



A Population Pharmacokinetic Study of Salmeterol in Asthmatic Patients Using Two Dry Powder Inhalers

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Objectives: To apply population pharmacokinetic (PK) modeling in order to describe the concentration-time (C-t) profile of salmeterol (SAL) in asthmatic patients after administration of two dry powder inhalers: the multi-dose (Fluticasone / Salmeterol via Diskus® 250/50 mcg/inhalation, Reference device) and a novel single-dose device (Fluticasone / Salmeterol via Elpenhaler® 250/50 mcg/inhalation, Test device).

Methods: SAL plasma C-t data were obtained from a single dose, two-sequence, two-period (2x4) bioequivalence study comparing two dry powder inhalers Test (T) and Reference (R) in 48 asthmatic subjects under fasting conditions. Non-linear mixed-effect modeling was applied to the C-t dataset of the afore mentioned study. Activated charcoal was not co-administered, leading to absorption of the SAL from both the lungs and the gastrointestinal (GI) tract. A pharmacokinetic model capable of describing the parallel lung and GI absorption was developed. The C-t data of SAL were fitted to one- and two-compartment PK models assuming first order elimination kinetics. The relative fraction of dose absorbed through the GI (R_{GI}) was set as a parameter estimated by the optimization process. Different residual error models (additive, proportional, combined, and exponential) were tested. The ‘period’ (i.e., occasion) and ‘treatment’ (i.e., T or R) effects were set as covariates in the structural model. Demographic characteristics were also evaluated as potential covariates. The entire work was implemented in Monolix v.4.3.

Results: A total of 45 subjects completed the study and were included in the PK analysis. **Fig. 1** shows the comparative mean plasma C-t profiles of SAL for the T and R products. A biphasic time course of the drug was observed, which indicates the presence of a parallel pulmonary and gastrointestinal absorption of SAL.

