EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES 28 (2006) 67–76

available at www.sciencedirect.com

SCIENCE DIRECT®

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

Stabilization of solid dispersions of nimodipine and polyethylene glycol 2000

*Nora Anne Urbanetz**

Institut für Pharmazeutische Technologie und Biopharmazie, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany

ARTICLE INFO

Article history:
Received 1 March 2005
Received in revised form 23 December 2005
Accepted 30 December 2005
Available online 10 February 2006

Keywords:
Ageing
Dissolution
Nimodipine
Polyethylene glycol
Povidone
Recrystallization
Solid dispersion
Supersaturation

ABSTRACT

Previous investigations revealed that solid dispersions consisting of 20% (m/m) nimodipine and 80% (m/m) polyethylene glycol 2000 prepared by the melting method, represent supersaturated solid solutions of nimodipine recrystallizing upon storage at +25 °C. The objective of this study was the improvement of the storage stability by preventing recrystallization. The first approach in order to prevent recrystallization was the development of thermodynamically stable solid solutions by using solvents aiming to enhance the solubility of nimodipine in the carrier material. As potential solubility enhancing additives, polyethylene glycol 300, poly(ethylene/propylene glycol) copolymer, polypropylene glycol 1020, propylene glycol, glycerol and ethyl acetate were evaluated. The second approach enhancing storage stability was the addition of recrystallization inhibitors to supersaturated solid solutions, thereby delaying the transformation of the metastable supersaturated system to the thermodynamically stable state. Macrogol cetostearyl ether, macrogol glycerol monostearate, polysorbate 60, cetostearyl alcohol, glycerol monostearate and sodium lauryl sulphate as well as hydroxypropylcellulose, butylmethacrylat-(2-dimethylaminoethyl)methacrylat-methylmethacrylat-copolymer, polyacrylic acid, polyvinyl alcohol and povidone K17 were included in the study. It could be shown that povidone K17 effectively prevents recrystallization in solid solutions containing 20% (m/m) of nimodipine during storage at +25 °C over silica gel thereby ensuring a substantial increase in the dissolution rate and degree of supersaturation in water. On the contrary, stabilization by solubility enhancement was only successful at drug loadings not exceeding 1% (m/m) using polyethylene glycol 300 as solubility enhancing additive.

1. Introduction

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal 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 (Leuner and Dressman, 2000). This may be achieved by incorporating the drug in a hydrophilic carrier material obtaining products called solid dispersions. Depending on the properties of both, drug and carrier, and depending on their ratio, a solid solution or a solid suspension of the drug in the carrier material may be formed. The mechanisms involved in solubility and dissolution rate enhancement include transformation of stable modifications into less stable ones or even into the amorphous state, reduction of particle size possibly to the molecular level as well as enhance-

* Tel.: +49 211 8114385; fax: +49 211 8114251.
E-mail address: NoraAnne.Urbanetz@uni-duesseldorf.de.
0928-0987/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejps.2005.12.009

ment of wettability and solubility of the drug by the carrier material.

However, if a solid dispersion represents a thermodynamically unstable system, it is prone to convert into a more stable state. Especially supersaturated solid solutions of the drug are subjected to recrystallization phenomena (Serajuddin, 1999).

Generally, there are two principles avoiding recrystallization. The first one is the transformation of a supersaturated into a saturated or even unsaturated system. This may be achieved by additives enhancing the solubility of the solute within the solvent. The obtained systems are thermodynamically stable at least with respect to the solute. The second principle is the inhibition of recrystallization by additives preventing the solute from crystallizing in a supersaturated solution. Although the obtained systems are thermodynamically unstable, the conversion into the thermodynamically stable state by recrystallization may be delayed effectively, thereby maintaining the properties of these systems throughout the shelf life of the product.

