International Journal of Pharmaceutics 412 (2011) 1–7

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Strategies for bringing drug delivery tools into discovery

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ARTICLE INFO

Article history:
Received 1 October 2010
Received in revised form 1 February 2011
Accepted 11 March 2011
Available online 21 March 2011

Keywords:
Drug delivery tool in discovery
In vivo model development
Nanoparticles
Alternate route of administration
Mechanism-based toxicity
Target delivery

ABSTRACT

The past decade has yielded a significant body of literature discussing approaches for development and discovery collaboration in the pharmaceutical industry. As a result, collaborations between discovery groups and development scientists have increased considerably. The productivity of pharma companies to deliver new drugs to the market, however, has not increased and development costs continue to rise. Inability to predict clinical and toxicological response underlies the high attrition rate of leads at every step of drug development. A partial solution to this high attrition rate could be provided by better preclinical pharmacokinetics measurements that inform PD response based on key pathways that drive disease progression and therapeutic response. A critical link between these key pharmacology, pharmacokinetics and toxicology studies is the formulation. The challenges in pre-clinical formulation development include limited availability of compounds, rapid turn-around requirements and the frequent un-optimized physical properties of the lead compounds. Despite these challenges, this paper illustrates some successes resulting from close collaboration between formulation scientists and discovery teams. This close collaboration has resulted in development of formulations that meet biopharmaceutical needs from early stage preclinical in vivo model development through toxicity testing and development risk assessment of pre-clinical drug candidates.

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Abbreviations: DMPK, drug metabolism and pharmacokinetics; ADME, absorption distribution, metabolism and excretion; DMSO, dimethyl sulfoxide; PD, pharmacodynamics; API, active pharmaceutical ingredients; POC, proof of concept; CNS, central nervous system; IN, intranasal; IV, intravenous; SD, spray dried; GRAS, generally recognized as safe; PET, positron emission tomography; HT, high throughput; HPMC-AS, hypromellose acetate succinate; PVP, povidone; PGP, P-glycoproteins; BCS-, biopharmaceutics classification system; SLS, sodium lauryl sulfate; AUC, area under the curve; HPC, hydroxyl propyl cellulose; MN, micronucleus; IT, intratracheal; DNP, dinitrophenol; LO, Lead optimization; TV, target validation; LI, lead identification.

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0378-5173/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2011.03.024

1. Introduction

Early assessment of in vivo efficacy and toxicological assessment of potential drug candidates depends upon effective delivery to the desired therapeutic target. While this usually can be accomplished with simple formulation strategies, sometimes creative technological solutions are needed in order to drive drug absorption to the target in order to answer key questions. This paper shares some examples where formulations have made an impact during discovery with regards to decisions around target validation, efficacy, and safety.

1.1. Rationale for an integrated discovery and development team

R&D expenditure in the last few years has increased by 80%, while productivity decreased by 43% (Mark Crawford, 2010). This poor return on investment and reduced productivity is the subject of investigation and scrutiny in the Pharma Industry. Despite the increase in sophisticated sales forecasts and market analyses to enhance predictions of success, the rate of producing blockbusters has not improved over the last 20 years (Munos, 2009). It is obvious that there are underlying causes that are either not fully understood or are not being addressed properly. In a review by DiMasi et al. (2003), a major factor for many of these failures was determined to be the high attrition rate in drug development. The taxonomy of the risks showed that efficacy and toxicity are the major cause of attrition (Ismail and John, 2004; Fearn, 2000; FDA, 2004) (Fig. 1). In addition, the pursuit of therapeutic targets that have notoriously unpredictive animal efficacy models (i.e., CNS, oncology) does not favor success in Phase II or III clinical trials (Booth et al., 2003; Roberds et al., 2001).

A survey of these failures and successes calls for measures to rethink the strategy, goals, and efficiency of drug discovery. In older models, medicinal chemistry worked closely with drug metabolism and pharmacokinetics (DMPK) to understand the absorption, distribution, metabolism and excretion (ADME) of the candidate without a thorough understanding of how the compound was delivered in the animals under study. Most of the approaches for delivery focused on solubilization and generally used DMSO as the vehicle. As highlighted in several references addressing formulation support during discovery (Bailey et al., 1996; Railkar et al., 1996; Venkatesh and Lipper, 2000; Chaubal, 2004; Saxena et al., 2009; Maas et al., 2007), use of dimethyl sulfoxide (DMSO) may provide an easy formulation; however, these types of formulations do not reflect those used in development stages and thus provide an inflated absorption outcome. To address this issue, it has been recognized (Bailey et al., 1996; Railkar et al., 1996; Venkatesh and Lipper, 2000; Chaubal, 2004; Saxena et al., 2009; Maas et al., 2007)

