

**Polymeric Micelles for
Parenteral Drug Delivery:
Application to Paclitaxel
(Genexol-PM)**

**David Young, Sung Chul Kim, Jaewon Yu,
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Outline

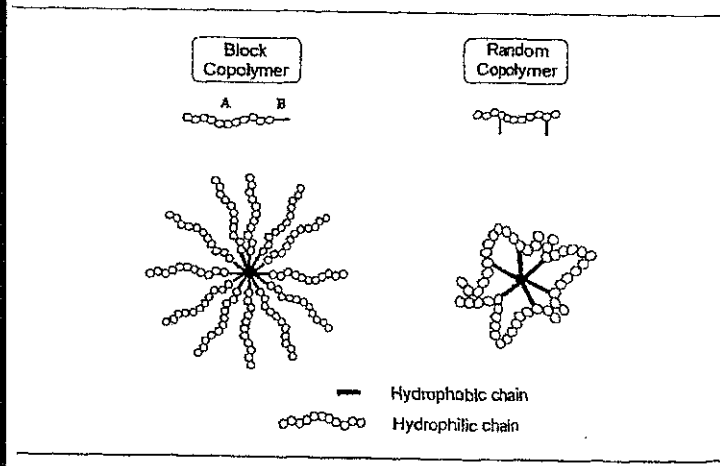
- Polymeric micellar formulations for parenteral delivery
- Genexol-PM (polymeric micellar formulation of paclitaxel)
- In vivo response to Genexol-PM
- Conclusion

Polymeric Micellar Formulations for Parenteral Delivery

What Happens in Micellization?

- Surfactants self-associate to form micelles and aggregates where hydrophobic regions are shielded from aqueous contact by hydrophilic regions
- The hydrophobic region provides an environment where hydrophobic compounds can be solubilized
- The aggregate and micelle structure depend on the type of surfactant and solution condition (e.g, pH, temperature, ionic strength).

Figure 9.2.2 Schematic representation of block and random copolymer micelles. Reproduced from Jones and Leroux (1999) with permission. [Source: Reprinted from *Eur. J. Pharm. and Biopharm*, 48, M. C. Jones and J. C. Leroux, Polymeric micelles—a new generation of colloidal drug carriers, p. 102, 1999, with permission from Elsevier Science.]



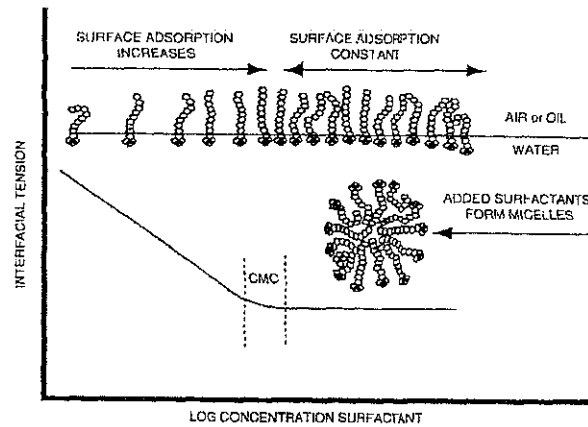
General Characteristics of Polymeric Micelles

- The surfactants used are actually copolymers composed of several different monomer units
- The copolymers have hydrophilic and hydrophobic components
- Poorly aqueous soluble compounds can be solubilized within the hydrophobic core and within the head group at the surface of the micelle

General Characteristics of Polymeric Micelles

- Micelles are dynamic structures with a frequent exchange of monomer surfactant between the micelles and the solution
- The self-association of the surfactant decreases interfacial tension

