



BIOEQUIVALENCE TRIALS SIMULATION TO SELECT THE BEST ANALYTE FOR ACETYLSALICYLIC ACID



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INTRODUCTION

The analyte (parent drug or metabolite) to be evaluated in bioequivalence trials is still today a controversial issue, with different solutions in EMA and FDA guidance: both guidelines generally recommended measuring the parent drug bioequivalence, but the situations in which are recommended the measurement of metabolite are different.

OBJECTIVE

The objective is to evaluate which analyte (parent drug or metabolites) is more sensitive to detect changes in the quality of the test medicinal product, in the case of acetylsalicylic acid (ASA).

MATERIALS AND METHODS

The semiphysiological model used (figure 1) has been adapted to ASA performance. The dose is orally administered, as a solid form in a single dose scheme. The solved ASA in lumen is absorbed into enterocytes. It has been established a limited time to allow the absorption process: the operative absorption time (OAT). After drug absorption, ASA is partially metabolized in the enterocytes (intestinal first pass metabolism), and in the liver (hepatic first pass metabolism). Once ASA reaches the systemic circulation, it is rapidly distributed in one compartment. The ASA is eliminated by intestinal and hepatic metabolism and in a small fraction by renal excretion. The SA is formed as result of ASA metabolism, it is distributed in one compartment and it is eliminated by renal excretion and by intestinal and hepatic metabolism producing SU. Finally, the SU is distributed in one compartment and it is eliminated unchanged by renal excretion.

Different scenarios depending on the in vivo dissolution constant of the test formulation and dose have been considered.

The studies were simulated using NONMEM VI.

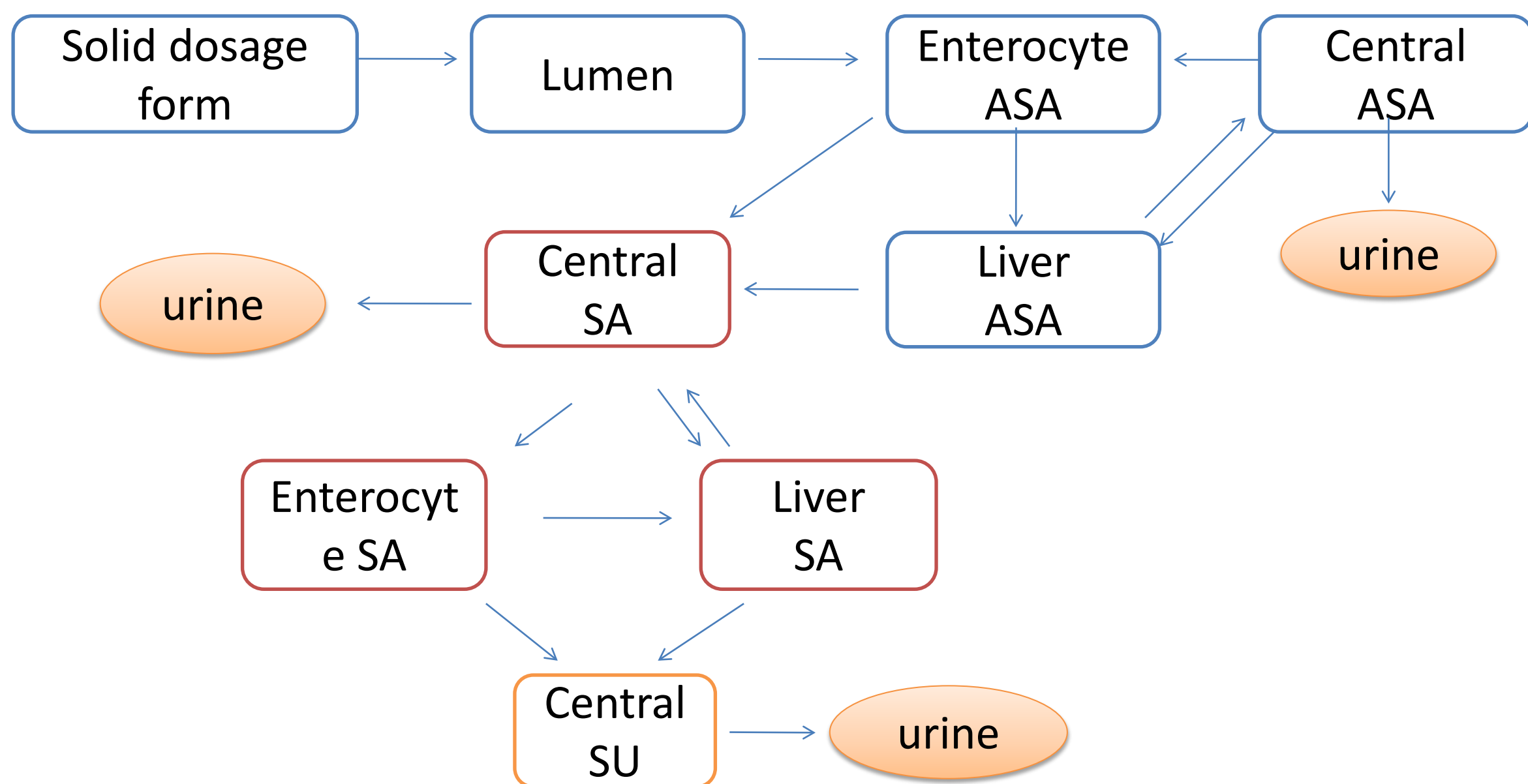


Figure 1. Schematical representation of the ASA's release, absorption and disposition.

