REVIEW ARTICLE

Formulation development for cancer compounds – Biopharmaceutical issues and perspectives

Nuggehally R Srinivas

Integrated Drug Development, Suramus Biopharm, 77, 10th Cross, 29th Main, J.P. Nagar, Bangalore

The development of formulations for anti-cancer drugs imposes challenges owing to the different physicochemical attributes of the compounds as well as the need to deliver the compound to the desired target and/or tumor sites. In this article we present case studies to discuss recent formulation related work for both paclitaxel and topotecan. As enumerated by the case studies, biopharmaceutical and pharmacokinetic challenges are imposed in design and optimization of suitable dosage forms for both intravenous and oral drug delivery. The focus is on selection of excipients which may play additional role(s) in contributing towards the disposition of both paclitaxel and topotecan.

Key words: *Anti-cancer compounds, biopharmaceutical, cytotoxics, paclitaxel, topotecan, pharmacokinetics*

INTRODUCTION

Regardless of the intended delivery, parenteral or oral, formulation development is an important aspect in delivery of oncology compounds given the difficulties imposed by both physicochemical attributes of the compounds and the biological targets/receptors it intends to interact.[1-4] In this context, the present day trends offer a variety of formulation opportunities to due to technical advancement in the field, better know-how of various delivery options and through thorough knowledge of excipients being used. In spite of the profound knowledge in the field, there appear to be many challenging issues in the development of suitable formulations for several anti-cancer compounds. Some of the challenges may be partly due to attempts to switch certain drug substances from an approved route of administration to another one. For instance, there have been several attempts to formulate intravenously approved compounds such as paclitaxel or docetaxel for oral dosing.[5,6] Other kinds of challenges may also arise because of attempts to overcome some of the natural barriers of oral absorption by circumventing the profound effects of efflux transporters such as P-glycoprotein pumps (pgp).[7]

Address for correspondence:
Dr. Nuggehally R Srinivas, Suramus Biopharm 77, 10th Cross, 29th Main J.P. Nagar I Phase Bangalore - 560 078, India.
E-mail: Srini.suramus@yahoo.com

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SCOPE

This note intends to discuss a few case studies recently presented in literature to illustrate innovative thinking and challenges involved in the formulation of anti-cancer compounds. It also provides views on biopharmaceutical, pharmacokinetic and drug development challenges. The two selected compounds for this brief overview are: a) paclitaxel, a tubulin inhibitor, to serve as an example for both intravenous and oral routes of administration and b) topotecan, a topo isomerase I inhibitor, to serve as an example for oral route of administration.

CASE STUDY OF PACLITAXEL

Cemaphor-based formulations for intravenous and oral use

Intravenous

Chu *et al.* (2008) have showed the influence of cremaphor-EL excipient on the disposition and pharmacokinetics of paclitaxel administered by the intravenous route. The authors used two cremaphor-EL based formulations of paclitaxel: a) the original formulation that contained 50% v/v of cremaphor-EL excipient (i.e. Genaxol); b) a modified formulation that contained 2.5 fold lower quantity of cremaphor-EL excipieint (20% v/v Genetaxyl).[8]

The pharmacokinetic evaluation for the two formulations of paclitaxel was carried out in cancer patients who received an intravenous dose equivalent to 175 mg/m^2 of either Genaxol or Genetaxyl formulations administered as a standard three-hour infusion.[8] Interestingly, although the paclitaxel dose remained constant for the

two formulations, the pharmacokinetic parameters showed distinct and conspicuous differences. The peak concentration (C_{max}) for total paclitaxel (protein bound plus unbound fraction) for Genetaxyl (2.25 μg/mL) appeared to be two-fold lower as compared to Genaxol (4.43 μg/mL), which further translated into a two-fold difference in area under the concentration time curve values (AUC) between Genaxol (14.3 μg.h/mL) and Genetaxyl (7.85 μg.h/mL) formulations.[8] However, the elimination half-life values appeared to be similar between the two formulations (11 h for Genaxol versus 14 h for Genetaxyl).[8] On the contrary, examination of the unbound fraction of paclitaxel revealed a different picture - the AUC parameter for Genetaxyl (1.17 μg.h/ mL) was about two-fold higher than that of Genaxol (0.62 μg.h/mL).[8] While the clearance values for the total paclitaxel revealed faster clearance after Genetaxyl formulation; it was reversed if unbound clearance values for paclitaxel were considered. Since the volume of distribution parameters were not presented in this report, it was not possible to assess the differences of that parameter between the two paclitaxel formulations. Therefore, this study unequivocally confirmed the role of excipient such as cremaphor EL in modulating the pharmacokinetics of paclitaxel.[8] Although the underlying mechanism has not been elucidated the higher cremaphor content may entrap paclitaxel and restrict its distribution to tissues and/or organs. On the other hand, with lower cremaphor content it could be envisaged that paclitaxel was more readily available for distribution into tissues, especially the liver (where metabolism is occurring) and/or kidneys (to facilitate urinary excretion). To underscore observations from this study another formulation that contained albumin bound nano particles of paclitaxel behaved in a similar fashion to that of Genetaxyl formulation.[9]

