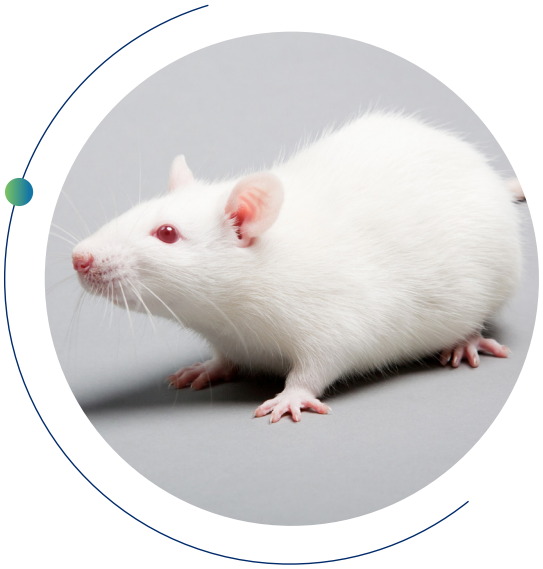
AURIGENE
PHARMACEUTICAL SERVICES

Case Study

Solid dispersion development to enhance solubility and oral bioavailability for rodent toxicology studies

Background:

- Develop oral liquid dosage form of an IND candidate (small molecule) suitable for chronic toxicology studies in rats.
- Must meet required systemic exposure and shall be dose proportional.
- Developed vehicle or used excipients shall be safe for chronic preclinical toxicology studies.



Challenges:

- Low oral bioavailability
- Practically insoluble in bio relevant media
- Basic in nature with precipitation potential at intestinal pH
- Salt did not improved solubility
- Poorly soluble in lipid excipients so limited scope for LBDDS

Aurigene solution:

- Assessment of biopharmaceutical properties indicated solubility limited oral absorption. Hence, two approaches solid dispersion and nanosuspension were evaluated to enhance oral bioavailability.
- API was crystalline and showed significant increase in solubility on ionization. These two physicochemical properties were used for solid dispersion formulation development.
- Solid dispersion and reconstitution vehicle was developed to result in enhance soluble content with minimum precipitation at intestinal pH.
- Nanosuspension was prepared by 'top down technology' using bead mill.

Outcome:

- Dose depended target systemic exposures were obtained by enhancing solubility through *in situ* salt and amorphization using solid dispersion approach

Highlights:

- Target systemic exposure was achieved with developed solid dispersion based solution formulation
- Dose dependent increase was observed
- Due to increase in oral bioavailability, required highest toxicology dose got lowered which hugely reduced API requirement for 90 days GLP toxicology studies.

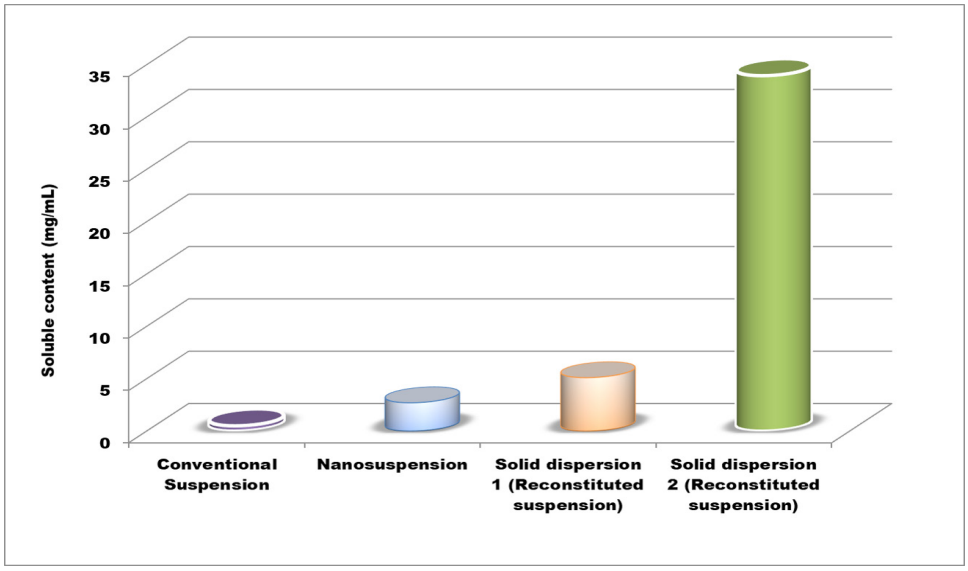


Figure-1: Soluble content in liquid formulation for dosing in various formulation approaches and compositions

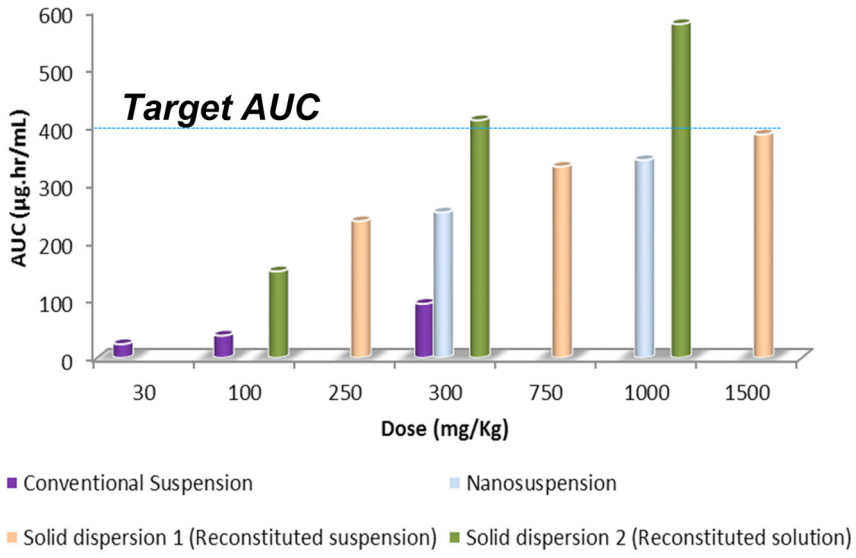


Figure-2: Systemic exposure from various formulation approaches in rodent species

Thank You

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