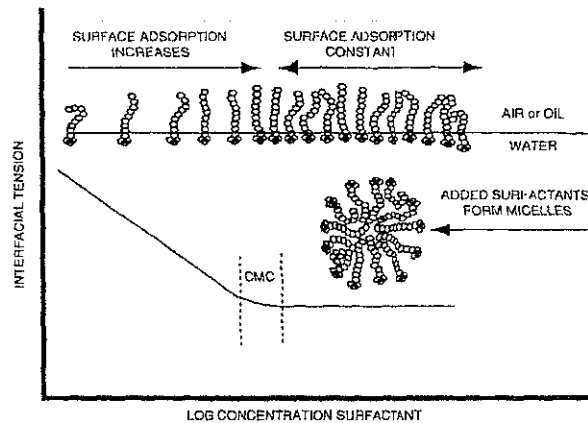
Figure 9.1.4 Schematic showing surfactant adsorption. Surfactants adsorb strongly to an air-water interface or a water-oil interface (top). The accompanying reduction of interfacial tension (in accordance with the Gibbs adsorption equation, i.e., Equation 1) ceases in a narrow concentration range (the critical micellization concentration: CMC). At concentrations above this range, added surfactants will aggregate to form micelles. [Source: Reprinted from *Surfactants in Cosmetics*, 1985, edited by M. M. Rieger, p. 56, by courtesy of Marcel Dekker, Inc.]



General Characteristics of Polymeric Micelles

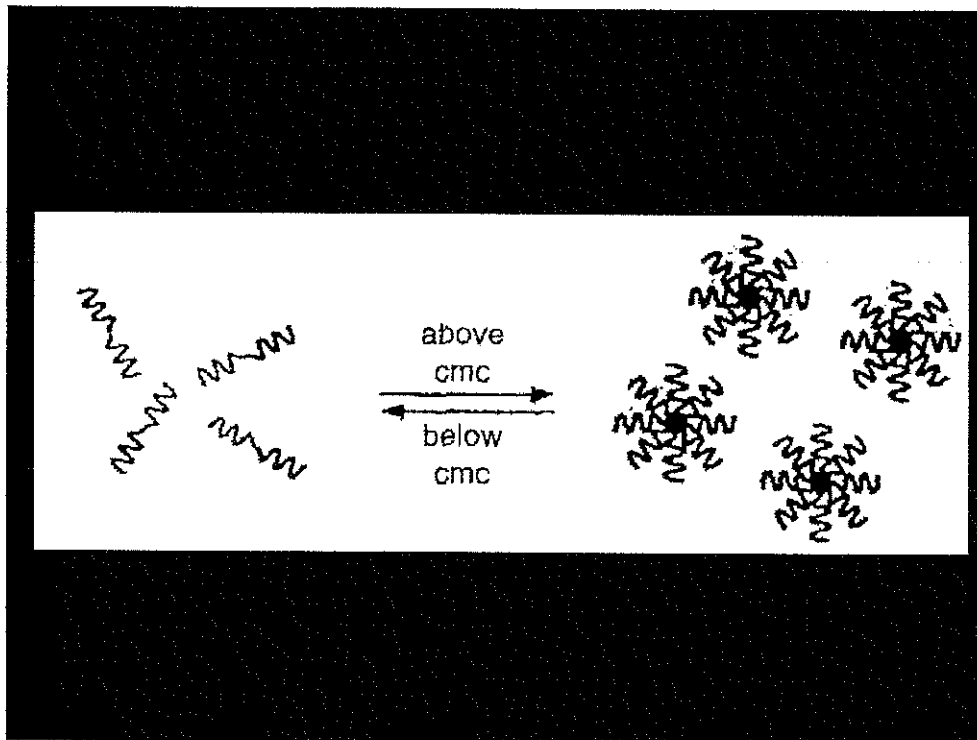
- Polymers can
 - Have lower toxicity,
 - Prevent adsorption of immunoglobulins,
 - Adhesion of drug micelles onto surfaces of phagocytes,
 - Circulate in blood stream without immobilization in capillaries,
 - Be biodegradable

Figure 9.1.4 Schematic showing surfactant adsorption. Surfactants adsorb strongly to an air-water interface or a water-oil interface (top). The accompanying reduction of interfacial tension (in accordance with the Gibbs adsorption equation, i.e., Equation 1) ceases in a narrow concentration range (the critical micellization concentration; CMC). At concentrations above this range, added surfactants will aggregate to form micelles. [Source: Reprinted from *Surfactants in Cosmetics*, 1985, edited by M. M. Rieger, p. 56, by courtesy of Marcel Dekker, Inc.]



