its first passage in the portal blood through the liver to the systemic circulation (Birkett, 1991).

The extent of hepatic first pass effect is influenced by (i) site of absorption, (ii) intracellular residence time of drug molecules in enterocytes; as the residence time in the enterocytes increases then the metabolism is more extensive, (iii) diffusional barrier between the splanchnic bed and the enterocytes; lower diffusibility allows for longer residence time, (iv) mucosal and portal blood flow and (v) substrate concentrations (Younggil, 2001).

In cases where drugs undergo extensive first pass metabolism, higher doses are needed to reach intended efficacy. However this increase results in increasing the incidence of adverse events and may lead toxicity. Therefore, in order to overcome this issue, drugs are usually formulated as prodrugs where they are converted to the active moiety upon metabolism or in other cases they are given through routes of administration other than oral route; these routes bypasses hepatic first pass metabolism such as sublingual (e.g. nitroglycerin), transdermal patches (e.g. timolol) or rectal (e.g. propranolol). Although these routes of administration increase the bioavailability of the active ingredient without the need to increase the dose and encountering subsequent issues related to it, yet each of these routes has its own obstacles; skin irritation in case of transdermal patches is reported and buccal mucosa presents a barrier for rapid drug absorption.

The pharmacokinetics can be altered by previous or co-administration of certain medicaments, supplements or even food, which is referred to as drug interactions. There are several types of drug interactions: (i) pharmaceutical interactions, (ii) pharmacokinetic interactions, and (iii) pharmacodynamics interactions (Aronson, 2004).