would be consistent with one of the key metabolism sites in CsA (*N*-demethylation at [MeLeu]^4) being blocked by an ethyl group. However, the remaining portion of the drug undergoes extensive metabolism and no single metabolite has been reported.

CsA displays a selective distribution profile in blood, with the major fraction being found in erythrocytes ($\sim$58%), while the portion of drug in the plasma is extensively bound by the lipoprotein component.[172] The distribution of CsA into erythrocytes appears to be a saturable process that can be affected by co-administration of certain excipients. A demonstration that Cremophor EL can significantly increase the plasma concentration in rats of a given dose of CsA was supported by the finding that this excipient also limited the erythrocyte uptake of the drug.[173] Alisporivir demonstrates a concentration-dependent distribution profile when examined *in vitro*. At low blood concentration (<0.06 μM), 90% of the compound was found in the erythrocyte fraction, which fell to 30% as the blood concentration was increased to 2 μM.[174] A commensurate increase in the proportion of the drug in plasma was observed at higher blood concentrations.[174] Pharmacokinetic data published for SCY-635 indicate that the compound has little plasma exposure when delivered at low doses to humans but that a supra-proportional increase in the plasma fraction occurs as the dose level is raised. These data support a model wherein the drug is initially taken into an erythrocyte fraction until such point that this compartment is saturated whereupon the compound 'spills' into the plasma.[175]

CsA was recognized early to be an inhibitor of the P-gp efflux transporter and a modified CsA derivative, PSC-833, was actively studied as a chemo-sensitizer to anti-cancer agents such as vinblastine by preventing the P-gp-mediated efflux of the latter from MDR cancer cells.[176] A study of the SARs of CsA metabolites as inhibitors of P-gp indicated that most of the primary metabolites of CsA are weaker inhibitors of P-gp than the parent molecule; however, for the closely related analog CsG, demethylation at [MeLeu]^4 resulted in a significant increase in P-gp inhibition.[177] CsA is a well-known inhibitor of hepatic transporters, including the organic anion transporters (OATPs) and the multi-drug resistance protein transporters, including Mrp-2.[169] The concentration required to inhibit by 50% many of these transporters by CsA falls within the range of clinically used blood levels of the drug and notable drug–drug interactions involving CsA and drugs such as statins have been observed.[178] One of the main adverse events noted during clinical studies of alisporivir in HCV-infected patients was an elevation of plasma bilirubin levels that could be ascribed to the inhibitory activity of alisporivir on the key hepatic transporter responsible for clearing bilirubin from blood, Mrp-2.[78] *In vitro* studies confirmed a significant inhibition of Mrp-2 by alisporivir. However, the finding that SCY-635 is significantly less inhibitory toward several transporters such as Mrp-2 and OATP indicates that SARs can be established to avoid unwanted interactions.

These characteristics of cyclosporine and its derivatives demand that care be taken when initially studying the pharmacokinetic properties of a new compound.