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An Alternative Solution for Peptide Drug Development

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Abstract: Polypeptide molecules are now a significant source of new chemical entities in the pharmaceutical industry. When exploring structure activity relationships of potential peptide sequences for various targeted receptors, medicinal chemists often encounter structures which have the desired affinity and specificity for the target, but which are intractable as potential drug molecules because of problems related to solubility or chemical stability. Significant cost and time are added to development cycles though the process of exploring alternative structures that will overcome such problems. A more expeditions approach to enabling a candidate molecule to be formulated as a drug would offer significant benefits in cost and time savings. Herein we introduce a novel concept for resolution of stability and solubility problems confronting formulators working with peptide drug molecules. Aprotic solvents such as Dimethyl Sulfoxide are shown to be safe and effective solvents for injectable peptide drugs, and are shown to offer long term shelf stability for such molecules in liquid formulations. The aprotic solvent technology obviates the need for costly and time consuming lyophilization processes. Its ability to increase solubility while obviating pH effects enables delivery of well tolerated small volume therapeutic doses. The technology also obviates the effect of pH and coupled with its ability to increase the concentration of peptide, affords a parenteral dose volume that is reduced and which spares the patient exposure to irritation that can be introduced by pH outside the range of neutrality.

Keywords: Peptides, Drug Formulation, Aprotic Solvents, Dimethylsulfoxide

1. Introduction

If the job of a medicinal chemist was “only” to identify and synthesize a molecule that had optimal affinity and specificity for a targeted receptor, while showing minimal or no off target effects or toxicities, success might come more quickly and more frequently. It often does not because in addition to the aforementioned properties, a candidate drug molecule must also be amenable to formulation and well tolerated delivery to patients, while retaining stability and potency under conditions of handling, manufacturing, packaging, transport and storage that are amenable to the environmental realities of commerce.

Often a great deal of time, money and effort are spent at molecular modeling workstations and in synthesis labs, trying to develop tweaks to a molecule that will improve its solubility, stability, or impart some other property that makes it suitable for a particular delivery route. This is particularly true with peptide molecules. In 1963. Dr Bruce Merrifeld, spawned a revolution in medicinal chemistry with his brilliant conception of a solid phase sequential synthesis scheme for polypeptide molecules. [1] Merrifield’s work and those who followed, enabled peptide molecules and analogs to be synthesized quickly, inexpensively and in sufficient quantity to be evaluated for biological activity. Whether looking at the nervous system, the circulatory system, hormonal systems, the immune system, or virtually any other life process, peptides have been identified which play significant roles, forming the basis for their vast and expanding potential as drug candidates. Peptide based drugs now generate several billions of dollars in annual pharmaceutical revenues and looking across industry and academia, one can identify hundreds of new candidates in various stages of development at any given point in time [2].

A significant limitation of peptide molecules as pharmaceutical agents is they are subject to degradation by several mechanisms during storage and handling. Peptides are labile to water, and pH, which are also essential to their function. Water mediated degradation pathways are arguably the most significant set of factors that impact peptide drug formulations. Hydrolysis, aggregation, fibrillation,

deamidation and other side chain reactions are all water and/or pH mediated. [3] To preserve function in drug formulations, virtually all peptide and protein-based drug products undergo a lyophilization process in order to remove water to keep them intact until they are rehydrated at the point and time of use. Medicinal chemists often attempt to explore structural changes in peptides to limit phenomena such as aggregation or fibrillation without significantly impacting their pharmacological activity and toxicity. A good example of this was the development of Pramlintide as a functional analog of the human Amylin peptide. [4] The insertion of three proline residues allowed the molecule to be isolated at useful concentrations without aggregation yet retain its ability to function pharmacologically. Other examples exist, one being the adoption of Salmon Calcitonin as a human therapeutic, primarily because it showed high potency as well as solubility at drug concentrations without fibrillation and subsequent precipitation, which cause its human version to be problematic as a drug product [5].

It is the purpose of this review to describe a very simple and elegant solution to some of the stability and solubility problems that confront medicinal chemists and their formulating partners when exploring peptide molecules for drug use.

2. A Novel Approach to Solvation

In 2015, Neuswanger et. al. published results of research on the use of polar aprotic solvents, such as Dimethyl Sulfoxide (DMSO) as a solvent vehicle for drug formulation [6]. This approach has now been demonstrated to enable dissolution of numerous problematic peptides, while maintaining their chemical and physical integrity and potency in solution for extended periods of time at ambient temperatures. Many drug formulators and development teams have been quick to assume that such solvents are unacceptable for drug use, particularly as injections, but this is in fact not the case. Scientists at Xeris Pharmaceuticals Inc. have now demonstrated the utility and clinical efficacy of several peptide and non-peptide drugs formulated in aprotic solvent systems. The company has received regulatory approvals to market some of these products in both the US and Europe.