In order to obtain solid dispersions with favorable dissolution characteristics and sufficient storage stability the combination of different carrier materials seems to be a useful approach, which also has been successfully applied by Suzuki and Sunada (1997) to nifedipine solid dispersions. The authors were able to obtain solid dispersions with amorphous nifedipine by combining nicotinamide or ethylurea as carrier material with hydroxypropylmethylcellulose, whereas the combination of polyethylene glycol 6000 and hydroxypropylmethylcellulose did not show any supersaturation and the X-ray diffraction pattern revealed peaks of crystalline nifedipine. This was attributed to the fact, that hydroxypropylmethylcellulose could not be dissolved in the fused polyethylene glycol resulting in an insufficient recrystallization inhibition of nifedipine. However, nicotinamide may exert a pharmacological effect, and therefore, it is not the first choice as carrier material for solid dispersions. Furthermore, its melting point of 129 °C means a certain drawback for the preparation of solid dispersions by the melting method. Cogrinding of nifedipine with a combination of polyethylene glycol and hydroxypropylmethylcellulose as proposed by Sugimoto et al. (1998) did not change the drug from crystalline to amorphous, either. Similarly, the miscibility of the recrystallization inhibiting component with the carrier material is described to be essential for exerting a recrystallization inhibiting effect by Suzuki and Sunada (1998), who investigated povidone, polyvinyl alcohol and pullulan as recrystallization inhibitors in combination with nicotinamide. Veiga et al. (1993) attributed the enhanced dissolution rate of oxodipine from solid dispersions containing polyethylene glycol 6000/polysorbate 20 to the mere wetting effect of polysorbate 20, as polysorbate 20 did not mix with polyethylene glycol 6000. Furthermore, Sjökvist et al. (1991, 1992), Sjökvist Saers et al. (1993), Aldén et al. (1992, 1993, 1994) and Wulff and Aldén (1995) as well as Wulff et al. (1996) extensively studied solid solubility of griseofulvin in solid dispersions containing polyethylene glycols and different surface active additives as combined carriers. The effect of polyethylene glycols and surface active additives as combined carrier materials on the dissolution rate of nifedipine has been investigated by Law et al. (1992), as well as Mura et al. (1999) examined the effect on the dissolution rate of naproxen.

Previous studies on solid dispersions containing 20% (m/m) of nimodipine and 80% (m/m) of polyethylene glycol 2000 prepared by the melting method, have been reported to show ageing phenomena depending on preparation and storage conditions (Urbanetz and Lippold, 2005). Solid dispersions shock frozen at −20 °C exhibited a fast dissolution rate and an about four-fold supersaturation of the drug in the dissolution medium with respect to the intrinsic solubility of the drug. Storage at +25 °C over silica gel led to a complete loss of the supersaturation effect within 1 day of storage at +25 °C over silica gel. This observation could be attributed to the recrystallization of the initially molecularly dispersed drug within the carrier material. In contrast, solid dispersions slow cooled at +25 °C did not show any supersaturation effects at all. Therefore, the objective of the present study is to find additives preventing nimodipine from recrystallization in these systems during preparation and storage at +25 °C.

2. Materials and methods

2.1. Materials

Cetostearyl alcohol (Lanette® O), glycerol monostearate (Cutina® GMS), sodium lauryl sulphate (Texapon® K12) and macrogol cetostearyl ether (Eumulgin® B3) were given by Henkel KGaA, D-Düsseldorf. Ethyl acetate was received from Merck KGaA, D-Darmstadt, glycerol from Caesar & Loretz GmbH, D-Hilden, hydroxypropylcellulose (Klucel® GF-EP) from Hercules GmbH, D-Düsseldorf, nimodipine from Bayer AG, D-Leverkusen, polyacrylic acid (Carbopol® 974 P) from B.F. Goodrich, Cleveland, USA, polyethylene glycol 300 from Clariant GmbH, D-Burgkirchen, polyethylene glycol 2000 from Hoechst AG, D-Frankfurt am Main, macrogol glycerol monostearate (Myrij® 49) and polysorbate 60 (Tween® 60) from ICI Specialty Chemicals GmbH, D-Essen, poly(ethylene/propylene glycol) copolymer (Pluronic® L61) from C.H. Erbslöh KG, D-Düsseldorf, butylmethacrylat-(2-dimethylaminoethyl)methacrylat-methylmethacrylat-copolymer (Eudragit® E100) from Röhm GmbH, D-Darmstadt, polypropylene glycol 1020 from Chemische Werke Hüls AG, D-Marl, polyvinyl alcohol (Polyviol® W25/190) from Wacker Chemie GmbH, D-München, povidone K17 (Kollidon® 17 PF) from BASF AG, D-Ludwigshafen and propylene glycol from ARCO Chemie, NL-Rotterdam.

2.2. Methods

As nimodipine is sensitive to light, preparation and characterization of nimodipine-containing material have been performed under subdued light.

2.2.1. *Preparation and storage of solid dispersions containing 1% (m/m) of nimodipine and 99% (m/m) of polyethylene glycol 2000 or a mixture of 19% (m/m) of polyethylene glycol 300 and 80% (m/m) of polyethylene glycol 2000*

Solid dispersions containing 1% (m/m) of nimodipine, 99% (m/m) of polyethylene glycol 2000 or a mixture of 19% (m/m)