Journal of Pharmaceutical Research Vol. 10, No. 2, April 2011 : 51-59.

A PROFILE OF PACLITAXEL

Siddiqui S[1*]. Kumar S[2], Siddiqui AA[2], Kataria S[2], Paliwal S[3]

[1]Subramanium College of Science and Technolgy, Holambi Khurd, New Delhi -110 082.
[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi -110 062.
[3] Department of Pharmacy, Banasthali University, Banasthali Vidyapeeth, Rajasthan - 304 022, India.

Received on : 07.02.2011 Revised : 16.03.2011 Accepted : 31.03.2011

ABSTRACT

Treatment of cancer is a challenge to physicians, and it requires multiple treatments. But the role of paclitaxel cannot be neglected in cancer treatment. It is the most promising anti tumour agent. As the drug has poor water solubility, number of alternative controlled release formulations has been developed having variety of dose regimens to overrule the limitations of cremophor based formulation. More advanced Drug delivery systems includes Nanoparticles, Microemulsion, Liposomes, Oncogel, Microspheres, Cyclodextrin complex, etc. Also the drug has flexible structural aspects hence lots of modifications are possible in the structure.

Keywords: *paclitaxel; cremophor; nanoparticles; formulations.*

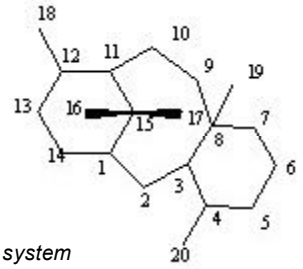
INTRODUCTION

Cancer in general terminology is group of diseases caused by abnormal and unrestricted growth of cells. It has high morbidity and mortality, being the second most cause of all death after cardiovascular diseases. Treatment of 'gulma' [cancer] by using herbs was described in the first surgical treatise from India, *Sushruta Samhita*, as far back as 2500 BC, and Ayurveda also described treatment of cancer with certain plants[1]. *Eber Papyrus* described the same in 1500 BC[2]. Since then, numbers of natural products with diverse chemical structure have been isolated for anti-cancer agents out of which paclitaxel are one of the novel broad spectrum drug.

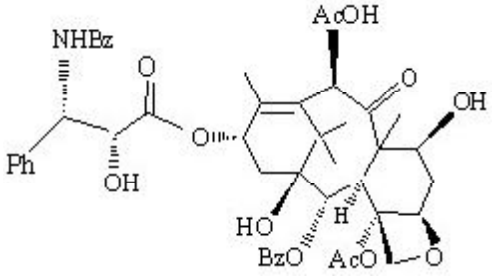
Paclitaxel, tax-11-en-9-one,5β,20-epoxy-1,2α,4, 7β,10β,13α,hexahydroxy-4,10-diacetate-2-benzoate-13-α-phenylhippurate, a poly-oxygenated naturally occurring diterpene alkaloid, was first isolated by Wall and Wani from the bark of *Taxus brevifolia*. Paclitaxel is one of the broadest spectrum anticancer agent approved by the Food and Drug Administration FDA for the treatment of advanced ovarian cancer[3-5]. Today, it is considered as one of the most important chemotherapeutic drugs in cancer chemotherapy for clinical treatment of cancer of lungs, head, neck, bladder, AIDS related Kaposi's sarcoma, and endometrial cancers etc[6-12]. Paclitaxel is found in the bark of yew trees [Taxus] which grows extremely slowly & having very low yield[13]. So alternate routes have been investigated for the production of paclitaxel which include production in plant suspension, biotechnical method, fungal resources, total synthesis and semi synthesis. Paclitaxel exerts its action by binding microtubules and causes kinetic suppression (Stabilization) of microtubule dynamics[14]. The paclitaxel arrest the cell cycle at mitotic phase & causes the cytotoxicity. Paclitaxel is hydrophobic in nature due to which suitable vehicle is required for delivery of paclitaxel.

CHEMISTRY OF PACLITAXEL

Paclitaxel has the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It consists of a taxane nucleus to which an uncommon four-membered oxetane ring is linked to C_4 and C_5 and an ester is attached at C_{13}.



1. Taxoid ring system



2. Paclitaxel

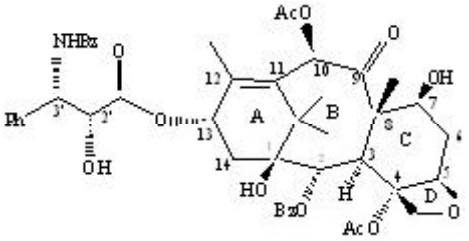
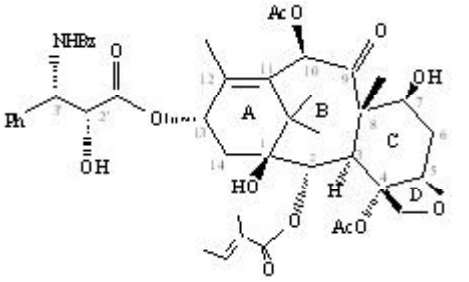
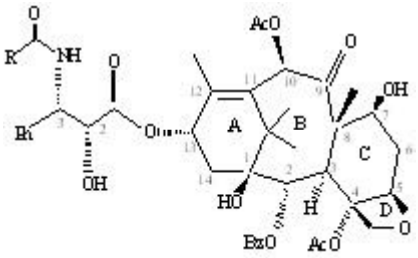
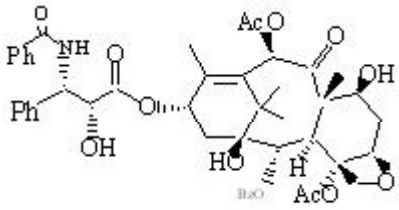
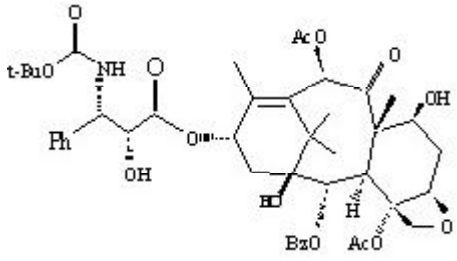
STRUCTURE ACTIVITY RELATIONSHIP

