Transitioning to the future.

Keith Horspool

Editorial Board, Journal of Excipients and Food Chemicals

Editorial

KEY WORDS: Novel excipients, continuous manufacturing, sub-optimal CMC properties, solubility enhancement, biologics formulations, surfactants, drug delivery

Welcome to the 15th volume of the Journal of Excipients and Food Chemicals (JEFC) 2024. It is my pleasure to introduce myself as the new Editor for this publication. To quote the ubiquitous Taylor Swift on X (2015); "This is a new year. A new beginning. And things will change". For The Journal of Excipients and Food Chemicals (JEFC), this means a new perspective that stems from my thirty-plus year career in the pharmaceutical industry, working on new product development and drug delivery.

The JEFC was started in 2010 by Dr Shireesh Apte based on his recognition of ongoing and future trends in excipients and food chemicals. This special edition of the JEFC is dedicated to Dr Apte, and those who worked with him, to recognize their magnificent contributions to taking the Journal from a concept to an established publication that continuously provides contemporary information to the scientific community it serves.

The importance of excipients has increased significantly through the last decade or so during which many new chemical entities (NCE) products, and certain drug classes (e.g., most products containing HCV polymerase inhibitors for the treatment of hepatitis C virus infections) have been enabled by new materials to achieve the necessary drug product performance. Similarly, many recently launched new biotherapeutic products (NBPs) have required the inclusion of novel excipients/new materials to achieve the requisite performance (e.g., oligonucleotide products containing specific lipids essential for stability and activity).

These crucial applications of new materials have been reflected in several JEFC editorials by Dr Apte and review articles such Dr Moreton's somewhat prophetic publication entitled "Excipients to the year 2025 – and beyond!" (republished here on pages 4 - 15) (1). This paper describes the various activities that have improved the quality of excipients and medicinal products, including harmonization of excipient pharmacopeial monographs. It highlights emerging areas at that time (such as continuous manufacturing), that are now fully accepted and widespread activities within pharma; and increasingly, in the biotherapeutics industry. Changing from batch manufacturing for solid dosage forms to continuous manufacturing practices has required greater understanding of material properties as well as advanced engineering for development of robust processes. It will continue to garner more interest in

*Corresponding address: HorspoolConsulting, Connecticut, USA, E-Mail: 125krh@gmail.com

both new chemical entity (NCE) and new biological entity (NBE) product development based on the opportunities to improve the effectiveness, and the quality, of drug product supply. Dr Moreton alludes to these benefits while also highlighting the importance of excipient consistency to facilitate the success of continuous solid dosage form production.

Significantly, this publication reflects on the emergence of biotherapeutics and some early challenges in their development as well as the implications of NCEs with poor chemistry, manufacturing and controls (CMC) properties that require formulations to overcome deficiencies such as low drug solubility, or permeability. It is encouraging to note that since the publication, excipients have enabled important products containing active pharmaceutical ingredients (APIs) with sub-optimal CMC properties; e.g., Rybelsus™ (*semaglutide*) that contains salcaprozate sodium, SNAC, to increase oral bioavailability; and certain new biologics (such as Onpattro™ (*patisiran*)), that is formulated as a lipid nanoparticle for delivery to hepatocytes. The potential of new excipients to generate new and improved drug products, has gradually been recognized by companies, and regulatory organizations, such as FDA, as indicated by Dr Moreton. Collaborative efforts between the pharmaceutical/biotech industry, excipient organizations (IPEC), the FDA, and the USP, subsequently led to the FDA's Novel Excipient Review Pilot Program launched in 2021.

Challenges in the approval of novel excipients/new materials has led to pre-existing excipients being utilized differently than in the past. This is the emphasis of the paper from Drs Kollamaram and Williams entitled "The effect of the composition of polysorbate 80 grades on their physicochemical properties" (republished here on pages 16 - 24) (2), that describes the use of polysorbates in formulations containing monoclonal therapeutics. The unprecedented application of these excipients to improve formulation stability of these very different drug products led to issues with product quality that allegedly caused a recall of marketed batches of product. Initial findings of this kind created consternation in the pharma/biotech industry leading to substantial scientific effort to understand the reasons for this issue. In the final analysis, the quality and stability of the polysorbates being used in certain monoclonal formulations were shown to be implicated in the product issues. Scientific understanding of excipients, their chemical composition and properties (including stability), physical characterization and material science underlying their production and performance are all important topics for the JEFC.

