, 10-deacetylcephalomannine and cephalomannine.

To obtain good absorption and therapeutic efficacy, drugs should be in the solution form. Therefore, having an ideal aqueous solubility is very important parameter for preparation of a dosage form. One of the most important clinically problems of taxanes, is poor aqueous solubility that caused low dissolution rate and absorption. So, enhancing the solubility of this category of drugs is increasingly employed to enhance their bioavailability and therapeutic efficacy. Various methods have been employed for the enhancement of solubility of taxanes including ether, ester and carbonate prodrugs, conjugation, inclusion complexation, micellar solubilization, microemulsion and liposome-based formulation which are briefly reviewed in this work.

#### Search Method

The articles are searched from SCOPUS database by key keywords of solubility enhancement of PTX, solubilization of PTX, cosolvent system of PTX, solubility enhancement of DTX, solubilization of DTX, and cosolvent system of DTX. Totally 50 articles were related to the subject which the purpose of this article is a review of all techniques reported for the enhancement of taxanes' solubility.

# Reported Techniques for Solubility Enhancement of Taxanes

#### Prodrugs

Prodrugs are bioreversible derivatives that release the active drug after metabolism, then exert the desired pharmacologic effect. Prodrugs can be utilized as a tool

for improving physicochemical, biopharmaceutical, or pharmacokinetic properties of pharmacologically active agents. Prodrug design goals include:<sup>7</sup>

- Providing sufficient chemical stability
- Covering unacceptable taste or odor
- Reducing irritation
- Decreasing first-pass or presystemic metabolism
- Increasing solubility and bioavailability

Two main mechanisms for prodrug activation are hydrolysis and bioprecursors activation by a biosynthetic reaction.

Golik *et al.*<sup>8</sup> synthesized phosphonooxymethyl ether derivatives of PTX (Figure 4) and their salt forms. They reported that the solubility of sodium salts of compounds (3-6) was 1000-folds more than PTX and solutions were stable at pH 7.4 and 37 °C. Prodrugs conversion rate is rapidly and PTX detected in plasma, tumor and liver after 15 min. The efficacy of prodrugs 4 and 6 was investigated against implanted M109 murine tumor.In a similar dose, the efficacy of compound 6 against M109 was comparable to PTX but the antitumor efficacy of compound 4 was less than PTX.

Polyethylene glycol (PEG)- valine citrulline (VC)paminobenzylcarbonyl (PABC)-PTX, compound 7 (Figure 5), was synthesized as a prodrug of PTX by Liang et al.9. PABC and VC were used as spacer and substrate of cathepsin B, respectively to link PEG and PTX to each other. The synthesized prodrug showed more antitumor effects than PTX and the control conjugate (PEG-PTX). The aqueous solubility of compound 7 has improved about 1000 times compared to PTX which decrease its side effects. A dose of 10 mg/Kg of PTX and compound 7 was administered then hepatotoxicity was investigated. The cathepsin B sensitivity of conjugate exhibited no apparent hepatotoxicity whereas PTX showed pyknosis in liver cells. Some C-2' and C-7 phosphate derivatives of PTX were also synthesized by Vyas et al.10 which show significant increase in aqueous solubility compared to PTX. But, the results obtained from anti-tumor activity in mice showed that these phosphate derivatives were poor candidates for PTX prodrugs. In other work, Ueda et al.<sup>11</sup> synthesized a similar prodrug (Figure 6) by adding a phosphonoxyphenylpropionate ester group at the C-2'or C-7 position which is activated by phosphatase in the body according to Figure 7. The high water solubility of compound 8 improved the anti-tumor activity in compared with compound 9 and PTX.

![](_page_2_Figure_11.jpeg)

Entry	R <sub>1</sub>	R <sub>2</sub>
(3):	CH <sub>2</sub> OPO(OH) <sub>2</sub>	Н
(4):	Н	CH <sub>2</sub> OPO(OH) <sub>2</sub>
(5):	CH <sub>2</sub> OPO(OH) <sub>2</sub>	CH <sub>2</sub> OPO(OH) <sub>2</sub>
(6):	CH <sub>2</sub> OPO(OH) <sub>2</sub>	$\mathrm{CO}_2\mathrm{C}_2\mathrm{H}_5$

Figure 4. Phosphonooxymethyl ether prodrugs of PTX

![](_page_2_Figure_14.jpeg)

Figure 5. Structure of PEG-VC-PABC-PTX prodrug

![](_page_3_Figure_1.jpeg)

![](_page_3_Figure_2.jpeg)

Compound 8

Figure 7. Schematic mechanism of phosphatase action on phosphonoxyphenylpropionate esters of taxol

Compound 14 (canadensol) as a highly water-soluble prodrug was synthesized by Skwarczynski *et al.*<sup>12</sup>. This prodrug was obtained by O–N intramolecular acyl migration of the isobutyryl group (Figure 8) which was pH-dependent. Under physiologic condition (pH 7.4), the solubility of compound 14 was reported as 2.26 g.L<sup>-1</sup> that showed the 10-folds increase in aqueous solubility. 'O–N acyl-like' migration reaction was also studied for the design of a DTX prodrug which was a possible strategy but it is difficult to apply.

