Abstract

Particle Formation of Poorly Water Soluble Drugs & their Incorporation into Polymeric Films for Enhanced Oral & Transdermal Drug Delivery

Active Pharmaceutical Ingredients (APIs) are the main components of drug delivery systems. The physical characteristics of APIs such as particle size, size distribution, polymorphic form and crystallinity play a crucial role in the effectiveness of APIs. These properties not only affect the powder flow behavior but also significantly influence the dissolution rates and hence their bioavailability. Nearly 40% of the New Chemical Entities (NCEs) identified by the pharmaceutical industry fall in the category of being poorly water soluble, i.e. in Biopharmaceutical Classification System (BCS) class II and IV drugs. Poor aqueous solubility of drugs and limited drug absorption results in poor bioavailability which is the major problem encountered during pharmaceutical formulation development. This work was therefore focused on enhancing the efficacy of poorly water soluble drugs by formulating these (BCS class II and IV) drugs as ultrafine particles in aqueous suspensions and incorporating drug particles into polymeric films for effective transdermal drug delivery. Reduction in particle size increases the interfacial area for dissolution and hence enhances drug dissolution rates and increases the effectiveness of drug action. Further, the use of drug loaded films can improve the bioavailability since the polymeric films can either be used for transdermal drug delivery or for sublingual delivery. Such a route of drug administration can take advantage of highly vascularized nature of oral or buccal mucosa where drug can directly enter into a systemic circulation without having to pass through hepatic first-pass metabolism.

In this thesis, Fenofibrate and Curcumin were used as model drugs. Fenofibrate is a lipophilic drug used to lower cholesterol levels in blood whereas Curcumin is a naturally occurring ingredient found in turmeric (*Curcuma longa*). Curcumin is known to exhibit anti-inflammatory, antimicrobial and anticancer properties. Liquid Anti-Solvent (LAS) precipitation technique was used to produce aqueous suspensions of drug particles and different grades of hydroxyl propyl methylcellulose (HPMC) were used to produce polymeric films loaded with drug particles. These films were then evaluated for their effectiveness for *in-vitro* drug release.

Sonoprecipitation of fenofibrate was carried out in the presence of different additives. The particle size and morphology were found to be significantly affected by mixing conditions and the use of additives. In order to understand the mechanism by which additives control fenofibrate particle growth and affect particle morphology, intermolecular interactions between additive and fenofibrate were simulated using molecular dynamics simulations. HPMC was found to be the most suitable additive to produce submicron particles while ultrasound helped in stabilizing fenofibrate particles in all the cases. Powder X-ray Diffraction (PXRD) analysis indicated no polymorphic change in the precipitated fenofibrate particles where all the precipitated fenofibrate particles were found to be Form I particles, a stable polymorphic form of fenofibrate. Particles precipitated with Tween 80 exhibited a needle-like morphology whereas fenofibrate particles precipitated with HPMC and Polyvinyl Pyrrolidone (PVP) showed a plate-like morphology. The particles precipitated with Bovine Serum Albumin (BSA) resulted in a mixture of rod and plate-like morphology. The dissolution rate of fenofibrate particles precipitated with additives and ultrasound was highest (about 99% in 6 hrs) as compared to the fenofibrate particles precipitated with additives and without ultrasound. Thus, HPMC was found to be the most effective additive for FNB while PVP was found to be the least effective additive.

