Metaxalone Nanoformulation Utilizing SoluMatrix™ Technology

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ABSTRACT SUMMARY
iCeutica Inc. has developed SoluMatrix™ dry milling technology capable of producing stable drug particles in the sub-micron size range. This technology has been applied to the muscle relaxant metaxalone for the development of a 300 mg nanoformulated immediate release tablet dosage form with enhanced dissolution properties relative to commercial metaxalone products.

INTRODUCTION
It is estimated that at least 40% of active drug substances in development have performance limitations due to poor water solubility1,2. These limitations often lead to suboptimal properties such as poor bioavailability, lack of fed/fasted equivalence and difficulty in determining the optimal dose. By decreasing the drug particle size to less than 1 micron, the surface area and surface interactions are positively enhanced resulting in improved dissolution and an improved and more repeatable pharmacokinetic profile. However, the increase in surface energy present in nanometer-sized drug particles can result in spontaneous aggregation into a more thermodynamically stable state1. SoluMatrix™ technology allows for the production of stable nanometer-sized drug particles through a dry milling process in which the particles are stabilized by an inert matrix material comprising conventional pharmaceutical excipients. This process has been scaled up for the production of larger clinical and commercial scale batches. The technology has been used to develop an immediate release tablet formulation of metaxalone with improved dissolution properties relative to a conventional formulation.

EXPERIMENTAL METHODS
Sub-micron sized metaxalone drug particles were prepared by dry milling metaxalone drug substance (40%) together with lactose monohydrate and sodium lauryl sulfate in an attritor mill containing stainless steel grinding media. The total batch size was approximately 1 kg. Milled powder was discharged out the bottom of the mill and collected for analysis and further processing. The size distribution of the milled metaxalone particles was measured using a Malvern Mastersizer 3000 laser particle size analyzer equipped with a Hydro MV liquid sample cell module containing an aqueous dispersing medium. Moisture uptake of milled powder was studied by exposing the sample to a constant temperature of 40˚C and varying the relative humidity from cycles of 0% to 90% to 0% using a SMS Dynamic Vapor Sorption Analyzer. Powder was compressed into tablets with a dry granulation process. Briefly, the milled powder was blended with binder, disintegrant, and lubricant, and then converted into free-flowing granules using a roller compaction system (TFC-Lab Micro, Freund Vector). These granules were blended with additional disintegrant, binder, and lubricant and compressed to yield tablets of 300 mg potency. These tablets were tested for content uniformity, impurities and dissolution at initial, 2 week and 4 week time points. Stability conditions were 25˚C/60%RH and 40˚C/75%RH. Physical properties such as hardness and friability were also determined. Dissolution of the 300 mg metaxalone SoluMatrix™ tablets was compared to commercially available 800 mg metaxalone tablets. Dissolution was done in a Sotax Dissolution Apparatus with 1000 ml of 0.01 N HCl (pH=2) at 37˚C using Type 2 Apparatus (paddle) set to a rotational speed of 100 rpm. Aliquots of the dissolution test solutions were
filtered and analyzed using an in-line UV spectrophotometer at a detection wave length of 271 nm.

RESULTS AND DISCUSSION
The nanoformulation of metaxalone shows a significant reduction in particle size relative to the unmilled metaxalone (Fig. 1). The Dv10, Dv50, and Dv90 of the milled metaxalone each show a >100 fold decrease in magnitude relative to the unmilled metaxalone (Figure 1, Table 1).

![Figure 1](image1.png)

**Figure 1:** Particle size distribution (PSD) of milled vs. unmilled metaxalone

<table>
<thead>
<tr>
<th>Table 1: PSD Milled vs. Unmilled Metaxalone</th>
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<td>Dv10 (μm)</td>
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<tr>
<td>Unmilled</td>
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<td>Milled</td>
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Dynamic vapor sorption shows moisture uptake of less than 0.8% and little to no hysteresis between sorption and desorption curves indicating only surface absorption i.e. little to no bulk absorption.

Dissolution of the metaxalone nanoformulation tablets (Fig. 2) shows that 100% of the dose is dissolved in the first 60 minutes. This is in great contrast to the 800 mg commercial product which shows that less than 2% (10.8 ± 0.3 mg) of the drug is dissolved in the first 60 minutes. This result demonstrates the improved performance of nanoformulated tablets as compared to commercial tablets. Dissolution of the nanoformulated metaxalone tablets shows no difference after 2 and 4 weeks under 25°C/60%RH and 40°C/75%RH conditions (Fig. 2).

Content uniformity was measured on 10 nanoformulated 300 mg tablets and demonstrated a % drug content of 98.5% of label claim and an acceptance value of 2.39 indicating a uniform distribution of drug between tablets.

Impurity studies were done on both tablets and milled powder. No significant increase in impurities was seen over the 4 week stability study.

![Figure 2](image2.png)

**Figure 2:** % Dissolution of 300 mg nanoformulated tablets at initial and 4 week stability time points compared to 800 mg commercial tablets. pH=2 (0.01 N HCl)

The physical characteristics of the nanoformulated tablets included a tablet hardness value of 144.8 ± 12 N and an acceptable friability value of 0.1752%.

CONCLUSION
Sub-micron metaxalone drug particles were produced using iCeutica’s dry milling SoluMatrix™ technology. The milled drug powder was successfully compressed into tablets with good physical properties and rapid dissolution in-vitro. The tablets also displayed acceptable stability after storage at both ambient and accelerated conditions for 4 weeks.

REFERENCES