Introduction
Kidney is a complex and heterogeneous organ composed of vascular as well as tubular components. It plays a vital role in the excretion of metabolic wastes and in the regulation of extra-cellular fluid volume, electrolyte composition and acid base balance. It synthesizes and releases hormones too. Because of its complex structure and function it is a frequent site of injury following exposure to chemicals or during drug treatment. Any toxic insult to the kidney can have profound effect on total body homeostasis and metabolism.

Fortunately, the kidneys are equipped with a variety of detoxification mechanisms and have considerable functional reserve and regenerative capacities. The damage does not become apparent until up to 2/3rd of the renal parenchyma is damaged and by this time it becomes irreversible. Further, many toxic chemicals target preferentially discrete cell type, but adjacent morphologically different cells are unaffected. This selectivity has made the in life assessment of nephro toxicity still more difficult.

Detection of early stages of renal damage by making in-life observations is thus a big challenge because of technical limitation of methods routinely employed for this purpose. Toxicity studies aiming to unmask the nephro toxic potential of a foreign chemical or drug are in need a lot of refinement and improvement for early detection of such type of adverse effect. Various in-vivo and in-vitro models have been used for early and reliable discovery of nephro toxicity.

Urinalysis and blood analysis provide a relatively easy assessment of overall renal functional integrity and provide some insight into the nature of nephro toxic insult. Measurement of urine volume, osmolality, pH, and urine composition are important parameters of urine analysis. The parameters of blood examinations are BUN, creatinine, protein, sodium, potassium, calcium, phosphorous and hematocrit, which can provide information about functional impairment of kidney.

Conventional assessment of nephro toxicity includes urinalysis, serum clinical chemistry and histopathology to provide a reasonable profile of the functional and morphologic effects of a chemical on kidney. Because nephro toxicants can exert adverse effects on various parts of the kidney, resulting in alterations of different functions, a variety of tests need to be performed. The most sensitive and reliable tests appear to vary depending on the nature of the toxicant, specific site of damage in the nephron, as well as with the experimental conditions. Furthermore, it has been
found that pre-renal and post-renal mechanisms could lead to damage to kidney tissue and a foreign substance not acting directly on kidney could also be responsible for adverse effects on the renal structure or function. The need for detecting truly nephro specific toxicants was thus evident.

*In vitro* test systems provide possible answer for the detection of site specific nephro toxicants. There are several *in vitro* test systems including renal cortical slices, isolated perfused kidney, primary renal cell culture and renal cell lines. *In vitro* test for renal toxicity has been proposed as a means by which chemicals of concern may be prioritized for further *in vivo* screening. The combination of *in vivo* and *in vitro* methods may yield optimal information on the spectrum of effects of drugs and chemicals on kidney. *In vitro* assays are more reproducible; provide easier end points, present no problems with respect to route of exposure, and metabolic differences. The aim is to reduce the use of animals and increase the rate of screening. With all these advantages there are number of limitations too with the *in vitro* techniques. These models have limited life span of 2 to 24 hours. Primary cultures of renal cells and established renal cell lines exhibit longer life span of 2 weeks but in comparison to the *in vivo* conditions exhibit the differentiated functions to a lesser degree.

On review it appears that the suitable endpoint(s) are still lacking with the available test systems. For screening purposes, the most relevant and sensitive end points for the assessment of toxicity need to be determined because these endpoints vary for different *in vitro* test systems. Kidney has large amount of reserve and only one-third of the organ is sufficient to carry out the required excretory, homeostatic functions for the body. Damage to this important organ manifests only when a large portion of its tissue is rendered nonfunctional or dead. Commonly a battery of tests is employed to evaluate the renal damage under experimental condition which includes assessment of different parameters in blood, urine or tissue culture media; some challenge/stress tests; and finally the histological studies.

A large body of information exists regarding the type, site and mechanism of action of nephrotoxicants. The site of nephro selective action of these toxicants within the kidney appears to be very specific. We intend to make use of this information for preparing a laboratory approach of detection of reversible / irreversible renal injury. Attention would be focused to identify the biomarkers of damage occurring at different sites in the nephron.
The proposed work is thus, addressing the need of defining a suitable approach for early detection of renal damage and measurement of functional reserve capacity of kidney for timely identification of individuals specifically prone to renal damage.

**Objectives of study**

Kidneys have the ability to hide its defects, so it is very essential to have a test system through which one can assess the nephro toxicity of a drug or a chemical in its very early stages. In the present study we compared the different test systems with different drugs at their specific action sites. The overall aim of the work was to identify the test system(s) and parameter(s) which have the ability to make a bridge between the *in vitro / in vivo* gaps. The objectives, therefore were as follows:

- To assess the suitability of different models of site-specific, reversible / irreversible renal injury

- To evaluate the practical utility of various biomarkers of renal damage occurring at different sites in the nephron

- To develop a suitable approach for the functional reserve of kidney and detection of abnormal susceptibility to renal damage.