Critical Parameters for Solubilization, Micelle Formation

- Critical Micelle Concentration (CMC) is the concentration of copolymer surfactant:
 - Which minimizes the interfacial surface tension, allowing for surfactant self-association for micelle formation
 - Below which only single chains are present and above which single chains and micelles coexist
- CMC is a function of:
 - Surfactant (type of copolymer, hydrophobic-hydrophilic regions of copolymer)
 - Condition of solution (e.g., pH, temperature, ionic strength)



Critical Parameters for Solubilization, Micelle Formation

- Critical Micelle Temperature (CMT) is the temperature:
 - Below which only single chains are present
 - Above which single chains and micelles coexist
- CMT is a function of:
 - Surfactant (type of copolymer)
 - Condition of solution (e.g., pH, concentration of copolymer, ionic strength)

Figure 9.2.6 (A) Phase diagram of 17R4 in water. Regions I, II, and III are the one-phase unimer region, one-phase micelle region, and two-phase region of two immiscible isotropic solutions, respectively. (B) Phase diagram of 164 in water. Also, three phase regions are shown. See text for an explanation of the symbols and curves. [Source: Reprinted from *Macromolecules*, vol. 27, by Z. Zhou and B. Chu, Phase behavior and association properties of poly (oxypropylene)-poly (oxyethylene)-poly (oxypropylene) triblock copolymer in aqueous solution, p. 2699, with permission from American Chemical Society.]

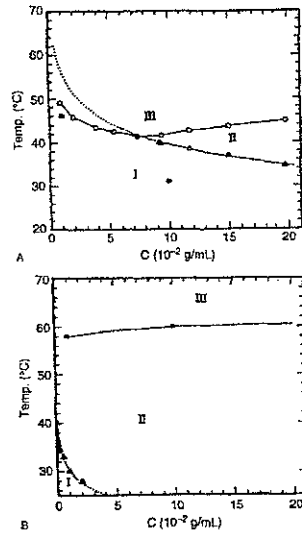


Table 9.2.2
Solubilizing Capacities and Partition Coefficients of Diazepam
as a Function of Temperature, Taken from Lin and Yang (1987)

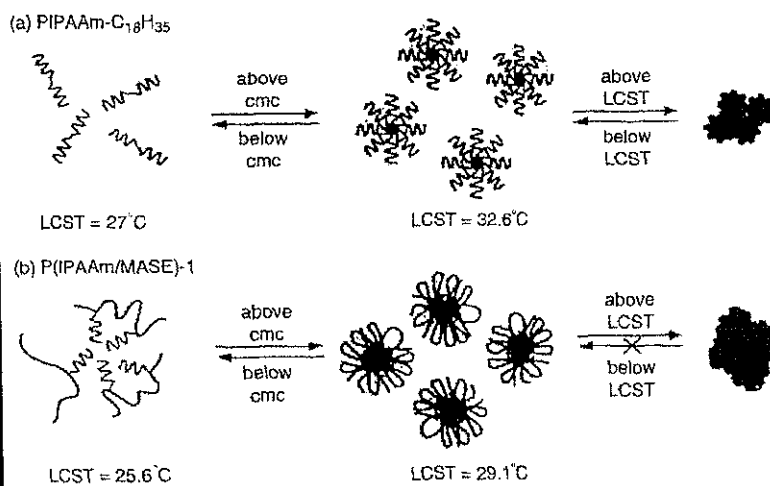
Pluronics	Solubilizing Capacity*			Partition Coefficient (K_m)		
	25° C	37° C	50° C	25° C	37° C	50° C
F-68	0.0253	0.0522	0.1811	272.32	460.37	1292.76
F-88	0.0334	0.1206	0.3167	358.77	1059.43	2464.44
F-108	0.0342	0.3751	0.6771	367.38	3326.63	4294.74

*units: mol diazepam/mol Pluronic

Critical Parameters for Solubilization, Micelle Formation

- Lower Critical Solution Temperature (LCST)
 - Temperature above which the polymer solution phase separates
 - Solution with the single chains and micelles can both phase separate (usually at different temperatures)