RESULTS

The simulated population plasma concentration-time profile fits the experimental curves of the literature, so the model is considered validated. The analyte sensitive to the decline in quality is the ASA, and the decrease of ratios of AUC and Cmax is more noticeable with increasing dose (Figure 2). The percentages of bioequivalence when drugs are not bioequivalent is lower for the parent drug, and this percentage decreases with increasing dose. However, when there is a large difference between reference and test dissolution rate constant values, in case of 1000 mg of administered dose, AUC ratio of SA becomes more sensitive than ASA.

This is because at that dose, SA concentration in the enterocytes and liver is around Km (Km=12.42 mg/L), while at the other concentrations SA concentrations are much lower or higher than Km value (Figure 3).

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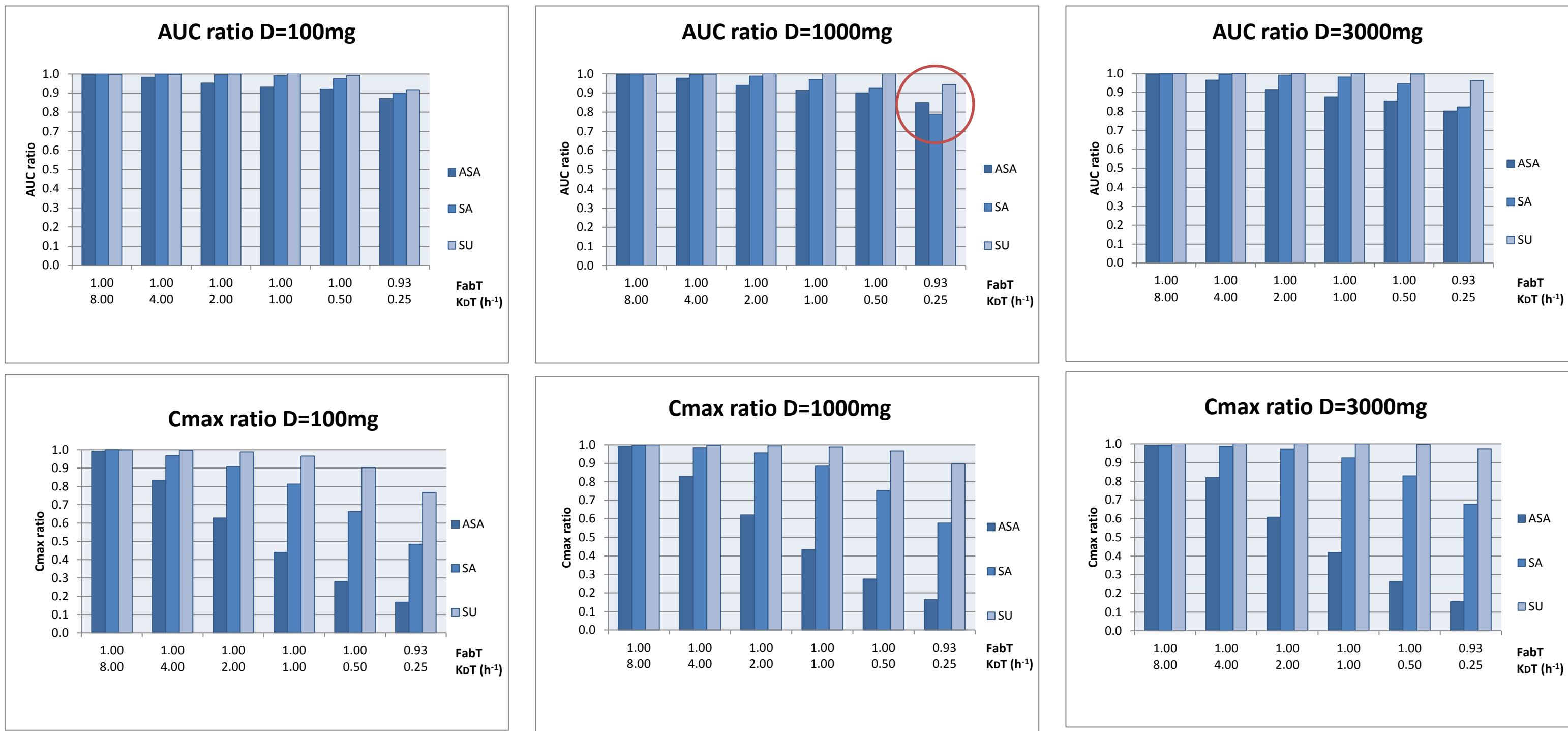


Figure 2. AUC (up) and Cmax (down) ratios of ASA, SA and SU obtained with the different KD of the test medicinal product and with the different absorbed fractions of the parent compound, at doses of 100, 1000 and 3000 mg of ASA.

