The Use of Polysorbate Excipients in BoNT/A formulations and Potential Underlying Immunological Implications

Michael Uwe Martin[1], Jurgen Frevert[2], Je-Young Park[3], Haiyan Cui[4,5], Andy Curry[6], Wei Qi Loh[7], Kathlea Newland[7*]

1 Independent Researcher, 31832 Springe, Germany. 2 Merz Pharmaceuticals GmbH, 60318 Frankfurt am Main, Germany.
3 Apkoo-Jung Oracle Dermatology Clinic, Seoul 06022, Korea. 4 Department of Plastic and Cosmetic Surgery, Tongji Hospital, School of Medicine, Tongji University, Shanghai 200092, China. 5 Institute of Aesthetic Plastic Surgery and Medicine, Tongji University, Shanghai 200092, China. 6 Merz Aesthetics, Raleigh, NC 27615, USA.
7 Merz Asia Pacific Pte. Ltd., Singapore 138589. * Presenting author.

For more study details:

Doi:/10.3390/toxins17120598

Introduction and Objectives

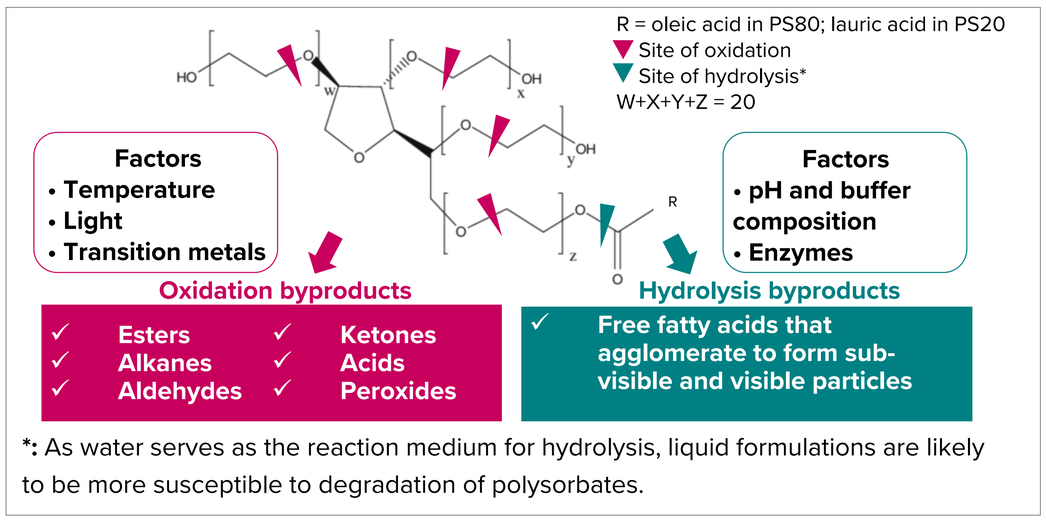
Polysorbates, including polysorbate 20 (PS20) and polysorbate 80 (PS80), are being increasingly used as non-human-derived stabilizing excipients in botulinum neurotoxin type A (BoNT/A) formulations. This shift from the use of human serum albumin (HSA) was driven by perceived concerns regarding potential infectious agent transmission, despite HSA's long record of safe use. **The objective of this review is to clarify the immunological implications of polysorbate excipients in BoNT/A formulations, aiming to inform real-world practice and formulation strategies by integrating chemical, mechanistic, and clinical perspectives.**

Findings

Chemical nature and degradation

- Polysorbates are a class of synthetic non-ionic surfactants, prone to degradation via hydrolysis and oxidation pathways to generate various byproducts (**Figure 1**).
- These reactive byproducts can chemically alter proteins such as BoNT/A, or lead to aggregates, which may affect product quality and lead to immune activation.

Figure 1. Summary of the oxidative and hydrolytic degradative pathways of polysorbate.



*: As water serves as the reaction medium for hydrolysis, liquid formulations are likely to be more susceptible to degradation of polysorbates.