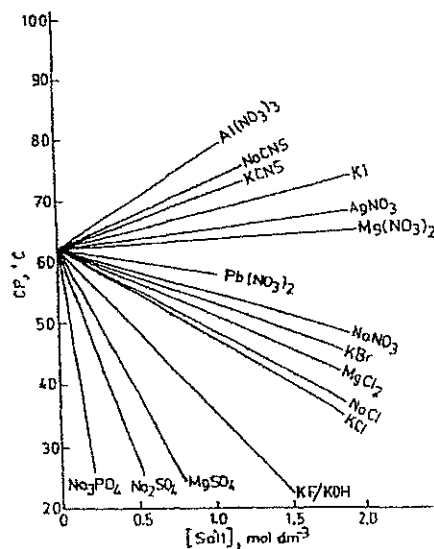
Figure 9.2.7 Schematic of micellar structure and thermoresponsive reversibility of PIPAAm- $C_{18}H_{35}$ and P(IPAAm-MASE)-1. [Source: Reprinted from *J. Controlled Release*, 53, I. E. Chung et al., effects of molecular architecture of hydrophabically modified poly (N-isopropylacrylamide) on the formation of thermoresponsive core-shell micellar drug carriers, pp. 119–130, 1998, with permission from Elsevier Science.]



Critical Parameters for Solubilization, Micelle Formation

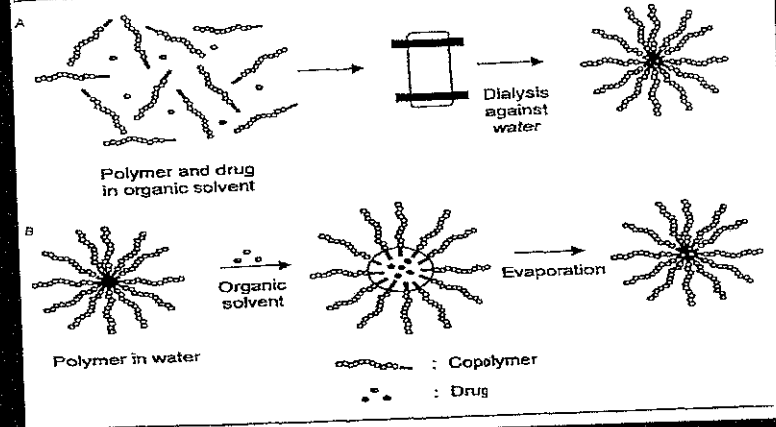
- Micelle Size
 - Sensitive to same conditions as CMC
- Hydrophile-Lipophile Balance (HLB)
 - Expression of hydrophilic and hydrophobic character of the surfactant
- Excipients (e.g., inorganic salts)

Figure 9.2.8 Cloud point of L-64 in aqueous salt solutions. [Source: Reprinted from *J. Macromol. Sci.-Pure Appl. Chem.*, A30, K. Pandya et al., Effect of additives on the clouding behavior of an ethylene oxide-propylene oxide block copolymer in aqueous solution, pp. 1-18, 1993 by courtesy of Marcel Dekker, Inc.]



Manufacturing Process

Figure 9.2.18 Drug loading of polymeric micelles by the dialysis (A) and the oil-in-water emulsion methods (B). Reproduced from Jones and Leroux (1999) with permission.

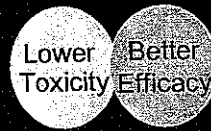


Genexol-PM Formulation

Objectives

1. Maximizing the water solubility of paclitaxel
2. Minimizing the systemic toxicity related to vehicle

Maximizing the administrable amount of paclitaxel

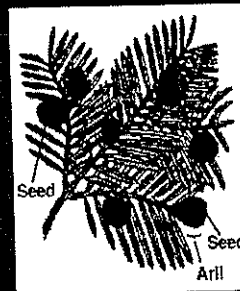


Genexol®-PM

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Paclitaxel

- Isolated from the bark of *Taxus brevifolia* in 1971
- Promotes the polymerization of tubulin into microtubules and inhibits depolymerization
- Approved for treatment of different types of cancer
- Poor solubility in water (0.7 ~ 30 $\mu\text{g}/\text{ml}$)



