

INJECTABLE DRUG DEVELOPMENT

TECHNIQUES TO REDUCE PAIN AND IRRITATION

Edited by

Pramod K. Gupta

and

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Parenteral products significantly contribute to global health by providing effective and immediate therapy through direct delivery of therapeutic compounds to the patient. However, as with most routes of delivery, parenteral drug administration has both real and perceived disadvantages. The two potential disadvantages that are typically associated with parenteral therapy are tissue damage and injection pain. Whether this pain is real or imagined makes little difference to the patient, and there exists a significant literature that both highlights the pain caused by injectable drug products and offers methods to reduce these effects.

The first section of this chapter provides a strategy that can be used to develop a parenteral product. Emphasis is placed on the two formulation parameters, pH and tonicity, that are usually associated with tissue damage and injection pain. It is through the adjustment of these parameters that the product formulator can minimize adverse effects. The second section of this chapter describes administration techniques used by

healthcare professionals to reduce tissue damage or pain caused by commercial parenteral products. By recognizing the potential risks these alterations may confer to commercial formulations (such as decreased product stability or modified efficacy), the formulator will be better prepared to support the “real-world” use of the product.

FORMULATION DEVELOPMENT

The development strategy for parenteral products is similar for all products. The challenge is in the details of solving the physical/chemical difficulties encountered with a specific molecule within the timeline allowed for development. This section provides a parenteral product development outline with an emphasis on two formulation parameters, pH and tonicity, which may be modified to minimize tissue damage and pain caused by a parenteral product.

The activities necessary to develop a parenteral product can be placed into the following three broad areas: preformulation, formulation, and scale-up. While there are alternative development perspectives, all development ultimately needs to accomplish the same activities. Preformulation includes the characterization of the bulk drug plus initial screening for excipient compatibility with the drug. Formulation activities include the identification and selection of a suitable vehicle (aqueous, nonaqueous, or cosolvent system), necessary excipients with appropriate concentrations (buffers, antioxidants, antimicrobials, chelating agents, and tonicity contributors), and the container/closure system. Scale-up activities aid in moving the product to a manufacturing site (although not discussed here, references are available to provide guidance).

Preformulation

Preformulation studies provide fundamental data and the experience necessary to develop formulations for a specific compound. Activities are initiated and experiments performed for the purpose of characterizing specific and pharmaceutically significant physicochemical properties of the drug substance. These properties include interactions of the drug with excipients, solvents, packaging materials, and, specifically relating to the subject of this book, biological systems. These investigations also evaluate the drug under standard stress conditions of temperature, light, humidity, and oxygen. Many of these factors should be considered critically prior to animal testing, since these data will influence activities such as samples prepared for toxicology and animal testing, solubilization techniques, and design of subsequent studies.

Areas of specific interest during preformulation are provided in outline form below, along with an outline of additional characterization information needed to formulate a protein drug substance. Since analytical methods are usually developed concurrently with the preformulation data and then refined during formulation activities, the team must effectively communicate and collaborate to ensure appropriate assays are used to obtain data having sufficient accuracy and precision.

Preformulation Physicochemical Properties

1. Molecular weight
2. Color
3. Odor
4. Particle size, shape, and crystallinity
5. Thermal characteristics
 - 5.1. Melting profile
 - 5.2. Thermal profile
6. Hygroscopicity
7. Absorbance spectra
8. Solubility
 - 8.1. Selected solvents (water, ethanol, propylene glycol, polyethylene glycol 400, plus others as necessary)
 - 8.2. pH profile
 - 8.3. Temperature effects
 - 8.4. Partition coefficient
9. Stability
 - 9.1. Selected solvents
 - 9.2. pH profile
10. Ionization constant (pK or pI)
11. Optical activity

Additional Characterization for Protein Drugs

1. Physical stability
 - 1.1. Aggregation
2. Solubility
3. Chemical stability
 - 3.1. Beta-elimination
 - 3.2. Deamidation
 - 3.3. Isomerization/cyclization
 - 3.4. Oxidation
 - 3.5. Thiol disulfide exchange
4. Analytical methods
 - 4.1. Fluorescence spectroscopy
 - 4.2. Electrophoresis
 - 4.3. Calorimetry
 - 4.4. Size exclusion chromatography
 - 4.5. Reverse phase high performance liquid chromatography (HPLC)
 - 4.6. Circular dichroism
 - 4.7. Mass spectrometry
 - 4.8. Light scattering

