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Enhancing the Solubility of Poorly Water-Soluble Drugs in the Presence of Nano-Emulsion Particles

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INTRODUCTION

Aqueous solubility of drug substances is an important parameter in preformulation studies of a drug product. Several drugs are sparingly water-soluble and pose challenges for formulation and dose administration. Literature indicates that a solution of drug in an organic solvent can be injected into an IV fluid that forms a relatively stable solution of drug for infusion (Mozzi et al., 2002 and Wright et al., 2005). The current study focuses on the influence of different types of nano-emulsions and the particle size of the nano-emulsion on the solubility of different APIs.

MATERIALS AND METHODS

APIs and IV fluids used in the current study include:

1. Ibuprofen, USP (Spectrum Chemical Manufacturers Corp.)
2. Ketoprofen, USP (Spectrum Chemical Manufacturers Corp.)
3. Benzocaine, USP (Universal Preserv-a-Chem)
4. Mupirocin, USP (Biogal Pharmaceutical Works)
5. Ketoconazole, USP (Noramco Inc.)
6. Intralipid ™ (IL), 20% (Baxter Healthcare Corp.)
7. Normal saline (NS), 0.9% sodium chloride, USP (Baxter Healthcare Corp.)
8. 5% dextrose solution (D5W), USP (Hospira, Inc.)

Nano-emulsions:

The following nano-emulsions were prepared in the laboratory:

1) Nano-emulsion-I (NE-I): 5% light mineral oil, emulsifiers (emulsifying wax, PEG 7 glyceryl cocoate) and water.
2) Nano-emulsion-II (NE-II): 5% medium-chain triglycerides, emulsifiers (emulsifying wax, PEG 7 glyceryl cocoate) and water.

Nano-emulsions were prepared by mixing the oil and water phases under high-speed homogenization (~7000 rpm) followed by microfluidization (3 passes) at ~18000 psi using a microfluidizer M110 (Microfluidics, Inc.). Intralipid™ 20% was used as supplied and after microfluidization (3 passes) at ~18000 psi. Microfluidization of Intralipid™ (Micro-IL) decreased the particle size from 265 to 188 nm.

Each API was dissolved in ethanol at 3-16% (wt/wt) depending on the solubility limit of API in ethanol. Typically 5% (wt/wt) ethanolic solution of the API was injected into: a) NE-I, b) NE-II, c) IL, d) Micro-IL, e) mixtures of nano-emulsions with NS or D5W, and f) mixtures IL with NS or D5W. The solubility was monitored for 72 hrs at room temperature (20-23°C).

Solubility of Ketoprofen, Benzocaine, Ketoconazole, and Mupirocin was determined via a UV spectrophotometer (Pharma Spec UV-1700 [Shimadzu]), whereas Ibuprofen solubility was determined via a UPLC (Ultra Performance Liquid Chromatography; Waters Corp., Milford, MA). The particle size of Intralipid™ and nano-emulsions was determined using a Zetasizer Nano-S (Malvern Instruments, Westborough, MA).

RESULTS

Table 1: Particle size of different nano-emulsions as determined by Zetasizer Nano-S.

Nano-Emulsions	Particle Size, nm
Intralipid™ (IL)	265
Microfluidized Intralipid™ (Micro-IL)	188
Nano-emulsion-I (NE-I)	75
Nano-emulsion-II (NE-II)	68

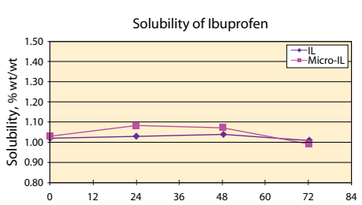

Fig. 1: Solubility of Ibuprofen (% wt/wt) monitored for 72 hrs at room temperature in Intralipid™ (IL) and microfluidized Intralipid™ (Micro-IL).

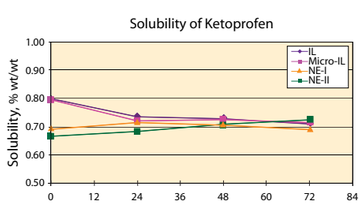

Fig. 2: Solubility of Ketoprofen (% wt/wt) monitored for 72 hrs at room temperature in Intralipid™ (IL), microfluidized Intralipid™ (Micro-IL), and nano-emulsions I and II (NE-I and NE-II respectively).

