NANOMEDICINES INNOVATION NETWORK
RÉSEAU D'INNOVATION NANOMÉDECINES

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Repurposing an Anticancer Agent for Liver Fibrosis Therapy

Enhancing the Oral Bioavailability of Sorafenib Using Chitosan Nanoparticles for Liver Fibrosis Mitigation

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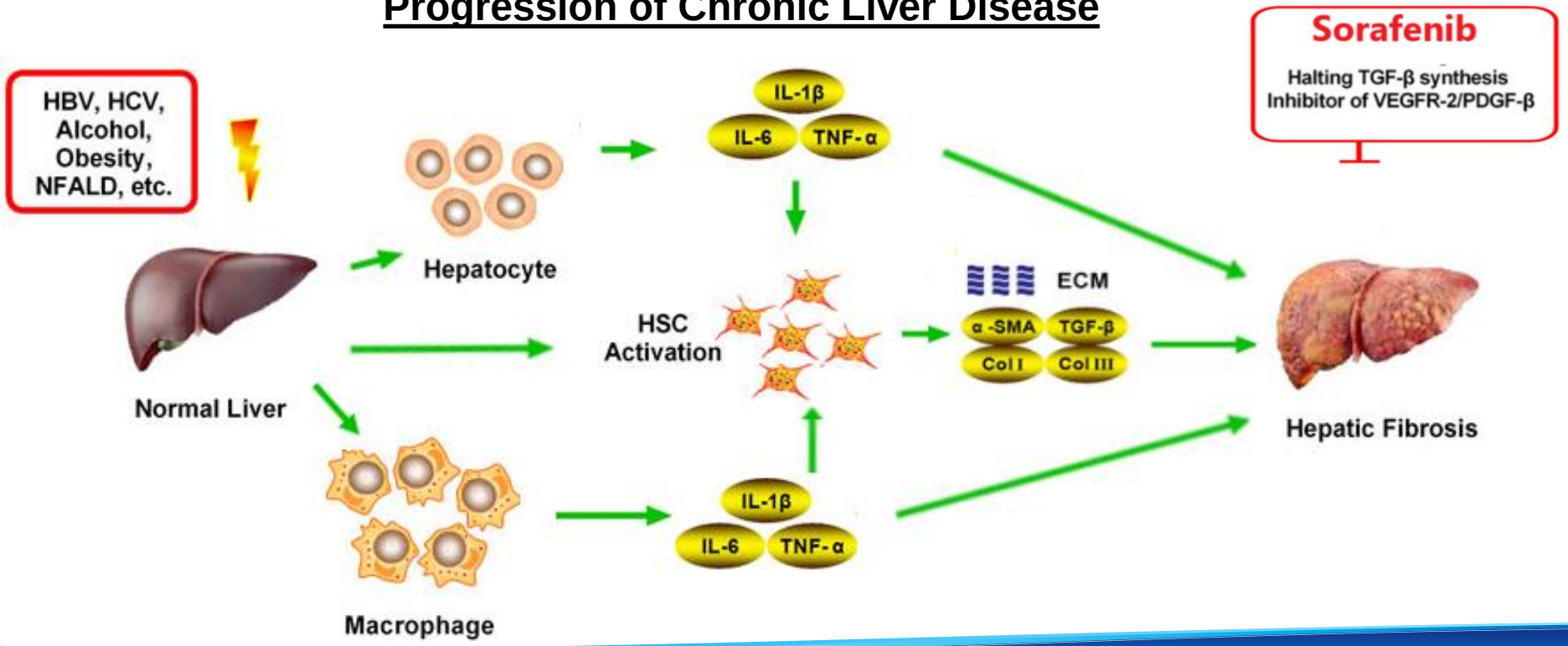
Liver Fibrosis