Compound 10

![](_page_3_Figure_7.jpeg)

C2<sup>'</sup> and C7 modified derivatives of PTX (Figure 9) were synthesized as an ester of malic acid prodrugs by Damen *et al.*<sup>13</sup>. All prodrugs were stable in plasma (pH 7.4) and showed improved aqueous solubility, antitumor effect, and less cytotoxicity. The compound 17 was prepared in sodium salt form which showed the highest solubility as about 60 times more than PTX. It should be noted that the antitumor activities of prodrugs 16 and 17 were similar to PTX. Skwarczynski *et al.*<sup>14</sup> synthesized photo triggered PTX by using 7-N,N-diethylamino-4-hydroxymethyl coumarin as a photolabile group to 2'-benzoyl-paclitaxel which could increase PTX's aqueous solubility by converting it to chloride and be activated at 430.6 nm without decomposition. After activation by light, the cleavage of the carbamate induces O–N acyl migration to end up with PTX. Liu *et al.*<sup>15</sup> applied a PEG-DTX conjugate (Figure 10) for the enhancement of DTX solubility. Low molecular weight PEG was conjugated to DTX by an ester linker. The critical micelle concentration (CMC) and micelle diameter were found 0.88 g.L<sup>-1</sup> and 46 mm, respectively. The cytotoxicity of PEG-DTX formulation was lower than DTX and aqueous solubility was increased about 7000-times.

![](_page_4_Figure_3.jpeg)

Figure 10. Synthesis of PEG-DTX conjugate

![](_page_5_Figure_1.jpeg)

Figure 11. Structure of 2' and 7-PEG esters of PTX

2' and 7-PEG esters of PTX (Figure 11) were reported by Greenwald *et al.*<sup>16</sup> which compounds 22, 26 and 27 are 2'-PEG ester and compound 25 is a 7-PEG ester. The solubility of compound 22 was > 666 g.L<sup>-1</sup> which show an >165260-folds increase in compared to PTX. PEG increased solubility and made the controlled release formulation.

DTX-glucose (DTX-G), DTX-lactose (DTX-L) and DTX-sialic acid (DTX-S) were investigated as prodrugs of DTX by Park and his co-workers.<sup>17</sup> Succinyl group was used as a linker which was hydrolyzed by esterase enzyme in the body. The esterification occurs in 2-OH group of DTX and the solubility increased 155, 1042 and 1043.6 folds for DTX-G, DTX-L and DTX-S, respectively.

Henni-Silhadi *et al.*<sup>18</sup> investigated carboxymethylpullulans polymers such as  $\text{CMP}_{49}\text{C}_8$  and  $\text{CMP}_{12}\text{C}_8$  (Figure 12) for the solubilization of DTX and benzophenone. The solubility was increased via  $\text{CMP}_{49}\text{C}_8$  polymer by

![](_page_5_Figure_6.jpeg)

Compound 28

## Figure 12. Structure of carboxymethylpullulans polymers

the formation of self-assembled nanoaggregates with a hydrophilic shell and hydrophobic inner core.

Zhang *et al.*<sup>19</sup> developed a new prodrug for PTX based on the formation of multi-covalent bonds between gold nanoparticles and PTX by DNA linkers (Figure 13). The obtained conjugate significantly increased the solubility of

![](_page_5_Figure_11.jpeg)

Figure 13. Schematic formation of Au-PTX prodrug

PTX about 50-folds. Also, this strategy decreased cancer cell line resistance to PTX.

Other similar works for solubilizing PTX and DTX by prodrug formation were reported by Niethammer *et al.*<sup>20</sup>, Feng *et al.*<sup>21</sup>, Khmelnitsky *et al.*<sup>22</sup>, Nakamura *et al.*<sup>23</sup>, Li *et al.*<sup>24</sup>, Greenwald *et al.*<sup>25</sup>, Du *et al.*<sup>26</sup> and Ma *et al.*<sup>27</sup> which the details of each method are summarized in Table 1.

## Inclusion complex formation technique

Inclusion complex is a host and guest interaction between a compound with a hydrophobic inner cavity and a nonpolar drug. The most frequently used host molecules are cyclodextrins (CD<sub>s</sub>). The enzymatic hydrolysis of starch by CD-glycosyltransferase produces CD. CDs are crystalline, water soluble, cyclic and oligosaccharides. Three forms of CD are  $\alpha$ -CD,  $\beta$ -CD, and  $\gamma$ -CD can be used in parenteral products, but  $\beta$ -CD should not be administered as it causes renal failure.<sup>28</sup>

Dordunoo *et al.*<sup>29</sup> studied the effect of CD derivatives on the solubility of PTX at 37 °C and pH range of 1-9. Higuchi and Connors method was used for solubility determination.<sup>30</sup> The solubility and stability of PTX increased in the presence of CDs and may be appropriate for ophthalmic, intra-peritoneal or intravesicular administrations. The highest increase in the solubility obtained by 2-hydroxypropyl (HP)  $-\beta$ -CD. The solubility of PTX in 50% aqueous mixture of HP $\beta$ CD was 3.2 g.L<sup>-1</sup> at 37 °C (2000-folds increase in compared with PTX solubility).

Hamada *et al.*<sup>31</sup> were used 11 types of modified CDs for the enhancement of aqueous solubility of PTX. The solubility of PTX in DM- $\alpha$ -CD solution was reported to be 8.1±0.11 µmol L<sup>-1</sup> that show the high solubility among the various investigated types of modified CDs. PTX-DM- $\beta$ -CD increased the ratio of polymerization/depolymerization compared to PTX alone that this result showed the activity of PTX is maintained in the PTX- DM- $\beta$ -CD complex.