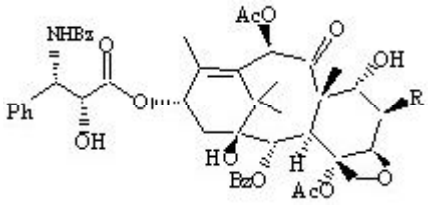
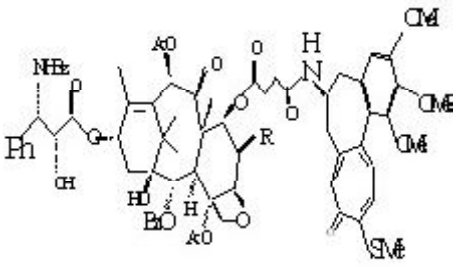
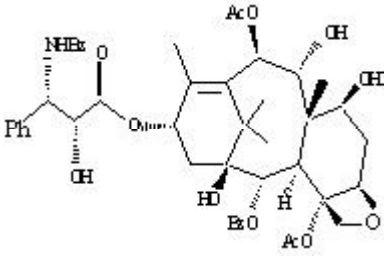
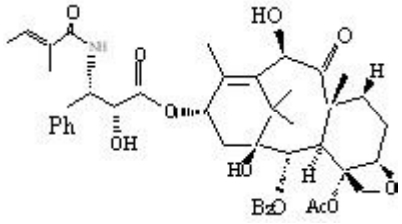
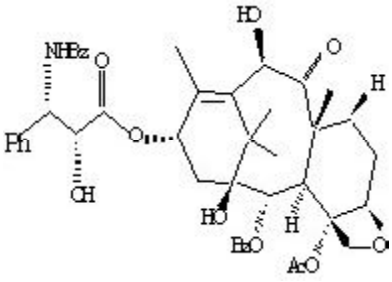
Structure activity relationship (SAR) investigations of taxanes have been carried out for seeking higher activity towards tumors and less toxicity towards normal tissues. General structure of paclitaxel includes Toxoid ring system with A, B, C, D rings. It is known that certain modifications at certain positions in the molecule results in great differences in activity. The modification of paclitaxel can be divided into two parts:

***Correspondence :** seemi.siddiqui1@gmail.com

A) MODIFICATIONS OF SKELETON

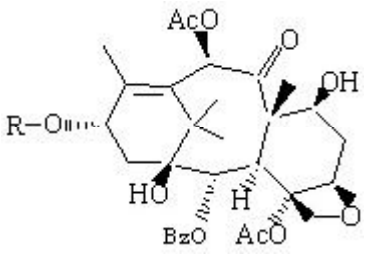
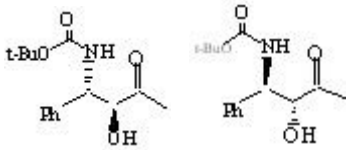
The skeleton of paclitaxel includes the A, B, C and D rings in the diterpene part, which has eight oxygenated positions at positions **1**, **2**, **4**, **5**, **7**, **9**, **10**, and **13**.

MODIFICATION	STRUCTURAL OUTCOME
Modifications at C_1 Position A series of analogues without C_1 -OH were prepared for studying microtubule stabilization and cytotoxicity. Position is not important for the activity of paclitaxel[15].	 3
Modifications at C_2 *Position* SAR studies at the C_2 position showed that both the nature and stereochemistry of the 2-benzoyl group are of great importance for activity. 2-Debenzoyl-2-tigloyl paclitaxel (4), the first natural analogue of paclitaxel with a modified ester group at C_2, retained microtubule-binding activity, but displayed decreased cytotoxity as compared to paclitaxel and 2-debenzoyl-2-senecioyldocetaxel analogue. These results suggest that C_2 benzoyloxy is essential for activity[16].	 4
Modifications at C_4 PositionC_4 modified analogues include 4-deacetylpaclitaxel, 4- deacetoxypaclitaxel, and 4-ether, ester, carbonate and carbamate derivatives. 4-Deacetylpaclitaxel (5) and 10-acetyl-4-deacetyldocetaxel (6)[17] were inactive in the microtubule assembly assay. Compound (5) also showed no cytotoxicity towards several tumor cell lines[18].	 5 R=Ph 6 R= t-BuO
These results illustrate the importance of the 4-acetyl moiety for microtubule binding. Chordia *et al*. reported two 4 deacetoxypaclitaxel derivatives (7 and 8), which were significantly less active than paclitaxel in microtubule assembly and cytotoxicity assays[19]. This result again indicates that an ester substituent at C_4 is essential for the biological activity.	 7 R=Ac 8 R=H
Oxetane Moiety at C_4-C_5 Position The presence of the oxetane ring was shown to be essential for the bioactivity of paclitaxel. In order to clarify the role of the oxetane oxygen atom, several groups synthesized paclitaxel analogues with nitrogen, sulfur and other heteroatom's[20-21]. Compounds with nitrogen were inactive in cytotoxicity assays. These results suggested a specific interaction of the heteroatom with the protein.	 9