Formulation

Formulation activities include the identification and selection of a suitable vehicle (aqueous, nonaqueous, or cosolvent system), necessary excipients with appropriate concentrations (buffers, antioxidants, antimicrobials, chelating agents, and tonicity contributors), and the container/closure system. The formulator is interested in the same list of activities given for pre-formulation; however, the activities are focused on specific excipients and characterization of the formulation. The principles of formulating a parenteral product have been outlined by several authors, although most do not specifically include the evaluation of tissue damage or pain caused by injection of the final product. This is likely due to the assumption that

deviation of pH or tonicity from physiological conditions causes these effects. It is, however, important to consider that a product may cause tissue damage with little associated pain, pain with little tissue damage, or both pain and tissue damage. Therefore, the models utilized to assess either the pain or tissue damage associated with a product need to be selected carefully. Several complementary methods may be needed, and these models are provided throughout this book.

Significant formulation activities begin with initial preformulation data and knowledge of the specific route of administration. These data provide the formulator with the requirements and limitations for the final formulation. Due to the location of human pain receptors, formulation approaches to reduce pain are more critical for subcutaneous (SC) and intradermal injections and less critical for intramuscular (IM) and intravenous (IV) administration.

Injection volume is one of the most important considerations in the formulation development of a commercial product. This volume is selected based on the proposed injection route. Since veins have a relatively large volume and blood flow rate, a product administered by the IV route can have a volume greater than 10 mL; as the volume increases, the delivery rate may need to be controlled. This is in contrast to IM injections, which are normally limited to 3 mL, SC injections to 1 mL, and intradermal injections to 0.2 mL. Recommended maximum injection volumes are author dependent but not radically different.

Thus, the factors that need to be considered in evaluating the hemolysis caused by a product include both the quantity and proportions of the substances and how rapidly the blood dilutes the product. The data in Table 17.1 provide some perspective on the vascular system's capability of diluting an injected IV product, in terms of both volume and rate. The choice of solvent is dependent both on the route of administration, which

Table 17.1. Physical Characteristics of the Arteriovenous System

Anatomical Section	Volume (cm ³)	Velocity (cm/sec)
Aorta	100	40
Arteries	325	40–100
Arterioles	50	10–0.1
Capillaries	250	0.1
Venules	300	0.3
Veins	2,200	0.3–5
Vena cava	300	5–30

as noted above imparts volume limitations, and on drug solubility in the selected solvent. IV injections are typically restricted to dilute aqueous solutions to ensure compatibility with the blood; however, IM or SC injections allow for oily solutions, cosolvent systems, suspensions, or emulsions. Pain, soreness, and inflammation of tissues are frequently observed in the administration of parenteral suspensions, particularly with products having a high solid content.

A third important consideration in the development of a parenteral product is compatibility of the formulation with the tissue. An isotonic solution is less irritating, causes less toxicity and pain, and minimizes hemolysis. An isotonic product, however, is not always the goal since for SC or IM injections a hypertonic solution may facilitate drug absorption. Having an isotonic product is, however, very important for intraspinal injections, where the fluid circulation is slow and abrupt changes in osmotic pressure can contribute to unwanted and potentially severe side effects.

The choice of acceptable excipients in parenteral product development remains limited compared to other dosage forms, due to concerns of injection safety and feasibility of sterilization. In order to avoid uncertainty and reduce development time, most formulators select excipients successfully used in marketed products. A short list of commonly used additives, their functions, and typical concentrations is given in Tables 17.2 and 17.3. As the number of biotechnology products increases, excipients such as human serum albumin (HSA), amino acids, and sucrose are finding increasing utility. In Europe, the use of animal-derived excipients such as HSA and some polysorbate surfactants has become problematic due to the increasing concern with bovine spongiform encephalitis (BSE). This concern is expanding to the rest of the world and has impact on the selection of excipients.

An excipient selected for a parenteral product may serve one or more purposes. For example, benzyl alcohol is primarily a preservative; however, it has a transient local anesthetic property. Dual roles may help in the goal to minimize both the number of product ingredients and their quantity. The justification for each selection will become a part of the formulation development report.

