Evaluation of Apisolex™ for Parenteral Use: Solubilizing Poorly Soluble Small Molecules and PROTACs

Jianyan Wang[1], Sanjib Saha[1], Stacey Marden[1], Hsin-Chieh Chen[1], Paresh Chothe[3], Aixiang Xue[2], Eric Gosselin[3], Wenzhan Yang[1], Liping Zhou[1], Annette Bak[1]

[1]Advanced Drug Delivery, Pharmaceutical Sciences, R&D, AstraZeneca, Boston, US; [2]Animal Science and Technologies, R&D, AstraZeneca, Boston, US; [3]Oncology Drug Metabolism and Pharmacokinetics, R&D, AstraZeneca, Boston, US

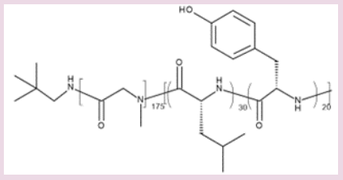
2019039

Abstract

Delivering poorly soluble small molecules and proteolysis-targeting chimeras (PROTACS) at relatively high doses as injectables could be very challenging. Apisolex™ LY, a novel multiblock copolymer comprising a poly(sarcosine) block and a D,L-mixed poly(amino acid) block shows promise in substantially enhancing API solubility for parenteral applications. It is non-toxic, non-immunogenic, biocompatible, and biodegradable. We carefully selected five model compounds with challenging formulations and conducted a comprehensive evaluation of Apisolex™ LY . The result demonstrated that Apisolex™ LY significantly improved the solubility of the tested compounds, exhibiting compatible or superior solubilization power over conventional solubilizing excipients.

Introduction

- Apisolex™ LY exhibits the potential to increase the solubility of hydrophobic APIs with simple formulation techniques. The resulting formulation can be lyophilized and reconstituted in water or saline prior to use.
- We evaluated Apisolex™ LY solubilization performances using various formulation processes.



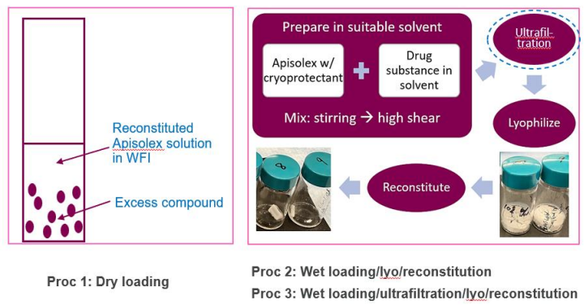
Methods

- Model compounds with diverse physchem properties were selected (Table 1)
- Apisolex™ LY was evaluated with dry loading, wet loading/lyophilization and wet loading/ultrafiltration/lyophilization processes via micelle formation. (Figure 1 & 2)

Table 1 Physchem properties of model compounds

Compound	MW	Ion Class	pKa	cLog P	Aq. Solubility (µg/mL)@pH7.4
CPD 1	1438	zwitterion	3.7, 12.9 (A) 9.0, 5.5 (B)	14	<1
CPD 2	1545	zwitterion	3.7, 13.1 (A) 9.0, 5.4 (B)	14	<1
CPD 3	430	neutral	2.1 (B)	3	17
CPD 4	946	zwitterion	4.7 (A), 3.5, 8.5 (B)	10	<1
CPD 5	471	weak base	4.7 (B)	2	<1
CPD 6	470	weak base	3.8 (B), 11.6 (A)	4	<1

