Enhancing Oral Bioavailability of Sorafenib and Mitigating Liver Fibrosis using modified Chitosan-Sorafenib-Loaded nanoparticles

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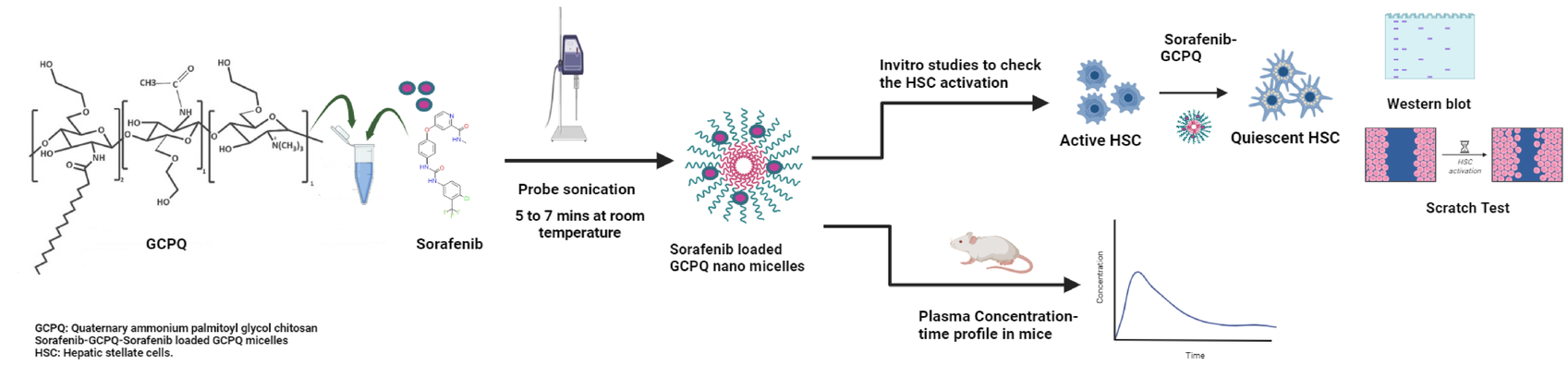
1. Introduction

Liver fibrosis, a consequential response to chronic liver injury, is characterized by excessive extracellular matrix (ECM) accumulation. If untreated, fibrosis can progress to cirrhosis, increasing mortality risk. Inhibition of overly active hepatic stellate cells (HSC) by sorafenib can decrease collagen and ECM deposition, a hallmark of liver fibrosis. However extended use of sorafenib is associated with adverse effects. We propose to develop sorafenib-loaded GCPQ (quaternary ammonium palmitoyl glycol chitosan) polymeric micelles, to achieve enhanced bioavailability and sustained release and consequently enhanced tolerability to the formulation.

2. Methodology

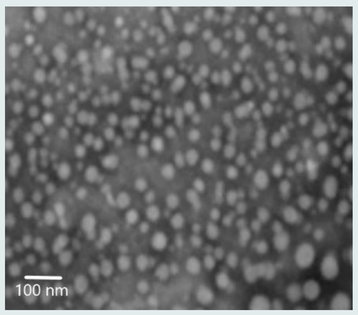


GCPQ: Quaternary ammonium palmitoyl glycol chitosan
Sorafenib-GCPQ-Sorafenib loaded GCPQ micelles
HSC: Hepatic stellate cells.

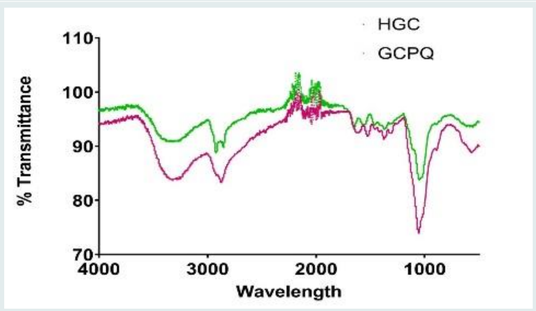
Schematic illustration of the synthesis of Sorafenib-loaded GCPQ polymeric micelles and subsequent *In-vitro* and *In-vivo* studies.

3. Characterization

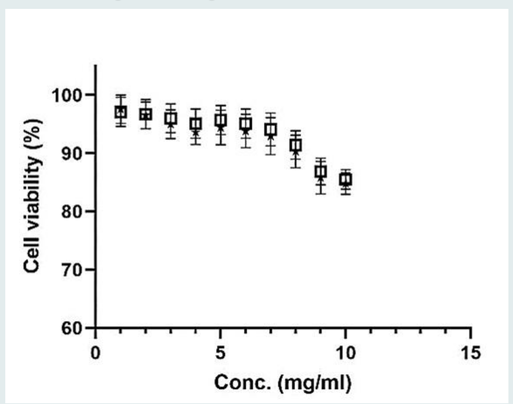
Transmission electron micrograph of Sorafenib- GCPQ micelles



