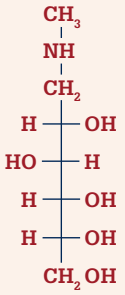
A counter ion that fulfils all needs

The solubility of an active drug substance is critical to a successful dosage delivery. Dr Steffen Denzinger, **Merck Millipore**'s head of technical marketing pharma raw materials, reveals how meglumine can improve the solubility of an anionic drug.

During the formulation of pharmaceutical drugs, many properties must be optimised to create an active pharmaceutical ingredient that will be delivered in the right amount, at the right time, at the right place in the body in order to achieve the desired effect. In addition to classical properties such as dissolution and disintegration for solid dosage forms, or stabilisation for liquid dosage forms that can be supported by excipients, the solubility of the active drug substance is critical to success.

For liquid dosage forms, aqueous solubility under the right buffer conditions plays an important role for the successful storage of a pharmaceutical drug. Even more important is solubility under physiological conditions within the body, a property that is independent from the chosen dosage forms.



The structural formula of meglumine. Under physiological conditions, the amine is partly protonated, resulting in a weak cationic counter ion.

Enhancing solubility

Interestingly, the solubility of new drug substances has been decreasing. Fortunately, additives can help change the solubility of active drug substances. One option for enhancing solubility is complexation of the drug substance. This can be achieved by, for example, cyclodextrines forming stable aggregates; however, kinetics of the release from these complexation agents has to be studied in order to ensure the pharmacokinetics of the active drug substance remain adequate.

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Another option involves the chemical transformation of a drug molecule by changing the protein kinase A (pKa) of the drug through the formation of an applicable salt. In most instances, the salts resulting from the synthetic routes of chemical entities are the sodium, calcium or potassium salts in the case of anionic moieties, which are numerous among known drug substances. All the counter ions are derived from strong bases with pKa values above 12. Nevertheless, a large number of active ingredients are derived from rather weak acids. Therefore, the solubility of such actives can be enhanced significantly by exchanging these counter ions with weaker organic counter ions with pKa values of 8-9.

Meglumine as a counter ion

Selecting the right counter ion for a drug substance is an important factor for enhancing the solubility of a drug. A counter ion frequently used to enhance the solubility of active ingredients is N-Methyl-D-glucamin, known as meglumine, which is an amino sugar derived from sorbitol with a pKa of 8.03. Meglumine is used to replace sodium because it has a comparable osmotic activity and is impermeable towards cell membranes. Examples of current products with meglumine as a counter ion are meglumine antimonate (for human use) and flunixin meglumine (for animal use). Meglumine is also widely used in the manufacturing of contrast media in combination with iodine containing compounds.

As the counter ion closely interacts with the drug substance, the quality and supply chain security of the manufacturing process for these substances should be considered carefully. For human use, the quality standard both in purity and the manufacturing process should be equal to the standard of the API itself. As such, manufacturing with a tight quality control under an ICH Q7/A standard provides the most security and peace of mind.

Unfortunately, organic counter ions such as meglumine, tromethamine or piperazine are frequently derived from technical sources due in part to a lack of suppliers who can offer grades manufactured under cGMP.

Improving bioavailability

Merck Millipore provides meglumine that fulfils the stringent requirements of drug manufacturers. Its meglumine is an API grade that is accompanied by full documentation including DMF and CEP.

Counter ions of this quality open new possibilities for drug manufacturers. Therefore, Merck Millipore will dedicate itself to offer more such materials as it strives to help drug manufacturers to enhance the bioavailability of drugs. ■

Further information
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