Docosome: Liposomes of Docetaxel Freeze dried powder filled in vials to be reconstituted for intravenous injection

IDENTIFYING LICENSING PARTNERS



Delhi — Bangalore — Pune — California

Presentation Plan

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INTRODUCTION TO DOCOSOME

A Patented product in India, Docosome is a product which contains Docetaxel and is available as dry powder for reconstitution before Intravenous administration.

Docetaxel is mainly indicated for treatment of cancer by virtue of being a Broad Spectrum anti-neoplastic agents. It is a BCS class IV drug with log P of 2.4 and practically insoluble in water.

DOCOSOME: USPs



DOCOSOME : COMPLETED STUDIES



Long Term
 Accelerated
 Reconstitution
 Stability Studies

In- vitro cell
 cytotoxicity against
 MCF-7 cell lines

In-vivo
pharmacokinetic and
pharmacodynamic
study of docetaxel

TECHNOLOGY OFFER Vitamin E TPGS functionalized of Liposomes of Docetaxel

TRADE-DRESS

• Freeze dried powder filled in vials to be reconstituted for intravenous injection.

• About 58.73-fold increase in *in-vitro* cell cytotoxicity against MCF-7 cells of docetaxel (DTX) upon incorporation in to vitamin E TPGS functionalized liposomes (TPGS-liposomes-DTX) as compared to free drug when incubated for 48 h.

CRITICAL PRODUCT PERFORMANCE

• About **12.73-fold and 21.31-fold enhancement in circulation half-life** of docetaxel upon incorporation in to TPGS-liposomes-DTX(TPGS-Liposomes-Docetaxel) as compared to Taxotere[®] and free drug, respectively.

• About **80.21 % reduction in the tumor burden** in case of large tumors (>1000 mm3) and almost complete reduction in tumor volume (non-measurable) in case of small tumors (<1000 mm3.) after 10 days upon intravenous administration of TPGS-liposomes-DTX in contrast to **170 % increase in tumor burden in case of untreated animals**.

CRITICAL PRODUCT PERFORMANCE.....Continuation

- The developed formulation does not pose any vehicle associated toxicity and hence does not require any concomitant use of corticosteroids as found in case of Taxotere[®].
- Data available for stability of formulation at accelerated stability conditions is for 6 months, carried out as per ICH guidelines. Parameters evaluated include particle size, PDI and assay.
- The developed formulation showed significantly lesser hepatotoxicity and nephrotoxicity as compared to marketed formulation Taxotere[®].

> ADVANTAGES OF DOCOSOME

- The excipients used in formulation are **GRAS listed**, relatively **inexpensive** and readily **available**.
- The formulation has been designed based on **optimization strategy** and is also compatible for **QbD approach**.
- Significant increase in the preclinical therapeutic efficacy and safety profile of the developed formulations will have significant improvement in the patient compliance and thereby marketability.

> **DEVELOPMENT STATUS**

• Laboratory scale; Data available for *in vitro* cell cytotoxicity against MCF-7 cell lines, *in vivo* pharmacokinetics and pharmacodynamics at preclinical level and stability studies for 6 months at accelerated conditions as per ICH guidelines.

> TECHNICAL SPECIFICATIONS

• Surface modified liposomes loaded with DTX for targeted delivery at tumor site and reduced toxicity were developed. The developed system comprises of TPGS which is amphipathic and hydrophilic and exhibits the characteristics of a typical surface active agent (HLB 13-15) which suggests that it can also be used as an emulsifier, solubilizer, absorption enhancer, and a vehicle for lipid based drug delivery formulations. It is further reported to enhance the cytotoxicity of various anticancer drugs and inhibit P-glycoprotein mediated multi-drug resistance (MDR), thereby increasing the overall therapeutic efficacy of the formulation.

BRIEF BACKGROUND

Cancer :

- Uncontrolled growth of abnormal cells in the body
- Second leading global killer, accounting for 12.5% of all deaths across the world.
- Efficacy of conventional therapies enhances by utilizing the targeting potential of the nanoparticles.

Liposomes:

- Highly effective in cancer therapeutics.
- Major breakthrough in the field of liposomes technology that came is Pegylated liposomes, which can easily evade recognition by reticuloendothelial system (RES).
- The half life of liposomes is raised from several minutes to several hours, changing their pharmacokinetics from saturable and dose dependent to dose independent.
- Recently, vitamin E TPGS (D- α -tocopheryl PEG 1000 succinate) has been successfully utilized in numerous drug carrier formulations like microemulsions, micelles, nanoparticles and solid dispersions. TPGS is the one of the most investigated ester with reference to drug solubilization and drug delivery of poorly water soluble drugs.

> DRUG PROFILE

• Docetaxel (DTX) is an antineoplastic agent belonging to the second generation of the taxoid family and was taken as model drug to establish the effectiveness of the developed formulation strategy.

