

***PHARES* Drug Delivery AG**

Muttenz, Switzerland

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Instant Loading of Lipid Dispersions With Insoluble Pharmaceutical Actives

Nuremberg, Germany

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Room Paris

PHARES Company Information

- Located in MuttENZ, just outside Basel, Switzerland
- Move to Switzerland from UK, December 2000
- Founded 1985
- Privately owned

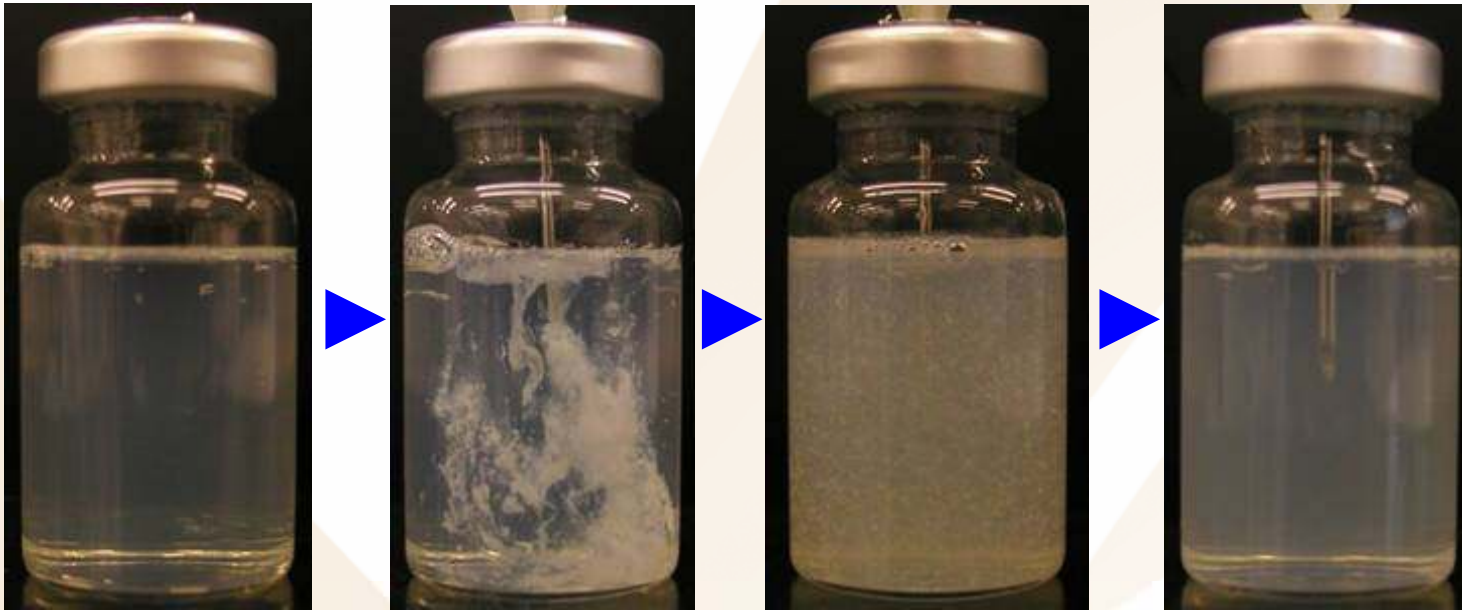
Introduction:

SupraVail™ Instant Solubilization System

- Two bottle system:
 - 1) Placebo Lipid Dispersion
 - 2) Transfer Medium: drug in organic solvent
- The two are mixed together, organic drug concentrate is diluted with water, two possible outcomes:
 - 1) Drug precipitates
 - 2) Drug partitions into phospholipid bilayer

System is designed to safely direct all drug into the lipid bilayer.

