Aim and Objectives

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2.1 Significance

Following oral administration, dissolution of the drug molecule in the gastrointestinal tract is a prerequisite for the absorption process. Up to 40 per cent of new chemical entities discovered by the pharmaceutical industry today and a number of already existing drugs are poorly soluble or lipophilic compounds. For poorly water-soluble drugs (BCS class II and IV), the maximum achievable intra-luminal drug concentration may limit absorption. The introduction of high-throughput screening and combinatorial chemistry in drug development has resulted in a shift such that more new chemical entities suffer from limited aqueous solubility and/or poor dissolution properties.

In the era of research and development, plenty of techniques are developed for solubility enhancement of poorly soluble drugs but these techniques often have some limitations like scale up, cost effectiveness, instability, biocompatibility, toxicity, regulatory requirements etc. Some of them are listed in table 2.1. There is a continuous need to explore new and ideal approach to enhance the aqueous solubility of these compounds.

Table 2.1 Problems associated with established formulation techniques.

Formulation technique	Associated problem
Micronization	⊕Difficult to control particle size, shape, morphology, surface properties and electrostatic charges. ⊕High energy process causes crystal disruption. ⊕Unstable and chances of recrystalization on storage.
Salt formation	⊕High reactivity with atmospheric CO_2 and H_2O cause precipitation of poorly water soluble drugs. ⊕Epigastric distress due to high alkalinity.
Spray drying	⊕Thermal stress and degradation of pharmaceuticals. ⊕ Use of organic solvents.
Hot melt extrusion	⊕ Not suitable for thermolabial pharmaceuticals.
Solvent evaporation	⊕ Difficulties in removing solvent residue. ⊕ Toxicity potential of organic solvents.
Conventional method of solid dispersion	⊕ Laborious and expensive method. ⊕ Difficult for moisture sensitive drugs. ⊕ Phase separation and crystallization. ⊕Stability of drugs and vehicles.
Precipitation	⊕ Not universally acceptable technique.

	⊕Needs to be stabilized. ⊕ Interference of solvent residue.
Milling	⊕ Residue from milling media ⊕ Large batches difficult to produce due to size of milling chamber
Homogenization	⊕ Thermal stress and degradation of Pharmaceuticals. ⊕Great experience needed.
pH adjustment	⊕Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli.
Co-solvency	⊕Uncontrolled precipitation occurs upon dilution with aqueous media. ⊕As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered.
Microemulsion	⊕The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent. ⊕The tolerability of formulations with high levels of synthetic surfactants may be poor in cases where long term chronic administration is intended. ⊕Formulations containing several components become more challenging to validate.
Complexation	⊕ Toxicity issues of complexing agents. ⊕ Necessity to evaluate various physical properties i.e. forces which imparting in complexation. ⊕ Dilution of system may still result in precipitation.
Supercritical fluid process	⊕ Critical control of the system parameters are essential like the density, transport properties (such as viscosity and diffusivity), and other physical properties(such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both.

2.2 Aim and Objectives

The aim of this study was envisaged to prepare a formulation which can enhance the solubility of a poorly soluble drug. It was hypothesized that incorporating drug in nano-sized mesoporous silica material will enhance its solubility which in turn may help in enhancing the absorption through gastro-intestinal tract and ultimately the bioavailability.

Keeping this aim in perspective, the specific objectives of the investigation were therefore:

1) Review of the literature with special reference to mesoporous silica materials, their synthesis, properties, evaluation techniques and cytotoxicity.
2) Preparation/synthesis of mesoporous nanoparticles (MSNs) and their characterization.
3) Loading of drug in the MSNs, optimization of procedure and characterization.
4) *In-vitro* dissolution studies of the prepared drug loaded MSNs.
5) Stability studies of drug loaded MSNs.
6) Cytotoxicity studies of drug loaded MSNs.

On the basis,

1) Methotrexate and Dasatinib were selected for the investigation.
2) Analytical methods for both the drugs were developed for different analytical studies.
3) MCM-41 and MSU-H were selected as mesoporous silica materials for preparing MSNs.
4) The selected drugs were loaded into the pores of prepared MSNs and the process was optimized.
5) The drug loaded MSNs were characterized by SEM, TEM, DSC, FTIR, Nitrogen adsorption isotherm and XRD methods.
6) *In-vitro* dissolution studies were performed in different dissolution media and *in-vitro* dissolution data were compared with that of commercialized formulations.
7) The cytotoxicity of prepared and drug loaded MSNs were performed by using K-562 and L-132 cell lines.