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### **Preparation and Characterization of Letrozole-Loaded Poly (D,L-Lactide) Nanoparticles for Breast Cancer Therapy**

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#### Introduction

Breast cancer has been ranked first as the most prevalent type of cancer and the leading cause of cancer-related mortality among women worldwide. Letrozole (LTZ), an aromatase inhibitor, has been shown to be an effective and relatively safe agent for the treatment of hormonally-positive breast cancer in postmenopausal women. However, the drug suffers from poor water solubility and rapid metabolism, leading to low oral bioavailability, and thus, lower anticancer effects at target sites. Interestingly, polymer-based nanoparticles (NPs) have been reported to be effective drug delivery systems as integrating drugs into these carriers have presented substantial improvements in drugs tissue distribution and tissue selectivity with superior pharmacokinetic profiles. Therefore, this study was designed to incorporate LTZ into an FDA approved polymer; poly (D,L-Lactide) (PDLLA) nanoparticles to improve its physiochemical properties and bioavailability.

#### Methods

Emulsion-solvent evaporation technique was used to produce LTZ-PDLLA NPs. Briefly, 250 mg PDLLA was mixed with different w/w ratios of LTZ (10-30%) in 20 ml dichloromethane. The prepared solution was slowly poured via a syringe into an aqueous phase (140 ml) to form an emulsion which was followed by a two-step sonication. The emulsion was sonicated using Branson® B5510 ultrasonic cleaner at 40 KHz frequency for 30 minutes, vortexed for 2 minutes, then sonicated again for another 30 minutes. Solvent was allowed to evaporate completely by stirring for 2 hours at room temperature. The resultant dispersed particles were centrifuged at 8500 rpm, 5 oC for 2 hours. Supernatant was discarded and the pellet comprising the NPs was dried under vacuum over 48 hours. The obtained

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NPs were characterized using Scanning Electron Microscope (SEM), Zetasizer, Differential Scanning Calorimeter (DSC), X-Ray Diffractometer (XRD), & Ultra Performance Liquid Chromatography (UPLC).

## Results

LTZ-PDLLA nanoparticles were prepared with a high yield that reached 85%. The NPs were spherical in shape with smooth surfaces across all LTZ loadings. An increase was seen in particle size from 242 nm to 365 nm upon increasing LTZ concentration from 0% to 30% w/w. Such finding was expected since larger contents of LTZ would definitely contribute to the increase in the diameter of the enclosing polymer. Particles were polydisperse in general with a polydispersity index (PDI) ranging from 0.38 to 0.44 and this was mainly due to the fact that non-uniform force was applied to each droplet injected into the aqueous medium while producing the emulsion. DSC and XRD analyses confirmed the crystalline nature of LTZ that was lost after being incorporated into the amorphous polymer, PDLLA. This will have a great impact on the dissolution rate and later on the release rate from PDLLA in which amorphous particles tend to be released easily and in a more controlled fashion than crystalline counterparts. The actual content of LTZ loaded inside PDLLA was expressed as entrapment efficiency and calculated via UPLC analysis through subtracting the amount of LTZ present in the supernatant from the initial amount of LTZ added in each formulation. Very high entrapment efficiency was obtained with all formulations ranging from 87.9% with 10% LTZ-PDLLA up to 96.7% with 30% LTZ-PDLLA. As such, high concentrations of LTZ can be delivered to the target sites with minimum drug loadings.

## Conclusion

LTZ-PDLLA nanoparticles were successfully prepared with high entrapment efficiency using emulsion-solvent evaporation technique. The physicochemical properties and entrapment efficiency were dependent on LTZ concentration. Future work should focus on reducing the wide size distribution by formulating monodisperse particles which would allow uniform tissue distribution and longer sustained release actions upon administration. Additionally, in-vitro testing is needed to evaluate the efficacy and safety of the new formulations.