Drugs of the Future 2012, 37(12): 879-883

CCC: 0377-8282/2012
DOI: 10.1358/dof.2012.37.12.1899643

MEETING REPORT

THE IMPORTANCE OF (BIO)PHARMACEUTICAL PROPERTIES IN SUCCESSFUL DRUG DESIGN

HIGHLIGHTS FROM THE SOCIETY OF MEDICINES RESEARCH SYMPOSIUM, HELD ON OCTOBER 4TH, 2012 – NATIONAL HEART AND LUNG INSTITUTE, KENSINGTON, LONDON

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SUMMARY

The pressing challenge pharmaceutical scientists can often be faced with is dealing with drug development candidate molecules with suboptimal drug delivery or pharmaceutical properties. Using the Biopharmaceutical Classification System, analysis of marketed products suggests ≈30% fall into class II, demonstrating exemplary permeability but poor solubility. However, this figure rises to ≈70% when the analysis is applied to candidates coming through the development pipeline. Challenges with biopharmaceuticals often reside around achieving stability, minimizing immunogenicity, optimizing pharmacokinetics and providing, from the patient viewpoint, more convenient and better management of drug delivery. This symposium brought together international experts from both industry and academia to discuss pharmaceutical and biopharmaceutical properties, and strategies to optimize development and minimize developmental impact. Small-molecule new chemical entity topics included a formulation road map for oral delivery, assessment of Chemistry, Manufacturing, and Controls (CMC) developability using material efficiency indices, preclinical assessment of amorphous solid dispersions and case studies of the use in the development of compounds with poor aqueous solubility, and new insights into solubilization, supersaturation and precipitation behavior of active pharmaceutical ingredients. Biopharmaceutical topics focused on strategies for optimizing delivery and pharmacokinetics.

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THE FORM AND THE FORMULATION – STRATEGY FOR ORAL DELIVERY

Professor Graham Buckton (UCL, School of Pharmacy, U.K.) opened the symposium with a discussion on logical approaches to preclinical and early clinical formulations of small-molecule new chemical entities (NCEs). A "do what is needed when it is needed" philosophy was suggested as a sensible strategy to employ, highlighting that too much work undertaken before human proof of concept remains to be established could be a costly mistake, both in time and formulation.

As a starting point, establishing whether the free form of active pharmaceutical ingredients (APIs) formed a stable non-hygroscopic

crystalline form that dissolved at a reasonable level was suggested. With regard to dissolution rate, one parameter open to manipulation is crystal size, where size reduction and increase in exposed surface area can lead to significantly increased rates. Micronization and microfluidization represent techniques employed, with the latter delivering ultra-small particle size reduction at the submicron level. Simple powder in capsule or tablet form was suggested as a dose option to support phase I clinical trials.

If the API contains an ionizable functional group, then salt formation represented a further strategy to control dissolution rate. Unlike crystal size reduction, salt formation presents the opportunity to improve API stability. A further difference also resides in the ability of salt formation to not only increase dissolution rate, but offer the option, if required, of reducing the dissolution rate. Professor Buckton described a salt selection decision tree where a handful of crystalline salts should be evaluated for hygroscopicity, followed by solubility measurements and polymorphism studies, where salts showing little tendency for multiple polymorphs or solvates would rank high in the selection of a final salt form.

Although a reproducible crystalline-free form or salt may have been noted in discovery batches of the drug candidate, it was recommended that polymorphism be conducted as standalone studies, where controlled conditions can be applied to establishing the true extent of polymorphism tendency, and which form represented the most thermodynamically stable form. If the API lacked an ionizable functional group, and therefore salt formation no longer represented an option, consideration should be given to co-crystal formation, using, as the preferred technique, solvent-based crystallization.

As the drug candidate transitions across the development phases, it was suggested that different work packages be applied to consideration of the physical form: at preclinical/phase I a small polymorphism and if necessary salt/co-crystal screen, while at phase II larger optimization of the form, and at phase III an intellectual property (IP) screen to extend patent life and protect company profitability.

