CHAPTER 3: AIMS AND OBJECTIVES

3.1. Aims

- The study aimed to enhance the efficacy and efficiency of the selected drug candidate by formulating a MSNs type nano framework.
- To enhance the solubility and in turn bioavailability of poorly soluble anti-cancer drugs viz., Raloxifene (RLX) and Bexarotene (BXR) by developing MCM-41 and MCM-48 types of mesoporous silica nanoparticles.
- To prepare a targeted drug delivery for RLX and BXR such that the drug exclusively reaches cancer cells sparing or causing least damage to healthy cells.

3.2. Objective:

- The major objective of the proposed study was to develop a mesoporous silica based nano drug delivery system to enhance the solubility and possibly bioavailability of the selected drug candidates.
  I. RLX and BXR, the selected both the drugs belong to BCS class II and IV facing the solubility and/or permeability issues. Therefore, a strategy was adopted with the aim of enhancing the solubility and permeability of the selected active pharmaceutical candidates.
  II. The efficiency of formulated nanoparticles was enhanced by attaching the targeting moiety on the external surface of the MSNs which would aid their amassment inside the tumor cells by either passive or active targeting mechanism and will efficiently reduce the toxicity or the adverse effect by avoiding the healthy cells.
- Considering these, the specific objectives of the present study were:

I. Synthesis, characterisation and solid-state evaluation of mesoporous silica nanoparticles (MSNs) *i.e.* MCM-41 and MCM-48
II. Drug (RLX and BXR individually) loading and thorough characterisation of formulated nanoparticles for their particle size, surface area, particle uniformity *etc.*
III. To synthesise pH and target based mesoporous silica nanoparticles by Surface modification of MSN followed by further characterisation to confirm success of surface modification
IV. To perform *in vitro* release study in different dissolution and diffusion media

V. To perform *in vitro* cytotoxicity study

VI. To perform the cellular uptake study

   a. Qualitative cellular uptake study by confocal microscopy

   b. Quantitative cellular uptake study by flow cytometric analysis

VII. To perform apoptosis study to know the cell death mechanism

VIII. To perform *in vivo* animal study

   a. Bioavailability enhancement study

   b. Bio distribution study

   c. Toxicity study

IX. To perform the stability study of engineered formulations

The overview of the entire journey of work has been summarized here (figure 3.1-3.3).

