Dissolution Optimization and Solid Dispersion Feasibility Approaches for an Anti-HIV Drug Candidate

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ABSTRACT SUMMARY
A poorly water-soluble anti-HIV drug candidate was assessed with regard to its suitability to formulation as a solid dispersion. While traditional carrier screening was straightforward, dissolution and supersaturation assessments seemed to disconnect from dosage form experience in rats and dogs. An optimized dissolution approach was generated which seemed to be more biorelevant and reflective of in vivo bioavailability.

INTRODUCTION
Contemporary drug pipelines often contain complex drug candidates which are increasingly difficult to formulate based on (1) poor water-solubility and (2) limiting dissolution rates. While this is a widespread problem, certain therapeutic areas often suffer disproportionately from these issues including antiviral therapeutics. This is punctuated by the observation that of the 13 current approved solid dispersions, 5 contain antiviral medications. Anti-HIV medications figure prominently in this list with examples including: ritonavir (Norvir®), ritonavir and lopinavir (Kaletra®) and etravirine (Intelen®). While efforts continue to search for medicinal chemical solutions to formulation difficulty, target space and oral bioavailability space are often misaligned and expanding formulation space continues to be of interest.1

R157753 is a potentially useful anti-HIV drug candidate with a good in vitro antiviral efficacy (ED50~2 nM) and low cytotoxicity (>39 μM)2,3. The compound is poorly water-soluble and has limited oral bioavailability from a drug suspension in the rat and dog. In order to improve the probability of success of this drug candidate, solid dispersion concepts were considered by assessing interactions with glassy carriers, evaluation of supersaturation and drug release using specially designed in vitro dissolution assays.

EXPERIMENTAL METHODS

Materials. R157753 was obtained from Janssen Research and Development, Beerse, Belgium and demonstrated a purity of >95%. The following excipients were used in the studies: hydroxypropyl cellulose (HPC) 150-700 mPa.s (Aquelon Belgium N.V., Doel-Beveren, Belgium), hydroxypropylmethyl cellulose (HPMC) 2910 5 mPa.s (Aqualon, Hercules, Zwijndrecht, the Netherlands), polyvinylpyrrolidone – co- vinyl acetate (PVP VA64) (BASF AG, Ludwigshafen, Germany), polyvinylpyrrolidone (PVP) K30 (BASF AG, Ludwigshafen, Germany), Cremophor RH40 (BASF, Hamm, Belgium), PEG400 (Sigma-Aldrich, Bornem, Belgium). 2-Hydroxypropyl-β-cyclodextrin (HPβCD) was obtained from Roquette (Lestrem, France) and was characterized by a degree of substitution of 4.2 based on an FT-IR method. All other materials and solvents were obtained from Sigma-Aldrich (Bornem, Belgium) or Janssen Pharmaceutica (Beerse, Belgium).

Methods. Differential scanning calorimetry (DSC) was completed using a Perkin-Elmer DSC-7 differential scanning calorimeter (Perkin-Elmer, Norwalk, CT, USA) equipped with a liquid nitrogen subambient accessory (Perkin-Elmer, Norwalk, CT, USA). For supersaturation testing, the drug, in a dimethylformamide (DMF) solution (100 mg/mL), was added in small aliquots (using a Hamilton syringe) to a stirring (600 rpm) solution of the excipient (10 mL, 2.5% w/v in SGF (without pepsin) at 37 °C). When a precipitate was visually perceptible, the addition was stopped and the media sampled, filtered and analyzed for the compound using UV spectrophotometry. Dissolution rate was determined using a USPII containing 900 mL of 0.1 N HCl, thermostated to 37 °C and operating at a paddle speed of 100 rpm. Films or other formulations were incorporated into a Teflon cup fitted with a sinker. For optimization assessments, the dissolution media was altered using both organic modified and other solvents and solvent mixtures. Animal pharmacokinetics and antiviral data were obtained from the literature.2,3

RESULTS AND DISCUSSION
R157753 is a diarylpyrimidine (DAPY)-type anti-HIV reverse transcriptase and chemically related to etravirine.2

The compound is characterized with a pKa <3, a high log P (>5) and is practically insoluble in aqueous media. The predicted human doses range from 200 to 400 mg. A screen of pharmaceutically acceptable vehicles identified PEG400 as a useful solvent providing a drug solubility of 6.7 mg/g. Both PEG solutions and micronized suspensions (in 0.5% w/v HPMC) were administered to rats and dogs. Solution vehicles provided for AUC values (mg•h/mL) of 8.2 in the dog (10 mg/kg) and 0.1 in the rat.