Antimicrobials

Preservatives are always included in a product when multiple doses will be drawn from a single vial unless the drug itself is bacteriostatic. The addition of an antimicrobial is not a substitute for good manufacturing practices; however, many times they are added to single-use containers. They are specifically excluded from large-volume products intended for infusion. In some cases, as with benzyl alcohol, the excipient may have multiple functions. Therefore, the decision whether or not to include a preservative in a single-use product may be product specific. The rationale

Table 17.2. Additives Commonly Used in Parenteral Products

Substance	Concentration (percent)
Antimicrobial	
Benzalkonium chloride	0.01
Benzethonium chloride	0.01
Benzyl alcohol	1–2
Chlorobutanol	0.25–0.5
Chlorocresol	0.1–0.3
Metacresol	0.1–0.3
Phenol	0.5
Methyl p-hydroxybenzoate	0.18
Propyl p-hydroxybenzoate	0.02
Butyl p-hydroxybenzoate	0.015
Antioxidants	
Acetone sodium bisulfite	0.2
Ascorbic acid	0.1
Ascorbic acid esters	0.015
Butylhydroxyanisole (BHA)	0.02
Butylhydroxytoluene (BHT)	0.02
Cysteine	0.5
Monothioglycerol	0.5
Sodium bisulfite	0.15
Sodium metabisulfite	0.2
Tocopherols	0.5
Glutathione	0.1
Surfactants	
Polyoxethylene sorbitan monooleate	0.1–0.5
Sorbitan monooleate	0.05–0.5

for any preservative addition should be a part of the product development report.

Common antimicrobial agents are given in Table 17.2. These agents are grouped into five chemical classes: quaternary ammonium compounds, alcohols, esters, mercurials, and acids. The alcohols and esters are commonly used in parenteral products. The quaternary compounds, which are commonly used in ophthalmic products, are not compatible with negatively charged ions or molecules.

Table 17.3. Common Buffers Used in Parenteral Formulations

Buffer	pK _a	Usual Buffering Range
Acetic acid	4.8	3.5–5.7
Citric acid	3.14, 4.8, 5.2	2.1–6.2
Glutamic acid	2.2, 4.3, 9.7	8.2–10.2
Phosphoric acid	2.1, 7.2, 12.7	2–3.1, 6.2–8.2
Benzoic acid	4.2	3.2–5.2
Lactic acid	3.1	2.1–4.1
Ascorbic acid	4.2, 11.6	3.2–5.2
Tartaric acid	3.0, 4.3	2.0–5.3
Succinic acid	4.2, 5.6	3.2–6.6
Adipic acid	4.4, 5.28	3.4–6.3
Glycine	2.34, 9.6	1.5–3.5, 8.8–10.8
Malic acid	3.4, 5.1	2.4–6.1
Triethanolamine	8.0	7–9
Diethanolamine	9.0	8.0–10.0
Tromethamine	8.1	7.1–9.1

The literature reports interactions of the parabens with surfactants and formation of molecular complexes with gelatin, methylcellulose, polyvinyl pyrrolidone, and polyethylene glycol. These interactions may decrease preservative efficacy. Some antimicrobial compounds, such as benzyl alcohol, may be adsorbed by the container closure. Thus, microbial preservation must be demonstrated for the final formulated product.

Buffers

The buffer system establishes and maintains the product pH. A specific buffer system is selected such that the pK_a of the system is within one pH unit of the pH desired for the product. A list of common buffers is provided in Table 17.3. The selection of the product pH is based on the stability of the active drug. When alternative buffers are available, a comparison of their respective effects on stability will usually aid in the final choice. The acetate buffer system is not a good choice for a lyophilized product due to the volatility of acetic acid. Loss of acetic acid results in a pH shift when the product is reconstituted. The pH of solutions containing a phosphate buffer system have been shown to shift during cooling due to precipitation of sodium phosphate species. These pH shifts during freezing may cause

damage to a protein. Since the specific buffer and the buffer capacity can contribute to injection pain, these effects should be evaluated in the selection of the buffer. Each species of the buffer system affects the tonicity of the final product; this influence must be considered during product development. For example, as the pH of a formulation containing monosodium phosphate is adjusted, the disodium salt is formed and contributes to product tonicity.

Antioxidants

Preformulation data will identify compounds sensitive to oxidation. Free radicals or molecular oxygen mediates oxidation, and several alternative stabilization approaches are available. In many cases, several approaches are utilized concurrently. One approach is lowering the product pH, which, according to the Nernst equation, increases the oxidation potential of the drug and thus increases stability. When oxygen contributes to degradation, it can be displaced during the filling operation by “bubbling” an inert gas such a nitrogen or argon gas through the solution prior to filling the vials. Additionally, the container headspace can be overlaid with the inert gas. An antioxidant may be useful if further protection is necessary. The specific antioxidant selected should have a lower oxidation potential than the drug. Several antioxidants and concentrations should be evaluated because, in many cases, a single agent is not sufficient. Sulfites are associated with allergic reactions in some patients. This reaction has a rapid onset and is not always confirmed by an oral challenge. Despite this reaction potential, sulfites may be used in a formulation if necessary to stabilize a life-saving product.

