2. AIM AND OBJECTIVES

Dramatic changes in the demographic profile of a society can be correlated to an increasing incidence of cancer. This is true especially in developing countries like India. A multitude of antineoplastic agents have been discovered and synthesized in the last three decades. Among them, Irinotecan is an effective chemotherapeutic agent that is widely prescribed for advanced colorectal cancer as first or second line treatment. Irinotecan has also been shown to be active in gastric cancer, non-small cell lung cancer; alone or in combination with other cytotoxic agents. Unfortunately, majority of the conventional cancer chemotherapies have relied only on oral and bolus administration of antineoplastic agents and the patients are frequently exposed to peak drug concentrations, which are well above the toxic levels. On the other hand, critical therapeutic levels are not always maintained for sufficiently long time for effective treatment of neoplasms. Ideally, for effective cancer chemotherapy, a relatively constant antineoplastic drug concentration should be maintained within the narrow range between the minimum therapeutic level and the toxic dose level for prolonged period of time. By doing so, the systemic toxicity commonly associated with treatment of antineoplastic agents can be avoided. Hence, the strategy of identifying new methods of drug delivery for existing antineoplastic agents like Irinotecan is more feasible and rewarding.

Irinotecan is a prodrug; converted to the active cytotoxic molecule SN38 predominantly by the action of liver carboxylesterases. The efficacy of Irinotecan is limited by this hepatic activation that results in a low conversion rate, high interpatient variability, and dose-limiting gastrointestinal toxicity. The purpose of this study was to formulate a novel drug delivery system to bypass this hepatic activation and thus reduce the gastrointestinal toxicity and interpatient variability compared to Irinotecan. Liposomes have raised considerable interest as drug carriers in cancer chemotherapy by virtue of their ability to control the release rate and alter the biodistribution of encapsulated drugs. Their versatility, biocompatibility, biodegradability and lack of immunogenecity confer them intrinsic advantages as pharmaceutical devices for drug delivery.
The role of estimation of drugs in the biological fluid has a wider scope in today’s scientific field especially, in bioavailability and bioequivalence, new drug development, drug abuse, clinical pharmacokinetics, and drug research. These are highly dependent on accurate measurement of drugs in biological fluids. Estimation of the drugs present in the biological fluid can be performed using various methods; but HPLC and LC-MS methods are considered to be more suitable because of their sensitivity and ruggedness. This choice can also be attributed to their extreme specificity, linearity, precision and accuracy.

2.1 AIM OF THE RESEARCH WORK
The present study, aims at developing stable liposomal formulation of Irinotecan and evaluating the pharmacokinetic and toxicokinetic variables in suitable rat model.

2.2 OBJECTIVES
1. Development of liposome formulation of Irinotecan
2. Development and validation of analytical method for Irinotecan by LC-MS/MS in accordance with ICH guidelines
3. In vitro evaluation of liposomes
4. Bioanalytical method development and validation for estimation of Irinotecan and its metabolite SN-38 in rat plasma using LC-MS/MS as per FDA guidelines
5. In vivo evaluation of liposomes
   - Pharmacokinetic evaluation of liposomes and data handling
   - Toxicokinetic evaluation of liposomes and data handling
   - Organ toxicity study