Distinct immune pathways leading to potential downstream effects with BoNT/A treatment

Immunological outcomes, including immunogenicity and hypersensitivity, have been broadly associated with polysorbates; implications in the context of BoNT/A use are presented in **Table 1.**

Table 1. Potential immunological outcomes with polysorbate excipients. IgE: immunoglobulin E

	Immunogenicity	IgE-mediated hypersensitivity	Non-IgE-mediated hypersensitivty
Mechanistic pathway	Adjuvant-like effects of polysorbates can indirectly contribute immune cell recruitment, and enhanced antigen uptake by dendritic cells	Repeated exposure and sensitization to polysorbates and its byproducts lead to the downstream activation of mast cells and basophils	Polysorbates can directly activate mast cells, resulting in non-IgE- mediated reactions
Clinical presentation	Loss of efficacy over time	Hypersensitivity symptoms such as itching, swelling, urticaria	
Detection methods	Binding antibody assays, e.g., ELISA; Neutralizing antibody tests (i.e., mouse hemidiaphragm assay)	Skin prick or serum specific IgE tests against polysorbates	Increase in circulating complement mediators, e.g., C3a/C5a without IgE involvement

Clinical experience with polysorbate-containing BoNT/A formulations

Although published real-world data on polysorbate-containing BoNT/A formulations (**Table 2**) are limited, isolated cases of hypersensitivity and immunogenicity in clinical trials have been reported.

Table 2. BoNT/A formulations with polysorbate excipients. RTU: ready-to-use

Generic/Code Name	Form	Polysorbate content
DaxibotulinumtoxinA	Lyophilized	PS20 (0.1 mg per vial)
RelabotulinumtoxinA	Liquid	PS80 (1.6 mg per vial; 1.1 mg/mL)
AbobotulinumtoxinA RTU	Liquid	PS80 (0.1 mg per 1 mL)
MT10107	Lyophilized	PS20 (1.0 mg per vial)
NivobotulinumtoxinA	Liquid	PS20 (0.094 mg per vial)

Clinical data of polysorbate-containing BoNT/A

- In a study for moderate-to-severe glabellar lines administering three doses of daxibotulinumtoxinA over a 36–84 week follow up in 2691 patients, one adverse event of hypersensitivity assessed as possibly related to the intervention was reported.[1]
- Among 357 patients treated for cervical dystonia with up to four doses of daxibotulinumtoxinA over 52 weeks of follow-up, one patient developed NAbs de novo and was positive throughout follow-up. Although attributed to prior rimabotulinumtoxinB treatment, cross-reactivity across toxin subtypes is thought to be unlikely.[2]
- For 595 patients treated for up to 5 total doses of abobotulinumtoxinA RTU, with mean follow-up of up to 377.2 days, no neutralizing antibodies (NAbs) were observed, but hypersensitivity reactions were noted in two patients (0.3%)[3]
- There were indications of treatment-induced NAb development in two individuals out of a total of 556 patients who received up to three treatment cycles of nivobotulinumtoxinA for the treatment of glabellar lines and/or lateral canthal lines, with follow-up until 360 days.[4]

Risk mitigation strategies

Repeated exposure to BoNT/A across multiple uses, alongside growing intradermal application in aesthetic treatments may raise the risk of immune reactions, underscoring the importance of appropriate risk mitigation.

Manufacturers need to optimize manufacturing processes by monitoring degradation, and ensure stringent control of manufacturing and storage parameters.

Clinicians should adhere to proper storage and handling protocols, make informed decisions in product selection, and document potential immunological reactions.

References: 1. U.S. Food and Drug Administration. Multidiscipline Review: NDA 761127. 2. McAllister, P et al. Mov. Disord. Clin. Pract. 2025, 12, 1764–1773. 3. Swedish Medical Products Agency. Public Assessment Report: Alluzience; Swedish MPA: Uppsala, Sweden, 2022. 4. Coleman,W et al. Aesthet. Surg. J. 2025, 45, 404–413

Conflicts of interest: Michael Uwe Martin serves as an ad hoc consultant and speaker for Merz Pharma GmbH & Co., KGaA. Jürgen Frevert serves as a consultant for Merz Pharma GmbH & Co., KGaA. Je-Young Park has received grants from Merz Aesthetics and serves as an advisory board member and speaker for Merz Aesthetics. Cui Haiyan declares no conflicts of interest. Andy Curry is an employee of Merz Aesthetics. Wei Qi Loh and Kathlea Newland are employees of Merz Asia Pacific Pte. Ltd.