One of the first molecules to be studied by the Xeris team, led by Dr. Steven Prestrelski, was the important metabolic peptide glucagon [7]. Glucagon became available as a drug for injection following the advent of insulin therapy and is provided to insulin users as a rescue drug for acute hypoglycemia. The original formulation was a lyophilized powder that is meant to be reconstituted at the point and time of use, and once reconstituted the drug must be injected almost immediately or it will aggregate and come out of solution. Glucagon has a very short stability interval once dissolved in water. The Xeris team demonstrated that when formulated in DMSO, along with appropriate levels of other components to enable it to achieve a functional pH when it meets the aqueous microenvironment at the site of injection, glucagon retained stability and pharmacological activity for many months (now 36) as a liquid even when stored at room temperature. This discovery allowed glucagon to be formulated as a ready to inject liquid that could be packaged in a convenient pen injector device, making it an improved rescue drug for episodes of hypoglycemia following insulin use. (See figure 1).

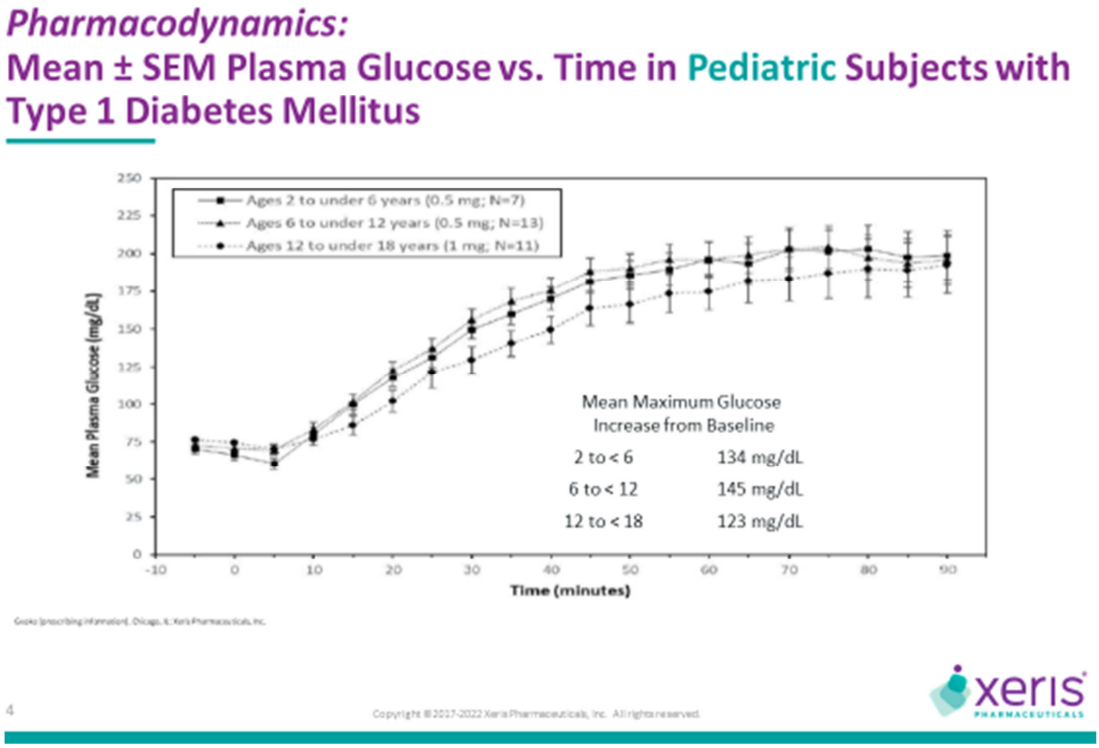

Figure 1. *Pharmacodynamics: Mean±SEM Plasma Glucose vs. Time in Pediatrics Subjects with Type 1 Diabetes Mellitus.*

It is noteworthy that throughout their animal studies and human clinical trials, Xeris did not note signs of injection site irritation or pain that were significantly different from the aqueous formulation. More recent data suggest that there are fewer injection site related complaints with their formulation. The Xeris formulation of glucagon is approved by FDA and is marketed in the United States as Gvoke (R) glucagon injection in a single use rescue pen device and in a pre-filled syringe [8]. It is marketed in Europe and the UK as Ogluo (R) glucagon injection in the same packages.