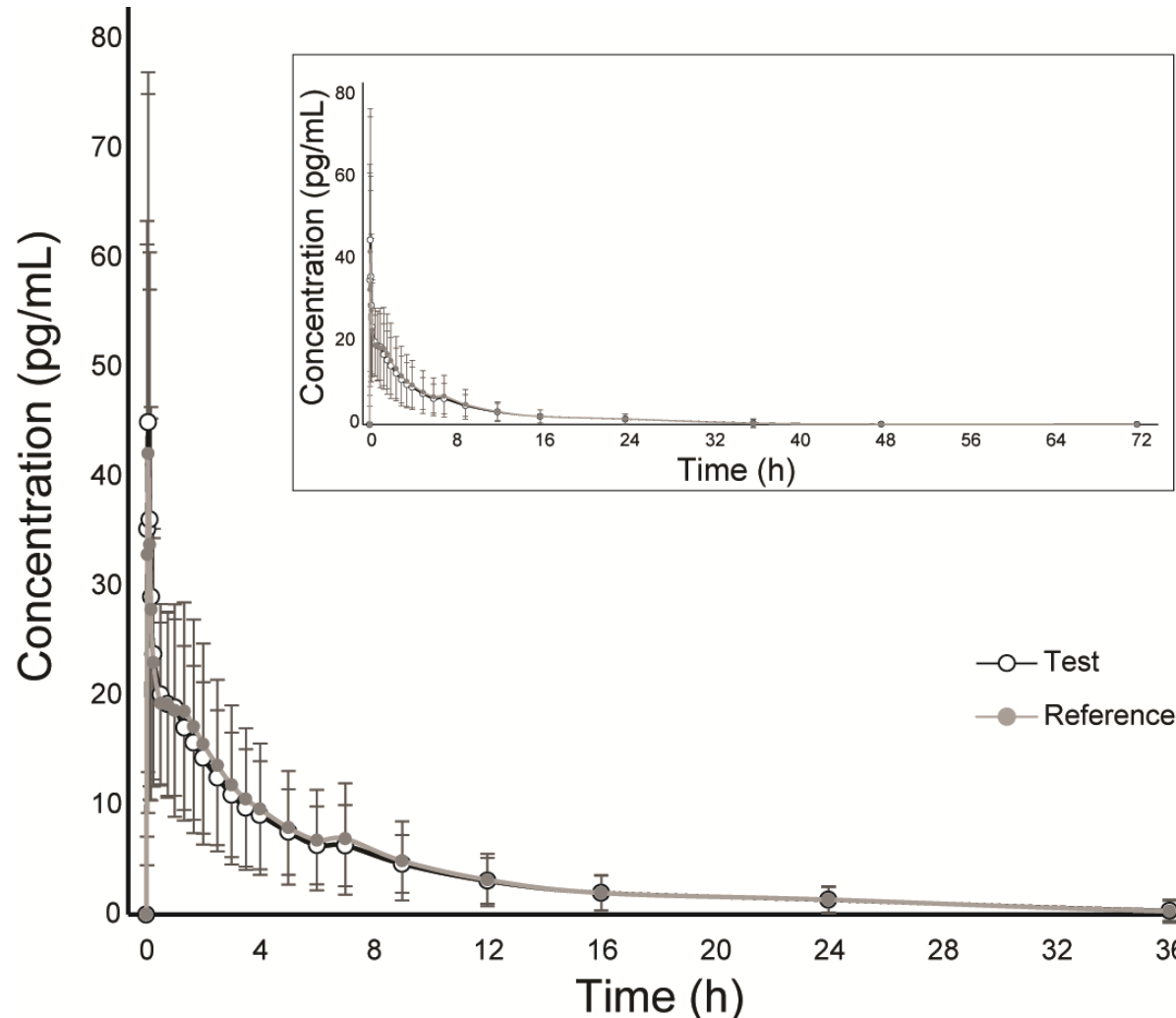


Fig. 1. Mean plasma concentration profiles of salmeterol for the test and reference dry powder inhalers.

An Mlxtran code, describing the parallel pulmonary and GI absorption was developed. SAL plasma concentrations were best described by a two-compartment disposition model combining two parallel absorption processes: a first order absorption from the GI and a very rapid absorption (like IV bolus) from the lungs. Elimination was considered to take place in the central compartment following first order kinetics. A proportional error model led to the optimum performance. **Fig. 2** is a schematic representation of the SAL pharmacokinetics following inhaled administration.

