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Solubilization Methods for Paclitaxel and Docetaxel: An Overview

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Abstract

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 achievement for solubilization of taxanes are reviewed and critically discussed regarding their pharmaceutical and chemical applications.

KEY WORDS: Paclitaxel; Docetaxel; Taxanes; Poor water-solubility; Solubilization methods.

Introduction

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.¹ 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) (Fig. 1), which are being utilized in chemotherapy of breast, head, neck, ovarian and non-small cell lung (NSCL) cancers.²⁻⁴ These drugs inhibit mytosis by binding to the B-tubulin subunit of microtubules and induce apoptosis by preventing depolymerization of microtubules (Fig. 2). Adverse effects of taxanes which are summarized in Fig. (3).

PTX, a diterpene ester derived from the Pacific yew tree, was isolated for the first time in 1971 from *Taxus brevifolia*.⁵ It found in the forests of North-West Canada and the USA. The solubility of PTX in water is about 0.0003 g.L⁻¹. 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.⁶

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:⁷

- 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.⁸ synthesized phosphonooxymethyl ether derivatives of PTX (Fig. 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.⁸ 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.

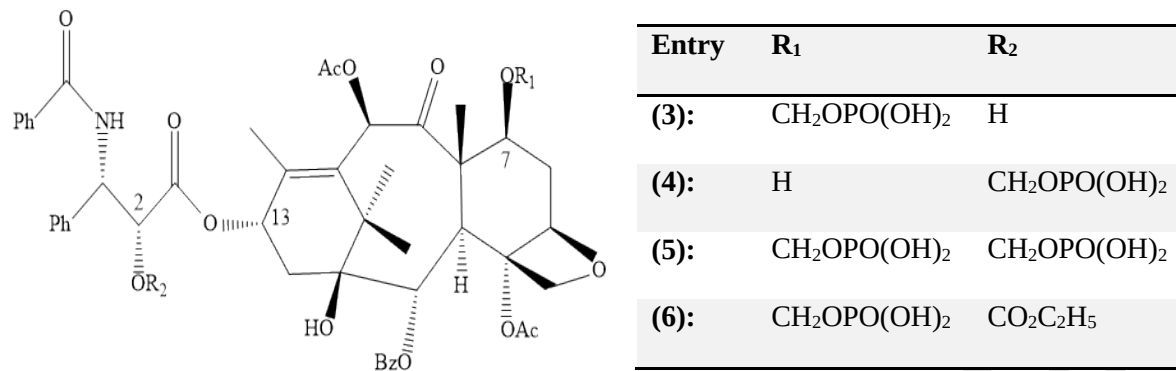


Fig. (4). Phosphonooxymethyl ether prodrugs of PTX.

Polyethylene glycol (PEG)- valine citrulline (VC)- paminobenzylcarbonyl (PABC)-PTX, compound 7, (Fig. 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.

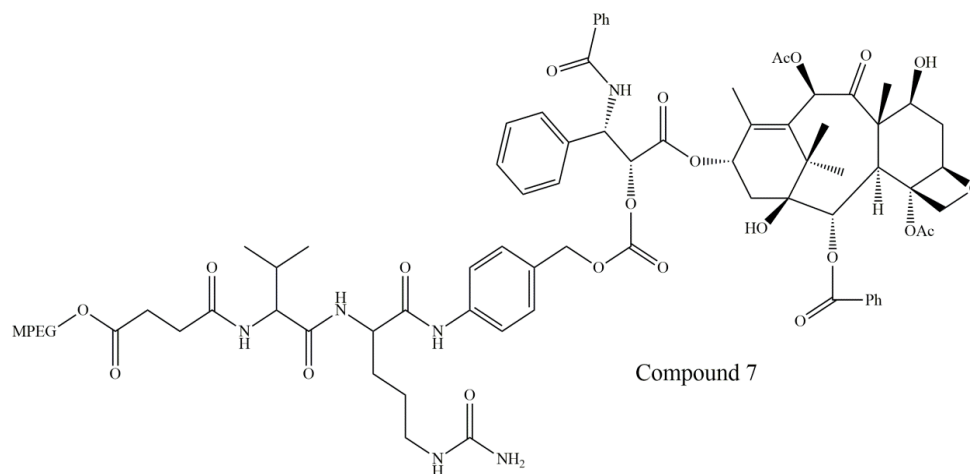


Fig. (5). Structure of PEG-VC-PABC-PTX prodrug.

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.¹¹ synthesized a similar prodrug (Fig. 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 Fig. (7). The high water solubility of compound 8 improved the anti-tumor activity in compared with compound 9 and PTX.

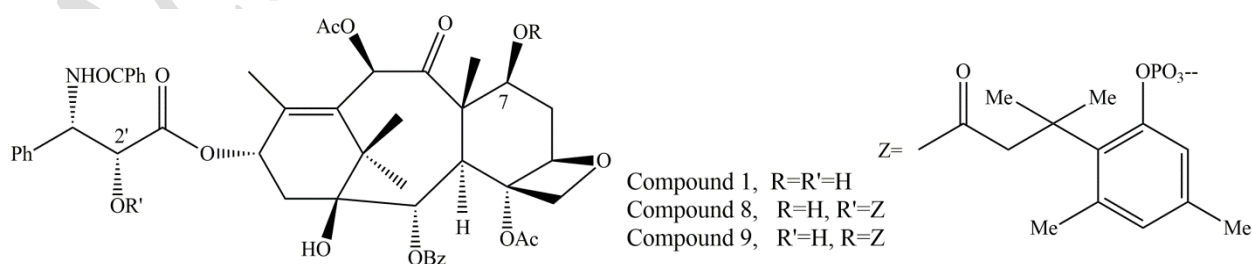


Fig. (6). Structure of phosphonoxyphenylpropionic acid esters of taxol.

