Chapter I

Introduction
1. Introduction

In the recent years, research in drug discovery to tackle the increasingly varied health and medical issues has resulted in the upsurge of new chemical entities (NCEs) with drug-like properties but with low water solubility and inadequate bioavailability, especially those that are to be delivered via oral administration\(^1\). The number of such NCEs has mushroomed so immensely and currently almost 70\% of such new drug candidates have shown poor aqueous solubility. 65\% of human body is comprises of water and thus, a drug molecule must be water soluble at least to an extent and also be acceptably bioavailable. Poorly water soluble molecules tend to get eliminated from the gastrointestinal (GI) tract even before they can fully dissolve and get absorbed into the systemic circulation, consequently, result in in poor bioavailability and poor dosage proportionality, significantly affecting their clinical translations\(^3\). Dose augmentation would be an obvious solution for such cases and would probably warrant the drug’s optimal therapeutic concentration in the blood. However, upon oral administration, dose augmentation may cause an increased chance local toxicity in the GI tract affecting adversely the overall patient compliance\(^4\). Moreover, from an industrial perspective, dosing a large amount of Active Pharmaceutical Ingredient (API) would elevate the manufacturing cost of the pharmaceutical drug product. Thus, such poorly water soluble drugs are disadvantageous with considerable undesirable clinical effects like inter-patient variability, higher patient costs, inefficient treatment, and more importantly increased risks of toxicity and side effect profiles.

Instead of going for completely new drugs to overcome the adverse effects of a prescription, introducing advanced formulations goes a long way in reducing the associated risks, as well as time and capital invested in drug development and manufacturing. Most approaches that have been developed to enhance the dissolution rate as well as bioavailability of poorly water soluble drugs include either alterations to the drug moiety itself or the design of specific formulations to alter its crystal habit. Physical modifications are generally aimed at increasing the wettability, or the surface area, the solubility, and typically focus on particle size reduction\(^5,6\) or creation of amorphous (highly disordered particle states).
1.1. Poorly water soluble drugs

The BCS (Biopharmaceutical Classification System) is a scientific framework classifying a drug substance based on two pertinent factors that are crucial to the bioavailability of a drug; (i) aqueous solubility and (ii) intestinal permeability. Taking into account these two characteristics, that define the extent of oral absorption from solid oral dosage forms, coupled with the dissolution characteristics, the BCS classifies drugs into four classes. Among the four classes, the Class II and Class IV drugs of the BCS are associated with poor solubility and limited dissolution characteristics. The major challenge with the design of oral dosage forms of these drugs mostly lies with their poor bioavailability. Aqueous solubility plays a major role for dosage forms like oral and parenteral formulations. It is one of the important parameters to achieve the desired concentration of drug in systemic circulation and subsequently obtain the required pharmacological response. Poorly water soluble drugs often require high dosing amounts in order to reach the required therapeutic plasma concentrations after oral administration. Any drug to be absorbed must be present in the form of its aqueous solution at the site of absorption. Thus, these compounds with low solubility are associated with poor absorption and bioavailability, inadequate solubility for oral as well as intravenous (IV) dosing. These negative characteristics encountered adversely affect their development resulting in increased development cost and time, and the burden shifted to patient (frequent high-dose administration).

There are numerous approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs. The strategies are preferred on the basis of aspects like properties of drug under consideration, nature of excipients, and kind of intended dosage form.

Most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration. In fact, most NCEs are poorly water soluble drugs, not well-absorbed after oral administration which can detract from the drug’s inherent efficacy, Moreover, most promising NCEs, despite their high permeability, are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, therefore, that there is a small absorption window. Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability. Therefore, a major challenge of the
pharmaceutical industry is related to strategies that improve the water solubility of such drug products.