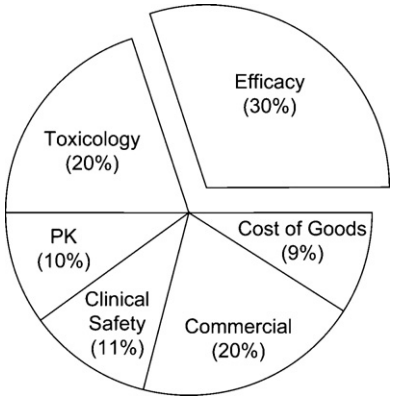
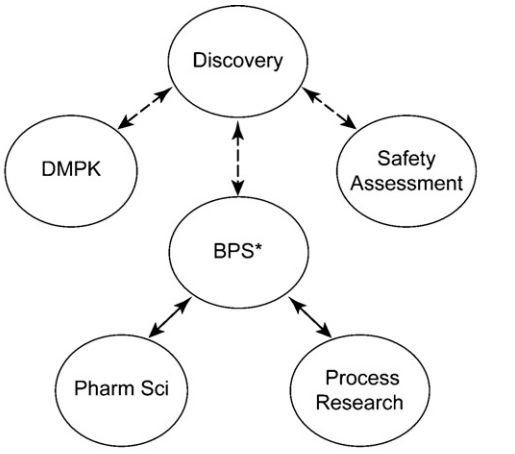


Fig. 1. Reasons for attrition in the clinic based on 2000 survey; taken from reference (Ismail and John, 2004).



*Basic Pharmaceutical Sciences (BPS)-Interface between discovery and development scientists

Key Features:
- Lead Optimization focus
- Lead Optimization team member
- Limited support for Target Validation/Lead ID in model
- Single point of contact for functional capabilities
- Dedicated resources
- Align Pharm Sci + PR resources in problem solving
- Provide a line of sight for development

Fig. 2. Integrated collaborative model with Basic Pharmaceutical Sciences Interface with other functional areas in discovery and key features of the interface model.

that the pharmaceutical industry has to evolve such that closer collaboration between functional areas, as illustrated in Fig. 2, is realized. This would lead to co-location of the team members that are dedicated to bringing molecules through discovery into development. This will allow the teams to understand and solve the problems during discovery allowing for disciplined decisions to select quality candidates. It is clear that the team members have to understand the development space to minimize the risks and liabilities of the candidate before progressing into development. In other words, drug discovery would need to be conducted without borders to allow dedicated development scientists to facilitate medicinal chemistry, pharmacology and biology. Efforts will need to be enhanced for delivering not just Phase I compounds but also a safe and effective commercializable drug that is differentiated from existing therapies. Therefore, studies during the discovery phase needs to include: (1) efficacy in animal models using appropriate formulations to ensure exposure and pharmacodynamic (PD) effects, (2) physical and biopharmaceutical properties of active pharmaceutical ingredient (API) that are amenable to downstream development, (3) compounds that meet ADME requirements and (4) are de-risked around toxicological concerns.

1.2. Current state of discovery

To understand the gaps and where there are opportunities to collaborate, we need to dissect the drug discovery process. It basically includes three typical phases (Fig. 3): target validation, lead identification and lead optimization. These phases all have their individual complexities and can have many feedback loops to each other and downstream to decisions early stages of development. Thus, it is important to aim for high compound quality early on because challenges live with the drug development program throughout its lifetime, including later stages of development.

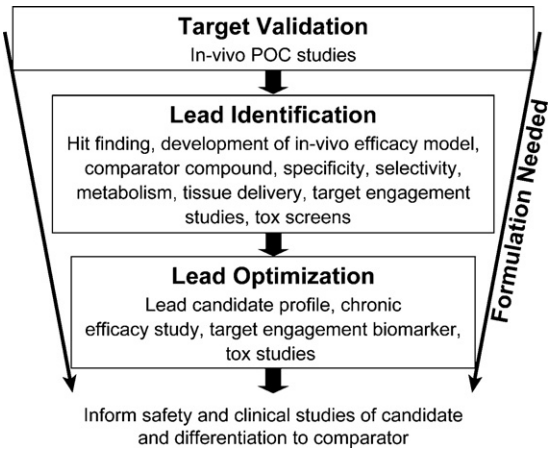


Fig. 3. A typical drug discovery process linking formulation needs through the different phases.

In the target validation phase, one or several targets are studied to determine their role in the mechanism of a given disease state. Recent publication of the FDA "Critical Path" initiative (FDA, 2004) stresses the importance of translational research and the development of tools such as biomarkers and appropriate animal models for efficacy and toxicological testing which may potentially impact the selection of appropriate candidate for clinical development. The challenge for biomarkers is to allow earlier, more robust drug safety and efficacy measurement. Because of the multifaceted nature of optimal in vivo models and/or biomarker development, the research operating plans for the selection and applications of these models should have input from each functional area including formulations, such that a holistic approach can be taken to make the appropriate decisions. At the lead identification stage, discovery teams face a different challenge in using un-optimized leads for developing in vivo efficacy models to determine the specificity and selectivity of the lead. Finally, in lead optimization, a lead candidate emerges via SAR studies which use profiling to inform on efficacy, PK, toxicology and differentiation from comparators (as needed) to arrive at a single or small set of development candidates.

