Formulation of Liver-Specific PLGA-DY-635 Nanoparticles Loaded with the Protein Kinase C Inhibitor Bisindolylmaleimide I.

Shkodra B, Press AT, Vollrath A, Nischang I, Schubert S, Hoeppener S, Haas D, Enzensperger C, Lehmann M, Babic P, Benecke KJ, Traeger A, Bauer M, Schubert US (2020) Formulation of Liver-Specific PLGA-DY-635 Nanoparticles Loaded with the Protein Kinase C Inhibitor Bisindolylmaleimide I. *Pharmaceutics* 12(11), PubMed

ILRS Authors

Petra Babic

Projects

Endoplasmatic reticulum turnover and outcome of sepsis
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Abstract

Bisindolylmaleimide I (BIM-I) is a competitive pan protein kinase C inhibitor with anti-inflammatory and anti-metastatic properties, suggested to treat inflammatory diseases and various cancer entities. However, despite its therapeutic potential, BIM-I has two major drawbacks, i.e., it has a poor water solubility, and it binds the human ether-à-go-go-related gene (hERG) ion channels, potentially causing deadly arrhythmias. In this case, a targeted delivery of BIM-I is imperative to minimize peripheral side effects. To circumvent these drawbacks BIM-I was encapsulated into nanoparticles prepared from poly(lactic-co-glycolic acid) (PLGA) functionalized by the near-infrared dye DY-635. DY-635 served as an active targeting moiety since it selectively binds the OATP1B1 and OATP1B3 transporters that are highly expressed in liver and cancer cells. PLGA-DY-635 (BIM-I) nanoparticles were produced by nanoprecipitation and characterized using dynamic light scattering, analytical ultracentrifugation, and cryogenic transmission electron microscopy. Particle sizes were found to be in the range of 20 to 70 nm, while a difference in sizes between the drug-loaded and unloaded particles was observed by all analytical techniques. In vitro studies demonstrated that PLGA-DY-635 (BIM-I) NPs prevent the PKC activation efficiently, proving the efficacy of the inhibitor after its encapsulation, and suggesting that BIM-I is released from the PLGA-NPs. Ultimately, our results present a feasible formulation strategy that improved the cytotoxicity profile of BIM-I and showed a high cellular uptake in the liver as demonstrated in vivo by intravital microscopy investigations.

Identifier

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