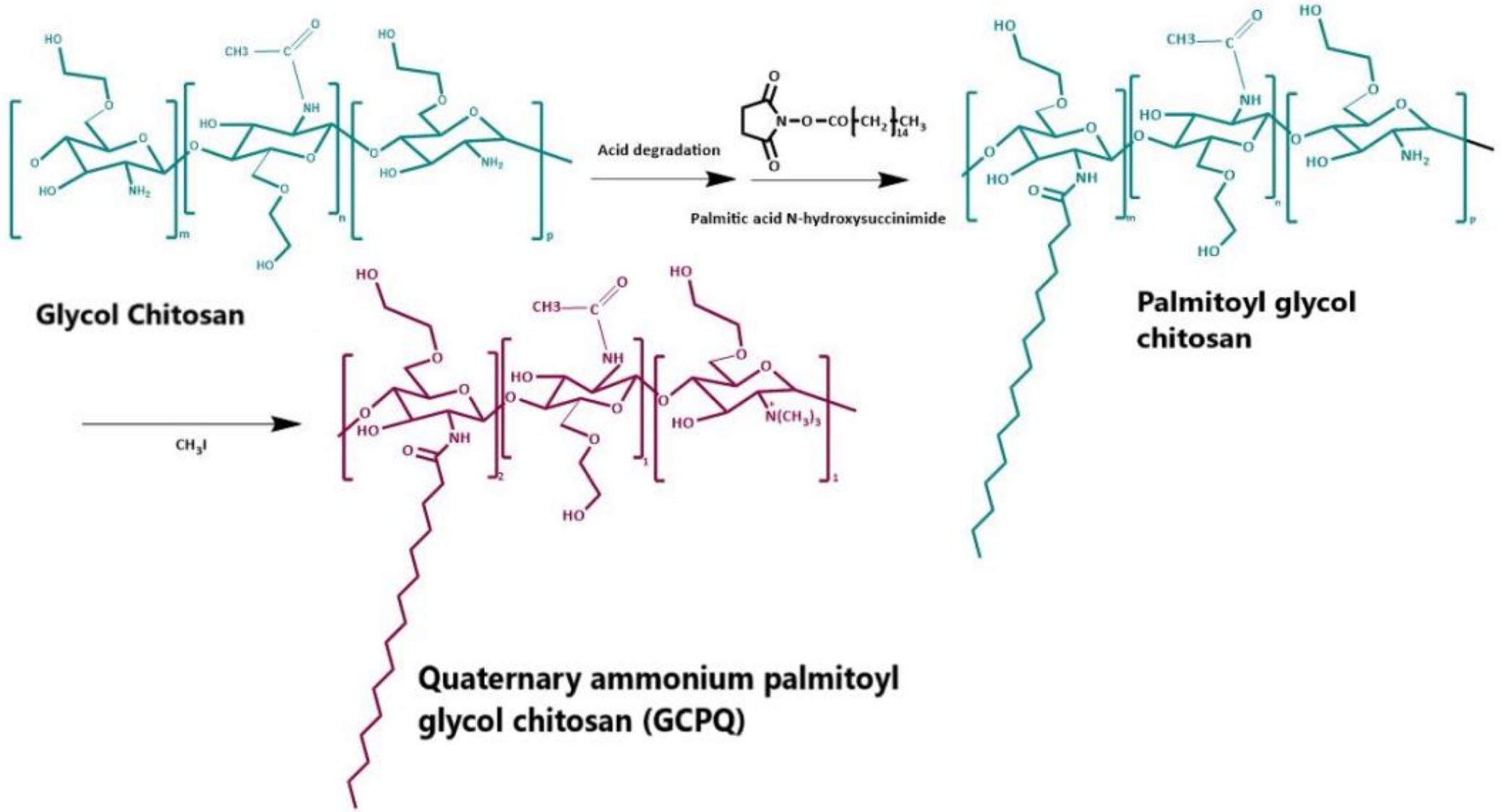
Liver fibrosis is the clinical corollary of **chronic liver diseases** and involves excessive accumulation of extracellular matrix proteins replacing the normal tissue.

Chronic liver disease is progressive in nature and a leading cause of mortality and morbidity across the world. accounted for 2.2% of deaths and 1.5% of disability-adjusted life years worldwide in 2016.

