

# Significant improvement of oral bioavailability of a poorly soluble compound

Jeffrey Grunkemeyer<sup>1</sup>,

Dorla Mirejovsky<sup>2</sup>

Luigi Lenaz<sup>2</sup>

Jacques Quinton<sup>1</sup>

Mathew Leigh<sup>1</sup>

Peter van Hoogevest<sup>1,3</sup>

<sup>1</sup> Phares Drug Delivery AG Muttens Switzerland <sup>2</sup> Spectrum Pharmaceuticals Inc. Irvine CA USA

<sup>3</sup> Adjunct Professor Department of Pharmacy University of Basel Basel Switzerland \*Corresponding author Tel: +41 (61) 317 9040 Fax: +41 (61) 317 9050 E-mail: info@phares.biz

## Introduction & Objectives

The extremely low solubility of some pharmaceutical actives can make oral delivery of such compounds very challenging. This challenge is even greater when the required dose is high.

The objective of this study was to significantly improve the bioavailability of a proprietary compound (Spectrum Pharmaceuticals, Inc.) which demonstrates extremely low solubility at the acidic pH values of the stomach. Coupled with improved bioavailability was the need to boost the dose and achieve higher drug loading in the delivery form. A final and equally important requirement was to develop a delivery form suitable for oral delivery using pharmaceutically acceptable excipients with production processes employing standard pharmaceutical manufacturing equipment.

## Methods

All excipients used were available in cGMP qualities and commercial quantities. Rat PK studies were conducted and bioanalysis was performed by RCC Ltd., Itingen, Switzerland, where plasma samples were taken using the automated AccuSampler®.

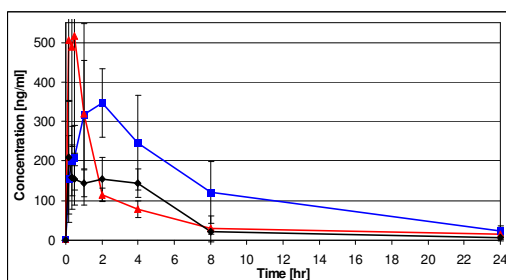


Fig. 1. Mean plasma profiles [ng/ml] ± S.D. (n = 4), of the test compound in male rats after oral administration formulations: -■- PNM and -▲- MLM, compared to -◆- the reference potassium salt solution.

## Results & Discussion

### Formulations:

#### 1) SupraVail® Membrane Lipid Matrix (MLM) / Phospholipid affinity of acid form:

In order to evaluate the possibility to use phospholipids to solubilize the acid form and prevent precipitation upon dilution the affinity of the acid form was determined with diacyl (VP100), monoacyl (VP814) phospholipids, as well as with a diacyl lipid with a higher level of negatively charged lipids (VP45). The phospholipid affinity was not very high at acidic pH. Nevertheless, at a drug to lipid ratio of 1 to 5, VP45 was able to solubilize 1.85 mg/ml. The VP45-based MLM formulation was dosed in liquid form.

#### 2) SupraVail® Porous Nano Matrix (PNM) / Highly porous adsorbents to maximize dissolution rate:

The dissolution rate can often be boosted by greatly increasing the specific surface area of the compound. This is achieved by coating highly porous (100-300 m<sup>2</sup>/g) and highly disperse (~300 nm diameter) adsorbents with the drug. Several silicate-based adsorbents were evaluated, and a drug loading of 30% by weight was achieved. The dry PNM formulation was suspended in water before administration.

#### 3) Control / potassium salt solution:

The potassium salt has a solubility ~100 mg/ml at pH > 7.0. After oral administration of salt, the acid is formed in the stomach. The acid form has a solubility of 0.030 and 1.41 mg/ml, at pH 1.0 and 7.0, respectively. As a reference formulation, the potassium salt was dissolved in water before oral administration.

### Pharmacokinetic Results:

The pharmacokinetic results are summarized in Figure 1 and Table 1. The Administration of the control (salt solution) resulted in a poorer bioavailability compared to the two formulation approaches.

The MLM formulation demonstrated the highest and most rapid C<sub>max</sub> in the study; this is consistent with the observation that phospholipids were able to solubilize some of the acid form, permitting a fraction of drug to behave as a pseudo solution and demonstrate rapid absorption, while the rest of the active was an insoluble precipitate. MLM formulations are most effective with compounds demonstrating a higher phospholipid affinity than the test compound, permitting 100% solubilization of the active and preventing precipitation.

The C<sub>max</sub> of the PNM formulation indicated a less rapid dissolution than the MLM formulation. Sustained plasma levels up to 8 hr after administration indicate significant absorption in the intestine. The higher pH in the intestine, the highly particulate nature of the PNM carrier as well as the high specific area of the drug substance together contribute to effective and prolonged drug absorption in the intestine. For compounds requiring higher drug loading and actives without a high phospholipid affinity, PNM is a viable formulation alternative.

	C <sub>max</sub> [ng/ml]	T <sub>max</sub> median [h]	Terminal t <sub>1/2</sub> [h]	AUC <sub>0-inf</sub> [ng h/ml]	AUC boost [%]
MLM	590.5	0.3	3.6	1350.3	146
PNM	367.2	1.5	4.2	3264.5	353
Control	257.3	1.1	4.2	924.2	—

Tab. 1. Pharmacokinetic parameters of the test compound after oral administration in rats.

## Conclusions

- For this particular poorly soluble compound, the bioavailability follows the following: PNM formulation > MLM formulation > salt form
- The AUC of the SupraVail® Porous Nano Matrix formulation was superior to the other two formulation strategies
- SupraVail® Porous Nano Matrix formulations can deliver drugs for absorption in the intestine
- Complete solubilization of lipophilic compounds using the SupraVail® Membrane Lipid Matrix can result in absorption similar to that of true solutions



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