



1) What is pH adjustment?

Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change.

2) Which administration route is our pH technology suitable for?

pH adjustment can in principle be used for both oral and parenteral administration.

Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 – 7.4. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to consider.

In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines.

3) Which types of compound are suited to pH adjustment?

Ionizable compounds that are stable and soluble after pH adjustment are best suited. The compound types may be acids or bases or zwitterionic. It can also be applied to crystalline as well as lipophilic poorly soluble compounds.

4) How does pH adjustment work to increase bioavailability?

The solubility of the poorly soluble drug is increased compared to water alone, so if compounds can permeate through the epithelium orally, the fraction of orally absorbed drug may be increased. pH adjustment is also frequently combined with co-solvents to further increase the solubility of the poorly soluble drug.

If the precipitation upon dilution is fine or amorphous, bioavailability can be increased due to an increased concentration gradient and enhanced surface area for dissolution. In situations where the drug precipitates into poorly soluble particles that require dissolution and do not rapidly redissolve, bioavailability may not be sufficiently increased.

5) Which Phares services use the pH technology?

This approach is used frequently in Survey as pre-clinically pH adjustment is a good technique to assess the efficacy of poorly soluble drugs due to its universality and relative simplicity. However, if precipitation of the poorly soluble drug occurs uncontrollably after contact with a pH at which the drug is much less soluble (oral as well as parenteral), the interpretation of the results may be misleading. In our Speed service, this approach may be an ideal approach if the pH is not extreme and it is well tolerated. However, it may be less attractive to assess the pre-clinical toxicity of poorly soluble drugs if toxicity is observed after multiple administrations. In these situations, precipitation at the injection site and damage of the injection site may be limiting, particularly if the insoluble compound has to be administered intravenously at a high dose and an extreme pH.

Also, during the development of clinical dosage forms in our Icebreaker service, although pH adjustment may be simple from technological perspective, it may cause undesired tolerability at the injection site if a non physiological pH is used.

6) Advantages and disadvantages of pH adjustment

Advantages

- Simple to formulate and analyze
- Simple to produce and fast track
- Uses small quantities of compound, amenable to high throughput evaluations

Disadvantages

- Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability
- Tolerability and toxicity (local and systemic) related with the use of a non physiological pH and extreme pHs
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms

7) Scale-up of pH adjusted formulations

The production of pH adjusted formulations of a poorly soluble drug is usually straightforward. They can be produced aseptically if compound is unstable to heat or produced dry if susceptible to hydrolysis.

8) Phares pH adjustment expertise

Phares has developed smart ways of rapidly identifying if pH adjustment is a suitable approach. We also examine the precipitation behaviour of drugs from pH adjusted formulations after dilution in media which are relevant for the *in vivo* situation.

Coupled with Phares' experience in salt forms, we can help identify if pH adjustment and counter ions can provide advantages over free forms.

9) Commercial products using pH adjustment

Phenytoin Injection (Epanutin® ready mixed, Pfizer) 50mg/ml with propylene glycol 40% and ethanol 10% (1.1 mmol Na⁺ per 5 ml ampoule) is an example of a pH adjusted formulation containing co-solvents.

KEY SERVICES:

