

# Proposomes: A Nano-formulation approach for targeted skin delivery National University of Singapore

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Tofacitinib (TOF) is an FDA approved to treat rheumatoid arthritis via the oral administration. It is a JAK inhibitor which has recently gained interest in the oral treatment of skin disorders such as psoriasis, atopic dermatitis and baldness. However, the oral administration shows systemic side effects such as decreased neutrophil counts, opportunistic infections, and increased cholesterol level. Therefore, the topical delivery of TOF can be ideal by reducing the risk of systemic exposure, in addition to provide targeted therapy at the site of drug action. However, TOF shows minimal absorption via skin. Hence, the objective of this study was to enhance its skin delivery using non-invasive approaches. The liposomes based on propylene glycol named as proposomes loaded with TOF (TOF-proposomes) have been investigated. The effect of varied proposomes compositions with fixed amount of TOF (SPC; 1% to 3%, and propylene glycol; 20% to 40%) were studied. The stability, morphology, particle characteristics, entrapment efficiency and in vitro drug release, skin permeation and skin toxicity using bioengineered skin were assessed. The proposomes were uniform in size with sufficient entrapment efficiency to deliver the Janus kinase (JAK) inhibitor into the skin in non-invasive manner. The average particle size of the proposomes were ranging 219-317 nm with PDI <0.3 and the zeta potential ranging -4 mV to -7 mV. The entrapment efficiency was 38-58% with enhanced skin permeability of 4-11 folds as compared to control, and relatively slow in vitro release in comparison to control. The amount of propylene glycol in proposomes would affect the CMC and hence, the number of proposomes for drug delivery. The composition of proposomes found to affect the skin permeation and deposition into epidermal and dermal layer. The SPC and PG synergistically affect the tight junctional possibly by reversible redistribution of tight junctional proteins. The transfollicular pathway as one of the mechanism for proposome absorption was clearly evident. The better and deeper absorption of two fluorescent probes with different log P value was supportive for delivery of other drugs as well. It was effective and biocompatible for topical application. The blank proposomes and TOF-proposomes were non-toxic. It was physically stable as compared to ethosomes and prevented the degradation of TOF as well. The proposomes were stable for 6 months at least, and shown to improve the stability of the incorporated TOF as compared to TOF solution in water. Overall, the proposomes were effective and safe for topical application. It can be utilized for passive targeting of drugs for epidermal, dermal and transdermal drug delivery for skin and other medical applications by varying the composition of PG and SPC.