In the overall discovery process, whether these are proof-of-concept pre-clinical studies, biomarker development or mechanism-based toxicity studies, the conclusive evaluation is through an in vivo study. As such, formulation can influence API release rate, the PK profile, oral absorption and hence the PD effect. Hence, involvement of development scientists in this space can have a profound contribution to decision-making to enable the "fail fast/fail cheap" paradigm, reducing costs and downstream resources. Consequently, use of appropriate formulations and/or route of administration can be useful in the development of appropriate efficacy and toxicity models and thus enable studies previously inaccessible using conventional approaches.

2. Formulation approaches in discovery

Numerous publications (Chaubal, 2004; Saxena et al., 2009; Maas et al., 2007; Wilson, 2010; Niwa and Hashimoto, 2008; Strickley, 2008; Gad et al., 2006; Li and Zhao, 2007) have documented significant formulation efforts during drug candidate profiling. However, only a few reports address the challenges associated with development of formulations to support early discovery stages, where an effective formulation can assist in developing in vivo models. Furthermore, the paucity of appropriate early formulation approaches available for discovery have often led to excessive animal usage with inexplicable results.

In order to properly provide formulation support for early discovery, it is essential to understand the challenges facing a formulator at this stage of development. During lead identification, a small team is typically assembled to understand the biology of the target. At this stage, chemists spend little time on optimizing leads, nor do they prepare large quantities of material to allow for elaborate studies. The compounds are typically un-characterized and may not provide the optimum exposure needed to understand the efficacy or toxicity. In vivo models (mostly rodent) are developed in a drug substance amount sparing approach using un-optimized leads. Besides the time constraints for formulation support, inappropriate physico-chemical properties, and lack of sufficient quantity of API for proper formulation development, other challenges include ensuring that the content of the formulation does not interfere with the outcome of the model and that the route of administration does not interfere with key experimental apparatus such as telemetry transmitters.

Effective strategies for accelerating the discovery process can be implemented by understanding the challenges in supporting early discovery via different formulation approaches. In several references (e.g. Chaubal, 2004; Saxena et al., 2009), it was noted that non-GRAS (Generally Recognized as Safe) solubilizers can be used since studies are normally acute and needed quick results. However, it is also important to note that the excipients need to be innocuous in the models being used to ensure that no false responses are generated. Because of limited availability of compound, miniaturization of formulation development approaches such as use of a high throughput (HT) format is required. Close collaboration with biologists and pharmacologists is crucial to understand the issues with exposure and determine what available technologies can enable delivery of the active to the site of action. Alternate routes of administration also might be helpful in enabling key studies that address issues with a compound. For example, to evaluate PK–PD relationships, parenteral routes of administration may be useful, since plasma concentrations can be better predicted and controlled. However, when leads are optimized and materials are readily available, oral activity needs to be evaluated as well because of the differences in metabolic profile between various routes. Finally, maximization of exposures through formulation intervention is usually needed to evaluate toxicity of the compound and thus, better validated pre-clinical candidates and preclinical proof of concept (POC) study effectiveness.

A focused solubility-enhancing formulation screen based on the characteristics of the compound can expedite formulation selection using limited API. We have developed a HT solubility screen which enables rapid and efficient selection of formulations. In this system, vehicles comprised of pH buffers, surfactants, emulsions, and selected solubilizers are scaled down to well microtiter plate formats and automated with a robotic liquid-handling system. Powder API (~1 mg) is aliquoted into the wells manually or via an automated powder dispenser such as a Powderinium. When the drug in the vehicle reaches its solubility limit, the dissolved materials are measured by turbidity, optical microscopy and/or UV absorption. The fully automated measurement system is able to determine solubility of 2–5 compounds within 24 h using about 10 mg of solid materials. The solubility of the compound, along with other methods to predict and understand the pharmacokinetics of the drug as it is released in the body are critical for success. For example, *in vitro* methods such as dissolution in biorelevant media have also been suggested in the literature (Li and Zhao, 2007).

2.1. Case Studies

2.1.1. Resolving mechanism based toxicity

Dogs are most often used as the non-rodent species in toxicity studies. In this case study, emesis was observed after multiple oral

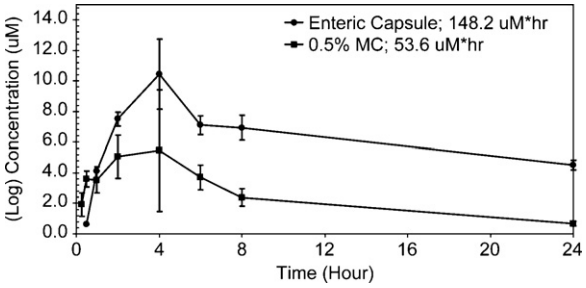


Fig. 4. Oral PK evaluation of compound 1 in dogs: dosed in 6 size "00" human enteric capsules. (-●-) vs 0.5% Methocel solution (-■-) at 100 mpk (n = 3 dogs).

dosing of compound 1 to dogs which contributed to lower exposure with no toxicity findings. Unfortunately, switching to an alternate species was not possible since historical data were generated in dogs. Upon further investigation, it was determined that the cause of emesis was due to local release of gastrin from drug in the stomach and not due to systemic exposure. Furthermore, because of the low aqueous solubility of compound 1, parenteral formulation at high doses was not feasible and thus, may not have provided high enough exposure to understand the toxicity of this series of compounds.

