Docetaxel and Disulfiram Loaded Tumor Extracellular pH Responsive Nanocarrier for Targeting Cancer Stem Cells

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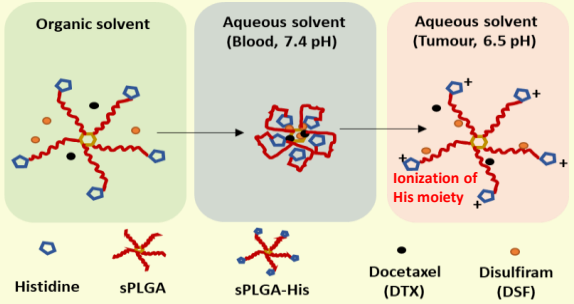
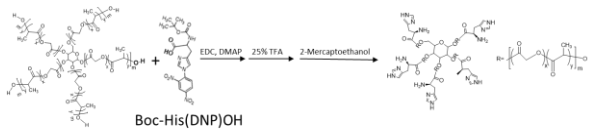
Introduction

DTX is a potent anticancer agent; DSF is an anti cancer stem cell (CSC) agent. DTX and DSF combination is having a good synergistic activity in 2D and 3D *in-vitro* breast cancer models. For the effective distribution of DTX and DSF to tumor at pre-determined ratio (based on their combination index value), a pH sensitive nanoparticle (NP) was prepared by using histidine conjugated star-shaped PLGA.

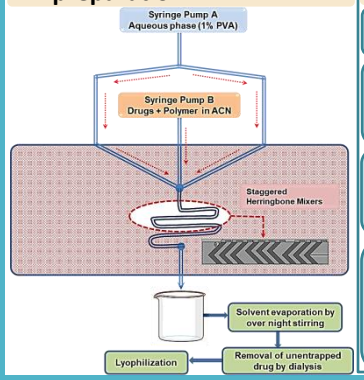


Methods

Schematic of pH sensitive polymer synthesis



NP preparation



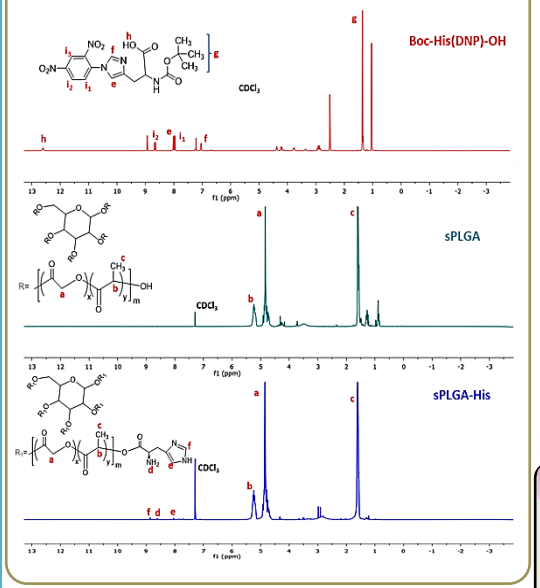
Evaluation

- Polymer characterization by NMR and FTIR
- Physicochemical characterization of NPs, such as drug entrapment, loading, size, PDI, pH sensitive destabilization, and drug release
- Invitro efficacy on 2D MCF7 model; cytotoxicity by MTT assay, cellular internalization and distribution analysis using DiI loaded NPs
- In-vitro efficacy on 3D (spheroid) MCF7 model; cytotoxicity by LDH assay, spheroid penetration using DiI loaded NPs and ROS generation with drug loaded NPs using DCFDA assay, CSC markers (Oct4 & SOX2) expression by RT-PCR

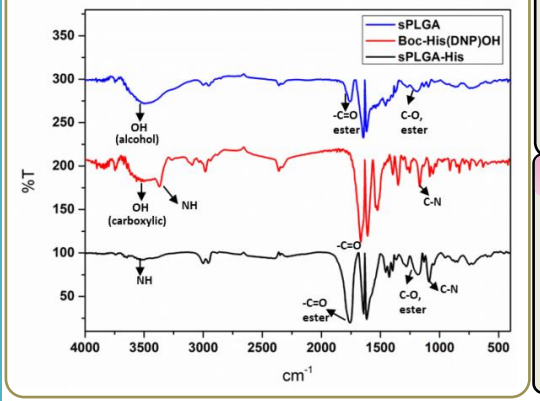
Results

Structural characterization :

