Predicting the Pharmacokinetics of Topically Applied Ketoprofen using Mechanistic Physiologically-based Pharmacokinetic Modelling

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Abstract

A Mechanistic Dermal Absorption Model (MechDermA) model has previously been developed [1] and included in the Simcyp Simulator platform. The model has recently been expanded to account for multi-dimensional "brick and mortar" skin structure and to handle various drug formulations (multi-phase multi-layer (MPML-)MechDermA. Performance verification of this model has included testing its ability to simulate local and systemic exposure of topically applied compounds of diverse chemical classes (acids, bases, neutral and ampholytes), formulations (gels, creams, ointments, patches), and clinical study designs (site and duration of application, single and multiple dosing).

Ketoprofen is one of the most widely used topically applied anti-inflammatory drugs. The MPML_MechDermA model was used to predict local and systemic exposure after topical application of ketoprofen, using basic physicochemical and systemic disposition parameters from previous studies; without fitting of any of the dermal model parameters.

Methods

A Physiologically Based Pharmacokinetics (PBPK) model was developed using physicochemical and intravenous clearance parameters for ketoprofen. The model was first used to simulate systemic PK following intravenous bolus [2] and infusion [3]. Having confirmed the model ability to provide a good prediction of intravenous pharmacokinetics, it was then advanced to dermal applications.

A systematic review was conducted, and 12 clinical studies were identified in which ketoprofen topical applications were used. Data were available for generic gel, fastum gel, solution, and patch formulations. Application sites included the back, knee and upper arm. Endpoints included concentrations in systemic circulation (plasma), as well as local at site of application (muscle, dermis, subcutis fat and synovium).

Clinical trial simulations were performed for each study, matching the age ranges, gender ratios and number of participants in each trial. Specific formulation parameters were incorporated wherever possible including formulation pH, viscosity and vehicle molar volume. Fastum and generic gel were represented as emulsion as they are emulsion gels. The droplet diameter for each formulation were included, which are used to calculate the permeation of the compound between dispersed and continuous phases, which has an impact on the amount available for skin absorption.

An evaporation model was included for the solution formulations. This has a dynamic impact on the rate of absorption. As volume of the vehicle reduces, the concentration of the solution left behind increases. The evaporation rate was predicted in Simcyp using a mechanistic model based on the vehicle vapour pressure and air velocity.

Results

Of the 12 clinical studies simulated, nearly all of them gave reasonably good prediction of the observed clinical data. This included capturing the effect of the site of application (due to local skin physiology), different formulations, and both systemic and local concentrations.