Understanding the thermodynamic stability relationship among polymorphs of API is a necessary step for drug formulation development. Knowledge of such relationship enables identification of a stable polymorphic form at the prevalent conditions. Curcumin, a pharmaceutically active ingredient found in herbal spice turmeric, exists in three polymorphic forms; a monoclinic form (Form 1) and two orthorhombic forms (Form 2 and Form 3). However, thermodynamic stability relationships among curcumin polymorphs have not been ascertained yet. One part of the work was therefore focused on understanding thermodynamic stability relationships among curcumin polymorphs. During purification of curcumin, the pressure applied for vacuum evaporation of organic solvent was found to significantly affect the polymorphic outcome. Curcumin Form 2 was found to precipitate when the vacuum pressure in the range of 100-200 mbar was used whereas Form 1 was obtained when pressure in the range of 300-400 mbar was used. Thus, higher pressure was found to result in the nucleation of a stable form (Form 1) which also involves significant hydrogen bonding among curcumin molecules whereas lower pressures were found to facilitate nucleation of a metastable form (Form 2) in accordance to the Ostwald rule of stages. Application of the Burger and Ramberger rules such as heat of fusion, entropy of fusion and heat of transition rules indicates that the thermodynamic stability relationships among the curcumin polymorphs are of monotropic type with Form 1 being the most stable form. The irreversible transformations of Form 2 to Form 1 and that of Form 3 to Form 1 confirmed through DSC heating and cooling cycles and variable temperature XRD studies further prove that monotropic relationships exist between Form 1 and Form 2 and Form 1 and Form 3. Also, Solution Mediated Transformations (SMT) of polymorphic mixtures at 0, and 25 ^{o}C to Form 1 confirm that Form 1 is the most stable form among all three forms. The van't Hoff plot prepared based on the solubility of curcumin polymorphs in ethanol did not show any point of intersection between the

solubility curves of these polymorphs which once again confirms that these polymorphs are monotropically related to each other. It can therefore, be summarized that the curcumin polymorphs are monotropically related to each other and the monoclinic form (Form 1) is the most stable form among three curcumin forms.

One aspect of the work was carried out to demonstrate that continuous LAS precipitation process can successfully produce aqueous suspensions of ultrafine particles of curcumin with narrow size distribution and desired polymorphic form. The use of ultrasound during precipitation process has a tremendous impact on particle size, size distribution, polymorphic form, and suspension stability. It prevents uncontrolled particle growth due to annealing of particle surface and also decreases the mixing time and increases the nucleation rates during LAS precipitation. Mixing time obtained during precipitation with ultrasound is 100 times lower than that without ultrasound. The polymorphic form of the precipitated particles can also be controlled by using ultrasound and additive. Orthorhombic curcumin form was found to precipitate when ultrasound and additives were used and a monoclinic form was found to precipitate when precipitation was carried out without ultrasound and additives. The observations made in this work demonstrate that by the judicious choice of additives and different process conditions like sufficient use of ultrasound, a highly scalable continuous LAS precipitation process can be developed to produce ultrafine particles of curcumin with desired particle size and polymorphic form. Further, this process can also be used for continuous precipitation of other poorly water soluble drugs.

Next, we focused on precipitation of ultrafine particles of curcumin polymorphs at higher drug loading and their incorporation into polymeric films for transdermal drug delivery. Curcumin polymorphs i.e., Form 1 (monoclinic), Form 2 (orthorhombic) and Form 3 (orthorhombic), was precipitated using LAS precipitation incorporated into polymeric films

in order to test their efficacy for transdermal drug delivery. Curcumin particles obtained at higher curcumin concentrations from acetone solutions in presence of ultrasound and additives were found to precipitate as stable Form 1. However, the particles obtained at high curcumin concentrations from DMSO solutions (with ultrasound and additives) were found to precipitate as metastable Form 3. The cytotoxicity of curcumin polymorphs was studied on SK-MEL 28 cell line. The free radical scavenging activity of Form 3 was found to be highest, followed by Form 2 and Form 1. Form 3-loaded films showed higher release profiles, both at the pH of 5.5 and 7.4. These studies imply that wound healing might accelerate for Form 3 loaded films as compared to Form 2 and Form 1 loaded films and that the films prepared in this work are suitable candidates for transdermal drug delivery.

To summarize, this work provides a basic understanding of particle formation process which can be used to control the particle morphology and polymorphism of poorly water-soluble drugs during LAS precipitation. It was found that particle size, polymorphism and morphology can be altered by mixing conditions and the use of additives both at batch and at a continuous mode of precipitation. Thus, judicious choice of precipitation conditions can significantly impact and modulate the dissolution profiles of the precipitated drug particles. This work also presents a systematic evaluation study to assign thermodynamic stability relationship between the polymorphs which is very important in understanding the occurrence domains of several polymorphs. Moreover, it is shown that the patches made of HPMC [with triethyl citrate (TEC) as a permeation enhancer] serve as an effective drug carrier for curcumin in the transdermal drug delivery. Curcumin Form 3 exhibits the highest release and permeation profiles among all the curcumin polymorphs studied in this work.