International Journal of Pharmaceutics 533 (2017) 145–155

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Research paper

Improving the wetting and dissolution of ibuprofen using solventless co-milling

Sophia Varghese, Chinmay Ghoroi*

DryProTech Lab., Chemical Engineering, Indian Institute of Technology Gandhinagar, Palaj, Gandhinagar, 382355, Gujarat, India

ARTICLE INFO

Keywords:
Solid dispersion
Co-milling
Strain
Defects
Hydrophilicity
Wettability
Dissolution

ABSTRACT

The wetting and dissolution of a BCS class II drug (Ibuprofen) is enhanced by solventless solid dispersion technique using co-milling. The co-milling is performed in a planetary ball mill using 1:1 wt. ratio of Ibuprofen (drug) and Microcrystalline cellulose, MCC (excipient). The improvement in wettability and dissolution after co-milling are compared with the raw ibuprofen, ball-milled ibuprofen without any excipient and v-blend mixture of ibuprofen with an excipient. The changes in crystal level properties and reduction in crystallinity due to co-milling are measured using Powder X-ray diffraction (P-XRD) and Differential Scanning Calorimetry (DSC) respectively. The increased interaction between ibuprofen and MCC as well as hydrogen bond formation is confirmed by Fourier Transform Infrared Spectroscopy (FTIR). The morphological changes are observed by optical microscopy and Field Emission Scanning Electron Microscopy (FESEM). The miscibility of drug and excipient and evidence of formation of glassy solutions are demonstrated by Modulated Temperature Differential Scanning Calorimetry (MTDSC) and Raman microscopy. The surface energy and wetting properties are determined using Inverse Gas Chromatography (IGC) and sessile drop method respectively. The results show that co-milling generates defects, strain, and reduction in crystallite size (changes in crystal level properties) which are responsible for the improvement of wetting and dissolution (96% in 90 min). Also, with increase in co-milling time, the polar surface energy increases and the hydrophobic ibuprofen drug surface transforms into hydrophilic surface due to increase in −OH groups of MCC on the ibuprofen surface. The present work quantified all the above-mentioned parameters including the acidic and basic parameters of co-milled ibuprofen using IGC. The technique improves the wetting and dissolution of hydrophobic drugs. It can be very well extended to BCS class II and IV drugs in the presence of different hydrophilic excipients.

1. Introduction

Improving the bio-availability of dissolution limited drugs (BCS Class II) is the major challenge for many pharmaceutical industries. Several well-known drugs such as ibuprofen, danazol, carbamazepine, indomethacin, itraconazole, griseofulvin belong to this class of drug (Kawabata et al., 2011). These drugs have low solubility and high permeability. Thus, improving the dissolution of these hydrophobic drugs can be beneficial for pharmaceutical industries (Kawabata et al., 2011; Khadka et al., 2014). There is several methods to improve the dissolution of such drugs. Particle size reduction or micronization is one of the widely used top down approaches to improve the solubility of drugs using different types of mills such as ball-mill (Khadka et al., 2014) and fluid-energy mill (Han et al., 2011). The milling of drug reduces the drug particles to few micron or submicron levels only. Amorphization of certain drugs such as piroxicam, budesonide, naproxen, and indomethacin is also reported which provides larger surface area and thus improves the wettability and dissolution (Khadka et al., 2014).

However, milling of powder also offers certain disadvantages such as the coarser particles are turned into finer ones which are more energetic (Han et al., 2011; York et al., 1998) due to increase in surface energy. This increases the interactions among particles and exhibits increased cohesiveness and forms a larger aggregate which is responsible for reduced dissolution (Han et al., 2013; Nikghalb et al., 2012). In-order to overcome this challenge usage of surfactants during milling and wet milling is preferred (Khadka et al., 2014).

The solid dispersion technique is one of the promising techniques to improve the solubility of hydrophobic drugs. This technique is mainly accomplished by solvent, melting methods (Kaushal et al., 2004; Liu et al., 2013; Nikghalb et al., 2012; Vasconcelos et al., 2007) and co-milling (Barzegar-Jalali et al., 2010; Lim et al., 2013; Liu et al., 2013; Nikghalb et al., 2012; Rojas-Oviedo et al., 2012). Solid dispersion forms dispersed phase which exists in different forms such as eutectic

* Corresponding author.
E-mail address: chinmayg@iitgn.ac.in (C. Ghoroi).

http://dx.doi.org/10.1016/j.ijpharm.2017.09.062
Received 11 June 2017; Received in revised form 19 September 2017; Accepted 22 September 2017
Available online 23 September 2017
0378-5173/

mixtures, glass solutions (Forster et al., 2001; Teja et al., 2013). This technique offers certain advantages such as reduction of particle size as well as the crystallinity of drug. It produces particles with higher porosity and prevents the formation of agglomeration. Free flowing powders are produced with increased wettability which improves their bioavailability (Vasconcelos et al., 2007).

However, *solvent assisted* and melting method of solid dispersion has its drawbacks such as difficulty in complete removal of solvent, high preparation cost (Vasconcelos et al., 2007), degradation of drugs processed with polymers at high temperatures (Pattnaik et al., 2015), etc. In contrast, *solventless co*-milling or co-grinding of drugs with various excipients such as lactose, MCC, starch (Vogt et al., 2008), etc. is a promising green approach of solid dispersion (Pattnaik et al., 2015).