**1.2. Drug delivery**

Drug delivery involves specific administering of drugs within the body. It also includes enabling systemic pharmacokinetics. It is typically concerned with both quantity and duration of drug presence. Drug delivery is often approached via a drug's chemical formulation, but it may also involve medical devices or drug-device combination products. Drug delivery is a concept heavily integrated with dosage form and route of administration, the latter sometimes even being considered part of the definition.\(^21\) Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Drug release involves diffusion, degradation, swelling, and affinity-based mechanisms.\(^22\) Current efforts in the area of drug delivery include the development of targeted delivery in which the drug is only active in the target area of the body (for example, in cancerous tissues) and sustained release formulations in which the drug is released over a period of time in a controlled manner from a formulation. In order to achieve efficient targeted delivery, the designed system must avoid the host's defense mechanisms and circulate to its intended site of action.\(^23\)

Most common methods of drug delivery include i) noninvasive peroral (through the mouth) ii) Topical (skin) iii) Transmucosal (nasal, buccal/sublingual, vaginal, ocular and rectal) iv) inhalation route and v) Parental (IV, IM, IA, ISp etc). Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products.\(^24\)

Oral drug delivery is the simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their
bioavailability and reduce side effects. Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs. These can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties.

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II substances according to the Biopharmaceutics Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids.

1.3. Bioavailability

It is the fraction of an administered dose of unchanged drug that reaches the systemic circulation, one of the principal pharmacokinetic properties of drugs. By definition, when a medication is administered intravenously, its bioavailability is 100%. However, when a medication is administered via other routes (such as orally), its bioavailability generally decreases (due to incomplete absorption and first-pass metabolism) or may vary from patient to patient. Bioavailability is one of the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosages for non-intravenous routes of administration.

Improvement of bioavailability of poorly water soluble drug remains one of the most challenging aspects of drug development. By many estimates up to 40% of new chemical entities discovered by the pharmaceutical industry today are poorly water soluble compounds. Together with the permeability, the solubility behavior of a drug is a key determinant of its bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples are griseofulvin, digoxin, phenytoin, sulphathiazole etc. With the recent arrival of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.
1.4. Dissolution

The dissolution of a drug administered in the solid state is a pre-requisite for efficient subsequent transport within the human body. This is because only dissolved drug molecules/ions/atoms are able to diffuse, e.g. through living tissue. Thus, generally major barriers, including the mucosa of the gastro intestinal tract, can only be crossed after dissolution. Consequently, the process of dissolution is of fundamental importance for the bioavailability and, hence, therapeutic efficacy of various pharmaco-treatments. Different physical phenomena are involved in the process of drug dissolution in an aqueous body fluid, namely the wetting of the particle’s surface, breakdown of solid state bonds, solvation, and diffusion through the liquid unstirred boundary layer surrounding the particle as well as convection in the surrounding bulk fluid.

Many drugs are administered in the solid state to the patient, e.g. in the form of crystalline particles, which are compressed into tablets. Upon contact with aqueous body fluids the drugs dissolve and cross various barriers in the living organism to reach their target sites. Importantly, only dissolved (individualized) molecules/ions/atoms (and molecular conglomerates of limited size) can diffuse (but not micro/macro-sized drug crystals or amorphous particles). Thus, if a drug exhibits very low solubility in water and/or if its dissolution rate at the site of administration is very low, only minor amounts of drug become available for diffusion. This might result in insufficient drug concentrations at the site of action (e.g. a receptor in the brain) and the failure of the treatment in vivo, despite a potentially ideal chemical structure of the drug to interact with its target site.

The most frequently applied mathematical theories quantifying drug dissolution are the Noyes–Whitney equation, Nernst–Brunner equation and Hixson–Crowell equation. According to the IUPAC, the term “dissolution” is defined as “The mixing of two phases with the formation of one new homogeneous phase (i.e. the solution).” (IUPAC). The term “dissolution” describes the mixing of the two phases, resulting in the formation of a new homogeneous phase: the “solution” (and the boundary between the two initially separated phases disappears). In the case of a solid drug particle, which dissolves in an aqueous body fluid, one of the phases is the drug (e.g. in the form of a crystal or amorphous particle), and the other phase is an aqueous liquid (here we consider pure water for reasons of simplicity). The process of “drug dissolution”: is the mixing of the two
phases, resulting in the formation of a new homogeneous phase – the aqueous drug solution (the
drug and water molecules being intensively mixed at the molecular level).