Examples of antioxidants include sodium bisulfite, ascorbic acid, glutathione, and propyl gallate. Sodium bisulfite tends to react irreversibly with the double bonds found in aldehydes and some ketones, and frequently results in a significant loss of biological activity. Epinephrine forms a bisulfite addition product, as do other sympathomimetic drugs having ortho- or para-hydroxybenzyl alcohol derivatives. The meta-hydroxy alcohol does not react with sodium bisulfite. Sulfites are converted to sulfates in the oxidation reaction, and if small amounts of barium are present, a precipitate will form.

Chelating Agents

Chelating agents are used to increase the solubility of a drug or to impart some product stability. Compounds such as ascorbic acid, citric acid, and ethylenediaminetetraacetic acid chelate metals, which would otherwise catalyze oxidation reactions, and provide measurable benefits for some products.

Surfactants

Surfactants are used to solubilize a drug and, for protein products, to minimize adsorption of the protein on surfaces. Most polysorbates are derived from animal sources, and their use in Europe is becoming problematic due to the increasing concerns with BSE. This concern is expanding to the rest of the world and will impact in the selection of excipients. Several suppliers are beginning to offer polysorbates from vegetable sources. Polysorbates can contain peroxides that may adversely affect product stability and, as for all excipients, specifications will need to be established.

Tonicity Agents

The active drug and each excipient contribute to the tonicity of the formulation. When the tonic contribution of these combined ingredients is not sufficient to provide an isotonic solution, then tonicity agents, such as dextrose, sodium chloride (NaCl), sodium sulfate, or mannitol can be added. Additional details are provided in the osmolality section below.

In summary, formulation activities focus on the selection of the solvent, the necessary excipients (buffers, antimicrobials, antioxidants, chelating agents, surfactants, and tonicity agents) with corresponding concentrations, the container/closure system, and on demonstrating adequate stability.

Focus on Osmolality, Cosolvents, Oils, and pH

The contribution of isotonicity in reducing injection pain is not always clear but, at a minimum, it may reduce tissue irritation. Injection pain may occur during and immediately following product administration but may be delayed or prolonged, with an increase in severity with subsequent injections. Pain can be difficult to assess because significant patient variation exists, and there are few preclinical methods for evaluation.

Literature describing pain associated with parenteral products has focused on three areas: osmolality, cosolvents, and pH. This is a pragmatic focus since osmolality and pH are easy to measure. Unfortunately, the adjustment of pH and osmolality may not be possible for some formulations due to physical or chemical stability of the product. In other products, the drug molecule may be inherently painful when injected. In both of these cases, formulations must be delivered at a low drug concentration or in complex formulations (such as emulsions or liposomes), in an attempt to “hide” the drug from pain receptors. Due to volume constraints, these are not always a viable alternative for IM or SC injections, leaving the formulator to design the best possible product and otherwise relying on the health professional to further minimize the injection pain at the time of administration. Since these formulations pose significant development

issues, most formulators optimize the pH and isotonicity and provide information on appropriate dilution for administration.

Osmolality

The primary purpose for adjusting product osmolality is to minimize red blood cell lysis, tissue damage, and pain when the product is administered. An isotonic solution provides an electrolyte environment that allows human erythrocytes to maintain “tone.” If cells are placed into a hypertonic solution, the cells may lose water and shrink (crenation). If placed in a hypotonic solution, the water moves into the cells, which can then swell to the point of breaking. Thus, the formulator’s goal is to develop a product that, when administered, will be as close to isotonic as possible. In fact, the British Pharmacopoeia states that aqueous solutions for SC, intradermal, or IM injections should be made isotonic if possible. Unfortunately, there is no formulation solution for a product that is hypertonic. The necessity for administration in a diluted form or by slow infusion is appropriately noted in the product package insert.

Common agents used to adjust tonicity of a product include dextrose, NaCl, mannitol, and sodium sulfate. Care must be taken if sodium sulfate is selected for a product packaged in barium-containing glass, because even extremely small amounts of leached barium can lead to the precipitation of barium. Since all ingredients contribute to the tonicity of the product, it is necessary to measure or calculate the contribution of each and then, if necessary, adjust the product tonicity with additional agents.

