active metabolites can be formed from an inactive parent drug (prodrug). In general, all tissues can metabolize drugs, but the liver, GIT and lungs are the major sites for drug metabolism in humans. The strategic location of the liver relative to the portal circulation and the high level of enzymes capable of metabolizing foreign substances regarded the liver as one of the major sites responsible for drug metabolism (Raffa 2010). Drug metabolism is divided into two phases; phase I and phase II metabolism. Primary hepatocyte culture is used to study the expression and function of enzymes responsible on drug metabolism including cytochromes P450, drug-drug interactions, and the mechanisms of cytotoxicity and genotoxicity (Bu and Mashek 2010; Gomez-Lechon *et al.* 2004; Gonçalves *et al.* 2007; Saito *et al.* 2010; Schmidt *et al.* 2005).

1.1.4.1 Phase I metabolism

Phase I reactions take place in the cytoplasm, mitochondria, and the microsomes, which are a subcellular component containing membrane-associated enzymes on the smooth endoplasmic reticulum (Raffa 2010). Phase I reactions (oxidation, hydrolysis and rarely, reduction) are concerned with the addition or unmasking of polar groups, which is mediated by a large family of cytochrome P450 enzymes (Leucuta and Vlase 2006). These reactions result in small changes making a drug more hydrophilic and also provide a functional group that is used to complete phase II reactions. However, some drugs do not necessarily undergo phase I metabolism prior to phase II metabolism (Leucuta and Vlase 2006; Smith *et al.* 2012).

Phase I metabolism occurs during drug absorption, mainly in the liver as well as in the gut wall before reaching systemic circulation. The presystemic metabolism determines