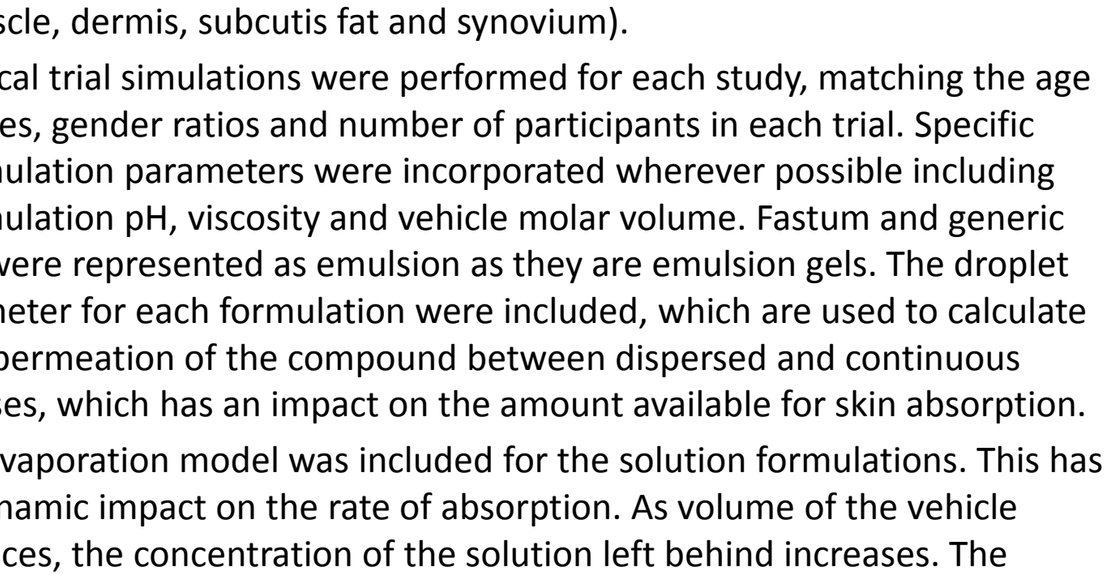


Figure 1. Clinical trial simulation of multiple applications of Fastum gel (Ballerini 1986) Left: mean and 95% prediction intervals, Right: individual simulations. The model captures the large observed variability between individuals.

Results (cont)

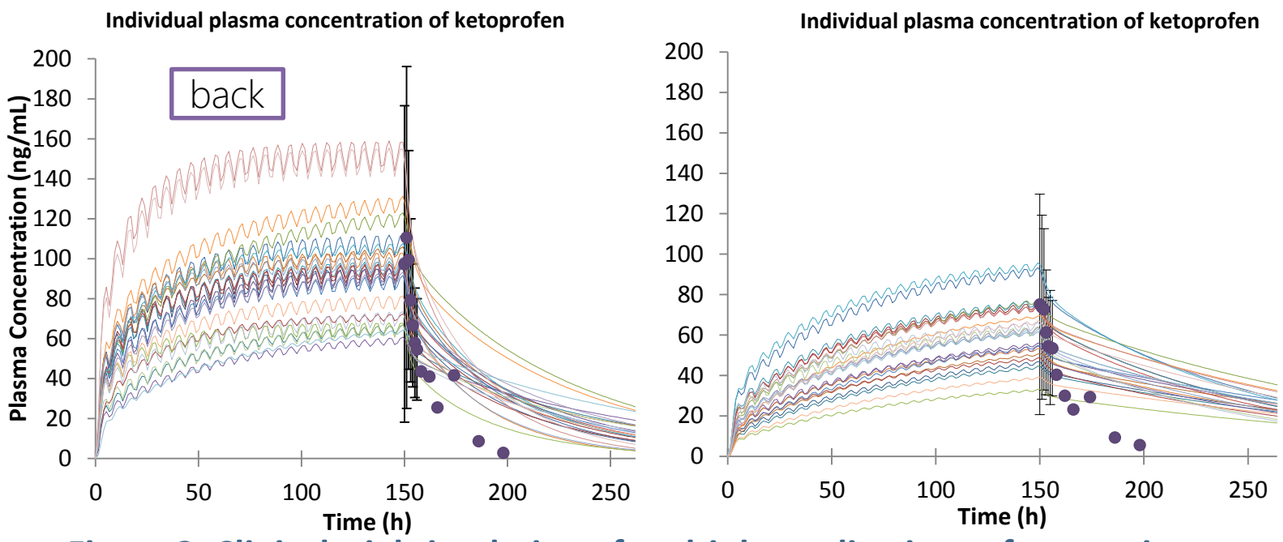


Figure 2. Clinical trial simulation of multiple applications of a generic ketoprofen gel with different application sites (Shah 1996). The model correctly captures differences in exposure and variability between application sites, as a result of local skin physiology.