Professor Buckton then went on to briefly describe the use of cyclodextrin inclusion and mixed glyceride systems, highlighting the self-emulsifying drug delivery system (SEDDS) and self-microemulsifying drug delivery system (SMEDDS). In the case of the lipid-based systems, several dose options were suggested to support phase I studies, ranging from the use of soft gel, liquid or molten-filled hard gelatin capsules, or absorption of the lipid formulation, to cellulosic excipients and a fill powder capsule or tablet strategy.

The final area Professor Buckton discussed was the amorphous state, which represents the least ordered and most thermodynamically unstable solid state. Nevertheless, there is great interest in amorphous solid dispersions, where amorphous API is stabilized by a polymer-based system as an effective formulation approach to dealing with Biopharmaceutical Classification System (BCS) class II drug candidates. Currently, there is debate as to what controls the amorphous stability in such formulations. One view is centered on the glass transition temperature (Tg), where a high Tg, brought about by the stabilizing effect of the polymer, can be correlated with increased stability. A second view focuses on favorable interactions at the molecular level between the polymer and amorphous API, such as hydrogen bonding, which can be demonstrated using spectroscopic techniques (e.g., poly-[vinylpyrrolidone] [PVP] and indomethacin). Generally, the manufacture of amorphous solid dispersions is via dissolution of both the drug candidate and polymer in a volatile solvent, followed by rapid removal of the solvent by spray drying. Alternatively, melt extrusion can be employed, where a co-melt of the drug candidate and polymer is extruded through a heated screw to produce a solid extrude. The effectiveness of this approach depends on the drug and polymer exhibiting similar melting points and being totally miscible. For heat-sensitive drug candidates, the spray drying technique may be the more suitable process to adopt. Professor Buckton discussed, through case studies, some of the challenges of pursuing an amorphous solid dispersion, where processing conditions, feed concentration and effects of solvent can lead to variability in stability. For early-phase work, it was suggested that little characterization is required, while for late-phase studies, extensive understanding of the method of manufacture and stability was critical to ensure success.

PRECLINICAL ASSESSMENT OF CMC DEVELOPABILITY OF DRUG CANDIDATES AS AN INTEGRAL PART OF THE TRANSLATIONAL PRODUCT DEVELOPMENT STRATEGY

Dr. Andrey Peresypkin (Vertex Pharmaceuticals, Inc., U.S.) discussed the common occurrence of the selection of drug candidates with minimal CMC input that are aggressively pushed into preclinical and first-in-man studies. To support his case, Dr. Peresypkin described a weak base (pK_a = 4) Vertex drug candidate possessing moderate permeability but limited solubility in aqueous systems (< 0.1 mg/mL @ pH 2-9). Both crystalline and lipid formulation strategies failed to deliver a formulation path, leaving the project reliant on pursuing an amorphous solid dispersion formulation. To deliver stability and required solubility, the amorphous solid dispersion relied upon the use of an aggressive vehicle in 20% Captisol®/1% HMPC-AS/1% PVP. Although this formulation gave excellent parent drug exposures in early toxicology studies, projection of the quantities of Captisol®/HMPC-AS/PVP required to support late-phase clinical studies, based on predicted human doses, suggested an unrealistic dosing schedule.

To help estimate the CMC risk of potential drug candidate molecules, Vertex has introduced the concept of material risk factors (MRFs). The MRFs are designed to be done using 100- to 2000-mg quantities of API in a rapid and efficient manner, covering a range of formulation options (amorphous, crystalline, nanosuspensions, etc). The use of a traffic light color system linked to time zones is used to depict the degree of MRF, as shown in Figure 1.

Dr. Peresypkin described how the MRF concept has been applied to different formulation options. Vertex has established a robotic work

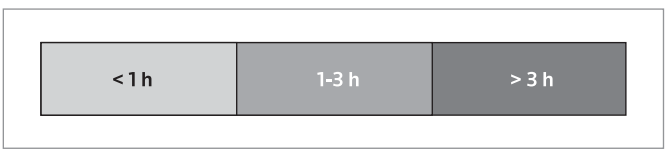

Figure 1. Rank order color scheme for material risk factors (MRFs).