For clinical studies, enteric coated tablets or capsules are often developed for drugs that are known to have an irritant effect on the stomach (i.e., aspirin). The coating protects the formulation from the acidic environment of the stomach but breaks down rapidly at the lower acidic pH of the intestine. Since dogs can be dosed using human capsule formulations, an enteric coated capsule was used to mitigate the emesis during the toxicity study. To prepare a small batch of the enteric coated capsules, compound 1 was manually filled in capsules which were then hand treated with Eudragit E100 (a methacrylic ester copolymer) coating solution, such that the capsules would not release their contents in the gastric pH range (pH 1-5). The capsules were then dried under vacuum under a steady stream of air at 127 mm Hg for 30 minutes. Three coats were applied per capsule to ensure enteric coating integrity. By avoiding local exposure in the stomach, the risk of stomach irritation was reduced which prevented emesis and hence, increased exposure by 3-fold (Fig. 4). This increase in exposure allowed the compound to achieve a dose limiting toxicity, which provided the needed safety margin to start the human clinical program. This approach of using a well-known clinical formulation technology to quickly understand the preclinical mechanism of toxicity allowed for resolution of the exposure challenge prior to entering clinical studies.

2.1.2. Enabling in vivo model development

Another challenge for preclinical pharmacology is delivery to the central nervous system (CNS). In this example, a CNS compound 2 had low permeability and was a P-glycoprotein (pgp) efflux substrate, both of which contributed to low brain uptake from systemic circulation. Furthermore, the molecule had a MW ~ 500, underwent hepatic metabolism, had poor water solubility (<2 μg/ml) and a log P of ~5. There is growing evidence (Illum, 2000; Yamada, 2007) in the literature suggesting that direct nose to brain delivery of drugs via an intranasal (IN) route is possible via transport pathways that circumvent the blood brain barrier. Compound 2 was used to confirm the nasal to brain route in a proof of concept study using imaging techniques. A high throughput solubility screen of potential vehicles was performed to determine a vehicle that would solubilize compound 2 with an addition of the mucoadhesive Chitosan to enhance retention in the nasal cavity. An aqueous formulation consisting of 10% ethanol with 0.5% Chitosan was selected for the IN route and the same formulation without Chitosan was used for the IV arm dose. Consequently, an IN formulation was administered for compound 2 and compared to an intravenous (IV) formulation using a dose of 130 μg [^{3}H] compound 2 in Sprague Dawley rats. The IN formulation had similar content to the IV formulation with a lower volume of application to the nose to ensure limited drainage to the throat and minimize absorption due to swallowing. Radioactivity levels were determined at 5 mins, 0.5,1, 2 and 6 hrs post-dose in brain (especially hypothalamus), in plasma, and liver (Fig. 5). CNS exposure was also evaluated after IN vs IV dosing. The hypothalamus/plasma concentration ratio after IN