Patterson et al. (2007) performed solid dispersion using three different methods such as spray drying, solvent method, and ball-milling and observed that high energy ball-milling has a potential to form glassy solution (Patterson et al., 2007). Riekes et al. (2014) studied the co-grinding technique to improve the hydrophilicity of nimodipine. They observed an enhancement in bio-pharmaceutical property due to increased hydrophilicity and hydrogen bond formation without any significant change in particle size distribution. Similarly, Mallick et al. (2013) studied the compaction and dissolution of co-milled ibuprofen and MCC (Avicel PH 101) with different weight% of Aerosil (colloidal silicon dioxide). Improvement in the compaction and dissolution of the tablet was observed for different blends of MCC owing to reduced crystallinity confirmed from DSC studies. However, the role of surface energetics including the acid/base nature of surface as well as changes in crystal level properties such as defects, dislocations, and strain which dictate the wetting and dissolution behaviour of drugs is not explored in the literature. In this work, we have investigated these aspects and their effect on improving the wettability and dissolution of ibuprofen without the addition of any nano-material (colloidal silicon dioxide).

The objective of this work is to improve the wettability and dissolution of ibuprofen without using any solvent and melting methods. The present work focuses on the use of an alternative solventless approach ("co-milling"). In this work, ibuprofen and MCC are milled together (co-milling) and the improved performance of wetting and dissolution is reported. The changes in the crystal level properties (defects, strain, crystallite size) due to co-milling are quantified using P-XRD. Also, with increase in co-milling time the changes in the polar surface energy and acidic and basic characteristics of the ibuprofen drug surface is studied using (Inverse Gas Chromatography). Formation of the glassy solution, drug excipient compatibility is also predicted using glass transition temperature with the help of MTDSC and Raman microscopy.

2. Experimental

2.1. Materials

Ibuprofen was obtained as a gift sample from (BASF, Ludwigshafen Germany), and MCC (Avicel PH105, FMC Biopolymers) was used for milling and co-milling. De-ionised water (Millipore, USA) was used as a test liquid for carrying out wettability studies using sessile drop method. IGC experiments were performed using non-polar alkane probes-decane (Spectrochem, India), nonane (Merck, USA), octane (Spectrochem, India) heptane (RANKEM, India) and polar probes such as dichloromethane (Finar, India) and ethylacetate (Finar, India).

2.2. Milling and Co-milling process

Ball-milling of ibuprofen and co-milling of drug (ibuprofen) and excipient (MCC) was carried out in a planetary ball-mill (Insmart systems) in 500 ml zirconia bowl. The zirconia balls used were of 10 mm diameter. The powder to ball ratio was maintained as 1:2. Ibuprofen was milled without any excipient for 10 min. For co-milling, ibuprofen, and MCC were taken in 1:1 weight ratio operated at 100 rpm for 10 min and 20 min. Prior to milling and co-milling ibuprofen and MCC, both the powders were first passed through 30 mesh BSS sieve, and the co-milled mixture was premixed in v-blender at 15 rpm for 20 min. After co-milling for 10 min, off-time of 5 min was given in between and some amount of sample was withdrawn while maintaining powder to ball weight ratio of 1:2.

2.3. Particle size and morphology (Optical microscopy and scanning electron microscopy)

Particle size analysis was performed using laser diffraction particle size analyzer (CILAS, Model 1190) in dry mode. The particle size distribution for as received ibuprofen, MCC, v-blended and co-milled mixtures was determined.

The surface morphology for as received samples, ball-milled ibuprofen, v-blend mixtures, as well as co-milled samples was characterized using optical microscopy (Carl Zeiss Axio Scope. A1) and FE-SEM (JEOL JSM 7600F, USA). FE-SEM was performed with a working distance of 7–9 mm and voltage of 5 kV.

2.4. Raman microscopy

Confocal laser dispersion Raman microscope (REINSHAW plc, U.K) using 785 nm NIR laser was used. Mapping was carried out for 20 μm × 20 μm region with a higher resolution of 1 cm^{-1} with confocal depth profiling with step size 0.1 μm. Raman microscopy was carried out for co-milled mixtures at different times to study the miscibility and presence and of drug and excipient rich areas after co-milling.

2.5. Powder X-Ray Diffraction (PXRD)

To determine the crystallinity of drug and the excipients XRD analysis was carried out using Powder X-ray diffraction (Bruker D8 Discover) with Cu Kα, operating at 40 kV and 30 mA. Scan speed was kept as 0.2s/step while a step size of 0.02 and scanning range (2θ) from 5 to 50. Powder XRD of ibuprofen, MCC, ball-milled ibuprofen, v-blend mixtures and co-milled mixtures were performed. All the experiments were carried out at room conditions. Initially for ibuprofen as received and ball-milled for 10 min was compared to check if the reduction in its crystallinity was taking place and to observe the changes in its crystal properties respectively. Also for v-blend mixture and co-milled mixtures, similar studies were carried out.

While Strain in lattice was determined by Debye-Scherrer equation

$$\varepsilon = \frac{\beta}{4tan\theta} \quad (1)$$

Crystallite size was calculated using following equation:

$$D = \frac{0.9\lambda}{\beta cos\theta} \quad (2)$$

Where, ε = Strain, β = Full Width Half Maxima (FWHM)
D = Crystallite size, λ = Wavelength

2.6. Fourier Fourier Transform Infrared Spectroscopy (FTIR)transform infrared spectroscopy (FTIR)

Fourier transform infrared spectroscopy was used to analyze the functional groups present in the powders using Perkin Elmer Spectrum GX FTIR Spectrometer. Drug and excipient interactions were studied from FTIR. The samples were prepared by conventional KBr method where KBr pellets comprises of 200 mg KBr powder and 2 mg of sample to be analyzed.