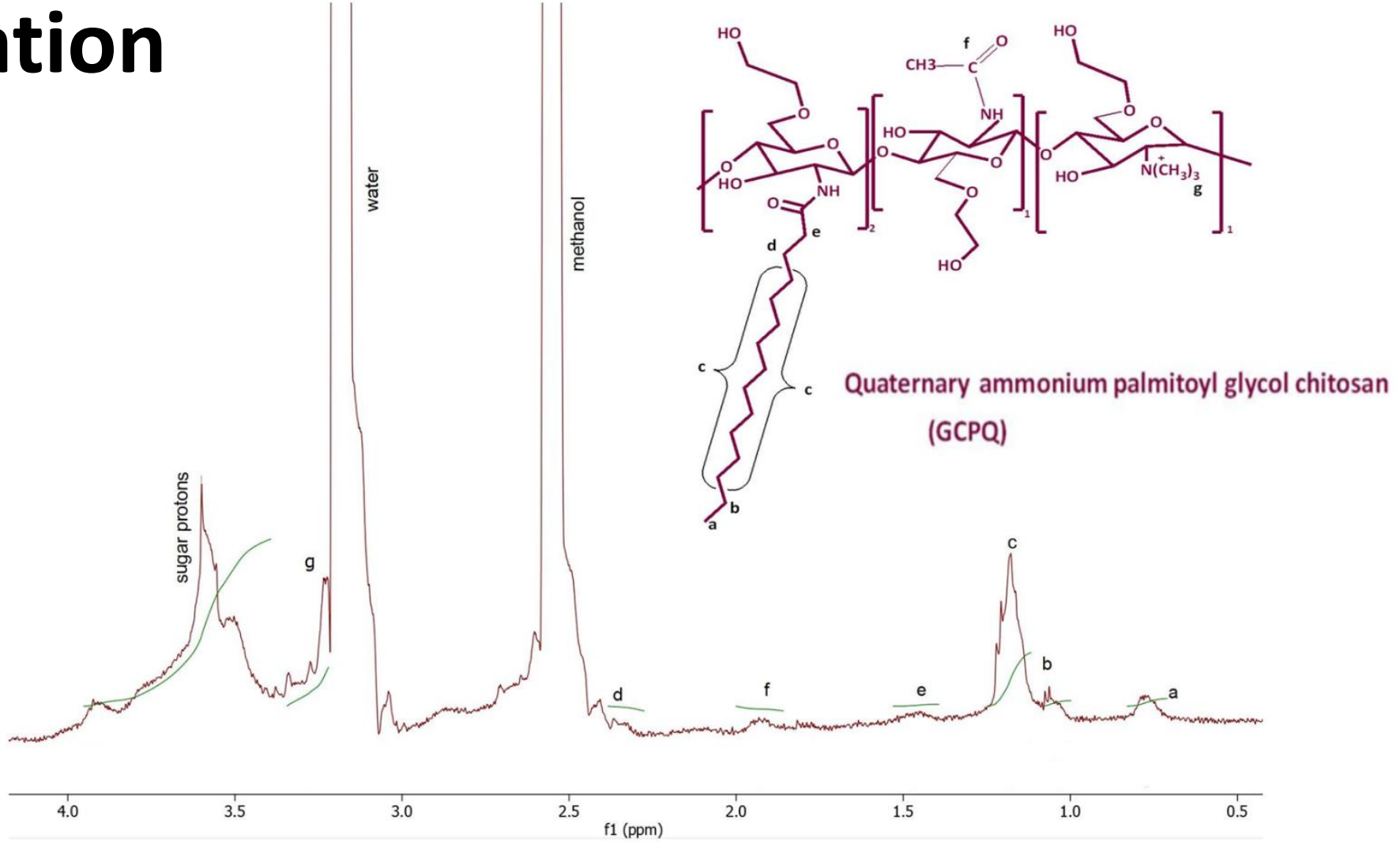
Progression of Chronic Liver Disease



Development of Modified Amphiphilic Polymer with Optimized Hydrophilic-Lipophilic Balance (HLB) and Stability