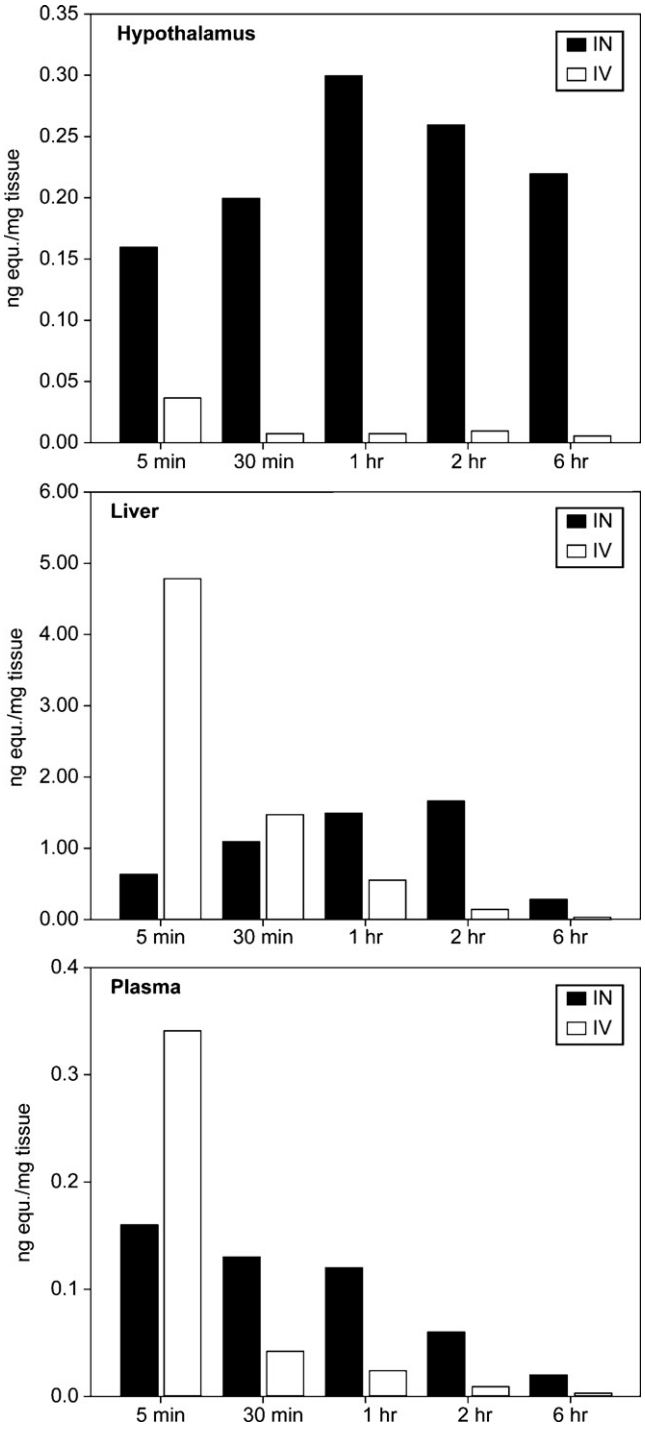


Fig. 5. Concentrations (ng equivalent/mg tissue) of [^{3}H] compound 2 in Sprague Dawley rats at 130 μg/rat (n = 1/time point) after intranasal (IN) or intravenous (IV) administration. (40 μCi/rat, 20 μl/nostril for IN) in hypothalamus, liver and plasma at specific time points.

was 1 to 11 compared to 0.1 to 2 after IV dosing. The nose to brain approach was more API sparing and produced higher brain target exposure. This case illustrates the power of using an alternate route of delivery to target drug to the brain, thus enabling diagnostic tool development.

2.1.3. Enabling dose limiting toxicity studies

In another case, a lead optimization team was asked to "derisk" a potential candidate. As toxicity is one of the leading causes of attrition in the clinic, good safety margins are imperative to reach proof of concept in clinical studies. To better assess the margins at the discovery stage, non-GLP rat and non-rodent dose limiting toxicity studies were performed. A study design with dose duration of up to 1 week was employed with intent to obtain at least 20× safety margin. However, before initiation of such toxicity studies, a road map like that described in Fig. 7 Maas et al. (2007) and Fig. 1 Li and Zhao (2007) was used to identify a conventional formulation that would provide the maximum exposure possible to define the dose limiting toxicity. Since compound supplies were limited, *in vitro* studies coupled with in vivo studies were carried out to assess the oral bioavailability. Physicochemical characterization along with information on solubility in aqueous and biorelevant media was critical to assist in selecting the formulation to support toxicity studies.

In this specific case study, compound 3 existed as a crystalline free base that was poorly soluble in water but highly permeable and hence, drug dissolution was the rate limiting step for absorption. Table 1 summarizes the low aqueous and non-aqueous solubility of compound 3, where no acceptable solution formulation was found for in vivo testing. Spray dried (SD) amorphous solid dispersions (i.e., amorphous drug–polymer composites stabilized with hydroxypromellose acetate succinate HF grade) are well-known in the literature as an effective means of improving solubility and subsequent bioavailability of BCS II drugs (Jung et al., 1999; Leuner and Dressman, 2000; Moser et al., 2008a,b; Shanbhag et al., 2008). Amorphous solid dispersions can also achieve acceptable exposure at the high doses required for the preclinical toxicity studies and thus, can provide a line of sight to clinical oral solid dosage form development. Furthermore, spray drying techniques do not depend on the physical form of the API. For compound 3, an HT screening of the different polymer and SD solvents as described in Moser et al. (2008a,b) and Shanbhag et al. (2008) was initially performed to help optimize the components for the amorphous dispersion. The screen was conducted on a 96 well-plate using a solvent casting approach. A total of 10 mg API was used with varying concentrations of selected polymers and surfactants. The solubilized mixture (in either acetone or methanol) was dispensed into each well and evaporated. The dried film was analyzed with a HT xRPD and optical microscopy for crystallinity. Once the combinations of polymer or additional surfactant concentrations were identified, the composition of the spray dried material was selected. This was followed by scale-up feasibility using a laboratory scale spray dryer with 100 mg API. The resulting amorphous dispersion of compound 3 (50% drug loading with HPMCAS-HF) was then suspended in 0.5% methylcellulose (Methocel) with sodium lauryl sulfate (SLS) as a wetting agent. Fig. 6 compares the dose proportionality of the crystalline form in 10% Tween 80, amorphous API in Methocel and the suspended formulation of the spray dried materials. At the lowest dose of 10 mpk, the exposure was similar for all three formulations. However, as the dose was increased (100 mpk), solubility of the crystalline phase limited the absorption of the compound, hence giving a lower exposure. Note that exposure from the amorphous form API in Methocel is still comparable at this mid-dose to the amorphous spray dried suspended materials. Finally, as expected, the amorphous dispersion at 750 mpk, provided a significant increase in exposure (4X AUC as compared to the crystalline phase (Fig. 6)). This result is consistent with literature findings (Leuner and Dressman, 2000; Moser et al., 2008a,b; Shanbhag et al., 2008) for supersaturated solutions stabilized by polymers. This approach allowed for a maximization of exposure to define the dose limiting toxicity with the needed turnaround time for formulation support.