flow system where nonaggressive amorphous solid dispersions can be made using spray dry technology on the 100-mg scale and evaluated for solubility in biorelevant media under set conditions (1-hour simulated gastric fluid [SGF]/3-hour simulated intestinal fluid [SIF]), with any undissolved solids analyzed by X-ray powder diffraction (XRPD). While the solubility data can highlight amorphous vehicle optimization, analysis of the XRPD data can be used to assess the onset of crystallization, which can be captured by MRF metrics and used to stability rank the different amorphous solid dispersion formulations. In the case of formulations based on nanosuspensions, where Vertex has developed a fast, efficient process utilizing only 5 mg of API, the particle size growth is assessed after stirring in the same biorelevant media as above, with MRF metrics used to rank nanosuspension integrity. By evaluating the growth of the most stable form, MRF metrics can be used to rank the stability of metastable form suspensions, which often deliver enhanced solubility and oral exposure compared to the most stable form. Dr. Peresypkin showed how the MRF metrics could be used to quickly and efficiently identify optimized formulations for in vivo testing, the results from which could be used to suggest the likely formulation path to the clinic.

An adaption of the MRF concept to maximum absorbable dose (MAD) and predicted human efficacious dose (HED) was discussed. In this case, the metrics are based on ranges of the MAD/HED ratio using the traffic light system depicted in Figure 2.

Dr. Peresypkin suggested that input of a range of solubilities from different formulation forms (e.g., crystalline vs. amorphous) to the MAD equation could help begin to establish a quick read on the likely clinical path forward.

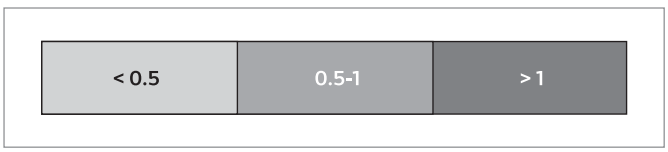

Figure 2. Rank order color scheme for maximum absorbable dose (MAD)/human efficacious dose (HED).

PRECLINICAL ASSESSMENT OF AMORPHOUS SOLID DISPERSIONS: FRIEND OR FOE?

Dr. Mark Saunders (Kuecept, U.K.) re-emphasized the current industry-wide increase in insoluble drug candidates, stating that > 75% of drugs in development exhibited poor aqueous solubility characteristics, with solubilities of 0.1 µg/mL or less not uncommon. Of the several formulation strategies available to address poor solubility/dissolution, it was suggested there is an ever-increasing interest in the use of amorphous solid dispersions to enhance kinetic solubility. However, considerable effort is required for identifying suitable polymeric materials to stabilize the amorphous drug in the solid state, as well as in an aqueous suspension required for oral dosing in pharmacokinetic (PK) or long-term toxicology studies. Dr. Saunders discussed some of the challenges in the preclinical assessment of solid amorphous dispersions.

For early preclinical assessment, spray drying techniques are often used to prepare amorphous solid dispersions. However, it was suggested that the resulting drug-loaded microparticles are often suboptimal from a handling viewpoint, in particular exhibiting high static tendency, poor flow properties and cohesivity. In addition, the microparticles exist in a low bulk density (0.1-0.3 g/cm^3), which on suspending into higher-density aqueous-based dosing vehicles (density of water 1 g/cm^3) leads to a high concentration of drug-loaded particles floating on the surface. Dr. Saunders described a technique developed at Kuecept to densify the microparticles, called ProRelease™, in which amorphous microparticles are prepared by an emulsification/slow solvent evaporation approach. Yields for the process are high, with ProRelease™ microparticles exhibiting good flow properties, and more importantly, a bulk density around 1 g/cm^3, which leads to a more uniformly dispersed suspension.