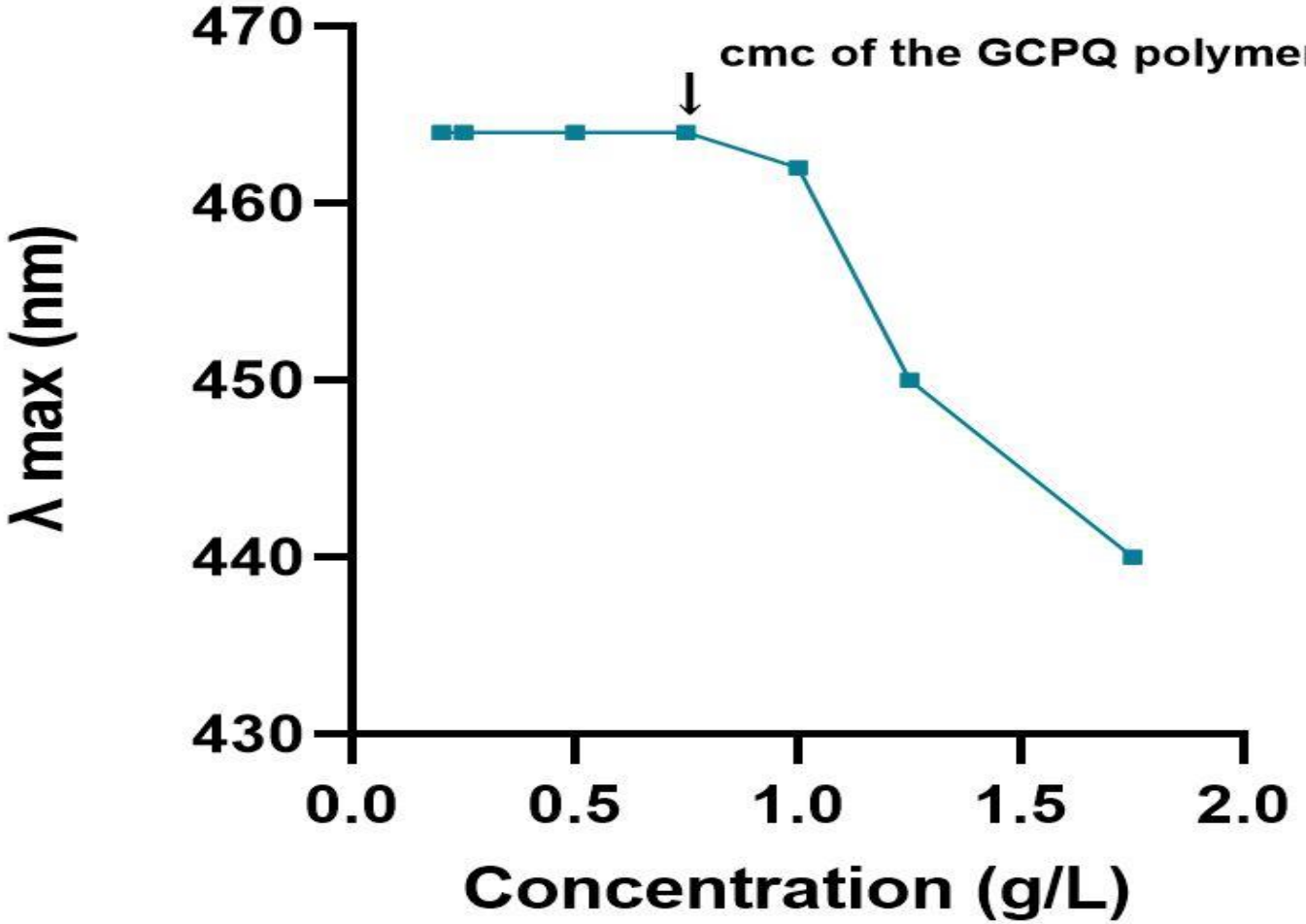
Characterization



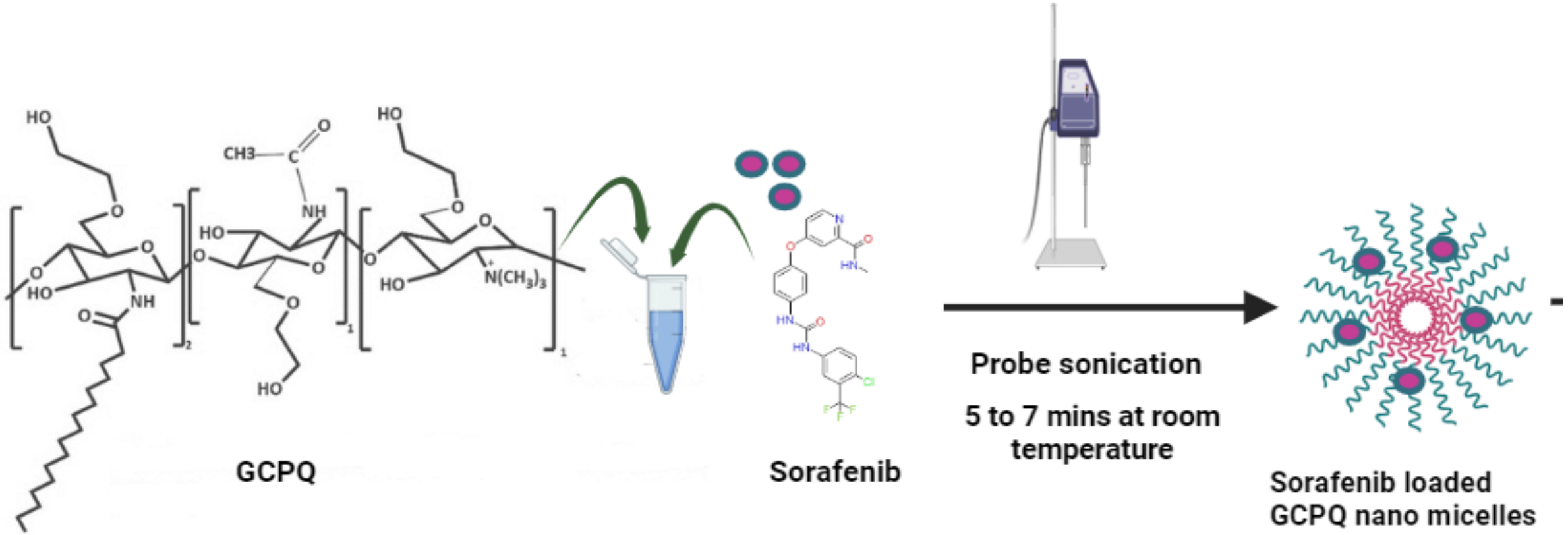
H^1 NMR of GCPQ. NMR peak spectrum is integrated for sugar backbone (1), palmitoyl group (0.15) and quaternary ammonium group (0.20)

