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Evaluation of oral exposure increase for poorly soluble compounds with dissolution-improving formulations

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Purpose

Poorly soluble compounds often fail to achieve the target plasma exposure in safety studies. Although solubilized and nanocrystal formulations may be prepared to improve the exposure, we cannot determine the most effective formulation before preparation. To address the issue, we tried to develop a workflow for improving exposure with solubilized and nanocrystal formulations by evaluating the plasma exposure of seven poorly soluble compounds in rats after oral administration.

Conclusion

We have developed the workflow to increase the oral exposure of poorly soluble compounds with the dissolution-improving formulations in rats. The increase ratio in plasma AUC by the formulations was estimated with high probability. Furthermore, no notable adverse effects were observed in any vehicle groups of the formulations in the 2-week toxicity study in rats. The results indicated that this workflow would be useful for estimating the applicability of these formulations before preparation to poorly soluble compounds, and for improving rat plasma exposure after oral administration in safety studies.

Formulations in this study

Formulation	Solubilized	Nanocrystal	MC suspension
Characteristics	• Solution • Vehicle: DMSO or NMP / Gelucire® 44/14 (1:9 v/v)	• Suspension • d50 ≈ 0.3 μm • Vehicle: 0.5% Tween 80 (w/v), 5% HPC (w/v)	• Suspension • d50 ≥ 3 μm • Vehicle: 0.5% MC
Application	• Based on toxicological findings by the vehicle of the formulation	• All toxicity studies	• All toxicity studies

Compounds in this study (BCS Class II)

Compound	logD	Thermodynamic solubility (μg/mL)			Permeability (nm/sec)
		JP2nd	FaSSIF-V2	FeSSIF-V2	
Danazol	3.68	0.39	2.2	38	260
Atovaquone	4.25	<0.00026	0.014	5.2	12
Aprepitant	4.07	0.0037	4.3	83	94
Cilostazol	2.14	6.1	7.4	16	260
Felodipine	3.60	0.37	13	203	114
Itraconazole	4.73	<0.0013	0.0072	0.29	79
Phenytoin	2.20	30	27	53	111

Proposed workflow

Solubilized formulation

Confirmation of the use of the formulation:
- Are the toxicity findings by the vehicle of the formulation acceptable?
- Is the calculated increase in the in vivo Fa sufficient?

Yes → Development of the formulation:
- Does the compound remain dissolved when the formulation was mixed with an aqueous solution?

Yes → **Applicable**
No → Not applicable

No → Not applicable

Nanocrystal formulation

Confirmation of the use of the formulation:
- Is the increase in calculated Fa due to the hypothetical decrease in particle size of the formulation sufficient?

Yes → Development of the formulation:
- Is the increase in calculated Fa due to the observed decrease in particle size of the formulation sufficient?

Yes → **Applicable**
No → Not applicable

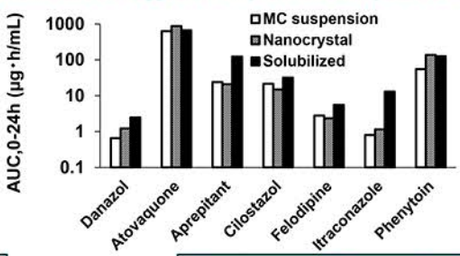
No → Not applicable

Results *Estimation of the formulated effect on plasma exposure*

[1] Acquisition of in vivo rat AUC at three formulations

AUC values were increased by solubilization and nano-sizing.

✓ Plasma AUC in rats after oral dosing at a dose of 100 mg/kg as MC suspension, nanocrystal formulation, and solubilized formulation were obtained.

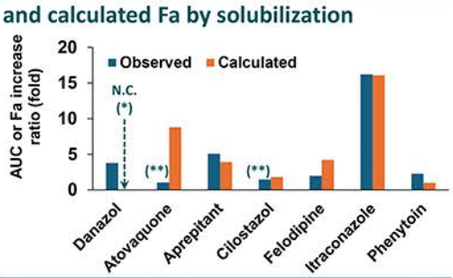


Solubilized formulation

[2] Calculation of rat Fa increase by solubilization

✓ Fa at MC suspension was calculated, assuming that non-hepatic elimination was negligible and that Fg = 1.
✓ Fa increase ratio was calculated using the reciprocal of Fa at MC suspension.

