A quantitative structure-permeability relationship model for split-thickness skin absorption, reasoning for the choice of the database.

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Introduction

. The skin is the largest organ in the human body, protecting the body from xenobiotic invasion.

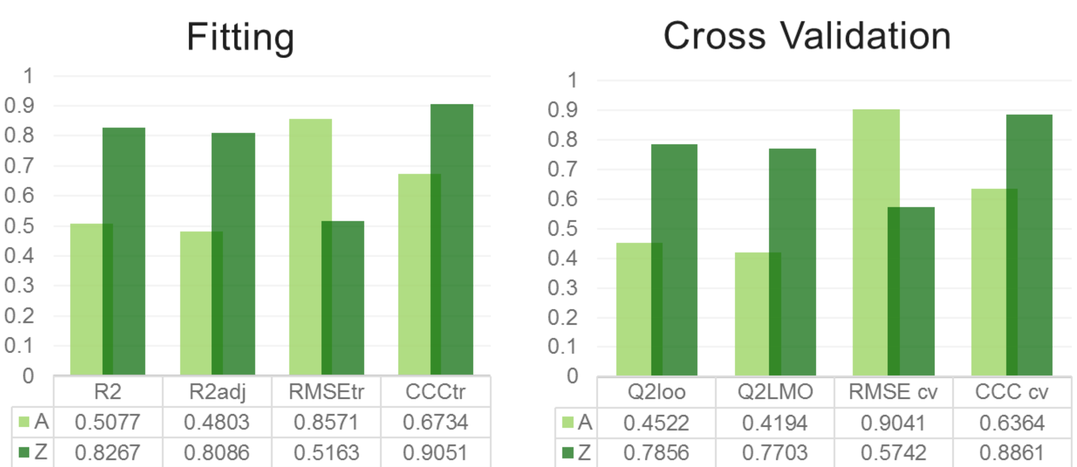
- Local and systemic drugs may be administered through the skin, therefore there is the need to measure the permeability of the skin.
- The use of *in vivo* or *in vitro* techniques is time-consuming, moreover, it is not possible to assess the permeability of compounds not yet synthesised.
- An alternative option can be the development of Quantitative Structure-Permeability Relationships (QSPRs).
- Knowing that permeability can be affected by different experimental conditions, the aim of this study is to build a QSPR based on uniform and consistent experimental conditions, but with a significant database size.

Methods

. Two different databases were compared: the first one, the database Z, was obtained only from Zhang et al (3), the second one, the database A, was created from multiple literature sources, fulfilling the following conditions:

- Data (log Kp values) were obtained by an *in vitro* diffusion system;
- The membrane was human stratum corneum and viable epidermis;
- The donor solvent was an aqueous solution;
- No permeation enhancement technologies were used;
- No association with other chemicals were considered.

- The geometrical structures of all the compounds retrieved were optimized with MM2 forcefield and common 1D-, 2D-, 3D- descriptors, and fingerprints were generated.
- Both the datasets were homogeneously split in training and test set with a ratio of 4:1.
- A wide range of Multi Linear Regression models were built using a stepwise forward selection method.
- The calculation was prolonged until 7 descriptors, the 10th fold of the smallest training set.
- The models selected were validated computing fitting, internal validation, and external validation parameters. For each of these parameters category a desirability function was calculated ($MCDM_{fit}$, $MCDM_{cv}$, and $MCDM_{ext}$, $MCDM_{all}$) according to the Multi-Criteria Decision Making (Keller et al., 1991).



	R2	R2adj	RMSEtr	CCCtr
A	0.5077	0.4803	0.8571	0.6734
Z	0.8267	0.8086	0.5163	0.9051

	Q2loo	Q2LMO	RMSE cv	CCC cv
A	0.4522	0.4194	0.9041	0.6364
Z	0.7856	0.7703	0.5742	0.8861

	R2ext	RMSE ext	CCC ext
A	0.5859	0.8223	0.6931
Z	0.7383	0.6304	0.8579

	MCDM fit	MCDM cv	MCDM ext	MCDM all
A	0.5727	0.5194	0.5382	0.543
Z	0.8563	0.8096	0.734	0.7984

Figure 2 Statistical values for the two different databases considered.

Results and Discussion

. Multiple permeability constant (Log K_p) values (304) for 186 different compounds were collected, and the descriptors for 182 compounds were generated (database A). Among them, 96 compounds constituted the database Z.

- For the compounds with more than one permeability data the average has been calculated and 14 compounds with standard deviation above 0.5 were excluded. The response distribution of each training and test set is shown in Figure 1.