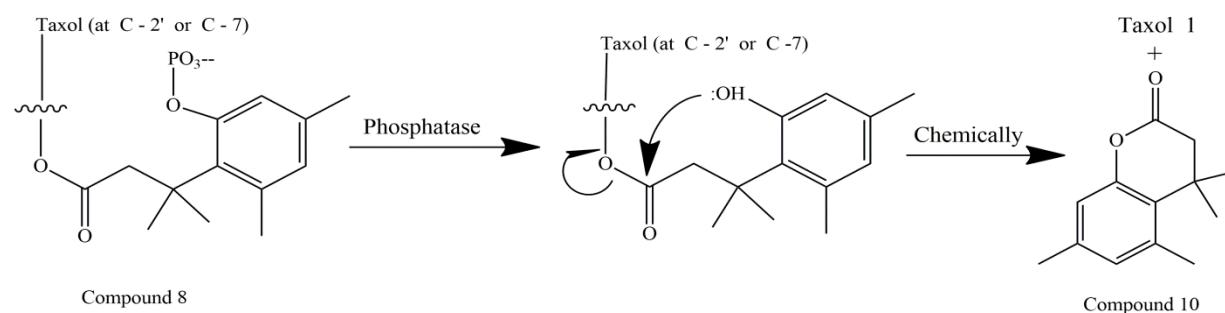


Fig. (7). Schematic mechanism of phosphatase action on phosphonoxyphenylpropionate esters of taxol.

Compound 14 (canadensol) as a highly water-soluble prodrug was synthesized by Skwarczynski et al.¹². This prodrug was obtained by O–N intramolecular acyl migration of the isobutyryl group (Fig. 8) which was pH-dependent. Under physiologic condition (pH 7.4), the solubility of compound 14 was reported as 2.26 g.L^{-1} 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.

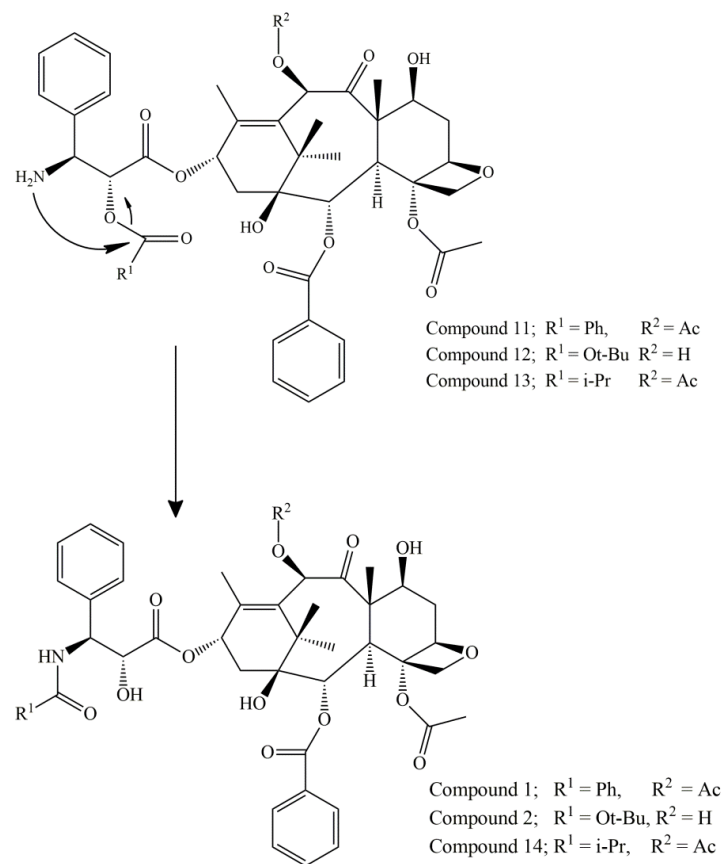


Fig. (8). The O–N acyl migration reaction of taxoid prodrugs.

C2' and C7 modified derivatives of PTX (Fig. 9) were synthesized as an ester of malic acid prodrugs by Damen et al.¹³. 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.

