

OxaPEGylation technology for API properties

In the second of two articles, **Dr Andreas Meudt** and **Dr Sebastian Würtz** of **Archimica** show how oxa acids can be used in pharmaceutical applications*

Polyethyleneglycol (PEG) is among the most important commercial polyethers. It is a neutral biodegradable, non-toxic polymer and has low chemical reactivity, unless it is modified with functional groups. Functionalised PEGs with one or two terminal carboxylic groups are known as polyglycolic acids or oxa acids.

These have unique physical and chemical properties, notably good solubility in water and organic solvents, a wide liquid range, good heat stability and outstanding complexing properties for metal ions. For this reason, they have found widespread commercial applications as complex ligands or ligand precursors for transition metals, solvents for inks, fuel additives, high temperature lubricants and components for high-technology polymer blends in golf balls.

Oxa acids with one or two carboxylic functional groups are water-soluble compounds with defined chain lengths that are non-toxic and non-irritating (Figure 1). Therefore, they have found commercial application in the cosmetics sector as active compounds in creams, lotions and shampoos. Compared to the commonly used carbon α -hydroxy or dicarboxylic acids, oxa acids exhibit higher water solubility and desquamatory activity.

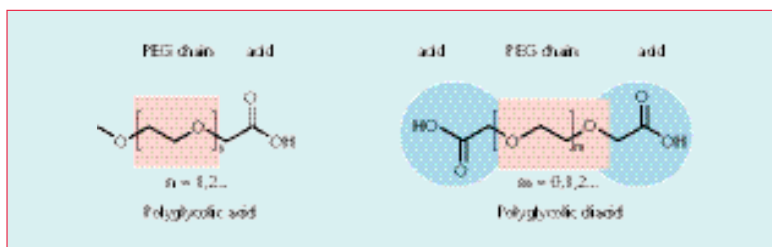


Figure 1 - (above) **Mono- & homodifunctionalised oxa acids**

Figure 2 - (bottom) **Different PEGylation methods for peptides or APIs**

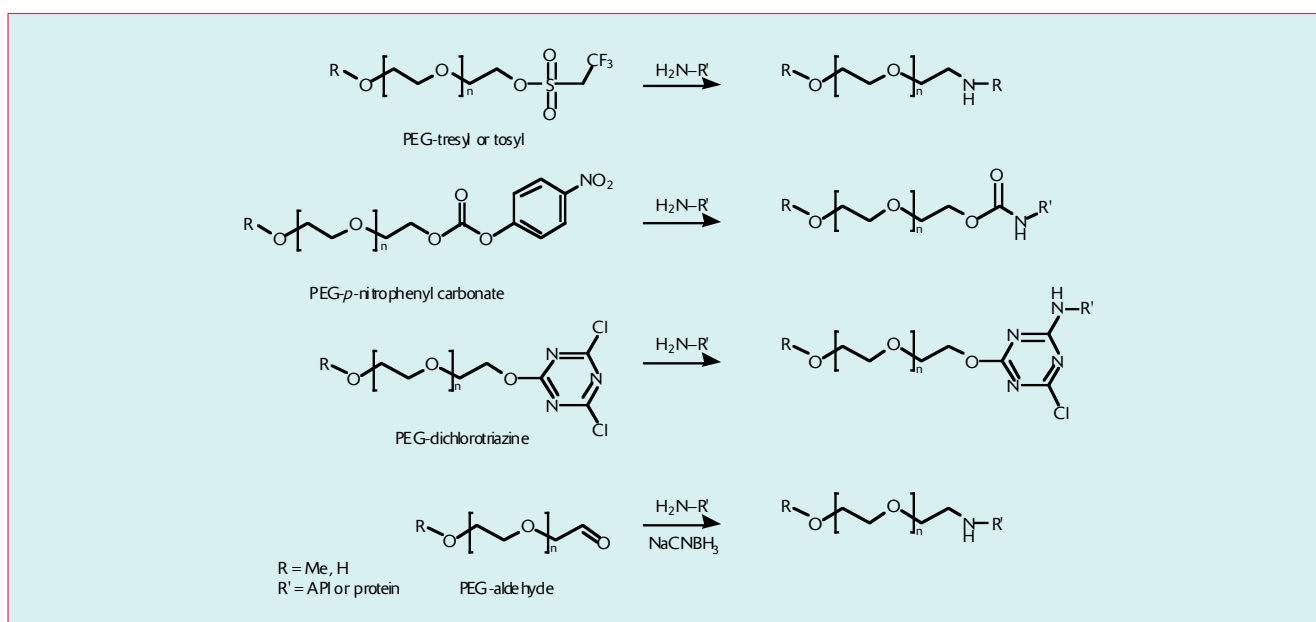
Figure 3 - (below) **T3P-mediated oxaPEGylation of APIs under mild conditions**

