Biopharmaceutics, formulations and exposure

While the mantra for exciting drug discovery is target, medicinal chemistry, and *in vitro/in vivo* biology, the early drug development success leading to a positive clinical proof of concept studies is largely predicated by biopharmaceutics, formulations, and drug exposure. As it is largely an unchartered territory when it comes to novel chemical entities (NCEs), the skills of a formulator to be practical, pragmatic, and innovative would be put to a litmus test. This is because the success of delivering and maximizing the exposure in humans is dictated by the chosen formulation options to overcome the biopharmaceutical challenges imposed by the NCE. The editorial is written in the context of providing perspectives on "Biopharmaceutics, Formulations and Exposure" that are key to make an informed decision on the developability aspects of the compound as it is declared a "drug candidate" and enters the challenging phase of drug development.

Being in the pharmaceutical industry for over two decades and having participated in scores of translational medicine programs across all therapeutic areas, aimed to gather proof of concept evidence in human subjects, I have realized that optimization of developability factors is of paramount importance to ensure that the decision to advance the compound is solely based on the inherent ability (or lack of it) of the NCE to modulate the target to produce the purported pharmacological activity and/or pharmacodynamic response. After all, one should not be asking the question, if I had only used another formulation, altered the permeability considerations, or avoided the efflux mechanism(s), perhaps the exposure would have been adequate for the NCE to provide the right signals in the Phase 2a – proof of concept (POC) study.

As NCEs are getting synthesized and tested in the early discovery phase, several developability-oriented screens are instituted to reduce the risk of a wrong selection of NCEs having poor solubility, permeability, and/or *in vitro* cytochrome P450 liability. However, it needs to be appreciated that some promising compounds that have exceptional *in vitro* activity may have to be dropped if it fails to meet the "developability" target profile. While it may seem it is a pretty harsh decision to throw away a series of NCEs based on certain *in vitro* criteria, I have learnt over time that such a decision can save enormous resources and time if the NCE precisely fails to achieve adequate plasma concentrations to elicit the desired pharmacological/pharmacodynamic and/or surrogate biomarker activity in the clinic. Many pharmaceutical companies have learnt to accept the harsh reality of drug failures due to significant developability issues that are totally unrelated to the target and/or the biology considerations of the NCEs.

While it is a dream to discover a NCE that has absolutely no developmental-related issues, from my experience one has to be contended with selecting the so-called best NCE in the series and then putting together a strategy to make it more amenable for development. It should not come as a surprise to the readers that it may be a great strategy to pick a NCE solely based on its anticipated potential to offer an edge from a developability perspective despite the fact that it did not top the list in terms of *in vitro* potency. Once the NCE is chosen, the role of the formulator becomes challenging since he/she needs to first understand the "biopharmaceutics" attributes of the NCE and devise a delivery system that maximizes the exposure of the NCE both in preclinical species and humans. Hence, in today's global drug development paradigm, it is imperative that the NCE needs to be equipped with right attributes to avoid surprises. Needless to say biopharmaceutics plays a dominant role and going hand-in-hand formulation options are of paramount importance.

In simplistic terms, biopharmaceutics could be extremely tricky if the inherent issues of the compound linked to solubility and/or permeability comes in the way of drug absorption to achieve adequate systemic exposure in animals/humans. Generally, the biopharmaceutical challenges are strongly correlated to the dose size of the NCE and is expected to significantly hamper the *in vivo* absorption beyond a certain dose threshold is reached. The present day biopharmaceutics classification system (BCS) prepares the drug developer to be aware of imminent challenges imposed by the NCE if there is a requirement of certain dose size for adequate plasma/blood levels. The formulation options are primarily driven by the expected dose size and the extent of biopharmaceutical hurdles that need to be addressed.

In a simple case study, the "drug candidate" needs formulation work for the required investigational new

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DOI: 10.4103/0973-8398.63972

www.asiapharmaceutics.info

drug (IND) toxicology studies in rodent and non-rodent (dog/monkey) species. While, it is customary to make a 0.5% carboxymethylcellulose (CMC) suspension of the NCE to support rodent studies, it may become important to use the same or similar dosage form planned to be used in humans in the non-rodent study, if feasible. However, this would become a moot point if the sponsor simply wants to test the same suspension formulation that was used in rodent studies both in non-rodent species and in man. Nevertheless, the challenge for a drug formulator is to understand the biopharmaceutical properties of the NCE as it relates to drug absorption when given in solid dosage forms. Hence, it is customary to devise a three-way or four-way crossover study in dogs (if it is the chosen toxicology species) where three different formulations of NCE are tested with a reference NCE formulation (either a solution or suspension). The formulation options could be neat filled drug (i.e. NCE) capsule and other variants that include addition of certain excipients (solubility enhancers or permeability enhancers) that may enhance drug absorption as necessitated by the biopharmaceutical challenge inherent to the NCE. The exposure data obtained from this simple three-way or four-way crossover study in dogs would enable to make the decision on the choice of the formulation to be used in IND toxicology testing in dogs (or other non-rodent species) and subsequently for the first time human dosing of the NCE. While the decision is largely data driven, it is important to build certain contingency in the planning. For instance, if the exposure difference between the neat filled drug capsule versus capsule containing drug + other excipients is small (i.e.<20%), it may be pragmatic to chose the neat filled option for human dosing.