Table 1
Solubility of compound 3 in biorelevant media and common conventional formulation.

Vehicle	Solubility (mg/ml)
pH 2, 0.01 N HCl	0.0003
pH 4, 50 mM acetate buffer	0.0003
pH 7, 50 mM phosphate buffer	0.0002
H_2O	0.0002
SGF	0.0003
FaSSIF	0.004
FeSSIF	0.013
0.5% Methocel	0.0008
0.5% Methocel/0.24% SDS	0.0094
10% Tween 80	0.488
20% Vitamin E TPGS	1.02
Imwitor:Tween 80	1.28
PEG400	4.82

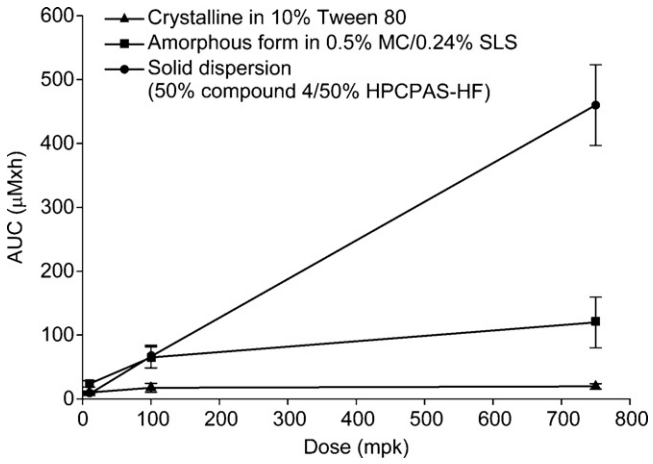


Fig. 6. Dose proportionality of compound 3 in 10% Tween (-▲-) as the crystalline form; in 0.5% Methocel/0.24%SDS as the amorphous form (-■-) and in solid dispersion at 50% drug loading dispersed in HPMC-AS polymer given as a suspension in Methocel (-●-) from 10 mpk to 750 mpk dosed at 5 ml/kg in Sprague Dawley rats ($n = 4$).

2.1.4. Addressing micronucleus studies

In oncology programs, additional toxicity screens are often performed during discovery to ensure that genotoxicity issues are adequately addressed. The in vivo micronucleus assay is one of a battery of tests used in toxicological screening for potential genotoxic compounds. This study requires a formulation that can provide the highest exposure to detect clastogenic and aneugenic activity in the peripheral blood and hence provide the safety margin required to support the clinical studies. In this example, compound 4 was identified as the lead, which existed as a crystalline form and provided low oral exposure. However, when administered in a 10% Tween 80 vehicle as a suspension with particle size of <10 μm, plasma levels of about 5× the safety margin with saturation of absorption at lower doses were observed. Since particle size seemed to have a profound effect on the rate and extent of absorption, a nanosuspension was evaluated. A platform recipe for the nanosuspension using polymer and surfactant was developed using a low energy milling procedure (i.e., ball milling). Agglomeration potential and rate were carefully controlled using stabilizers such as 1% hydroxyl propyl cellulose (HPC-SL) and ionic surfac-

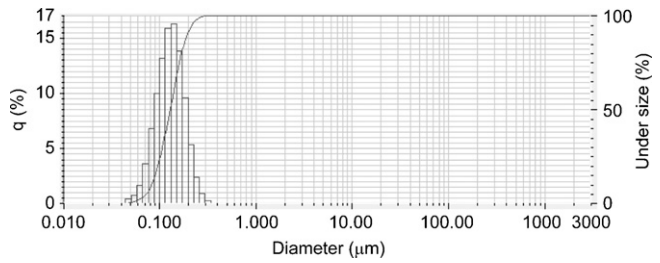


Fig. 7. Particle size distribution of compound 4 as a nanosuspension.

tants (0.05% SLS). The nanosuspension was prepared by weighing the API directly into a plastic eppendorf tube and adding the needed HPC-SL and SDS in water. Particle reduction was performed using zirconium beads added in the suspension and milled for 48 h before dosing. Fig. 7 shows the particle size distribution of the prepared nanosuspension. Compound 4 showed a dramatic increase in exposure to 85× safety margin (Fig. 8) when a stable nanosuspension was administered along with improved dose proportionality up to 750 mpk. Even at this high exposure, the micronucleus (MN) assay showed negative activity which provided the discovery team confidence in the evaluated structural series.

