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Research paper

Enhancement of griseofulvin release from liquisolid compacts

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ABSTRACT

The potential of hydrophilic aerogel formulations and liquisolid systems to improve the release of poorly soluble drugs was investigated using griseofulvin as model drug. The in vitro release rates of this drug formulated as directly compressed tablets containing crystalline griseofulvin were compared to aerogel tablets with the drug adsorbed onto hydrophilic silica aerogel and to liquisolid compacts containing the drug dissolved or suspended in PEG 300. Furthermore, the commonly used carrier and coating materials in liquisolid systems Avicel® and Aerosil® were replaced by Neusilin®, an amorphous magnesium aluminometasilicate with an extremely high specific surface area of 339 m^2/g to improve the liquisolid approach.

Both the liquisolid compacts containing the drug dissolved in PEG 300 and the aerogel tablets showed a considerably faster drug release than the directly compressed tablets. With liquisolid compacts containing the drug suspended in PEG 300, the release rate increased with rising fraction of dissolved drug in the liquid portion. It could be shown that Neusilin® with its sevenfold higher liquid adsorption capacity than the commonly used Avicel® and Aerosil® allows the production of liquisolid formulations with lower tablet weights.

1. Introduction

Since the implementation of combinatorial chemistry and high throughput screening for the investigation of new chemical entities, the molecular weight and lipophilicity of drugs increase and this in turn decreases water solubility [1]. Especially poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) represent a technological challenge, as their poor bioavailability is solely caused by poor water solubility resulting in low drug absorption [2]. Therefore, new technologies increasing the solubility and thus drug release are looked for. Release enhancement of poorly soluble drugs may be achieved by an increase in the drug solubility, the drug surface area, or by formulating the drug in its dissolved state: Several methodologies such as micronization [3], co-grinding [4,5], formulation of inclusion complexes [6], solid dispersions [7,8], and lipid based formulations [9] such as self-emulsifying drug delivery systems (SEDDS) have been introduced with different success.

Adsorption of drugs to hydrophilic silica aerogels has been shown to be a promising technique for drug release enhancement [10–12]. This methodology also allows a long-time stabilization of amorphous drugs. Upon contact with fluids, the structure of hydrophilic aerogels collapses and a fast release of the loaded drug takes place.

One of the most promising approaches for release enhancement is the liquisolid technique [13–19]. Liquisolid systems as described by Spireas [13,14] are composed of a non-volatile, water miscible liquid vehicle, solid drug particles, and selected excipients, namely the carrier and coating materials. The liquid portion, which can be a liquid drug, a drug suspension, or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface, which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. Liquisolid compacts of poorly soluble drugs containing the drug dissolved or suspended in a solubilizing liquid vehicle provide enhanced drug release due to an increased drug solubility, a high surface area of the drug, and an improved wettability of the drug particles [20,21]. Accordingly, this optimized drug release allows an improved drug absorption in the gastrointestinal tract and thus a higher oral bioavailability [22,23].

Stability studies with liquisolid systems containing various drugs [18,24–26] showed that storage at different conditions neither had an effect on the hardness nor on the release profiles of liquisolid compacts. This indicates that the technology is a

Abbreviations: BCS, biopharmaceutics classification system; SEDDS, self-emulsifying drug delivery system; PEG, polyethylene glycol; RH, relative humidity; LS, liquisolid; RESS, rapid expansion from supercritical solutions.

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promising technique for release enhancement, which is not associated with any physical stability issues.

Besides drug release enhancement, the liquisolid approach is a promising technique because of the simple manufacturing process, low production costs, and the possibility of industrial manufacture due to the good flow and compaction properties of the liquisolid formulations.

To calculate the required amount of powder excipients (carrier and coating materials), a mathematical approach for the formulation of liquisolid systems has been developed by Spireas [27].

Depending on the excipient ratio R of the powder substrate, an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load, named "liquid load factor" (L_f), is not exceeded.

The terms "acceptable flow" and "acceptable compressibility" imply the desired and thus preselected flow and compaction properties, which must be met by the final liquisolid formulation.

R represents the ratio between the mass of the carrier (Q) and the coating (q) materials present in the formulation:

$$R = Q/q \quad (1)$$

L_f represents the ratio between the mass of the liquid portion W and the carrier materials Q:

$$L_f = W/Q \quad (2)$$

With the desired amount of liquid, the amount of carrier and coating material can be calculated if the liquid load factor L_f is known.