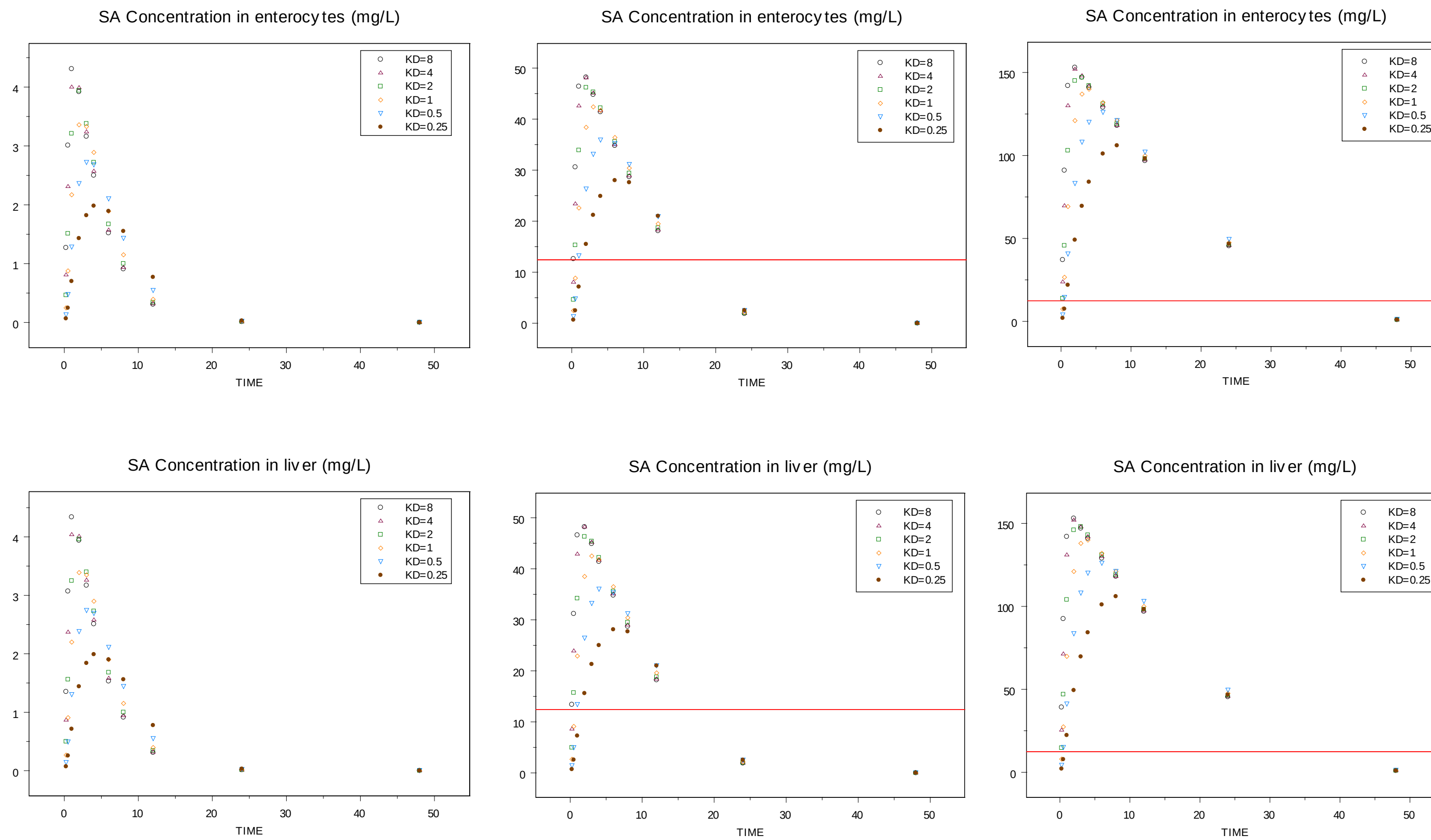


Figure 2. SA Concentrations (mg/L) in enterocytes (up) and liver (down), obtained for three dose levels: 100 mg (left), 1000 mg (center) and 3000 mg (right). The red line represents the Michaelis-Menten constant value (Km=12.42 mg/L)

CONCLUSION

The ASA is more sensitive than its metabolites to detect the decrease in pharmaceutical quality. However, the measurement of first generation metabolite provide additional information to the parent drug when its concentrations in the metabolic cells are around the Michaelis-Menten constant.