PREFACE

Chemotherapy induced nausea and vomiting (CINV) is one of the main side effects of cancer therapy. Functional Living Index-Emesis (FLIE) which assesses quality of life of cancer patients, suggest that CINV has intense negative effects on quality of life of patients. CINV occurs in two phases; acute phase and delayed phase. Acute CINV occurs within 1–2 h of chemotherapy administration and can last for up to 24 h while delayed CINV occurs more than 24 h after chemotherapy administration. The three main receptors involved in the regulation of nausea and vomiting are 5-hydroxytryptamine (5-HT3) receptor, neurokinin-1 (NK-1) receptor, and dopamine (D2) receptor. Because the onset of acute and delayed CINV often overlap after the initial day of chemotherapy, it remains a challenge to determine an appropriate antiemetic regimen, as patients may require alternate treatment regimens. Limited efficacy and resistance to existing monotherapy can be addressed by incorporating multiple drugs in single drug delivery system. Multiple drugs interact with multiple targets and can achieve better efficacy and/or less toxicity than monotherapy in practice. Identifying the appropriate molecules for combination and suitable drug delivery system for incorporating them is crucial from formulation development perspective. Present investigation reports the preparation of Amisulpride-Granisetron dual-drug loaded Janus microspheres for effective treatment of both acute and delayed phases of CINV. The microspheres were prepared from Poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) polymers using water-oil-water (W/O/W) emulsion-solvent evaporation method. The microspheres were optimized using quality by design approach to find out the best drug: polymer ratio and process parameters which can provide the desired Quality target Product Profile (QTPP). Dual drug loaded microspheres were characterized in terms of morphology, particle size, drug loading and entrapment efficiency and in-vitro drug release. The desired dose and theoretical drug release for both drugs were estimated using in-silico model developed in Gastroplus^{TM} which should provide sustained drug release up to one week. The pharmacokinetic data from existing marketed formulations were used to validate the developed formulation. The developed dual drug loaded microspheres provided sustained drug release up to one week providing better patient compliance and efficacy. Virtual bioequivalence (VBE) studies showed the bioequivalence between sustained release and multiple dose immediate release formulations. Further, predictive IVIVC was developed to establish safe space for the formulations. The adopted in-

vitro and in-silico approach offers great platform for design and development of polymeric systems with single or multiple drugs.

This idea and concept can further be extended to other products with minimal use of in-vivo studies. This approach is currently widely used by generic companies in 505(b)(2) NDA approach, where costly in-vivo studies can be waived using published data from existing marketed formulations. The 505(b)(2) pathway allows use of different salt/polymorph of API, change in formulation, change in strength or use of combination of drugs where safety and efficacy of individual drugs has already been established. The use of in-silico modelling has been encouraged by regulatory agencies due to their capability in predicting different dosing scenarios in different group of populations, drug-drug interaction studies and developing long-acting dosage forms based on immediate release pharmacokinetics. Thus, the present research work can serve as benchmark strategy for other such disease areas using combination of drugs with known safety and efficacy profiles.