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Overcoming the Challenges of Low Drug Solubility in the Intravenous Formulation of Solithromycin

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ABSTRACT

Solithromycin is a fluoro-ketolide (a fourth-generation macrolide) antibiotic that has been undergoing clinical trials for the treatment of community-acquired bacterial pneumonia. In this study, development of the tri-amino acid–buffered solithromycin intravenous (IV) formulation was performed to minimize the occurrence of infusion-associated local adverse events (infusion-site pain or phlebitis) observed in patients who received the tartaric acid–buffered IV formulation with a lower buffered capacity during phase I clinical trials. Development of the tri-amino acids–buffered solithromycin IV formulation was achieved using a dynamic *in vitro* precipitation model. Computational modeling also supports the superiority of the amino acid-buffered formulation over the tartaric aid–buffered formulation.

Introduction

Solithromycin is a fourth-generation macrolide antibiotic that completed 2 phase 3 clinical trials (oral and IV to oral switch) for the treatment of community-acquired bacterial pneumonia (CABP).[1] Solithromycin, the first fluoro-ketolide used in human clinical trials, shows higher efficacy and has a broader spectrum than other macrolide antibiotics such as azithromycin and erythromycin.[2]

In addition to its oral formulation, solithromycin was formulated for IV infusion delivery to treat patients in an acute care setting. During an early phase I study, several patients receiving the IV formulation experienced infusion-site–related pain and phlebitis. This article describes the development of a solithromycin formulation that was designed to minimize the potential for drug precipitation on infusion which can cause infusion-site–related injuries.

Background

The structure of solithromycin is shown in Figure 1 below. Solithromycin, which has a low aqueous solubility at pH 7.4, is a dibasic compound with ionization constants of $pKa_1 = 3.94$, $pKa_2 = 9.44$. Having the 2 basic ionizable functional groups allows the use of pH control to increase the aqueous solubility of the drug to clinically relevant levels.

The total solubility (S_T) of a dibasic drug as a function of solution pH can be estimated using the exponential form of the Henderson-Hasselbalch equation.[3]

$$S_T = S_u\left(1 + 10^{pKa_2 - pH} + 10^{pKa_1 + pKa_2 - 2\times pH}\right) \quad (1)$$

where S_u is the aqueous solubility of the unionized form of the drug. Differences between Henderson-Hasselbalch–derived solubility data and data obtained experimentally are often due to aggregation of dug molecules[4] as well as the formation of insoluble salts of the drug and its counter-ion.[5]

During intravenous administration, the infusion solution of the formulation is injected into the blood stream which is naturally buffered at pH 7.4. Thus, on mixing with blood, a formulation

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0022-3549/

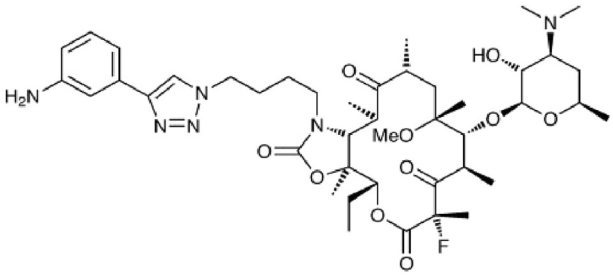

Figure 1. Structure of solithromycin.

containing a basic drug solubilized in a low pH solution will experience the processes of dilution and titration simultaneously. The effect of dilution on the concentration of a drug (C_{drug}) is linear and can be determined by the following formula[6]:

$$C_{drug(diluted)} = C_{drug} \times f_{form} = C_{drug} \times (1 - f_{blood}) \quad (2)$$

where f_{form} is the volume fraction of formulation and f_{blood} is the volume fraction of blood. A simple correlation between f_{form} and f_{blood} during IV administration can be done by considering matching the injection rate to a theoretical blood flow rate (5 mL/min) in the forearm vein. Assuming complete mixing of the blood and drug formulation, the relationship of f_{form} and f_{blood} can be expressed in Equation 3.

$$\frac{f_{form}}{f_{blood}} \approx \frac{r_{inj}}{r_{bloodflow}} \quad (3)$$

where r_{inj} is the injection rate of the formulation and $r_{blood\ flow}$ is the blood flow rate.