Figure 1. Chemical Structure of R157753
(40 mg/kg).\(^2\) Suspensions generated exposures that were >10-fold lower suggesting the need for formulation enablement. To assess possible solid dispersion approaches (with e.g., processing using melt extrusion, bead coating or spray-drying), the interaction of possible carriers and the drug candidate were assessed using melt blending and film casting as well as through the use of supersaturation testing.

Differential scanning calorimetry indicated that R157753 has a high melting point (300 °C) with a high heat of fusion (130 J/g). Given this high melting point and based on possible thermal instability, it was of interest to assess whether the drug candidate could dissolve in molten polymers rather than attempting to co-melt the binary mixture. Data from the DSC suggested that PVPK30, PVP-VA 64, HPC and possibly HPMC and HPMCD acted as solvents for R157753 based on area of the endothermic melting event. Based on screening results, PVP K30 was selected for further assessments. A 1:3 ratio of the drug to the polymer generated a Tg of 155 °C for the dispersion.

Supersaturation assessments were completed using PVP K30 with the addition of a surfactant (Table I). In the experimental set-up assessed, little or no supersaturation was observed in the presence of PVP K30 while the addition of Cremophor RH40 increased the extent and duration of supersaturation marginally. Interestingly, PEG400 was also not useful in this test even though important exposures were observed in test animals.

Table I. Supersaturation Assessment of R157753 (in DMF) in the Presence of Various Excipients (Conc. in mg%)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0.1 N HCl</th>
<th>PVP</th>
<th>PVP-RH40</th>
<th>PEG400</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>ND</td>
<td>ND</td>
<td>0.50</td>
<td>ND</td>
</tr>
<tr>
<td>30</td>
<td>ND</td>
<td>ND</td>
<td>0.38</td>
<td>ND</td>
</tr>
<tr>
<td>60</td>
<td>ND</td>
<td>ND</td>
<td>0.34</td>
<td>ND</td>
</tr>
<tr>
<td>120</td>
<td>ND</td>
<td>ND</td>
<td>0.32</td>
<td>BD</td>
</tr>
</tbody>
</table>

ND – below the limit of detection

Cast films were generated based on the screening data. Materials were prepared from a 1:3 mixture of Cremophor RH40:PVP K30 containing R157753. DSC of the films confirmed the formation of a solid dispersion and stability assessments indicated little or no degradation had occurred. In vitro dissolution was completed and the film provided for measurable drug levels at 5 and 15 min after sample addition to the dissolution bath. By 30 min, the drug had precipitated from the dissolution bath. These results suggested a re-evaluation of the dissolution method. Based on dog and rat data, the method appeared to be underdiscriminating and a more biorelevant dissolution set up was sought.\(^4\) Dissolution was optimized as a function of animal data by screening various solvents and solvent systems. Improved results were generated using a solvent system containing 1:1 H$_2$O:THF. Under these conditions, in vivo behaviour of the solution and suspensions were correlated at least in rank order. The suggested PVPK30/Cremophor RH40 film was potentially superior based on this assay.

Figure 2. Drug release from a Micronized Suspension, a PEG solution and a Cast Film using an optimized Dissolution Method.

CONCLUSION

Difficult-to-formulate drug candidates have to be carefully assessed to connect drug delivery needs with compound requirements. Inappropriate application of technologies can lead to exaggerated development complexities with associated aggregated risk, cost and dilated timelines. Appropriately biorelevant screening tools should be carefully considered in the selection of both enabling technologies and processing approaches.

REFERENCES