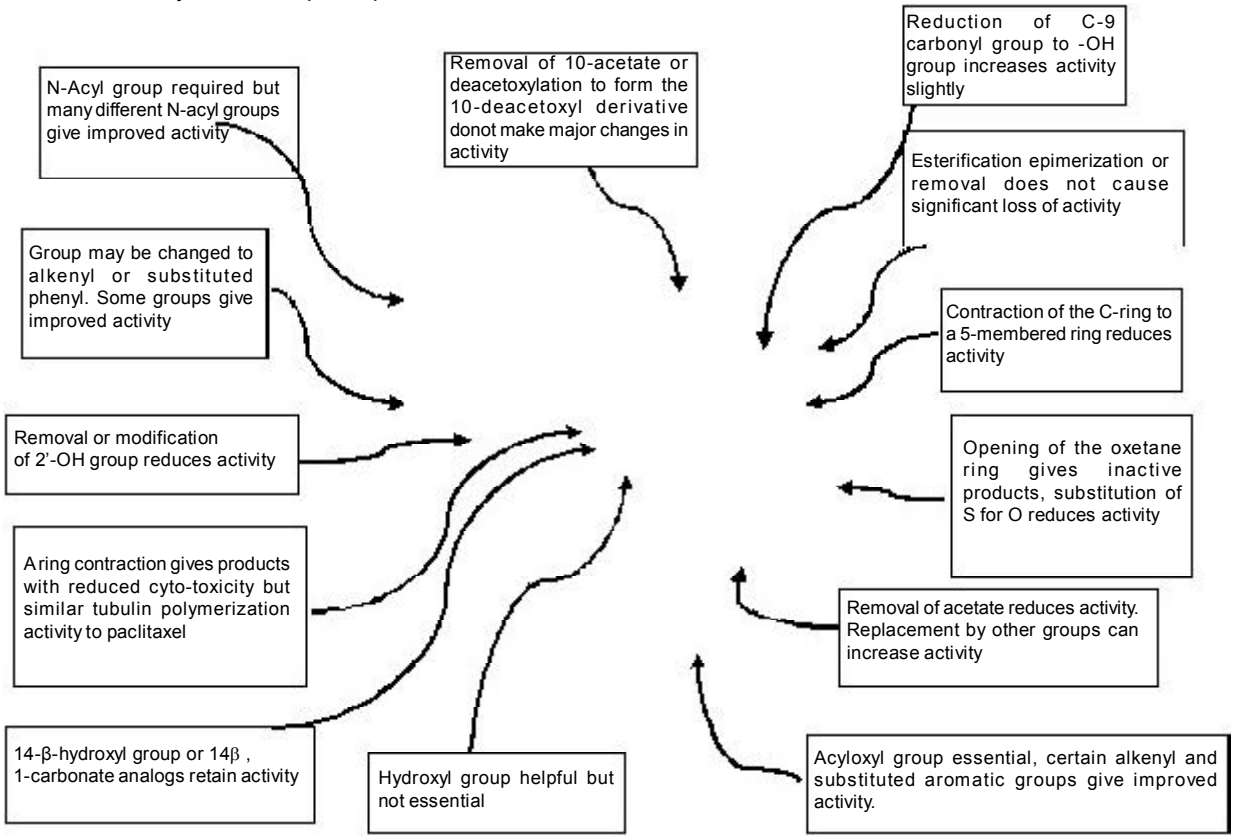
MODIFICATION	STRUCTURAL OUTCOME
Modifications at C_6 Position The compounds (10) and (11) were synthesized and evaluated for their *in vitro* cytotoxicity towards the human colon cancer cell line. Aminopaclitaxel (11) was significantly less active than paclitaxel, but the azido analog (10) was 2- to 3-fold more cytotoxic than paclitaxel[22].	 10 R=N_3 11 R=NH_2
Modifications at C_7 Position The derivatization of the C_7 hydroxyl or change of its stereochemistry has no significant effect on anticancer activity of the molecule. Although Esterification at C_7 resulted in loss of *in vitro* microtubule assembly activity, but not cytotoxicity. These observations suggested that esters at C_7, which tend to improve water solubility, might serve as useful prodrugs of paclitaxel[23]. Hence, the C_7 position was frequently modified to act as prodrugs for increasing the water-solubility of paclitaxel.	 12
Modification at C_9 Position Studies on the modification at C_9 imply that the functional group at C_9 may be one effective factor of the tubulin binding site in addition to two further key tubulin binding regions at the C_{13} ester side chain and the oxetane ring of paclitaxel. Klein reduced the C_9 carbonyl group to a hydroxyl group and obtained compound (13), whose cytotoxicity was higher than that of paclitaxel[24].	 13
Modifications at C_{10} Position Previous studies on naturally occurring taxanes indicated that acetylation of the C_{10} hydroxyl group is not essential for the anti-tumor activity. Modifications at C_{10} position do not decrease the activity of analogues. Both 10-deacylcephalomannine (14) and 10-deacylpaclitaxel (15) obtained from *Taxus wallichiana* showed considerable cytotoxicity and also affected microtubule disassembly[25].	 14  15

B. MODIFICATION OF SIDE CHAIN

Paclitaxel contains C_{13} side chain, which is essential for cytoxicity of paclitaxel. Modification at $C_{2'}$, and $C_{3'}$ Position are of having significant effect on antitumor activity.