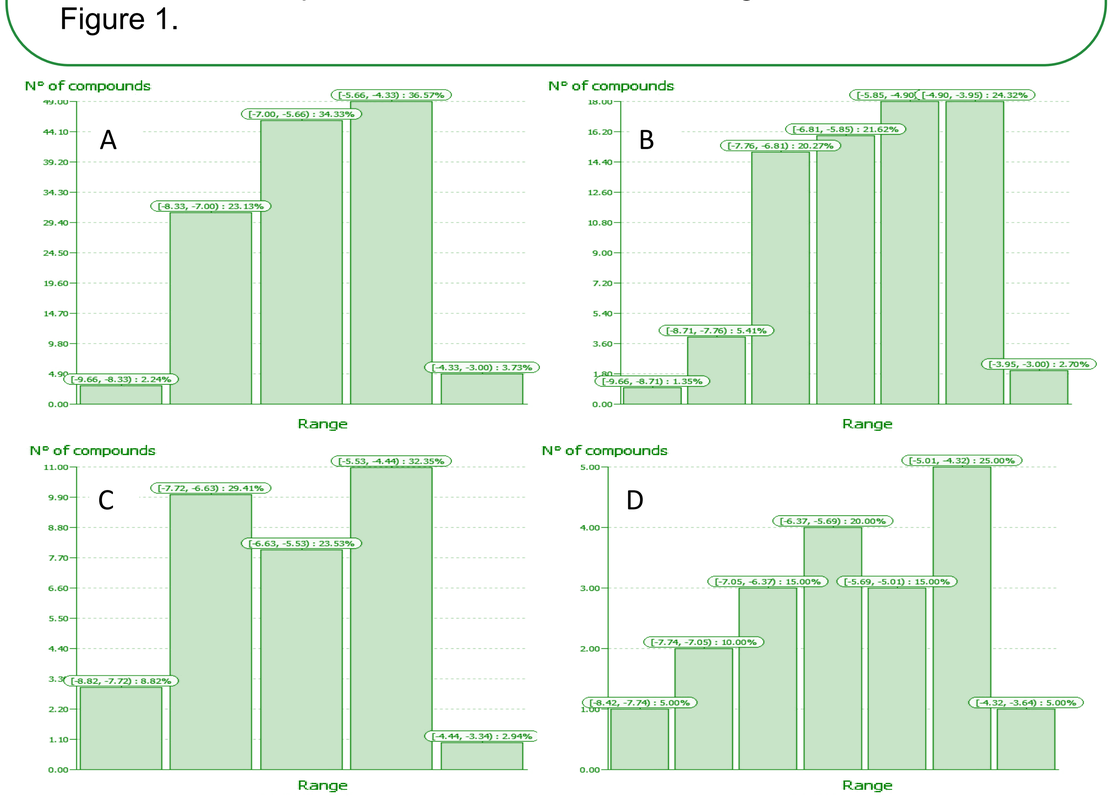


Figure 1 Test and training set response distribution. A) Training A, B) Training Z, C) Test A, D) Test Z.

- The fitting, cross validation, external validation and Multi-Criteria Decision Making parameters are shown in Figure 2. According to the values retrieved, the model built with the database A, originated from multiple experimental sources, is not considered predictive, contrary to database Z.
- Figure 3 shows the predicted Log Kp vs the expected endpoint for the training and the test set of each database. Among the descriptors that constitute the best-performing model, originated from dataset Z, the first two of them, Crippen LogP and the number of donor H bond, are known to be correlated with the permeability.

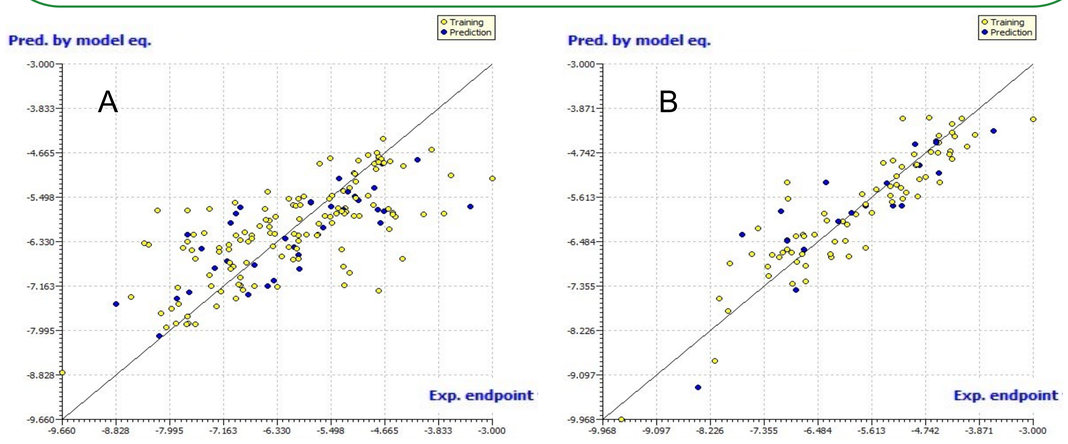


Figure 3 Predicted Log Kp by model equation vs. Expected values. A) A database, B) Z database.

Conclusion

The strong superiority of the one-source model compared to the multi-source one leads to consideration that the inter laboratories variation represent a source of error in QSPR development. As previously shown by Johnson (Johnson et al., 1995), even monitoring the main experimental factor variations, it is not possible to find an obvious explanation to this inter laboratory variability.

The same kind of observation can be found in other studies (Degim et al., 1998, Abraham et al., 1997, Samaras et al., 2012, Van de Sandt et al., 2004, Chilcott et al., 2005), confirming that models obtained with data coming from different sources can bring with them an atavistic, non-removable, fundamental error. Having avoided this error and properly validating the model, it is possible to use it as an effective tool to predict the permeation of a wide variety of compounds through stratum corneum and viable epidermis.

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