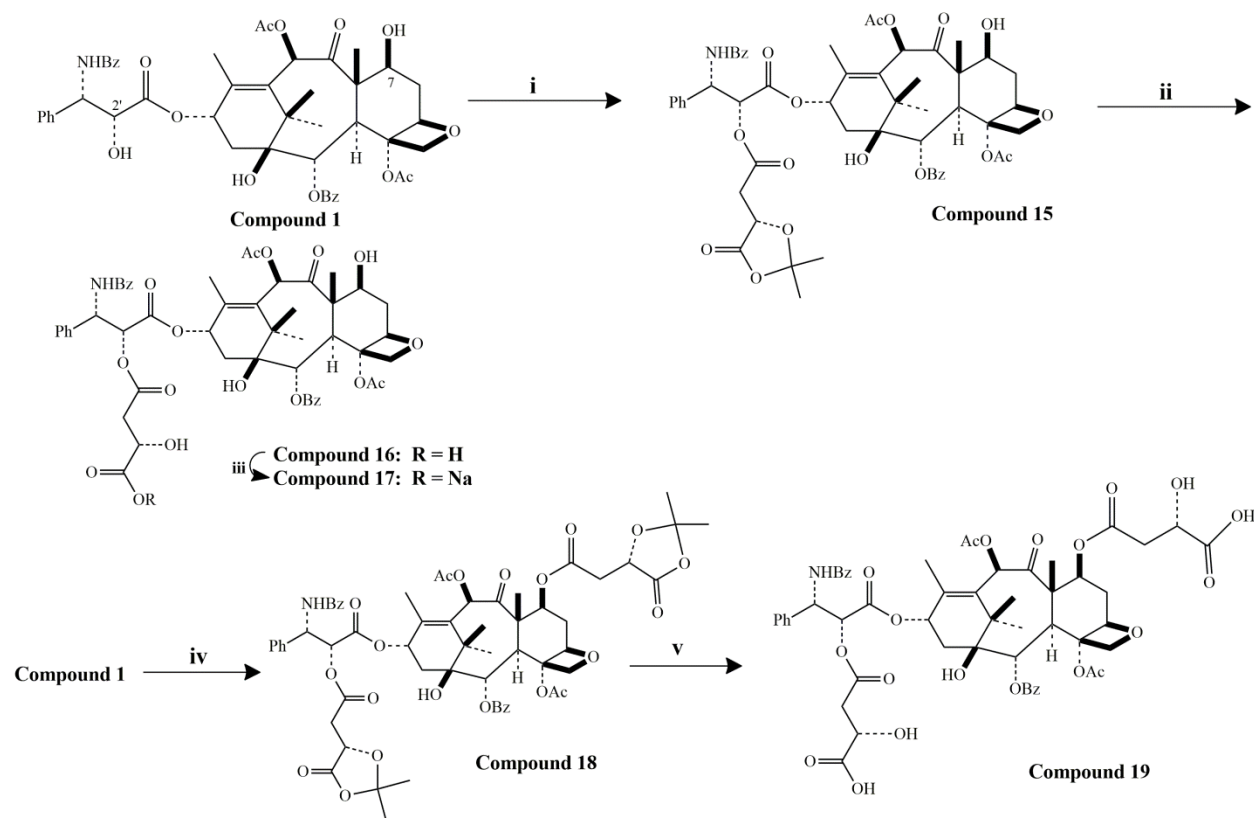


Fig. (9). Synthesis of malylyl PTX.

Skwarczynski et al.¹⁴ 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. Li et al.¹⁵ applied a PEG-DTX conjugate (Fig. 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⁻¹ and 46 nm, respectively. The cytotoxicity of PEG-DTX formulation was lower than DTX and aqueous solubility was increased about 7000-times.

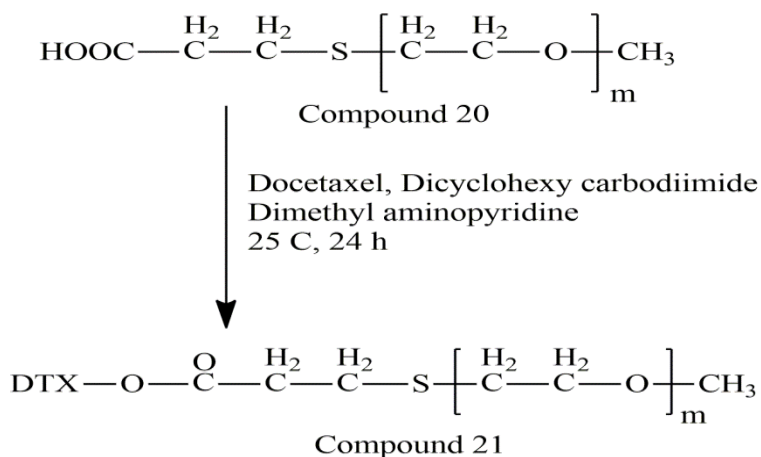


Fig. (10). Synthesis of PEG-DTX conjugate

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

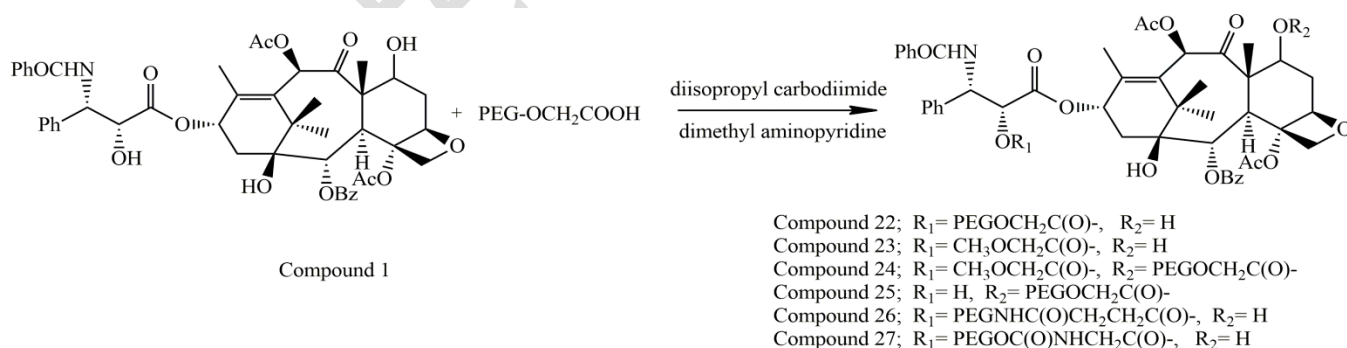
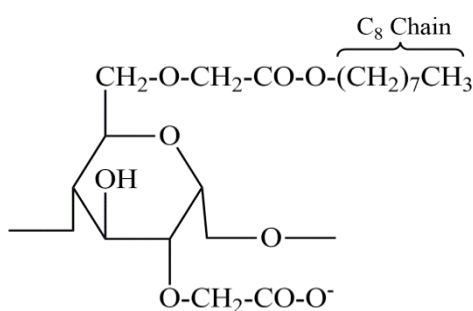


Fig. (11). Structure of 2' and 7-PEG esters of PTX.

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-workers¹⁷. 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.¹⁸ investigated carboxymethylpullulans polymers such as CMP₄₉C₈ and CMP₁₂C₈ (Fig. 12) for the solubilization of DTX and benzophenone. The solubility was increased via CMP₄₉C₈ polymer by the formation of self-assembled nanoaggregates with a hydrophilic shell and hydrophobic inner core.



Compound 28

Fig. (12). Structure of carboxymethylpullulans polymers.

Zhang et al.¹⁹ developed a new prodrug for PTX based on the formation of multi-covalent bonds between gold nanoparticles and PTX by DNA linkers (Fig. 13). The obtained conjugate significantly increased the solubility of PTX about 50-folds. Also, this strategy decreased cancer cell line resistance to PTX.

