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Extemporaneous preparation strategy for early phase clinical studies

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ABSTRACT

Extemporaneous preparations (EPs) of investigational drugs, which are compounded at the clinical study site by a pharmacist, are being increasingly used in early phase clinical studies to accelerate the development of new medicines. The successful application of EP strategies in clinical studies requires 'fit-for-purpose' formulation design and preparation processes, as well as administration procedures that are safe, flexible, cost-effective, and simple to adapt by a compounding pharmacist at the clinical site. DNS-7801 is a weakly basic investigational compound that exhibits a higher aqueous solubility at lower pH with its solubility dropping off precipitously with increase in pH. This phenomenon is known to result in potential risk of variable and decreased exposure *in vivo*. Combination of citrate buffer at pH 3.0 and hydroxypropylbetadex enabled formulation of DNS-7801 solutions that were stable as formulated and up on manipulation for oral administration. The solutions were compatible with apple juice, used to mask (blind) the potential taste differences between the placebo and DNS-7801 solutions when dosing study subjects. The oral administration of the solutions resulted in dose proportional C_{max}, $AUC_{0\text{-}24}$, and $AUC_{0-\infty}$ of DNS-7801 in non-elderly and elderly subjects. A key advantage of the use of an EP approach with DNS-7801 was the flexibility in dose selection that this approach offered because DNS-7801 concentration in the preparation and/or volume could be readily adjusted based on real-time cohort data.

1. Introduction

The pharmaceutical industry is under increasing pressure to accelerate the discovery, development, and delivery of new medicines while maintaining quality and keeping cost increases under control. First-in-human and other initial clinical studies in investigational drug development focus on gaining an early understanding of the safety, tolerability, and pharmacokinetic characteristics of a drug and are crucial for expedited 'go-no go' decision making. Given the high rate of attrition of investigational drugs in early phase development, practices which reduce the total time and effort expended prior to arriving at key early decision points can lower the cost of developing new drugs and may also accelerate the investigational new drug (IND) application process for getting novel drugs into the clinic.

Extemporaneously compounded oral preparations have historically been used when a required dose or dosage form is unavailable commercially or for individualized dosing (Allen, 2008; Dupuis et al., 2009; Ernest et al., 2012; Garg et al., 2011; Gupta and Khan, 2013; Lam, 2011; Nahata and Allen, 2008; Nunn et al., 2012; Pabari et al., 2012; Standing and Tuleu, 2005). As a result, in such instances these drugs are often prepared extemporaneously as oral liquids using commercially available tablets or capsules. The concept of extemporaneous preparations (EPs) has been widely used in pediatric practice due to its potential to provide age appropriate and easily swallowable liquid doses (Allen, 2008; Ernest et al., 2012; Gupta and Khan, 2013; Nunn et al., 2012; Standing and Tuleu, 2005). The concept is also being used for anticancer drugs typically available as solid dosage forms, such as tablets and capsules, which can be challenging for patients with difficulties in swallowing a tablet or capsule (Dupuis et al., 2009; Lam, 2011).

In recent years, EPs, which are compounded at a clinical site by a pharmacist, are being increasingly used in early phase drug development (e.g., Phase 1) and small scale clinical studies for new chemical entities (NCEs) (Clinicaltrials.gov, 2018). These preparations can be relatively simple such as solutions, suspensions, and powder filled capsules. More advanced preparations such as extemporaneously prepared matrix tablets and osmotic capsules have also been reported in the literature (Thombre et al., 2014).

Use of 'fit-for-purpose' liquid EPs during early phase and small scale clinical studies offers several advantages (Mathews et al., 2013). While there are also some potential disadvantages (Table 1), these liquid EPs importantly enable rapid development of an investigational compound,

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Table 1
Potential advantages and disadvantages of using extemporaneously prepared oral liquids in early phase and small scale clinical trials.

Advantages	Disadvantages
Greater dosing flexibility by varying drug concentration in oral liquid and/or dosing volume	Availability of fewer clinical sites that can accommodate extemporaneous preparation handling and have trained pharmacy staff
Greater decision making flexibility: permits to wait for pharmacokinetic/safety data from an earlier cohort before making a decision on oral liquid concentration/dosing volume for the next cohort	Require dose preparations multiple times to accommodate multiple clinical study cohorts, multiple dosing schedule for multiple ascending dose (MAD) studies, and shorter product usage-life
Better suited for low (sub-mg to mg) doses, with acceptable dose uniformity, especially in case of oral solutions	Greater risk for preparation/dosing errors
Lower costs: reduced API needs, no multiple strength GMP clinical trial material manufacturing and packaging, no long-term stability, no pre- and post-use equipment cleaning steps	Need for taste masking for blinding purpose
Shorter time to arrive at final formulation as it requires only short-time stability, no process scale-up/optimization	Microbial contamination risk
Easier to swallow	Pharmacokinetic bridging study generally needed before starting Phase 2, resulting in increased costs and lengthened timelines
Potential for earlier IND filing	Potential bioinequivalency challenges between the early phase oral liquid and later phase solid dosage form, especially for poorly soluble compounds (BCS Class II and IV)
Simpler program termination process, if warranted	

more simplified termination of development efforts for compounds that will not be progressed further, and reduction of resources spent on full development, i.e., manufacture of multiple strengths of clinical trial materials under Good Manufacturing Practices (GMP) and execution of long-term stability studies. Unlike fixed-strength solid dosage forms, such as tablets and capsules, liquid EPs offer flexibility in dose selection because compound concentration in the preparation and/or dosing volume can be readily adjusted based on real-time cohort data, which is important during early clinical evaluation where safety and therapeutic index are still being established (Mathews et al., 2013).