Measuring Osmolality. Determination of osmolality is performed by measuring one of the four colligative properties, which depend only on the number of “particles” in the solution: (1) osmotic pressure elevation, (2) boiling point elevation, (3) freezing point depression, and (4) vapor pressure elevation. Of these methods, freezing point depression and vapor pressure elevation are most commonly utilized. These methods are relatively easy to perform and reasonably accurate. Commercial instruments are readily available.

Iso-osmolality, as determined by physical methods such as freezing point depression or vapor pressure reduction, is different from isotonicity determined by biological methods such as erythrocyte hemolysis. This difference is important since cells do not always behave as semipermeable membranes, and measuring biological compatibility by direct methods will identify problematic molecules that can cause lysis or tissue damage. Urea is the most frequently cited example of such a molecule; a 1.8 percent solution of urea has the same osmotic pressure as NaCl at 0.9 percent, but causes cell lysis. Other compounds that have specific cellular effects include glycerin, propylene glycol, and boric acid.

Although physical methods such as freezing point depression and vapor pressure are valuable tools in formulation development and quality control of the product, it is imperative to have direct methods to measure the effect of the product on red blood cells and tissue. Methods to evaluate cellular effects are given below, and methods to evaluate tissue effects are provided in other chapters of this book. The references provide additional information, and formulators are encouraged to include them in their library.

Determining Tonicity (Hemolysis). A common in vitro method to evaluate a product is by measuring erythrocyte hemolysis. Typically the release of hemoglobin from the damaged cells is measured spectrophotometrically; however, a more sensitive method is to directly observe the changes in cell volume. An aqueous isotonic NaCl solution is used as the standard. Several protocols are available that describe incubating the product with erythrocytes suspended in defibrinated blood for a specified time, centrifuging to separate the erythrocytes and ghost cells, and then using a spectrophotometer to determine the absorbance of the supernatant versus a standard at 520 nm. Solution to blood ratios of 100:1 have been used. Concerns that this ratio is not realistic and can often give misleading results has lead investigators to use dilutions of 1:10—a complete reversal of proportions—with no hemolysis found.

Others have evaluated product effects by directly observing variations of red blood cell volume when suspended in solution. This method is more sensitive to small tonicity differences than the hemolysis method.

An alternative method to determine the compatibility of a product with blood is proposed by Ito et al. (1966). The coil planet centrifuge (CPC) method was originally developed to examine dynamic membrane properties of erythrocytes. The system comprises three instruments: the CPC itself, gradients for preparing the solution having an osmotic gradient in a coil, and a scanning spectrophotometer for recording a hemolytic pattern of the sample coil. The CPC is a specific centrifuge that rotates at 1,600 rpm around the main axis at a constant temperature of 37°C, while the coil holder fitted with coils rotates at 16 rpm. The design of this equipment ensures that the centrifugal force is constant irrespective of the distance from the main axis. It has been found that measuring the hemolysis of oil injections and those of high concentration or viscosity by this method is difficult, if not impossible.

The “osmogram” output shows red blood cell hemolysis as a function of the osmotic gradient. The hemolytic pattern of injections are divided into the following four patterns:

1. Hemolysis is remarkable, or erythrocyte is coagulated and does not move.

2. Hemolysis takes place gradually and then continues or is shifted to the side of high osmotic pressure.
3. No change is observed.
4. Pattern is shifted to low osmotic pressure, indicating stabilization of the erythrocyte membrane.

This method may provide valuable information for the evaluation of parenteral products; however, the full potential of the method is unknown since there is little information available.

Calculating Tonicity. Several methods used to calculate tonicity are summarized below.

(1) The method of NaCl equivalents expresses tonicity in terms of the amount of drug equivalent to NaCl since, in most cases, when an aqueous solution is iso-osmotic with 0.9 percent NaCl, it will be isotonic with physiologic systems. The NaCl equivalent value, *E*, is defined as the weight of NaCl having the same osmotic effect as 1 g of the drug. A 1 percent NaCl solution has an equilibrium freezing temperature of -0.58°C and is given a NaCl *E* value of 1.00. The freezing temperature of serum is -0.52°C , equivalent to the freezing temperature of a 0.9 percent NaCl solution. Therefore, if a 1 percent solution of a specific compound has a freezing temperature of -0.058°C , then it has an *E* value of 0.1. Thus, 1.0 g of this compound will have the same tonic value as 0.1 g of NaCl; to prepare 100 mL of an isotonic solution containing 1 g of this substance, 0.8 g of NaCl must be added. *Remington's* (Gennaro 1995) has an extensive list of NaCl equivalents for specific excipients and drugs.

