A VIEW ON THE USE OF APROTIC SOLVENTS IN PARENTERAL DRUG FORMULATIONS

In this article, Michael Neely, Consultant to Xeris Pharmaceuticals, presents a review and discussion of the status of aprotic solvents as a solubilising vehicle for parenteral drug formulations in the context of the industry's increasing interest in biologic drugs.

A review of the literature surrounding aprotic solvents produces but a scant bibliography citing their use in parenteral drug formulations, and a look at the current array of marketed drug products shows that only a very few employ such solvents. Given the potential benefits that non-aqueous systems might present to certain types of drug formulations, especially for biologics susceptible to water-mediated degradation, the dearth of industry experience invites some speculation as to why the approach has not been more widely explored. To try to explain this observation, there are several questions whose answers may be revealing. Relevant questions include:

- How much do formulators know about aprotic solvents and their properties?
- Are there prevailing assumptions in academia and industry about the safety and suitability of aprotic solvents for parenteral administration?
- Is existing equipment for formulating and packaging in the pharmaceutical industry a deterrent to alternative approaches?
- To what extent are non-aqueous solvents compatible (or incompatible) with existing parenteral filling equipment and packaging systems?
- What additional formulation modifications might be necessary to make aprotic formulations stable, safe and effective?
- How do regulatory agencies view aprotic solvents, and what additional risks or delays might the use of these solvents introduce to the approval process?

Biomolecules, such as proteins and peptides, comprise a large segment of new drugs currently in development. While recent research on formulation approaches for these drugs has been heavily focused on non-parenteral routes of administration, biomolecules remain most readily amenable to parenteral delivery. Accordingly, for developers looking to achieve rapid market entry, drugs that require precise dosing, or for APIs that are very high cost where alternative delivery routes are economically infeasible, parenteral formulation remains the most viable option.

Protein- and peptide-based drugs are often packaged and distributed as lyophilised products. This is because these molecules are susceptible to several water-mediated degradation pathways, such as hydrolysis, as well as various pH-dependent oxidation or reduction reactions that affect their amino acid side chains. When concentrated in aqueous solution, certain peptides are also prone to forming insoluble aggregates. Lyophilisation renders these molecules stable for extended periods of time, making them suitable for commercial distribution in the pharmaceutical supply chain. A downside is that lyophilised drugs require reconstitution prior to administration, which presents additional handling requirements, a potential risk of contamination and can easily result in over- or under-dilution. Moreover, once reconstituted, many of these drugs have a very short shelf life, and some must be administered immediately or discarded.

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Michael E Neely
Consultant
T: +1 314 608 0715
E: mneely@xerispharma.com

Xeris Pharmaceuticals, Inc
180 North LaSalle Street
Suite 1600
Chicago, IL 60601
United States

www.xerispharma.com

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The rationale for considering a non-aqueous solvent for parenteral delivery of protein or peptide drugs includes considerations of several factors, including:

- Stability
- Solubility
- Safety
- Efficacy
- Compatibility with containers, closures and injection devices
- Manufacturability
- Regulatory approval
- Patient acceptance.

Until very recently, the only non-aqueous polar solvent that could be found in commercial parenteral formulations is N-methyl pyrrolidone. This solvent is typically present at concentrations of around 30–60% in several extended-release depot injection drugs containing peptide drug substances. More recently, formulations of the sugar-regulating peptide hormone, glucagon, have been approved for marketing using dimethyl sulfoxide (DMSO) as the solvent. In this unique formulation, DMSO proved to be a superior solvent because it eliminated water, and thereby water-mediated degradation. This allowed for an increased drug concentration and reduced injection volume due to greater solubility of the active, eliminated aggregation as a degradation pathway, and has proven to be shelf-stable for upwards of 24 months at room temperature.

So why are there so few examples of marketed drugs formulated in aprotic solvents, given the rise in biomolecule drug candidates and the many potential advantages and benefits such solvents offer with these molecules? A value proposition is the net of benefits less risks and, when risks are not well known or well understood, their perceived magnitude is increased. A lack of familiarity with aprotic solvents, specifically of their physical, chemical and toxicological properties, is probably one reason why they may not have received first line consideration.

"Many formulators may look at DMSO as a vehicle unsuitable for parenteral injection. However, a review of the literature shows that it has very low toxicity and, in clinical experience, is proving to be well tolerated in subcutaneous injections."

Many formulators may look at DMSO as a vehicle unsuitable for parenteral injection. However, a review of the literature shows that it has very low toxicity (it has a no-observed-adverse-effect level greater than 10 mg/Kg) and, in clinical experience, is proving to be well tolerated in subcutaneous injections. DMSO is widely available in United States Pharmacopoeia and European Pharmacopoeia grades from several suppliers. Moreover, the literature suggest that DMSO has antimicrobial properties that could be beneficial in sterile fill or aseptic processing operations.[1,2]

Whatever the reasons behind the reluctance to include aprotic solvents in a formulation approach, the lack of activity in this area of inquiry appears to have created a vacuum in the realm of intellectual property development, and the adage "nature abhors a vacuum" has proven true once again. A review of patents granted over the past half decade shows that a small handful of companies have begun to explore and develop the opportunities afforded by aprotic solvents as parenteral formulation vehicles. Indeed, a total of 13 US and 93 Ex-US patents claiming use of aprotic solvents as formulation solvents and/or the medical use of such formulations have been granted to a single company, Xeris Pharmaceuticals. Other patents have been issued claiming aprotic solvents as specific formulation components.

A look at some of the current patents shows that another issue with adoption of aprotic solvents might be that using them is not as simple as just substituting the aprotic solvent for water. It also appears to be critical that additional stability-promoting formulation components must be included to ensure the desired shelf life of the drug product is achieved. Such formulations result in a drug molecule that retains its structure and functional characteristics once it is introduced to the *in vivo* aqueous environment.

It will be interesting to see whether and how this technological opportunity manifests in the pharmaceutical industry as the pace of discovery and development of protein- and peptide-based biomolecules continues to increase.

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ABOUT THE COMPANY

Xeris Pharmaceuticals is a specialty pharmaceutical company that leverages novel formulation technology platforms to develop and commercialise ready-to-use liquid-stable injectables. The company

is focused on creating medicines that are easier to use, including its Gvoke® glucagon injection, which uses Xeris's technology to deliver ready-to-use solutions for patients and caregivers alike.

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ABOUT THE AUTHOR

Michael Neely retired in 2015 after a 42-year career in the pharmaceutical industry. He currently serves in a consulting role for business development at Xeris Pharmaceuticals. His experience spans multiple disciplines, including pharmaceutical manufacturing, research and development, business development and marketing.