MODIFICATION	STRUCTURAL OUTCOME
Modifications at the C_{13} Side Chain This side chain is essentially required in taxol for anticancer activity. The $C_{2'}$ hydroxyl is important for activity. When this hydroxyl is protected, activity is reduced to a great extent. $C_{3'}$ aryl group is critical, and is required for better activity. While amide's aryl group may be replaced by similar aryl or alkyl groups. On replacement with methyl group, activity is reduced 19-fold.	
Stereochemistry at $C_{2'}$ and $C_{3'}$ has a dramatic effect on activity. The (2´R, 3´S) isomer is significantly less active than natural (2´R, 3´S) isomer, but the (2´S, 3´S) and (2´R, 3´R) isomers shows comparable activity with the natural isomer[26].	*Where R is -*  16 17

Structure activity relationships of paclitaxel



MECHANISM OF ACTION

Paclitaxel kills the cancerous cell by cytotoxicity and apoptosis. Paclitaxel exhibit a unique mechanism of action it binds to microtubule and causes kinetic suppression (stabilization) of microtubule dynamics. Microtubules are actually cylindrical structure made up of proteins (mainly tubulin) that are involved in various cellular functions such as movement, ingestion of food, controlling the shape of cells, sensory transduction and spindle formation during cell division[27]. In normal case the tubulin polymerizes to microtubule and again microtubulin converts into tubulin. This whole routine process exists in equilibrium state. But Paclitaxel mainly binds to microtubules, rather than to tubulin dimers[28]. The binding site for paclitaxel is the N-terminal 31 amino acids of the β-subunit of tubulin in the microtubule[29], unlike the binding sites of colchicine, vinblastine and podophyllotoxin for GTP. The microtubules formed due to paclitaxel action are not only very stable but are also dysfunctional. The cancerous cells lack a checkpoint to detect the absence of spindle and attempt to continue the cell cycle leads to cell death[30].

1.Normal case

Tubulin ⇌ Microtubulin (Polymer) → Microtubulin bundles

→ Normal cell cycle

2. In case of Taxol

Tubulin (monomer) ⇌ Microtubulin (Polymer) → Stable bundles of microtubulin Size=22A°

→ Defective cell cycle, new cells without spindles; instant cell death

Paclitaxel kills cancerous cells through the induction of apoptosis by p53-independent pathways.

PHYSICAL PROPERTIES AND PHARMACOKINETICS

Paclitaxel is white to off-white crystalline powder. It is highly lipophilic, insoluble in water and melts at around 216-217 °C. The generally accepted dose is 200–250 mg m^{-2} and is given as 3 and 24 h infusion. Pharmacokinetics of paclitaxel shows wide variability. Terminal half-life was found to be in the range of 1.3–8.6 h (mean 5 h)[31] and the steady-state volume of distribution was found to be ~87.1 m^{-2}. The drug undergoes an extensive P-450 mediated hepatic metabolism and less than 10% drug in the unchanged form is excreted in the urine[32]. Most of the drug is eliminated in feces. More than 90% of the drug binds rapidly and extensively to plasma proteins[33]. The highest concentration of the paclitaxel following a 6-h infusion in rats was found to be in lung, liver, kidney and spleen and was essentially excluded from brain and testes[34].

PACLITAXEL DOSE AND DRAWBACKS OF THE FORMULATIONS

Paclitaxel has a low therapeutic index, and the therapeutic response is always associated with toxic side-effects[35-36]. It should be only used when the potential benefits of paclitaxel therapy outweigh the possible risks.

In the early development of paclitaxel, a high incidence of acute hypersensitivity reaction characterized by respiratory distress, hypotension, angioedema, generalized urticaria and rash were observed. It is generally felt that the vehicle Cremophore EL (Polyoxyethylated castor oil vehicle and dehydrated alcohol) contributes significantly to the hypersensitivity reactions, leading to peripheral neurotoxicity, neutropenia, etc. An additional problem linked to the CrEL solvent is the leaching of plasticizers from PVC bags and infusion sets used routinely in clinical practice. Consequently CrEL formulation need to be prepared and administered in either glass bottles or non- PVC infusion systems with inline filtration. This leads to the need of search of alternative formulations of paclitaxel. The maximum tolerated dose (MTD) of paclitaxel administered by a 3-h infusion to patients with solid tumors was found to be 225–240 mg m^{-2} without any hypersensitivity reactions but resulted in hypotension[37]. A summary of Therapeutic Efficacy and Toxicities is presented in Table 1.