Genexol®-PM

SAMYANG CORPORATION

Current Formulation: Taxol® (BMS)

- Composition (a vial)
 - Paclitaxel: 30 mg
 - Cremophor EL / Ethanol (1/1, v/v): 5 ml
- Disadvantages
 - Hypersensitivity reactions
 - Premedication required
 - Dose limitation



Genexol®-PM

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Alternative Formulations of Paclitaxel

Formulations	Solubility of paclitaxel (mg/ml)
✓ Co-solvents/Emulsions	0.2 ~ 75
Soybean oil	0.3
PEG 400 (75%)	31
Triacetin	75
✓ Liposomes	1.0
✓ Nanocapsules	0.6
✓ Mixed micelles	0.4 ~ 1.3
✓ Prodrugs	
C-2' esters	up to 666
C-7' esters	~10
✓ Cyclodextrins	0.02~34.1
✓ PEG-Cyclodextrin Micels	30-50

Genexol®-PM

SAMYANG CORPORATION

Product Description



☐ **Pharmaceutical Form**
Lyophilisate for reconstitution

☐ **Compositions**

Paclitaxel (Genexol [®])	100 mg
mPEG-PDLLA	500 mg
Lactose anhydrous	250 mg



Genexol[®]-PM

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What is GENEXOL[®] ?

GENEXOL[®] is the Samyang Genex's trade name of the anticancer drug, Paclitaxel



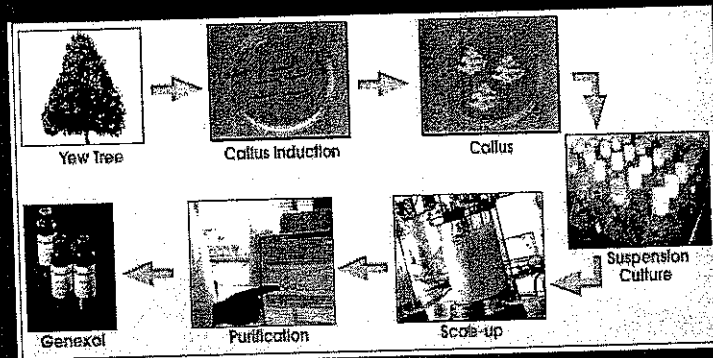
$C_{47}H_{51}NO_{14}$, F.W. 853.9, m.p. 213-216

Genexol[®]-PM

SAMYANG CORPORATION

GENEXOL® (PACLITAXEL)

GENEXOL® is a registered trademark of Samyang Genex for Paclitaxel and is manufactured from the explants of *Taxus chinensis* by plant cell culture technology under cGMP.



Estimated Capacity (2003) : 100 kg

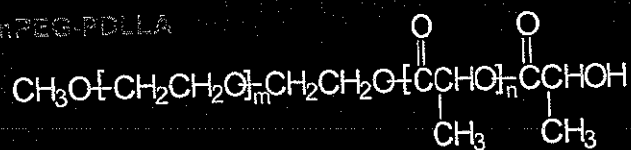
<http://www.genexol.com>

Genexol®-PM

SAMYANG CORPORATION

METHOXY POLY(ETHYLENE GLYCOL)- POLY(D,L-LACTIDE)

mPEG-PDLLA



- Average Molecular Weight : 3,700 Daltons
- Polydispersity : 1.02 ~ 1.2
- PEG content : 54 wt %
- Synthesized by ring opening polymerization
- Forms stable micelles

GMP

Genexol®-PM

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Determination of Critical Micelle Concentration (CMC)

Surfactants	CMC (mg/ml)
mPEG-PDLLA	0.007 ^{a)}
Lutrol F68	0.5
Sodium Lauryl Sulfate	1.0

^{a)}determined by spectrofluorometer (HITACHI F 4010)

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Biocompatibility Studies of mPEG-PDLLA

