

A Standardized Procedure for Preparing an Intravenous Dosing Vehicle for Poorly Soluble Research Compounds



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Purpose

Evaluate a standardized in situ intravenous administration technique for solubilizing poorly soluble research NCEs.

Methods

A simple 2 step protocol (Figure 1) to produce standardized solubilization dosing vehicles for increasing the solubility of 5 model drugs with low water solubility (Table 1) was evaluated. The commercially available intravenous dosing vehicle (*Lead Select IV Discovery Kit*, www.ephares.com) comprises a Transfer Medium (Liquid A) and sterile Lipid Dispersion (Liquid B). This Kit uses the technique of Instant Solubilization [1] to increase the solubility and prevent precipitation upon intravenous parenteral administration of insoluble compounds. The lipid dosing vehicle has very low toxicity and should be slowly infused.

Figure 1 Preparation Protocol

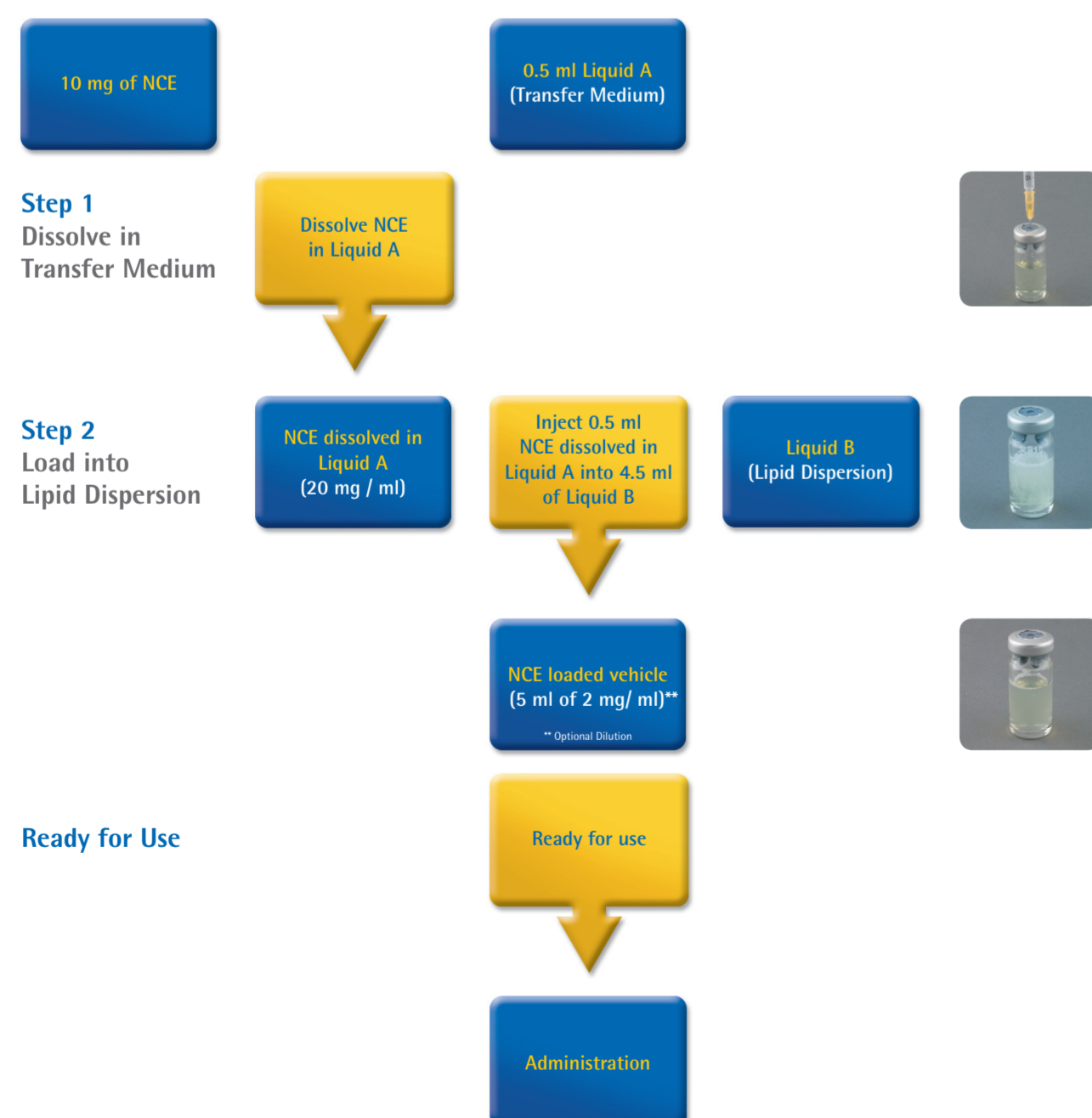


Table 1 Summary of Model Compounds Examined

| Compound | Candesartan | Carbamazapine | Celecoxib | Dexamethasone | Fenofibrate |
|----------|-------------|---------------|-----------|---------------|-------------|
| MW | 441 | 237 | 381 | 392 | 361 |