In the pharmaceuticals industry, functionalised PEG derivatives have found widespread application in the derivatisation of proteins, or PEGylation. The use of biologically active proteins as therapeutics suffers from short circulation half-lives, immunogenicity, protolytic degradation and low solubility.¹

The most successful approach to overcoming these limits has been to mask the surface of the protein by covalent bonding with PEG.² In 1977, Abuchowski found that PEGylated proteins are non-immunogenic and non-antigenic active conjugates with significantly increased *in vivo* circulation half lives.³

This effect is mainly attributed to the increased molecular size and altered surface of the bioactive peptide by the PEG polymers.^{4,5} In addition thermal stability and solubility in water and organic solvents is increased. Today, the PEGylation of bioactive peptides is state of the art and has become an important application for functionalised PEG derivatives.

The conversion of an activated PEG derivative with the free amino functions of a pharmaceutically active protein seems to be the most obvious strategy for an efficient PEGylation. Due to the low reactivity of unfunctionalised PEG, all PEGylation strategies start with the formation of electrophilic PEG derivatives.



This can be accomplished by the conversion of the terminal alcohol function into good leaving groups by means of sulphonylation or the formation of reactive carbonates. Another approach is by derivatisation with a reactive spacer like triazine derivatives or by the oxidation of the terminal alcohol to the more reactive aldehyde function (Figure 2).

The major drawbacks of these strategies are the use of toxic reagents, the formation of toxic by-products, slow reactivity or low selectivity.⁶ In all cases, the formation of an active PEG derivative is required and the subsequent separation of the PEGylated protein from the by-products formed during the reaction can be troublesome.⁷

The derivatisation of APIs with PEG moieties could improve the bioavailability of drugs, thanks to the improved properties mentioned above. However, due to the relatively high costs of producing pharmaceutically active compounds, any subsequent derivatisation of drugs has to be as efficient as possible.

In addition, the quality of the PEG building block is a crucial parameter to achieving reproducible PEGylation of the respective drugs. The efficient coupling of unfunctionalised amino, hydroxy and thiol groups of APIs with oxa acids to the corresponding amides or (thio)esters offers a new chemical PEGylation strategy.

T3P (propane phosphonic acid anhydride) is a highly reactive coupling and dehydrating agent that Archimica offers in various solvents, like EtOAc and DMF. T3P-mediated coupling of amines and alcohols, including various functional groups with carboxylic acids to form amides, peptides and esters, is an established procedure for the industrial manufacture of APIs.⁸

This procedure can be used for the efficient coupling of oxa acids with amine or alcohol functional groups. In this case, the

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carboxylic acid function of the oxa acid can be used directly in the coupling without further modification. In addition the consequent by-products are non-toxic and can easily be separated by aqueous extraction. Because of the additional oxygen atom of the PEG chains introduced via this route, this method is termed oxaPEGylation (Figure 3).

As well as the advantages of PEGylated bioactive compounds, the oxaPEGylation strategy offers some key benefits. Oxa acids with various defined chain lengths and high purity are available and the reaction offers a high functional group tolerance, with low epimerisation and easy work-up and purification. In addition, the T3P-mediated coupling of various functional groups with oxa acids to form peptides and esters is mild and highly efficient, as well as generally being high-yielding.^{9,10,11}

* - Also contributing to this article was Dr Jörg Jung of Archimica

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