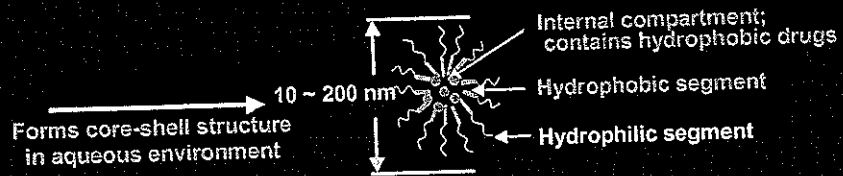
Test Items	Results
Irritation: Intracutaneous Tox.	No irritation
Sensitization	No sensitization
Genotoxicity	No mutagen
Hemo-compatibility	No hemolysis
Cytotoxicity	No cytotoxicity
Sub-chronic toxicity:i.v.	No toxicity
Systemic toxicity	
Material mediated pyrogen	Non-pyrogenic
Bacterial endotoxin	No endotoxin

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GENEXOL-PM

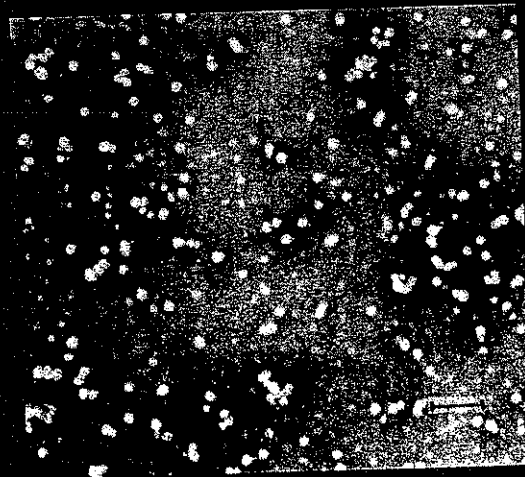
Amphiphilic Block Copolymer



Average Particle Size of Genexol®-PM (after reconstitution) ... 20~50 nm

Genexol®-PM

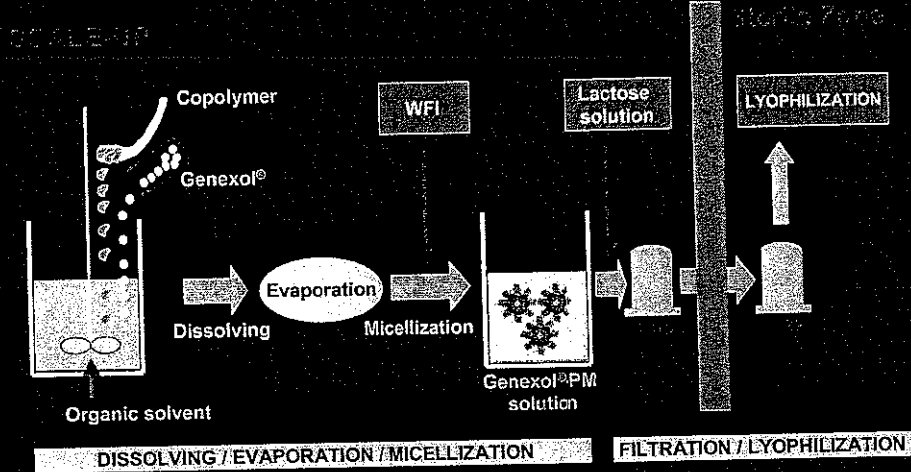
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GENEXOL®-PM

Manufacturing Summary

GMP



Genexol®-PM

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GENEXOL®-PM



- ✓ Mw : 3,700
- ✓ Pd : 1.02 - 1.2
- ✓ Ring opening polymerization
- ✓ PEG content : 54 wt%

- ✓ Paclitaxel
- ✓ Mw : 853.9
- ✓ Solubility in water : ~1 µg/ml
- ✓ Plant cell culture
- ✓ Samyang Genex Co.

