The use of non-ionic surfactants to enhance the solubility of poorly water-soluble drugs in liquid systems for parenteral applications

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Introduction

In the current pharmaceutical market, APIs in the pipeline continue to exhibit poor water solubility, and many estimates indicate that this fraction will continue to grow. In order to increase the intrinsic solubility of these drugs, there are many viable technology-based methods, which include amorphous solid dispersions, self-emulsifying systems, nanosuspensions. However, it is also critically important to evaluate simple liquid systems, particularly, parenteral formulations which utilize concentrations of non-ionic surfactants as a highly effective means to dissolve poorly water-soluble drugs. These applications are then introduced into the body through common parenteral routes, such as intramuscular, subcutaneous, intravenous or intradermal applications. It is also important to note that the majority of approved poorly water-soluble drugs are still administered parenterally.[1]

While these systems remain one of the most effective methods to bring drugs to market, very little efforts are spent investigating the solubilizing excipients. For example, it is common to utilize formulations containing polysorbates (polysorbate 80 and polysorbate 20), but there are additional surfactants that are as potent as solubilzers, with less known side effects. In this work, the use of two surfactants designed for use in parenteral formulations are explored, Kolliphor® HS 15 (Polyoxyl 15 Hydroxystearate) and Kolliphor® ELP (Polyoxyl-35 Castor Oil). Furthermore, while many formulators have „rules of thumb“ or preferred solubilizers, the ability to understand the effects of concentration as well as other physicochemical properties on the resulting solubility are also not well understood. A novel instrument, the Pion inForm was utilized within this work in order to map solubilization capacity of a representative poorly water-soluble drug as a function of concentration and system pH in order to better understand how these surfactants function.

Materials and Methods

Kolliphor® HS 15, or Polyoxyl 15 Hydroxystearate (USP/NF), Macrogol 15 Hydroxystearate (Ph. Eur.) is a non-ionic surfactant consisting of an ethoxylated hydroxystearate. This excipient was designed specifically to exhibit a low histamine release for fewer side effects when utilized as a parenteral excipient; an example of such data is shown in Table 1.[2, 3] For the experiments utilized herein, the product was heated to 50°C, lightly homogenized and introduced to the aqueous buffered system. A molecular depiction of Kolliphor® HS 15 is shown in Figure 1.

	Haemolytic activity [% Haemolysis]			Serum histamine level (beagle dogs) [nM]		
	0.1%	1%	10%	0	15 min	60 min
Kolliphor® HS 15	0	0	8.7	5	220	8
Polysorbate 80	0	0	11.1	3	>50000	247

Table 1: Haemolytic activity and serum histamine level of Kolliphor® HS 15 compared to benchmark Polysorbate 80[2]

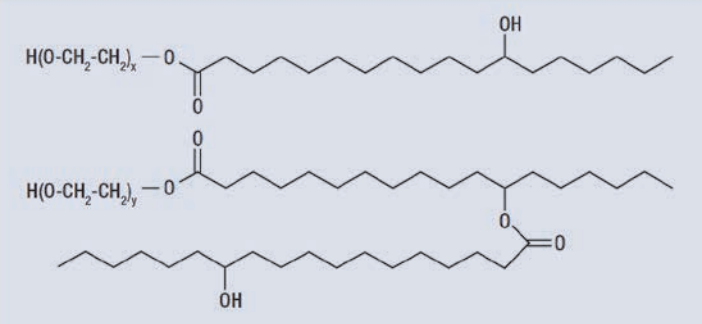


Figure 1: Representative chemical structure of Kolliphor® HS 15[2]

Kolliphor® ELP, known as Polyoxyl-35 Castor Oil (USP/NF) and Macrogolglycerol ricinoleate (Ph. Eur.) is a BASF purified version of Polyoxyl-35 Castor Oil, or Kolliphor® ELP. In contrast to the unpurified version, Kolliphor® ELP exhibits a lower viscosity, lower water content (≤0.5%), low levels of potassium, and free fatty acids, known to interact with sensitive APIs. Prior to use, it was fully liquified at 50°C and lightly homogenized, then dissolved in buffered aqueous solutions. The molecular formula is represented in Figure 2.

The model compound studied here was Danazol and studied at saturated and supersaturated conditions. Key drug properties are shown in Table 2.[4]

Solubilization capacity and effect of concentration and pH were measured utilizing the Pion inForm; this instrument is shown in Figure 3. Solubilizers Kolliphor® HS 15, Kolliphor® ELP, were tested as solubilizers in poorly water-soluble drug formulations. pH values were tested at 2, 4, 6 7.4 and 9, while concentrations of solubilizer ranged from 0 to 10%.