^{1}H NMR

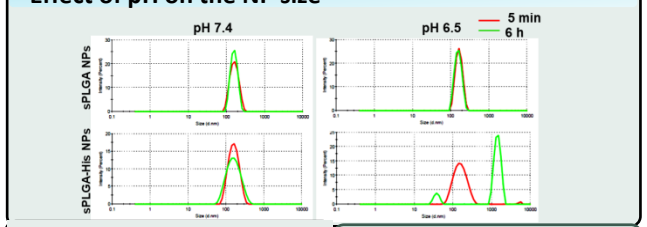


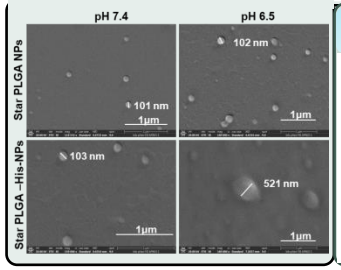
FTIR



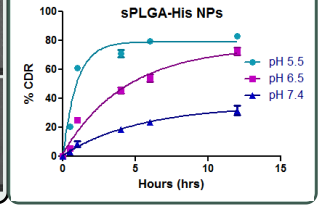
Physicochemical characterization of NPs:

Effect of pH on the NP size



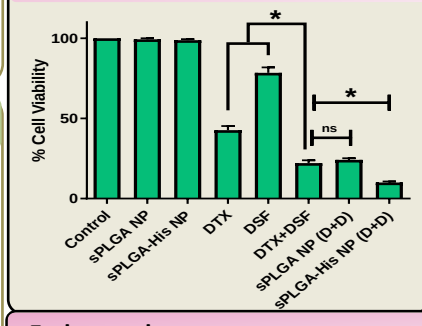


Effect of pH on drug release

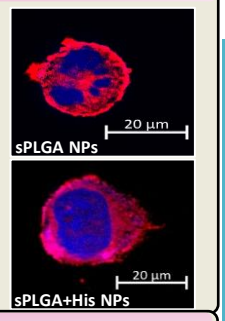


Efficacy against 2D tumor *in-vitro* model:

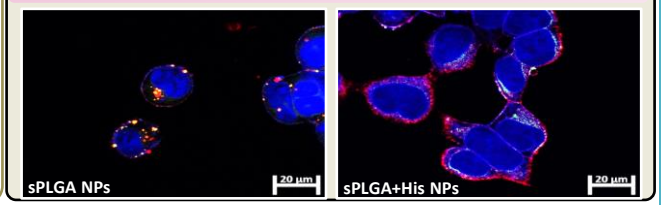
Cytotoxicity



Internalization

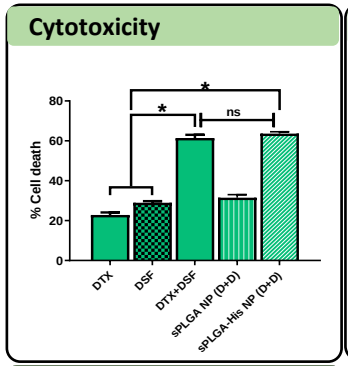


Endosomal escape

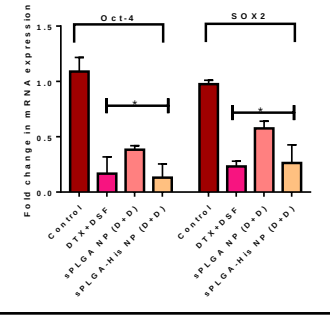


Efficacy of NPs against 3D tumor *in-vitro* model:

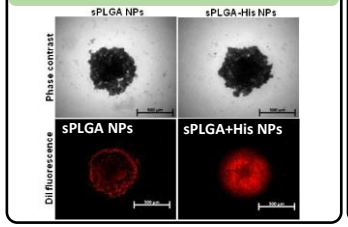
Cytotoxicity



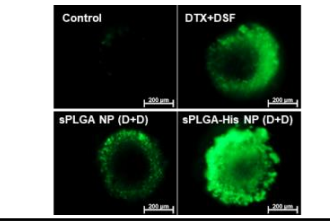
CSC marker analysis



Tumor spheroid penetration



ROS analysis



Conclusion

- A **novel pH sensitive polymer** (sPLGA-His) was synthesized.
- DTX+DSF at 1:10 molar ratio loaded NPs (~150 nm) were prepared using the pH sensitive polymer by microfluidic technology. sPLGA-His NPs has **shown excellent pH sensitive destabilization and drug release**.
- Drug loaded **pH sensitive NPs has shown more cytotoxicity than non-pH sensitive NPs** in 2D *in-vitro* tumor model which may be due to the quick **endosomal escape** exhibited by them .
- The pH sensitive NPs has shown **higher cytotoxicity along with reduction of CSC markers (Oct4 and SOX2) in 3D tumor model,** which may be due to the **increased ROS generation and also better drug distribution to spheroid core**.

Acknowledgements

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