

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

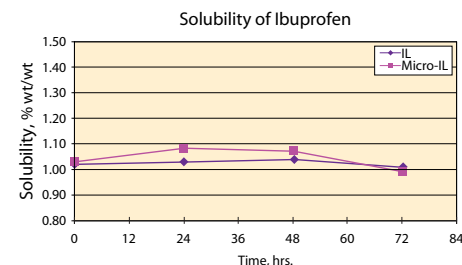


Fig. 1: Solubility of Ibuprofen (% wt/wt) monitored for 72 hrs at room temperature in Intralipid™ (IL) and microfluidized Intralipid™ (Micro-IL).

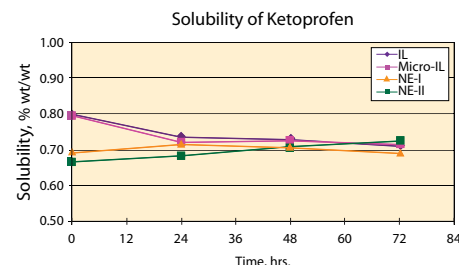


Fig. 2: Solubility of Ketoprofen (% wt/wt) monitored for 72 hrs at room temperature in Intralipid™ (IL), microfluidized Intralipid™ (Micro-IL), and nano-emulsions I and II (NE-I and NE-II respectively).

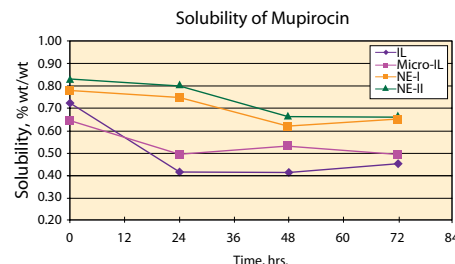


Fig. 3: Solubility of Mupirocin (% wt/wt) monitored for 72 hrs at room temperature in Intralipid™ (IL), microfluidized Intralipid™ (Micro-IL), and nano-emulsions I and II (NE-I and NE-II respectively).

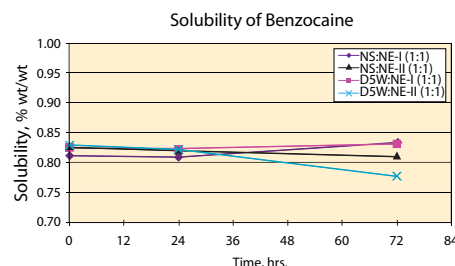


Fig. 5: Solubility of Benzocaine (% wt/wt) monitored for 72 hrs at room temperature in 1:1 (wt/wt) mixtures of nano-emulsions (NE-I and NE-II) with normal saline (NS) and 5% dextrose solution (D5W).

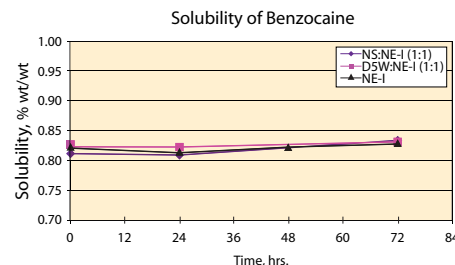


Fig. 7: Comparison of the solubility of Benzocaine (% wt/wt) in nano-emulsion-I (NE-I) and in the two mixed systems of 1:1 (wt/wt) mixtures of NE-I with normal saline (NS) and with 5% dextrose solution (D5W). Solubility was monitored for 72 hrs at room temperature.

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.

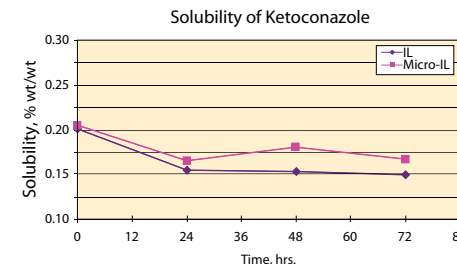


Fig. 4: Solubility of Ketoconazole (% wt/wt) monitored for 72 hrs at room temperature in Intralipid™ (IL) and microfluidized Intralipid™ (Micro-IL).

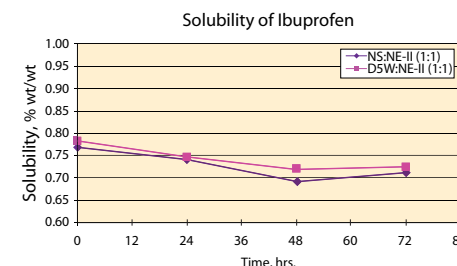


Fig. 6: Comparison of the solubility of Ibuprofen (% wt/wt) monitored for 72 hrs at room temperature in 1:1 (wt/wt) mixtures of nano-emulsion (NE-II) with normal saline (NS) and with 5% dextrose solution (D5W).

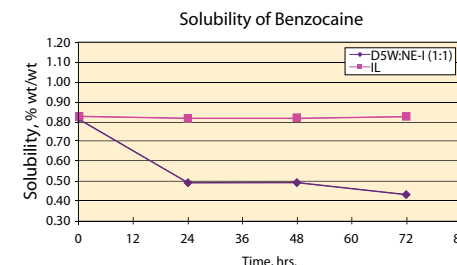


Fig. 8: Comparison of the solubility of Benzocaine (% wt/wt) in 1:1 (wt/wt) mixtures of Intralipid™ (IL) with 5% dextrose solution (D5W) and in Intralipid™ by itself. Solubility was monitored for 72 hrs at room temperature.

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 ethanolic 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^{-2} [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.

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