PEGylation in biophrmaceutics: and evolving strategy for enhanced therapeutic efficacy

TANAYA RAJESH KHIRAPATE, REEMA RANI, DR. RUPALI TASGAONKAR
Yadavrao Tasgaonkar Institute of Pharmacy

Abstract—
PEGylation is the process of attaching polyethylene glycol (PEG) chains to therapeutic molecules, it has played a transformative role in the development of biopharmaceuticals (1,9).
This strategy helps improve drug solubility, stability, and half-life, and has been especially valuable in protein- and peptide-based therapeutics (1,4).
Over the years, PEGylation has contributed to the success of multiple FDA-approved drugs, enhancing their performance and patient tolerability (1,10).
However, it is not without challenges (5,10).
The emergence of anti-PEG antibodies, potential loss of biological activity, and concerns about long-term PEG accumulation have highlighted the need for more refined approaches (3,5,13).
This review explores the basic science of PEGylation, examines its clinical applications, addresses current limitations, and looks ahead at innovative solutions shaping its future (4,9,10).

Keywords—**PEGylation, Biopharmaceutical, Immunogenicity, Drug delivery systems, Controlled release, Anti-PEG antibodies**

I. INTRODUCTION

PEGylation has become one of the most important strategies in pharmaceutical biotechnology for improving the performance of biologic drugs (1,9).

The process involves attaching polyethylene glycol (PEG), a biocompatible and water-loving polymer, to therapeutic molecules such as proteins, peptides, or nanoparticles (1,8).

This simple modification has a big impact, as it helps drugs stay in the bloodstream longer, reduces how often patients need to take them, and makes them less likely to trigger an immune response (4,10).

Today, more than 20 PEGylated drugs, including Pegasys for hepatitis C and Neulasta for chemotherapy-induced neutropenia, are used in clinical practice (1,9).

However, growing evidence of anti-PEG antibodies, hypersensitivity reactions, and PEG accumulation in tissues has sparked debate about its long-term safety (3,5,8).

This review looks at both sides: the proven benefits and the emerging concerns to provide a clear picture of where PEGylation stands today (9,10).

PEGylation: Mechanism & Chemistry

PEGylation works by chemically attaching polyethylene glycol (PEG) chains to specific sites on a therapeutic molecule, creating a protective, water-loving layer around it (4,9).

PEG itself is a flexible, highly soluble polymer that is generally well tolerated by the human body (1,8).

The attachment can occur at different points on the drug molecule, most commonly on lysine residues through amine groups (4,9).

Cysteine residues can also be targeted through thiol groups (4,6).

PEGylation may also occur at the N- or C-terminal ends of a protein (4,6).

There are two main strategies for this process (4,9).

Random PEGylation is simpler to perform but can reduce drug activity if the PEG chain blocks a critical functional site (4,10).

Site-specific PEGylation is a more controlled approach that targets a precise location to preserve biological activity (4,6).

PEG itself can be designed in different forms, including linear, branched, or multi-arm structures, depending on the desired therapeutic effect and the size of the target molecule (1,4).

Selecting the right PEG structure and conjugation site is crucial because it determines the drug's circulation time, stability, and overall clinical performance (4,10).

Clinical Applications

Many PEGylated drugs have made a real difference in clinical settings (1,9).

By increasing half-life and decreasing immunogenicity, they have led to better outcomes for patients and greater convenience for both doctors and caregivers (4,10).

This technology has been applied across multiple therapeutic areas, including oncology, viral infections, autoimmune disorders, and enzyme replacement therapies (1,9).PEGylation not only improves pharmacokinetics but also reduces systemic toxicity and side effects by allowing lower doses or more targeted delivery (10,11)

Examples include:
Oncology: Doxil (PEGylated liposomal doxorubicin) for cancer therapy.
Viral Infections: Pegasys (PEGylated interferon-alpha) for hepatitis C.
Autoimmune Disorders: Adagen (PEGylated adenosine deaminase) for severe combined immunodeficiency.

Enzyme Replacement Therapy: Krystexxa (PEGylated uricase) for gout.
Hematology: Neulasta (PEGylated filgrastim) for neutropenia.
Vaccines: Comirnaty and Spikevax (PEGylated lipid nanoparticles in mRNA vaccines).
Ophthalmology: Macugen (PEGylated aptamer) for age-related macular degeneration.
Diagnostic Imaging: PEGylated contrast agents.

