**Novel Injectable dual thermoreversible hydrogel for sustained intramuscular drug delivery**

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**Background and aims.** The primary aim of this study was to develop novel solid lipid nanoparticle (SLN)-loaded dual-reverse thermoreversible system (DRTS) for intramuscular administration of docetaxel (DCT) with sustained release and improved antitumor efficacy.

**Methods.** The DCT-loaded thermoresponsive SLNs were prepared by homogenization and membrane emulsification technique, after optimizing the concentration of lipid mixture (tricaprin and tricaprylin in 9:1 weight ratio), drug and surfactant at their respective weight ratio of 1.4/0.3/0.6. The DRTS were prepared by adding this DCT-loaded SLN in various poloxamer solutions followed by investigation of their rheological characterizations. In vitro release was executed in phosphate buffer solution (pH 7.4) and pharmacokinetic study was performed after its intramuscular administration to rats compared with the drug and hydrogel. Finally, antitumor evaluation of the DCT-DRTS was executed and compared with DCT-hydrogel, and DCT-suspension trailed by the histopathological and immune-histochemical analysis.

**Results.** The DCT-loaded SLN gave a mean particle size of about 157 nm and entrapment efficiency of around 93%. The DCT-DRTS was a solid at room temperature, and changed to liquid form at physiological temperature due to its melting point of about 32 °C. The mixture of poloxamer 188 (P 188) and poloxamer 407 (P 407) decreased the gelation temperature and gelation time, but increased the viscosity at 25 °C and gel strength of DRTS. In particular, the DRTS composed of [SLN/P 188/P 407 (2.3/7.5/6.5%)] with the gelation temperature of about 32 °C existed as liquid at room temperature, but gelled at 30-36 oC, leading to opposite reversible property of SLN. Thus, it was easy to administer intramuscularly, and it gelled rapidly inside the body. This DCT-DRTS gave a significantly increased dissolution rate of the drug as compared to the DCT-suspension, but significantly retarded as compared to the DCT-hydrogel, including the initial dissolution rate. Moreover, this DCT-DRTS gave significantly higher plasma concentration and 3.2-fold AUC values compared to the DCT-suspension, and lower initial plasma concentration and Cmax value compared to the DCT-hydrogel due to reduced initial burst effect. A meaningfully enhanced antitumor efficacy via reduced tumor volume and maintained body weight was observed from DCT-DRTS in tumor cell xenograft athymic nude mice. Additionally, substantially increased number of caspase-3 and PARP-immunoreactive cells and noticeably reduced number of CD31- and Ki-67-positive cells were observed in DCT-DRTS treated tumor masses.

**Conclusion/Discussion.** Overall, it can be concluded that DCT- DRTS with delayed release, reduced initial burst effect and improved antitumor efficacy would be recommended as an alternative for the DCT-loaded intramuscular pharmaceutical products.