Consideration of the modified Noyes-Whitney equation\textsuperscript{31} provides some hints as to how the
dissolution rate of Even very poorly soluble compounds might be improved to minimize the
limitations to oral availability:

\[
\frac{dC}{dt} = \frac{AD. (Cs − C)}{h}
\]

where, \(\frac{dC}{dt}\) is the rate of dissolution, \(A\) is the surface area available for dissolution, \(D\) is
the diffusion coefficient of the compound, \(Cs\) is the solubility of the compound in the dissolution
medium, \(C\) is the concentration of drug in the medium at time \(t\), \(h\) is the thickness of the diffusion
boundary layer adjacent to the surface of the dissolving compound.

The “dissolution rate” of a drug in a liquid is generally defined as the change in the concentration
of dissolved drug (individualized drug molecules/ions/atoms), \(dc\), in the time interval \(dt\): The main
possibilities for improving dissolution according to this analysis are to increase the surface area
available for dissolution by decreasing the particle size of the solid compound and/or by optimizing
the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to
ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent
solubility of the drug under physiologically relevant conditions.

Larger the surface area, higher will be the dissolution rate. Since the surface area increases with
decreasing particle size, which can be accomplished by conventional methods like trituration,
grinding, ball milling, fluid energy micronization, salt formation and controlled precipitation.
Although these conventional methods have been used commonly to increase dissolution rate of
drug, there are practical limitation with these techniques as the desired bioavailability enhancement
may not always be achieved. Therefore, formulation approaches are being explored to enhance
bioavailability of poorly soluble drugs. Some such formulation approaches that have been shown
to significantly enhance absorption of such drugs is to formulate solid dispersion nanosuspensions.\textsuperscript{32}

Since more than one third of the existing drugs are poorly water and the gastro-intestinal tract is
primarily an aqueous environment, solubilization of water-insoluble drugs is of great concern in
pharmaceutical research. The dissolution of a solid into a liquid has been widely studied\(^3\) and that the process is energy driven has been established. When administered as a crystalline entity, a higher energy is required to break down the crystal lattice and thus dissolve the drug. To lower the energy required to dissolve the drug forms the major aim of the pharmaceutical formulations used to administer these drugs. It is obvious that reduction in particle size of the drug to nanoscale becomes an effective way to increase the dissolution rates of drugs. However, in this phase the particles are highly unstable (rather metastable) and tend to spontaneously recrystallize. Thus, it becomes crucial that these metastable states must be stabilized in suitable stable matrices used to dose the drug.

In the recent years, the use of polymeric nanoparticles containing active pharma ingredients (APIs) have gained much interest in scientific and pharmaceutical areas as these are potential prospects for site-specific drug delivery, and thus optimization of drug therapy. By encapsulating the poorly soluble drugs in hydrophilic polymers, it is expected that three major characteristics of the dosage form will be altered leading to the enhancement of the dissolution characteristics, namely:

(a) decrease in particle size to nanoscale\(^35\)
(b) increase in surface area\(^36,37\)
(c) thinning of the hydrodynamic (diffusion) boundary layer\(^38\)

Formulations of nanodispersions in polymers have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. In these formulations, the drug molecules are dispersed molecularly but irregularly in the hydrophilic carrier and hence the drug remains in its highly energetic amorphous form. There are many views on the way the drugs are dispersed in the polymer matrix. Based on the manufacturing procedure, the nature of drug and that of polymer, the drugs can be dispersed as either disordered amorphous nanoparticles\(^39\), as crystalline entities \(^40\) or individual molecular species/ clusters\(^34\). Our endeavor would be to tailor make the synthesis routes in a manner that would result in reduction of the polymer dimensions also to nanoscale in an effort to make the dispersions more effective in carrying, stabilizing and releasing the drug particles that are encapsulated.
1.5. NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) like, ibuprofen, ketoprofen, flurbiprofen, naproxen, diclofenac, aceclofenac, indometacin, flufenamin, piroxicam, meloxicam, celecoxib, parecoxib, etoricoxib etc… are very commonly used as painkillers. Although very effective as pain killers and anti-inflammatory agents, these belong to the type II category of the biopharmaceutical classification system, indicating that, though these drugs have a relatively high membrane permeability, their bioavailability remains limited due to their poor (or rather sparing) solubility in aqueous media. In fact, currently about 40% or more of drugs in development and about 60% of molecules obtained directly from synthesis are poorly soluble in aqueous media. For example, it takes more than two hours for the drug piroxicam (an NSAID) to attain the maximum concentration after being administered orally.