Polymer	% age yield	Mw (kDa)	Mn (kDa)	PDI	% age palmitoylation	% age quaternization
GCPQ B2	71	14.6	14.3	1.02	15	20

Method could control the level of palmitoylation and quaternization and hence HLB of polymer

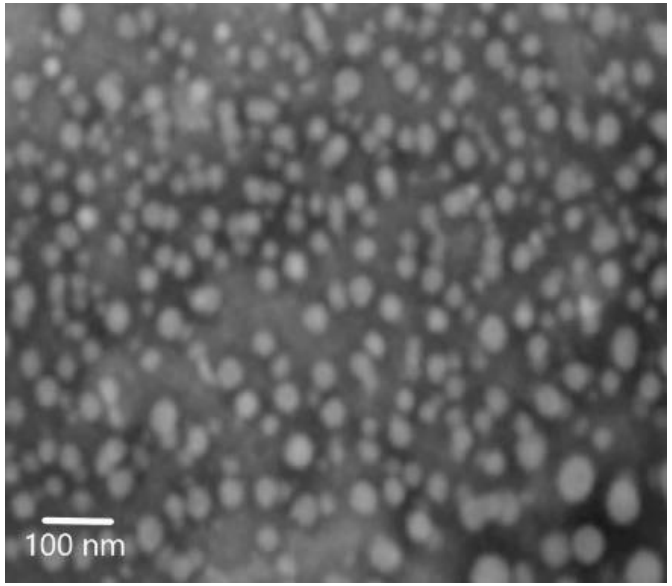


Critical micelle concentration (CMC) showed high stability under dilution conditions, as could happen in circulation



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

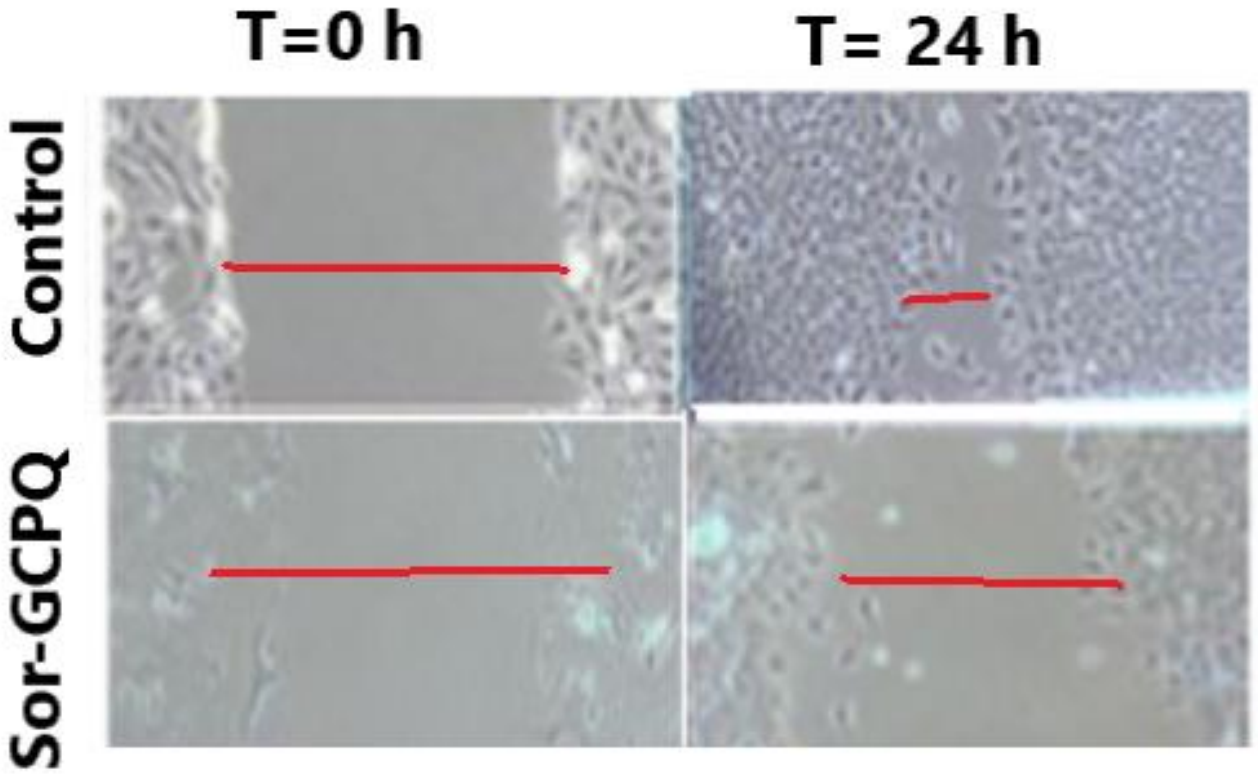
Polymer was used to load tyrosine kinase inhibitor drug: Sorafenib

