International Journal of Pharmaceutics 423 (2012) 496–508

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

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

Pharmaceutical nanotechnology

Preparation and characterization of hydroxypropyl methyl cellulose films containing stable BCS Class II drug nanoparticles for pharmaceutical applications

Lucas Sievens-Figueroa[a], Anagha Bhakay[a], Jackeline I. Jerez-Rozo[b], Natasha Pandya[a], Rodolfo J. Romañach[b], Bozena Michniak-Kohn[d], Zafar Iqbal[c], Ecevit Bilgili[a], Rajesh N. Davé[a,*]

[a] Department of Chemical, Biochemical, and Pharmaceutical Engineering, New Jersey Institute of Technology, United States
[b] Department of Chemistry, University of Puerto Rico, Mayagüez Campus, United States
[c] Department of Chemistry and Environmental Science, New Jersey Institute of Technology, United States
[d] Department of Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers-The State University of New Jersey, United States

ARTICLE INFO

Article history:
Received 7 October 2011
Received in revised form
29 November 2011
Accepted 1 December 2011
Available online 9 December 2011

Keywords:
Nanosuspensions
Media milling
BCS Class II
Pharmaceutical films
Hydroxylpropyl methyl cellulose

ABSTRACT

The design and feasibility of a simple process of incorporating stable nanoparticles into edible polymer films is demonstrated with the goal of enhancing the dissolution rate of poorly water soluble drugs. Nanosuspensions produced from wet stirred media milling (WSMM) were transformed into polymer films containing drug nanoparticles by mixing with a low molecular weight hydroxylpropyl methyl cellulose (HPMC E15LV) solution containing glycerin followed by film casting and drying. Three different BCS Class II drugs, naproxen (NPX), fenofibrate (FNB) and griseofulvin (GF) were studied. The influence of the drug molecule on the film properties was also investigated. It was shown that film processing methodology employed has no effect on the drug crystallinity according to X-ray diffraction (XRD) and Raman spectroscopy. Differences in aggregation behavior of APIs in films were observed through SEM and NIR chemical imaging analysis. NPX exhibited the strongest aggregation compared to the other drugs. The aggregation had a direct effect on drug content uniformity in the film. Mechanical properties of the film were also affected depending on the drug–polymer interaction. Due to strong hydrogen bonding with the polymer, NPX exhibited an increase in Young's Modulus (YM) of approximately 200%, among other mechanical properties, compared to GF films. A synergistic effect between surfactant/polymer and drug/polymer interactions in the FNB film resulted in an increase of more than 600% in YM compared to the GF film. The enhancement in drug dissolution rate of films due to the large surface area and smaller drug particle size was also demonstrated.

1. Introduction

The solubility of drug molecules is an important factor to take into account during the development and design of new drug products. According to the Biopharmaceutical Classification System (BCS), Class II drugs are characterized by their poor solubility and high permeation in the human body (Amidon et al., 1995). The hydrophobicity becomes essential for their transport properties through the cell membrane and their pharmacological action to be exerted in the desired tissue. Since these compounds have low solubility, limited bioavailability is observed (Krishnaiah, 2010; Kesisoglou et al., 2007). In order to overcome this limitation, a commonly used approach involves particle size reduction (Merisko-Liversidge and Liversidge, 2011; Liversidge and Cundy, 1995; Muller, 2011; Keck and Muller, 2006; Pu et al., 2009; Timpe, 2010; Gao et al., 2008; Pathak et al., 2005; Panagiotou and Fisher, 2008). By reducing the particle size it is expected that the dissolution rate will be increased as described mathematically by the Noyes–Whitney equation (Noyes and Whitney, 1897).

