Excipients in formulations for clinical trials: Getting it right the first time

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The advances made in the understanding of the mechanisms underlying the etiology and propagation of disease have resulted in a rapid proliferation of pharmacological targets. Very often, the excitement of the promise of a new target, therapeutic possibilities and potential profits overwhelm the recognition of the need for appropriate/adequate drug delivery. The identification/designing of molecules and the identification/validation of pharmacological targets, often carried out *in vitro*, have historically largely been insular pursuits disconnected from the 'downstream' processes of formulation development. Carried out in such a manner, they become inimical to the more pragmatic aspect of *in vivo* drug delivery, especially so, in an era characterized by APIs' with larger molecular weight and greater hydrophobicity.

The author has 'formulated' a variety of antineoplastic drugs for pharmaceutical companies intended for use in clinical studies. The companies were often start-ups and 'virtual' with little or no in-house formulation expertise and scarce funding, typical of 'idea' stage organizations. These drugs ranged from biological response and gene expression modulators, antisense oligonucleotides, monoclonal antibodies to 'conventional' small molecules usually targeted for intravenous administration. The 'strategy' in most instances was to get to the clinic as soon as possible or to administer to humans as soon as possible. The formulations therefore were lyophilized (often in a simple mannitol or sodium chloride matrix) for those APIs' that were water soluble, or formulated as nanosize suspensions (using simple surfactants) for water insoluble APIs'. Occasionally, esoteric methods such as evaporative drying from aprotic polar solvents was also employed. In none of these instances was any thought given to a judicious choice of excipients that would allow for a better clinical outcome.

The proof-of-concept (POC) is dependent, in no small part, on getting the API to its site of action and, preferably nowhere else, in sufficient amount over a specified time interval in order for it to exert its proposed effect at the pharmacological target receptor. Use of proper excipients is one of the tools in the 'tool-box' of enabling technologies, without which the probability of developing a successful drug product in a time efficient manner from a promising molecule is low.

An ignorant and therefore, nonchalant and indifferent attitude, bordering on the cavalier,

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toward excipients as potential enablers for drug delivery, creates a hubris in the early stages of the drug development process that serves to dismiss the pivotal role played by the excipients/delivery system as a contributory factor to the success of POC clinical studies. The result is an API that is poorly formulated (and hence sub-optimally bioavailable at its site of action), and unlikely to achieve statistical significance with regard to the clinical trial objectives.

Anachronistic paradigms that view the drug development process occurring in a series of sequential steps in the order of drug discovery, target validation, preclinical studies, preformulation, clinical studies, formulation, and regulatory filing need to be replaced by a parallel approach, wherein the drug delivery aspect is thoughtfully considered alongside drug discovery and target validation. Excipients have evolved to the point where there should really be no need for two formulations, one for the clinic and the other for the market, to exist. Decisions about which formulation to take to the clinic should focus not only on stability and expediency but also on projected *in vivo* performance.

Biopharmaceutical companies with 'molecule-centric' formulations demonstrating initial borderline phase I and II trials often follow subsequent trials with use of so called 'bridging' formulations for phase III studies. These bridging formulations almost always differ from the original ones in that they contain excipients that are designed to enhance clinical performance. A good many of such scenarios could be reduced if the right excipients were to be chosen up front, before beginning human clinical trials.

Significant expertise in formulation services is available at numerous well established academic institutions and with experienced pharmaceutical consultants, resources that can be availed of by start-ups' and 'virtual' companies from the 'idea' stage, before commencing clinical trials. The thought process in the early stages of drug development is 'molecule-centric', a paradigm that should be expanded to become 'molecule-delivery-centric'. Part of the problem is that the institutional, venture and 'angel' investing communities have a poor grasp of the drug delivery aspect of the business. The notion of the 'black-and-white' aspect of *in vitro*, 'molecule-centric' statistical significance is simpler and much more easily understood, as opposed to the more nebulous and challenging concepts of *in vivo* drug delivery. In order to obtain funding, the scientific community has had to accentuate the *in vitro* provable, intuitively understandable, statistically conformable, 'target validation' side of the 'business', which often has little or no bearing on human *in vivo* results. The table (on the next page) illustrates how 'molecule-delivery-centric' formulations may stand a better chance of demonstrating statistical significance in clinical trials.

Excipient manufacturers and associations like the International Pharmaceutical Excipients Council (IPEC) should endeavor to educate and inform, not only the pharmaceutical industry, but also the investing community, about the pharmacological efficacy enabling features of excipients and drug delivery systems. These excipients can either be chosen from those used and approved in marketed pharmaceutical products or from more esoteric 'research stage' molecules that are not yet in the FDA inactive ingredient guide (IIG). In the latter instance, even if the risks for the 'return on investment' seem significant purely from a regulatory standpoint, they may be anticipated to diminish considerably upon demonstration of statistical significance in clinical trials.

It is time that the Pharmaceutical community incorporated relevant excipients earlier in the drug development process to increase the probability of success in clinical trials and the return on investment, a shorter time to market and, ultimately, a greater probability to ease the suffering caused by disease.

Formulation issues in drug development

CHALLENGE	'MOLECULE-CENTRIC' CLINICAL FORMULATIONS	'MOLECULE-DELIVERY-CENTRIC' CLINICAL FORMULATIONS
API not water soluble	Use solvents such as DMA, DMSO, DMF to dissolve followed by dilution with water. Micronize and suspend API in water, lyophilize from organic solvent systems and administer using specific reconstitution directions.	Solubilizers, complexing agents
Insufficient bioavailability in animal models	Invasive administration such as Intrathecal or Intratumoral injection	Transfection enhancers, Cell or blood brain barrier penetrating peptides, lipid complexes, absorption enhancers.
Does not provide the desired Pharmacological response in animal models		Adjuvants for vaccines, Multidrug resistance reversants for antineoplastic drugs, lipid complexes, modulators of plasma protein binding and membrane transporters.
Non achievable synergistic blood concentrations for drug combinations	Usually not taken into consideration for clinical studies, directions for complex institutional protocols when administered as part of a 'cocktail'.	Ratiometric release agents, counterions
Is toxic or has dose limiting side effects	Co-administer with other API 'salvage agents' to reduce toxicity.	Lipid complexes, targeted (PEGlyated, folated, antibody directed) excipients
Does not prevent relapse/ recurrence	Not usually taken into consideration for clinical studies.	Assembly specific excipients targeting in vivo viral reserviors/sanctuaries.
Is not convenient to patient quality of life, comfort and/or compliance	Not usually taken into consideration for clinical studies.	Sustained/delayed release agents, bioactuators, excipients that facilitate non-invasive administration, inorganics used in bioabsorbable/biodegradable stents, sutures, implants/ scaffolds