The aim of the present study was to compare drug release from several tablet formulations using griseofulvin as model drug. The poorly soluble antifungal drug was formulated as conventional tablets containing crystalline griseofulvin, as aerogel tablets containing the drug adsorbed to hydrophilic silica aerogel, and as liquisolid compacts containing the drug dissolved in PEG 300. Liquisolid compacts containing the drug suspended in PEG 300 were investigated with regard to the influence of drug content in the liquid portion on drug release. Furthermore, the commonly used carrier and coating materials in liquisolid systems Avicel® and Aerosil®, respectively, were replaced by Neusilin® to improve the liquisolid approach. Due to its extremely high specific surface area of 339 ± 1 m^2/g as well as its good flow and tableting properties [28], this magnesium aluminometasilicate was assumed to allow a considerably higher liquid load factor, thereby enabling the preparation of liquisolid compacts with lower tablet weights.

2. Materials and methods

2.1. Materials

Griseofulvin, Fagron, Barsbüttel, Germany; Carbon dioxide (purity 99.9%), AGA Gas, Hamburg, Germany; hydrophilic silica aerogel microspheres, mean particle size 300 μm [29]; polyethylene glycol 300 (PEG 300), glycerol, and propylene glycol, Fagron, Barsbüttel, Germany; Avicel® PH200 (microcrystalline cellulose), FMC BioPolymer, Cork, Ireland; Aerosil® 200 (colloidal silica), Evonik, Darmstadt, Germany; Neusilin® US2 (magnesium aluminometasilicate), Fuji Chemical Industry, Toyama, Japan; Kollidon® CL (crospovidone), BASF, Ludwigshafen, Germany. All other reagents used were of analytical grade.

2.2. Determination of the particle size of the drug raw material

The particle size distribution of griseofulvin was determined in triplicate by laser diffraction using a dry dispersing system with a feeding air pressure of 1 bar (HELOS equipped with RODOS, Sympatec, Clausthal-Zellerfeld, Germany).

2.3. Solubility studies

The solubility of griseofulvin in three non-volatile liquid vehicles that are commonly used for the formulation of liquisolid compacts, namely, propylene glycol, polyethylene glycol 300 (PEG 300), and glycerol was determined by preparation of saturated solutions of the drug in these solvents and measuring their drug concentration: Excess griseofulvin was stirred in the above mentioned solvents for 48 h at 21 °C. Accurately weighed quantities of the filtered supernatants were further diluted with methanol and analyzed spectrophotometrically at 291 nm for their drug content. From these results, the solubility of griseofulvin (in percent [w/w]) in the respective liquid vehicle was calculated. Each experiment was carried out in triplicate.

2.4. Loading of silica aerogel microspheres with griseofulvin

Loading of silica aerogel microspheres with griseofulvin was performed by adsorption of the drug from its solution in supercritical carbon dioxide (solubility of griseofulvin in carbon dioxide: 1.6×10^{-3}% [30]).

To deposit the drug onto silica aerogel microspheres, the following procedure was used: A weighed amount of drug and aerogel microspheres, each wrapped in a filter paper, was placed in an autoclave (250 ml, built at the Hamburg University of Technology, Germany). The autoclave was sealed, heated to 40 °C, and carbon dioxide was pumped inside until a pressure of 180 bars was reached [31,32]. Under these conditions, the drug was completely dissolved and thus, adsorption to the aerogel took place. After 48 h, the pressure was released and the drug-loaded aerogel microspheres (300 μm) were removed. In previous studies, it could be shown by visual evaluation as well as electron microscopy that during impregnation of the aerogel with drug no crystallization occurs in the pores of the aerogel [30].

To determine the percentage of drug in the loaded aerogel, a weighed amount of aerogel microspheres was dispersed in methanol. The solution was stirred for at least 20 min to ensure complete dissolution of the drug. The concentration of the drug in methanol was analyzed spectrophotometrically at 291 nm (1 cm quartz cells, 8453, Agilent Technologies, Santa Clara, USA). Based on these data, the percentage of drug in the loaded aerogel was calculated. Each experiment was carried out in triplicate.

2.5. Preparation of directly compressed tablets

A conventional tablet formulation with micronized griseofulvin and an aerogel tablet formulation with griseofulvin adsorbed to hydrophilic silica aerogel were prepared with each tablet containing Kollidon® CL as disintegrant, Avicel® as binder, and 1.5 mg of drug. The percentage of drug of the hydrophilic silica aerogel microspheres was determined to 3.0 ± 0.1% [w/w], and therefore, each tablet contained 50 mg of drug-loaded silica aerogel. To ensure that tablet disintegration is not the rate-limiting step and drug release is not hindered by slow disintegration of the dosage form, 5% [w/w] Kollidon® CL was added to all formulations. All ingredients were mixed for 5 min in a Turbula blender (T2F, Willy A. Bachofen, Muttenz, Switzerland) and compressed into tablets with an instrumented single punch press (EXI, Fette, Schwarzenbek, Germany) equipped with flat faced punches of 10 mm diameter. For each tablet, 300 mg of the powder blends was filled manually into the die and compressed at a compaction speed of 16 strokes/min. The compaction force was adjusted to achieve a minimum tensile strength of 1 MPa [33]. All experiments were performed at 21 °C/45% RH.