Prestrelski coined the term Xerisol^{TM} to describe this aprotic solvent formulation platform because it incorporates the Greek word "Xeris" which means dry, and "sol" to indicate solution. The technology platform has since demonstrated additional significant benefits. It has been shown to be effective for formulating difficult to dissolve small molecules as well as peptides. [9] Furthermore, it also allows peptides that require different pH to achieve aqueous solution to be co-dissolved at relatively high concentration. Xeris is now completing phase 2 clinical trials on a combined formulation of human insulin and pramlintide, both of which are deficient in type 1 diabetics and which function naturally as partner hormones in healthy glucose metabolism. [10] The co-formulated product under study is a liquid subcutaneous injection which is demonstrating improved glucose control in the study populations. The early clinical data are sufficiently promising that the company is actively seeking a partner to carry the drug forward into further Phase 2 and Phase 3 studies. (See Figure 2).

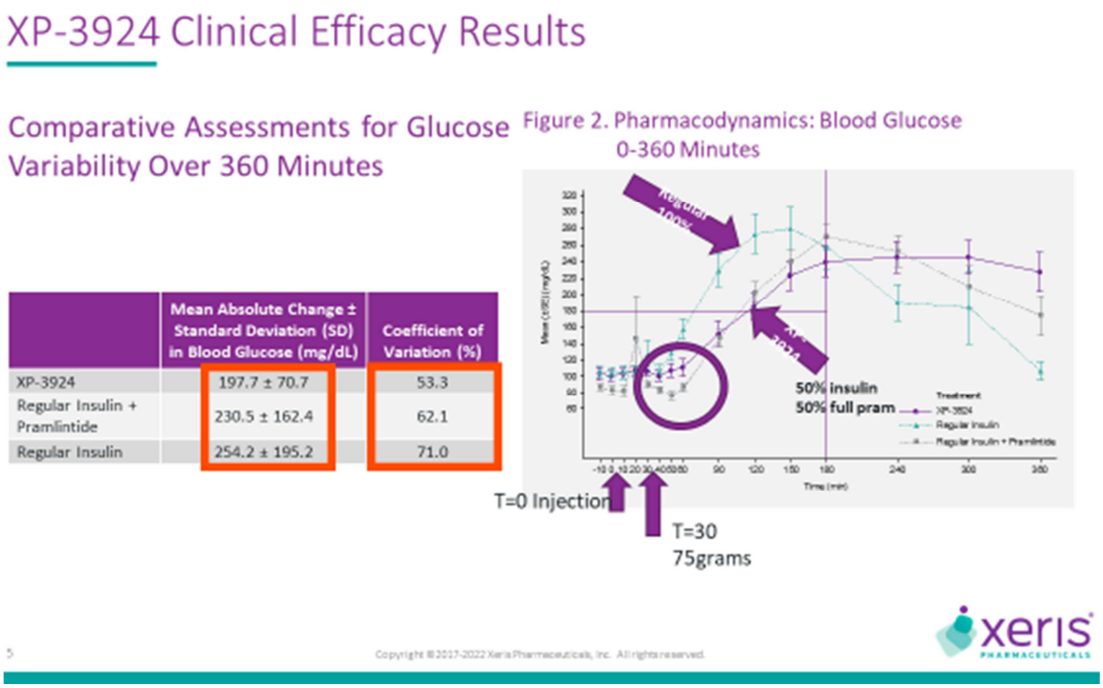

Figure 2. *XP-3924 Clinical Efficacy Results.*

The ability to dissolve multiple peptides in a single solution could yield significant benefits to those seeking to develop "cocktail" drugs such as multiple peptide antigen vaccines, or other co-formulated peptide combinations that might be imagined for various endocrinological disorders, peptide antibiotic mixtures, etc. It also merits consideration for use by those developing personalized medicines based on peptides, where it may offer a nearly "Plug and Play" formulation approach that yields a commercially viable product sparing the time and expense of complicated lyophilization process development.

3. Conclusion

For Medicinal Chemists and peptide drug developers seeking to bring benefits to patients efficiently, expeditiously and perhaps less expensively, this formulation approach would appear to offer significant value. The fact that Xeris has assembled an extensive patent estate around the technology platform also creates potential value in that whereas a molecule may not be patentable, such as the case for a natural molecule, a drug created using the patented formulation technology would be protected, and thus enable the developer to enjoy enhanced commercial value for an extended time period. This should spark interest among pharmaceutical companies seeking to extend product life cycles, and also among those seeking to develop and market bio similar drugs that are off patent. Xeris is actively seeking licensees for this technology platform, making its potential benefits available to others in the pharmaceutical industry.

Clinically proven success with a non-aqueous solvent system suggests that for a significant problem set confronting medicinal chemists who work in the domain of peptide molecules, the solution may in fact be "the solution" rather than modifying the structure of the molecule, an idea worth considering as they pursue therapeutic goals.

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