

3 Chapter 3: Rationale and Objectives

The ethanolic extract of the *Piper longum* fruit and its phytoconstituents have been well investigated for their anticancer activity against melanoma through *in-vitro* and *in-vivo* tumor models. Irrespective of promising reports on anticancer activity, the poor solubility of the majority of contained phytoconstituents and the obstruction by major skin barrier, i.e., Stratum corneum (SC) of skin, restrict their therapeutic use through oral and transdermal routes, respectively. In order to realize the actual therapeutic property, two novel formulations, SD and TFG of standardized extract (PLFEE), were developed and optimized using the QbD approach. To our knowledge, no reports are available for the standardized PLFEE-loaded SD and TFG for the effective treatment of melanoma. Further, the combination of Soluplus[®] & Tween[®]80 as excipient in SD and the combination of Phospholipon[®] 90 H as membrane former, Tween[®] 80 as edge activator, and Xanthan gum as gelling agent is not explored for the development of TFG of standardized PLFEE for the melanoma therapy. The SD formulation has been designed, statistically analyzed, and optimized using a CCD-based QbD approach to obtain the best formulation with high saturation solubility. Similarly, the TFG was designed statistically to develop the best formulation with low Z_{avg} , maximum % EE, and optimum flexibility.

The optimized SD and TFG were characterized for their physicochemical properties, pharmaceutical properties, *in-vitro* and *in-vivo* anticancer activity in the C57BL/6 murine model. The combination of oral SD and transdermal TFG F2 was explored 1st time for the *in-vivo* anticancer activity against murine melanoma. Further, the *in-vivo* anticancer activity of SD and TFG were evaluated with a standard anticancer drug i.e., dacarbazine as adjuvant therapy.

Objectives

- Authentication, extraction, marker-based standardization, and residual solvent analysis of PLFEE
- QbD-based formulation of SD of standardized PLFEE, its *in-vitro* and *in-vivo* anticancer activity evaluation in melanoma-bearing C57BL/6 mice
- QbD-based formulation of TFG of standardized PLFEE, its *in-vitro* and *in-vivo* anticancer activity evaluation in melanoma-bearing C57BL/6 mice
- Comprehensive anticancer activity evaluation of both the optimized formulations and marketed drug in melanoma-bearing C57BL/6 mice