One of the key challenges in developing amorphous solid dispersions is imparting sufficient physical stability to prevent conversion to the slower dissolving and less soluble crystalline state, both in the solid form and, more importantly, within an aqueous or biorelevant environment. Polyethylene glycol (PEG), PVP and hydroxypropyl methylcellulose (HMPC) are common nonionic polymers used to form amorphous solid dispersions. Unfortunately, these polymers tend to be hygroscopic and absorb significant amounts of water. In the solid form, this is reflected in a lowering of the Tg and a propensity to trigger crystallinity, which can be monitored using XRPD. Dr. Saunders showed, however, that the Tg can be significantly lowered in biorelevant media, to the point where fast hydration and gel formation ensues, leading to significant drug crystallization. To circumvent this phenomenon, replacing the neutral polymers, which dissolve over the entire pH range, with ionic polymers, which are pH-sensitive and less hygroscopic, was suggested. Examples of ionic polymers discussed included the acidic polymers Eudragit L and S, the enteric polymers HPMC-AS and Eudragit 100, which dissolve at pH > 6 and are used for modified release, and the reverse enteric polymers Eudragit E and Kollicoat Smartseal 30D, which dissolve at pH < 5 and are used for immediate release.

Dr. Saunders showed the beneficial effects of turning to this strategy by comparing and contrasting the amorphous solid dispersions of a drug made with a neutral polymer versus that made with Eudragit E. The amorphous solid dispersion using Eudragit E as the polymeric matrix retained an amorphous state, while at the same time delivering a superior dissolution profile, when exposed to an aqueous environment, compared to the amorphous solid dispersion made with the neutral polymer, which showed drug precipitation and a reduced kinetic solubility through a crystallization process, which was confirmed from XRPD studies.

USE OF AMORPHOUS DISPERSIONS IN THE DEVELOPMENT OF COMPOUNDS WITH POOR AQUEOUS SOLUBILITY: CASE STUDIES FROM DISCOVERY TO COMMERCIALIZATION

Dr. Rod Ketner (Bend Research, U.S.) gave a fascinating talk on the company's strategies for formulating poorly soluble compounds and describing the formulation strategies they employ in drug discovery through to commercialization of the product. He gave insight into

the ideal development program, with optimization strategies inserted sequentially into the development program, but likened it in reality to fast-to-man and at times a rescue mission, where reformulation was vital for the progression of the compound to commercialization.

Dr. Ketner described the strategies that Bend uses to interrogate the compound´s solubility and enhance bioavailability, emphasizing that they had worked with over 700 compounds, from which > 450 have advanced through preclinical animal studies, with > 65 compounds further advancing through phase I-III clinical trials.

Dr. Ketner's description of their formulation-enhanced discovery tools showed how their elegant biomodels can be used to predict oral absorption, intraocular, pulmonary, intraarticular and targeted delivery. When used in combination with the API physical and chemical properties, these biomodels can predict the effect of solubilization on absorption, dose-escalation, food effect, fraction of dose absorbed, allometric scaling and sensitivity analysis. He then went on to describe the polymer choices for solid dispersions and described their work with HPMC-AS, and a case study testing an HPMC-AS spray-dried dispersion (SDD) drug in fasted state intestinal media with or without gastric exposure. Physical stability is also assessed at Bend using increasing melt temperature versus relative humidity. Prediction of the stability of a formulation can be made with the assessment of stability at different temperatures and humidity, and Dr. Ketner shared a number of the analytical tools that Bend uses to monitor stability. Of interest was the accelerated aging of the formulation utilizing aggressive stability conditions using thermal activity monitoring. The graph of heat of crystallization versus time showed a sigmoidal response, and the crystallinity and residual amorphous drug could be confirmed at points along the curve by high-resolution XRPD and modulated differential scanning calorimetry (mDSC). Dr. Ketner described the customized spray drying equipment that they have developed with clients to fulfill their needs, and the scale-up process that is available at Bend Research to go from a formulation screen at the start of formulation development to commercialization, with a number of dosing options available for spray-dried dispersions (SDDs). At the end of his talk, Dr. Ketner described three compounds and the strategies used to formulate them. These compounds included an API with low organic solubility, an API with a high propensity to crystallize and chemically unstable as an amorphous form, and lastly, an API which was a viscous oil.