TABLE 1: *Summary of Therapeutic Efficacy and Toxicities*

a) Tumors responding to paclitaxel	Ovarian cancer, breast cancer, head and neck cancer, small cell lung cancer, colon cancer, multiple myeloma, melanoma, Kaposi's sarcoma
b) Dose limiting toxic effects	Neutropenia, mucositis, neurotoxicity, hypersensitivity
c) Different systems	
Cardiovascular	Asymtomatic bradycardia, atrioventricular conduction blocks, atrial arrhythmias, ventricular tachycardia, ischemia
Hematological	Neutropenia, thrombocytopenia
Hypersensitivity	Dyspnea with bronchospasm, urticaria, hypotension
Neurotoxicity	Peripheral neuropathy, transient myalgia, scintillating scotamata
Gastrointestinal tract	Mucosities, nausea, vomiting, diarrhea
Hepatotoxicity	Elevation of liver function tests
Others	Alopecia, myopathy, fatigue, pulmonary lipid embolism

PRODUCTION OF PACLITAXEL

Natural Resources

It is difficult to obtain sufficient quantities of the compound from its natural sources. Paclitaxel constitutes only 0.01-0.03% of the dry weight of the bark of the pacific yew tree[38]. In addition, several other taxane including 10-DAXP, 10-DAB III, and cephalomannine have been obtained from the needles, which can be used for semi-synthetic production of paclitaxel. At present, the culture of seedlings and the growth of yew trees in plantations have been widely considered as the most feasible method to obtain paclitaxel and its precursors.

Biotechnological Approaches

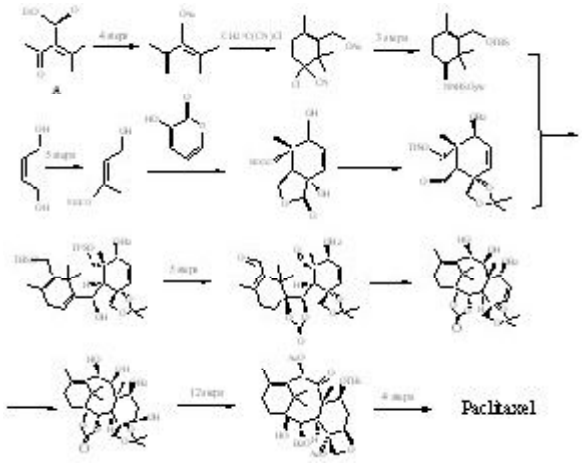
These include plant tissue cultures, cell suspension cultures, hairy root cultures, recombinant microorganisms and the induction of paclitaxel biosynthesis in cell culture systems. Especially *Taxus* cell cultures have been considered as a promising means for paclitaxel production[39].

Fungal Resources

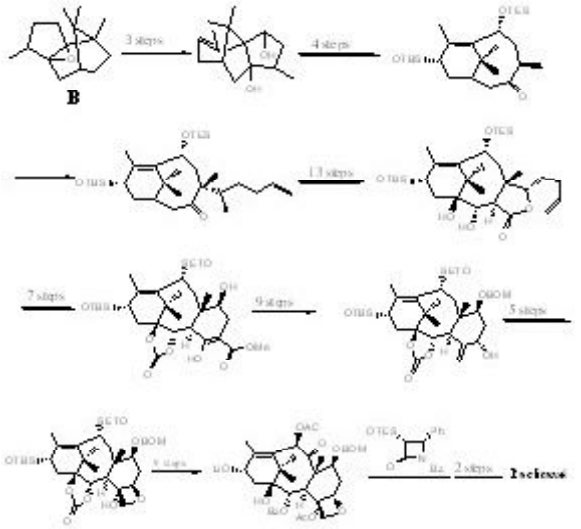
In 1993, Stierle *et al*. were the first to report a paclitaxel producing endophytic fungus, *Taxomyces andreanae,* which was isolated from yew trees[40]. Although the yield of paclitaxel was only as low as 24-50 ng/L, the greatest problem of using fungal fermentation for paclitaxel production represents very poor and unstable yields.

Total Synthesis

Total synthesis of paclitaxel is a challenge, because of four complicated rings (A, B, C rings and the oxetane ring) and 11 chiral centres in the molecule. Nicolaou[41-44] and Holton[45-46] describe two different schemes (Scheme 1 & 2) for total synthesis of paclitaxel from **compound A** (2-Acetyl 3-methyl-but-2-enoic acid ethyl ester) and **compound B** (4-Methyl-1-(1,2, 2 trimethyl-cyclopentyl)-6-oxa bicycle[3.1.0]hexane) respectively as precursor.



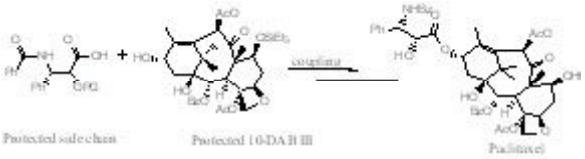
Scheme 1. *Total synthesis of paclitaxel by Nicolaou*



Scheme 2. *Total synthesis of paclitaxel by Holton*

Semi-Synthetical Production

The semi synthetic production of paclitaxel *via* the coupling of a phenylisoserine moiety with protected 10-DAB III has been extensively studied[47](Scheme 3).