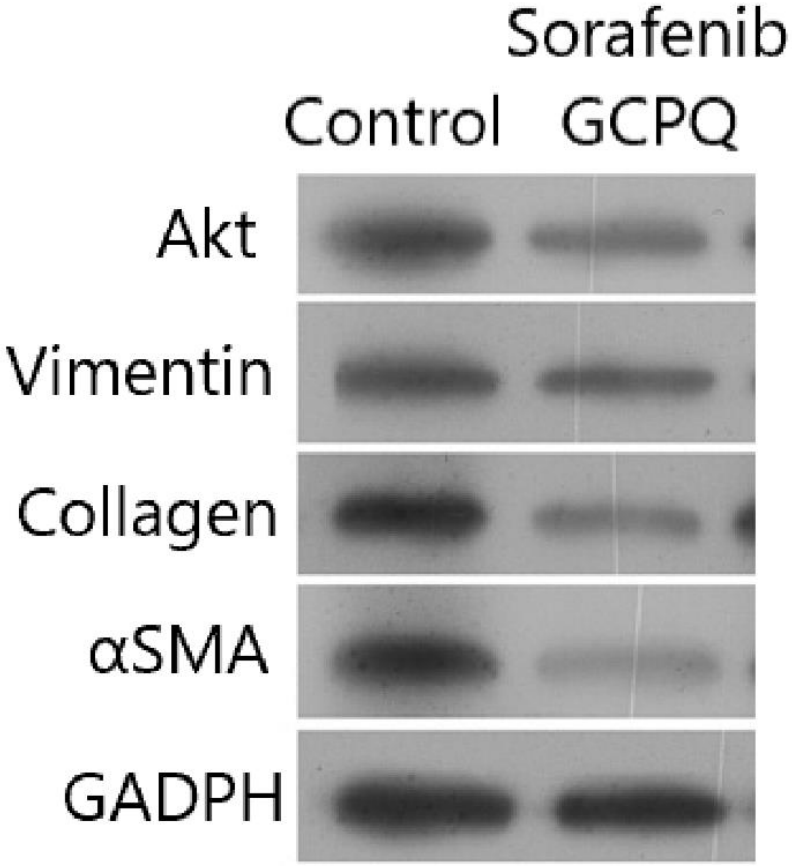


TEM image of Sot-GCP15Q20 showing micelles of around 60 ± 10 nm.

Formulation	Polymer – drug ratio	% Encapsulation efficiency		Size (nm)	PDI	Zeta potential (mV)
GCP15Q20	1:1	99.62 ± 1.62	99.6 ± 1.64	78	0.32	32.6

