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Review

Tolerability of hypertonic injectables

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ABSTRACT

Injectable drug products are ideally developed as isotonic solutions. Often, hypertonic injectables may have to be marketed for a variety of reasons such as product solubilization and stabilization. A key concern during product formulation development is the local and systemic tolerability of hypertonic products upon injection. This report reviews and discusses the tolerability in terms of local discomfort, irritation, sensation of heat and pain, along with other observed side effects of hypertonicity in both *in-vitro* systems and *in-vivo* animal and human models. These side effects clearly depend on the degree of hypertonicity. The sensation of pain among different injection routes seems to follow this order: intramuscular > subcutaneous > intravenous or intravascular. It is recommended that the upper osmolality limit should be generally controlled under 600 mOsm/kg for drug products intended for intramuscular or subcutaneous injection. For drug products intended for intravenous or intravascular injection, the recommended upper limit should be generally controlled under 1000 mOsm/kg for small-volume injections (≤100 mL) and 500 mOsm/kg for large-volume injections (>100 mL). Several options are available for minimization of hypertonicity-induced pain upon product administration.

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1. Introduction

The main goals in formulation development for injectable products are to control the product solubility, to extend/optimize product storage stability, and to maximize both local and systemic tolerability upon injection. These three aspects are interrelated and needed to be considered together (Fig. 1). There are many factors that can potentially affect the local tolerability of an injectable drug product. One such factor is the osmolality of drug product solutions for administration. Therefore, osmolality of an injectable product is a key parameter, which formulation scientists need to consider during product development.

The osmolality of an injectable product would ideally be the same or similar to that of the body fluid. In many cases, however, hypertonic (or in rare cases, hypotonic) drug product formulations have to be developed. This is because different types and amounts of formulation excipients are needed for drug efficacy, safety and/or stability. This is especially the case for high-concentration biological products, which may need excessive amount of stabilizers in a product formulation. Some commercial product solutions for intravenous injection were found to be extremely hypertonic with an osmolality of >>1000 mOsm/kg (*e.g.*, digoxin, phenytoin, phenobarbital, *etc.*) (Pereira-da-Silva et al., 2002). These hypertonic solutions may cause tonicity-related discomfort/pain, which could be inherently associated with a particular drug and/or excipient(s) and observed as a confounding side effect. Nonetheless, product labels should list injection-related pain under Adverse Reactions, and if pain is a significant safety concern, it has to be listed under Warnings and Precautions, as required by FDA (2013).

Is there an upper limit in osmolality of a drug product that is tolerable upon injection? This review tries to address this question by summarizing the concept of osmolality and tonicity, and *in-vitro* and *in-vivo* tolerability to hypertonicity. Based on the literature data, an upper osmolality limit for an injectable product is recommended. Several options are described for minimization of hypertonicity-induced pain upon product administration.

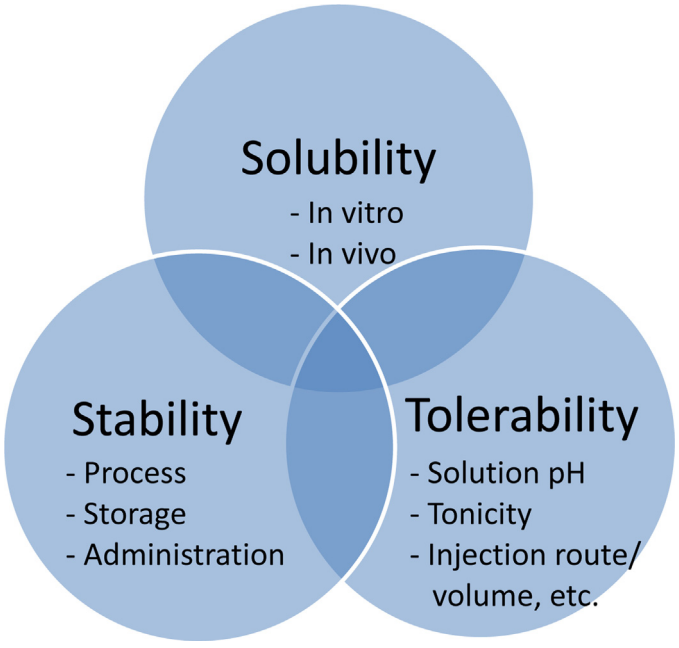

Fig. 1. Key aspects for consideration in product formulation development and their overlapping relationships.

2. The concept of osmolality and tonicity

Osmolality (osmolarity) is a measure of the osmotic pressure exerted by a solution across a perfect semi-permeable membrane, which allows free passage of water and completely prevents movement of a solute(s). Osmolality, a physical property of a solution, is equal to the total concentration of all ionizable (*e.g.*, NaCl) and non-ionizable (*e.g.*, sugar) species/particles, as described by the following equation:

$$\text{Osmolality} = \Sigma(\Phi n C)$$

where Φ is the osmotic coefficient accounting for the degree of molecular dissociation; n is the number of particles of dissociation; and C is the molal concentration of a solute. With respect to a reference solution, a test solution can be iso-osmotic (equal), hyperosmotic (higher), or hypo-osmotic (lower) in osmolality.

Tonicity is a measure of the osmotic pressure that a substance can exert across a cell membrane relative to blood plasma. For a substance that can't cross cell membranes, tonicity is practically identical to osmolality. Human plasma has an osmolality of about 0.3 Osm/kg (300 mOsm/kg), therefore a 0.15 mol/kg NaCl solution may be said to be isotonic with plasma, assuming that neither Na^+ nor Cl^- can cross cell membranes freely (almost true). Solutions having a greater (or lower) osmolality than 300 mOsm/kg are hypertonic (or hypotonic).

There are two common methods in measuring the osmolality—freezing point depression (FPD) and vapor point deficit (VPD). The most commonly-used osmometer in modern laboratories is based on freezing point depression because it is accurate, sensitive to all types of solutes and easy to use (Schmelzer et al., 2000). A between-day variation of <1% in measurement can be easily achieved in a range of 0–2000 mOsmol/kg with a sample volume of 20 μL (Koumantakis and Wyndham, 1989). For biological samples, variation can be slightly higher due to temperature variation during measurement, sample storage and handling (Bohnen et al., 1992). Alternatively, osmolality can be also calculated rather accurately based on the concentration of all solutes, using the above equation. It was demonstrated that the mean difference was negligible (up to 0.5 mOsmol/kg) between the calculated and measured osmolality of patients' blood samples by freezing point depression (Fazekas et al., 2013).

Accurate measurement of the osmolality of a body fluid may be required in a clinical setting, as an abnormal value may provide evidence for certain types of diseases. For examples, plasma hyperosmolality has been used as an indicator for dehydration or hyperglycemia (Seifarth et al., 2004) (Arieff and Carroll, 1972) and marker for early frailty/low survival in elderly patients (Stookey et al., 2004) (O'neill et al., 1990), and tear hyperosmolality for dry eye (Stahl et al., 2012). Therefore, administration of isotonic drug product formulations is highly recommended, so as not to change the state of physiological tonicity upon drug administration.

3. *In-vitro* and *in-vivo* tolerability to hypertonicity

The *in-vitro* and *in-vivo* tolerability to hypertonicity has been widely studied and reported. These studies can be divided roughly into three major categories—*in-vitro* cell systems, animal studies and human trials.