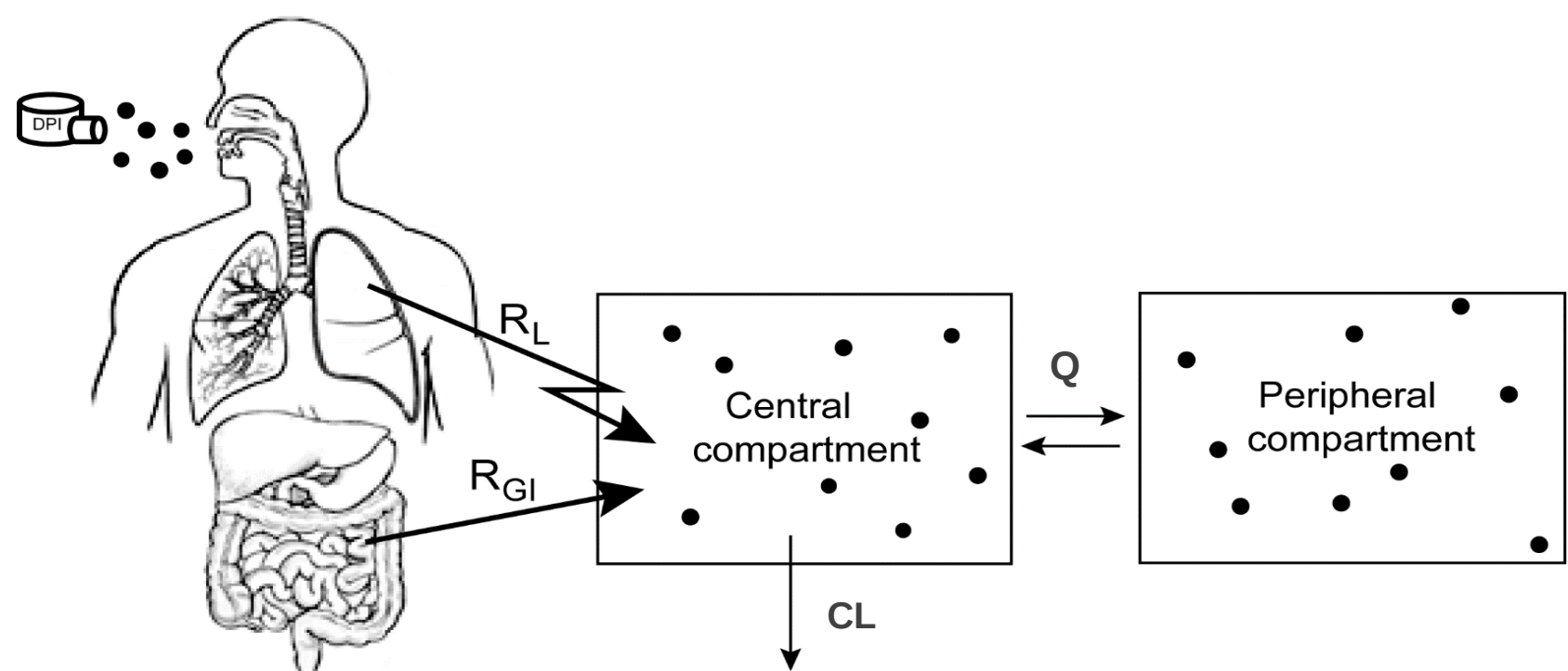


Fig. 2. Schematic representation of the two-compartment model of SAL describing the complex absorption (from lungs and GI) after inhaled administration.

The estimates of the population parameters and their statistics are listed in **Table 1**. The estimated R_{GI} value was found equal to 85%, which suggests a high gut deposition of SAL. Gender was found to be a significant covariate for clearance (CL/F). Male subjects showed 26% higher clearance compared to females. Body weight was found to be a significant covariate for the volume of distribution of the central compartment (Vc/F). A 10 % increase in body weight will result in a 24 % increase in Vc/F.

Table 1. Estimated population pharmacokinetic parameters for SAL.

Parameter	Mean (RSE%)	BSV% (RSE%)
Ka (h ⁻¹)	0.325 (8)	58.31 (8)
R _{GI}	0.85 (2)	12.95 (8)
CL/F (L/h)	408 (9)	45.41 (10)
Vc/F (L)	218 (13)	79.81 (12)
Vp/F (L)	2,970 (13)	83.60 (5)
Q/F (L/h)	339 (10)	65.96 (8)
Covariate effects		
Gender on CL/F	- 0.309 (34) (p = 0.003)	-
Weight on Vc/F	0.021 (45) (p = 0.027)	-
Residual error model		
b	0.16 (1)	-

The derived population PK model was capable for describing adequately the plasma C-t data of SAL (**Fig. 3-5**). All the obtained goodness-of-fit criteria and the diagnostic plots reveal that the final PK model exhibits adequate predictive ability.