#### Table 1. Details of reported prodrugs for taxanes solubilization

Compound number	Drug	Prodrug	Туре	Solubility enhancement	Remarks	Ref.
29	ΡΤΧ	$Ph \underset{O}{\overset{O}{\overset{O}{\overset{O}{\overset{O}{\overset{O}{\overset{O}{\overset{O}{$	Carbonate	50-folds	Prodrug is activated, pH dependently, by hydrolytic cleavage of the carbonate moiety	20
30	ΡΤΧ	$\begin{array}{c} AcO & O \\ C_{6}H_{5}COHN & O \\ C_{6}H_{5} & 2' \\ OCH_{2}CO-AA-O \\ HO \\ OCOC_{6}H_{5} & O \\ HO \\ OCOC_{6}H_{5} & O \\ OCO$	2'-PTX prodrugs	-	PEG as solublizing moiety and amino acids as spacers	21

#### Table 1. Continued.

![](_page_7_Figure_2.jpeg)

#### Solubilization of Taxans

#### Table 1. Continued.

![](_page_8_Figure_2.jpeg)

#### Table 1. Continued.

![](_page_9_Figure_2.jpeg)

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#### Table 1. Continued.

![](_page_10_Figure_2.jpeg)

Cho *et al.*<sup>32</sup> developed a complexation based-method by using modified cyclooligosaccharides for the improvement of PTX solubility. To modification of CD and cyclosophoraoses (CyS) with a biotin group, mono-6-amino CyS and mono-6-amino- $\beta$ -CD were reacted with N-hydroxysuccinimide ester of biotinamidohexanoic acid at 60 °C and primed biotinylated CyS and  $\beta$ -CD. Biotinyl CyS and biotinyl  $\beta$ -CD have increased the solubility of PTX 10.3- and 3.7-folds, respectively.

Baek *et al.*<sup>33</sup> used an inclusion complex between PTX-solid lipid nanoparticles (PS) and HP- $\beta$ -CD to enhance the solubility of PTX. Surface-modified PTX-incorporated solid lipid nanoparticles with HP- $\beta$ -CD (smPSH) was prepared by a modified hot sonication method at 80 °C. The solubility of PS and smPSH showed 15- and 17-folds increase compared to PTX. The smPSH indicated 1.2-time higher AUC and toxicity compared to PS. Also, an increase about 5.3-folds in cellular uptake of smPSH was observed compared to PTX.

#### Micellar solubilization

Surfactants are surface-active agents that have polar and non-polar parts. There is four types of surfactant including anionic, cationic, zwitterionic and nonionic. Surfactants used as wetting agents, emulsifiers, foaming agent, detergents and dispersants. Micelles are formed above the CMC when surfactant self-assembled in an aqueous environment. Micelles are commonly used as solubilizing agents.<sup>34</sup>

Zhou and his co-workers<sup>35</sup> used a linear dendritic block copolymer for solubilization of

PTX. Block copolymer  $B_{16}E_{42}$  Poly(amidoamine) [BE-PAMAM], a linear-dendritic block copolymer, was used as a surfactant which was prepared by reacting between the poly(butylene oxide) (B)–poly(ethylene oxide) (E) block copolymer  $B_{16}E_{42}(BE)$  with a G<sub>2</sub>PAMAM dendrimer. The solubilization method was solvent loading technique. At room temperature, the optimum CMC for BE and BE-PAMAM copolymers were reported 0.41 and 0.59 g.L<sup>-1</sup>, respectively. The solubility of PTX was improved about 3700-times in 2% (w/v) solution of BE–PAMAM copolymer at 37 °C. Varma *et al.*<sup>36</sup> studied the effects of D-α-tocopheryl PEG 1000 succinate (vitamin E-TPGS) on the solubility and bioavailability of PTX. The CMC concentration of TPGS was above 0.2 g. L<sup>-1</sup>. The water solubility of PTX was increased about 38-folds in the presence of 5 g.L<sup>-1</sup> of TPGS. The AUC and bioavailability of PTX in co-administration with TPGS, are enhanced about 1.5- and 6.3-folds, respectively. Some other similar studies performed on solubilization of PTX and DTX are summarized in Table 2 and the conditions of each method are explained.

Microemulsions are homogeneous, thermodynamically stable and transparent systems that their droplet size is 5–140 nm. In four studies, microemulsions were applied for solubility enhancement of taxanes. Three microemulsion formulations including Cremophor EL/PG, cremophor RH40/Transcutol and cremophor EL/Transcutol were developed and evaluated by Yin *et al.*<sup>37</sup> for the improvement of DTX solubility. Pseudoternary phase diagrams were used for the optimization of microemulsion systems. The size of microemulsion drops was 30 nm. The antitumor activity and cytotoxicity of

