Preface

Amorphization is a well-known method used for increasing the solubility and dissolution of poorly water-soluble drugs. The drug's amorphous form is formulated as amorphous solid dispersion (ASD) where the amorphous drug is uniformly dispersed in the polymeric matrix. Since no energy is required to break the crystal structure in amorphous form, higher apparent solubility and noticeably quicker dissolution can be attained as compared to the crystalline form.

To withhold the drug in the amorphous state is very challenging as the amorphous form of solid posses' high thermodynamic energy as compared to its crystalline counterpart. The type and the concentration of the polymers have the most significant role in providing the stability to the amorphous state of drug. There is no single polymer which can guarantee the stability of all amorphous drug. Till date there is no rationale for selection of an appropriate polymer for the preparation of a stable ASD. By using polymer with high glass transition temperature (T_g) drug can be stabilized by antiplasticization effect in which the overall T_g of the ASD increases hence the drug's recrystallization doesn't happen. Yet, only T_g is not the sole indicator of the stability of any ASD. Another approach is to evaluate the chemical interaction like formation of drug-polymer hydrogen bonding or ionic interaction between the drug and the polymer. There are evidences that these interactions increase the crystallization inhibition, affects the molecular mobility and hence the physical stability of the ASD. Hence, the selection of polymer is a amalgamation of all these factors working together towards the stability of the ASD.

The current work involves grading of three widely used polymers for preparing a thermodynamically and kinetically stable amorphous solid dispersion (ASD) of a neuroprotective drug Riluzole (RLZ) by evaluating the drug-polymer interactions. Polymers were screened based on their chemical interaction with RLZ and ability to

inhibit the crystallization of the drug. Detailed computational studies were performed to quantify the non-bonding interactions between RLZ and the modelled structures of polymers; polyacrylic acid (PAA), polyvinylpyrrolidone vinyl acetate (PVP VA) and hydroxypropyl methyl cellulose acetate succinate (HPMC AS) for calculating the interaction energies of drug/polymer complex. Experimental validation of the obtained results was done by thermal, microscopic and spectroscopic tools and drug-polymer miscibility studies. Selection of a polymer was done using the above studies.

In addition to the selection of polymers, the role of polymers in changing the surface properties in terms of wettability and polarity were explored using contact angle method and surface chemistry. These studies confirmed the increase in the surface polarity and hence the enhanced ability of ASD formulations to interact with water. This study established a correlation between the surface properties and the dissolution profile of various drugs present in different types of formulations. Further formulations with different drug and polymer ratio were prepared and characterized for solid state properties and dissolution profile. The formulation with best dissolution profile were carried forward for in vivo pharmacokinetic studies in rats. Pharmacokinetic parameters of the final formulation were calculated and compared with the parameters of the marketed formulation. Later, a Physiological Based Pharmacokinetic (PBPK) model of rats for marketed tablet and RLZ ASD was developed by incorporating physiological differences between species and then extrapolated to humans and validated by comparing the modelled outcome with published human pharmacokinetic data. Further, the model was used to predict different exposure scenarios, and the simulated data was compared with observed data points. The developed model was able to predict the RLZ concentration in multiple compartments. Since RLZ is neuroprotective in action hence, its effect on the

cognitive functions was tested. Along with this, the effect of repetitive dosing on the liver enzyme levels were also evaluated.

The overall findings of this study can lead to a rationale behind the selection of polymer for the formulation of a stable ASD which will have enhanced dissolution and pharmacokinetic properties. The developed PBPK model can be used to estimate the concentration of drug in different compartments including the target organ or the organ where toxicity is likely to occur. This will ultimately help in designing a dosage form which will ensure superior stability, dissolution, pharmacokinetic and pharmacodynamic effect and show lesser toxicity.

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