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Introduction

A common problem experienced in the early development of drugs intended for parenteral, especially intravenous, administration is the solubilization of a slightly soluble or water insoluble active ingredient. Drug solubilization has been the subject of many scientific articles and textbooks (referenced throughout this article); yet despite this attention and available literature, product development scientists still encounter significant difficulties in solving their solubility problems.

Theories of solute solubilization are not easy to understand. Solubilization processes are amazingly complex and require a fair amount of expertise in physical chemistry to interpret and apply current theoretical models. Much of the literature deals with solubilization theory and does not offer much practical help to the inexperienced scientist under a lot of pressure to find a solution to his/her solubility problem.

This article intends to help the scientist in early drug formulation design for parenterally administered drug products by reviewing pertinent literature on solubilization and reducing it to simple approaches one can use to solve solubility problems. The classical theories of solubility, and how they relate to pharmaceutical systems of interest will be reviewed and practical applications discussed. Because of the common concerns regarding cosolvent toxicity and acceptability by medical and regulatory bodies, we also will treat this topic in some detail.

I. Pertinent Theory of Solubilization of Drugs

Solubility theories deal with conversion of a substance from one state to another, and the equilibrium phenomena that are involved. Through pioneering work of Henry, Raoult and van't Hoff in the late 1800's, the properties of various solutions have been defined in theories. These early theories form the basis by which more complex systems, such as those encountered in the biological sciences, are compared and understood.

No single theory can adequately explain solubility behavior of uncharged molecules in a variety of solvent systems. Each theory is suited for select combinations of solutes and solvents where certain intermolecular forces are assumed to predominate, or conversely, be absent. The classical theories of solubility have been explained most simply in terms of intermolecular interactions. *Ideal solution theory* assumes solute-solute, solvent-solvent and solute-solvent interactions are completely uniform in strength and nature. An example of a solution behaving ideally is a non-polar solute in a non-polar solvent such as naphthalene in benzene. *Regular solution theory* evolved to account for the imbalance of intermolecular interactions that often occur between dissimilar systems of a solute and solvent. The focus of this theory are systems of low polarity such as steroids in hydrocarbon solvents. *Extended regular solution theory* incorporated additional parameters such as dispersion, polar and hydrogen-bonding interactions into regular solution theory. Various approaches have been used to represent these molecular interactions, leading to a variety of models to predict and explain solubility behavior of polar solutes in polar systems, each with different approximations and assumptions (1–4).

In most pharmaceutical systems, the routine application of these models to predict solubility and simplify formulation development is complex. Most drugs of interest are ionizable, contain polar polyfunctional groups, and are capable of forming multiple hydrogen bonds. The majority of parenterally acceptable cosolvents—such as propylene glycol, polyethylene glycol, ethanol and water—are capable of self association through hydrogen bond formation. Such interactions may alter solvent structure and, as a result, influence solubility in an unpredictable manner (1). Examples of this phenomena are deviations from log-linear solublization of nonpolar solutes in a polar cosolvent system (5). For the models to adequately describe solubility behavior, proper weighting must be assigned to the relative importance of competing self-associations and strong intermolecular interactions. Currently this is being modeled by various computer intensive group-contribution approaches, some of which allow for the mutual interactions of various functional groups (1).

In the biological sciences, many solutes of interest are capable of acting as acids or bases. In an ionizing media such as water, they may dissociate into ions which are usually highly water soluble. To what extent a molecule is ionized in an aqueous solution is largely dependent on its pKa and the pH of the media. The Henderson-

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Hasselbalch equation is a mathematical expression of this relationship (3). In formulation development, consideration of the amount of un-ionized drug in solution is helpful to avoid unexpected precipitation of this form. As the pH of a drug solution is changed, the amount of free acid or base may increase and eventually exceed the limited solubility of this form. It is possible to calculate the pH of precipitation and of maximum solubility, if the pKa of the molecule and the solubility of the un-ionized and ionized forms are known (3, 6). Generally, two pH units above or below the pH_{max} value establishes the desired pH for formulation. For drug molecules with multiple ionizable groups these equations are more complicated to apply and so experimentally generated solubility data are usually collected.

Through our own experience, we find that theory gives us some direction with respect to experimental approaches, but we still need to rely on the empirical experimentation to screen for systems which offer the most promise in solubilizing water-insoluble drugs.