Figure 1 Processes used for evaluation

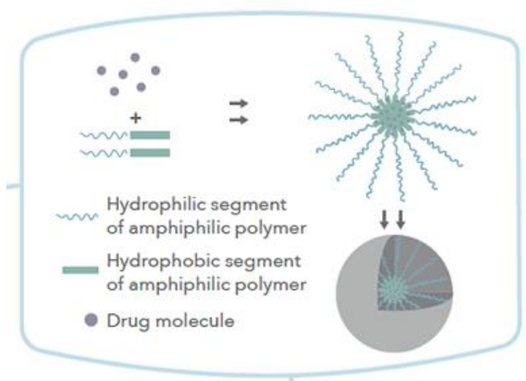


Proc 1: Dry loading

Proc 2: Wet loading/lyo/reconstitution

Proc 3: Wet loading/ultrafiltration/lyo/reconstitution

Figure 2 Polymer micelle technology



Results

Evaluation of dry loading method

Table 2 Improvement of solubility in presence of 6% Apisolex

Compound	Sol in water (mg/mL) & pH	Sol in 6% Apisolex (mg/mL) & pH	Fold increase in solubility
CPD 1	0.000027 (6.50)	0.073 (7.43)	2700
CPD 3	0.101 (6.42)	1.844 (4.59)	18
CPD 4	ND (7.52)	0.352 (4.95)	NA
CPD 5	0.00079 (6.34)	0.129 (4.21)	163
CPD 6	0.000032 (6.70)	0.0031 (4.40)	96

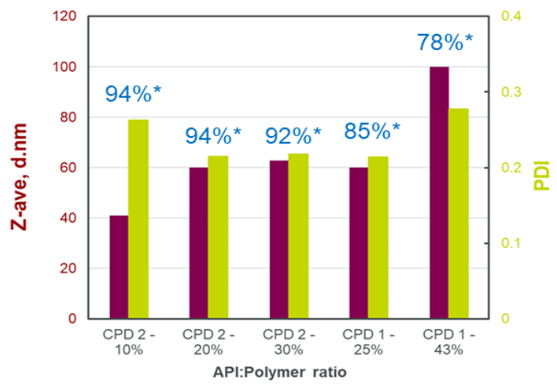
Evaluation of mixing/lyophilization process

Table 3 Improvement of solubility using process 2

Compound	Sol (mg/mL) in formulation w/15% Api.	Fold incr. in sol vs. water	DL (API : Apisolex)	Sol with best excipients (mg/mL)
CPD 1	6-14	222K-519K	10	3.3 (30% SBECD)
CPD 3	29-30	287-297	20	23.7 (20% HPBCD)
CPD 4	21-22	NA*	14	7.2 (30% SBECD)
CPD 5	0.64	810	<5	0.027 (1% Tween 80)
CPD 6	0.063	2594	<5	w/prodrug approach

Introduction of helper solvent (e.g. DMSO) improves drug loading efficiency

Figure 3 Higher drug loading achieved with helper solvent and subsequent ultrafiltration step

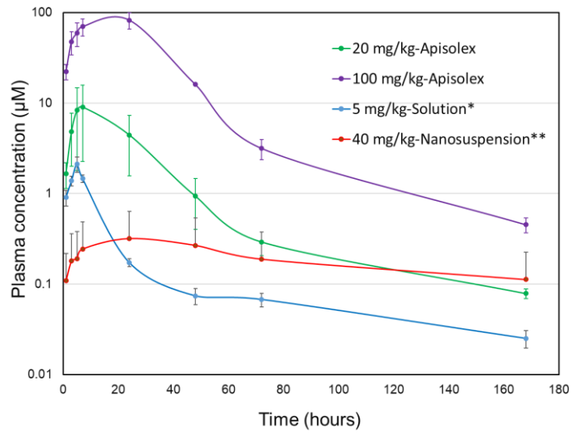


(*) Encapsulation efficiency

Pharmacokinetic studies of Apisolex™ LY based formulations

Reconstituted Apisolex based formulations of CPD 2 via Proc 3 were dosed subcutaneously in mouse for pharmacokinetic studies (Figure 4).

Figure 4 Subcutaneous PK of CPD 2 Apisolex™ LY based formulations vs. conventional formulations



(*) 50% w/v Kleptose solution / 40% v/v Kolliphor HS15 solution / PEG 400 / water 40/40/3/17 v/v
(**) 4% PVP/2% AOT in water.

Conclusions

Apisolex™ LY has demonstrated the potential to effectively address solubility challenges of poorly soluble small molecules and PROTACs, enabling their preclinical evaluations at reasonably higher doses. Significant PK exposure enhancements over nanosuspensions were demonstrated No adverse effects were observed when administrated subcutaneously at a 15% w/v level.

References

[1] www.lubrizol.com/-/media/Lubrizol/Health/Campaigns/Apisolex-Brochure---Injectable-Solubility-Enhancement.pdf

Acknowledgements

The authors would like to thank Lubrizol Life Science for providing Apisolex™ LY samples for the evaluation.