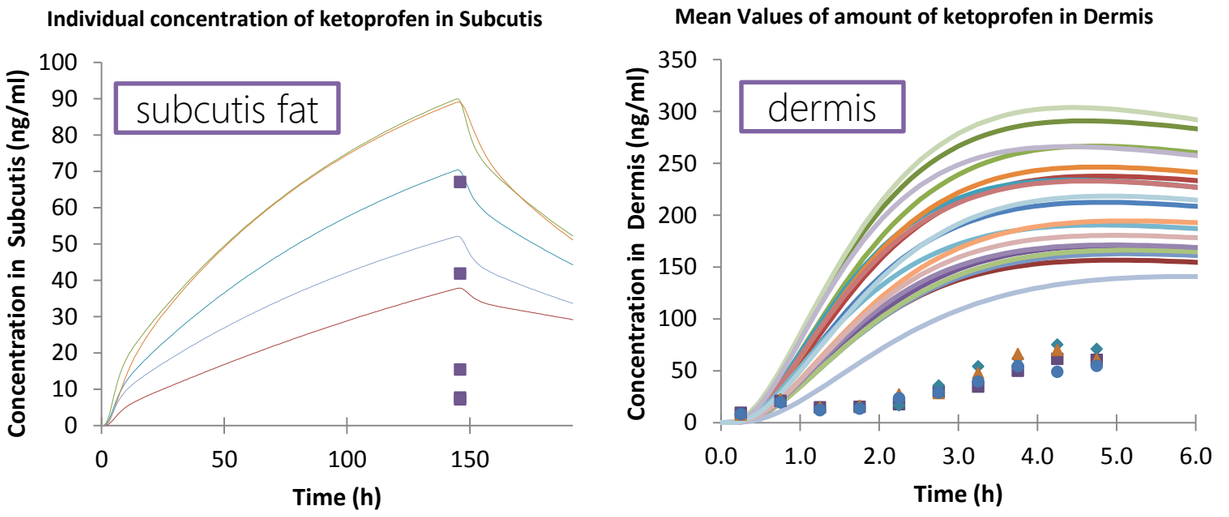
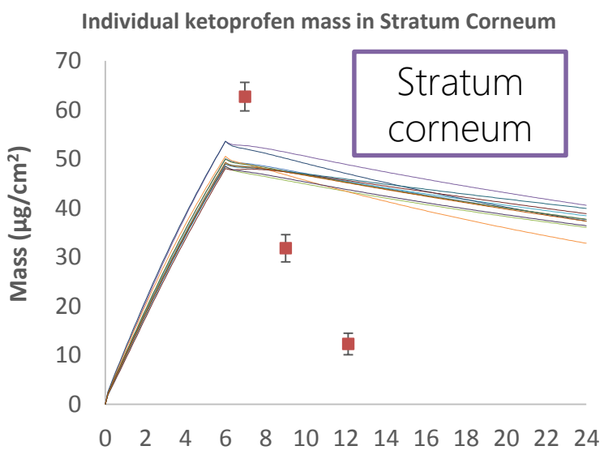


Figure 3. Prediction of local tissue concentrations from single applications of ketoprofen patch (left) (Osterwalder 2002) and fastum gel (right) (Tettey-Amlalo 2009)

Even in the worst performing cases, where some aspects of the kinetics of the formulation was not captured due to unavailability of input data, the prediction of the extent of exposure was well within observed range. The results show mechanistic PBPK can benefit the topical drug development however the suitable inputs to parameterize the model are crucial to accurately predict the dermal drug disposition.

Figure 4. Prediction of mass in the stratum corneum following application of a generic ketoprofen gel. Clearance from the straum corneum is underpredicted. The model could be further improved by optimising formulation parameters. Even in this example, the overall extent of exposure is well predicted.



Conclusions

The MPML-MechDermA model as implemented within the Simcyp simulator (V17) was able to predict dermal absorption of ketoprofen from various application sites. Absorption is affected by both the local skin physiology and drug-dependent parameters; including formulation-specific effects, such as viscosity, pH, and the mean diameter of droplets.

References

Ballerini 1986, Int J Clin Pharm Res VI(1) 69-72., Puglia et al. 2008, International Journal of Pharmaceutics 357, 295–304., Osterwalder et al. 2002, Arzneim.-Forsch./Drug Res. 52, No. 11, 822–827., Shah et al. 1996, Pharm Res 13(1).,Tettey-Amlalo 2009, EJPS 36, 219–225.

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