FTIR Spectra of Hydrolyzed glycol chitosan and GCPQ

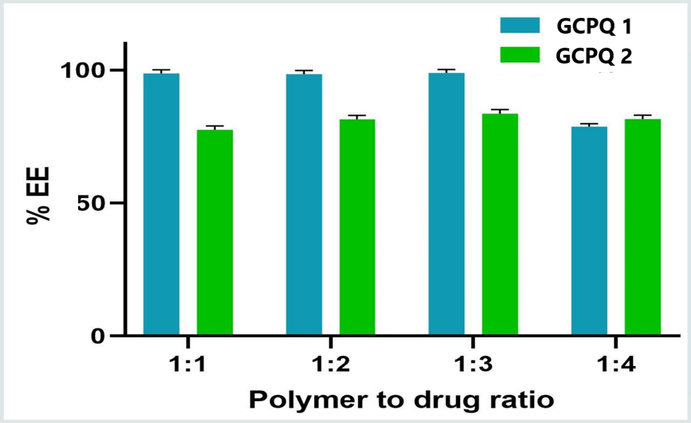


Cell Viability study



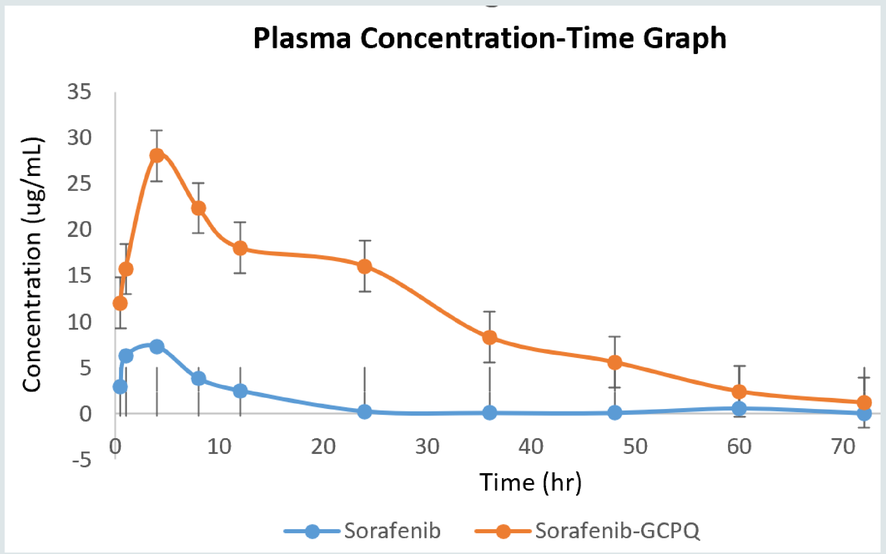
In vitro Cell Viability of Sorafenib-GCPQ micelles against HepG-2 cells over a period of 10 h, with the standard error of the mean (SEM), n=5. Paired t-test.

4. Drug Loading



Percentage encapsulation efficiency of Sorafenib in GCPQ micelles at different polymer-drug ratios with two types of GCPQ polymers having different functionalization. The sonication was done at 75 % of the maximum power, for 2min with a pulse of 10 seconds with an interval of 15 seconds.

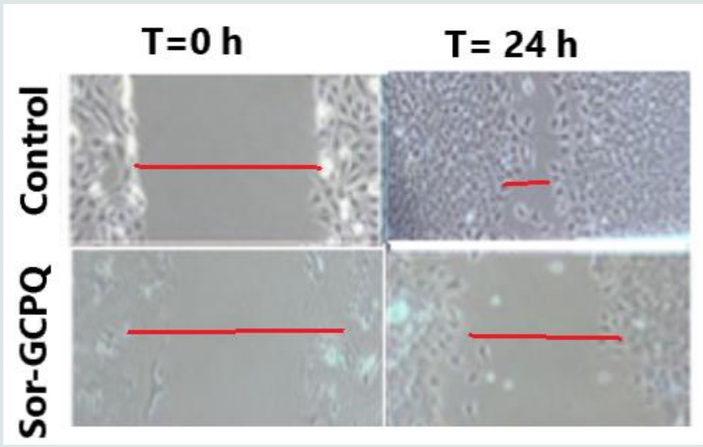
5. Pharmacokinetic Study (mice)



Representative plasma concentration-time profile after oral administration of Sorafenib solution (20 mg/kg) and Sorafenib-GCPQ formulation (Sorafenib 20mg/kg, GCPQ 72 mg/kg) in Balb-c mice over a period of 72 h. Plasma concentrations were measured using HPLC, n=7

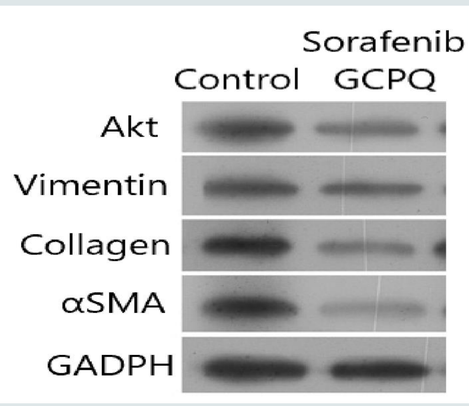
	C max (ug/mL)	T max (h)	T1/2 (h)
Sorafenib (Sol)	**28.04**	**4**	**28**
Sorafenib-GCPQ	**7.32**	**4**	**9**

6. In-vitro HSC Wound Healing Assay



Sorafenib-loaded GCPQ micelles (Sor-GCPQ) inhibit liver cell migration. Cell migration was assessed by wound-healing assay in the human hepatic stellate cells (HSC) LX-1.

7. In-vitro Protein Expression Study



Western blot analysis of protein expression levels in activated hepatic stellate cells treated with sorafenib-loaded GCPQ micelles.

Acknowledgements