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Influence of chemical nature of carrier materials on the dissolution behavior of racemic ibuprofen

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ABSTRACT

The poor aqueous solubility of ibuprofen due to its hydrophobicity limits the bioavailability of the drug in the aqueous environment of the human body. Therefore particle deposition experiments were performed with ibuprofen and different carrier materials. Furthermore, the dissolution behavior of the untreated ibuprofen and the ibuprofen loaded carriers has been investigated at 310 K and pH = 2.0 and pH = 5.5.

The results of this investigation demonstrate that drug loadings up to 50 wt% drug onto silica materials could be achieved and that the drug loading increases nearly linear with increasing surface area of the silica materials. Furthermore, the study reveals that the highest dissolution rate was obtained with β-cyclodextrin and that the dissolution rate of all materials investigated increases with increasing pHvalue.

1. Introduction

One of the biggest challenges in pharmaceutical research is to improve the bioavailability of orally applied drugs since the bioavailability of these mainly poorly water soluble compounds depends strongly on the size, particle size distribution and morphology of the particles. It is well known that especially in case of anti-inflammatory drugs such as ibuprofen or naproxen, which are highly permeable but poorly water soluble (class II of the Biopharmaceutical Classification System [1]) the bio-absorption process is strongly limited by the dissolution behavior in aqueous media. Due to this, there is an enormous need for the development of efficient technologies, which increase the dissolution behavior. Until today, several ways are known to improve the drug solubility and dissolution behavior, for example the use of surfactants or co-solvents, solid dispersions or lipid-based formulations [2]. Other suitable ways to increase the solubility are complex formation with cyclodextrins or the reduction of the particle size [2,3]. Conventional particle size reduction methods like milling, spray-/freeze drying or grinding show different disadvantages (broad particle size distribution, thermal or chemical degradation of the product etc.). To prevent these drawbacks new methods like processing with supercritical fluids (SCF) [4,5] are under examination because they are characterized by liquid like densities whereas mass transfer properties (diffusion and viscosity coefficients) resemble more those of gases [6]. CO_2 is considered as a suitable solvent since it is non-toxic, non-flammable, inexpensive, and allows the production of a solvent-free and dry product [4]. Despite this, the low critical data (T_c = 304 K, p_c = 7.4 MPa) allow moderate process conditions.

Reliable and well-known methods to form submicron or nano-sized particles are the rapid expansion of supercritical solutions (RESS) or various modifications such as CORESS (coprecipitation during rapid expansion of supercritical solutions), RESOLVE and RESSAS (rapid expansion of supercritical solutions into liquid or aqueous solutions) [5,7–15]. Numerous investigations have shown that the particles formed by these processes enhance the dissolution rate of poorly soluble active ingredients in aqueous media at pH values ranging from 2 to 7.4 [5,8,15].

However, submicron particles are difficult to handle and to include into solid dosage forms. Therefore, measures to incorporate poorly water-soluble drugs into appropriate solid dosages forms receive increased attention. In general, different techniques, such as kneading, grinding, co-precipitation, and freeze-drying, can be used to incorporate poorly water-soluble substances into a fast dissolving hydrophilic carrier. The drawbacks of these methods are high processing temperatures or the need to require the use of organic solvents that can be found as residual in the product. To overcome this, Türk et al. developed the controlled particle deposi-

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tion process (CPD) [8,16]. The key idea behind CPD is to dissolve the drug in a supercritical fluid, followed by permeation of the supercritical mixture into the pores of a carrier and subsequent precipitation of the drug inside the pores caused by a fast pressure drop in the system. Thus, the attractive feature of CPD is the possibility to produce solvent-free, drug loaded carrier particles in a single processing step. Among others, a suitable group of carrier material are cyclodextrins [16–21]. Besides the formation of inclusion complexes between drugs and cyclodextrins the supercritical impregnation of aerogels [22,23], porous silicas [24,25], polymers [26,27], microcrystalline cellulose pellets and hydroxyethylcellulose [28], sugar cubes [28] etc. with drugs are used. Furthermore, coated tablets with optimized drug release profiles can be produced. Thereto it must be pointed out that the choice of the carrier material and its interaction with the drug molecule determines whether accelerated or retarded dissolution behavior is achieved.

2. State of the art

The following two chapters give a short overview (that cannot pretend to be complete) of published knowledge classified according to two different concepts that are, among others, currently considered as a viable option to obtain an improved dissolution behavior of poorly soluble drugs in aqueous media.

2.1. Cyclodextrins (CDs)

CDs have indeed been explored extensively as additives in the pharmaceutical industry due to their unique ability to host and solubilize hydrophobic guest molecules including poorly water-soluble drugs. The most common cyclodextrins are α-, β- and γ-CD. These natural CDs consist of six, seven or eight glucopyranose units, and are characterized by a hydrophilic surface and a hydrophobic cavity. Due to their high water solubility and the ability to form inclusion complexes with hydrophobic molecules [3,29] CDs are often used in different pharmaceutical applications.

Already in 1999 van Hees et al. started investigations about the preparation of a piroxicam/β-CD complex [30]. By treating a physical mixture of both components with $scCO_2$ for 3 h (T = 423 K and p = 45 MPa) a complete inclusion of 94% was achieved.

