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# Conference Report: Out of This World – Sound Bites from the Excipient World Conference & Expo, May 13-15, 2024

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Conference Report

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Having been absent from the Excipient World Conference & Expo for a couple of years it was exciting to witness the progress made in developing this meeting into a continually evolving environment for everyone interested in this area. The organizers, with a brilliant sense of irony, invited guest speaker, Lee McIntyre, (Boston University), to present on "How to Talk to a Science Denier". This outstanding lecture provided advice on the importance of empathy to translate science to skeptics, etc., to an audience that is anything but denying science. On the contrary, over three days, more than 250 participants contributed to, and participated in, more than 30 sessions including workshops, lectures, and fireside chats. These events illuminated the diverse universe of Excipient World that has grown in its scope and ambition to include innovative science, key quality topics, and crucial applications of excipients for development of small molecule and biologics human pharmaceuticals as well as veterinary medicines. The following selected insights are designed to provide high-level awareness of many of the topics covered at the conference.

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The conference began with educational workshops, one led by Professors Polli and Hoag (University of Maryland) focused on "Excipients 101" and the other, a Biologics Summit run in conjunction with the Controlled Release Society, dealing with "Breakthroughs in Drug Delivery and Medical Devices". This session highlighted technologies for targeted delivery of drugs to specific locations in the body via various routes of administration. Dr Kevin Warner (Alucent Biomedical Inc.) described drug coated balloons indicated for the treatment of obstructive lesions in arteries and veins. Specifically, the contribution of excipients to critical quality attributes of paclitaxel drug coated balloons including an overview of key attributes and the impact on product performance. Data highlighted how excipients play a role in facilitating adhesion of the drug to the balloon, release of the drug coating from the balloon surface into the vessel wall and residence of the drug at the treatment site. Dr Bo Michniak-Kohn (Rutgers University), reviewed applications of microneedles for drug and vaccine delivery. The microneedle concept is based on using needles long enough to by-pass the stratum corneum and short enough to avoid the pain

sensation by preventing intrusion into the dermis where there are blood vessels and nerves. Several formats are available for microneedle construction including solid or hollow microneedles, coated microneedles (that typically have a drug and polymer/co-polymer in the coating), and dissolving microneedles (comprising an excipient and drug formed into needles.) Several companies are advancing these technologies such as NanoPass' Microject TM that has been used in over 70 completed and ongoing clinical trials (according to the company website).

An elegantly pragmatic liquid embolic system (LES) for treatment of stroke was presented by Dr Thanasis Touris (Medtronic Neurovascular). A stroke occurs when the brain cannot receive blood or oxygen because blood vessels are either blocked or have burst. The Onyx™ LES consists of ethylene vinyl alcohol copolymer with DMSO as a solvent along with a radiopaque tantalum component (for confirming location of the device). This system is delivered to the aberrant blood vessel using a microcatheter whereupon the DMSO solvent rapidly dissipates causing the polymer to precipitate. The resulting polymer "cast" cuts off circulation to the aberrant/susceptible vessel, in what is referred to as peripheral embolization. The concept of in situ forming polymer systems was continued by Professor Diane Burgess (University of Connecticut) in a talk on long-acting injectable drug products including microsphere systems. Numerous polymer-based long-acting injectable products have been marketed over the last few decades including Perseris® (*in situ* forming polymer depot) and Risperdal Consta® (pre-formed microspheres). Professor Burgess' focus was primarily on work developing valuable methodologies that generate robust *In vitro in vivo* (IVIVC) correlations that can be used to develop alternative presentations of these complex injectable systems, and to develop greater insights on the role of various components in achieving the desired drug release profile.

Another workshop focused on the theme of 3D printing: Emerging Technologies and Functionality of Polymeric Excipients in Drug Product Development. Implementation of this technology to fabricate multicompartment solid oral dosage forms for use in clinical trial was presented by Dr Derrick Smith (Merck). Dr Smith provided a detailed case study of the development of this fascinating approach to explore the developability of new drug candidates. Judicious selection of polymer (PVA), combined with engineering and modeling expertise, was used to optimize a printed dosage form "capsule" that is robust and reproducible enough to be used in the clinic. The objective was to have a delivery system that could provide drug release with both a delayed burst and controlled release. One application of the system is to allow BCS Class II and IV drugs (low solubility-high permeability, and low solubility-low permeability respectively) to be delivered to various regions of the GI tract to assess regional delivery potential. The dosage form is provided to the clinical site where it is filled *in situ* with the drug, and other components necessary to solubilize it, prior to dosing. Challenges in the procurement of pharmaceutical quality excipients/materials were mentioned as impediments to the progress of 3D printing and this was a theme further exemplified in a presentation by Dr Sagar Narala (Ashland). Five different 3D printing methods were outlined along with the major applications: Material extrusion (e.g., Fused Deposition Modeling, FDM), binder jet printing (e.g., powder bed inkjet printing), powder bed fusion (e.g., selective laser sintering), material Jetting (drop on demand), and photopolymerization (e.g., stereolithography). Numerous polymers excipients have been used in work conducted so far but all speakers highlighted numerous limitations that affect their use and the need to increase the scope of the polymer portfolio to enable this area to become a more viable manufacturing option for the industry. Currently a range of materials have been utilized such as cellulosic polymers, polyvinyl polymers and bioresorbable polymers. Challenges due to excipient material properties differ across the various printing techniques with issues such as thermoplasticity temperature (potential API stability consequence) and filament brittleness being two considerations in polymer selection for FDM. This theme of material selection for 3D printing was continued by Dr Krizia Karry (BASF) who also showed a case study involving nifedipine (see later).