Different compounds can be used to adjust solution tonicity. For example, in the above calculation, 0.8 g of NaCl was needed to render the solution isotonic. If, however, dextrose is desired to adjust tonicity, then the amount of dextrose would be

$$(1 \text{ g dextrose}/0.16 \text{ g NaCl}) \times 0.8 \text{ g NaCl} = 5 \text{ g dextrose}$$

A comparison of measured osmolality to calculated values using the NaCl equivalent method shows agreement within 10 percent; for most systems this is sufficiently accurate.

(2) The freezing point depression method uses “*D*” values having units of $^{\circ}\text{C}$ per x percent of drug. The *D* values for some drug compounds can be obtained in the literature.

(3) The *V* value of a drug is the volume of water used to dissolve a specific weight of drug to prepare an isotonic solution. The purpose of this method is to prepare an isotonic solution of the drug and then to dilute this to the desired final concentration with a suitable isotonic vehicle. This method is most commonly used for ophthalmic preparations. Values for commonly used drugs are available in the literature.

(4) Other calculations such as the L_{iso} method can be used for estimations when values for a specific compound are not available. The mathematical relationship of L_{iso} to the NaCl equivalent, E , is:

$$E = 17 (L_{iso}/M)$$

where M is the molecular weight of the compound. Average L_{iso} values for different types of compounds are given in Table 17.4.

Cosolvents and Oils

Cosolvents are commonly used to enhance drug solubility and stability. Cosolvents may include ethanol, propylene glycol, polyethylene glycols, and glycerin. These components have intrinsic effects on biologic tissue and can alter the properties of other excipients, thus influencing the tissue damage or pain caused by the product. There is a dearth of literature on the pain caused by cosolvents, but there is also a growing body of knowledge on the tissue damage that they can cause. It is not certain that tissue damage is always directly correlated with injection pain, but minimization of both pain on injection and potential for tissue damage should be included in the product development plan.

In studies by Brazeau and Fung (1989a, b), moderate concentrations of organic cosolvents (20 to 40 percent v/v) show the following relative myotoxicity ranking: propylene glycol > ethanol > polyethylene glycol 400. These investigators also discovered that total myotoxicity equaled the sum of the individual myotoxicity of each component, with the exception of preparations containing polyethylene glycol 400, which apparently has a protective effect.

Table 17.4. Average L_{iso} Values for Different Types of Compounds

Compound Type	L_{iso}	Example
Nonelectrolyte	1.9	Sucrose
Weak electrolyte	2.0	Phenobarbital, boric acid
Di-divalent electrolyte	2.0	Zinc sulfate
Uni-univalent electrolyte	3.4	Sodium chloride
Uni-divalent electrolyte	4.3	Sodium sulfate, atropine sulfate
Di-univalent electrolyte	4.8	Calcium chloride
Uni-trivalent electrolyte	5.2	Sodium phosphate
Tri-univalent electrolyte	6.0	Aluminum chloride
Tetraborates	7.6	Sodium borate

Consideration must also be given to cosolvent effects on other product excipients. Since most buffers are conjugates of a weak acid or base, the polarity shift caused by cosolvents may shift the pK_a of the buffer species. It is best to evaluate biological compatibility using direct biological methods, because cosolvents may have both specific cellular effects and indirect excipient effects.

Another class of nonaqueous vehicles used in parenteral formulations are the fixed oils, including corn, cottonseed, olive, peanut, sesame, and soybean. Oils of vegetable origin are selected because they can be metabolized, are liquid at room temperature, and will not rapidly become rancid. To remain liquid at room temperature, a fixed oil must contain unsaturated fatty acids, which, when present in excessive amounts, can cause tissue irritation. The U.S. Pharmacopeia (USP) includes specifications for rancidity, solidification range of fatty acids, and free-fatty acids. The formulator may include antioxidants, such as tocopherol (a natural component of many fixed oils) to prevent the product from becoming rancid.

pH

A product buffer system is selected to help maintain an environment in which the drug is stable throughout the commercial shelf life of the product. These systems are composed of a weak acid or base and a corresponding salt. The ratio of these species determines the pH, and the concentration provides a buffer capacity to resist pH changes due to product degradation or container-closure interactions. A buffer system is most efficient at its pK_a , thus, buffers are generally chosen within one pH unit of the desired product pH.

The buffer concentrations typically chosen for a product range from 1 to 2 percent, although higher concentrations of up to 5 percent have been used with citrate buffers. The more a pH deviates from physiological conditions and the higher the buffer capacity, the more likely the product will contribute to tissue damage or injection pain. Table 17.3 provides a list of acceptable buffers with pK_a values and usual pH buffer ranges.