Numerous investigations on the formation of ibuprofen/CD inclusion complexes and their dissolution behavior have been performed in the past [8]. Charoenchaitrakool et al. have investigated the complex formation of methyl-β-CD and ibuprofen [19]. At T = 308 K and p = 22 MPa high ibuprofen loadings of 10.8 wt% that are close to a 1:1 complex (13.6 wt%) were reached. In comparison to a physical mixture the dissolution behavior of the $scCO_2$ treated mixture was significantly enhanced at pH = 5.5 during the initial period. This behavior can be explained by the amorphous nature of the product and its improved wettability.

The $scCO_2$ based impregnation of β-CD with ibuprofen was investigated by Türk et al. applying the CPD process at T = 313 K and p = 25.7 MPa [16]. High loadings up to 88 mol% were obtained. Furthermore the dissolution behavior of an unprocessed physical mixture was compared to the CPD products and untreated ibuprofen at pH 2.0 and 5.5. All inclusion complexes showed an improved dissolution behavior in comparison to untreated ibuprofen, whereas the CPD products offered the best dissolution behavior. Furthermore CPD experiments performed by Hussein et al. showed an improved dissolution behavior of CPD impregnated β-CD [17]. Under process conditions of T = 313 K and p = 24.4 MPa ibuprofen loadings of 2.8 wt% on β-CD powder [17] and 17.4 wt% on β-CD granules [31] were obtained.

Tozuka et al. investigated the effect of different CDs, in particular β-CD, dimethyl-β-CD and trimethyl-β-CD, on the inclusion complex formation with racemic ibuprofen [18]. Within the process conditions investigated a complex formation occurred only with trimethyl-β-CD while no inclusion formation between ibuprofen und β-CD was observed after processing with $scCO_2$.

Banchero and Manna investigated the influence of lysine on the formation of ketoprofen/CD complexes [32]. In this study lysine was selected as co-solvent and yields up to 92% on β-CD and 83% on 2-hydroxypropyl-β-CD were achieved at T = 343 K and p = 30 MPa. Furthermore the authors reported that increased drug loadings could be achieved if water was used as an additive during the impregnation step [32,33].

2.2. Mesoporous silica carriers

The possibility to fine-tune the pore size, surface area and the surface chemistry in ordered mesoporous materials such as MCM-41 (i.e. Mobil Composition of Matter or Mobil Crystalline Materials) and SBA-15 (i.e. Santa Barbara Amorphous type material) enables the improvement of the dissolution behavior of poorly soluble drugs since these ordered materials easily liberate adsorbed hydrophobic compounds into aqueous media. However, until now, only a small number of studies investigated the SCF based deposition of drugs onto these mesoporous silica materials.

Ni et al. investigated the deposition of ibuprofen on SBA-15 at 310 K and 17 MPa [25]. Depending on the ibuprofen concentration in the $scCO_2$ high loadings up to 42 wt% were obtained. However, adding a small amount of ethanol (5 ml) to the system the drug loadings were decreased from 37 wt% to 8 wt%. Nevertheless, all samples showed a fast drug release in a simulated body fluid (SBF). Hillerström et al. used liquid CO_2 to impregnate MCM-41 with ibuprofen and this method led to a high drug content of 0.3 g ibuprofen/g SiO_2 [34]. If additives such as acetone, cyclohexane or methanol were used, the drug loadings were significantly decreased due to a competition between the H-bonds on the surface Si-OH-groups, the additive and the ibuprofen molecules. All samples showed an improved dissolution performance in aqueous media compared to the untreated crystalline ibuprofen [35].

Li-Hong et al. impregnated MCM-41 with ibuprofen at T = 313 K and pressures ranging from p = 20–30 MPa [24]. Thereby the impregnation time was fixed to 2 h and drug loadings up to 38.6 wt% were achieved. Additional dissolution experiments were performed at 310 K and the results showed that after 15 min a drug release of 50% and of 90% after 60 min was reached. In comparison thereto samples, which were prepared by the organic solvent immersion method (OSIM) reached lower loadings (15.1 wt%) but showed an improved dissolution behavior. The authors explained this result by the differences in the drug location inside the pores. Thereby they assumed that the molecules that were deposited by SCF impregnation are deposited deeper inside the pores than those molecules deposited by OSIM. The latter case facilitates a faster transfer of the molecules from the silica matrix to the aqueous solution that leads to a fast drug release.

Charnay et al. studied the influence of different solvents (dimethyl sulfoxide, methyl methacrylate, dimethylformamide, ethanol, and hexane) and loading procedures on the deposition of ibuprofen in mesoporous MCM-41 [36]. The experiments showed that a decrease of the solvent polarity results in an increase of drug loading, that ibuprofen could be loaded with a high efficiency into MCM-41 (up to 0.59 g/g) and that the loading extent is influenced by the loading procedure. Additional dissolution experiments performed in a simulated gastric (pH = 1.2) and intestinal fluid (pH = 7.4) showed a rapid and nearly 90% release of the ibuprofen molecules after 60 min.

Vallet-Regi et al. investigated the effect of pore sizes on drug loading and dissolution behavior [37]. In these investigations MCM-41 materials were synthesized by using two different surfactants

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