RESEARCH ENVISAGE & PLAN OF WORK

Aim:

The present research work was aimed at development, optimization and characterization of two types of nanoparticulate systems: (A) Nanostructured Lipid Carriers (NLCs) of PTX, Gen and the combination of PTX+ Gen (B) PLGA based polymeric nanoparticles of, PTX, Gen and the combination of PTX+ Gen for achieving improved and safe treatment of ovarian cancer.

Objective:

Objective of the study was to achieve better treatment of ovarian cancer by developing nanoformulation of PTX, Gen and their combination.

Rationale of the study:

Paclitaxel is a first line chemotherapeutic drug but the marketed formulation (Taxol) sufferers from the disadvantage of hypersensitivity reactions to the patient after administration which are due to the presence of Cremophore EL as a solvent used to solubilize the highly lipophilic drug. Moreover, Paclitaxel also causes serious side effects like neutropenia to the patients which are dose related side effects. So, it was the need of the hour to have some alternative formulation of Paclitaxel for the treatment of ovarian cancer with the absence of any serious side effects and could release the drug for a prolonged period of time to reduce the dosing frequency and also to reduce the dose of the PTX which is costly, therefore, the therapy will become economically

viable. Further, Genistein, an isoflavenoid also known as "Phytoestrogen" also exhibits anticancer, antioxidant and anti proliferation properties and has more potential for ovaries as it binds to the estrogen receptors present there. So, it was hypothesized that, if paclitaxel could be entrapped into lipid as well as in polymeric matrix, the nanoparticles can provide sustained release and due to passive targeting of tumor by EPR effect; they will be more effective at the site of action without causing toxicity to the normal tissues. Also, with the entrapment of genistein along with paclitaxel in a synergistic ratiometric drug combination, the anticancerous effect will be more pronounced and the side effects will be lesser due to protective properties of genistein and also due to reduction of dose and dosing frequency of paclitaxel, which will also produce a cost effective treatment of the ovarian cancer.

Plan of work:

- **Preformulation studies:**

- HPLC method development and validation for the estimation of Paclitaxel (PTX), Genistein(Gen) and their combination (Gen+PTX)

- Synergism analysis of ratiometric drug combination based on Chau Talalay principle.

- **Formulation development and optimization**

- Screening of components for the formulation of nanostructured lipid carriers

- Screening of parameters by Placket Burman design

- Optimization by Box-Behnken Design
- Formulation of Nanostructured lipid carriers (PTXNLCs, GenNLCs & PTX+Gen NLCs)
- Optimization of polymeric nanoparticles by Box-Behnken Design
- PLGA based polymeric nanoparticles (PTX, Gen & PTX+Gen loaded)`

❖ **Physicochemical characterization studies**

- Particle size & PDI
- Zeta potential
- Entrapment Efficiency
- TEM(Transmission Electron Microscopy) & AFM (Atomic Force Microscopy)
- Stability

❖ **In Vitro evaluations**

- In vitro release
- In vitro cytotoxicity
- Haemolysis and Platelet Aggregation

❖ **In vivo evaluations**

- Pharmacokinetic studies
- In vivo anticancer activity of dual drug loaded formulations.
- Biochemical estimations.