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Review

If Euhydric and Isotonic Do Not Work, What Are Acceptable pH and Osmolality for Parenteral Drug Dosage Forms?

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ABSTRACT

Parenteral products should aim toward being isotonic and euhydric (physiological pH). Yet, due to other considerations, this goal is often not reasonable or doable. There are no clear allowable ranges related to pH and osmolality, and thus, the objective of this review was to provide a better understanding of acceptable formulation pH, buffer strength, and osmolality taking into account the administration route (i.e., intramuscular, intravenous, subcutaneous) and administration technique (i.e., bolus, push, infusion). This evaluation was based on 3 different approaches: conventional, experimental, and parametric. The conventional way of defining formulation limits was based on standard pH and osmolality ranges. Experimental determination of titratable acidity or *in vitro* hemolysis testing provided additional drug product information. Finally, the parametric approach was based on the calculation of theoretical values such as (1) the maximal volume of injection which cannot shift the blood's pH or its molarity out of the physiological range and (b) a dilution ratio at the injection site and by verifying that threshold values are not exceeded. The combination of all 3 approaches can support the definition of acceptable pH, buffer strength, and osmolality of formulations and thus may reduce the risk of failure during preclinical and clinical development.

Introduction

During drug product development, nonclinical safety studies are performed to support clinical trials and marketing authorization for pharmaceuticals.[1,2] As an added precaution, the first clinical trials ("entry into human") usually start with a relatively low systemic exposure in a small number of healthy volunteers. The formulation that is being brought forward into nonclinical and clinical testing needs to take into account physical and chemical stability, manufacturability, and local and systemic tolerability, in addition to regulatory and pharmacopeial requirements. Although physicochemical parameters like pH, osmolality, buffer concentration, their process-related acceptance criteria, and impact on stability are part of a state of the art drug product formulation development, the definition of what is accepted in terms of tolerability in a clinical setting is more controversial and not straightforward.

Solutions for injection of infusion may require a pH or osmolality, which are clearly outside the physiological (euhydric and isotonic) range, often for solubility or stability reasons. In those cases, only a sound understanding of physiological, anatomic, physical, and chemical mechanisms of the parenteral administration at the injection site and during infusion will provide enough insight into the suitability of a formulation for the nonclinical and clinical studies. Especially, small molecule parenteral dosage forms are often characterized by a pH and osmolality significantly deviating from ideal target values. Although biologics in most cases can be developed toward isotonicity, the pH values may also deviate from euhydric pH because of stability reasons. For example, antibodies are often formulated around pH 5.5-6.5, and G-CSF is around pH 3-4. Biologic formulations often contain a buffer, and buffering capacity thus also needs to be considered in connection with target pH. In cases where lyophilisates are reconstituted in less volume, for example, to achieve higher concentration antibody formulations for administration,[3] the tonicity may also be hypertonic.

Parenteral products should aim toward being isotonic and euhydric (physiological pH). If this is not achievable, as a general rule, excessive values of pH and osmolality should be avoided as much as possible to minimize or prevent local damage on vascular endothelium and circulating blood cells. However, because many parameters play a crucial role in terms of local tolerance (e.g., administration site and route of administration, vein selected, related venous blood flow, injection volume, infusion time, infusion

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duration, residence time in subcutaneous [s.c.] or intramuscular [i.m.] tissue, diffusion into surrounding tissues),[4] no well-defined and generally recognized pH, buffer strength, and osmolality limits are available.

To evaluate the appropriateness of a formulation with regard to pH, buffer, and osmolality related to sufficient systemic and local tolerance, 3 different approaches can be considered: conventional, experimental, and parametric.

The *conventional approach* is knowledge based and consists in choosing pH and osmolality within the usual ranges of literature. The difficulty of this approach is that those ranges can vary considerably depending on the reference chosen as shown in later sections. Furthermore, they often do not sufficiently take other crucial parameters into consideration such as buffer capacity of the formulation, administration site, injection volume, injection duration, or frequency of administration.

A second approach is based on *experimental* data from either (1) titratable acidity measurements or (2) *in vitro* hemolysis tests. The titratable acidity measurements are used to determine the buffer strength of a solution at nonphysiological pH values, whereas the *in vitro* hemolysis test characterizes the risk of cell membrane damage after contact with a parenteral injection solution. The advantage of the experimental approach is that it is product specific and, at least for hemolysis testing, includes a biological component such as a direct contact with the (red blood) cell membrane. Hemolysis testing can be considered as a simple *in vitro* model for local tolerance. However, it provides no information about systemic toxicity, for example, interaction with the whole blood volume.