Table no. 1 Examples of some PEGylated drugs

Drug	Condition Treated	PEGylated Form	Benefit
Filgrastim	Neutropenia	Pegfilgrastim	Longer half-life, fewer doses
Asparaginase	Leukemia	Pegaspargase	Lower immune response
Interferon-α	Hepatitis C	Peginterferon-α	Improved patient adherence
Doxorubicin	Cancer	PEG-liposomes (Doxil)	Targeted delivery, less toxicity

II. LIMITATIONS & CHALLENGES

While PEGylation has brought major advances in drug delivery, it is not without limitations (5,10).
Ongoing research and clinical experience have highlighted several challenges that need to be addressed to ensure safe and effective use of PEGylated therapeutics (9,10).

Anti-PEG Antibodies and Immune Reactions

Contrary to early assumptions, PEG is not always invisible to the immune system (3,13).

Some patients have pre-existing anti-PEG antibodies, while others develop them during treatment (3,13).

These antibodies can clear PEGylated drugs from the body too quickly, a phenomenon known as Accelerated Blood Clearance (5,12).

They may also reduce therapeutic efficacy (5,10).

In some cases, they can trigger mild to severe immune reactions (3,8).

A growing number of clinical reports have documented this issue, especially in patients receiving repeated PEGylated treatments or vaccines (8,12).

Reduced Bioactivity

In some cases, attaching PEG randomly to a molecule can interfere with its ability to bind to receptors or perform its intended function (4,10).

If a PEG chain blocks an enzyme's active site, the drug may become less effective (4,9).

This limitation has driven increased interest in site-specific PEGylation strategies (4,6).

Accumulation and Long-Term Safety

PEG is not readily metabolized by the body, particularly in high-molecular-weight forms (5,10).

As a result, PEG may accumulate in tissues such as the liver, spleen, and kidneys during chronic treatment (5,8).

Although no definitive long-term toxicities have been established, the clinical implications of PEG accumulation remain uncertain (10,12).

Recent Innovations

To overcome the limitations of conventional PEGylation, researchers are developing more advanced approaches that improve precision and safety (4,9).

These innovations aim to preserve therapeutic efficacy while minimizing immunogenicity and long-term risks (10,12).

Site-Specific PEGylation

Site-specific PEGylation enables controlled attachment of PEG molecules to defined protein positions (4,6).

This approach ensures that critical functional domains remain intact (4,6).

As a result, drugs retain biological activity while benefiting from extended circulation time (4,9).

Studies on GLP-1 analogs have demonstrated that N-terminal PEGylation significantly prolongs half-life without compromising efficacy (4,10).

Similar success has been observed in monoclonal antibodies and therapeutic enzymes (6,9).

Smart or Stimuli-Responsive PEGs

Smart PEG systems are engineered to respond to biological triggers such as pH or enzymes (10,11).

pH-sensitive PEGs detach in acidic tumor environments, enabling localized drug release (11,12).

Enzyme-cleavable PEGs activate drugs selectively at disease sites (10,11).

These systems reduce off-target toxicity while improving therapeutic precision (11,12).

Exploring Alternatives to PEG

Concerns regarding PEG immunogenicity have driven the development of alternative polymers (2,10).

Poly(2-oxazoline) exhibits PEG-like stealth properties with lower immunogenicity (2,4).

Hyperbranched polyglycerols show excellent biocompatibility and biodegradability (4,9).

Dextrans have long been used in drug delivery and plasma expansion (1,9).

Polysialylation has demonstrated reduced immunogenicity while maintaining drug activity (6,7).

III. FUTURE PERSPECTIVES

The future of PEGylation depends on balancing benefits with emerging safety concerns (10,12).

Screening for anti-PEG antibodies may become part of personalized treatment planning (3,13).

Advances in site-specific conjugation will improve reproducibility and scalability (4,6).

Biodegradable and immunologically neutral polymers such as PASylation and XTENylation are gaining attention (9,10).

These developments reflect a shift toward safer and more precise drug delivery platforms (10,12).

IV. CONCLUSION

PEGylation has revolutionized biologic drug delivery by improving half-life and patient convenience (1,9).

However, immune responses and safety concerns highlight the need for continued innovation (5,10).

Emerging strategies such as site-specific PEGylation and alternative polymers offer promising solutions (4,10).