Oral

The rationale for using the modified cremaphor EL based formulation (Genetaxyl) was that unlike the 50% v/v formulation of paclitaxel, there would be lesser micellar entrapment of paclitaxel and therefore, would provide a better environment for absorption of paclitaxel through the gastrointestinal regions.[8] From a biopharmaceutics perspective it was considered important to present readily available paclitaxel for oral drug absorption and it was thought that the 20% v/v cremaphor-EL containing paclitaxel formulation would be best suited for this work. Since palcitaxel was subjected to first pass metabolism, it was thought that a combination with cyclosporin A would enhance its oral bioavailability.[8] Although it was previously shown that the combination was not effective,[10] it was postulated that 20% v/v cremaphor based formulation would behave much differently than the 50% v/v cremaphor-EL based formulation tested earlier.[8] In this oral bioavailability study a single dose of cyclosporine A was chosen (i.e., 10 mg/kg) and combined with three doses of Genetaxyl (60, 120 and 180 mg/m^2).[8] The pharmacokinetic data revealed less than dose proportional increase in the C_{max} and AUC values for paclitaxel as a function of dose. For example, when the doses increased 1:2:3, the C_{max} increased in a proportion of 1:1.1:1.6, whereas, AUC increased in a proportion of 1:1.2:1.5, suggesting that there might have been saturation in the absorption process of paclitaxel. It also appeared that the oral bioavailability of paclitaxel was not enhanced in the presence of cyclosporine A when compared to historic values.[8] Therefore, it appeared there was a biopharmaceutic challenge of : a) understanding the requirements to formulate paclitaxel to overcome the inherent saturation barrier in the gastrointestinal tract; b) pinpointing the exact region that would promote the maximum absorption of paclitaxel when administered by oral route.

CASE STUDY OF TOPOTECAN

Yamagata *et al.* (2008) have conducted an interesting study to elegantly demonstrate the role of certain excipients for significant improvement in the oral bioavailability of topotecan.[11] The strategy, from a biopharmaceutic perspective is to block the efflux transporter pumps lined up in the intestine which limit the oral absorption of several drugs including topotecan. Accordingly, this study was designed to block the breast cancer resistance protein (BCRP/ ABCG2) in the intestine by carefully chosen excipients.[11]

The study was performed using two strains of mice – wild type and double BCRP knock-out (-/-) to study the effects of BCRP transport under very rigorous experimental conditions. The chosen excipients for the study were the ones used in formulation work for anti-cancer compounds, Tween 20 and Pluronic 85. In order to fully appreciate and comprehend the pharmacokinetic disposition of topotecan in the two strains of mice, a dose response curve was constructed with varying dose concentrations of both Tween 80 (50, 100 and 250 mg/kg) and Pluronic 85 (100, 250 and 500 mg/kg). The inclusion of both oral and intravenous dosing of topotecan enabled to ease out the 'presystemic' effects of excipients on oral bioavailability and resulted in an unbiased data interpretation of topotecan. Both excipients were administered approximately 15 minutes prior to either oral or intravenous dose administration of topotecan.[11]

In wild type mice, regardless of the excipient chosen, the oral exposure (AUC) increased as a function of the dosing concentration of the excipient. For example, the AUC values for topotecan increased by 53 and 99% at doses of 50 and 100 mg/kg of Tween 20 respectively as compared to wild type. Similarly, the AUC values for topotecan increased by 33 and 99% at doses of 100 and 250 mg/kg of Pluronic 85. However, at the highest dose tested for both Tween 20 and Pluronic 85, the AUC values diminished. In contrast, when orally administered, the two excipients had minimal effect on the intravenous pharmacokinetics of topotecan suggesting that the probable roles of these excipients were confined to the intestinal absorption of topotecan.[11]