2.1.5. Determining site of action and target exposure

For an inhalation program, pulmonary administration (directly to the lung) for local treatment of respiratory disease offers numerous advantages over other routes of administration. Since small animal models are used in such studies, pulmonary delivery is highly problematic. The techniques for delivering drugs to mouse or rat lungs include inhalation chambers, nose only aerosol exposure and intra-tracheal (IT) instillation (Driscoll et al., 2000). The inhalation chamber and nose-only aerosol exposure are the main techniques used in inhalation toxicology, but they are rarely used in pharmacology studies since lung deposition is difficult to determine. Moreover, only a small amount of the drug is inhaled by the animal during this process. IT administration was used in this experiment instead because it is easy to administer and the administered dose is readily quantifiable. Moreover, only a small amount

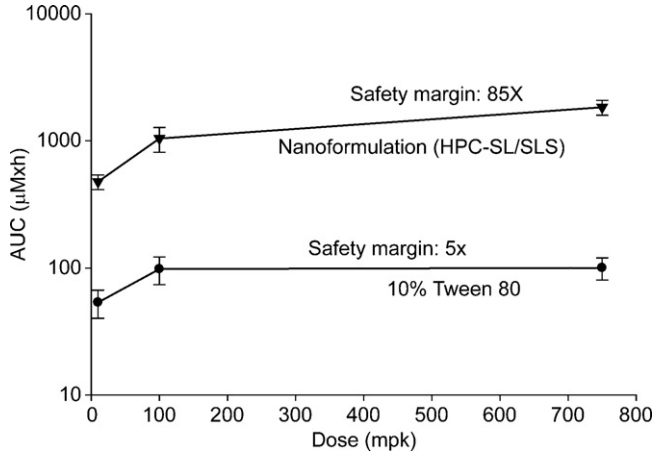


Fig. 8. Oral dose proportionality results of crystalline compound 4 in 10% Tween 80 and in 1% HPC-SL/0.05% SDS nanoformulation from 10 to 750 mpk in Sprague Dawley rats ($n = 4$) given at 5 ml/kg.

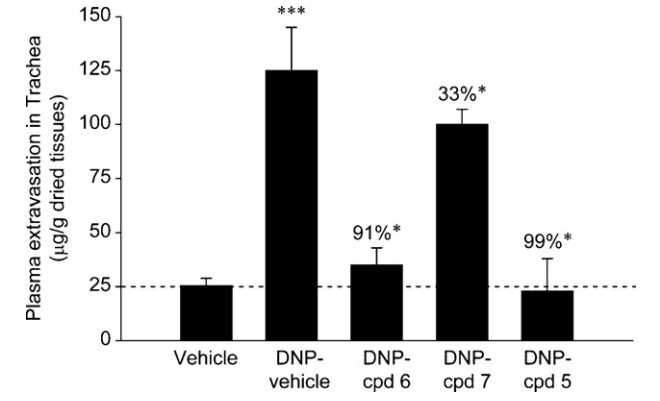


Fig. 9. Plasma extravasation in rat trachea following an intra-tracheal administration of DNP and intra-tracheal administration of 5.2 mpk nanoformulation of compound 5,6 and 7 in rats ($n = 3$) [$^{***}P < 0.001$ compared to vehicle, $^{*}P < 0.05$ compared to vehicle–DNP challenge].