SupraVail™ Instant Solubilization System



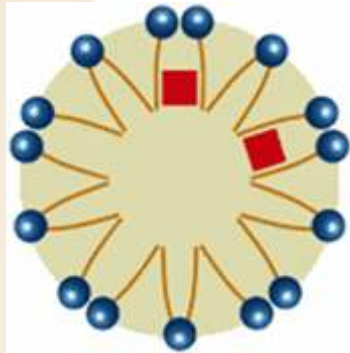
Placebo lipid dispersion is clear and translucent

Organic drug concentrate mixes with lipid dispersion

Drug partitions into the lipid phase within seconds

Drug loaded lipid dispersion is again translucent

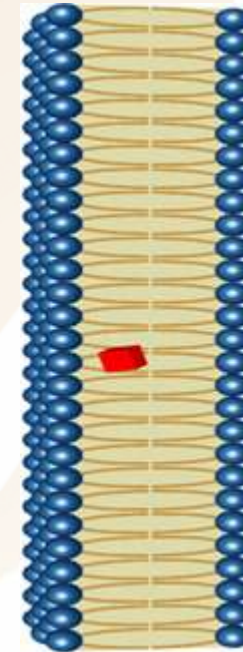
Rationale of Lipid Mediated Delivery of Poorly Water Soluble API's



Lipid Drug Complex (Donor)

Micelles, emulsions, liposomes

Drug molecularly dispersed in lipid domain



Lipid Domain (Acceptor)

Epithelial membrane

Lipoproteins, etc.