Among the methods used for particle size reduction the use of wet stirred media milling (WSMM) has received much attention because of the effectiveness in producing microparticles and nanoparticles (Bhakay et al., 2011; Merisko-Liversidge and Liversidge, 2011; Merisko-Liversidge et al., 2003). WSMM has been extensively used to formulate nanoparticles of drugs that are poorly soluble into nanosuspensions that can be used orally or can be used in ocular delivery, intravenous administration and dermal applications (Mauludin et al., 2009; Shegokar and Müller, 2010; Rabinow et al., 2007; Petersen, 2006; Piao et al., 2008; Hernandez-Trejo et al., 2005). In order to take advantage of the bioavailability enhancement it is necessary for the particle size to be preserved after administration. In general, this becomes problematic since particles tend to aggregate due to their large surface area and need to be stabilized (Bilgili et al., 2006; Mende et al., 2003; Peukert et al.,

* Corresponding author. Tel.: +1 973 596 5860; fax: +1 973 642 7088.
E-mail address: dave@adm.njit.edu (R.N. Davé).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.12.001

2005). Without a means to functionalize the surface, nanoparticles will tend to aggregate to a less energetic state. Polymers and surfactants are used as stabilizers to minimize particle aggregation (Van Eerdenbrugh et al., 2009). The stabilizers adsorb on the surfaces of the drug particles and provide an ionic or steric barrier (Merisko-Liversidge et al., 2003; Ploehn and Russel, 1990).

A significant amount of the work in the literature has focused on process improvement, characterization and stability of nanosuspensions (Choi et al., 2005; Verma et al., 2011; Van Eerdenbrugh et al., 2009). Stability of nanosuspensions could become challenging and therefore solid dosage forms are preferred (Bhakay et al., under review; Van Eerdenbrugh et al., 2008c). Solid dosage forms are also considered more attractive due to their convenience and consumer preference aspects. However, in order to prepare them, nanosuspensions have to be dried, which would likely lead to agglomeration of the nanoparticles, poor re-dispersion and poor recovery of nanoparticles (Heng et al., 2010; Bhakay et al., under review; Van Eerdenbrugh et al., 2008a,b; Lee and Cheng, 2006; Lee, 2003; Kim and Lee, 2010; Choi et al., 2008; Hu et al., 2011; Cheow et al., 2011). Most of the transformation of nanosuspensions into solid products presented in literature use well known unit-operations such as freeze-drying, spray-drying, pelletization and granulation (Van Eerdenbrugh et al., 2008a; Müller et al., 2006). Further processing of those powders in capsule filling or compression into tablets can also be performed (Vergote et al., 2001; Heng et al., 2010). In previous work, Desieno and Stetsko (1996) described the use of carrier particles, such as sugar or microcrystalline cellulose, coated with films containing nanoparticles utilizing WSMM. They showed re-dispersion and size preservation of the nanoparticles from the coated carrier utilizing stabilizers. Wax based pellets loaded with nanocrystalline ketoprofen have also been studied and the enhancement in dissolution compared to the microcrystalline form shown (Vergote et al., 2001). While the transformation of nanoparticles from WSMM to common solid dosage forms has been presented, the integration of WSSM into polymer films remains to be well studied. Polymer films can be an effective carrier of nanoparticles to mitigate the aforementioned problems and enhance dissolution of poorly water-soluble drugs, hence integration of WSSM into polymer films is warranted.

Polymer films (PF) have great potential over other dosage forms for delivery of poorly soluble drugs since they provide distinct advantages over other oral formulations including larger surface area which leads to rapid disintegration and dissolution in the oral cavity and increased bioavailability (Dixit and Puthli, 2009). This allows for a more rapid and controlled wetting in the oral or buccal environment. PF are easy to swallow and are a convenient dosage form and this has also led to improved acceptability and compliance among the geriatric and pediatric patients. PF also exhibit manufacturing advantages including continuous manufacturing capabilities that enable full product characterization when incorporated with in-line monitoring using Process Analytical Technologies (PAT) (Dixit and Puthli, 2009). Even though the interest in pharmaceutical films has increased based on publications and patents (Boateng et al., 2010; Matthews et al., 2008; Garsuch and Breitkreutz, 2010; Mendoza-Romeroa et al., 2009; Li and Gu, 2007; El-Setouhy and Abd El-Malak, 2010; Perumal et al., 2008; Bess et al., 2010; Yang et al., 2010, 2011), more research is needed in order to overcome potential limitations and increase the general patient acceptance.

