Use of In Vitro Release Test (IVRT) Method for Formulation Development of Semisolid Investigational New Drugs (IND)
A. Mahajan, K. Thakkar, V. Nalamothu, R. Klein
Tergus Pharma, LLC

Purpose
In-vitro release testing (IVRT) is a powerful tool for characterizing semi-solid products. Appropriately developed IVRT methods can be sensitive to differences in physicochemical properties in the formulations. The present study describes release profiles of several Investigational new drug formulations. The experimental design included development and manufacture of different formulations followed by determination of release profiles. The release profiles along with other tests were used to select a prototype to be used for Pre-clinical and Phase I clinical studies.

Methods
Eight creams containing two different drug substances and various penetration enhancers and functional excipients were prepared with same preservatives, buffers and solvents while the difference being four penetration enhancers PE1, PE2, PE3 and PE4. The formulations were tested for release rates using multi-station Vertical Diffusion cell system and PVDF membrane as the barrier. The samples obtained from vertical diffusion cells were analyzed using HPLC. The parameters such as membrane interference, media selection, dose discrimination and method robustness were evaluated while developing an appropriate release rate method.

Results
A robust IVRT method demonstrating dose discrimination was developed for determination of release rates of active pharmaceutical ingredients from cream products. Several Formulation development approaches led to use of optimum penetration enhancers to obtain desired release profiles specific to each active. The cream product 2A containing Alcohol based Penetration enhancer PE1 showed highest release rate for both the actives amongst all the formulations while some of the structure forming excipients contributed towards to better release rates than most of the formulations.

Conclusion
The release profiles of both actives followed the same rank order in all formulations tested. Since two actives have very different physicochemical properties, the release profiles are dictated by the formulation components such as penetration enhancers and NOT the drug substance. Hence the release rates were the major indicators in selection of ideal formulation for next stage in product development. This shows that IVRT is a useful tool to screen various prototype formulations. The study described here integrates IVRT with formulation development strategies to develop and select candidates for Pre-clinical toxicological studies and/or Phase I clinical trials.