Buffer systems are in an equilibrium that is sensitive to temperature and the concentration of each species. Each species in this equilibrium may contribute differently to product osmolality. There may be an error in estimating the contribution to osmolality of each species at room temperature, since the most common method to measure osmolality is by freezing point depression. Cutie and Sciarrone (1969) demonstrated for boric acid, Sorensen, and Palitzsch buffers that if formulated to be isotonic as measured by freezing point depression, the solutions may be slightly hypertonic at 37°C. Sodium tetraborate has, in fact, been demonstrated to have a NaCl equivalent (E value) of 0.45 at 37°C but 0.35 at 0°C, a 23 percent change. For most formulations, this is not of physiological significance;

however, it should not be discounted for those formulations where close tolerance to isotonicity is necessary.

A vapor pressure osmometer provides an alternative to the freezing point method and may be particularly useful when the data for temperature and concentration effects on ionization constants are not available. A limitation of the vapor pressure method includes interference by volatile substances such as ethanol.

POST-FORMULATION PROCEDURES

Despite efforts to minimize or eliminate pain through formulation optimization, some products remain painful when injected. The literature is replete with suggestions on how to reduce pain during the administration of a product. Unfortunately, much of these data are incomplete or seemingly contradictory. Deficiencies in the research conducted on children's pain have been noted, and the point is frequently made that children are short-changed with respect to pain management. Post-formulation efforts to alleviate pain which are discussed in this chapter are included in the following categories: pH, additives or solvent adjustments; devices or physical manipulations, and psychological.

pH, Additives, and Solvents

Drugs stable only in acidic conditions are purposefully formulated to ensure an adequate commercial shelf life. Because these acidic products are associated with injection pain, sodium bicarbonate is extemporaneously added prior to administration to more closely match physiological pH (pH 7.3). This approach appears to successfully reduce the pain caused by local anesthetics; however, studies with other products have been equivocal. For anesthetics, this increased pH will alter the stability of the product and may result in the precipitation of the less soluble, nonionized species. The amount of sodium bicarbonate that can be safely added is variable given the range of anesthetic products (pH of 3.5 to 5.5), the concentration of sodium bicarbonate, and other variables.

The reduction in pain for anesthetic products does not appear to be entirely due to the increased pH of the solution. The indirect effect of increasing product pH is to shift the equilibrium of anesthetics to the uncharged species that may diffuse more rapidly and consequently inhibit pain perceptions. Individual drugs or drug species (charged or uncharged) may have different intrinsic pain induction potential, independent of pH. The study design and product ingredients must be considered when evaluating data, because some excipients such as benzyl alcohol have local anesthetic properties.

Another extemporaneous technique is to add lipids to the commercial formulation. This method shifts more of the drug from the aqueous phase and has been successful in reducing injection pain for methohexital and propofol. Such additions need to be supported by studies to verify product stability, similar pharmacokinetics, and efficacy.

Clinicians also minimize or eliminate injection pain by topical administration of local anesthetics, which decrease pain sensation, or nitroglycerin ointment, which dilates local blood vessels and promotes absorption of the irritating substance. Although of interest to the formulator, these topical approaches do not pose formulation issues.

Devices and Physical Manipulations

Parenteral administration techniques will affect the magnitude of the pain. These include the practical training received by healthcare professionals; proper selection of administration equipment; and manipulation of the injection rate, injection site, and temperature. The formulator should note how health professionals may use the product and consider the need for pertinent data during product development.

Parenteral administration techniques are part of a nurse's education. This practical training is aimed at increasing the comfort of the patient and efficiency of the nurse. The references given at the end of this chapter provide additional detail and information on less common parenteral routes of administration.

Subcutaneous Injection

Drugs recommended for SC injection include nonirritating aqueous solutions and suspensions contained in 0.5 to 2.0 mL (target 1 mL or less) of fluid. The needle sizes are 25 gauge 5/8 in. length for an average adult and 25 gauge 1/2 in. length for an infant, child, elderly, or thin patient. After cleaning the area with an alcohol sponge, allow the skin to dry before skin penetration to avoid the stinging sensation caused by the alcohol entering the subcutaneous tissue.

With the nondominant hand, grasp the skin around the injection site firmly to elevate the subcutaneous tissue, forming a 1 in. fat fold. This provides rigidity for needle entry. Tell the patient "you will feel a prick as the needle is inserted." Holding the syringe in the dominant hand with the needle bevel up, insert the needle quickly in one motion. Release the patient's skin to avoid injecting the drug into compressed tissue to minimize irritation of nerve fibers, confirm the needle is in the tissue, and inject slowly. After the injection, remove the needle quickly. Cover the skin and massage the site gently (unless contraindicated as with heparin or insulin) to help distribute the drug and reduce pain.