NSAIDs have similar absorption characteristics and are considerably lipophilic molecules. Although absorption of these molecules occurs throughout the gastrointestinal tract, an acidic environment better promotes the absorption of NSAIDs which as weak acids, are less ionized in gastric juice and therefore absorbed by the mechanism of ionic or diffusion trapping.

The three most popular classes of NSAIDs are:

- Enolic derivatives
- Propionic acid derivatives and
- Acetic acid derivatives

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NSAIDs have similar absorption characteristics and are considerably lipophilic molecules. Although absorption of these molecules occurs throughout the gastrointestinal tract, an acidic environment better promotes the absorption of NSAIDs which as weak acids, are less ionized in gastric juice and therefore absorbed by the mechanism of ionic or diffusion trapping. Since the use of nanocarriers for dissolution enhancement has been established as effective dosage forms for solid systems with reduced dosing amount, the bioavailability of these drugs can be effectively improved by polymeric nanostructures. The use of amphiphilic polymers can be used for quick release of the drug at low, as well as, high pH media.

In this work, novel nanoformulations of NSAIDs in several hydrophilic and amphiphillic polymers have been explored and evaluated. The methods of synthesis of the nanodispersions include wet chemical methods like solvent evaporation, microemulsion (single and double emulsion methods) followed by solvent extraction, and nanoprecipitation. Due to increased emphasis and importance to green chemistry, a few solvent-free synthetic procedures like wet ball milling have also been explored.

The characterization techniques used to evaluate the nature, purity of phase and other properties of the nanodispersions include fourier transform infrared spectroscopy (FTIR) (for evaluating the interactions between polymer and drug); x-ray diffraction (XRD) and differential scanning calorimetry (DSC) (for evaluating the crystallinity and the purity of phase in the dispersions; dynamic light scattering (DLS) (for particle size distribution); and field emission scanning electron microscopy (FESEM) (imaging and confirmation of particle size). Although there are many methods to in vitro dissolution testing, the USP (United States Pharmacopeia) type II apparatus is the most popular and scientifically accepted technique and so is the method of choice for this work.

1.6 Nanoformulations
Since more than one third of the existing drugs are poorly water soluble and the gastro-intestinal tract is primarily an aqueous environment, solubilization of water-insoluble drugs is of great concern in pharmaceutical research. The dissolution of a solid into a liquid has been widely studied and that the process is energy driven has been established. When administered as a crystalline entity, a higher energy is required to break down the crystal lattice and thus dissolve the drug. To lower the energy required to dissolve the drug forms the major aim of the pharmaceutical formulations used to administer these drugs. It is obvious that reduction in particle size of the drug to nanoscale becomes an effective way to increase the dissolution rates of drugs. However, in this phase the particles are highly unstable (rather metastable) and tend to spontaneously recrystallize. Thus, it becomes crucial that these metastable states must be stabilized in suitable stable matrices used to dose the drug.

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1.7 Potential of Nanoformulations and Problem Domain
With a plethora of advantageous applications, in an unprecedented manner, nanomedicine has radically revolutionized and galvanized the science, technology and research of biomedical engineering. The applications of nanomedicine ranges from the nanomaterials and biological devices, to nanoelectronic biosensors and drug delivery to futuristic applications such as biological machines. Current problems for nanomedicine involve understanding the issues related to toxicity and environmental impact of nanoscale materials (materials whose structure is on the scale of nanometers, i.e. billionths of a meter). Distinguished with superior dissolution enhancements and high solubility efficiencies, nanofomulations are known to expedite the highly sensitive design of drug-polymer composites.