II. Formulation Design

Usually, the first approach used to increase the solubility of an insoluble drug in water is to form more water soluble salts. Berge and co-workers (7) wrote what is now a near classic review of salt form strategies acceptable for pharmaceuticals. If salt formation is not possible, e.g. too unstable, or does not render the molecule sufficiently water soluble, a series of formulation approaches may be investigated. Table I summarizes these general strategies. Often a useful approach to increase the aqueous solubility of an ionizable drug is pH adjustment. The next approach most frequently tried is the use of water-miscible cosolvents. Other approaches to be discussed briefly include the use of surface active agents and complexing agents. Development of emulsified and colloidal drug delivery systems for intravenous administration are becoming more widely and successfully applied. They may confer to the entrapped or associated drug significantly different proper-

TABLE I
Summary of Parenteral Formulation Approaches

Approach	Examples	Important Formula Considerations	Useful Tests
pH adjustment	pH 2 to 12	Drug stability pH ions to buffer or adjust pH Drug precipitation upon infusion drug concentration use of buffer/buffer capacity infusion rate Formula irritation isotonicity infusion rate & duration drug vs vehicle drug precipitation	pH rate profile pH solubility profile Freezing point depression *In vitro* precipitation model *In vivo* phlebitis model *In vitro* cell lysis studies
Cosolvent	Polyethylene glycol Propylene glycol Ethanol Dimethylacetamide	Systemic toxicity total cosolvent administered Drug precipitation upon infusion drug concentration infusion rate Formula irritation isotonicity infusion rate & duration drug vs vehicle drug precipitation	Mixture studies for maximum solubility *In vitro* precipitation model *In vivo* phlebitis model *In vitro* cell lysis studies
Surface Active Agents	Polysorbates Poloxamers Cremophor EL Lecithin Bile salts	Hypersensitivity in animals Formula irritation isotonicity infusion rate & duration drug vs vehicle	*In vivo* phlebitis model *In vitro* cell lysis studies
Complexing Agents	Cyclodextrans Water-soluble vitamins	Purity of excipients and drugs Formula irritation isotonicity infusion rate & duration drug vs vehicle	Phase solubility diagrams *In vivo* phlebitis model *In vitro* cell lysis studies
Dispersed Systems	Emulsions Liposomes Nanoparticles	Sterility Particle size Pharmacokinetics Stability	Particle size

ties from the free form, providing the opportunity to prolong drug presence in the bloodstream or to alter disposition in the body. "Heroic" methods, reported in the literature for various cancer drugs, will also be reviewed although these methods use types and amounts of excipients that probably would not commonly be considered approvable for intravenous administration.

The basis for reliable formulation development is accurate determination of solubility. Traditional methodology is the "equilibrium method" (8) where excess drug is added to the solvent system, and some means of agitation is employed under constant temperature. Samples are withdrawn, filtered, and analyzed for drug concentration over a period of time and equilibration is demonstrated by uniformity of the data over the time interval. For sparingly soluble drugs where equilibria are slow, accurate determinations of solubility may be difficult. Useful techniques in these instances include using highly specific analytical methods to detect parent compounds, minimizing the amount of excess solid added, and assuring sufficient equilibration time (1). Solid state factors and batch-to-batch variation (different polymorphs, hydration state, crystallinity, crystal homogeneity, and impurities) may affect reproducibility of drug solubility determinations.

A. pH Adjustment

Current FDA approved marketed parenteral products range in pH from 2 to 11. A comprehensive listing of these products may be found in Table II. For biocompatability reasons, formulation of injectables within the pH ranges of 4 to 8 is most common. However, to achieve sufficient drug solubility, a pH outside this range may be necessary.

The pH at which a product is formulated is usually determined from the pH solubility and pH rate profiles of the drug (9). A recent example of their application to aid parenteral formulation development is CI-988, a cholecystokinin-B receptor antagonist (10).