Scheme 3. *Semi synthesis of paclitaxel*

FORMULATION OF PACLITAXEL

Paclitaxel was earlier formulated in a vehicle composed of 1:1 blend of Cremophor EL (polyethoxylated castor oil) and ethanol which is diluted with 5–20-fold in normal saline or dextrose solution (5%) for administration. Taxol, the most popular formulation of Paclitaxel has serious drawbacks including:

- Cremophor EL contributes serious allergic reactions[48].
- Leaching of plasticizers from PVC bags and infusion sets[49].
- Increase systemic exposure to paclitaxel.
- Lack of specificity
- Poor solubility
- Low bio distribution

To overcome these drawbacks several novel drug delivery systems are formulated for Paclitaxel as shown in Table 2.

Table 2: *Formulations of Paclitaxel with their advantages*

FORMULATION	DESCRIPTION	GOAL / ADVANTAGE	THERAPEUTIC USE	EXPERIMENTAL STUDY
Nab Paclitaxel (ABI-007, Abraxane)	Paclitaxel protein bound particles, and does not employ Cremophor EL solvent system.	Preferentially accumulate in tumor beds and facilitate the portioning of nab Paclitaxel in tumor tissue, also there is no danger of leaching plasticizers from infusion bags or tubing	Breast cancer	• Phase I – evaluation of safety, MTD and antitumor activity. Dose range 80-375 mg/m2 every 21 days in 19 patients. • Phase II – breast cancer patients were chosen. Patients receive either nab Paclitaxel at 175 mg/m2 (n=43) or 300 mg/m2 (n=63) administered I.v over 30 min every 3 weeks. • Phase III – To demonstrate noninferiority of nab Paclitaxel when compared with Paclitaxel
Paclitaxel loaded PLGA nanoparticles	Paclitaxel is loaded as poly (lactic acid-co-glycolic acid) nanoparticle by interfacial deposition method	• Particles are suitable for I.v administration and therapeutic index of drug is improved. • Significant improvement in drug specificity of action and also there is ease of preparation.	Lung cancer	Cell line study was done using human small cell lung cancer cell line.
Surgically implanted CR, biodegradable polilactobiate microspheres (PACLIMER)	Poly phosphoester polymer (DAPG-EOP) backbone and drug encapsulated in microspheres at 10%w/w loading by dissolving both substances in ethyl acetate.	Safely bypass blood brain barrier and deliver Paclitaxel to malignant brain tumors	Malignant brain tumors	• In vivo biodistribution study is done in rats in group of 4 at 1 and 3 days after implant. • In vivo study of Paclitaxel was performed as intracranial implants in Fischer 344 rats in presence or absence of 9L gliosarcomas.
Paclitaxel microemulsion	Microemulsion prepared using drug having particle size 11.2 nm.	Paclitaxel injection (Taxol) causes hypersensitivity reactions, but no allergic reactions occur using microemulsion.	Myelomas	Hypersensitivity evaluation was done using guinea pigs divided into 2 groups A and B and observe scratch, sneeze, erect hair, twitch, dyspnea, ataxism, shock or death was observed. Further pharmacokinetic study was done using 180 SD male rats in a group of 5 rats.
Paclitaxel loaded gelatin nanoparticles	Paclitaxel is loaded in gelatin	Selective delivery of drug in high concentration to tumor bearing bladder while minimizing the systemic exposure.	Superficial bladder cancer	In vivo evaluation of Paclitaxel penetration in bladder tissues was conducted in 4 male beagle dogs. • Intravesical dose of Paclitaxel loaded gelatin nanoparticles containing 1000 µg of drug dispersed in 20 ml of saline was instilled in bladder. A graph was obtained which shows decline of urine Paclitaxel concentrations as a function time in dogs.
Microemulsion containing PLGA	Microemulsion prepared by self microemulsifying drug delivery system (SMEDDS) (a mixture of ,tetraglycol, cremophor ELP, Labrafil 1944 and drug emulsion containing PLGA	Improve release characteristics without any property change and weight loss of PLGA	Breast cancer and human ovarian cancer	In vivo antitumor activity test was done by s.c injection of 0.1ml of SKOV-3 human ovarian cancer cell suspension to the right flank of female nude athymic mice.
Paclical	Mixed micelles preparation developed by Oasmia Pharmaceutical, Sweden in which an amphiphilic synthetic derivative of retinoic acid replaced cremophor EL vehicle.	Effects caused by Cremophor EL in Taxol can be overruled.	leukemia	In vivo hollow model of 3 cell lines namely leukemia CCRF-CEM and myeloma RPMI 8226/S cell lines were used