The temporally challenging concept of 6D printing was just one on many intriguing concepts in the final presentation session of the workshop (Professor Mohammed Maniruzzaman, University of Mississippi). Various printed geometrical formats possible with this incredibly versatile method for fabrication were outlined with several systems already licensed for commercialization purposes. Pharmaceutical applications of the more elaborate and complex printed designs are still in the conceptual phase of experimentation although intriguing examples appeared to offer the possibility of creating printed systems that can undergo shape transformation in response to a specific stimulus. Other innovations in this session included a presentation and live demonstration of the Free-D Molding technology for rapid prototyping (Dr Daniel Treffer, MeltPrep GmbH). Vacuum compression Molding (VCM) is the basis of the technology that involves three basic steps: vacuum compaction, melting and then cooling. Advantages of the system are that it can produce homogeneous samples with defined geometry, there is no loss of material in sample preparation, and it is a rapid and straightforward process that usually produces a sample in less than 10 minutes. It is possible to generate amorphous solid dispersions or polymer implants with minimal amounts of active compatible with formulations during the early phases of development when drug quantities are often extremely limited. Molds can also be custom made to produce complex samples such as nasal implants and bone screws. The technology is a small, bench-top, system suitable for laboratory generation of samples for evaluation using *in vitro* and *in vivo* models.

The role of excipients to enable delivery of poorly soluble drugs continues to be of significant interest based on the sustained abundance of "beyond the rule of 5" compounds in pharma portfolios. Several lipid-based oral dosage forms of poorly soluble drugs have been marketed in soft gelatin capsules including cyclosporine, ritonavir, amprenavir, naproxen sodium. Challenges with this approach is that it requires specific know-how and manufacturing capabilities, and dosage forms may have stability issues (potential API solid form transformation), or issues with sealing/leakage. Incorporation of lipid formulations into an adsorbent binder to render compressible powders offers a way to convert from soft gels to tablets. A novel adsorbent composition generated by co-processing of mesoporous silica, microcrystalline cellulose and co-povidone has been developed by JRS Pharma. It can adsorb oils up to 25% by weight and remains compressible. The technology is a promising alternative for delivery of poorly soluble drugs using more conventional tablet processing rather than soft gelatin capsules. Using dexamethasone as a model drug, nanosized drug (used to increase the surface area and to facilitate dissolution) layered on to isomalt pellets with fluid bed processing was presented as another approach (from Beneo Palatinit GmbH) to deliver drugs with poor CMC properties. The resulting pellets can also be coated to produce dual release profiles with an initial high dose followed by a sustained release component to the formulation. Other applications of excipients highlighted included their role in pulmonary delivery for pharmaceutical and biological actives (Barentz) as well as in veterinary medicines that require flavor excipients that have good stability and palatability for successful formulation (Pet Flavors).

*In silico* tools offering expedited development by virtual selection of excipients through to full formulation design are available in various organizations including ZoomLab™, an online tool for digitally guiding formulation of poorly soluble drugs. One application of this system (presented by Dr Krizia Karry, BASF) was exemplified in development of a prototype solid dispersion formulation of the DCS Class IIb drug, nifedipine, with polymers predicted to offer the best performance. Dr Gerrit Vreeman (University of Minnesota) explained how prediction of tableting performance based on novel in-die compressibility characterization can also provide time and material sparing development. The methodology utilizes a combination of powder testing with the Styl'One Evolution system (capable of operating with powder quantities less than 100 mg), with mathematical modeling to determine intrinsic powder and material properties.

Profiling studies can be conducted in minutes with less than 1 gram of material. The idea is to use predictive formulation design to identify formulations with a high probability of processability success and robustness rather than empirical formulation selection with subsequent problem resolution. A spin-off start-up, Nu Compaction, is currently under development for performing compaction and analysis services. Of course, the conference would not be complete without showcasing uses of the capacious field of artificial intelligence (AI). Emphasis in the conference was on the fit of AI with pharma supply chain integrity/ quality and AI applications to increase understanding of variability in the manufacture of excipients.