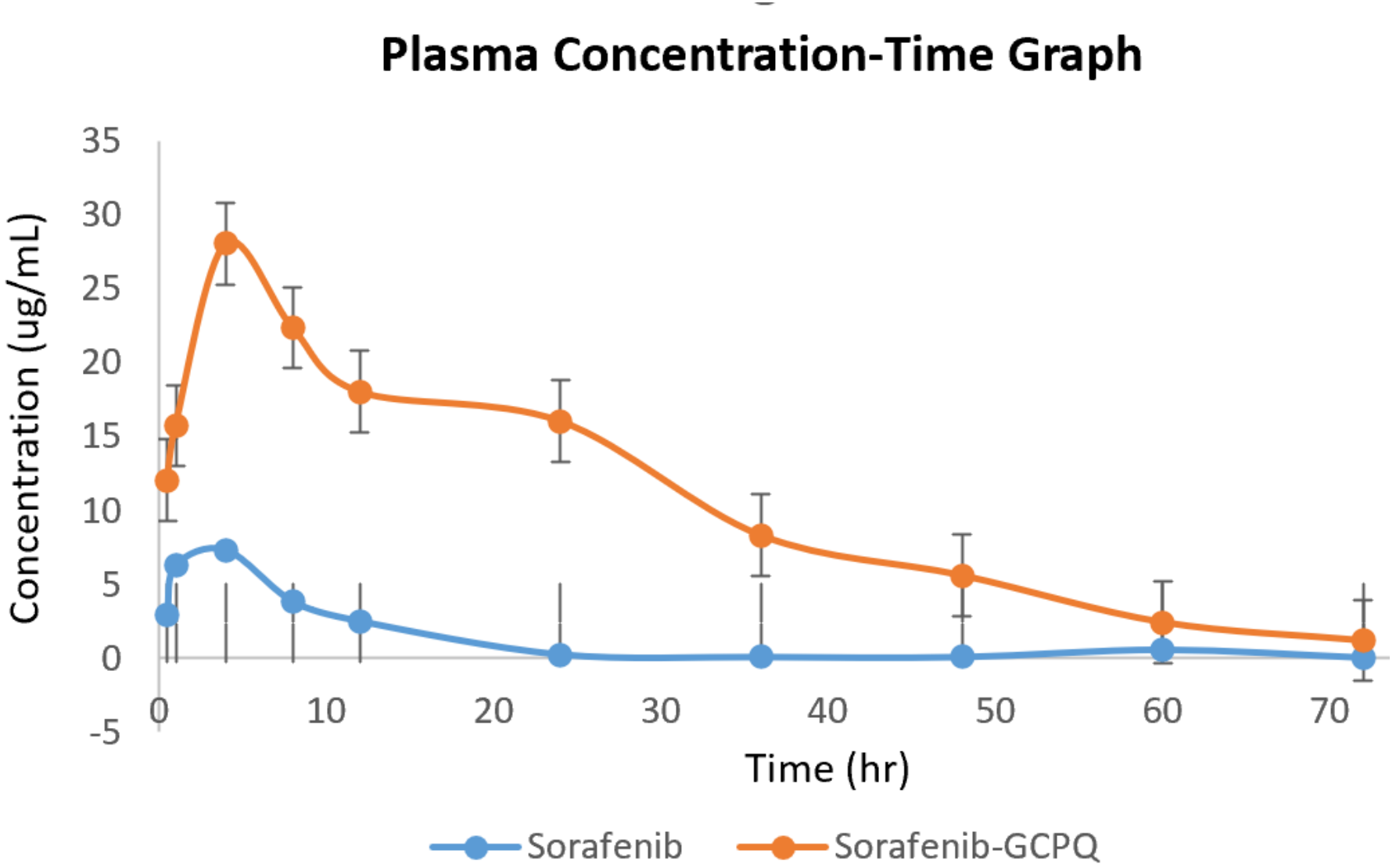
Physical characteristics of the Sot-GCP15Q20 Np's prepared by using different polymer to drug ratio.



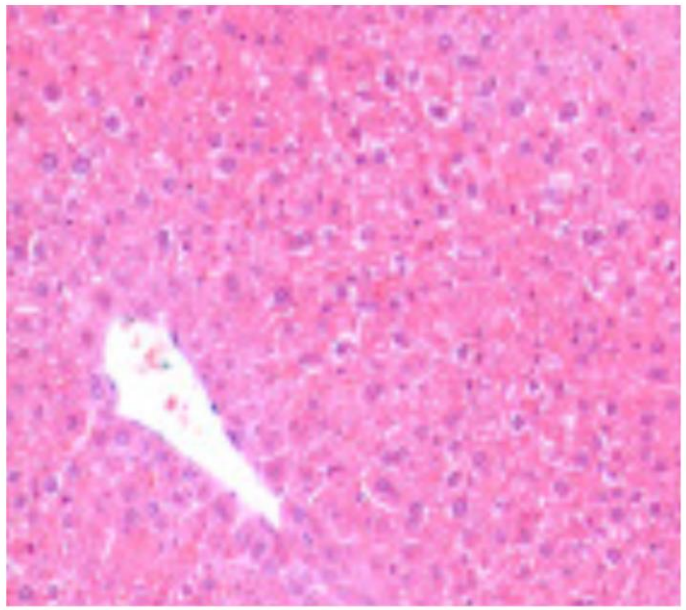


In-vitro tests showed decreased activation of hepatic stellate cells when treated with sorafenib-loaded GCPQ nanoparticles (Sor-GCPQ) compared to untreated cells in a scratch test using HepG2 cells and western blot analysis.