Solubilization was determined by dissolution at 37°C for 2 hours at desired, buffered pH value. If no equilibrium concentration was obtained, the test was repeated with longer time trials. Drug and additives were pre-weighed into empty vessels. The volume of ISA-Water (0.15 M NaCl) and Acetat-Phosphate-Buffer depends on the content of additive using in the trial. For simplicity, a density of 1g/ml is assumed for the aqueous media. The ratio of ISA-Water to Acetate-Phosphate-Buffer is always set to 1:9. The overall amount of aqueous media + additive is 40ml, and thus respectively 40g. The trials were completed using the conditions in Table 3.

Reference spectra was utilized within refinement using blank media including representative solubilizers. API concentration was included in a supersaturated state; refinement was completed using standard published method in accordance with GI Dissolution; the last 10 points measured by the UV probe were averaged as the Solubility Value of the API. Plots were created using MODDE software.

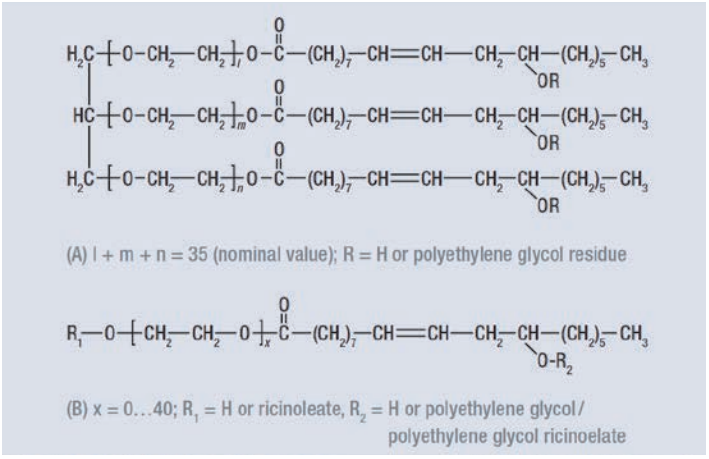


Figure 2: Representative chemical structure of Kolliphor® ELP[2]

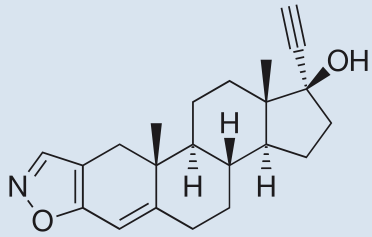
Danazol

Synthetic Steroid
337.46 g/mol
LogP: 3.62
pKa: 0.25
Solubility: 0.0176 mg/mL

Table 2: Drugs properties of Danazol as model drug for solubility

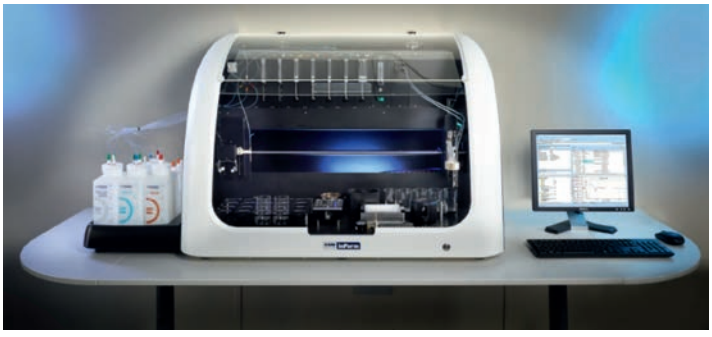


Figure 3: Pion InForm® utilized for measuring drug concentration rapidly at different pH values

Additive Content (%)	ISA-Water (mL)	Buffer (mL)	Solubilizer (g)
1	35.64	3.96	0.4
2.5	35.1	3.9	1
5	34.2	3.8	2
7.5	33.3	3.7	3
19	32.4	3.6	4

Table 3: Tested formulation concentrations

Results

In general, non-ionic surfactants are generally considered to be relatively pH independent as solubilizers, notwithstanding the pH effects on the API itself. Danzol (pKa = 0.25) in particular is not known to exhibit strong pH effects as it has no clearly defined acidic or basic groups. This was shown clearly at low concentrations of solubilizer, where little difference at different pH values was observed. However, at higher concentrations, the pH effects start to emerge. Figure 4, exhibits the raw data obtained from the Sirius inForm using solubilzer Kolliphor® HS 15, and in Figure 5, solubilizer Kolliphor® ELP.

In an effort to better visualize the data, additional trials were conducted and replotted as a surface plot reported in Figure 5, and Figure 6.

Using this method, the pH effects are much more clearly visible and focusing around a clear area of increased solubility. Through this method, a pH effect for Danazol, a very poorly water-soluble API with no defined acidic or basic group, clearly enhanced solubility in the pH range of 4 for Kollphor® HS 15 (Figure 1), and pH of 3 for Kolliphor® ELP (Figure 2). This has strong implications on the formulation of parenteral dosage forms where surfactant concentrations can easily reach nearly half the formulation.