Solubilization (Physical stability)

The % drug solubilized immediately after loading and after 24 hours at three temperatures (fridge, room temperature (RT) and 40°C) was determined by filtration of the loaded vehicle followed by HPLC and microscopic observation. To verify the increase in solubility was not due to presence of solvent or supersaturation, controls were also carried out by performing the procedure without lipid dispersion.

Dilution

The proportion of drug solubilized after dilution 1 to 10 with 5 % glucose was determined after filtration followed by HPLC.

Chemical stability

To verify whether chemical degradation interferes with the results, the chemical stability of the compound loaded vehicle after 24 hours was investigated by HPLC.

Speed of preparation

The time required for preparation for each drug loaded vehicle was also noted.

Results and Discussion

% Solubilization (Physical stability)

The results of the solubilization experiments before and after dilution of the loaded vehicle are shown in Table 2.

Table 2 Summary of Solubilization Experiments

| Time Point of Measurement | Solubilization Unit | Candesartan | Carbamazapine | Celecoxib | Dexamethasone | Fenofibrate |
|---------------------------|---------------------|-------------|---------------|-----------|---------------|-------------|
| T0 | mg / ml | 2.0 | 2.1 | 1.9 | 1.9 | 1.9 |
| T24 (Fridge) | % solubilized of T0 | 99.5% | 99.2% | 100.7% | 99.3% | 98.8% |
| T24 (RT) | % solubilized of T0 | 98.8% | 97.6% | 98.6% | 99.9% | 98.9% |
| T24 (40°C) | % solubilized of T0 | 96.5% | 99.3% | 101.3% | 99.4% | 98.1% |
| T24 (Fridge) dil. | % solubilized of T0 | 95.4% | 99.2% | 97.2% | 100.0% | 106.1% |
| T24 (RT) dil. | % solubilized of T0 | 89.1% | 97.2% | 95.3% | 92.8% | 99.8% |
| T24 (40°C) dil. | % solubilized of T0 | 93.4% | 100.8% | 99.5% | 102.9% | 107.3% |
| T0 Control | mg / ml | 0.167 | 0.972 | 0.058 | 0.449 | 0.107 |
| T24 (Fridge) Control | mg / ml | 0.184 | 0.558 | 0.045 | 0.368 | 0.015 |

At a compound concentration of 2 mg/ml, visual and microscopic inspection of the drug loaded dispersions were sufficient to detect possible precipitation. No precipitation was observed at T0 and T24 hours at the three temperatures tested. This was also verified and confirmed by HPLC.

The controls demonstrated that the solvent (10 %) after loading was not significantly contributing to the increased solubility for most compounds.

Dilution

Precipitation did not occur 24 hours after a x10 fold dilution with 5 % glucose for any of the compounds.

Chemical Stability

The chemical stability for each compound was checked (results not reported) and found not to change significantly after 24 hours at any of the conditions studied.

Ease of Preparation

The first step (dissolving compound in the transfer medium) took the longest time. The time needed was approximately at most 15 minutes. The second step (loading) took 5 minutes and the (optional) dilution step took an additional 5 minutes.

Conclusions

The loading procedure was found to be highly reliable for the 5 compounds tested at 2 mg/ml

- Amount of compound required: ca. 5 to 10 mg
- Inspection of concentrate: Visual or HPLC
- Inspection after dilution: HPLC (depends upon level of dilution)
- Physical stability after dilution: No precipitation at T0 and T24 (fridge, RT and 40°C)
- Preparation time: ca. 15 to 25 minutes per compound

The compound loaded formulations are suitable for rapidly determining absolute bioavailability, early pharmacokinetic performance and fundamental efficacy of a poorly soluble compound after parenteral intravenous administration without precipitation.

[1] Van Hoogevest, P., Rogue, V., Brumec, M., Schwebel, H., Grunkemeyer, J.L., Leigh, M.L.S., Instant solubilisation of poorly water-soluble drugs by in-situ loading of aqueous phospholipid dispersions, suitable for parenteral administration Journal of Parenteral Drug Association (2006), 60 (6), 277-377.