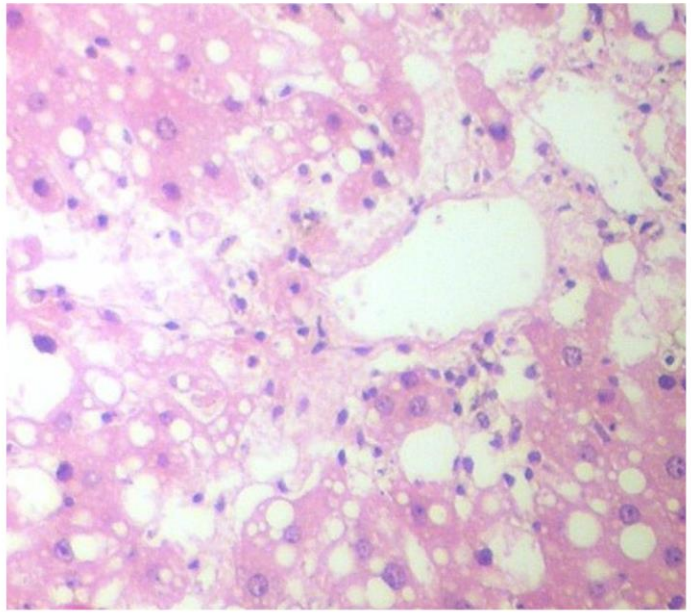
In-vivo Pharmacokinetics in Mice showed Improved Relative Bioavailability of Oral Sorafenib-GCPQ vs Oral Sorafenib tosylate



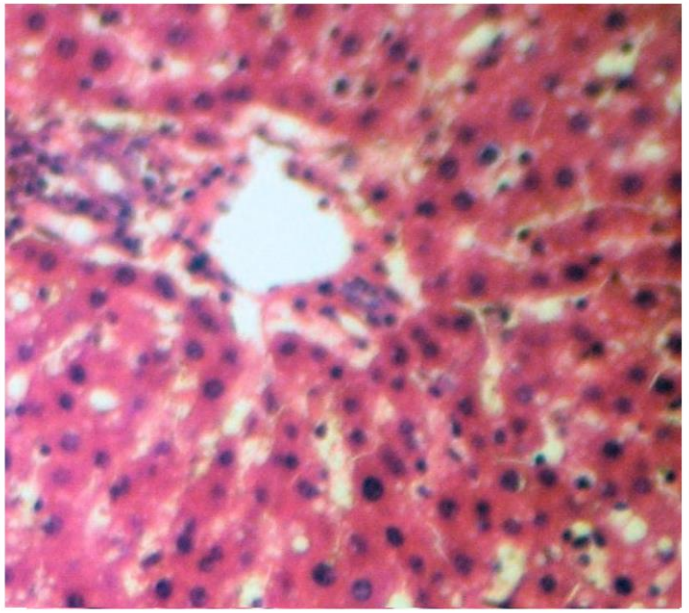
Plasma concentration-time profile after oral administration of Sorafenib solution (20 mg/kg) and Sorafenib-GCPQ formulation (Sorafenib 20mg/kg, GCPQ 72 mg/kg) in Balb-c mice over a period of 72 h. Plasma concentrations were measured using HPLC, n=7



Control



Saline/CCL4



Treated/CCL4

H/E-stained liver tissues of mice; control, untreated, and treated with Sorafenib-GCPQ. The treatment group received Sorafenib-GCPQ OD orally at a dose of 20 mg/kg, n=7

Next Steps

Multi-dose studies

Toxicology studies

Combination drug formulation development

Thank you!

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Acknowledgments

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Supplementary

HI was determined as described earlier [Qu et al, biomacromolecules,2006] using a ratio of molar fraction of quaternary ammonium groups/monomer (Q) to the molar fraction of palmitoyl groups/monomer (L), as given by following equation.

$$\%\ Palmitoylation = \left(\frac{\frac{Integration\ value\ of\ N-palmitoyl\ methyl\ protons}{3}}{\frac{Integration\ value\ of\ sugar\ protons}{9}} \right) * 100 \qquad 0\text{-}1$$

$$\%\ Quaternization = \left(\frac{\frac{Integration\ value\ of\ trimethyl\ protons}{9}}{\frac{Integration\ value\ of\ sugar\ protons}{9}} \right) * 100 \qquad 0\text{-}2$$

And HI=Q/L is also called QPR i.e., ratio of quaternization to palmitoylation was determined using following equation.

$$QPR = \frac{mole\ \%\ quaternization}{mole\ \%\ palmitoylation} \qquad 0\text{-}3$$