SMALL-SCALE SOLUBILITY AND DISSOLUTION ASSAYS: NEW INSIGHTS INTO SOLUBILIZATION, SUPERSATURATION AND PRECIPITATION BEHAVIOR OF APIs

Mr. Karl Box (Sirius, U.K.) gave a talk on the SiriusT3 analytical platform that they have developed. The SiriusT3 will measure pK_a, logP, solubility and supersaturation of ionizable drugs, and also measure dissolution rates of ionizable and neutral drugs. Mr. Box shared the data obtained for 84 marketed drugs which showed that a simple plot of logP versus logS separated the compounds by BCS class (1). Mr. Box gave a good description of supersaturation and explained the spring and parachute concept, where the utilization of crystalline salt forms and precipitation inhibitors can be used to improve oral adsorption (2, 3).

The talk then shifted to a description of the method for measuring solubility run on the SiriusT3 instrument, which is called CheqSol (4), which stands for "**Ch**asing **Eq**uilibrium **Sol**ubility", and he described the utilization of CAVASOL® W7 HP (hydroxypropyl-β-cyclodextrin), which is a water-soluble cyclodextrin. The inclusion complex formation of a poorly soluble apolar hydrophobic guest with CAVASOL® W7 HP in water results in an increase in the water solubility of the guest. By the addition of CAVASOL® W7 HP, the solubility of the API can be increased, and with increasing percentage levels of CAVASOL® W7 HP there is a significant improvement on the excipient gain factor (EGF) and the total solubility enhancement (SF × EGF). Alternative strategies for increasing solubility were discussed, including the effect of Labrasol, which is a mixture of PEG esters, a small glyceride fraction and free PEG, with a mean molecular weight between 200 and 400. Labrasol can also be deployed as a SMEDDS, a wetting agent and a bioavailability enhancer (associated with P-glycoprotein inhibition). Mr. Box showed how the Hoffman equation, along with the differential scanning calorimetry (DSC) data, can be used to estimate amorphous solubility and solubility advantage.

Mr. Box then described their new Sirius dissolution assay, which has advantages over the existing assays in that it is a small-scale assay that can be used to provide information on dissolution, solubility and precipitation behavior of pharmaceutical drug compounds at four different pHs to stimulate the passage through the gastrointestinal tract, along with the inclusion of a lipid layer to simulate the absorption process in the gastrointestinal tract.

STRATEGIES FOR NEW PROTEIN THERAPEUTICS: FROM BETTER PEGYLATION TO SOLID DOSAGE FORMS

The final two talks of the symposium were chosen with the purpose of presenting a broader understanding of the current challenges in drug delivery. Both talks focused on methodologies and delivery applications associated with biotherapeutics. Professor Steve Brocchini (UCL, School of Pharmacy and the Institute of Ophthalmology, and PolyTherics, Ltd., London, U.K.) opened this session. He introduced the subject by pointing out that a number of good protein-based therapeutics exist, but their efficacies could be improved by reformulation to yield better half-lives, reduce immunogenicity and provide alternative dosing formats. Professor Brocchini described how his research has been focused on the improvement of these in vivo properties of protein-based therapeutics. To achieve these ends, his laboratory has been involved in developing innovative strategies for protein PEGylation, the covalent conjugation of a protein to PEG. PEGylation is a clinically proven strategy that enables the circulation half-life of protein-based therapeutics to be increased. However, most PEGylation methods in use for the production of clinical preparations yield heterogeneous mixtures that are generated using nonspecific and inefficient coupling procedures (5).

In his talk, Professor Brocchini presented data demonstrating innovative approaches for the site-specific conjugation of PEG to either thiol (5) or imidazole (6) protein moieties (i.e., cysteine or histidine residues). Many biotherapeutics (e.g., Fabs) contain thiol groups as paired cysteines in a disulfide bond. Methods were described that used new PEGylation reagents that selectively alkylated both sulfurs derived from a reduced native disulfide to generate disulfide-bridged PEG-Fabs. PEG-Fabs prepared according to this new

methodology were homogeneous preparations and demonstrated similar binding affinities to clinical preparations, regardless of the PEG molecular weight used for conjugation (5). Professor Brocchini also showed data describing a generic approach for PEGylation of *N*- or *C*-terminal histidine-tag residues present on recombinant protein molecules. This methodology involved the generation of PEG-bissulfones that were subsequently used to conjugate one or two molecules of PEG by alkylation of the imidazole group. The resulting formulations were stable, bioactive and demonstrated extended half-lives in circulation. These half-lives increased as a function of the increasing sizes of the PEGs used in these studies (6).