Additional formulation variables to be considered are the necessity of a buffer, buffer capacity, and drug concentration. These can influence supersaturated drug concentrations in the bloodstream, a condition that may lead to *in vivo* drug precipitation. The blood is very efficient at pH neutralization and normally maintains a narrow pH range of 7.38 to 7.42. For example, a low incidence of phlebitis was observed in the rabbit ear vein model when solutions over the pH range of 3 to 11, with buffer concentrations of approximately 0.3 M, were administered in a single small volume (1 mL) bolus dose (11). Simple screening tests consisting of a computational model where drug solubility is plotted as a function of dilution, and *in vitro* dilution experiments were shown to be effective tools in evaluating the ability of the pH-solubilized drug to remain in solution dilution (12, 13). Davio et al. (14) showed that *in vivo* precipitation of the pH-solubilized drug ditekiren was dependent upon drug concentration and infusion rate. Low concentration drug solutions, which are rapidly diluted below saturation solubility, and rapid infusions were preferred to minimize precipitation.

The most commonly used buffer components in parenteral products and their pKa's are; citric acid (3.13, 4.76, 6.40), acetic acid (4.76) and phosphoric acid (2.15, 7.20, 12.33). When buffers are employed, the stability of the molecule must also be considered, since it may be influenced by the ions in solution (9). Examples of buffer catalyzed solution degradation include famotidine, a histamine H2 receptor inhibitor (15) and loracarbef, a zwitterionic cephalosporin (16).

B. Use of Cosolvents

In recent years, surveys of FDA-approved parenteral products (17–19) show five water-miscible cosolvents—glycerin, ethanol, propylene glycol, polyethylene glycol, and N,N,-dimethylacetamide—as components of sterile formulations (Table III and IV). Cosolvents are employed in approximately 10% of FDA approved parenteral products. They are useful because they may often provide exponential increases in solubility (20) and also allow exclusion of water for compounds susceptible to hydrolysis.

Investigation of the solubilizing potential of various cosolvents may be approached empirically by determining the compounds solubility in cosolvent compositions similar to marketed products (21–23), or by one of several systematic approaches, such as log-linear solubility relationships or statistical experimental design.

In the study of log-linear solubility relationships, Yalkowsky and Roseman (20) investigated a range of solutes in binary cosolvent mixtures of ethanol, propylene glycol, and glycerin in water and discussed the closeness of fit of apparent solubility to a log-linear solubility equation. Briefly, this technique involves experimentally determining the solubility of a compound in increasing percentages of a cosolvent and generating a semi-logarithmic plot of the apparent solubility of the drug as a function of the volume-fraction of the cosolvent. Using the slope and the solubility of the compound in pure water, an equation may be written to describe the solubility in a binary system.

Assuming that the log-linear increases in solubility of individual cosolvents are additive, equations may also be written for ternary and quaternary mixed cosolvent systems (24). Mathematically, these relationships are described by the following equations:

Binary cosolvent system

$$\log C_x = \log C_w + \alpha_x f_x$$

Ternary cosolvent system

$$\log C_x = \log C_w + \alpha_x f_x + \alpha_a f_a$$

Quaternary cosolvent system

$$\log C_x = \log C_w + \alpha_x f_x + \alpha_a f_a + \alpha_b f_b$$

where C_W is the drug solubility in water; α's are the slopes of the semi logarithmic plots; C_x is the drug solubility; f is the volume fraction of the cosolvent; and the subscripts a, b, x denote the cosolvents A, B, and X

TABLE II
Examples of Marketed Parenteral Products with Solution pH Outside Range of 4 to 8 (18, 19)