Dr Kollamaram and Dr Williams' paper highlights studies that characterize various polysorbate 80 grades to determine whether certain properties (purity, oleic acid content) influence the properties and degradation of these materials being used for the formulation of biotherapeutics. Although there was no evidence that various polysorbate 80 grades exhibited significant differences in various properties, including the degradation profile on storage, the paper demonstrates a systematic method for characterizing certain components of excipients and the impact on certain properties. The focus of the paper on factors affecting excipient properties provides an additional perspective on polysorbates, and different grades thereof, that can influence formulation stability and prevent protein agglomeration which may be affected by various impurities in these materials. For instance, secondary oxidation products of polysorbates, aldehydes and low molecular weight carboxylic acids are reactive with proteins and can play a role in product quality. When considering new applications of existing excipients formulators should be aware of possible liabilities associated with poor understanding of how potential chemical and physical properties could compromise their attributes in unusual formulation applications.

Therapeutic targets being pursued by drug discovery in recent years have led to NCEs that disobey the "rule of five" convention previously used to guide lead selection and advancement of drug candidates with more desirable CMC properties, especially good solubility and permeability. As this trend has continued in discovery, pharmaceutical scientists have used less conventional formulations, such as amorphous solid dispersions (ASDs) to overcome limitations of the

active pharmaceutical ingredient (API). Numerous products have been launched using this approach that has required new methods for characterization, and alternative manufacturing methods (e.g., spray drying or hot melt extrusion) for the development of robust dosage forms. Typically, the formulations have the active moiety incorporated into a polymeric matrix to form the amorphous solid dispersion (ASD). The paper by Dr Telange *et. al.*, entitled "Glucosamine HCl-based solid dispersions to enhance the biopharmaceutical properties of acyclovir" (republished here on pages 25 - 41) (3), describes research investigating the use of a glucosamine HCl as a potential alternative to polymers for creating solubility-enhanced formulations. Studies described highlight the potential of novel excipients to generate drug delivery systems with superior performance than standard formulation approaches. The paper describes the preparation, characterization and performance testing of several prototype ASD formulations comparing them with the model compound, acyclovir, demonstrate relatively stable formulations with superior performance compared to the unformulated compound. The paper highlights the importance of characterization of these more complex systems and how to conduct appropriate in vitro tests to gain insights on performance.

Drug delivery has steadily increased its prominence in product development in an industry driven by more challenging therapeutic entities and, in some cases, more localized delivery (e.g., ocular implants and long-acting parenteral systems). The sound understanding of the design principles, supported by robust materials science, cannot be underestimated for the robust development of such unconventional systems. Excipients are an essential component of drug delivery systems which might require special grades to guarantee performance or to eliminate risks to the product (e.g., polymers with low levels of residual peroxides). This will continue to be an expanding field with opportunities for multidisciplinary research to develop the next generation of technologies, and manufacturing processes, that will increase facile development of the increasingly diverse array of therapeutic entities and modes of delivery.

I hope that you enjoy this special edition of the Journal of Excipients and Food Chemicals, that is dedicated to its founder, Dr Shireesh Apte, and collaborators working on the Journal. I would personally like to thank them for their tremendous contributions to this publication that would not have been possible without their passion, commitment and expertise.

REFERENCES

1 Moreton RC, J. Excipients and Food Chem. **10**, (2): 29-40, 2019.

2 Kollamaram G, Williams GR, J. Excipients and Food Chem. **12**, (3): 32-40, 2021.

3 Telange DR, Bhagat SB, Patil AT, Umekar MJ, Pethe AM, Raut NA, Dave VS, J. Excipients and Food Chem. **10**, (3): 65-81, 2019.