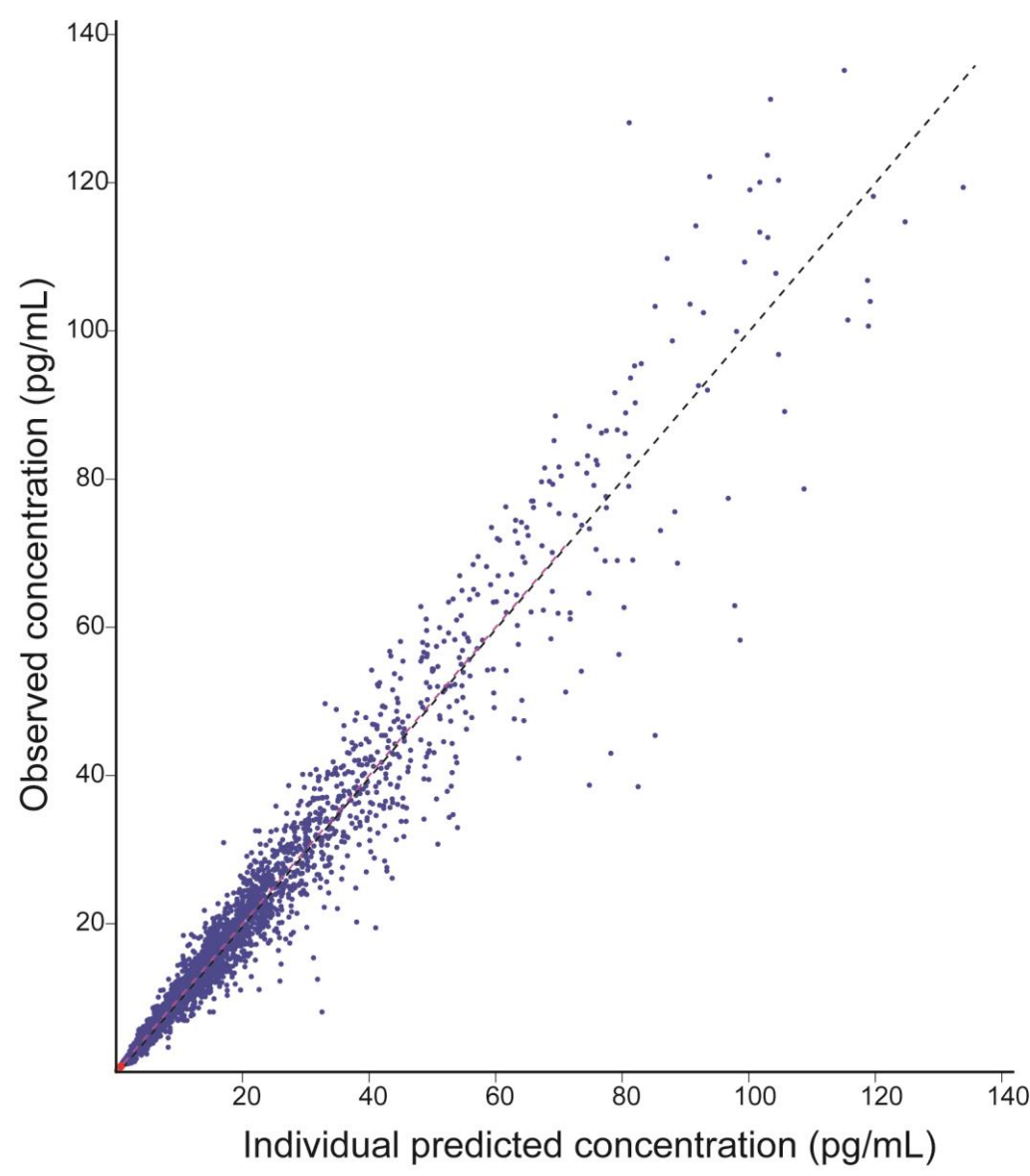


Fig.3. Individual predicted vs. observed plots for fluticasone and salmeterol.

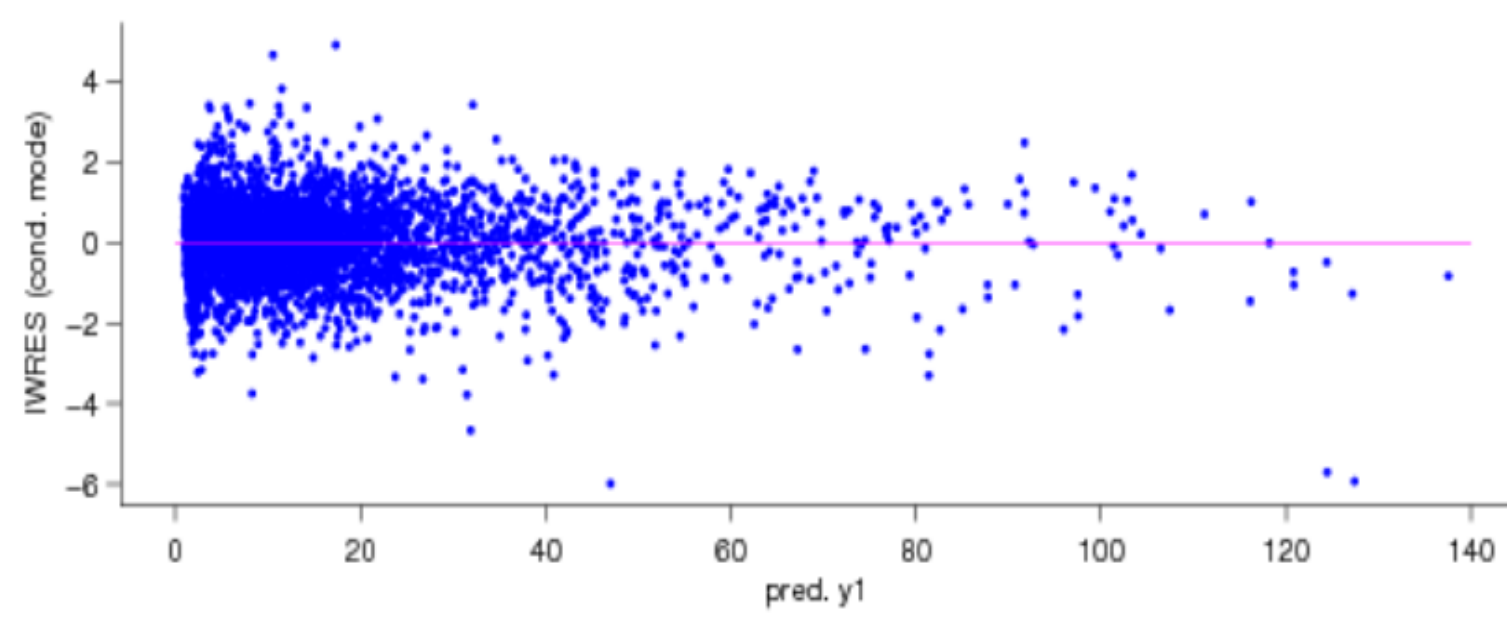


Fig.4. individual weighted residuals (IWRES) versus the individual predicted concentrations (IPRED)

