A Study into Upper and Lower pH Limits of Intravenous Products Delivered by Infusion

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1. Background
In the current portfolio of drugs in development, industry are finding a number of compounds with poor aqueous solubility.

One strategy to improve solubility is adjustments in pH. However, lack of solubility at pH of interest leads to formulations outside the pH guidelines (1-4).

Very high or low pH outside the current formulation guidelines are a cause for concern and impede development.

2. Purpose
The aim was to build confidence in the development of high and low pH infusions and bolus injections products.

To achieve this, current marketed intravenous products formulated at very low and high pH were studied.

The objectives were to conduct an extensive literature search and supporting laboratory experiments to construct a formulation risk assessment database for novel compounds.

The database will consist of formulation properties (e.g., pH, osmolality, volume) physicochemical properties (e.g. pKᵦ, log P) excipients, rate and site of administration.

This is to provide precedence for novel compounds formulated at high and low pH.

3. Method
Twenty products identified as having extreme pH and high volumes of administration were investigated. The study included literature and measured values.

Literature primary sources: Handbook of Injectable Drugs (5), PDR (6), Product Package Inserts and SPCs (7) were used to find the pKᵦ, log P, pH, volume, tonicity, excipients, rate of infusion and site of administration.

Measured: Each lyophile was reconstituted in a concentrated solution and administered into a central or large peripheral vein.

Little to no support is present in the literature to provide precedence for formulating outside the current pH limits for intravenous products.

4. Results

Product pH values from literature
All the products, except clarithromycin, lie outside the generally accepted pH range (Figure 3). The values were of the initial solution; the pH of the diluted infusion was not found in literature.

Product volumes from literature
The volume of the initial reconstituted vial or concentrated solution ranged from 1 to 25 ml.

Acid dissociation constant, pKᵦ
Many low pH products formulated at a pH two units below pKᵦ, fully ionised, whilst most high pH were not in this region (Figure 3).

Octanol: water partition coefficient, log P
Overall a greater proportion of drugs were found to be lipophilic, with a log P greater than 0.

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4. Results (Continued)

Measured pH values
The initial solution pH fit within the ranges from published sources. The pH of the infusion (unavailable in literature) was found to be lower than the initial pH and varied with the diluents used to prepare the product (Figure 4).

Measured osmolality
Reconstitution of the lyophiles with sodium chloride 0.9% was hypertonic and with water for irrigation was hypotonic (Figure 5). The final preparations were isotonic around 300 mOsm.

Rate and Site of administration
Most of the products were instructed to be infused slowly over an extended period of time and administered into a central or large peripheral vein.

Application to novel compounds
Development of compound X (Figure 4) was not supported by high pH infusions. Development of compound Y (Figure 1) is preceded by marketed low pH products.

5. Future Work
Collect irritancy data such as phlebitis risk to help understand which factor(s) (e.g. pH or osmolality) is responsible for pain.
Perform titration experiments to understand buffer capacity and how drug behaves in blood.
Compare generics to branded products as different manufacturers may incorporate different excipients.
Prepare infusions with other compatible diluents such as Ringer’s or Hartmann’s solution.

6. Conclusion
The key outcome was the construction of a map of extremely high and low pH of 20 intravenous products, which lie outside the current physiologically acceptable guidelines.

The data has been applied to two examples to demonstrate the study’s use in providing precedence to assess the risk of developing a novel formulation at extreme pH.
This will help develop a risk to benefit profile for formulators to consider formulating at high/low pH as an extra strategy to solubilise drugs.
Gaps were found in published literature for the final diluted pH and other physicochemical properties. Inconsistencies were also seen between resources. Therefore literature values need to be verified by measurement to use for development of novel formulations; which has been started with this study.