From the experience of having managed a number of early Phase I trials, there may be situations where there could be requirement of using two different formulations (liquid and solid) in first-in-man studies—especially if the planned dose escalation has to begun at very low dose sizes where it may be impractical to formulate a solid dosage form. Hence, it is a common practice to have suspension formulation supporting the first few dose escalations in man for NCEs and then switching to the solid dosage form would occur at a predetermined dose threshold for such NCEs. One key question to the drug formulator(s) would be on the dose strength/potency to support the solid dosage form strategy. It may be impractical to produce more than three or four dose strengths to support first-in-man testing as it would involve lot of development work, clinical trial manufacturing, and stability testing per the required norms added to the developmental costs, timelines, and risks of failure. Also, an important design consideration may be to distribute the strengths over the anticipated dose escalation range such that in between doses if required are covered by the use of multiple units of the existing strengths. While multiple units of capsule/tablet administration may not pose challenges, it may be a good idea to restrict the number of units to a maximum of 4 (or 6 in a worst case situation). This aspect may have to be factored if the sponsor wants to explore the first-in-man study of the NCE with a single strength of the solid dosage form. The increased number of units (8 or 10) of solid dosage forms may precipitate biopharmaceutical issues relating to drug dissolution and/or improper disintegration. The drug to excipient load may be another important consideration to keep in mind when designing formulations for first-in-man studies. While inclusion of certain excipients may impart pharmaceutical properties and/or solubility/permeability enhancement properties, the addition should be kept to a minimum since it may have a role to play in the biopharmaceutical challenges. In my experience, when the total capsule/tablet load approaches 3 to 4g due to multiple units (i.e. 6 × 500 mg tablets or 8 × 500 mg tablets), drug dissolution issues may surface causing plateau in the exposure of the NCE. It is not uncommon to see this phenomenon occurring at drug loads <2g depending on the inherent properties of the NCE.

The Phase I testing is a crucial phase for drug formulators along with clinicians, clinical pharmacologists, pharmacokinetists, etc for the simple reason that it provides the first platform to explore the exposure data of the NCE in relation to the dose delivered by the chosen formulation type. Also, it provides an opportunity to make a decision on the formulation options if the compound is deemed fit to go to subsequent clinical development. As the POC (i.e. Phase 2a) will likely happen at a limited dose range as opposed to Phase 1 testing, it would be less of challenge for the drug formulator to devise the dose formulation needed for this important phase of exploration. Also, the learning from the Phase I experience could also be easily incorporated in further design and/or tweaking of the existing formulation of the NCE.

While many pharmaceutical companies are keen to keep developmental costs under control, there may be opportunity to the drug formulator to think of simple and less expensive ways of formulating the NCE. However, regardless of the chosen formulation strategy, it is important to establish stability of the drug product for the duration of envisaged clinical testing. The key factors that drive the formulation optimization is related to dose size and exposure requirements. The Phase I testing would not only establish the safety and tolerability profile of the NCE but also would provide information on exposure, an important surrogate of efficacy. The decision to proceed to Phase 2a should also encompass the confidence in the chosen formulation to provide the needed exposure requirements. Hence, switching of the formulation that was tested in Phase I need to be judiciously considered factoring the risks of POC failure due to the lack of exposure due to an unknown formulation variable. Therefore, it is a common practice not to change the formulation (or make minimal tweaking, if necessary) once found satisfactory in the Phase I testing.

In summary, this commentary is intended to drive the

message that the critical success factors to enable an unambiguous POC testing of the NCE is largely driven by the considerations taken by the formulator. While creativity and skills of the formulator will be challenged by many NCEs, if not all of them, the success is driven by a clear understanding of the biopharmaceutics requirements of the NCE and devising formulation(s) that produce adequate exposure to elicit a target-related response in the intended clinical POC study.

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FORM IV

Statement about ownership and other particulars about newspaper ***(Asian Journal of Pharmaceutics)*** *to be published in the first issue every year after the last day of February*

1.	Place of publication	:	Mumbai
2.	Periodicity of its publication	:	Quarterly (January, April, July and October)
3.	Printer's Name	:	Medknow Publications & Media Pvt. Ltd.
	Nationality	:	Indian
	Address	:	B5-12, Kanara Business Center, Off Link Road, Ghatkopar (E), Mumbai - 400075, India Phone: 91-22-6649 1818
4.	Publisher's Name	:	Mr. Narendra Nahata, Chairman, B. R. Nahata Smriti Sansthan
	Nationality	:	Indian
	Address	:	B. R. Nahata Smriti Sansthan, B. R. Nahata College of Pharmacy, Mhow-Neemuch Road, Post Box No.6, Mandsaur 458001, MP Phone: 91-7422-255734, Fax: 91-7422-255504
5.	Editor's Name	:	Dr. V B Gupta
	Nationality	:	Indian
	Address	:	C/o. B R Nahata College of Pharmacy-SIRO, Mhow-Neemuch Road, P. B. # 6, Mandsaur – 458001, Madhya Pradesh, India.
6.	Names and addresses of individuals who own the newspaper and partners or shareholders holding More than one per cent of the total capital.	:	B. R. Nahata Smriti Sansthan, Mandsaur

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