Strategies for Enhancing Oral Exposure of Water-Insoluble Compounds

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Abstract

Compounds with poor water solubility, especially BCS II compounds, present challenges in *in vivo* PK studies, accounting for 60% [1] of such compounds during the preclinical stage. With the advent of novel compounds derived from combinatorial chemistry and their integration with receptor binding endeavors, there has been a noticeable positive effect on the drive for enhanced potency. However, this progress has come at the cost of significant drawbacks in terms of physicochemical properties, especially the **poor aqueous solubility and high lipophilicity** exhibited by these compounds. In addition, achieving sufficient bioavailability after oral dosing is difficult due to their solubility dependence on pH, resulting in precipitation in the gastrointestinal (GI) environment. Various strategies have been employed in our DMPK department to mitigate compound precipitation, including **pH adjustment, co-solvent addition, cyclodextrin utilization, surfactant incorporation, and/or their combinations** [2]. This poster presents multiple strategies developed by our DMPK department based on the physical-chemical properties of compounds. These strategies are organized in a vehicle screening **decision-making tree** to facilitate rapid screening of suitable vehicles for **addressing solubility issues** encountered in *in vivo* PK studies.

Objectives

It is challenging to conduct in vivo PK studies for compounds with poor water solubility, particularly BCS II compounds. The poster presents several strategies developed by the DMPK department to address these challenges, including pH adjustment, co-solvent addition, cyclodextrin utilization, surfactant incorporation, and combinations thereof.

Methods

Step one: **Supersaturated Solubility Testing in Individual Reagents**. Maximum solubility of compound A was tested in 22 commonly used individual reagents belonging to four types of buffers, co-solvents, cyclodextrin, and surfactants. Six reagents were selected due to higher solubility and were used in step 2 testing. See details in the Table 1.

Table 1. Top 6 Solubility Results of Compound A

Type	Reagent	Solubility(mg/mL) （Top 6）
Co-solvents	DMSO	＞100
	PG	6
Surfactants	Cremophor RH 40	7.5
	Solutol HS 15	6.5
Cyclodextrin	20% SBE-β-CD in water	9
Buffers	0.2M Acetic acid buffer, pH=3.8	4

Step two: **Vehicle combination and Precipitation Model**
Vehicle combination to improve solubility was explored, with the following four combinations being commonly used: 1. cyclodextrin + buffer; 2. surfactant + buffer; 3. co-solvent + cyclodextrin + buffer; 4. co-solvent + surfactant + buffer. The four combinations can effectively address solubility issues for a significant proportion of compounds in the discovery stage. The obtained solution will be further screened through simulated GI fluid precipitation testing. See details in the Table 2.

Table 2. Solubility and Precipitation Results of Compound A (5mg/mL) in 10 vehicles and SGF/SIF

Compound A	Vehicle Combination	Appearance	Precipitation Testing	
			SGF, pH1.2	SIF, pH 6.8
Vehicle 1	15% PG + 10% Cremophor RH 40 + 75% (0.2M Acetic acid buffer, pH=3.8)	Hazy suspension	NA	NA
Vehicle 2	15% PG + 10% Cremophor RH40 + 15% SBE-β-CD in (0.2M Acetic acid buffer, pH=3.8)	Clear solution	No	No
Vehicle 3	15% PG + 15% SBE-β-CD in (0.2M Acetic acid buffer, pH=3.8)	Clear solution	No	Yes
Vehicle 4	5% Cremophor RH 40 + 95% (0.2M Acetic acid buffer, pH=3.8)	Clear solution	No	No
Vehicle 5	5% Solutol HS 15 + 95% (0.2M Acetic acid buffer, pH=3.8)	Clear solution	Yes	No
Vehicle 6	2.5% Cremophor RH 40 + 2.5% Solutol HS 15 + 95% (0.2M Acetic acid buffer, pH=3.8)	Clear solution	Yes	Yes
Vehicle 7	2.5% Cremophor RH 40, 2.5% Solutol HS 15, 18% SBE-β-CD in (0.2M Acetic acid buffer, pH=3.8)	Clear solution	No	No
Vehicle 8	20% SBE-β-CD + 2% HPMC E5 in (0.2M Acetic acid buffer, pH=3.8)	Opaque suspension	NA	NA
Vehicle 9	20% SBE-β-CD + 0.5% PVP-K30 in (0.2M Acetic acid buffer, pH=3.8)	Clear solution	No	No
Vehicle 10	20% SBE-β-CD + 0.2% SLS in (0.2M Acetic acid buffer, pH=3.8)	Opaque suspension	NA	NA

Four potential vehicles, vehicle 2, 4, 7, and vehicle 9, were selected based on their solubility and stability in SGF/SIF (simulated gastric fluid /simulated intestinal fluid) , which did not precipitate. However, vehicle 4 and vehicle 9 had less organic reagents composition than vehicle 7 and vehicle 2, respectively. Therefore, vehicle 4 and vehicle 9 were selected for oral administration to dogs and underwent further *in vivo* screening.

Results

The results in Table 3 identified that vehicle 4 and vehicle 9 showed significantly increased *in vivo* exposure compared to the results from the previous studies at the same dosage level. At the same time, the excipients literatures [3] show that the safety of SBE-β-CD is better than Cremophor RH 40 in oral administration. So vehicle 9 demonstrated superior vehicle performance in terms of animal tolerance, safety, and PK data assessment. Consequently, vehicle 9 was selected for the preclinical toxicity study.

Table 3. Comparison of PK Parameters for Compound A in Dogs following Oral Administration with Three Different Vehicles

Compound A	Vehicle Combination	Appear-ance	Dose Level (mg/kg)	C_{max} (nM)	AUC_{last} (nM*h)	Percentage Increase VS Previous Study (AUC, %)
Previous Study	20% PEG400/80% (10% HP-β-CD in water)	clear solution	10	200	500	NA
Vehicle 4	5% Cremophor RH40 + 95% (0.2M Acetic acid buffer, pH=3.8)	clear solution	10	500	1300	160
Vehicle 9	20% SBE-β-CD + 0.5% PVP-K30 in (0.2M Acetic acid buffer, pH=3.8)	clear solution	10	400	1600	220

Conclusion

Considering the physicochemical properties (e.g., solubility, lipophilicity) of compounds is crucial during the discovery stage to understand their biopharmaceutical properties and select appropriate vehicles. Through a series of *in vitro* precipitation models, we identified optimal vehicles that effectively address the issue of low bioavailability in poorly soluble compounds in *in vivo* PK studies. Moreover, an extensive historical database has been created to support the use of optimal vehicles for further toxicity studies.

References

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