BIOPHYSICAL MODELS IN DRUG DEVELOPMENT: 6-FLUOROQUINOLONE DERIVATIVES

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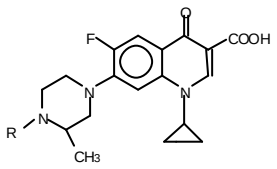
Introduction

Initial studies on the development of new drug candidates should not ignore the potential bioavailability problems inherent to the selected compounds, particularly, when they are intended to be orally administered, as is often the case. Experimental results obtained with preclinical permeability models such as *in situ* rat perfusion have demonstrated a good correlation with human experiments and therefore, it could be possible to classify drug candidates according to the proposed BCS (Biopharmaceutical classification system) with this animal models, especially with passively transported compounds.[1,2] In the present work a simple methodology for assessing and predicting passive absorption of drug candidates is presented and applied to three new fluoroquinolone derivatives.

Experimental Methods

Three new Ciprofloxacin derivatives were synthetised by CENAVISA S.A[3] Laboratories. The structures are represented in Figure 1.



R	Name
H	CNV97100
CH_2CH_3	CNV97102
$(CH_2)_3CH_3$	CNV97104

The methodology consists of the use of biophysical absorption models based on absorption-lipophilicity correlations to find the best derivative of a series.

Absorption was characterized by the permeability value (P_{eff}) determined by an *in situ* closed loop technique, on the whole intestine of male Wistar rats (six animals per compound). Quinolones were perfused in solution at a concentration low enough to avoid precipitation in the lumen (50 µg/mL). Lipophilicity was represented by n-Octanol partition coefficients. Analysis of the samples was carried out by reverse phase HPLC technique and fluorimetric detection.

Predictions of the permeability values for the new quinolones were based on a previously established absorption-partition correlation for a series of Norfloxacin and Ciprofloxacin derivatives. The Higuchi-Ho model was the biophysical model applied. It considers that the limiting step for absorption is located in the luminal aqueous barrier, where diffusion depends upon the molecular weight. The equation adapted as previously described[4] is:

$$P_{eff} = \frac{C \cdot K^{d}}{1 + E \cdot \sqrt{M} \cdot K^{d}}$$

where P_{eff} is the permeability value, M is the molecular weight, K is the partition coefficient and C, d, E are the fitting parameters. Equation was fitted to data by means of PCNONLIN 4.0 to estimate the parameters. A series of sixteen fluoroquinolones was used as exploratory population to find the equation parameters used to predict the permeability values of the three new derivatives.

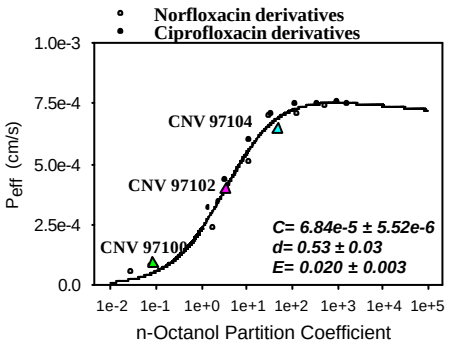
Results and Discussion

In Table 1 the experimental and calculated permeability values and the partition coefficient for the new fluoroquinolones are shown. The prediction error expressed as percentage is also outlined.

Comp.	K (SD)	Peff (cm/s) (SD)	Peff calc. (cm/s)	Error %
97100	0.09 (0.02)	1.86e-5 (1.49e-6)	1.70e-5	9.2
97102	3.47 (0.12)	7.97e-5 (8.47e-6)	7.57e-5	5.2
97104	48.0 (0.29)	1.29e-5 (7.96e-6)	1.29e-5	-0.3

Table 1

Figure 2 represents the absorption - partition correlation for the exploratory population of fluoroquinolones and the fitting parameters obtained[5].



The experimental permeability values found for the new derivatives are superimposed. Applying the biophysical model to the 16 homologous quinolones leads to a very significant correlation that allows a good prediction for the new derivatives. The lipophilicity increment from CNV97100 to CNV97104 produces a significant improvement in the permeability value. Such a modification could overcome the bioavailability problems that the parent compound (Ciprofloxacin) has.

The selection of a structure belonging to these series with some modifications to enhance antibacterial activity while maintaining the lipophilicity would be a useful way to carry out new drug development. As can be seen in Figure 2, lipophilicity seems to be the main factor governing fluoroquinolone absorption and the possible existence of an active process at intestinal level (i.e. an efflux process) does not appear to be relevant *in situ*.

Conclusion

The new 6-Fluoroquinolones reproduce the behavior predicted by the absorption-partition relationship previously obtained. This biophysical absorption model should be a powerful source of information in order to calibrate absorption potentialities and to prevent absorption failures.

References

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