- ✓ Polymeric micelles
- ✓ Size : 10 - 60 nm
- ✓ Genexol content : 16.7 %
- ✓ Solubility in water : ~50 mg/ml Genexol®
- ✓ Transparent in water

Genexol®-PM

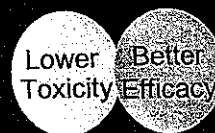
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Critical Parameters for Solubilization, Micelle Formation

- Critical Micelle Concentration (CMC)
- Critical Micelle Temperature (CMT)
- Lower Critical Solution Temperature (LCST)
- Hydrophile-Lipophile Balance (HLB)
- Excipients (e.g., inorganic salts)
- Manufacturing process as it relates to the above parameters (e.g., temperature of WFI since it can alter temperature of solution –CMT, LCST)

In Vivo Objectives

- Reduce Toxicity Higher Dose Administration
- Increase Tumor Site Concentration Maximize Therapeutic Efficacy
- Reduce Hypersensitivity Reaction Eliminate Premedication



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Acute Toxicity Study in Rats

- Animals : SPF Sprague Dawley Rat, 5 rats/sex per group

Compounds	LD ₅₀ (mg/kg)	
	Male ^{a)}	Female ^{a)}
Genexol [®] -PM	205.4	221.6
Taxol [®]	8.3	8.8
Genexol [®] -PM vehicle	>15,000 (2,000 mg)	>15,000
Taxol [®] vehicle	2,650 (17.3 mg)	2,430 (15.8mg)

^{a)}Dosing Scheme : single dose i.v. bolus

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5-Cycle Neurotoxicity Study in Mice

• Comparison:

- Genexol[®]-PM MTD > Taxol[®] MTD
- Genexol[®]-PM groups showed no important post-dosing reactions; Taxol[®] groups had post-dosing reactions to the vehicle
- Genexol[®]-PM groups showed distended abdomens and hair loss
- Genexol[®]-PM 120 mg/kg showed no important neurotox changes, while 280 mg/kg (840 mg/m²) produced neurotox seen around the end of 3rd cycle

Maximum Tolerated Dose (MTD)

	Genexol [®] -PM	Taxol [®]
Dosing scheme	Slow i.v. bolus over 5 min.	
Groups	0, 120 & 280 mg/kg 10/sex/group	0 & 9 mg/kg 10/sex/group
MTD	≥120 mg/kg	≥9 mg/kg

Genexol[®]-PM

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Pharmacokinetics of GENEXOL[®]-PM

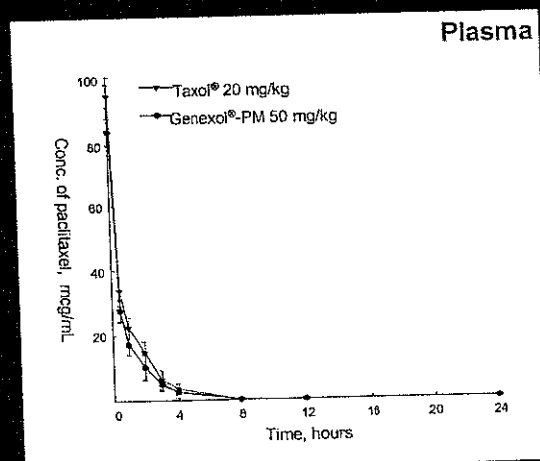
STUDY DESIGN

- Animal: Female C57BL/6 mouse ; 18~22 g
- Subcutaneous inoculation of murine B16F10 melanoma
- Treatment initiated after tumors reach 50-400 mm³
- Group and Dose:
 - Genexol[®]-PM (50 mg/kg, n=4)
 - Taxol[®] (20 mg/kg, n=4)

Genexol[®]-PM

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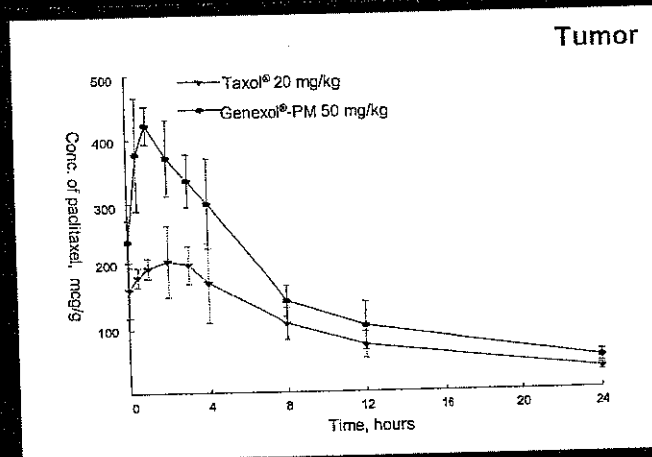
Pharmacokinetics of GENEXOL[®]-PM