Finally, the *parametric approach* is based on the calculation of theoretical threshold values such as the maximal volume of injection which will still keep the blood's pH or its molarity within the physiological range or an estimate of the dilution ratio at the injection site. As long as those threshold values are not exceeded, the formulation and its administration condition have at least no theoretical concern and may be considered within an experimental design for further assessment. The parametric approach provides some additional information but does not replace the conventional or the experimental approach. In fact, all approaches are complementary. Of course, such an evaluation is specific for a given product, formulation, and administration scheme, and only nonclinical and clinical studies will finally confirm the appropriateness of the drug product related to systemic and local tolerance and the assessment of safety (vs. efficacy).

Assessment via the Conventional Approach

pH Limits of Small- and Large-Volume Parenterals

For large-volume intravenous (i.v.) infusion administration, pH and osmolality recommendations are summarized in Table 1.[5]

For small-volume i.v. injection solutions (<100-mL nominal volume), broader pH ranges can be envisaged depending on the source of information: pH 4-9,[6] 3-10.5,[7] or 3-11.[4,8] On the other hand, when the risk of infiltration in subcutaneous tissue cannot be excluded, more restrictive pH ranges such as 5.5-8.5[9] are suggested, to avoid any risk of tissue damage.

Table 1
Recommendations of Infusion Nursing Society for Minimization or Prevention of Vascular Damage From Extremes in Infusate pH or Osmolarity[5]

Vessel	Blood Flow (mL/min)	Osmolarity (mOsm/L)	Solution pH
Superior vena cava	2000	>900	<5 or >9
Subclavian vein and proximal axillary vein	800	500-900	<5 or >9
Cephalic and basilica veins in the upper arms	40-95	<500	5-9

As summarized in Table 2, drug products within a broad range of pH values (2.55-11.15) are on the market, most likely to overcome solubility or stability constraints.

There are no major warnings about pain or irritation in the packaging inserts of the drug products listed in Table 2, although an injection solution with an extreme pH value is more likely to induce vascular irritation, inflammatory reactions, or pain. However, the physiological local reaction cascade depends on too many factors (injection volume, infusion rate, local blood rate, duration of infusion, needle diameter, injection depth, buffering capacity, viscosity, active ingredient, cosolvents, and so forth) to permit a direct correlation between the pH (as isolated parameter) and pain or local irritation, unless all other factors would be kept constant in a homologous test series. Therefore, in case of a low buffering capacity, a low injection volume, a slow injection rate (favoring an rapid dilution by blood close to the injection site), and a nonirritating active drug substance even an extreme pH (high or low) can be locally well tolerated and produce neither pain nor irritation. In contrast, for an injection solution such as promethazine hydrochloride, which has a relatively harmless pH (4.0-5.5), adverse reactions including burning, pain, thrombophlebitis, tissue necrosis, and gangrene are mentioned in the packaging insert.

Those examples show that a too restrictive use of pH acceptance criteria could unnecessarily jeopardize the feasibility of a parenteral drug product.

For small-volume injections, not only the dilution factor but also the time factor plays an important role with regard to local i.v. tolerance. In contrast to the almost instantaneous solubilization of lipidic cell membrane components in presence of a high concentration of cosolvents, acid or basic hydrolysis needs time. This is the reason why small-volume bolus injections can often be administered i.v. in a very broad pH range. This has been confirmed by animal studies[5,10] that concluded that a solution with a pH of 3-11 did not induce phlebitic changes when drugs were administered over a few minutes. However, the same studies showed that the local tolerance was highly dependent on the pH in case of a 6-hour infusion through peripheral vessels. Indeed, a solution with a pH of 4.5 resulted in a 100% incidence of severe phlebitic changes, a pH of 5.9 caused mild-to-moderate phlebitic changes in 50% of the animal subjects, a pH of 6.3 still caused mild damage in 20% of those subjects, and a pH of 6.5 caused no significant damage.[8,11,12]

To keep the risk of local irritation low, pH values should nevertheless be inside the target pH range of $3.5 \leq \text{pH} \leq 9.0$ (according to DailyMed database) unless for very compelling reason. Especially, alkaline solutions with significant buffering capacity should be preferably be avoided. In case of borderline pH, a slower infusion rate (e.g., 5-minute push instead of 1-minute bolus injection) will contribute to overcome or reduce the risk of local irritation and vein damage. The reason of a better local tolerance in that case is related to the infusion duration but to the increased drug product dilution by the blood flow at the injection site.

Osmolality Limits of Blood and Infusion Solutions

With regard to osmolality, hypertonic injection solutions with an osmolality >600 mOsm/kg[13] have been reported to possibly cause crenation (shriveling up) of red blood cells and significant pain. Hypotonic solutions with an osmolality about <150 mOsm/kg in contrast may cause hemolysis and pain at the site of injection. The limit of 240 mOsm/kg given in the European Pharmacopoeia for monoclonal antibodies[14] has already a considerable safety margin and seems a bit arbitrary acceptance criterion but is not the physiologically lowest limit conceivable for these products. Indeed, a hypotonic sodium chloride 0.45% infusion solution (154 mOsm/L)