[3] Comparison of increase in observed AUC and calculated Fa by solubilization



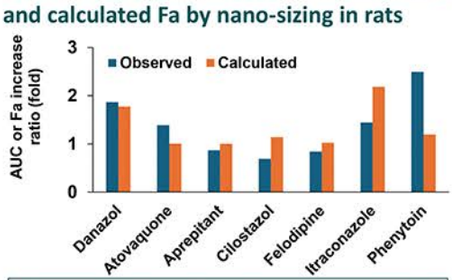
The calculated AUC increase ratio was within 3-fold of the observed one for 5 of 7 compounds.

Nanocrystal formulation

[2] Calculation of rat Fa increase by nano-sizing

✓ Fa values at MC suspension and nanocrystal formulation were calculated by the intestinal absorption simulator, BD Mini (BioavailabilityDesign LLC), assuming d50 = 3 μm (MC suspension) and 0.3 μm (nanocrystal). The ratio of Fa at nanocrystal to MC suspension was calculated.

[3] Comparison of increase in observed AUC and calculated Fa by nano-sizing in rats



The calculated AUC increase ratio was within 2-fold of the observed one for all compounds.

The increase ratio in plasma AUC by these formulations could be estimated with a high probability.

(*): Not calculated (N.C.) due to CLtotal > Qh.
(**): The compound was precipitated by mixing the formulation with an aqueous solution.

Safety assessment of the vehicles of the formulations

No notable adverse effects were observed in any vehicle groups (0.5%Tween 80/5%HPC, DMSO/Gelucire®44/14, and NMP/Gelucire®44/14). The following characteristic changes related to the dosing of Gelucire®44/14 or NMP were noted. Other findings were within our background data or spontaneous changes, and/or there were no related changes in histopathology.

Gelucire®44/14 :
○Decreased urine volume and increased specific gravity were noted in the DMSO/Gelucire®44/14 and NMP/Gelucire®44/14 groups. Protein and ketone bodies in urinalysis tended to be higher than in the control group due to concentrated urine.
○DMSO/Gelucire®44/14 and NMP/Gelucire®44/14 were melted at around 65℃ and then administered at around 45℃; the temperature at the dose did not affect the gastrointestinal tract in this study. Loose stools or diarrhea have been concerns; however, those findings were not noted under the condition of this study.

NMP :
○Urine color was deep yellow in all NMP dosing animals, but the grade was judged within normal. The NMP solution was colorless; however, this color change has been previously reported as a finding associated with NMP.

Methods

Physicochemistry:

Log D, solubility (JP2nd, FaSSIF-v2, FeSSIF-v2), membrane permeability (PAMPA)

In vivo rat pharmacokinetics:

i.v.; 0.1 mg/kg, p.o.; 100 mg/kg (0.5% MC suspension, nanocrystal formulation, solubilized formulation) to male CD(SD) rats (7–8 weeks old, n = 3). Plasma concentrations were measured and AUC for 0–24h was calculated.

In vivo rat 2-week repeated toxicity study:

Groups: 0.5% MC (control), 0.5% Tween 80/5% HPC, DMSO/Gelucire®44/14 (1:9), NMP/Gelucire®44/14(1:9)
p.o.; each vehicle 5 mL/kg/day to male CD(SD) rats (8 weeks old, n=6/group); Clinical signs, Body weights, Food consumption, Water consumption, Urinalysis, Hematology, Blood chemistry, Autopsy, Organ weights and Histopathology were evaluated.

AUC: Area under the plasma concentration curve
BCS: Biopharmaceutics classification system
CLtotal: total body clearance
DMSO: Dimethyl sulfoxide
d50: Median diameter in particle size distribution
Fa: Fraction absorbed from the gastro-intestinal tract
Fg: Availability from the gastro-intestinal tract to portal vein
HPC: Hydroxypropyl cellulose
MC: methylcellulose
NMP: N-Methyl-2-pyrrolidone
Qh: hepatic blood flow rate

COI disclosure information

Lead Presenter/Responsible Researcher
Teruki Hamada
I have no financial relationships to disclose.