Table 2. Details of reported micellar solubilization	n methods for taxanes solubilization
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Method	Drug	Solubility enhancement	CMC concentration	Remarks	Ref.
Dendrimer–TPGS mixed micelles	DTX PTX	DTX = 20.36 fold PTX = 34.95 fold	CMC of mixed micelles was 0.009%	Micelles were prepared by solvent casting method. G4 poly(amidoamine) PAMAM was acted as dendrimers.	38
Filomicelles and spherical micelles	ΡΤΧ	10,000-fold	CMC of 1.2 g.L <sup>.1</sup> for a sphere-forming	TPGS was acted as biodegradable surfactant. Diblock polymer poly (ethylene oxide)-b-poly (epsilon-caprolactone) was acted as non- ionic macromolecular surfactants. Micelles were prepared by co-solvent/ evaporation method	39
Hydrotropic block copolymer micelle system	PTX	-	CMC value for various type of PEG-b–P(2- VBOPNA) <sub>s</sub> is 0.0855 to 0.1285 g.L <sup>-1</sup>	PEG-b–P(2-VBOPNA) <sub>s</sub> was acted as surfactants. Micelle formation is pH-dependent ( in pH >2)	40
Mixed micelles (MM)	PTX	1414-fold for water- lecithin dispersions highest solubility (up to 570 mg/100 ml)	-	Micellar solution including: egg lecithin and sodium deoxycholate Poloxamer, PEG and benzalkonium chloride as co-surfactant	41
Hydrotropy	PTX	>100,000-folds	0.0028 to 0.5 mol.L <sup>-1</sup>	<i>N,N</i> -Diethylnicotinamide (NNDENA) was acted as surfactant	42
Soft micelles	РТХ	1200-fold for KXN441 5.2% (w/v) with CMC 3.6 mM 500-folds for KXN337 5.2% (w/v) with CMC 300mM 830-folds for KXN424, KXN437 and Solutol <sup>®</sup> HS15 5.2% (w/v)	KXN441 (3.4 μmol.L <sup>-1</sup> ) KXN437 (132 μmol.L <sup>-1</sup> ) Solutol <sup>®</sup> HS15 (130 μmol.L <sup>-1</sup> ) KXN 424 (104 μmol.L <sup>-1</sup> ) KXN 337 (300 μmol.L <sup>-1</sup> )	KXN441, KXN437, KXN424, KXN337 are soft surfactant. Micelle size is determined via dynamic light scattering. HPLC system is used for quantifying PTX by $C_{18}$ column and isocratic mixture of deionized water and acetonitrile at 30:70 Solubility measurements methods for equilibrium solubility determination require 24–48 h	43
Prodrugs micelles	ΡΤΧ	Solubilities >5 g.L <sup>.1</sup>	Micelle prodrug solutions were prepared at 0.5 µmol L <sup>-1</sup> (PEG-b PCL basis)	PEG-b-poly((caprolactone) was acted as amphiphilic block copolymer micelles.	44
Hydrotropic polymeric micelles	РТХ	6000-folds to 15 000-folds	The CMC values of PEG- <i>b</i> P(VBODENA) s were in the range 0.036-0.07 g.L <sup>-1</sup>	Micellar shell segment including: PEG block Core segment including: poly(2-(4- vinylbenzyloxy)-N,N diethylnicotinamide) (P(VBODENA)) block. N,N- Diethylnicotinamide (DENA)	45
Polymeric micelles	PTX	1 g. L <sup>.1</sup> in PMB30W	PMB30W concentration was higher than 9.0 g.L <sup>-1</sup>	Amphiphilic 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer was acted as the solubilizer.	46
Copolymer micelles	PTX	-	-	Pluronic copolymers of P123/F68 and sorbitan monopalmitate (Span 40) was used. Modified thin-film hydration technique were used for preparation of copolymer micelles.	47
Polymeric micelles (spherical and cylindrical micelles)	DTX	> 1000 folds	1 to 10 g.L <sup>-1</sup>	Poly(ethylene oxide)-block-poly(styrene oxide) (PEO-b-PSO) and PEO-b-poly(butylene oxide) (PEO-b-PBO) were acted as surfactant.	48
Polymeric micelles	DTX	-	CMC value of mPEG- PLA Lys(FB)2 at room temperature was measured to be as low as 0.00175 g.L <sup>-1</sup>	MPEG-PLA-Lys(FB)2 block was acted as copolymer. A solid dispersion-thin film hydration method was used for preparation of DTX-loaded micelles.	49
Copolymeric micelles	DTX	3000-folds	23 and 25 wt% of copolymer	Poly-(D,L-lactic acid-co-glycolic acid) (PLGA)-polyethylene glycol (PEG)-PLGA triblock was acted as copolymer DTX-loaded copolymer micelles was prepared by solvent casting method.	50

#### Solubilization of Taxans

microemulsion were not significant compared to DTX. The solubility of DTX in microemulsion form was 4056-6085 folds greater than DTX. Yin et al.<sup>51</sup> developed a new microemulsion system for bioavailability improvement of DTX. Microemulsion type was oil/water (O/W) system and its components were Capryol 90 (oil), Cremophor EL (surfactant) and Transcutol (co-surfactant). The solubility of DTX was obtained up to 30 g.L<sup>-1</sup>. The results showed that the inhibition of P-gp, permeability of DTX across the Caco-2 cell and bioavailability were improved by new microemulsion formulation. Gao et al.52 show that microemulsions as a carrier system decrease the toxic effects and can be an intravenous carrier for DTX. Temperature elevation method was used for the preparation of microemulsion of DTX. Soya oil and Miglyol 812 (about 10%) were used as the oil phase. 1.2% soybean lecithin, 0.3% Pluoronic F68, and 0.4 or 0.8 g.L<sup>-</sup> <sup>1</sup> DTX. The rational emulsions formulation, was obtained from solubility, distribution between oil and water, and degradation kinetic studies. The entrapment efficiency of the formulation was more than 90%, and it is stable at 4 and 25 °C for six months. Ma et al.53 developed an intravenous injectable microemulsion for DTX with lower toxicity, lower irritation, higher stability and high solubility. The components of microemulsion were including Brucea javanica oil, medium-chain triglyceride, soybean lecithin, Solutol<sup>®</sup> HS15 and PEG 400. Brucea javanica oil, an antitumor synergistic agent, contains oleic acid and linoleic acids. The droplet size and zeta potential were reported 13.5 nm and 41.3 mV, respectively.