The size of nanomaterials is similar to that of most biological molecules and structures; therefore, nanomaterials can be useful for both in vivo and in vitro biomedical development of diagnostic devices, contrast agents, analytical tools, physical therapy applications, and drug delivery vehicles.

The overall drug consumption and side-effects may be lowered significantly by depositing the active agent in the morbid region only and in no higher dose than needed. More than $65 billion are wasted each year due to poor bioavailability. A benefit of using the ‘nanoscale regime’ for medical technologies is that smaller devices are less invasive and can possibly be implanted inside the body, plus biochemical reaction times are much shorter. These devices are faster and more sensitive than typical drug delivery. The efficacy of drug delivery through nanomedicine is largely based upon: a) efficient encapsulation of the drugs, b) successful delivery of drug to the targeted region of the body, and c) successful release of the drug.

Complex drug delivery mechanisms are being developed, including the ability to get drugs through cell membranes and into cell cytoplasm. Triggered response is one way for drug molecules to be used more efficiently. Drugs are placed in the body and only activate on encountering a particular signal. For example, a drug with poor solubility would possibly be replaced by a drug delivery system where both hydrophilic and hydrophobic environments exist, improving the solubility. Drug delivery systems may also be able to prevent tissue damage through regulated drug release; reduce drug clearance rates; or lower the volume of distribution and reduce the effect on non-target tissue.

While dissolution is the primary attribute considered for the development of an ideal oral drug formulation another very important aspect that needs addressing, is the cost or expense associated
with the manufacture and actual scaling up application of the formulation technologies. Appealing to the humane side of our human existence with sympathy and concern, having the means and ways to achieve virtually anything today; we feel that it is imperative for us as responsible citizens of a global society, to also work towards the research, development and production of low-cost affordable pain relieving drugs that can be readily available for improving the living conditions, in service of those in need.

This opportunity to further improve upon the existing levels of drug efficacy was recognized by different research groups, which embarked on a quest of scientific exploration in an attempt to achieve this promising purpose. Towards this end, the technology of ‘nanoising’ the poorly soluble drugs in the presence of carrier nanoparticles has been identified as the most promising and exciting among the existing drug formulation technologies. The role of the carrier matrix in various drug formulations is the crucial part in the design and development of the nanoformulations which is the important subject of the present investigations in arriving at the right nanoformulation for some of the NSAID drugs.

*Polymer Matrix Engineering for the Development of Highly efficient NSAIDS.*

At this critical juncture, our research group was able to identify two important factors to improve upon; the addressing of which would facilitate the engineering, development and manufacture of cost effective, high-performance nanoformulations, with superior dissolution and solubility enhancements. They are as follows:

**Nanoising:** There are immense opportunities to get some novel drug delivery system by utilizing nanotechnology, because ‘Nanoising’ of drugs- Increase drug targeting ability, Reduce the dose needed, Enhance oral bioavailability , Decrease toxicity, Enhance solubility, Increase the stability of drug and formulation, Increase surface area, Enhance rate of dissolution Decrease drug resistance, Increase patient compliance.

In recapitulation, we have already elaborately discussed the various strategies employed by different research groups to improve the bioavailability enhancements. These involved the use of different synthesis routes, matching conditions, and the use of proper carrier. The effective use of the untapped potential of carriers, for promoting superior efficiency of the nanoformulations is highly imperative and essential. We have identified that the carriers as one of the most crucial
component of nanoformulations. Nanocarrier engineering involves the economical synthesis of the specific drug and carrier materials that are chemically, thermally and physically robust; followed by their subsequent incorporation as novel drug-polymer complexes to finally produce; nanoparticle based novel nanoformulations as superior drug formulations. Here, the choice of the carrier must be a low-cost material that would effectively enable highly efficient drug formulation, towards the generation of enhanced bioavailability associated with very high dissolution enhancements and solubility.