Intravenous hydrophobic Drug delivery API-1548	Porous particle formulation of Paclitaxel, formed by spray drying.	Rapidly dissolving formulation that could be administered as I.v bolus or short infusion.	Solid tumors	In vivo antitumor efficacy test in mice was done. Three API-1548 concentration was taken and I.v injection into tail vein was given once a day for 5 days and mice were observed for survival, tumor size and body weight.
DHA Paclitaxel	Docosahexanoic acid-Paclitaxel is a novel compound formed by covalently linking natural fatty acids DHA to Paclitaxel	Function as a prodrug and accumulate preferentially in tumor tissue.	Metastatic malignant myeloma	• Phase I: To characterize primary toxicity, MTD and pharmacokinetic profile, patients (n=24) with advanced refractory tumor were chosen. • Phase II: To determine efficacy and tolerability of DHA- Paclitaxel in patients (n=135) with Prostate cancer, breast cancer, malignant myeloma, gastric cancer, esophageal cancer. • Phase III: compare DHA - Paclitaxel with single agent dacarbazine for first line treatment of metastatic malignant myeloma.
Liposomal formulation of Paclitaxel	• Drug to lipid molar ratio, 1:20, liposomes prepared by polycarbonate membrane extrusion. • DPPC/DMPG/Mpeg-DSPE/Biotin PEG-DSPE in molar ratio 85:5:9.5:0.5	• Target folate receptors selectively • overcome vehicle toxicity associated with cremophor based traditional formulation.	tumors	Pharmacokinetic studies: Plasma clearance kinetics of liposomal formulation was compared to cremophor formulation and it was studied that liposomal formulation exhibited much longer half life.
Paclitaxel-β cyclodextrin complex	Drug entrapped in cage like structure of cyclodextrin	Increase aqueous solubility and formulation can be used for hyperthermic intraperitoneal chemoperfusion procedure (HIPEC).	Peritoneal carcinoma	Inclusion efficiency was checked using HPLC analysis
Nanoemulsified Paclitaxel using MPEG-PLGA diblock polymer	Nanoemulsified Paclitaxel using self emulsifying drug delivery system	Good biocompatibility, good solubilization of poorly water soluble drug and high concentration of drug in aqueous media.	Myelomas	Stability analysis was performed over nanoemulsified Paclitaxel.
Oncogel	• CR depot formulation of Paclitaxel in Regel • Non cremophor based formulation.	• Physically target Paclitaxel to tumor site with very little reaching circulation. • Can be used in combination therapy.	Superficially palpable tumors and esophageal carcinoma.	• 3 dose escalating clinical study have been done to date. • Phase I – Inpatients with superficially accessible advanced solid tumor, n=16 for open label study • Phase 2a – adjuvant therapy to R T in patients with esophageal cancer, n=11
Implexus implantable drug delivery system	Gelatin sponge impregnated with poly(lactide-co-glycolide) Paclitaxel (PLGA-PTX) microsphere. Loading of drug is 10%.	Intraoperative placement of PLGA-PTX sponge into surgical field in close proximity to mediastinal lymphatics after resection of primary lung cancer.	Lung cancer	Pharmacokinetic study in rats with regimens taxol 10mg/kg i.p/ PLGA-PTX 100mg/kg i.p/ Taxol 5mg/kg i.v Sponge containing PLGA – PTX 100mg/kg. Results showed that 100-400 fold increase of lymphatic drug exposure compared to I.v exposure.
Magnetic nanoparticle modified Paclitaxel	Prepared by mixing nanoparticles of Fe_3O_4 with water soluble polyaniline derivative SPAN16 and doping with HCl aqueous solution.	Surface of nanoparticles provide function-alized groups for binding enzymes inhibiting aggregation and increase stability allow contrast enhancement for magnetic resonance imaging and magnetic diagnosis.	Prostate cancer	Cell uptake study and in vitro cytotoxicity study was done.
Chitosan derived micelles loaded with Paclitaxel	N-octyl-N-(2-carboxyl-cyclohexamethenyl) chitosan derived micelles loaded with drug.	Selective control of drug concentration and distribution within tumor, excellent bioavailability, high drug loading content and markedly improved bio distribution of poorly water soluble drugs.	Malignant tumors	Characterization of micelles was done and CMC was measured.