## Liposome-based formulation

Liposome, a phospholipid dispersion in water, is a spherical and small vesicle that a water droplet surrounded by phospholipid bilayer membranes. It can be formed from cholesterol, non-toxic surfactants, sphingolipids, glycolipids, long chain fatty acids or membrane proteins.<sup>54</sup> They are usually utilized as drug carrier which encapsulated a wide variety of particles such as small drug molecules, proteins, nucleotides or plasmids. Liposomes can be used for improving the solubility of hydrophobic drugs.

Ceruti *et al.*<sup>55</sup> loaded PTX in conventional and PEGcoated liposomes. The stability, entrapment efficiency and solubility were improved in 2'-mPEG (5000)–PTX liposomes. The cytotoxic activity of this liposomal was no significant compared to the parent drug but half-life of 2'mPEG (5000)–PTX liposomes was increased.

Yang *et al.*<sup>56,57</sup> were also investigated the effect of PEGylated liposome formulation on solubility and stability of PTX. PEGylated liposome was prepared from  $S_{100}$  PC/CH/MPEG2000-DSPE (90:10:5 as a molar ratio) by the modified thin-film hydration method. Tween 80 (3% v/v) in the hydration media increased solubility of PTX up to 3.39 g.L<sup>-1</sup>. In compared to the conventional liposomes, the increase in biological half-life and decrease in uptake by reticuloendothelial system in PEGylated liposome were observed. Also, the PEGylated liposome exhibited higher

tumor growth inhibition effect.

#### Nanonization

Nanonization technique improved the dissolution rate and bioavailability of poorly soluble drugs by increasing the surface area to volume ratios of drugs.<sup>58</sup> He *et al.*<sup>59</sup> synthesized mesoporous silica nanoparticles (MSN) based on sol-gel method for the enhancement of PTX solubility. For the preparation of MSN, N-octadecyltrimethoxysilane and tetraethylorthosilicate in a mixture of solvents consist of deionized water, ethanol and ammonia (a molar ratio of 5:13:1) was used. Compared to free PTX, the MSN-PTX show a significantly increased solubility. The loading content of PTX in MSN increased when the solvent polarity decreased or the drug/carrier ratio increased.

#### Nanosuspension

Nanosuspension is a simple and applicable method to improve the aqueous solubility of drugs.<sup>60-62</sup>. Wang *et al.*<sup>63</sup> developed a new intravenous injectable nanosuspension for PTX with higher solubility and lower allergic reactions compared to classic formulation (PTX dissolved in ethanol and Cremophor® EL). Lyophilization of PTX nanosuspension via high-pressure homogenization improved both the chemical and physical stability of nanoparticles. This formulation increase clearance and decrease elimination half-life compared with PTX solution. Approved formulation of paclitaxel by the FDA in market is Abraxane which the drug surrounded by an albumin shell with an overall mean size of 130 nm.<sup>64,65</sup>

## Combination of cosolvency and surfactant solubilization methods

The classic formulation of PTX consist of 51% Cremophor EL (surfactant) and 49% ethanol (cosolvent) is used for improving the solubility of PTX.<sup>66</sup> It is administered as an intravenous (IV) infusion after dilution with dextrose 5% or lactated Ringer's solution.

## Conclusion

DTX and PTX belong to BCS class II and IV, respectively which their low solubility is the main challenge for developing an oral dosage form. Various techniques have been employed to improve the taxanes solubility. Among all the solubility improvement methods, prodrug formation is a frequently used technique which shows up to 165,000-folds increase in solubility in compared to the parent drug. However, many other methodologies including conjugation, inclusion complexation, micellar solubilization, hydrotropy and liposome-based formulation have been employed to enhance the solubility of taxanes that the details of each method were reviewed in this text. However, the development of nanotechnologybased methods such as nano-liposome formulations and nanoparticle-based prodrugs has progressed over the last years which can be considered for future studies.

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## **Author Contributions**

FP: Preparation of the original draft, ER: Editing the manuscript, SA: Drawing the figures and schemes, AJ: Supervising, Editing the manuscript. All authors read and confirmed the final version of the manuscript.

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## **Conflict of Interest**

The authors report no conflicts of interest.

## References

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90. doi: 10.1111/j.1530-0277.1997.tb042 56.x
- Ozols RF. Treatment of ovarian cancer: Current status. Semin Oncol. 1994;21(2 Suppl 2):1-9.
- Seidman AD, Reichman BS, Crown JP, Yao TJ, Currie V, Hakes TB, et al. Paclitaxel as second and subsequent therapy for metastatic breast cancer: activity independent of prior anthracycline response. J Clin Oncol. 1995;13(5):1152-9. doi:10.1200/ JCO.1995.13.5.1152
- Ojima I, Lichtenthal B, Lee S, Wang C, Wang X. Taxane anticancer agents: a patent perspective. Expert Opin Ther Pat. 2016;26(1):1-20. doi: doi:10.1517/13543776. 2016.1111872
- Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT. Plant antitumor agents. VI. Isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. J Am Chem Soc. 1971;93(9):2325-7. doi:10.1021/ja00738a045
- 6. Zeind CS, Carvalho MG. Applied therapeutics: the clinical use of drugs. 11th ed. Philadelphia: North American; 2018. p. 1264.
- Roche EB. Design of biopharmaceutical properties through prodrugs and analogs: a symposium. Washington DC: American Pharmacists Association; 1977.
- Golik J, Wong HS, Chen SH, Doyle TW, Wright JK, Knipe J, et al. Synthesis and antitumor evaluation of paclitaxel phosphonooxymethyl ethers: a novel class of water soluble paclitaxel pro-drugs. Bioorg Med Chem Lett. 1996;6(15):1837-42. doi:10.1016/0960-894X(96)00321-6
- Liang L, Lin SW, Dai W, Lu JK, Yang TY, Xiang Y, et al. Novel cathepsin B-sensitive paclitaxel conjugate: Higher water solubility, better efficacy and lower toxicity. J Control Release. 2012;160(3):618-29. doi: 10.1016/j.jconrel.2012.02.020
- Vyas DM, Wong H, Crosswell AR, Casazza AM, Knipe JO, Mamber SW, et al. Synthesis and antitumor evaluation of water soluble taxol phosphates. Bioorg Med Chem Lett. 1993;3(6): 1357-60. doi:10.1016/

