Pharmaceutical nanotechnology-based approaches to increase drug solubility and therapeutic efficacy of all-trans retinoic acid

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Background: Currently, more than 40% of commercialized drugs and 70-90 % of drug candidates are poorly water-soluble, resulting in erratic absorption, subtherapeutic plasma concentrations, and variable clinical outcomes. All-trans retinoic acid exhibits poor aqueous solubility (0.19 µg/mL), which limits its clinical usefulness. Traditional approaches such as salt formation, pH adjustment, and the use of co-solvents offer limited success and often come with stability or toxicity concerns. Nanotechnology has opened new avenues to overcome these challenges associated with traditional methods.

Methods: In this study, we developed a micelle/nanoemulsion based dual nanoparticulate system that combines the solubility enhancing properties of polymeric micelles with the efficacy boosting potential of nanoemulsions to improve the oral delivery of all-trans retinoic acid. Aqueous titration method was used to construct a phase diagram, from which the oil-in-water nanoemulsion region was identified. Drug-loaded TPGS micelles were prepared using the thin film hydration method. The formulated TPGS micelles were added to the aqueous phase in the oil-in-water nanoemulsion, resulting in the formation of a hybrid delivery system. The shake flask method was adopted to determine the drug solubility from the formulated hybrid system. Efficacy studies of the product were conducted using a λ-carrageenan induced hind paw oedema rat model (5 rats/ group) and were compared with a vehicle control (normal saline) and a drug suspension in normal saline. The treatment course lasted for 4 days, with the administration of 5mg/kg/p. o, BD in diseased rats. Histopathological examinations were carried out to assess the effects of hybrid system on the liver, kidneys, and heart of rats, and were compared with the control group.

Results: The formed hybrid system exhibited a 9.39 folds increase in the aqueous solubility of drug (2 µg/ml) as compared with pure drug in distilled water (0.23 µg/ml). The nanoparticulates in the formulation achieved a PDI of < 0.5, with an average particle size of 185.4 nm. The formed hybrid system had EE% 70%. Drug release was sustained for up to 48 hours, following a non-Fickian diffusion pattern. The stability study confirmed that the formulated system was clearly transparent in appearance, with no particle aggregation, indicating a uniform distribution of particles within the system, over a three months period under predefined conditions at 4 ℃, 25℃ and 37 ℃ with 60 % relative humidity. Relief from the disease was observed within 4 days of the treatment. The percentage inhibition of paw volume produced by the formulated hybrid system indicated a faster onset of the drug's anti-inflammatory action, confirming the high efficacy of the system. Histopathological examination of formed hybrid system administered rats did not show changed histopathology or harmful signs.

Conclusions: The formulated micelle–nanoemulsion hybrid system is a promising nanocarrier with tunable properties for enhancing the aqueous miscibility and oral delivery of lipophilic therapeutic agents.