Comparing dissolution, solubility, and trans-membrane flux of nanoparticle formulation of griseofulvin with micronized and un-processed drug

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INTRODUCTION

Recently, developed Zero Intercept Method (ZIM) enabling, for example, in situ concentration monitoring of free API being released from nanoparticles was applied to determine solubility and dissolution of griseofulvin formulated as nanosuspension. The effect of formulation was also studied through minimized dissolution-permeability setup (µFLUX) to determine if nanosuspension formulation improves flux of the griseofulvin through artificial membrane.

MATERIALS AND METHODS

Uniaxial pressure of griseofulvin (GSF-Uttreted) was purchased from Sigma (St. Louis, MO, USA); see chemical structure in Figure 1. GSF-Micronized was prepared by jet-milling technology using powder of GSF purchased from Chirag Pharma (Raejun NC, USA). GSF-Nanospension was prepared by suspending GSF-Micronized (10% w/w) in a mixture of HMPA (2.5% w/w), SLS (0.5% w/w) and deionized water. GSF-Nanospension was prepared with wet-milled milling technology using suspended GSF-Micronized (10% w/w) in a mixture of HMPA (2.5% w/w), SLS (0.2% w/w) and deionized water.

The particle size of the GSF-Micronized was characterized using laser light diffraction. For the nanosuspension the dynamic light scattering was used for particle size determination. Morphology of the samples was studied using scanning electron microscopy (SEM).

The flux of different forms of GSF through artificial membranes was studied in situ using the µDISS Profiler™ (Pion, Billerica, MA, USA). Figure 2). equipped with µFLUX apparatus (Pion, Figure 3); an add-on module consisting of four pairs of temperature controlled side-by-side permeability chambers mounted on top of the testing platform.

RESULTS AND DISCUSSION

Zero Intercept Method (ZIM™)

When nanoparticles are present in the solution they absorb light² effectively acting as another component in addition to the dissolved API. To determine concentration of dissolved API in the presence of nanoparticles a special analysis of the second derivative spectrum (Zero Intercept Method (ZIM)) was developed. In ZIM, the standard curve for nanoparticles is built by plotting 2nd derivative absorbance values at wavelengths where values of 2nd derivative spectra of dissolved API, 

\[A_{\text{2nd derivative}}(\lambda) = \text{constant} \]

equal to 0 (intercepts wavelength, Figure 6) versus amount of nanoparticles added. At these wavelengths, only nanoparticles contribute to the second derivative spectrum, i.e.,

\[A_{\text{2nd derivative}}(\lambda) = A_{\text{n}}(\lambda)\]

The plot of \(A_{\text{2nd derivative}}(\lambda)\) versus load of API from nanosuspension (µg/mL) will consist of horizontal portion where all nanoparticles dissolve and a sloping line when both dissolved API and nanoparticles present in the system, but only nanoparticles contribute to the derivative spectra, see Figure 7 for GSF-Nanospension.

The concentration of dissolved GSF in the presence of GSF-Nanospension was determined in situ by ZIM for 8 measurement channels and comparison with measured data done by equilibrium dialysis.

GSF-Nanospension Solubility in Water by ZIM

Average 13 ± 1.2 µg/mL

The slope of profiles, if doct shown in Figure 9, can be used to measure the flux of the GSF through artificial membrane.

Figure 10. Flux values measured using dialysis – time profiles in the nevirapin compartment (10 – 120 minute) with linear regression (equation 1) to create the profile of the time flux.

CONCLUSIONS

The study confirmed the ability of the ZIM to determine solubility of the nanoparticles in situ with no need for solid separation. Solubility of GSF from nanosuspension was the same as from powder forms.

Dissolution-permeability study of different forms of GSF suggested that microcrystallization of the GSF powder will not affect the absorption potential of the drug while creating nanosuspension of GSF may lead to improvement of its pharmaco-kinetic properties.

µFLUX apparatus offers potentials of in situ concentration monitoring by providing invaluable insight into effect of formulations on all three key physicochemical parameters: dissolution, solubility and flux of the material through membranes.

REFERENCES