S0960-894X(00)80348-0

- 11. Ueda Y, Mikkilineni AB, Knipe JO, Rose WC, Casazza AM, Vyas DM. Novel water soluble phosphate prodrugs of Taxol<sup>®</sup> possessing in vivo antitumor activity. Bioorg Med Chem Lett. 1993;3(8):1761-6. doi:10.1016/S0960-894X(00)80058-X
- 12. Skwarczynski M, Sohma Y, Kimura M, Hayashi Y, Kimura T, Kiso Y. O–N Intramolecular acyl migration strategy in water-soluble prodrugs of taxoids. Bioorg Med Chem Lett. 2003;13(24): 4441-4. doi:10.1016/j. bmcl.2003.09.020
- Damen EW, Wiegerinck PH, Braamer L, Sperling D, de Vos D, Scheeren HW. Paclitaxel esters of malic acid as prodrugs with improved water solubility. Bioorg Med Chem. 2000;8(2):427-32. doi:10.1016/S0968-0896(99)00301-6.
- 14. Skwarczynski M, Noguchi M, Hirota S, Sohma Y, Kimura T, Hayashi Y, et al. Development of first photoresponsive prodrug of paclitaxel. Bioorg Med Chem Lett. 2006;16(17):4492-6. doi:10.1016/j. bmcl.2006.06.030.
- 15. Liu J, Zahedi P, Zeng F, Allen C. Nano-sized assemblies of a PEG-docetaxel conjugate as a formulation strategy for docetaxel. J Pharm Sci. 2008;97(8):3274-90. doi:10.1002/jps.21245.
- Greenwald RB, Pendri A, Bolikal D, Gilbert CW. Highly water soluble taxol derivatives: 2'-polyethyleneglycol esters as potential prodrugs. Bioorg Med Chem Lett. 1994; 4(20):2465-70. doi:10.1016/S0960-894X(01)80411-X.
- Park MH, Keum CG, Song JY, Kim D, Cho CW. A novel aqueous parenteral formulation of docetaxel using prodrugs. Int J Pharm. 2014;462(1-2):1-7. doi:10.1016/j.ijpharm.2013.12.027.
- Henni-Silhadi W, Deyme M, Boissonnade MM, Appel M, Le Cerf D, Picton L, et al. Enhancement of the solubility and efficacy of poorly water-soluble drugs by hydrophobically-modified polysaccharide derivatives. Pharm Res. 2007;24(12):2317-26. doi:10.1007/s11095-007-9461-7.
- Zhang XQ, Xu X, Lam R, Giljohann D, Ho D, Mirkin CA. Strategy for increasing drug solubility and efficacy through covalent attachment to polyvalent DNA– nanoparticle conjugates. ACS Nano. 2011;5(9):6962-70. doi:10.1021/nn201446c.
- 20. Niethammer A, Gaedicke G, Lode HN, Wrasidlo W. Synthesis and preclinical characterization of a paclitaxel prodrug with improved antitumor activity and water solubility. Bioconjug Chem. 2001;12(3):414-20. doi:10.1021/bc000122g.
- 21. Feng X, Yuan YJ, Wu JC. Synthesis and evaluation of water-soluble paclitaxel prodrugs. Bioorg Med Chem Lett. 2002;12(22):3301-3. doi:10.1016/S0960-894X(02)00694-7.
- 22. Khmelnitsky YL, Budde C, Arnold JM, Usyatinsky A, Clark DS, Dordick JS. Synthesis of water-soluble paclitaxel derivatives by enzymatic acylation. J Am

Chem Soc. 1997;119(47):11554-5. doi:10.1021/ ja973103z.

