COVID-19 and vaccines: Excipient theory

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SUMMARY

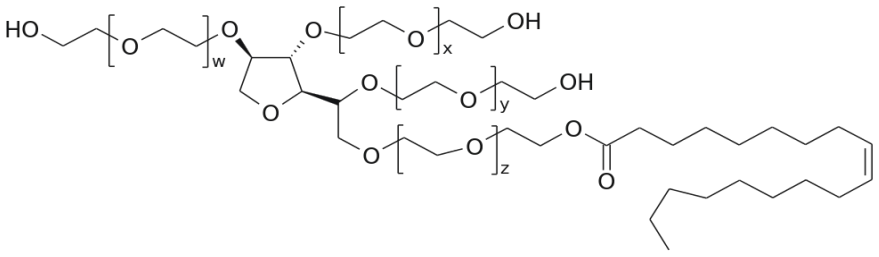
Polysorbates, polyethylene glycols and octylphenols are synthetic polyethers used as excipients in various biological drugs such as influenza and anti-COVID vaccines, and share epitopes with mannose polysaccharides present in glycoproteins on the outer surface of coronaviruses, which implies the risk of interfering with the immune system mannose receptors, and cause adverse reactions through three pathways:

- Excipient only: Cross reaction by activation of the complement by the excipient itself, observed with the first inoculations.
- Excipient + anti-PEG antibody: Type III hypersensitivity reaction, mediated by immune complexes, observed in subsequent inoculations.
- Excipient + anti-PEG antibody + coronavirus: Immunological interference after a viral infection, with a "Trojan horse" effect, postulated for severe COVID.

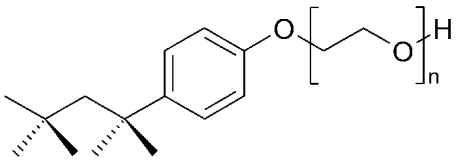
Key words: COVID-19 vaccines, excipients, polyethoxylates, polysorbates, polyethylene glycols, octylphenols, mannose, immune interference.

INTRODUCTION: SYNTHETIC AND NATURAL POLYETERS

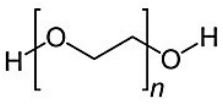
The nonionic surfactants most used as excipients in vaccines are polysorbates, octylphenols and polyethylene glycols (PEG), which are polyethoxylates produced by ethoxylation of fatty alcohols to make them more miscible with water. All three are structurally closely related in their main chain, formed by repeating groups of a polyether nature (1).



Polysorbate 80

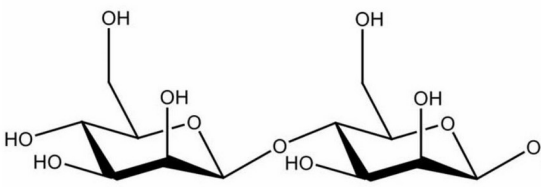


Octoxynol-9 (octylphenol)



Poliethylene glycol

These repeating synthetic chain structures OH - CH2 - CH2 - O - present on the surface of polysorbate and octylphenol micelles, as well as on the surface of pegylated nanoparticle micelles, also occur in natural polysaccharides such as mannose polymers (mannan) present in glycoproteins on the outer surface of viruses, bacteria and fungi, so they can be recognized as pathogen-associated molecular patterns (PAMPs) by the mannose pattern recognition receptors (PRRs) (2) of the innate immune system, and couple to them (3).



Oligomannose

After being administered parenterally, polyethoxylate excipients reach the bloodstream and spread throughout the body to reach small vessels and capillaries, contacting both vascular endothelial cells and blood cells, such as erythrocytes and platelets, and therefore can interfere with processes involving mannose receptors, which can be soluble or membrane bound.

I. UNION OF POLYETOXYLATE WITH MANNOSE RECEPTORS

Polyethoxylates can bind to soluble serum mannose-binding lectin (MBL) (2), and activate complement by promoting the generation of anaphylatoxin C3a, which mediates platelet activation (4). PEGs can generate complement activation products on a time scale of minutes (5). This explains the formation of thrombi observed after a first inoculation of a COVID vaccine, an anti-flu vaccine, or after a first administration of a biological drug.

Polyethoxylates can also bind to macrophage membrane mannose receptors and immature dendritic cells, sinusoidal liver endothelial cells, skin cells such as fibroblasts and keratocytes (6), and astrocytes and microglia (7), which could explain many other reactions described, such as liver (Amiodarone), skin, neurological...

II. UNION OF POLYETOXYLATE WITH ANTI-PEG ANTIBODIES

The polyether groups of polyethoxylates constitute repetitive epitopes that generate anti-PEG antibodies (1) in the spleen, in a process independent of type 2 T cells (TI-2), which gives rise mainly to IgM (8), but in the spleen can also occur isotype change from IgM to IgG (9), which increases its persistence in the blood.

This is a case of anti-drug antibodies (ADA), an important safety problem found with the use of biological drugs (10), this time linked to the excipient.

Before a second inoculation, either a 2nd dose of COVID vaccine, or a COVID vaccine after an anti-flu, or a 2nd administration of a biological drug, the polyethoxylate administered will

coincide in the blood with the previous anti-PEG antibodies, and can give rise to the formation of clinically important immune complexes, as they can lead to potential type III hypersensitivity reactions such as those of Rituximab (11).

At this point, it should be taken into account that an adjuvanted influenza vaccine contains 1,175 mg of polysorbate, whose molecular weight is 1,309.7 g / mol, which gives us 8.97 × 10-7 moles, and multiplying this amount by the constant from Avogadro ($6{,}022 \times 10^{23}$), we have the result of 540.000.000.000.000.000 antigenic polysorbate molecules, which are suddenly inoculated into the body.

III. ANTI-PEG ANTIBODIES AND VIRUSES: IMMUNE INTERFERENCE

Finally, it remains to evaluate the immune response of an individual with anti-PEG antibodies to contact with a virus with mannosylated epitopes, which will be recognized and bound by said antibodies. Here our theory of immune interference postulates that anti-PEG antibodies bound to viruses can interfere with their endocytosis by both macrophages and alveolar endothelial cells, and cause innate immunity to fail, which we postulate to explain the elevated severe COVID mortality in vaccinated old people (12).

DISCUSSION

The excipients of the medicines can cause adverse effects. Polyethoxylated surfactants are incorporated as excipients in many biological drugs, including influenza and anti-COVID vaccines, with observed adverse effects.

The shared chemical structures between the polyethoxylates and the oligomannose groups, which are recognized by the mannose receptors of the immune system, present a risk of cross-reactions that can result in adverse effects, such as thrombi.

The generation of anti-PEG antibodies also represents a risk of cross-reactivity both with new administrations of polyethoxylates, as well as between anti-PEG antibodies and viruses with mannose epitopes, which would explain both postinfusion reactions and overmortality in old vaccinates.

The mission of Pharmacovigilance is to provide data for the constant reevaluation of the benefit/risk balance of the drugs in use.

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