The future of bioconjugation lies in precision, personalization, and safety-driven design (9,10).

REFERENCES

[1] Alconcel, S. N. S., Baas, A. S., & Maynard, H. D. (2011). FDA-approved poly(ethylene glycol)–protein conjugate drugs. Polymer Chemistry, 2(7), 1442. https://doi.org/10.1039/c1py00034a

[2] Bludau, H., Czapar, A. E., Pitek, A. S., Shukla, S., Jordan, R., & Steinmetz, N. F. (2016). POxylation as an alternative stealth coating for biomedical applications. European Polymer Journal, 88, 679–688. https://doi.org/10.1016/j.eurpolymj.2016.10.041

[3] Garay, R. P., El-Gewely, R., Armstrong, J. K., Garratty, G., & Richette, P. (2012). Antibodies against polyethylene glycol in healthy subjects and in patients treated with PEG-conjugated agents. Expert Opinion on Drug Delivery, 9(11), 1319–1323. https://doi.org/10.1517/17425247.2012.720969

[4] Gonçalves, J., & Caliceti, P. (2024). Optimizing pharmacological and immunological properties of therapeutic proteins through PEGylation: Investigating key parameters and their impact. Drug Design Development and Therapy, Volume 18, 5041–5062. https://doi.org/10.2147/dddt.s481420

[5] Kozma, G. T., Shimizu, T., Ishida, T., & Szebeni, J. (2020). Anti-PEG antibodies: Properties, formation, testing and role in adverse immune reactions to PEGylated nanobiopharmaceuticals. Advanced Drug Delivery Reviews, 154–155, 163–175. https://doi.org/10.1016/j.addr.2020.07.024

[6] Lindhout, T., Iqbal, U., Willis, L. M., Reid, A. N., Li, J., Liu, X., Moreno, M., & Wakarchuk,

[7] W. W. (2011). Site-specific enzymatic polysialylation of therapeutic proteins using bacterial enzymes. Proceedings of the National Academy of Sciences, 108(18), 7397–7402. https://doi.org/10.1073/pnas.1019266108

[8] Padín-González, E., Lancaster, P., Bottini, M., Gasco, P., Tran, L., Fadeel, B., Wilkins, T., & Monopoli, M. P. (2022). Understanding the role and impact of poly (Ethylene glycol) (PEG) on nanoparticle formulation: Implications for COVID-19 vaccines. Frontiers in Bioengineering and Biotechnology, 10. https://doi.org/10.3389/fbioe.2022.882363

[9] Santhanakrishnan, K. R., Koilpillai, J., & Narayanasamy, D. (2024). PEGylation in Pharmaceutical Development: Current status and emerging trends in macromolecular and immunotherapeutic drugs. Cureus. https://doi.org/10.7759/cureus.66669

[10] Simberg, D., Barenholz, Y., Roffler, S. R., Landfester, K., Kabanov, A. V., & Moghimi, S. M. (2025). PEGylation technology: addressing concerns, moving forward. Drug Delivery, 32(1). https://doi.org/10.1080/10717544.2025.2494775

[11] Song, S., Sun, D., Wang, H., Wang, J., Yan, H., Zhao, X., Fawcett, J. P., Xu, X., Cai, D., & Gu, J. (2023). Full-profile pharmacokinetics, anticancer activity and toxicity of an extended release trivalent PEGylated irinotecan prodrug. Acta Pharmaceutica Sinica B, 13(8), 3444–3453. https://doi.org/10.1016/j.apsb.2023.01.011

[12] Wu, E., Guan, J., Yu, Y., Lin, S., Ding, T., Chu, Y., Pan, F., Liu, M., Yang, Y., Zhang, Z., Zhang, J., Zhan, C., & Qian, J. (2024). Exemplifying interspecies variation of liposome in vivo fat e by the effects of anti-PEG antibodies. Acta Pharmaceutica Sinica B, 14(11), 4994–5007. https://doi.org/10.1016/j.apsb.2024.07.009

[13] Yang, Q., Jacobs, T. M., McCallen, J. D., Moore, D. T., Huckaby, J. T., Edelstein, J. N., & Lai,

[14] S. K. (2016). Analysis of Pre-existing IgG and IgM Antibodies against Polyethylene Glycol (PEG) in the General Population. Analytical Chemistry, 88(23), 11804–11812. https://doi.org/10.1021/acs.analchem.6b03437