In BCRP knock out mice, the presence of either Tween 20 or Pluronic 85 had less of an influence on the oral

pharmacokinetics of topotecan implying that the excipients acted via the inhibition of the transporter pumps.[11]

Interestingly, the *in vitro* everted intestinal sacs prepared from both wild type and BCRP knockout mice supported the *in vivo* findings. It was observed that both Tween 20 and Pluronic 85 contributed for an accumulation of topotecan by an increased intestinal absorption rates in everted intestinal sacs prepared from wild type mice. However, the absorption rate appeared to be diminished in the everted sacs prepared from BCRP knockout mice.[11]

DISCUSSION

The case studies presented in this work highlight the importance of excipients in the delivery of cytotoxic drugs in the oncology area. While it was once thought that the role of an excipient may be to make the drug soluble it appeared that excipients may influence many other parameters which may all contribute for the total drug disposition of anti-cancer compounds.

If one takes paclitaxel as a casing point, earlier pharmacokinetic data gathered in cancer patients have postulated saturation of both distribution and elimination to possibly explain the nonlinear pharmacokinetics of paclitaxel.[12-15] However, this case study and other reports have postulated the entrapment theory of paclitaxel which would be influenced by the cremaphor dose.[16-19] More recently, Bullita *et al.* (2008) have proposed a mechanistic population model for paclitaxel pharmacokinetics from a cremaphor free tocopherol based nanoparticulate formulation.[20] Accordingly, a linear disposition and higher bioavailability for paclitaxel has been described due to the direct release of the drug at the target site.[20] In totality, all the pharmacokinetic data for paclitaxel gathered to date are reflective of the formulation dependent biopharmaceutical attributes which contribute to define the pharmacokinetic disposition of paclitaxel in cancer patients. Therefore, if a newer formulation of paclitaxel is devised with novel excipients, it is important to compare the biopharmaceutical attributes of the newer formulation in a well planned clinical pharmacokinetic/ pharmacodynamic study with the original formulation to understand and define the formulation dependent changes, if any, on the disposition of paclitaxel.

The case study of topotecan showed that formulators have an opportunity to choose certain excipients and at permissible concentration levels to enhance the oral bioavailability of certain substrates via BCRP transport pumps. Here the chosen excipient(s) are expected to manifest dual roles – improvement in the solubilization of the active substance and a transient blockade of the efflux transporter pumps (eg. Tween 20 and Pluronic 85). Such use has been extensively documented in literature for other anti-cancer compounds.[7,21,22] Recently, Yamagata *et al.* (2007) have provided a list of at least 10 excipients inclusive of Tween 20 and Pluronic 85, which could potentially block the P-glycoprotein (pgp) efflux phenomenon and promote improved transport and/or absorption of substrates.[23] These excipients were Cremophor EL, Cremophor RH40, Tween 80, Span 20, vitamin E TPGS, Brij 30, Myrj 52 and Gelucire 44/14.[23] Additionally, there were a few excipients which also had an inhibitory effect on BCRP efflux and it included Cremophor EL, Tween 20, Span 20, Brij 30 and Pluronic 85.[23]

Another important area for biopharmaceutical scientists and formulators would be to direct the delivery of anti-cancer drugs to the site of action since general routes of chemotherapy administration are expected to result in non-specific drug distribution. In this regard, Brown (2008) has proposed the use of polysaccharide hyaluronan to serve a dual purpose –excipient for chemotherapy and efficient transporter to tumor cells.[24] The application of the use of hyaluronan cytotoxin bioconjugates with potential to improve the therapeutic index for several important cancer drugs has been demonstrated.[24]

It should be noted that designing oral delivery systems for cytotoxic compounds is tricky for the simple reason that oral absorption characterization studies using gastrointestinal (GI) intubation methodology or gamma scintigraphy techniques typically followed for non-cytotoxic compounds,[25-28] to deliver the drug to specific regions of the GI regions, cannot be undertaken in healthy volunteers due to ethical constraints. The knowledge of GI absorptive region(s) is/are a critical piece needed for formulators to devise and optimize the drug formulations for an effective oral delivery of the drug substance. This is because of the variability observed in different GI regions with regard to local environment such as pH, fluid volume, transit times, absorptive surface etc. However, in spite of this setback, the reported work on paclitaxel, topotecan and other anti-cancer agents are indeed very encouraging and will set the stage for future innovations.

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