

Peak plasma concentration of rhein was reached 15-30 minutes after dosing. Binding of rhein to plasma proteins is >99%; area under the curve (AUC) is 20.9 mg/l.h after a single dose (50 mg) and 28.8 mg/l.h after repeated doses (50 mg/day for 5 days).

## 2. Protein binding

Rhein, a weak acid drug (pKa = 4-4.5); is present essentially in its ionized form in the plasma. Plasma protein-binding of rhein was almost 100% according to a radiochemical studies in 4 healthy volunteers (Fisher, 1994; Lang, 1994). Furthermore, consistent with subsequent clinical studies showing no drug interactions, bound rhein was not displaced by drugs that might be administered concomitantly, such as anticoagulants, anticonvulsants or non-steroidal anti-inflammatory drugs (Barre, 1992) as demonstrated by studies in vitro.

## 3. Metabolism and elimination

Diacerein is hydrolysed to rhein, the active metabolite, rapidly upon oral administration and before entering the systemic circulation as seen in figure 5. After a single 50 mg dose,  $19.6 \pm 11.3\%$  of the metabolites were excreted via the urine in the form of non-conjugated rhein while  $62.7 \pm 13.5\%$  was in the form of glucuroconjugated rhein and  $18.6 \pm 5.6\%$  in the form of sulphuronoconjugated rhein (Louchahi et al., 1991).