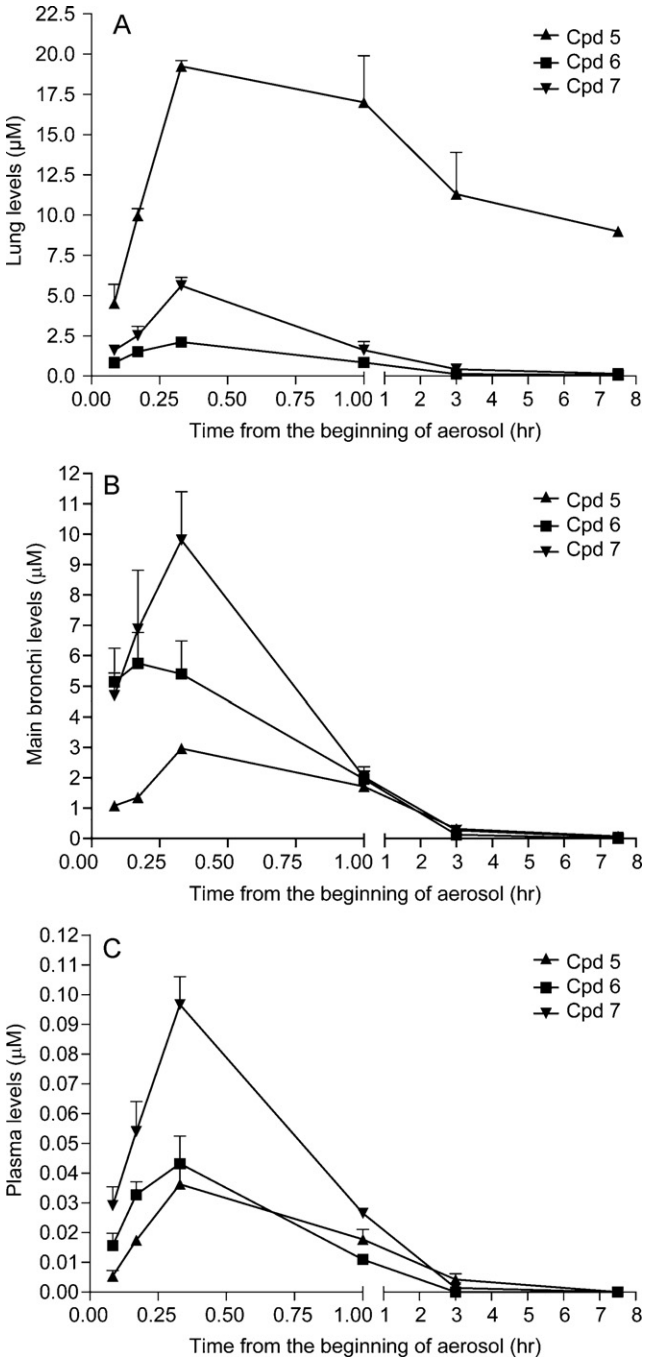


Fig. 10. Pharmacokinetic profile in the lung (A), main bronchi (B) and plasma (C) of the rats following intratracheal administration of 5.2 mpk of the nanoformulations of compound 5,6 and 7 in rats ($n = 3$).

of drug is required and there is minimal loss in the upper airway areas. The goal of this study was to detail the methodology for delivering the lead compound directly to the lung and evaluate the exposure levels in different parts of the lung and with systemic circulation. Additionally, the PD effects of the lead were also studied to help understand the deposition of the lead to the site of action. In this model, rats were passively sensitized with a dinitrophenol (DNP)-specific IgE. As a principal efficacy readout, plasma extravasation in the trachea was measured following IT administration of DNP. The systemic exposure was undesirable due to the compound adverse effects and thus, the compound was required to be localized to delivery in the lung. Three compounds, 5, 6 and 7 were administered IT using a nano-colloidal suspension to deliver a well-dispersed system, using a pipettor, directly into the trachea. All three compounds were crystalline and were easily milled to form nano-sized particles that could be suspended and remained physically stable during the duration of the studies. The suspensions were characterized pre-dose and post-last dose to assess the properties of the suspension used in the studies. No long term stability studies were required, since formulations were prepared fresh before each study. Fig. 9 shows that compounds 5 and 6 selectively blocked plasma extravasation in the trachea as indicated by >91% blockade compared to the DNP challenged case. Concomitant measurement of levels in plasma, bronchi and lungs showed that compound 5 (Fig. 10) exhibited the highest levels in the lung with low levels in bronchi and plasma suggesting that suitable levels might have been reached in the trachea where the PD endpoint is measured. By combining efforts on the nano-formulation platform with inhalation formulation development, incorporation of this model as part of the screening was quickly accomplished. Distribution of active after lung delivery can now be followed and relationship to efficacy can be established.

3. Concluding remarks

Stronger collaboration between discovery and development scientists is key to improving the process of selecting preclinical candidates that have a higher probability of success. Although more intensive pre-clinical formulation development may appear to prolong the discovery stage, meaningful data based on the effective delivery of the active molecule to the site of action is expected to enable faster go/no go decisions on moving programs into development. Furthermore, use of high throughput tools and technologies with well-designed experiments are essential for supporting the discovery scientists to advance the program from bench to the bedside. Providing elegant, custom formulations to discovery enables development of better pre-clinical models that can better predict clinical response. Understanding the preclinical in vivo models in collaboration with key discovery scientists coupled to an understanding of the toxicology of the mechanism helps identify which formulations will allow targeting the area of interest and thus, reduce the attrition rate of potential drug candidates. Challenges due to limited API supplies can be mitigated by miniaturization of the formulation development through the use of HT screens and small scale preparation equipment. In addition, understanding the physicochemical properties of the candidate and use of enabling formulation technologies such as spray drying and nanoformulations can further help in addressing the challenge of limited API availability. Finally, a holistic understanding of API, formulation vehicle, dose, exposures and concomitant efficacy enables scientists to better correlate study outcomes with provided test articles and thus, carve a development path forward with significant implications on downstream success of the product.

Acknowledgements

The authors gratefully acknowledge Hongshi Yu, Jenna Terebetski, Zhoupeng Zhang, James Ormes, Melaney Bouthillette, Lily Moy, for the examples included in this paper. The authors would also like to thank Sachin Mittal for his thorough reading of this manuscript.

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