pH (constituted)	pH Adjustment	Generic Name	Trade Name	Marketed Form	Routes
pH < 4					
3.2–4	Lactic acid, NaOH	Amrinone Lactate	Inocor (Sanofi Winthrop)	Solution	IB, IF
3.25–3.65	Benzenesulfonic acid	Atracurium Besylate	Tracrium (Burroughs Wellcome)	Solution	IB, IF
3		Chlordiazepoxide HCl	Librium (Roche)	Powder	IB
3–4		Benzquinamide HCl	Emete-Con (Roerig)	Powder	IM, IF
3.3–3.9	Lactic acid, HCl	Ciprofloxacin	Cipro I.V. (Miles)	Concentrate	IF
3–4	Citric acid	Dacarbazine	DTIC-Dome (Miles)	Powder	IB, IF
2.5–4.5	NaOH, HCl	Dopamine HCl	Intropin (DuPont)	Solution	IF
3.7–4.1	Citric acid, Na citrate	Diltiazem HCl	Cardizem (Marion Merrell Dow)	Solution	IF, IB
1.8–3.3		Doxycycline Hyclate	Vibramycin IV (Roerig, Elkins-Sinn)	Powder	IF
3–3.8	Lactic acid	Droperidol	Inapsine (Janssen)	Solution	IM, IF, IB
2.7–3.5	Lactic acid, ethyl lactate	Ergonovine Maleate	Ergotrate Maleate (Lilly)	Solution	IM, IB
3.2–3.8	Lactic acid	Fentanyl Citrate and Droperidol	Innovar (Janssen)	Solution	IM, IB, IF
2–3	NaOH/HCl	Glycopyrrolate	Robinul (Robins)	Solution	IM, IB
3–3.6	Lactic acid	Haloperidol Lactate	Haldol (McNeil)	Solution	IM
3–4		Labetalol HCl	Normodyne (Schering) Trandate (Glaxo)	Solution	IB, IF
3–4.2	NaOH, citric acid	Methyldopate HCl	Aldomet Ester HCl (Merck)	Solution	IF
2.7–3.5	Tartaric acid	Methylergonovine Maleate	Methergine (Sandoz)	Solution	IM, IF
3	NaOH, HCl	Midazolam HCl	Versed (Roche)	Solution	IM, IF
3.2–4		Milrinone Lactate	Primacor (Sanofi Winthrop)	Solution	IF
2–2.8		Minocycline HCl	Minocin (Lederle)	Powder	IF
3.5	Na citrate, citric acid	Nalbuphine HCl	Nubain (DuPont)	Solution	IM, IB
3–4	HCl	Naloxone HCl	Narcan (DuPont)	Solution	IM, IB, IF
3.3–4	Citric acid, Na citrate	Ondansetron HCl	Zofran (Cerenex)	Solution	IF
2.5–4.5	Acetic acid	Oxytocin	Pitocin (Parke-Davis)	Solution	IF
3–4	NaOH	Papaverine HCl	Papaverine HCl (Lilly)	Solution	IB, IF
2–3.8		Pyridoxine HCl	Pyridoxine HCl (Steris)	Solution	IM, IB
3–4	Tartaric acid, Na citrate	Tolazoline HCl	Priscoline HCl (Ciba)	Solution	IB, IM
pH > 8					
9.2	HCl/NaOH	Acetazolamide Na	Diamox (Lederle)	Powder	IM, IB, IF
10.5–11.6		Acyclovir Na	Zovirax (Burroughs Wellcome)	Powder	IF
8.6–9		Aminophylline	Aminophylline (Abbott, Elkins-Sinn, American Regent)	Solution	IB, IF
9.6–10.4		Amobarbital Na	Amytal Na (Lilly)	Powder	IM, IF
9.6	NaOH	Azathioprine Na	Imuran (Burroughs Wellcome)	Powder	IB, IF
8–10		Ampicillin Na	Polycillin-N (Apothecon) Totacillin-N (Beecham) Omnipen-N (Wyeth)	Powder	IM, IB, IF
8.5	Na_2HPO_4, NaOH	Betamethasone Na PO_4	Celestone Phosphate (Schering)	Solution	IB, IM
9.2–10	NaOH	Chlorothiazide Na	Sodium Diuril (Merck)	Powder	IB, IF
11.6	NaOH	Diazoxide	Hyperstat (Schering)	Solution	IB
9–10.5		Diethylstilbestrol Diphosphate	Stilphostrol (Miles)	Solution	IF
9.2	NaOH	Fluorouracil	Fluorouracil (Roche)	Solution	IB, IF
8–11	NaOH	Folic acid	Folvite (Lederle)	Solution	IB
8–9.3	NaOH	Lasix	Furosemide (Hoechst-Roussel)	Solution	IM, IB, IF
11		Ganciclovir Na	Cytovene (Syntex)	Powder	IF
8.1		Leucovorin Ca	Wellcovorin (Immunex, Burroughs Wellcome)	Powder	IM, IB, IF
9.5–10.5	Na carbonate	Methohexital Na	Brevital Na (Lilly)	Powder	IB, IF

IM = intramuscular, IF = intravenous infusion, IB = intravenous direct injection.

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