Oral Sustained Release Formulations Based on Coating a Nano-on-Bead Concept with a pH Sensitive Polymer

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ABSTRACT SUMMARY
A novel CNS drug candidate required a sustained release dosage form to provide for once-a-day doing as well as appropriate Cmax levels consistent with optimal safety and efficacy. Immediate release dosage forms included a liquid nanosuspension as well as a solid nano-in-tablet and a nano-on-bead concept. In order to develop a sustained release system, a coated bead approach was developed in which several pH sensitive/enteric coatings were applied. Dissolution testing as well as testing in the dog were applied as pharmaceutical and biopharmaceutical endpoints.

INTRODUCTION
Contemporary drug pipelines are often highly populated with poorly water-soluble drug candidates. The genesis of this situation is postulated to be rooted in the changing nature of the therapeutic targets of interest, the use of high throughput screening to identify drug candidates and current complexities with salt and polymorphic forms. Drug development is made even more convoluted when pharmacokinetic issues are superimposed on the pharmaceutical problems as in cases where the drug has a short plasma half-life or when safety and efficacy constraints require minimal plasma level variability. A germane example is a novel CNS drug, Compound A (free base), which is associated with a molecular weight of 416 g/mol, a melting point of 216 °C, is a weak base (pKa = 3.45), moderately lipophilic (log P = 3.1) and poorly soluble in water (<0.001 mg/mL) and with only a moderate tendency to complex with cyclodextrin (5 mg/mL in 20 % w/v HPC:CD). While several solubilizing technologies were applied, a nanosuspension was ultimately selected for first-in-human evaluation. The formulation contained the milled API and a stabilizer (HPMC:DOSS) at a ratio of 0.25:0.03 relative to the drug. The d50 of the nanodispersion was 150 nm. Dosing to man generated useful pharmacokinetics with increasing Cmax and AUC values as a function of dose. Conversion of the liquid nanosuspension to a solid dosage form was completed by either coating beads in a closed Wurster (nano-on-bead) or by spray-drying the aqueous nanosuspension and pressing the powder into a tablet (nano-in-tablet). These solid concepts gave similar exposures in man and provided for linear pharmacokinetics at the tested doses between 30 and 120 mg. The bioavailability was superior to that of the oral nanosuspension. Data from these studies also suggested that the dominate elimination half-life may be too short to ensure drug coverage after a single daily administration (effective plasma levels of 30-400 ng/mL) and that the Cmax-Cmin variation may be suboptimal. Both of these observations suggested that a sustained release dosage form may be of benefit. The design of such a system was complicated by the poor pharmaceutical properties of the compound. While a number of concepts were considered, one suggestion that was developed was applying a pH sensitive/enteric coating to the nano-on-bead concept to generate the required pharmacokinetic profile.

EXPERIMENTAL METHODS
Compound A was obtained from Janssen Research and Development, Beerse, Belgium and demonstrated a purity of >95%. Excipients were obtained from various sources including Aquelon Belgium N.V., Doel-Beveren, Belgium, BASF AG, Ludwigshafen, Germany, Sigma-Aldrich, Bornem, Belgium and Roquette, Lestrem, France. Nanosuspensions were prepared as previously reported using high energy Netzsch milling. Inert spheres (microcrystalline cellulose (MCC)) were coated with a nanosuspension using a Huttlin Uniball systems (Schopfheim, Germany). The nano-on-bead pellets were then overcoated with an enteric layer containing either Eudragit L30 D55 (for drug release at a pH of 5.5) or Eudragit L100 (pH 6), triethyl citrate and t alc. Enterically coated or uncoated pellets were then filled into hard gelatin capsules to generate a 60 mg drug dose. Dissolution studies were conducted using a USP II apparatus, 75 rpm containing 900 mL of (vessel 1) SGF (without pepsin), pH 1.2 and (vessel 2) 0.05 M phosphate buffer + 1% Tween80 (pH 6.8) and thermostated at 37 °C. All animal investigations were carried out in accordance with relevant national and international guidelines. Blood samples (3 mL in a collection tube containing EDTA) were taken at time 0, 5 min, 15 min, 30 min, 1, 2, 4, 8 and 24 h (and longer as needed). After collection, the samples were immediately protected from light and cooled to 0 °C in an ice bath. The sample were centrifuged at 1900 g for 10 min at 5 °C to separate the plasma and the separated plasma was removed, transferred to a second test tube and frozen. One hundred mL of the stored plasma was mixed with 50 mL of methanol containing an internal standard after which 200 mL of acetonitrile was added. The samples were then centrifuged at 10,000 g for 10 min. 150 mL of the supernatant was then transferred to an HPLC vial. The analysis was completed using a validated LC/MS/MS method with limits of quantitation of 5 ng/mL. Data was used to determine a number of pharmacokinetic parameters using WinNonlin ® Professional (Pharsight, Mountain View, CA). A non-compartmental analysis using the log-linear trapezoid rule with a log-linear extrapolation was applied.
RESULTS AND DISCUSSION

Design space input suggested at least two enteric coating materials might be of use including one which dissociated at a pH of 5.5 and one at a pH of 6 such that different regions in the intestine might be targeted. The Eudragit aqueous dispersion (L30 D55) was applied to the pH 5.5 release systems and the undispersed L100 to the pH 6 triggered pellets. Dissolution profiles were assessed in SGF (without pepsin) and in pH 6.8 buffer.

As demonstrated, the uncoated beads intended for immediate release provided for rapid drug availability with 100% of material available at 1 h. The release of drug from the coated systems was delayed with the pH 5.5 sensitive coating blocking release over an 8 h time frame and the pH 6 coating slowing significant release for approximately 2 h. In a media at pH 6.8, drug release is rapid in both presentations with approximately 40% release within 2 h for the pH 5.5 coating and ~60% within 1 h for the pH 6 system.

The biopharmaceutical fitness of these systems was then assessed in the dog based on a dose of 60 mg. Summarized data for AUC, Cmax and Tmax are provided in Figures 2.

Assessments in the dog suggested that the pH 6.0 coating not only increased exposure but also increased the Tmax consistent with the desired design elements as well as the in vitro dissolution profiles. The higher Cmax for the pH 6 coating material may be correlated with the behavior of the dosage form under acidic conditions.

CONCLUSION

Designing a modified release dosage form for a poorly water-soluble drug candidate was attempted using two formulation approaches including a nanosized API coated on a bead as well as an enteric layer designed to dissolve at either pH 5.5 or 6. The systems demonstrated useful in vitro and in vivo behavior and may be a starting points for human clinical materials.

REFERENCES