1.8 Outline of Thesis

After introducing the broad perspective of the thesis in Chapter I, the very important aspect in the promise of novel nanoformulations, the solubility, its importance and a detailed discussion of the various techniques for the enhancement of solubility and finally the special cases of Nonsteroidal anti-inflammatory Drugs (NSAIDS) have been presented in Chapter II.

Chapter III describes the principles of drug delivery: routes of drug delivery, delivery vehicles, targeting strategies, choice of route of administration and applications of nanotechnology in oral drug delivery and pharmacokinetics of drug absorption, distribution and elimination involving excretion and metabolism including the process of dissolution and nanoformulations in the dissolution enhancement.

In Chapter IV the concepts of bioavailability, the factors that influence bioavailability, has been introduced. A detailed account of drug dissolution, methods for dissolution enhancement and brief introduction of the mechanism of dissolution, factors influencing dissolution and nanoformulations for the enhancement of bioavailability have also been discussed in this chapter. A brief discussion on release kinetic modeling is also included in this chapter.

The various nanoformulations for overcoming poor solubility challenge are discussed in Chapter V. These include drug nanocrystals, first, second and third generation nanodispersions, nanoemulsions, and polymeric micelles.

Chapter VI deals with the materials required for the preparation of the proposed nanoformulations and the methodologies employed for realizing the improved characteristics of the formulations including the synthesis, characterization and actual measurements of the parameters associated with the betterment of the efficacy of the chosen drugs, formulation of the nanodispersions into
tablets and the characterization of the tablets, dissolution, phase solubility studies. A brief introduction to cell culture with special reference to caco2 cells and the procedures for cytotoxicity studies

In Chapter VII, we explore the use of aqueous based wet ball milling, an easy and scalable manufacturing process, to prepare nanoformulations of Naproxen and to evaluate and compare the effect of three different carriers, i.e. Gelucire 50/13, Soluplus® and PVP (Kollidon-25) on the physico-chemical characteristics of the nanoformulations and the drug dissolution enhancement in order to arrive at the best possible nanoformulation.

Chapter VIII is a report on two formulations of Piroxicam- Nanodispersions and Nanosuspensions. The comparative study of the properties of the nanodispersions of piroxicam made from a novel graft copolymer of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (Soluplus) and the linear polymer polyvinyl pyrrolidone (K 25), both the dispersions synthesized identically using solvent evaporation method. The results obtained from these analyses confirm that the drug is present in amorphous state in the dispersions. The in vitro dissolution characteristics of the tablets made from these powders were studied using the USP paddle dissolution apparatus (type II). The dissolution profiles showed that the nanodispersions have far higher dissolution rate than that of pure drug.

Aceclofenac is a new generational Non-Steroidal Anti-Inflammatory Drug (NSAID) whose bioavailability of the drug remains limited due to low aqueous solubility (0.058 μg/mL) and poor dissolution characteristics. Hence, improving its dissolution characteristics is of prime significance in order to establish its optimal therapeutic efficacy. In an effort to tackle this issue, we report the use of novel Soluplus®-based nanocomposites, prepared from emulsion templates, as effective drug loading agent for aceclofenac in Chapter IX.

Chapter X describes the design and engineering of Soluplus® as a polymeric carrier to support amorphous ibuprofen by preparing an aqueous slurry, and loading the drug onto the polymers by mechanical attrition of the slurry in a planetary ball mill resulting in enhanced dissolution rates. The increased dissolution were attributed to micellar solubilization and superior surface active properties of Soluplus®.
Chapter XI elucidates the *in-vitro* cytotoxicity studies of the nanoformulations highlighting in detail the culture procedure of Caco2 cells and the MTT assay. The cytotoxicity profiles of Naproxen-Soluplus®/Gelucire/PVP and Piroxicam-Soluplus/Gelucire nanoformulations are compared.

Finally an overview of the contents of the thesis highlighting the experimental results and their implications in the context of improved bioavailability of some of the selected NSAIDs has been given as Summary.

### 1.9 References