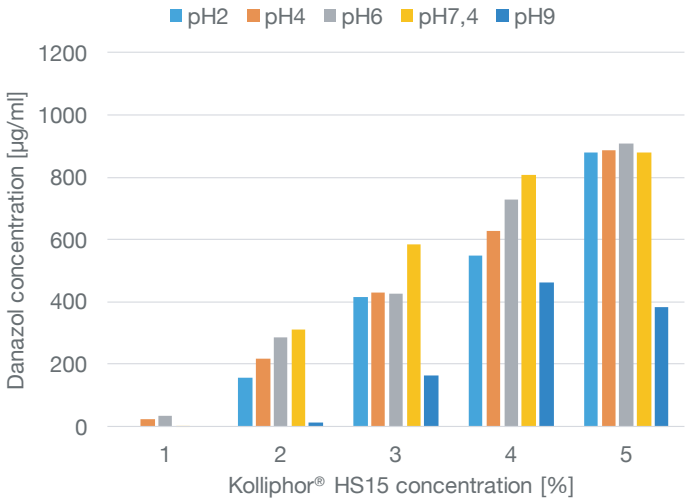


Figure 4: Danazol concentration as a function of Kolliphor® HS 15 concentration at various pH values

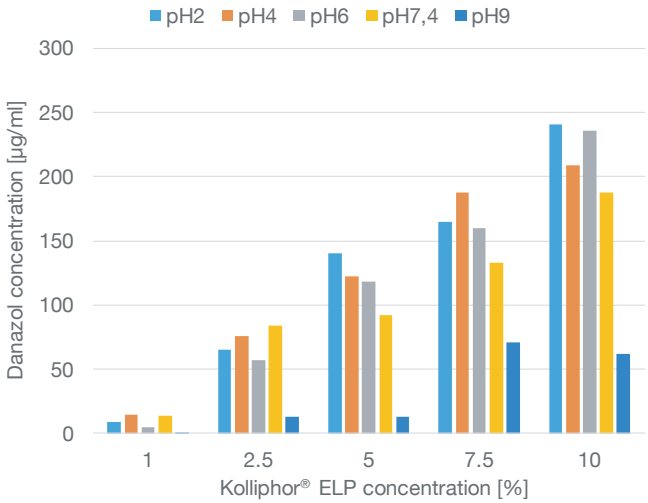


Figure 5: Danazol concentration as a function of Kolliphor® ELP concentration at various pH values

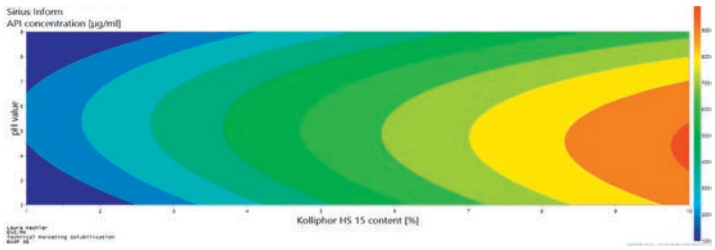


Figure 6: Danazol solubility as a function of pH and Kolliphor® HS 15 concentration

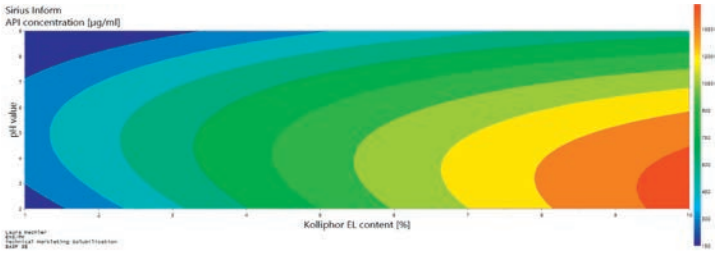


Figure 7: Danazol solubility as a function of pH and Kolliphor® ELP concentration

Conclusions

- A high throughput methodology for screening for drug solubility at different pH values with solubilizers was demonstrated using the Pion in Form.
- In this work, the solubilization capacity and behavior of parenteral solubilizers Kolliphor® HS 15 and Kolliphor® ELP were studied.
- It was uncovered that significant pH effects were apparent independent of API pKa, despite utilizing an API that exhibits little pH dependency on solubility, and non-ionic surfactants, also not known to exhibit a strong pH effect.
- Future work includes further evaluation of parenteral solubilizers with a wide breadth of applicable APIs.

References

[1] Parenteral Drugs: Tracking New Drug Approvals, Van Arnum, P., 2017.

[2] Reintjes, T., Solubility Enhancement with BASF Pharma Polymers – Solubilizer Compendium, October 2011.

[3] Rowe, R. Sheskey, P. J., Quinn, M. E.: Handbook of Pharmaceutical Excipients, 6th edition.

[4] Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006 Jan 1;34 (Database issue): D668-72.

BASF Excipients for Parenteral Use

The parenteral application requires excipients of highest quality standards. Solubilizers and co-solvents are the most widely employed excipients in the formulation of parenterals.

BASF offers a wide range of high-quality solubilization excipients and has an unparalleled understanding and experience in quality and regulatory affairs, as well as of the mechanisms of solubility enhancement.

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