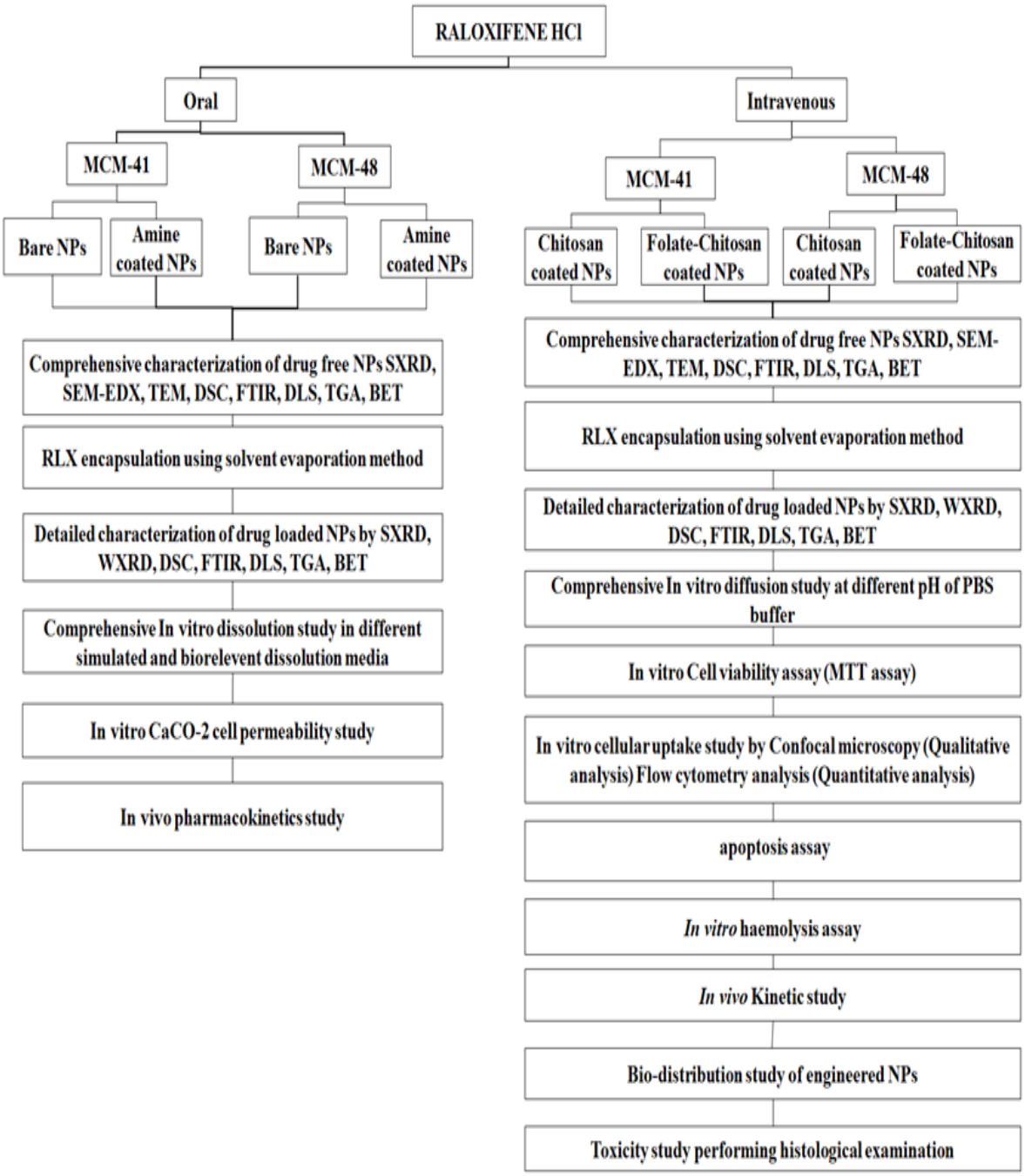

Figure 3.1: Schematic representation of work plan for RLX.