The concept of use of EPs derived from the commercially available tablets and capsules in pediatric practice (Allen, 2008; Ernest et al., 2012; Gupta and Khan, 2013; Nunn et al., 2012; Standing and Tuleu, 2005) and oncology (Dupuis et al., 2009; Lam, 2011) has been reported extensively. Those type extemporaneous formulations are usually prepared by simply crushing tablets or opening capsules from a commercial source and subsequently mixing with water or another diluent. PDA Technical Report No. 63 (Mathews et al., 2013) and United States Pharmacopeia (USP) Chapter ⟨795⟩ (US Pharmacopeia, 2017) provide compounders and pharmacists with quality and regulatory guidance for the extemporaneous preparation of formulations for dispensing and/or administration to humans or animals. Though it has been frequently mentioned in the literature and on the Food and Drug Administration (FDA) ClinicalTrials.gov website (Clinicaltrials.gov, 2018) the application and advantages of these preparations during early phase and small scale clinical studies for NCEs, detailed reports are scant. Unlike the EPs from a commercially available drug product, the EPs for NCEs being investigated for the first time in human require detailed planning and execution of formulations, preparation procedures, and precise clinical dose administration. The current manuscript reports in extensive details the design and execution of the EP strategy in the early phase clinical studies of an investigational compound, DNS-7801.

DNS-7801 is a phosphodiesterase type-1 (PDE 1) inhibitor, which is currently in Phase 1 development. The IND-opening first-in-human study, which was a randomized, double-blind, placebo-controlled, single-ascending dose (SAD) safety, tolerability, and pharmacokinetic study in healthy adult (including elderly) volunteers, utilized an oral solution formulation of DNS-7801 which was extemporaneously prepared at the Phase 1 clinical unit prior to dosing of each dose level cohort. In the current manuscript, we (a) describe the approach taken in the design of the liquid formulation of DNS-7801, including identifying potential oral solution compositions which are physically and chemically stable as formulated, as well as upon manipulation for administration to the clinical study subjects, (b) discuss in detail the extemporaneous preparation procedures (including color masking and taste masking) that were designed for implementation in a non-manufacturing environment (a Phase 1 clinical research unit) and are simple enough for the compounding pharmacist at the clinic site to easily follow in order to ensure product quality, patient safety, data integrity, and overall successful execution of the study, (c) present the first-in-human study design in which this approach has been employed, and (d) summarize the clinical pharmacokinetic results supporting the applicability of this methodology in early clinical development.

2. Materials and methods

2.1. Materials

The investigational compound, DNS-7801, was obtained from the GMP manufacturing process. Hydroxypropylbetadex, USP (Kleptose® HPB, Parenteral Grade, Roquette America Inc., Lestrem, France); citric acid, anhydrous, USP (Spectrum Chemical Mfg. Corp., Gardena, California); sodium citrate, dihydrate, USP (Spectrum Chemical Mfg. Corp., Gardena, California); D&C Yellow No. 10 (Sensient Colors, LLC, St. Louis, Missouri); and sterile water for injection, USP (Baxter Healthcare Corp., Deerfield, Illinois) were used in the preparation of the extemporaneous oral solutions. All the materials were tested and released as per the USP and in-house specifications. Commercially available apple juice (Apple Juice from Concentrate- Tree Top™) was used to dilute and taste mask the oral solutions before oral administration to the clinical study subjects.

Pyrex glass (borosilicate) media bottles with polypropylene screw caps (VWR International, Visalia, California) were used to prepare and store the oral solutions. BD amber oral dispensing syringes, 1 mL and 5 mL, with tip caps (Becton, Dickinson and Company, Franklin Lakes, New Jersey) and graduated medicine cups, 2 oz. (Medline Industries, Northfield, Illinois) were used to dispense and administer the oral solutions to the clinical study subjects. All the devices were used only once and disposed after each use to prevent any cross contamination.

Acetonitrile (HPLC grade, EMD Millipore, Billerica, Massachusetts); trifluoroacetic acid (reagent grade, JT Baker, Phillipsburg, New Jersey); and ultra-purified Milli-Q grade water (Millipore Corporation, Billerica, Massachusetts) were used for analytical testing. Biorelevant media used in the preparation of biorelevant fluids were obtained from Biorelevant.com Ltd. (London, UK). All the materials were used as received.

2.2. Methods

2.2.1. Screening of oral solution compositions

The preferred concentration of DNS-7801 in the oral solutions for the clinical studies was approximately 0.1 mg/mL–5.0 mg/mL. The variable concentration range of the compound in the solutions was