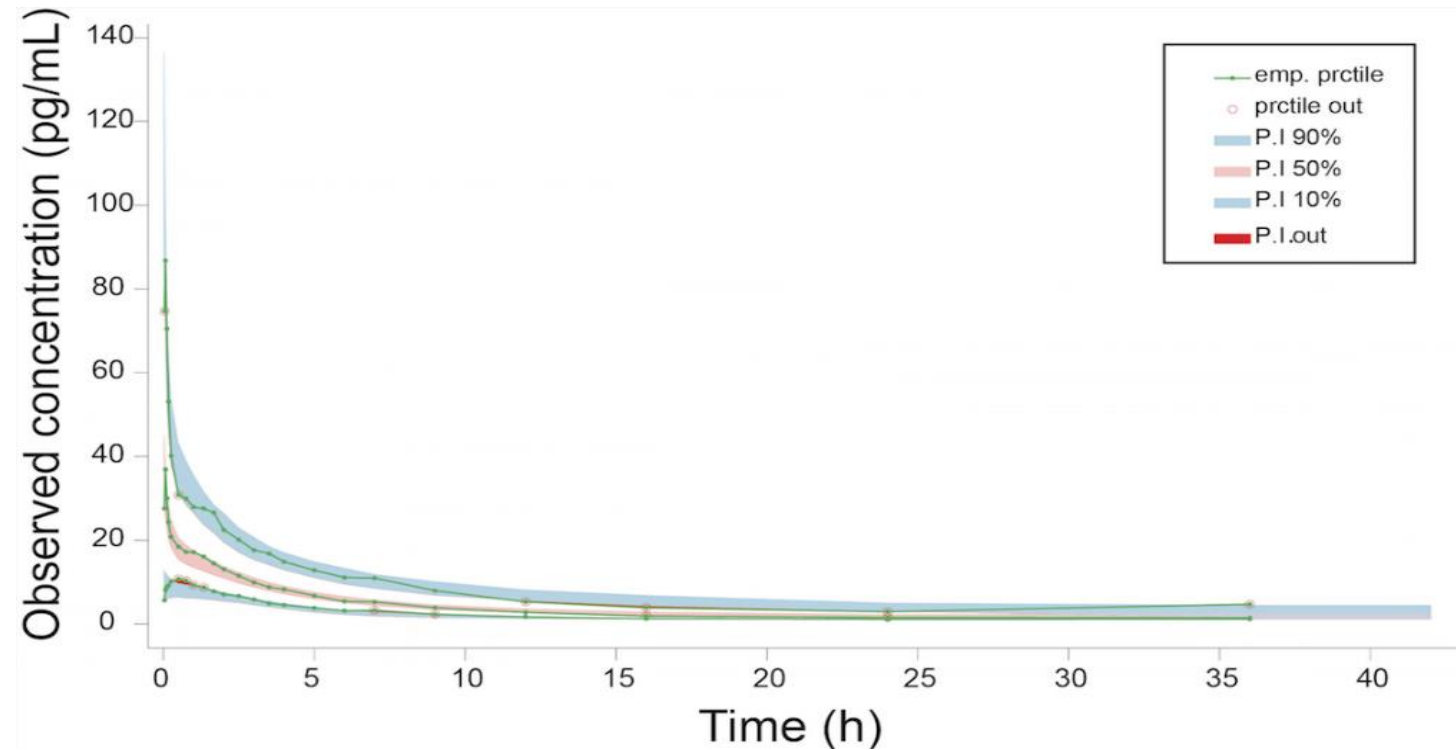


Fig.5. Visual predictive check (VPC).

Conclusions: The population PK analysis showed that a two-compartment PK model, with parallel (GI and lung) absorption describes successfully the C-t profile of SAL in asthmatic patients. A 85% of the inhaled dose of SAL was estimated to be deposited in the GI tract. Significant covariates affecting the pharmacokinetic parameters were identified. Women were found to exert less capability in eliminating SAL than men, while volume of distribution of the central compartment was shown to increase as body weight increases.

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Key: Ka: first-order absorption rate constant; R_{GI} : relative fraction of dose absorbed from the GI; Vc, Vp: volume of drug distribution of the central and peripheral compartments; Q: inter-compartmental clearance; CL: clearance; F: bioavailable fraction of dose; BSV(%): Between subject variability; RSE(%): percent relative standard error.