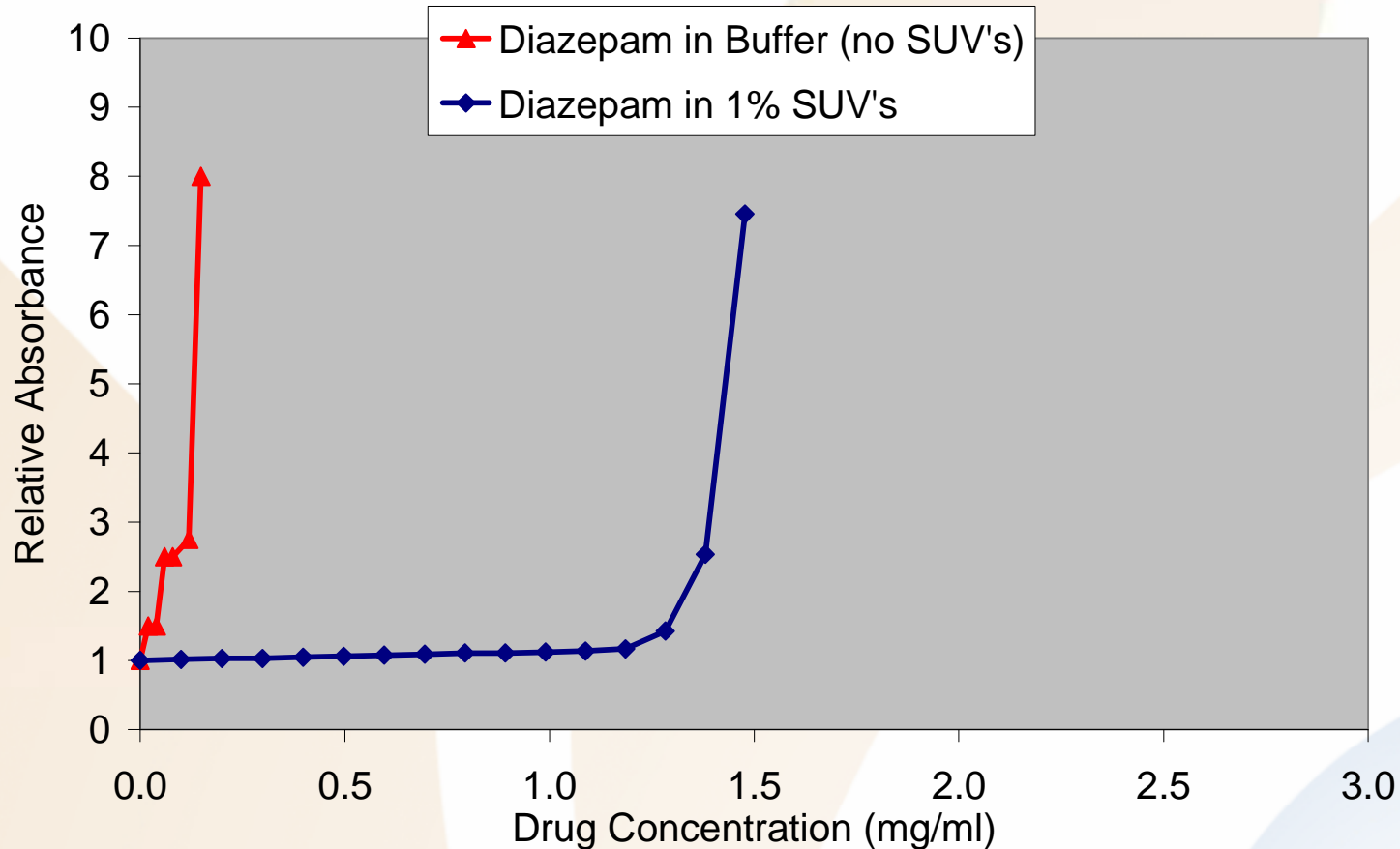
Placebo Lipid Dispersion

- 10% m/v Diacylphospholipids, soya or egg source
- Glycerol for isotonicity
- Buffer system for long term lipid stability
- High shear mixing to hydrate lipids followed by high pressure homogenisation
- Sterile filtration / aseptic filling
- Particle size typically 50-60nm
- Transmission important parameter

Transfer Medium

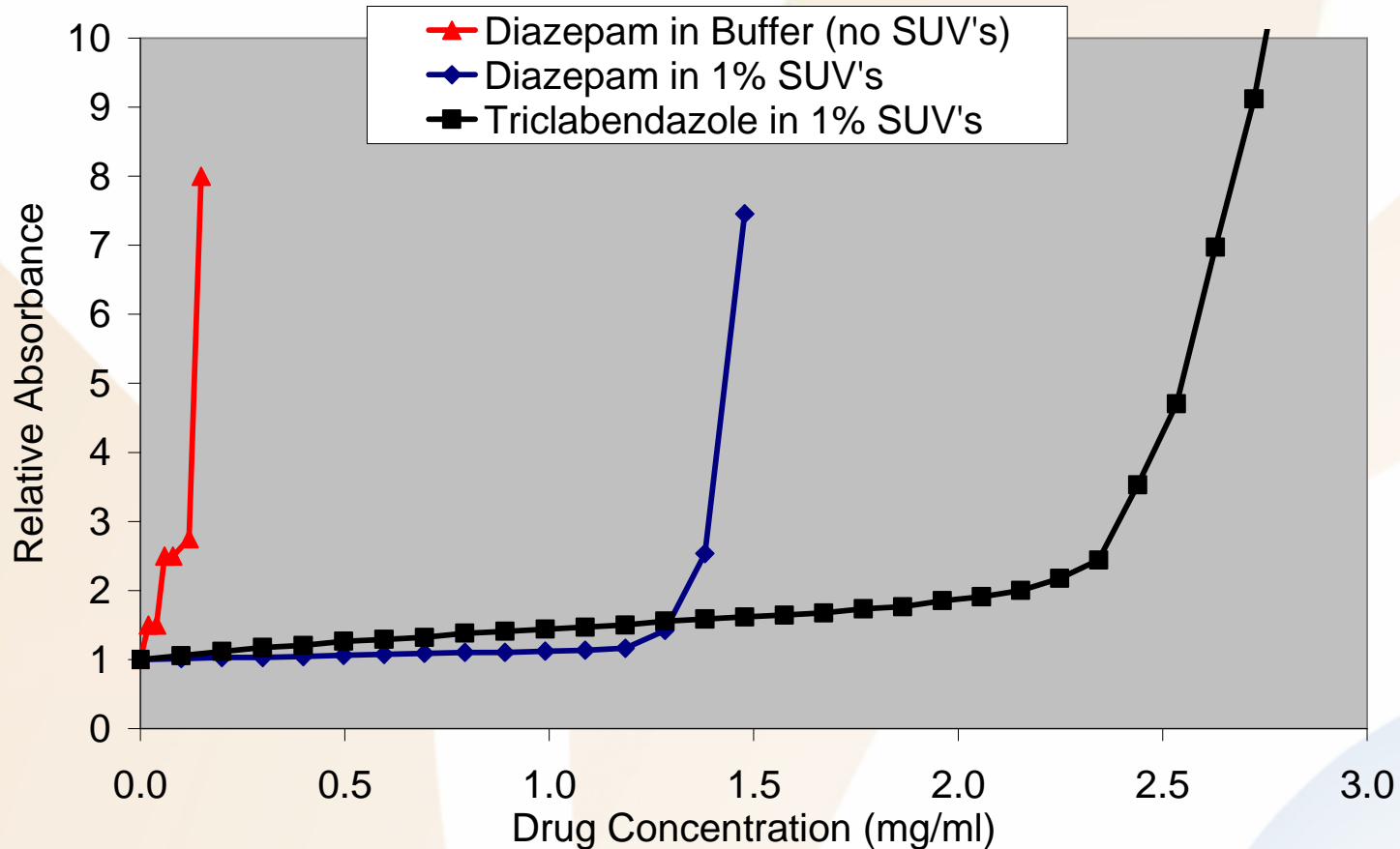
- Drug + organic solvent
- Maximum 10% w/v in final solution for infusion
- Parenterally acceptable solvents:
ethanol, polyethylene glycol, propylene glycol
- Choose solvent or mixture with best drug solubility
- Most significant constraint: viscosity