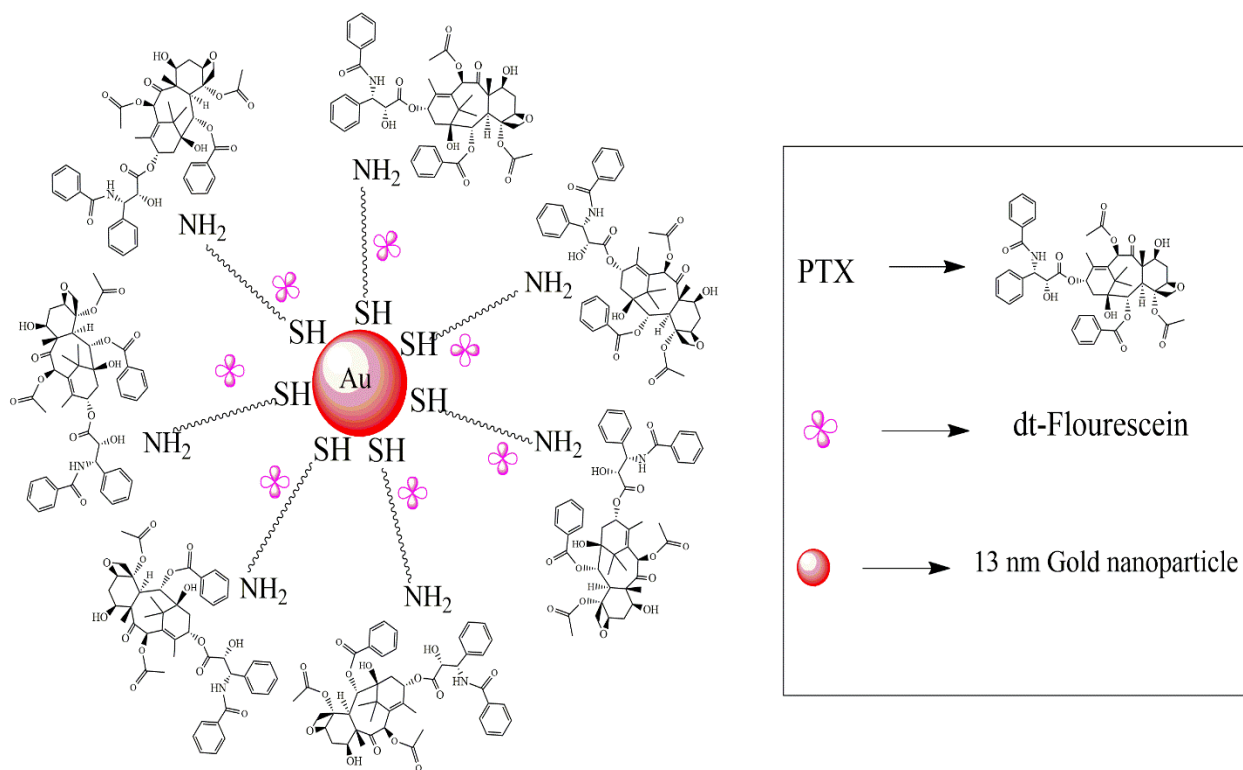


Fig. (13). Schematic formation of Au-PTX prodrug

Other similar works for solubilizing PTX and DTX by prodrug formation were reported by Niethammer et al.²⁰, Feng et al.²¹, Khmelnitsky et al.²², Nakamura et al.²³, Li et al.²⁴, Greenwald et al.²⁵, Du et al.²⁶ and Ma et al.²⁷ 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 (CDs). The enzymatic hydrolysis of starch by CD-glycosyltransferase produces CD. CDs are crystalline, water soluble, cyclic and oligosaccharides. Three forms of CD are α -CD, β -CD, and γ -CD. α - and γ -CD can be used in parenteral products, but β -CD should not be administered as it causes renal frailer.²⁸

Dordunoo et al.²⁹ 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.³⁰ 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) β -CD. The solubility of PTX in 50% aqueous mixture of HP β CD was 3.2 g.L⁻¹ at 37 °C (2000-folds increase in compared with PTX solubility).

Hamada et al. were used 11 types of modified CDs for the enhancement of aqueous solubility of PTX.³¹ The solubility of PTX in DM- α -CD solution was reported to be 8.1 $\pm$ 0.11 μ mol L⁻¹ that show the high solubility among the various investigated types of modified CDs. PTX-DM- β -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- β -CD complex.

Cho et al.³² 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- β -CD were reacted with N-hydroxysuccinimide ester of biotinamidohexanoic acid at 60 °C and primed biotinylated CyS and β -CD. Biotinyl CyS and biotinyl β -CD have increased the solubility of PTX 10.3- and 3.7-folds, respectively.

Baek et al. used an inclusion complex between PTX-solid lipid nanoparticles (PS) and HP- β -CD to enhance the solubility of PTX.³³ Surface-modified PTX-incorporated solid lipid nanoparticles with HP- β -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 are 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.³⁴

Zhou and his co-workers³⁵ used a linear dendritic block copolymer for solubilization of PTX. Block copolymer B₁₆E₄₂ 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 B₁₆E₄₂(BE) with a G₂PAMAM 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⁻¹, 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.³⁶ 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⁻¹. The water solubility of PTX was increased about 38-folds in the presence of 5 g.L⁻¹ 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.⁵⁰ for the improvement of DTX solubility. Pseudo-ternary phase diagrams were used for the optimization of microemulsion systems. The size of microemulsion drops was 30 nm. The antitumor activity and cytotoxicity of microemulsion were not significant compared to DTX. The solubility of DTX in microemulsion form was 4056-6085 folds greater than DTX. Yin et al.⁵¹ 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⁻¹. 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% Pluronic F68, and 0.4 or 0.8 g.L⁻¹ 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[®] HS15 and PEG 400. Brucea javanica oil, an anti-tumor 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.⁵⁴ 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.⁵⁵ loaded PTX in conventional and PEG-coated 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.^{56,57} were also investigated the effect of PEGylated liposome formulation on solubility and stability of PTX. PEGylated liposome was prepared from S₁₀₀PC/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⁻¹. In compared to the conventional liposomes, the increase in biological half-life and decrease in uptake by reticuloendothelial system in PEGylated liposomes 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.⁵⁸ He et al.⁵⁹ 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. It contains the poorly water-soluble drugs without any suspended material in dispersion.⁶⁰ Wang et al.⁶¹ 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.