• BCS class IV drug with log P of 2.4 and practically insoluble in water.

• The current formulation of docetaxel, Taxotere[®], contains Tween 80 and ethanol as the solvent, and adverse reactions due to either the drug itself or the solvent system have been reported in patients (e.g., hypersensitivity, fluid retention).

>IN -VIVO PHARMACOKINETICS

>FORMULATION CHARACTERISTICS

Parameters	TPGS-liposomes-DTX
Particle size	112.7 \pm 10.01 nm
PDI	0.18 ± 0.01
Zeta potential	$\textbf{-1.19} \pm \textbf{0.98} \text{ mv}$
Entrapment efficiency	83.63 ± 2.16
Particle drug loading	6.92 ± 0.18%

>CELL CYTOTOXICITY

Formulation	IC50 (μg/ml)
Free DTX	$\textbf{2.53} \pm \textbf{0.37}$
Liposomes-DTX	$\textbf{0.35} \pm \textbf{0.16}$
PEG-liposomes- DTX	$\textbf{0.16} \pm \textbf{0.05}$



Figure: Plasma Concentration Profiles of DTX after i.v. administration of DTX solution ,Taxotere, DTX loaded pain ,PEGylated and TPGS functionalised Liposomes in rats (2 mg/kg as DTX)

> Pharmacokinetic parameters of various DTX loaded formulations

Formulations	C30 (ng/ml)	AUC (ng*hml-1)	T1/2 (h)	MRT (h)
Free Drug	1708.675±25.4	4209.92 ± 34.22	0.95±0.08	1.6±0.28
Taxotere®	1575.84±41.34	4023.59±84.58	1.59±0.54	2.143±0.94
Lposomes-DTX	960.98±40.26	6012.41±401.283	3.32±0.612	4.89±0.952
PEG-Liposomes-DTX	896.84±29.61	13144.74±360.45	15.57±0.76	18.688±2.57

TPGS liposomes-DTX and PEG liposomes-DTX showed increase in half-life by 12.73 folds and 9.79 folds, respectively as compared to Taxotere[®] and 21.31 folds and 16.38 folds, respectively as compared to free DTX



Figure: Comparison of % change in tumor volume and % tumor burden of different formulation in large tumors (>1000) mm3)



Figure: Comparison of % change in tumor volume and % tumor burden of different formulations in small tumors (< 1000 mm³). (***=significant difference at p<0.001%,**=significant difference at p<0.001%,*=significant difference at p<0.05%)

- 170 % increase in the tumor volume in untreated animals
- ✓ 14.67 % decrease in tumor volume in large tumors (>1000 mm³) in free DTX
- ✓ 46.39% decrease in tumor volume in large tumors (>1000 mm³) in Taxotere[®]
- ✓ 80.21% reduction in tumor volume in large tumors (>1000 mm³) in TPGS-liposomes-DTX
- ✓ Complete reduction (non measurable) in tumor volume in small tumors (<1000 mm³) in TPGS-liposomes-DTX



difference at p<0.05, a=compared to control)

100 % mortality (instant death) in Taxotere without prophylactic and concomitant use of corticosteroids
 Severe tail necrosis in Taxotere even with prophylactic and concomitant use of corticosteroids
 100 % survival in TPGS-liposomes-DTX without prophylactic and concomitant use of corticosteroids
 No tail necrosis in TPGS-liposomes-DTX even without prophylactic and concomitant use of corticosteroids
 The developed formulations showed significantly lesser toxicity as compared to marketed formulation, Taxotere®
 The levels of biochemical parameters were comparable to that of control revealing negligible toxicity



Figure: Toxicity in tail of mice upon intravenous administration of various DTX loaded formulations

SUMMARY

The developed surface functionalized liposomes could be employed as effective tumor targeting carrier for delivery of various anticancer agents. The said formulation strategy exhibits following characteristics:

TPGS-liposomes-DTX were prepared by thin film hydration method and were found to have particle size 112.7 nm, PDI <0.2 and entrapment efficiency 83.63 %.

The developed formulation was freeze dried by a patented universal step wise freeze drying cycle using suitable cryoprotectants.

- Freeze dried formulation was found to be stable when stored in accelerated stability condition for 6 months.
- Significantly higher *in-vitro* cell cytotoxicity against MCF-7 cells of docetaxel was observed upon incorporation in to surface functionalized liposomes as compared to plain liposomes and free drug.
- Significant increase in the circulation half-life of docetaxel upon incorporation in to surface functionalized liposomes as compared to plain liposomes and free drug.
- Significantly higher decrease in the tumor burden in animals in DMBA induced breast cancer tumor model as compared to marketed formulation.

The developed formulation showed significantly lesser hepatotoxicity and nephrotoxicity as compared to marketed formulation.

≻IP STATUS:

Indian Patent Application and PCT filing under process.

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