- 23. Nakamura J, Nakajima N, Matsumura K, Hyon SH. Water-soluble taxol conjugates with dextran and targets tumor cells by folic acid immobilization. Anticancer Res. 2010;30(3):903-9.
- 24. Li C, Yu D, Inoue T, Yang DJ, Milas L, Hunter NR, et al. Synthesis and evaluation of water-soluble polyethylene glycol-paclitaxel conjugate as a paclitaxel prodrug. Anticancer Drug. 1996;7(6):642-8. doi:10.1097/00001813-199608000-00004.
- Greenwald RB, Pendri A, Bolikal D. Highly water soluble taxol derivatives: 7-polyethylene glycol carbamates and carbonates. J Org Chem. 1995; 60(2): 331-6. doi:10.1021/j000107a010.
- 26. Du W, Hong L, Yao T, Yang X, He Q, Yang B, et al. Synthesis and evaluation of water-soluble docetaxel prodrugs-docetaxel esters of malic acid. Bioorg Med Chem. 2007;15(18):6323-30. doi:10.1016/j. bmc.2007.04.002.
- 27. Ma YT, Yang Y, Cai P, Sun DY, Sánchez-Murcia PA, Zhang XY, et al. A series of enthalpically optimized docetaxel analogues exhibiting enhanced antitumor activity and water solubility. J Nat Prod. 2018;81(3):524-33. doi:10.1021/acs.jnatprod.7b00857.
- Uekama K, Hirayama F, Irie T. Cyclodextrin drug carrier systems. Chem Rev. 1998;98(5):2045-76. doi:10.1021/cr970025p.
- 29. Dordunoo SK, Burt HM. Solubility and stability of taxol: effects of buffers and cyclodextrins. Int J Pharm. 1996;133(1-2):191-201. doi:10.1016/0378-5173(96)04443-2.
- 30. Jouyban A, Fakhree MAA. Experimental and Computational methods pertaining to drug solubility. In: Acree Jr WE, editor. Toxicity and Drug Testing, New York: InTech Publisher; 2012. doi:10.5772/19206
- Hamada H, Ishihara K, Masuoka N, Mikuni K, Nakajima N. Enhancement of water-solubility and bioactivity of paclitaxel using modified cyclodextrins. J Biosci Bioeng. 2006;102(4):369-71. doi:10.1263/ jbb.102.369
- Cho E, Jung S. Biotinylated cyclooligosaccharides for paclitaxel solubilization. Molecules. 2018;23(1):90. doi:10.3390/molecules23010090
- 33. Baek JS, So JW, Shin SC, Cho CW. Solid lipid nanoparticles of paclitaxel strengthened by hydroxypropyl-β-cyclodextrin as an oral delivery system. Int J Mol Med. 2012;30(4):953-9. doi:10.3892/ ijmm.2012.1086
- 34. Taylor KM, Aulton ME. Aultons Pharmaceutics: The Design and Manufacture of Medicines. New York: Elsevier Health Sciences; 2013.
- 35. Zhou Z, D'Emanuele A, Attwood D. Solubility enhancement of paclitaxel using a linear-dendritic block copolymer. Int J Pharm. 2013;452(1-2):173-9. doi:10.1016/j.ijpharm.2013.04.075
- 36. Varma MV, Panchagnula R. Enhanced oral paclitaxel

absorption with vitamin E-TPGS: effect on solubility and permeability in vitro, in situ and in vivo. Eur J Pharm Sci. 2005;25(4-5):445-53. doi:10.1016/j. ejps.2005.04.003

- Yin Y, Cui F, Mu C, Chung SJ, Shim C, Kim DD. Improved solubility of docetaxel using a microemulsion delivery system: formulation optimization and evaluation. Asian J Pharm Sci. 2009;4(6):331-9
- 38. Pooja D, Kulhari H, Singh MK, Mukherjee S, Rachamalla SS, Sistla R. Dendrimer–TPGS mixed micelles for enhanced solubility and cellular toxicity of taxanes. Colloids Surf B Biointerfaces. 2014;121:461-8. doi:10.1016/j.colsurfb.2014.06.059
- 39. Cai S, Vijayan K, Cheng D, Lima EM, Discher DE. Micelles of different morphologies—advantages of worm-like filomicelles of PEO-PCL in paclitaxel delivery. Pharm Res. 2007;24(11): 2099-109. doi:10.1007/s11095-007-9335-z
- 40. Huh KM, Min HS, Lee SC, Lee HJ, Kim S, Park K. A new hydrotropic block copolymer micelle system for aqueous solubilization of paclitaxel. J Control Release. 2008;126(2):122-9. doi:10.1016/j.jconrel.2007.11.008
- Sznitowska M, Klunder M, Placzek M. Paclitaxel solubility in aqueous dispersions and mixed micellar solutions of lecithin. Chem Pharm Bull. 2008;56(1):70-4. doi:10.1248/cpb.56.70
- 42. Lee J, Lee SC, Acharya G, Chang CJ, Park K. Hydrotropic solubilization of paclitaxel: analysis of chemical structures for hydrotropic property. Pharm Res. 2003;20(7):1022-30. doi:10.1023/a:1024458206032
- 43. Alani AW, Rao DA, Seidel R, Wang J, Jiao J, Kwon GS. The effect of novel surfactants and solutol<sup>®</sup> HS 15 on paclitaxel aqueous solubility and permeability across a Caco-2 monolayer. J Pharm Sci. 2010;99(8):3473-85. doi:10.1002/jps.22111
- 44. Forrest ML, Yáñez JA, Remsberg CM, Ohgami Y, Kwon GS, Davies NM. Paclitaxel prodrugs with sustained release and high solubility in poly (ethylene glycol)-b-poly (ε-caprolactone) micelle nanocarriers: pharmacokinetic disposition, tolerability, and cytotoxicity. Pharm Res. 2008;25(1):194-206. doi:10.1007/s11095-007-9451-9
- 45. Lee SC, Huh KM, Lee J, Cho YW, Galinsky RE, Park K. Hydrotropic polymeric micelles for enhanced paclitaxel solubility: in vitro and in vivo characterization. Biomacromolecules. 2007;8(1):202-8. doi:10.1021/ bm060307b
- 46. Konno T, Watanabe J, Ishihara K. Enhanced solubility of paclitaxel using water-soluble and biocompatible 2methacryloyloxyethyl phosphorylcholine polymers. J Biomed Mater Res A. 2003;65(2):209-14. doi:10.1002/ jbm.a.10481
- 47. Gu W, Chen J, Patra P, Yang X, Gu Q, Wei L, et al. Nanoformulated water-soluble paclitaxel to enhance drug efficacy and reduce hemolysis side effect. J Biomater Appl. 2017;32(1):66-73. doi:10.1177/0885328217708458