While the concentration of the basic drug is decreasing linearly due to process of dilution, the buffered blood will also titrate the pH of the formulation back to 7.4. According to Equation 1, a rapid increase in pH will cause the solubility of the basic drug (using a low pH to increase solubility) to decrease exponentially. If the simultaneous processes of dilution and titration exerted by the blood on the formulation causes the solubility of the drug to fall below the drug concentration during mixing, a supersaturated solution is formed. This may ultimately lead to drug precipitation.

Drug precipitation that occurs when IV formulations are mixed with blood can cause infusion-site phlebitis.[7] In initial IV formulation development studies, the solubility of solithromycin was determined in many aqueous solutions which contained organic co-solvents, surfactants, cyclodextrins, and buffers. Solithromycin showed good solubility in low concentrations of tartaric acid solutions in lower pH range. Therefore, a lyophilized formulation (250 mg/vial) with tartaric acid and mannitol at pH 3.8 was developed for phase I clinical studies. Early in the phase 1 IV formulation development program, a lyophilized solithromycin tartaric acid-mannitol formulation, diluted in 0.45% sodium chloride to a concentration of 1.6 mg/mL and infused as single doses of 25 to 1000 mg and as multiple doses of 50 to 200 mg was evaluated. At higher single doses and multiple doses of 200 mg, several subjects experienced infusion-site–related pain and phlebitis. Precipitation of solithromycin due to the change on infusion from a low pH range (4 to 6) to a physiologic pH of approximately 7.4 was considered a potential contributor to the infusion-site reactions. Following these initial studies, extensive experiments were conducted to design the optimal infusion solution for solithromycin.

Materials and Methods

Materials

Solithromycin-free base and lyophilized product (tartaric acid-mannitol formulation) was provided by Cempra Pharmaceuticals, Inc. In addition, all buffers used in the formulations of this study were purchased from Ajinomoto and Sigma-Aldrich by Cempra and were of United States Pharmacopeia or National Formulary grade. All formulations tested were prepared according to instructions provided by Cempra and filtered using a 0.45-μm Polytetrafluoroethylene Acrodisc® syringe filter (Pall Life Sciences) before testing. Isotonic Sorensen's phosphate buffer (ISPB pH = 7.4), was prepared

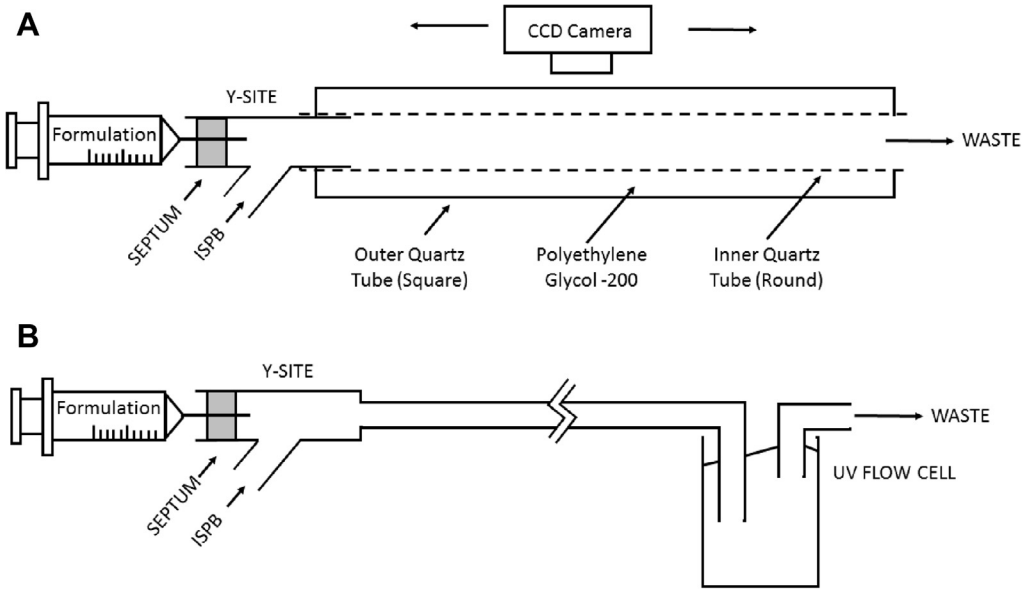

Figure 2. Illustration of the dynamic *in vitro* device used by Evans et al (a) and Johnson et al. (b).