Intradermal Injection

Intradermal injections are typically used only for local effects or diagnostic purposes in volumes of 0.5 mL or less. Needles of 26 or 27 gauge and 1/2 to 5/8 in. in length are used. The injection is given at a 15° angle about 1/8 in. below the epidermis at sites 2 in. apart. Stop when the needle bevel tip is under the skin and inject slowly; some resistance should be felt. A wheal should form; if it does not, the injection is too deep. Withdraw the needle at the same angle as the entry. Do not massage the site, as this may cause irritation.

Intramuscular Injection

IM injections deliver medication into highly vascularized deep muscle tissue. Because there are few sensory nerves in these tissues, pain is minimized when injecting irritating drugs. The volume for IM injection can be up to 5 mL, although it is typically less than 3 mL. A 20 to 25 gauge needle of 1 to 3 in. in length is used. Once the appropriate injection site has been selected and properly prepared, gently tap it to stimulate nerve endings and minimize pain when the needle is inserted. The gluteal muscles should not be used for a child under the age of 3, nor for someone who has not been walking for the prior year. Never inject into sensitive muscles, especially those that twitch or tremble when you assess site landmarks. Injections in these trigger areas may cause sharp or referred pain, such as pain caused by nerve trauma.

Intravenous Bolus Injection

Bolus drug administration is used when immediate drug effects are necessary, when the drugs cannot be diluted (diazepam, digoxin, phenytoin), or for drugs that are too toxic or irritating for other routes of administration. A 20 gauge needle is typically used. Bolus injections are given through the largest vein suitable, since the larger the vein, the more dilute the drug becomes, thus minimizing vascular irritation. An in-depth discussion of specific routes of administration, techniques, equipment, and cautions is readily available in the literature referenced at the end of this chapter.

Devices

Devices offer significant opportunities to reduce the fear and increase the consistency of parenteral injections. Some of these devices are needle free, with the product propelled through the skin under pressure. Some studies have demonstrated reduced pain during administration. These devices may affect the quality of a shear-sensitive macromolecule or alter drug

pharmacokinetics (PK) due to the pattern of drug deposition. For a given product, additional product or PK characterization may be necessary. These devices deliver subcutaneous injections; however, controversy remains on whether they can deliver an IM injection.

Other devices use “hidden” needles with guides that facilitate insertion of the needle and subsequent injection of the medication. These allow for reproducible injections. Their utility is dependent on the perception of the patient, the cost of the device, and the ease of use. These devices have been shown to be less painful and improve compliance for chronic administration of SC injections.

Temperature

Healthcare providers continually explore methods to increase the comfort of the patient by altering the temperature of the product or skin. Numbing the skin surface with ice or other means has successfully been used to reduce injection pain; in one case, injecting a cool solution before infusing the drug appeared to be successful in reducing pain. Changing the product temperature is more significant to the product formulator. Warming propofol to 37°C has been demonstrated to decrease the incidence of pain by 37 percent. Since both cooling and warming have been shown to reduce injection discomfort, it may be that some relief is provided by the quick, but transient temperature effects on the nociceptor receptors or pain mediators. The formulator should be aware that products might be either cooled or warmed by healthcare professionals and, therefore, consider the impact of temperature changes on the formulation during product development.

Psychological

The contribution of psychological factors to injection pain is substantial and has been considered in the design of the new devices mentioned previously. Psychology is used in the clinic to minimize injection pain, particularly in children. These are interesting and provided here for completeness.

The pain experience is influenced by age, physical, emotional, cultural, and, social factors as are the preferred control methods. A Gallup Poll stated that 58 percent of children rely on their own coping skills, such as thinking about something else to make shots bearable, and 47 percent said they specifically disliked needles. Perhaps we as healthcare providers can provide more assistance.

Several articles provide lists and examples of proactive psychological techniques shown to minimize injection pain, including distraction, honesty, and a demonstration of caring. Distraction asks the patient to focus on an image and and to use breathing techniques. The person giving the injection should be honest yet supportive while making general sympathetic statements that indicate the child can control pain. The child should

be involved in discussions, and all actions should be described before or as they are being performed.

The psychology and perception of pain are important factors in pain management and both the healthcare provider and formulator can effectively utilize the techniques mentioned above in the development, support, and administration of therapeutic products.

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