Loading Capacity Determination



Lipid : Drug ratio to fully solubilize Diazepam:
10 mg/ml : 1.2 mg/ml = 8.3 : 1

Loading Capacity Determination



Lipid : Drug ratio to fully solubilize Triclabendazole:
 $10 \text{ mg/ml} : 2.4 \text{ mg/ml} = 4.2 : 1$

Chemical & Physical Stability

Sample/ Storage Condition	Before filtration			After filtration		
	Assay in %	Aspect	Particle Size (nm)/PI	Assay in %	Aspect	Particle Size (nm)/PI
Before addition of DS solution		Opalescent, no visible particles	50.7 / 0.325			
Starting value immediately after mixing	100.4	Slightly turbid no visible particles	54.1 / 0.354	99.1	Opalescent, no visible particles	52.1 / 0.328
1 hour after mixing	98.7	Slightly turbid no visible particles	53.0 / 0.367	99.5	Opalescent, no visible particles	49.1 / 0.309
2 hours after mixing	98.9	Slightly turbid no visible particles	51.6 / 0.333	99.3	Opalescent, no visible particles	48.8 / 0.291
3 hours after mixing	98.9	Slightly turbid no visible particles	51.4 / 0.352	99.4	Opalescent, no visible particles	47.8 / 0.303
4 hours after mixing	99.6	Slightly turbid no visible particles	54.3 / 0.377	100.3	Opalescent, no visible particles	47.4 / 0.331

Short term physical and chemical stability of drug containing dispersion and influence of filtration through a 0.22 μm IV Express (Millipore) filter on the characteristics of the drug loaded lipid dispersion.

Dilution Behaviour

Storage Period	Particle Size (nm) / PI	Aspect
Start	52.7 / 0.391	Opalescent, no visible particles
10 minutes	52.8 / 0.411	Opalescent, no visible particles
30 minutes	58.1 / 0.416	Opalescent, no visible particles
60 minutes	54.1 / 0.377	Opalescent, no visible particles
24 hours*	55.2 / 0.398	Opalescent, no visible particles

* Stored at room temperature

Influence of 1:1 v/v dilution at room temperature with physiological glucose (5%) solution on the physical stability of the drug containing dispersion.

Advantages of SupraVai™ Instant Solubilization

- Physical stability of placebo dispersion much better
- Drug-loaded dispersion typically freeze dried (\$\$\$) to maintain chemical and physical stability
- High local and systemic tolerance
- Typical phospholipid dose during Total Parenteral Nutrition: >10 g i.v. / day

SupraVai™ Instant Solubilization

- No precipitation expected, drug is fully solubilised
- No “stealth” or depot properties
- No cholesterol added to stabilise lipid dispersion
- No targeting intended

Further Points

- Rapid release of drug payload to lipophilic blood components (phospholipids, lipoproteins):
 - + extremely high surface area
 - + single unilamellar vesicles
 - + liposomes disintegrate rapidly
- Instantly loaded lipid vesicles are transient solubilisers, a sort of biocompatible, “natural solvent”

Conclusions

- Viable formulation option for parenteral delivery of poorly soluble compounds
- Excellent local and systemic tolerability
- Enables rapid evaluation in both preclinical and clinical settings
- Placebo Lipid Dispersion is a universalised component of the system suitable for solubilizing a variety of different compounds, making it more economical

Contributors

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