Recognizing that environmental consciousness in industry can benefit the world, numerous presentations addressed the topic of sustainability and ways in which supply chains can be assessed, and optimized, to become more environmentally friendly. Sobering statistics highlight issues from the past that need to be addressed. Norman Richardson (BASF) shared several published statistics to indicate how pharma has had a substantial impact on the environment: Healthcare makes up more than 4.4% of net global climate emissions which, if converted as output by a country, would make this industry the 5$^{th}$ largest polluting "country" on earth. Pharmaceutical products account for between 20-33% of the health sector emissions and purportedly the pharmaceutical sector produces 55% more emissions than the automotive industry. In response, many pharma companies have introduced or participated in various programs to become more sustainable. Several have joined the Science Based Target Initiative (SBTI) with a goal to reduce their emissions within certain time frames. Product life cycles from end to end need to be addressed and this includes understanding the steps involved in the supply of materials purchased from excipient manufacturers. Maintaining a persistent focus on improvements to sourcing, business operations, etc., demonstrated how climate-conscious companies can achieve simultaneous benefits to the business and to the environment. Presenters from IMCD stated a few key considerations including sourcing and disposal of raw materials with minimal environmental impact, maximizing energy efficiency, and practices that conserve water. Taking a sustainable mindset extends to formulation and manufacturing choices. Examples included a comparison of tablets made using wet granulation (7 excipients, 7 hours drying time and use of 6 pieces of equipment) *versus* direct compression (5 excipients, no drying needed and only 3 pieces of equipment being used and cleaned). Similar benefits were mentioned for an example comparing roller compaction vs direct compression tablet manufacture and a topical example comparing emulsions prepared by hot or cold processes. More sustainable business processes can produce significant financial benefits as shown in the latter case study in which using a cold versus a hot process gave estimated savings of 67% in electrical cost, 37% savings in water cost and 17% saving in total production cost. Co-processed excipients represent another way to improve the efficiency and effectiveness of tablet manufacture. Silicified microcrystalline cellulose (Jalay Joshi, Biddle Sawyer) consists of a synergistic co-processed mixture (98%:2%) that imparts optimum compaction and superior flow to pharmaceutical formulations. Applications in direct compression, roller compaction and even wet granulation offer benefits to the overall efficiency of the manufacturing process (e.g., fewer steps, faster production) and improvement of product performance (e.g., reduced nitrite and nitrate risk, good content uniformity). A potential cost benefit of 25% savings were outlined for a conceptual high dose tablet product.

Excipient quality topics including an update on titanium dioxide, use of ion chromatography and mass spectrometry to detect nitrites in formulations and alternative analytical procedures for excipient quality control testing. The EXCiPACT Certification process was outlined as a tool to increase confidence that suppliers meet requisite quality and GMP practices for their materials. Similarly, a presentation on lean/ six sigma implementation demonstrated how the approach can support continuous improvement in excipient quality. Importantly, there were two keynote presentations by members of the FDA. Dr. Amanda Jones (Division of Bioequivalence I (DBI), in the Office of Bioequivalence (OB), Office of Generic Drugs (OGD)) focused on the FDA's Inactive Ingredient

Database (IID) that is an essential public source of excipient information for materials present in FDA-approved products. Information was presented on the IID and its use along with details of the ongoing efforts to constantly improve it for the future. Matt Dionne (Compliance Officer in the Office of Manufacturing Quality (OMQ)) described FDA's role in efforts to address the potential public health hazard of glycerin and other high-risk drug components contaminated with ethylene glycol or diethylene glycol, recently associated with poisoning outbreaks overseas. Other notable topics at the conference were, presentations from USP regarding its latest work on lipid nanoparticles and its future direction; several sessions focused on the importance of excipients in the development and commercialization of biotherapeutic products; a workshop on using IPEC Excipient Guides as a formulation development roadmap, and updates on issues challenging the industry such as the trends, risks, and regulations in today's excipient landscape.

So, let's face it, there was no denouncing of science at the out of this world Excipient World Conference & Expo. Its compact and dense format of compelling topics provided much to contemplate regarding the potential of excipients and their future direction.

Lastly, it seems appropriate to end with a note that at the conference I was fortunate enough to present the launch of the International Journal of Pharmaceutical Excipients (IJPE) and the role it will play in promoting excipient science and quality topics. Feedback was very positive and favorable, so it is exciting to follow up with this first issue of the IJPE containing an original research paper on polysorbate 80 together with a comprehensive review of dimethyl sulfoxide use in topical formulations. It is also encouraging to report that excellent progress has been made with establishing Editorial and Scientific Review Boards to enable the IJPE to begin its journey. I would like to extend my personal thanks, and the appreciation of IPEC-Americas, to all contributors for their support. This is also truly out of this world!