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.⁶² 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, hydrotrophy 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 nanotechnology-based 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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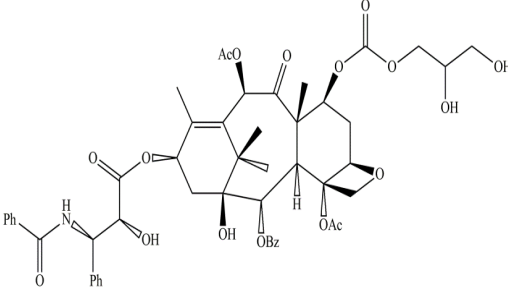
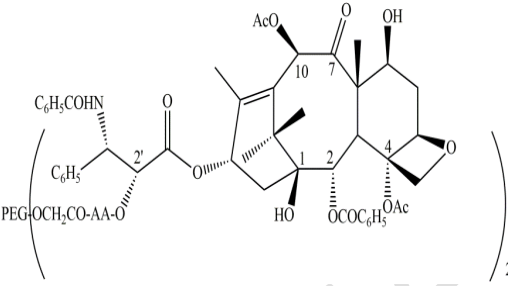
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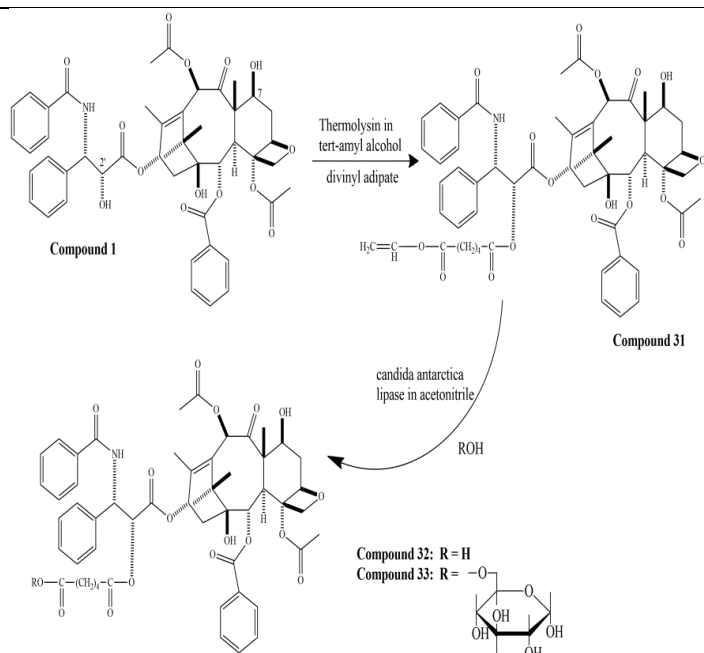
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Table 1. Details of reported prodrugs for taxanes solubilization

Compound number	Drug	Prodrug	Type	Solubility enhancement	Remarks	Ref.
29	PTX		Carbonate	50-folds	Prodrug is activated, pH dependently, by hydrolytic cleavage of the carbonate moiety	[20]
30	PTX		2'-PTX prodrugs	-	PEG as solublizing moiety and amino acids as spacers	[21]

31-33 PTX



Paclitaxel 2'-adipic acid (29) / paclitaxel 2'-adipoylglucose (30).

Enzymatic

Acylation at

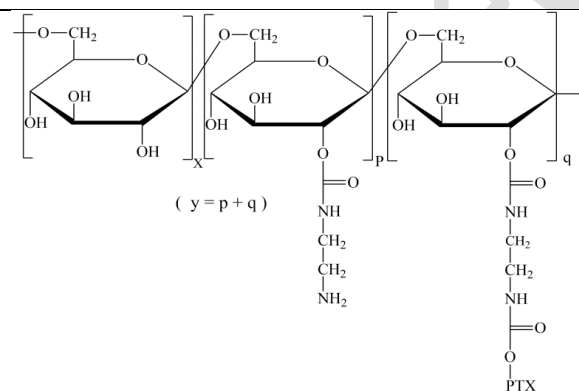
the 2'
position

1625-folds

Thermolysin is an
extremely regioselective
enzyme.

[22]

34 PTX

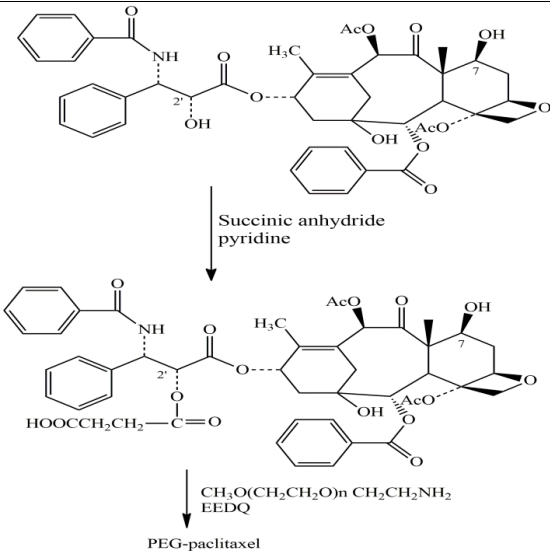
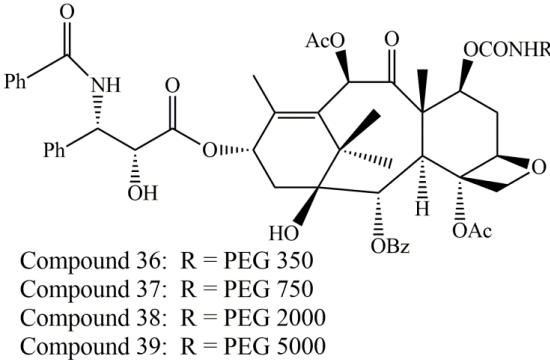


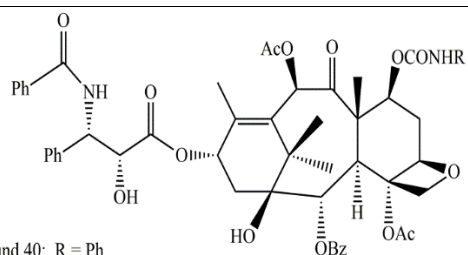
Conjugates
with dextran

2,700 folds

Folic acid was immobilized
for targeting by ionic
adsorption and covalent
bonding conjugation.