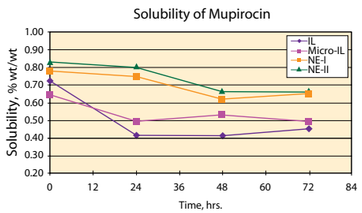

Fig. 3: Solubility of Mupirocin (% wt/wt) monitored for 72 hrs at room temperature in Intralipid™ (IL), microfluidized Intralipid™ (Micro-IL), and nano-emulsions I and II (NE-I and NE-II respectively).

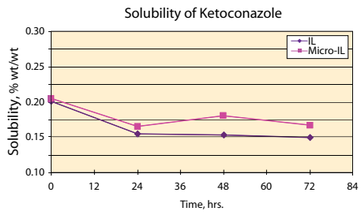

Fig. 4: Solubility of Ketoconazole (% wt/wt) monitored for 72 hrs at room temperature in Intralipid™ (IL) and microfluidized Intralipid™ (Micro-IL).

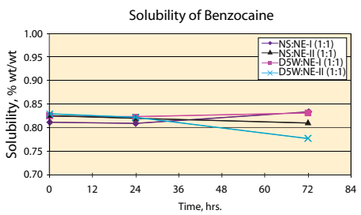

Fig. 5: Solubility of Benzocaine (% wt/wt) monitored for 72 hrs at room temperature in 1:1 (wt/wt) mixtures of nano-emulsions (NE-I and NE-II) with normal saline (NS) and 5% dextrose solution (D5W).

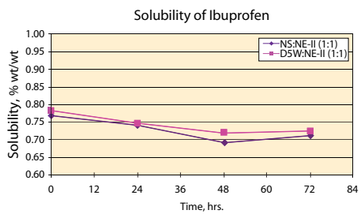

Fig. 6: Comparison of the solubility of Ibuprofen (% wt/wt) monitored for 72 hrs at room temperature in 1:1 (wt/wt) mixtures of nano-emulsion (NE-II) with normal saline (NS) and with 5% dextrose solution (D5W).

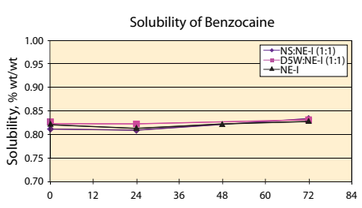

Fig. 7: Comparison of the solubility of Benzocaine (% wt/wt) in nano-emulsion-I (NE-I) and in the two mixed systems of 1:1 (wt/wt) mixtures of NE-I with normal saline (NS) and with 5% dextrose solution (D5W). Solubility was monitored for 72 hrs at room temperature.

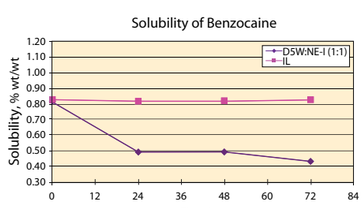

Fig. 8: Comparison of the solubility of Benzocaine (% wt/wt) in 1:1 (wt/wt) mixtures of Intralipid™ (IL) with 5% dextrose solution (D5W) and in Intralipid™ by itself. Solubility was monitored for 72 hrs at room temperature.

Nano-emulsions I and II showed good compatibility with both IV fluids NS and D5W. Data in Fig. 7 shows that in 1:1 mixtures (wt/wt) of NS or D5W with NE-I, solubility of Benzocaine is at the same level as in the NE-I by itself. However, in the mixed system of IL and D5W (1:1; wt/wt), solubility of Benzocaine dropped significantly compared to that in IL by itself (see Fig. 8), suggesting that the nature of nano-emulsion particles will influence the solubility of Benzocaine and that the dilution of the IL with D5W will reduce the solubility of Benzocaine.

DISCUSSION

When the ethanol solution of the drug was injected into water, it instantly precipitated the drug; however, when injected into a dispersion containing nano-emulsion particles, the drug did not precipitate. The enhanced solubility of APIs in the presence of nano-emulsions may be explained in two ways:

1) The ethanol solution of the API enters the core of the nano-emulsion particle, thus making it dissolve.
2) Nano-clusters are formed around the API particles before it crystallizes out from the ethanol solution.

Table 2: Solubility data for APIs in light mineral oil (LMO) and in medium-chain triglycerides (MCT) at room temperature.