Professor Brocchini concluded his talk with a brief presentation of recent studies from his group involving the development of a solid antibody tablet for use after ocular surgery. He described in detail complications that arise in wound healing and scarring related to incisions in the sclera. Clinical outcomes were often related to the skill of the surgeon and the time period in which the surgery took place. He explained that controlled release of biotherapeutics formulated as a solid could replace alternative delivery methods (injections) and potentially improve the quality of repair at the site of incisions. The data presented showed how tablets formulated from antibody, and created by direct compression, could be inserted into the sclera. The manner in which the tablet is inserted is similar to that described in a previously published study from Professor Brocchini's laboratory for a tablet formulation of the matrix metalloproteinase inhibitor ilomastat, used for the treatment of glaucoma (7). This approach, along with the others described above, exemplifies how considerable research is required to exploit the full potential of biotherapeutic medicines in formats suitable for use in clinical applications.

STRATEGIES TARGETING IMPROVED DELIVERY OF BIOPHARMACEUTICALS TO PATIENTS

Dr. Barry D. Moore (XstalBio, Ltd., Glasgow, Scotland) concluded the symposium by describing an interesting method for the production of dry powders with remarkable properties. These powders enable long-term storage and variable delivery of small and large macromolecular biotherapeutics. Dr. Moore highlighted a number of areas in the formulation and delivery of biopharmaceuticals where improvements needed to be made, including: 1) the need to increase the concentrations of macromolecular therapeutics (which often have low solubility); and 2) the need to reduce the requirement for cold chain storage of macromolecular therapeutics while maintaining their stability and activity. Monoclonal antibody therapies for cancer are an example of a therapeutic that would benefit from an increase in concentration. These biotherapeutics often require large doses, and therefore long periods of time for infusion, because of low solubility and sometimes poor potency of these macromolecules in current formulations. Therefore, the development of high-dose forms of antibodies, particularly for subcutaneous injection, represents a current need in the pharmaceutical industry.

In order to address challenges with the formulation of biotherapeutics, XstalBio has developed a novel platform that involves the production of protein-coated microcrystals (PCMCs). PCMCs are easily prepared by first generating a supersaturated solution of the protein of interest, plus a co-precipitant such as K_2SO_4, in a water-miscible solvent such as isopropanol or isobutanol. As the co-precipitant crystallizes under these conditions, the protein is excluded from the crystallization lattice and self-assembles on the surface of the resulting K_2SO_4 (or other carrier molecule) crystal faces. The resulting particles are water-soluble, and characteristics, such as particle morphology, protein loading and particle size, can all be optimized for a desired application by modifying the crystallization conditions. The technology is scalable and can be applied to the formulation of peptides, proteins or nucleic acids. Dr. Moore illustrated, using a number of different bioassays, that proteins such as insulin or antibodies formulated by this methodology showed excellent levels of response in bioassays even after a year of storage.

A second area of development involves modification of XstalBio's manufacturing processes, where a calcium phosphate (CaP) coating is added to the PCMCs in order to create controlled release of the biotherapeutics present in the formulation. This point was initially illustrated using a vaccine antigen that was immediately released to antigen-presenting cells in an uncoated formulation, but released with a delay (50% of material release after 8 hours) when a CaP coating was added to the formulation. Modifying the process of manufacturing the CaP coating allows the release time to occur over hours, days, and even weeks. The coating does not significantly affect particle size or long-term stability, and has been used for a range of biomolecules, including hormones, cytokines, growth factors, antibodies and vaccines. The versatility of the release and storage properties of XstalBio's formulations, and the ability to deliver these formulations by topical, pulmonary, nasal and oral routes, make this platform an advantageous choice for the delivery of a wide range of biotherapeutics in the future.

DISCLOSURES

K.A. Brown receives support from the National Institutes of Health (U.S.) and the Royal British Legion Centre for Blast Injury Studies at Imperial College (U.K.). M.S. Alavijeh, J.C. Holder and A.J. Ratcliffe are employees of Pharmidex, GlaxoSmithKline and Cellzome, respectively.

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