[23]

35	PTX	 Succinic anhydride pyridine $\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2\text{NH}_2$ EEDQ PEG-paclitaxel	Ester	PEG-PTX solubility was at least 200 g.L⁻¹ 1	PEG conjugate to PTX in 2'-position and succinyl group is acted as spacer.	[24]
36-47	PTX	 Compound 36: R = PEG 350 Compound 37: R = PEG 750 Compound 38: R = PEG 2000 Compound 39: R = PEG 5000	Carbamates and carbonates	4b (7444-14888) folds 9b – 9h (2.3-2836 folds) 4c and 4d (165260 fold)	PEG was added at the 7- position of PTX	[25]



Compound 40: R = Ph

Compound 41: R = H

Compound 42: R = CH₂CH₂OH

Compound 43: R = CH₂CH₂N₂H

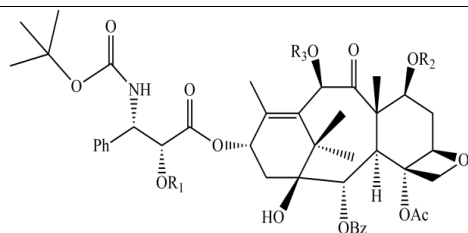
Compound 44: R = CH₂CH₂N₂O

Compound 45: R = CH₂CH(OH)CH₂OH

Compound 46: R = 1-deoxysorbitol

Compound 47: R = (CH₂)₃SO₃Na

48-55 DTX



Compound 48 R₁ = DL-malyl, R₂ = H, R₃ = H

Compound 49 R₁ = L-malyl, R₂ = H, R₃ = H

Compound 50 R₁ = D-malyl, R₂ = H, R₃ = H

Compound 51 R₁ = DL-malyl, R₂ = DL-malyl, R₃ = DL-malyl

Compound 52 R₁ = H, R₂ = DL-malyl, R₃ = H

Compound 53 sodium salt of compound 48

Compound 54 sodium salt of compound 49

Compound 55 sodium salt of compound 50

Ester

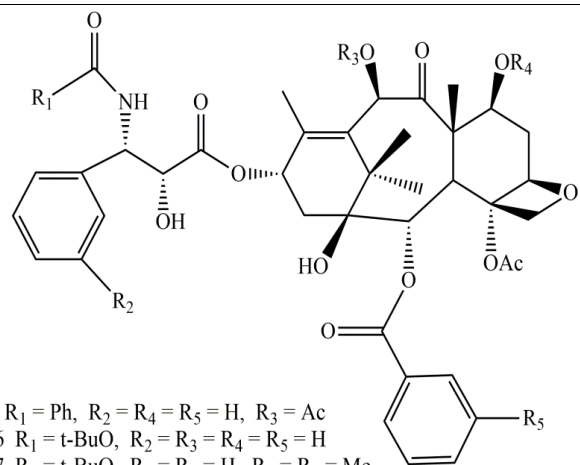
65-90 folds

Compounds were modified

in 2' position with malic
acid group

[26]

56-76 DTX



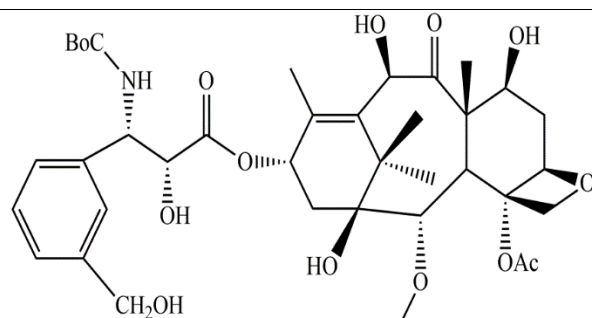
Compound 1 $R_1 = \text{Ph}$, $R_2 = R_4 = R_5 = \text{H}$, $R_3 = \text{Ac}$
 Compound 56 $R_1 = \text{t-BuO}$, $R_2 = R_3 = R_4 = R_5 = \text{H}$
 Compound 57 $R_1 = \text{t-BuO}$, $R_2 = R_5 = \text{H}$, $R_3 = R_4 = \text{Me}$
 Compound 58 $R_1 = \text{t-BuO}$, $R_2 = \text{CH}_2\text{OH}$, $R_3 = \text{Ac}$, $R_4 = R_5 = \text{H}$
 Compound 59 $R_1 = (\text{E})\text{-but-2-en-2-yl}$, $R_2 = R_3 = \text{H}$, $R_4 = \text{Propionyl}$, $R_5 = \text{azido}$
 Compound 60 $R_1 = \text{t-BuO}$, $R_2 = R_4 = \text{H}$, $R_3 = \text{Propionyl}$, $R_5 = \text{azido}$

C-2 and C-
3'prodrug

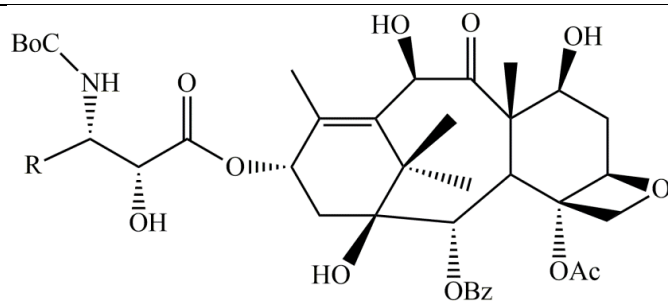
20-135 folds

Highest solubility
enhancement was obtained
by prodrug 3'C (0.0406).