- Elsabahy M, Perron MÈ, Bertrand N, Yu GE, Leroux JC. Solubilization of docetaxel in poly (ethylene oxide)-block-poly (butylene/styrene oxide) micelles. Biomacromolecules 2007;8(7):2250-7. doi:10.1021/ bm070226v
- 49. Qi D, Gong F, Teng X, Ma M, Wen H, Yuan W, et al. Design and evaluation of mPEG-PLA micelles functionalized with drug-interactive domains as improved drug carriers for docetaxel delivery. J Biomater Sci Polym Ed. 2017;28(14):1538-55. doi:09205063.2017.1333699
- 50. Gao Y, Ren F, Ding B, Sun N, Liu X, Ding X, et al. A thermo-sensitive PLGA-PEG-PLGA hydrogel for sustained release of docetaxel. J Drug Target. 2011;19(7):516-27. doi:10.3109/1061186X.2010.519031
- 51. Yin YM, Cui FD, Mu CF, Choi MK, Kim JS, Chung SJ, et al. Docetaxel microemulsion for enhanced oral bioavailability: preparation and in vitro and in vivo evaluation. J Control Release. 2009;140(2):86-94. doi:10.1016/j.jconrel.2009.08.015
- 52. Gao K, Sun J, Liu K, Liu X, He Z. Preparation and characterization of a submicron lipid emulsion of docetaxel: submicron lipid emulsion of docetaxel. Drug Dev Ind Pharm. 2008;34(11):1227-37. doi:10.1080/03639040802005057
- 53. Ma S, Chen F, Ye X, Dong Y, Xue Y, Xu H, et al. Intravenous microemulsion of docetaxel containing an anti-tumor synergistic ingredient (*Brucea javanica* oil): formulation and pharmacokinetics. Int J Nanomedicine. 2013;8:4045-52. doi:10.2147/IJN.S47956
- 54. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. J Mol Biol. 1965;13(1):238-52. doi:10.1016/S0022-2836(65)80093-6
- 55. Ceruti M, Crosasso P, Brusa P, Arpicco S, Dosio F, Cattel L. Preparation, characterization, cytotoxicity and pharmacokinetics of liposomes containing watersoluble prodrugs of paclitaxel. J Control Release. 2000; 63(1-2): 141-53. doi:10.1016/S0168-3659(99)00198-4.
- 56. Yang T, Cui FD, Choi MK, Cho JW, Chung SJ, Shim CK, et al. Enhanced solubility and stability of PEGylated liposomal paclitaxel: in vitro and in vivo evaluation.

Int J Pharm. 2007;338(1-2):317-26. doi:10.1016/j. ijpharm.2007.02.011

- 57. Yang T, Cui FD, Choi MK, Lin H, Chung SJ, Shim CK, et al. Liposome formulation of paclitaxel with enhanced solubility and stability. Drug Deliv. 2007;14:301-8. doi:10.1080/10717540601098799
- 58. Chen H, Khemtong C, Yang X, Chang X, Gao J. Nanonization strategies for poorly water-soluble drugs. Drug Discov Today. 2011;16:354-60. doi:10.1016/j. drudis.2010.02.009
- 59. He Y, Liang S, Long M, Xu H. Mesoporous silica nanoparticles as potential carriers for enhanced drug solubility of paclitaxel. Mater Sci Eng C. 2017;78:12-7. doi:10.1016/j.msec.2017.04.049
- 60. Patel VR, Agrawal YK. Nanosuspension: An approach to enhance solubility of drugs. J. Adv Pharm Technol Res. 2011;2(2):81-7. doi:10.4103/2231-4040.82950
- 61. Maghsoodi M, Montazam S, Rezvantalab H, Jelvehgari M. Response surface methodology for optimization of process variables of atorvastatin suspension preparation by microprecipitation method using desirability function. Pharm Sci. 2020;26(1):61-74. doi:10.34172/ PS.2019.52
- 62. Morteza-Semnani K, Saeedi M, Akbari J, Moazeni M, Seraj H, Daftarifard E, et al. Fluconazole nanosuspension enhances in vitro antifungal activity against resistant strains of *Candida albicans*. Pharm Sci. 2022;28(1):112-29. doi:10.34172/PS.2021.21
- 63. Wang Y, Li X, Wang L, Xu Y, Cheng X, Wei P. Formulation and pharmacokinetic evaluation of a paclitaxel nanosuspension for intravenous delivery. Int J Nanomedicine. 2011;6:1497. doi:10.2147/IJN.S21097
- 64. Jiang Y, Jiang Z, Wang M, Ma L. Current understandings and clinical translation of nanomedicines for breast cancer therapy. Adv Drug Deliv Rev. 2022;180:114034. doi:10.1016/j.addr.2021.114034
- 65. Rabinow B. Pharmacokinetics of drugs administered in nanosuspension. Discov Med. 2009;5(25):74-9.
- 66. Strickley RG. Solubilizing excipients in oral and injectable formulations. Pharm Res. 2004;21(2):201-30. doi:10.1023/b:pham.0000016235.32639.23