Genexol[®]-PM

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Pharmacokinetics of GENEXOL[®]-PM



Genexol[®]-PM

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In-Vivo Anti-Tumor Efficacy

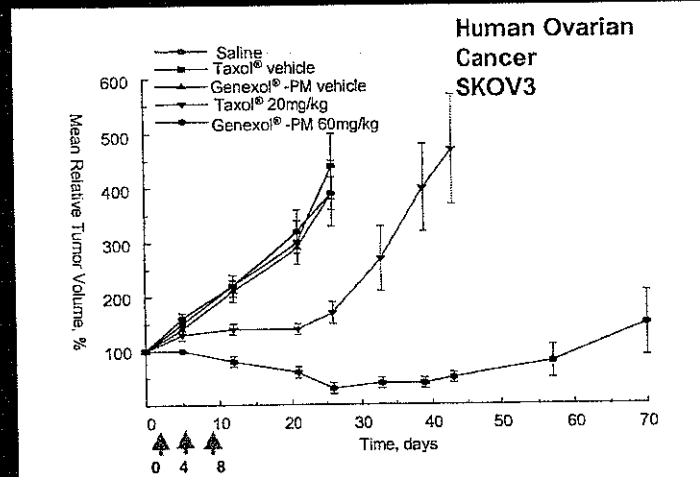
STUDY DESIGN

- Mice: Female nude (nu/nu) athymic mice; 22.0~34.0 g
- Subcutaneous implantation of human ovarian SKOV3 tumor
- Treatment initiated after tumors reach 50-300 mm³
- Intravenous bolus, Q1D x 3 (0, 4, 8 days)
- Group and Dose:
 - Salin (n=10)
 - Taxol[®] vehicle (n=10)
 - Genexol[®]-PM vehicle (n=10)
 - Taxol[®] (20 mg/kg; n=9)
 - Genexol[®]-PM (60 mg/kg; n=8-9)

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In-Vivo Anti-Tumor Efficacy



Genexol®-PM

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GENEXOL®-PM Phase I in Korea: Status

Patient's	Cancer	Dose (Paclitaxel mg/m ²)	Cycles	Status
1	Ampullar of Vater	135	2	Close-out, Progressive Disease
2	Chest Wall	135	9	No Change
3	Lung	135	4	Close-out, No Change
4	Lung	175	5	Partial Response
5	Esophagus	175	2	Close-out, No change
6	Lung	175	4	Close-out, Progressive Disease
7	Breast	230	3	Close-out, Progressive Disease
8	Adenocarcinoma	230	2	Close-out, Progressive Disease
9	Lung	230	2	Close-out, Progressive Disease
10	Kidney	230	1	Close-out, Progressive Disease
11	Ovary	230	2	TBD
12	Lung	230	1	TBD
13	Lung	300	1	Ongoing

Continuing : 300 mg/m² Next dose : 300 mg/m², 600 mg/m²

* 3-hour infusion, no premedication, dosed at same level every 3 weeks (cycle); tumor response measured every 2 cycles

Genexol®-PM

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GENEXOL®-PM US CLINICAL INVESTIGATION

- **Samyang has an IND in the US**
- **Phase I clinical studies are beginning**
- **Believe that Genexol®-PM has a significant clinical advantage over Taxol®**

Genexol®-PM

SAMYANG CORPORATION

Conclusions

- **Polymer Micelle formulations are a useful delivery system for parenteral administration**
- **Genexol®-PM has several advantages compared to Taxol®**
 - **Less toxic due to Cremopor EL free formulation**
 - **Increase in maximum tolerated dose (MTD)**
 - **More effective anti-tumor activity in accordance with the increased dose**
- **Genexol®-PM is being investigated in the US and in Korea as an alternative formulation with therapeutic advantages over Taxol®**

Genexol®-PM

SAMYANG CORPORATION

Acknowledge

- **Samyang**
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 - Staff

Scientific Advisory Board

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