[27]



- Compound 61 $R_1 = \text{azido}, R_2 = \text{H}$
 Compound 62 $R_1 = \text{methoxy}, R_2 = \text{H}$
 Compound 63 $R_1 = \text{trifluoromethoxy}, R_2 = \text{H}$
 Compound 64 $R_1 = \text{methoxy}, R_2 = \text{methoxy}$
 Compound 65 $R_1 = \text{methoxymethoxy}, R_2 = \text{H}$
 Compound 66 $R_1 = \text{cyano}, R_2 = \text{H}$
 Compound 67 $R_1 = \text{H}, R_2 = \text{H}$



- Compound 68 R = 3-formylphenyl
 Compound 69 R = 3-(methoxymethyl)phenyl
 Compound 70 R = 3-carboxyphenyl
 Compound 71 R = 3-((dimethylamino)methyl)phenyl
 Compound 72 R = 3-(2-hydroxyethyl)phenyl
 Compound 73 R = 3-hydroxyprop-1-ynyl
 Compound 74 R = (Z)-3-hydroxyprop-1-enyl
 Compound 75 R = (E)-3-hydroxyprop-1-enyl
 Compound 76 R = 3-hydroxypropyl

Table 2. Details of reported micellar solubilization methods for taxanes solubilization

Micellar solubilization method	Drug	Solubility enhancement	CMC concentration	Remarks	Ref.
				- Micelles were prepared by solvent casting method.	
Dendrimer–TPGS mixed micelles	DTX	DTX = 20.36 fold	CMC of mixed micelles	- G4 poly(amidoamine) PAMAM	[37]
	PTX	PTX = 34.95 fold	was 0.009%	was acted as dendrimers.	
				TPGS was acted as biodegradable surfactant.	
Filomicelles and spherical micelles	PTX	10,000-fold	CMC of 1.2 g.L ⁻¹ for a sphere-forming	- Diblock polymer poly (ethylene oxide)-b-poly (epsilon-	[38]

				caprolactone) was acted as non-ionic macromolecular surfactants. - Micelles were prepared by co-solvent/evaporation method.
Hydrotropic block copolymer micelle system	PTX	-	CMC value for various type of PEG-b-P(2-VBOPNA) _s is 0.0855 to 0.1285 g.L ⁻¹	- PEG-b-P(2-VBOPNA) _s was acted as surfactants. [39] - Micelle formation is pH-dependent in pH >2)
Mixed micelles (MM)	PTX	1414-fold for water-lecithin dispersions	-	- Micellar solution including: egg lecithin and sodium deoxycholate Poloxamer, PEG and benzalkonium chloride as co-surfactant [40]

		highest solubility			
		(up to 570 mg/100 ml)			
Hydrotrophy	PTX	>100,000-folds	0.0028 to 0.5 mol.L ⁻¹	<i>N,N</i> -Diethylnicotinamide (NNDENA) was acted as surfactant	[41]
		1200-fold for KXN441 5.2% (w/v) with CMC 3.6 mM	KXN441 (3.4 μmol.L ⁻¹) KXN437 (132 μmol.L ⁻¹) Solutol® HS15 (130 μmol.L ⁻¹)	- KXN441, KXN437, KXN424, KXN337 are soft surfactant.	
Soft micelles	PTX	500-folds for KXN337 5.2%	KXN 424 (104 μmol.L ⁻¹)	- Micelle size is determined via dynamic light scattering.	[42]
				- HPLC system is used for quantifying PTX by C ₁₈ column	

		(w/v) with CMC	KXN 337 (300 $\mu\text{mol.L}^{-1}$)	and isocratic mixture of deionized
		300mM	¹⁾	water and acetonitrile at 30:70
		830-folds for		- Solubility measurements methods
		KXN424, KXN437		for equilibrium solubility
		and Solutol [®] HS15		determination require 24–48 h
		5.2% (w/v)		
			Micelle prodrug	
			solutions were prepared	PEG-b-poly((caprolactone) was
Prodrugs micelles	PTX	Solubilities >5 g.L ⁻¹	at 0.5 $\mu\text{mol L}^{-1}$ (PEG-b	acted as amphiphilic block [43]
			PCL basis)	copolymer micelles.
		6000-folds to 15	The CMC values of	- Micellar shell segment including:
Hydrotropic polymeric micelles	PTX	000-folds	PEG- <i>b</i> P(VBODENA)s	[44]
				PEG block

			were in the range 0.036-0.07 g.L ⁻¹	Core segment including: poly(2-(4-vinylbenzyloxy)-N,N-diethylnicotinamide) (P(VBODENA)) block. N,N-Diethylnicotinamide DENA)
Polymeric micelles	PTX	1 g. L ⁻¹ in PMB30W	PMB30W concentration was higher than 9.0 g.L ⁻¹	Amphiphilic 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer [45] was acted as the solubilizer.
Copolymer micelles	PTX	-	-	- Pluronic copolymers of P123/F68 and sorbitan monopalmitate (Span 40) was used. [46]

				- Modified thin-film hydration technique were used for preparation of copolymer micelles.	
Polymeric micelles (spherical and cylindrical micelles)	DTX	> 1000 folds	1 to 10 g.L ⁻¹	Poly(ethylene oxide)-block-poly(styrene oxide) (PEO-b-PSO) and PEO-b-poly(butylene oxide) (PEO-b-PBO) were acted as surfactant.	[47]
Polymeric micelles	DTX	-	CMC value of mPEG-PLA Lys(FB)2 at room temperature was	- MPEG-PLA-Lys(FB)2 block was acted as copolymer.	[48]

			measured to be as low as	- A solid dispersion-thin film
			0.00175 g.L ⁻¹	hydration method was used for preparation of DTX-loaded micelles.
				- poly-(D,L-lactic acid-co-glycolic acid) (PLGA)-polyethylene glycol (PEG)-PLGA triblock was acted as copolymer [49]
Copolymeric micelles	DTX	3000-folds	23 and 25 wt% of copolymer	- DTX-loaded copolymer micelles was prepared by solvent casting method.