OILS	Solubility in Oils, mg/ml				
	Ibuprofen	Ketoprofen	Benzocaine	Ketoconazole	Mupirocin
LMO	7.36	ND	0.58	ND	ND
MCT	12.36	5.43	5.83	0.06	ND

ND: not detectable by UV spectrophotometer.

The nano-emulsions I and II used in the current study are comprised of light mineral oil and medium-chain triglycerides respectively. In general, solubility of APIs was not detectable (too low to be detected by UV spectroscopy) in LMO or very low (0.58 mg/ml for Benzocaine) except for Ibuprofen (~7 mg/ml). In MCT, Mupirocin was not detectable and Ketoconazole showed very low solubility (0.06 mg/ml), whereas Benzocaine, Ketoprofen, and Ibuprofen showed solubility at 5-12 mg/ml. Although Mupirocin is insoluble in LMO and in MCT, the nano-emulsions comprised of LMO (NE-I) or MCT (NE-II) showed significant increase in the aqueous solubility (see Table 3). This observation leads one to hypothesize that when an ethanol-drug solution is injected into the nano-emulsion, ethanol dissipates into the aqueous media and the nano-emulsion particles form nano-clusters around the drug before it precipitates. Ketoconazole, Ketoprofen, and Benzocaine also showed significant increase in aqueous solubility (see Table 3) compared to their solubility-in-oil phases (LMO or MCT; see Table 2), thus it supports the hypothesis of formation of nano-clusters to explain the enhanced solubility in the aqueous phase.

Formation of nano-clusters around the drug particle is thought to be similar to the "solvation" of solute by solvent molecules. In general, the enhanced solubility of API in nano-emulsion systems will depend on the compatibility of the API with the nano-emulsion particles.

Solubility of drug in the presence of nano-emulsion particles is subject to:

1) Stability of nano-emulsion particles
2) Temperature of storage: If nano-emulsion particles are not stable at 40°C, the drug will quickly precipitate. This behavior is the opposite of normal aqueous solubility, where solubility typically increases with temperature.

Table 3: Comparison of aqueous solubility of various APIs determined in the current study with that reported in the literature.

API	Reported Aqueous Solubility; mg/ml	Solubility from Current Study; mg/ml	Increase in Solubility; Fold
Ibuprofen	1.40×10^{-1} [1]	10.2	72
Ketoprofen	2.94×10^{-1} [2]	7.2	24
Benzocaine	4.00×10^{-1} [3]	8.1	20
Ketoconazole	8.70×10^{-5} [4]	1.6	18,390
Mupirocin	2.65×10^{-2} [4*]	4.6	173

[1]: Manrique and Martinez (2007)
[2]: Hadgraft et al. (2000)
[3]: Merck Index (2001)
[4]: as indicated at http://www.drugbank.ca
* calculated value

CONCLUSIONS

1. Data has shown that injecting ethanolic solutions of the APIs into nano-emulsions increased the solubility of the drug by 20-fold to >18,000-fold in aqueous media.
2. Solubility of API in the aqueous phase of nano-emulsions is dependent on the nature of nano-particles. The solubility may change with the dilution of the nano-emulsion.
3. Enhanced aqueous solubility in the presence of nano-emulsion is suspected to be due to a mechanism similar to that of "solvation" of solute particles. It is contemplated that the nano-emulsion particles trap the solute particles in nano-clusters that prevent the solute particles from crystallizing.

REFERENCES

Hadgraft, J., du Plessis, J., and Goosen, C. (2000) "The selection of non-steroidal anti-inflammatory agents for dermal delivery" *Int. J. Pharm.* **207:** 31-37.

Manrique, J. and Martinez, F. (2007) "Solubility of ibuprofen in some ethanol + water cosolvent mixtures at several temperatures" *Lat. Am. J. Pharm.* **26:** 344-354.

Mozzi, G., Benelli, P., Bruzzese, T., Galmozzi, M.R., and Bonabello, A. (2002) "The use of lipid emulsions for the i.v. administration of a new water soluble polyene antibiotic, SPK-843" *J. Antimicrob. Chemother.* **49:** 321-325.

Wright, D.W., Ritchie, J.C., Mullins, R.E., Kellermann, A.L., and Denson, D.D. (2005) "Steady-state serum concentrations of progesterone following continuous intravenous infusion in patients with acute moderate to severe traumatic brain injury" *J. Clinical Pharmacol.* **45:** 640-648.