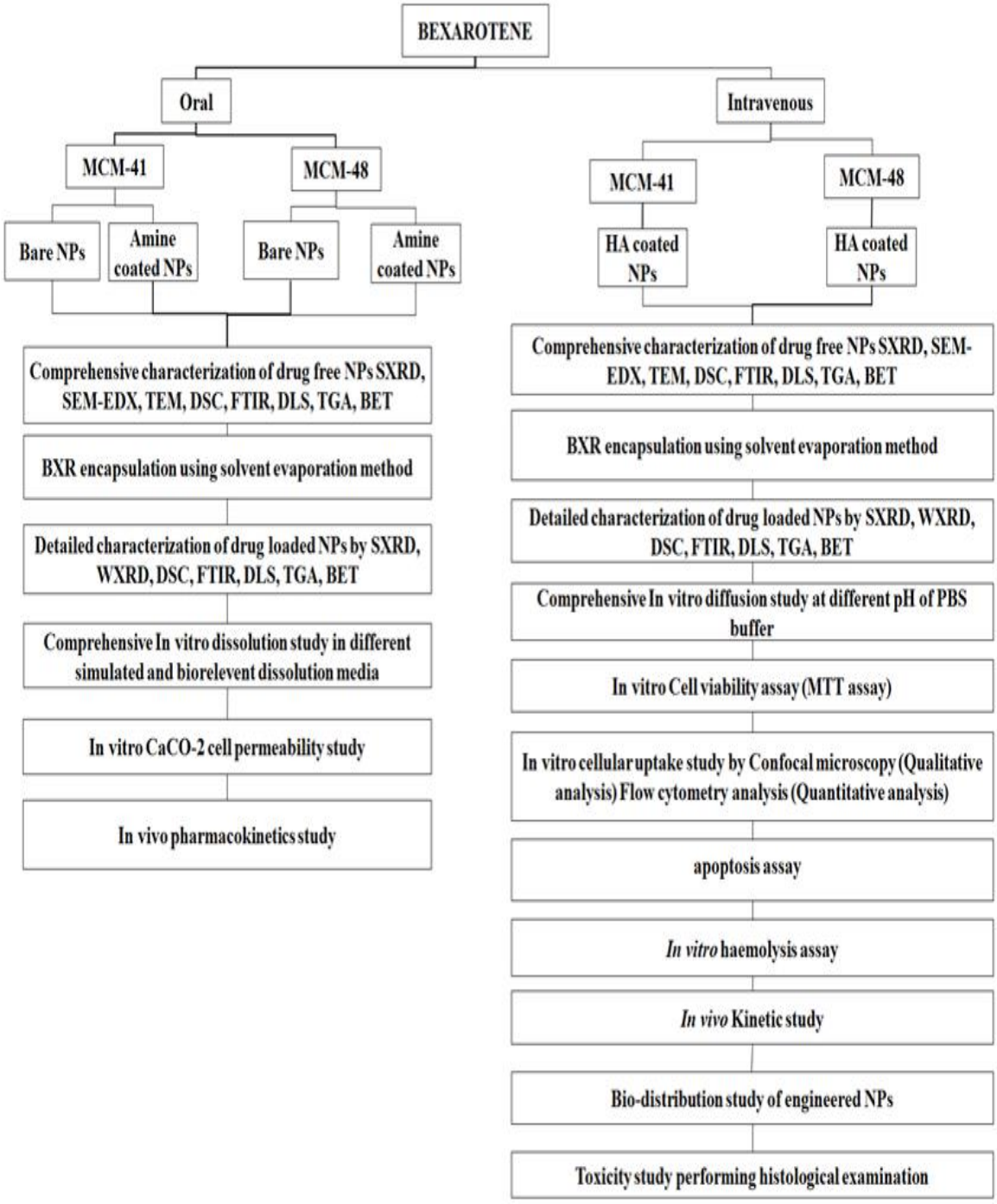

Figure 3.2: Schematic represenation of work plan for BXR

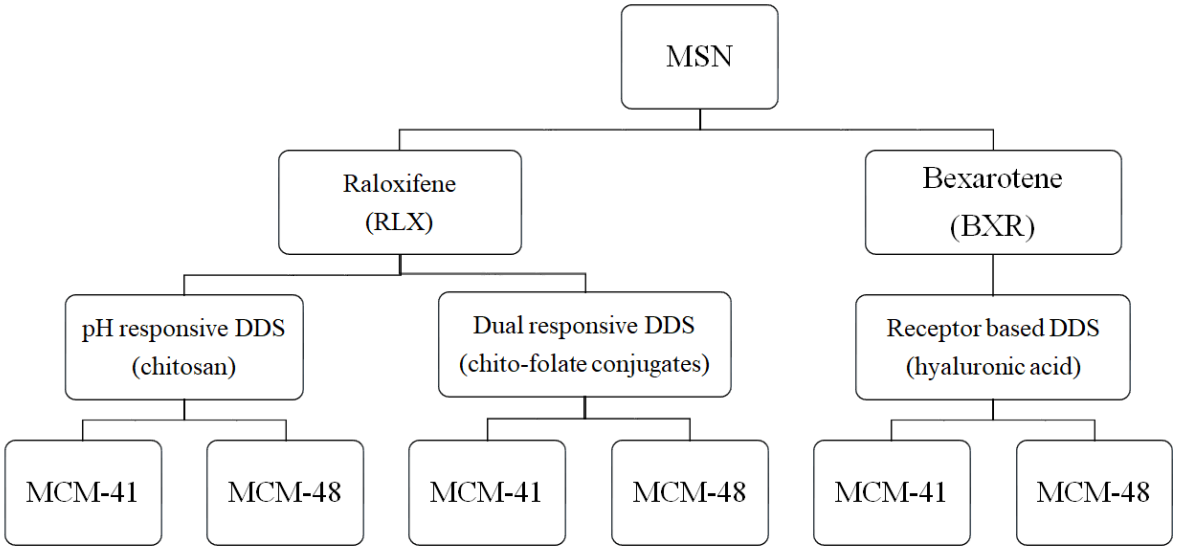

Figure 3.3: Overview of the formulation developed for RLX and BXR

3.3. Hypothesis:

- It is hypothesized that the oral bioavailability of RLX and BXR would increase by accommodating them inside the mesoporous silica nano framework. This would enhance their solubility and possibly bioavailability and would also improve their intra intestinal permeability performance.
- Cancer cells differ from normal cells in various aspects like having a more acidic pH, elevated GSH levels, over expression of certain receptors in various types of cancer. It is reported that folate and CD44 receptors are overexpressed in breast tumors. Hence, it was thought of great use and interest to synthesize MSNs which are surface coated with ligands such as folic acid and hyaluronic acid which can help in accumulating NPs at the targeted tumor site. This would ultimately lead to drug accumulation exclusively at the cancer site. Further, the pH responsive and receptor-based targeting approach may also be useful in minimizing the off-site toxic effects.

3.4. Expected Outcomes:

- An encapsulation of RLX and BXR in the nanoframwork would have potential to enhance the bioavailability which may prove to be helpful in the dose reduction and/or the frequency of drug intake.
- The surface modification by folate-chitosan conjugates and hyaluronic acid ligands, would target the drug delivery to tumor cells only and thereby it could decrease the adverse effect of the anti-cancer drug by minimizing the uptake by normal cells.