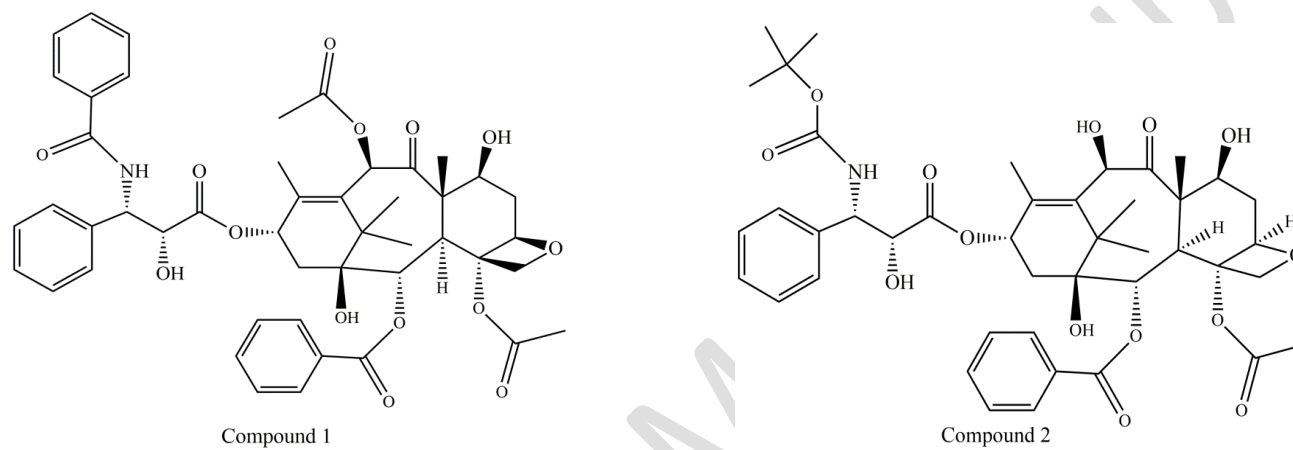


Fig. (1). Molecular structure of taxanes: paclitaxel (compound 1) and docetaxel (compound 2)

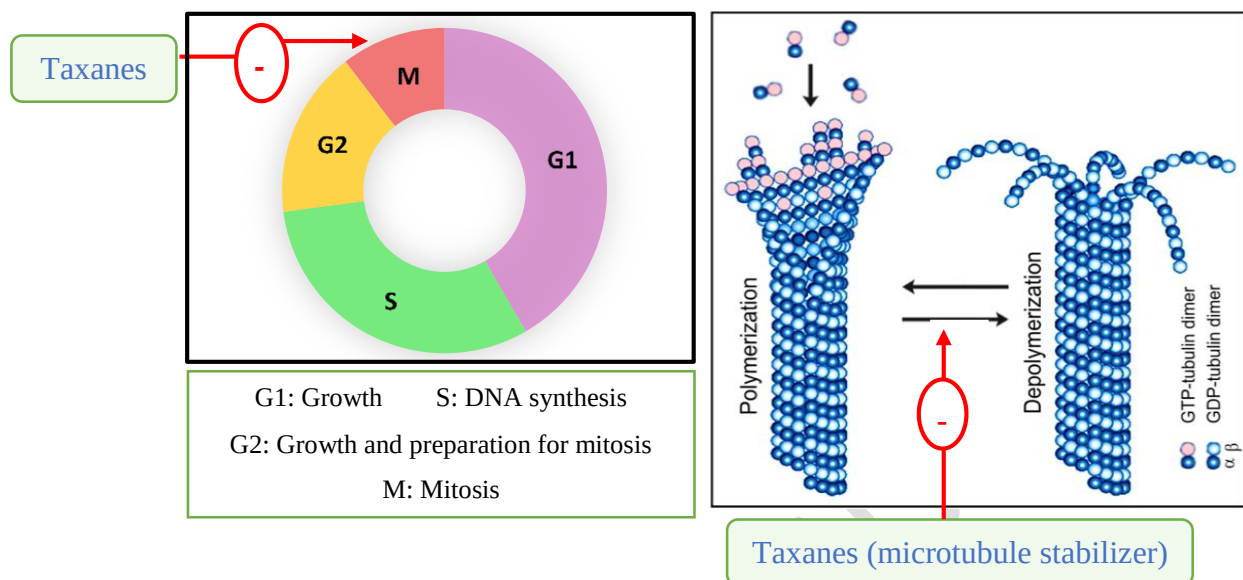


Fig. (2). Mechanisms of action of taxanes.

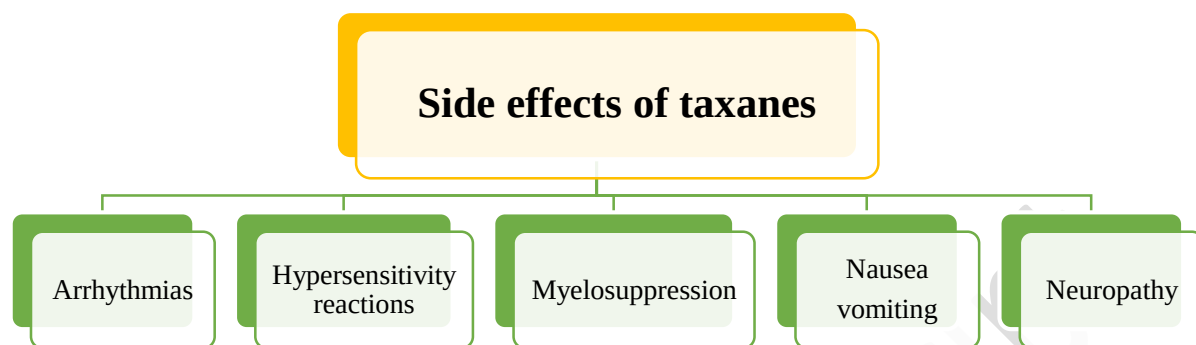


Fig. (3). Common adverse effects of taxanes.