

Caco-2/TC7 cell line characterization for intestinal absorption: a reliable in vitro model for the prediction of the oral dose fraction absorbed in human

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In vitro absorption studies of compounds across intestinal cell monolayers are easy to perform under controlled conditions. Various methodologies are available, however the good correlation between in vivo/in vitro passive intestinal drug transport makes the Caco-2 cells model a useful screening tool for this application.

Several clones have been isolated from Caco-2 cell line and characterized for their activities. Among them, TC7 clone was isolated from a late passage of the parental Caco-2 line and has shown to be similar in terms of paracellular transport and passive diffusion, whereas large differences were evidenced in the active transport, the expression of the brush-border-associated hydrolase, sucrase, isomaltase, the inducibility for the cytochrome P450 and P-glycoprotein-mediated active efflux.

In a recent study aimed at comparing the characteristics of 4 Caco-2 cell lines, it was concluded that TC7 clone expresses a more homogeneous population in terms of the most representative functions of the small intestinal enterocytes and exhibit more developed intercellular junctions.

On the basis of these characteristics, it was decided to check the suitability of Caco-2/TC7 as a predictive in vitro model for passive transport, in the framework of the EU A-Cute-Tox project.

27 compounds (including drugs and synthetic or natural chemicals) have been characterized for their absorption profile on Caco-2/TC7 cells cultivated on semi-permeable filters for 21 days. The absorption experiment has been performed with the highest non toxic concentration as determined in a preliminary set of cytotoxicity tests. The apparent permeability coefficient (Papp) has been extrapolated by calculating the passage of the test compound from the donor to the receiver compartment as a time function. The samples have been collected at time intervals and the concentration of the test compound analyzed by analytical methods (HPLC, GC, GC/MS).

A regression curve has been obtained plotting the in vitro Papp values and human fraction absorbed (FA, expressed as % of the administered dose) of reference compounds in order to extrapolate the unknown FA of the test compounds for which in vivo data were not available.

On the basis of the obtained results and the data elaboration, Caco-2/TC7 clone has shown to be a reliable model for passive diffusion, although some limits mainly due to technical difficulties related to in vitro methodologies are present and will be discussed. Beside the value of passive diffusion, the obtained results can be useful also to suggest the occurrence of active mechanisms, provided that a suitable experimental strategy is adopted.

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