Research in this field has focused on the incorporation of water-soluble drugs into film formulations (Jug et al., 2009; Nishimura et al., 2009; Schmidt and Bodmeier, 1999; Shimoda and Taniguchi, 2009). While water soluble drugs exist in the dissolved state or as solid solution, the water insoluble drugs have to be homogenously distributed in a film formulation in order to have an acceptable drug content uniformity. In recent patents (Yang et al., 2010, 2011) the process for making films with uniform distribution of components is described. The incorporation of poorly soluble particles into films or the issues involved when using microparticles or nanoparticles were not specifically addressed in these patents. Interactions between the drug molecule and polymer could also produce differences in the film properties (Nair et al., 2001). In this work we use a simple process for the preparation of films containing dispersed nanoparticles as the final dosage form for drug delivery applications. WSMM is used to produce stable BCS Class II drug nanosuspensions that are then transformed into polymeric films containing stable drug nanoparticles. The objective of this work was to demonstrate the feasibility and set the groundwork for the integration of WSMM with pharmaceutical polymer films formulations. A range of BCS Class II drugs that includes griseofulvin, fenofibrate and naproxen were used. The particle size distribution of the nanosuspensions and re-dispersion of the drug particles from films were investigated by utilizing laser diffraction. Distribution of drug particles in film was studied by NIR Chemical Imaging (Jérez Rozo et al., 2011). The influence of the drug molecule on the film mechanical properties was also studied. The morphology of the particles from suspensions and the structure of the films were observed by using Scanning Electron Microscopy (SEM). The crystallinity of drug particles before milling and in films was studied by X-ray diffraction (XRD) and Raman spectroscopy. The drug content for film containing nanoparticles with different thicknesses was studied, and the dissolution behavior was compared to different solid dosage forms and films containing microparticles.

Table 1
Physicochemical properties of the drugs.

Drug	Solubility (mg/l)	Molecular weight	Melting point (°C)	log *P*	Particle size (μm)		
					D_{10}	D_{50}	D_{90}
FNB	0.50	360.8	80.5	4.4	4.6	13.2	34.2
GF	8.99	352.8	220.0	3.5	5.2	11.8	23.6
NPX	17	230.26	153	3.0	3.2	11.5	26.7

2. Materials and methods

2.1. Materials

The drug molecules utilized were griseofulvin (GF; Sigma–Aldrich, Saint Louis, MO), naproxen (NPX; Medisia, NY, USA), and fenofibrate (FNB; Ja Radhe Sales, Ahmedabad, India). Chemical structures of the drug molecules are shown in Fig. 1. Sodium dodecyl sulfate (SDS) (Sigma–Aldrich, Saint Louis, MO) and low molecular weight hydroxypropyl methyl cellulose (HPMC; Methocel E15LV) (Dow Chemical) were used as a stabilizer. HPMC (Methocel E15LV) was also used as a film former. Glycerin (Sigma) was used as a plasticizer. All these materials were used without further processing.

2.2. Methods

2.2.1. Preparation of drug nanosuspensions

FNB, GF and NPX were chosen as the model BCS Class II drugs. The physicochemical properties of these drugs are given in Table 1. The initial particle sizes of all the drugs were slightly different as seen in Table 1. The formulation of the suspensions and the milling time for each of the drugs differed based on the optimization studies performed in our group. The formulation of the suspensions was optimized for all the drugs in a separate study, which was guided by the work in Bhakay et al. (2011, under review) and will be presented in a forthcoming paper. The HPMC concentration was kept constant at 2.5% (w/w) (wrt water) for all the drugs. The SDS concentration was 0.5% (w/w) (wrt water) for GF and NPX suspensions and was reduced to 0.075% (w/w) (wrt water) for FNB suspension. A low