CONCLUSION

Paclitaxel is one of the most important and broadest spectrum anticancer drugs approved by FDA for the treatment of cancer. This review provides a complete description of paclitaxel, its Synthesis, SAR, and Mechanism of action, Doses, Production and Formulations with special emphasis on its Novel drug delivery system. Also it highlights how these Paclitaxel formulations is an effective tool in the therapy of cancer.

ABBREVIATIONS USED

EL : Ethoxylated
CrEl : Cremophore ethoxylated
PLGA : Poly (lactic-co-glycolic acid)
DPPC : Dipalmitoyl phosphatidylcholine
DMPG : Dimyristoyl phosphatidylglycerol
DSPE : Distearoyl phosphatidylethanolamine
PEG : Polyethylene glycol
MPEG : Methoxy polyethylene glycol
CR : Cremophor
PTX : Paclitaxel
SPAnNa : Self-doped poly[aniline-cosodium N-(1-one-butyric acid) aniline]

REFERENCES

1. Chunekar K, Pandey GS. 1990. Bhavaprakasa Nighantu of Sri Bhavamisra (Indian Materia Medica). Chaukhambha Bharati Academy, Varanasi.
2. Hartwell J, *et al*. J Am Chem. 1951; 73: 2909-2916.
3. Rowinsky EK, *et al*. Sem Onc. 1992; 19: 646-662.
4. Rowinsky EK, *et al*. Ann Rev Med.1997; 48: 353-74.
5. Kingston DGI. Chem Commun. 2001; 10: 867-80.
6. McGuire WP, *et al*. Ann Int Med. 1989; 111: 273-9.
7. Holmes FA, *et al*. J Nat Cancer Inst. 1991; 83: 1797-805.
8. Rowinski EK, *et al* Pharmacol Ther. 1991; 52: 35-84.
9. Thigpen T, *et al*. Proc Am Soc Clin Oncol. 1990; 9: 156.
10. Einzig AI, *et al*. J Clin Oncol. 1992; 10: 1748-53.
11. Seidman A, *et al*. Proc Am Soc Clin Oncol. 1992; 11: 59.
12. Murphy WKJ, *et al*. Natl Cancer Inst. 1993; 85: 384-8.
13. Wani MC, *et al*. J Am Chem Soc. 1971; 93: 2325.
14. Schiff PB, *et al* Nature. 1979; 277: 665-667.
15. Kingston DGI, *et al*. J Org Chem. 1999; 64: 1814-22.
16. Gabetta B, *et al*. J Nat Prod. 1999; 62: 219-23.
17. Datta, A, *et al*. J Med Chem. 1994; 37: 4258-60.
18. Neidigh K.A, *et al*. Tetrahedron Lett. 1994; 35: 6839-42.
19. Chordia, M.D, *et al*. Tetrahedron Lett. 1994; 35: 6843-6.
20. Marder-Karsenti R, *et al*. J Org Chem. 1997; 62: 6631-7.
21. Gunatilaka AAL, *et al*. J Org Chem. 1999; 64: 2694-703.
22. Yuan H, *et al*. Tetrahedron. 2000; 56: 6407~14.
23. Deutsch H.M, *et al*. J Med Chem. 1989; 32: 788-92.
24. Klein LL, *et al*. Tetrahedron Lett. 1993; 34: 2047-50.
25. Georg GI, *et al*. J Org Chem. 1994; 59: 4015-8.
26. Guéritte VF, *et al*. J Med Chem. 1991; 34: 992-8.
27. Rowinsky E, *et al*. J Natl Cancer Inst. 1990; 82: 1247-1259.
28. Parness J, *et al*. J Cell Biol. 1981; 91: 479-487.
29. Rao S, *et al*. J Biol Chem. 1994; 269: 3132-3134.
30. Rowinsky E, *et al*. New Engl J Med. 1995; 332: 1004-1014.
31. Rowinsky EK, *et al*. Semin Oncol.1993; 20: 16.
32. Rizzo R, *et al*. J Pharm Biomed Anal. 1990; 8: 159.
33. Wiernik PH, *et al*. J Clin Oncol. 1987; 5: 1232.
34. Rowinsky EK, *et al*. Semin Oncol.1993; 20: 16.
35. Weiss R, *et al*. J Clin Oncol. 1990; 8: 1263-1268.
36. Nightingale S. J Am Med Assoc. 1992; 268: 1390–1393.
37. Kramer I, *et al*. Eur Hosp Pharm. 1995; 1: 37-41.
38. Kingston DGI. Pharmacol Ther. 1991; 52: 1-34.
39. Christen AA, *et al*. Proc Am Assoc Cancer Res. 1989; 30: 566-570.
40. Stierle A, *et al*. Science 1993; 260: 214-6.
41. Nicolaou KC, *et al*. J Am Chem Soc. 1995; 117: 624-33.
42. Nicolaou KC, *et al*. J Am Chem Soc. 1995; 117: 634-44.

43. Nicolaou KC, *et al.* J Am Chem Soc. 1995; 117: 645-52.

44. Nicolaou KC, *et al.* J Am Chem Soc. 1995; 117; 653-59.

45. Holton RA, *et al.* J Am Chem Soc. 1994; 116: 1597-8.

46. Holton RA, *et al.* J Am Chem Soc. 1994; 116: 1599-600.

47. Ojima I, *et al.* Tetrahedron. 1992; 48: 6985-7012.

48. Friedland D, et al. J Natl Cancer Inst. 1993; 85: 2036.

49. Venkataraman R, Am J Hosp Pharm. 1986; 43: 2800–2802.

50. Singla AK, et al. Int J Pharmaceutics. 2002; 235: 179.

51. Cristina F, et al. J controlled Release. 2002; 83: 273.

52. Khan W Li, et al. Clinical Cancer Research. 2003; 9: 3441.

53. He L, et al. Int J Pharmaceutics. 2003; 250: 45.

54. Ze Lu, et al. Clinical Cancer Research. 2004; 10: 7677.

55. Bok KK, et al. Int J Pharmaceutics. 2004; 286: 147.

56. Hassan S, et al. Cancer Chemother Pharmacol. 2005; 55: 47.

57. Straub JA, et al. Pharmaceutical Research. 2005; 22: 3.

58. Hennenfent KL, et al. Annals Of Oncology. 2006; 17: 735.

59. Jun WU, et al. Int J Pharmaceutics. 2006; 316: 148.

60. Bouquet W, et al. Europ J Pharmaceutics and Biopharmaceutics. 2007; 66: 391.

61. Lee, et al. Colloids and Surfaces. 2008; 313-314: 126.

62. Nancy L, et al. Advanced Drug Delivery Review. 2009; 61: 785.

63. Liu J, et al. American Association of Cancer Research. 2009; 69: 3.

64. Hua MY, et al. Biomaterials. 2010; 31: 7355.

65. Liu J, et al. Carbohydrate Polymers. 2010; 82: 432.