European Journal of Pharmaceutics and Biopharmaceutics 113 (2017) 97–107

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Preparation and tableting of long-term stable amorphous rutin using porous silica

Qionghua Wei [a], Cornelia M. Keck [b], Rainer H. Müller [a,*]

[a] Institute of Pharmacy, Department of Pharmaceutics, Biopharmaceutics & NutriCosmetics, Freie Universität Berlin, Kelchstr. 31, 12169 Berlin, Germany
[b] PharmaSol GmbH, Stubenrauchstr. 66, 12161 Berlin, Germany

ARTICLE INFO

Article history:
Received 10 July 2016
Revised 27 October 2016
Accepted in revised form 3 November 2016
Available online 12 November 2016

Chemical compounds studied in this article:
Rutin (PubChem CID: 5280805)
Tween 80 (PubChem CID: 5281955)
Dimethyl sulfoxide (PubChem CID: 679)

Keywords:
Amorphous drug
CapsMorph®
AEROPERL® 300 Pharma
Rutin oral bioavailability enhancement
Physical stability
Saturation solubility

ABSTRACT

Amorphous state of drugs increases the oral bioavailability, but typically faces physical stability problems. Amorphous rutin was generated and physically stabilized by encapsulating inside mesopores of porous AEROPERL® 300 Pharma and named as rutin CapsMorph® in this study. AEROPERL® 300 Pharma was loaded with rutin dissolved in DMSO containing Tween 80, and subsequently the solvent evaporated (wetness impregnation method). The loading process was monitored by light microscopy and scanning electron microscopy (SEM). X-ray diffraction (XRD) and differential scanning calorimetry (DSC) were used to confirm the amorphous state in AEROPERL® 300 Pharma. A loading of 20% of the rutin-AEROPERL® 300 Pharma mixture was obtained. The amorphous state proved to be stable over 2 years of storage at room temperature. Due to the amorphous state and the nanosize of the rutin in the mesopores, the kinetic saturation solubility increased to about 4 mg/ml (water, 0.1 M HCl, pH 6.8 PBS) compared to the maximum observed thermodynamic equilibrium solubility of rutin raw drug powder of only 74.48 ± 1.42 μg/ml in pH 6.8 PBS (=increase by factor about 54). The dissolution velocity also increased distinctly, e.g. about 96.1% of rutin dissolution from CapsMorph® powder in water within 5 min compared to less than 40% of raw drug powder after 3 h. Tablets were produced with rutin CapsMorph®, raw drug powder and their dissolution velocity compared to a marketed product. About 83.0–95.6% were released from the rutin CapsMorph® tablet within 5 min, compared to 42.7–52.5% from the marketed tablet after 3 h (water, 0.1 M HCl, pH 6.8 PBS). After dissolution the supersaturation level of rutin CapsMorph® remained over about 2 h, then solubility slowly reduced, but remained after 48 h still multifold above the thermodynamic rutin solubility. This should be sufficient for many poorly soluble drugs to achieve a sufficient bioavailability. For optimal exploitation of the supersaturation, a multiple step release system could be used, e.g. release of CapsMorph® particles every 2–3 h.

1. Introduction

Rutin, with an aromatic trimeric heterocyclic structure, is one of the most active bioflavonoids. As the glycoside form of quercetin it can be found in asparagus, the leaves and petioles of Rheum species and buckwheat, or the fruits of some other plants, especially in citrus fruits, like orange, grapefruit, lemon and lime [1]. Rutin is classified as vitamin P, which increases the strength of the walls of blood capillaries and regulates the permeability [2]. It also has the anti-inflammatory, antitumor, antibacterial effects [3,4]. Therefore, it is mainly regarded as a medicine with hypolipidemic, cytoprotective, antispasmodic and anticarcinogenic potency. In addition, another important function of rutin is antioxidant capacity because it can scavenge oxidizing species, superoxide radical and peroxyl radical [5]. However, the low oral bioavailability caused by the poorly water-soluble characteristic limited the introduction of effective rutin products onto the market as drug or nutraceutical.

Up to date different formulation approaches were performed to improve the solubility of poorly soluble drugs, e.g., nanocrystals [6,7], melt extrusion and generation of the amorphous drug [8,9]. Theoretically, amorphous drug is the first choice because it pos-

Abbreviations: AV, Avicel pH 101; DSC, differential scanning calorimetry; Ex, Explotab; HPLC, high performance liquid chromatography; MC, microcrystalline rutin; Mg, magnesium stearate; SEM, scanning electron microscopy; T, Talc; XRD, X-ray diffraction.

* Corresponding author.
E-mail address: nanoteam@gmx.com (R.H. Müller).

http://dx.doi.org/10.1016/j.ejpb.2016.11.009
0939-6411/

sesses higher aqueous solubility than crystalline material. Alternatively, with a reduction in size to nanodimension (<1000 nm), the saturation solubility of drug substance increases as well. These two advantages (amorphous and nanodimension) were combined by encapsulating (*Caps*) amorphous drug (*Morph*) in mesoporous materials (=*CapsMorph*® technology) [10]. The pores in mesoporous materials have typically a pore diameter between 2 and 50 nm. Encapsulated in the tiny space, drug remains long-term stable in the amorphous state and possesses a nano size, both of them contribute to enhanced saturation solubility Cs and dissolution rate dc/dt, thus to high bioavailability [11,12]. The methods loading drug into mesoporous material include solvent method and non-solvent method. In solvent method, organic solvent was used to dissolve and introduce hydrophobic drugs, via immersion way [13–15], wetness impregnation way [16–18], or fluidized bed way [19]. Super-critical CO_2 (SC-CO_2) method [20], melting method [21], co-grinding method [22], sublimation mass-transfer method [23] are different non-solvent methods performed to load drug into mesoporous carrier in last decades, without the using of organic solution.

The commercial mesoporous products include e.g., Syloid [24], Neusilin [25] and AEROPERL [10]. AEROPERL® 300 Pharma, introduced by Evonik (Essen, Germany), is a granulated form of colloidal silicon dioxide mesoporous material. It meets all the main requirements of a drug delivery material, such as sufficient mechanical strength, biocompatibility [26] and regulatory acceptance. In addition, AEROPERL® 300 Pharma possesses exceptional flowability due to its spherical particle shape, for which it can be easily used in tableting and capsule filling processes [27].

Tablets account for about 80% of the pharmaceutical market, ascribing to the easy implement of cost-effective large-scale production, the potential to control drug action and the possibilities for masking color and odor, and of course the patient-friendly ease of use [28,29]. In the present study rutin CapsMorph® powder was first formulated by incorporating rutin in the amorphous state into AEROPERL® 300 Pharma through the wetness impregnation method. The obtained formulation was transferred into a tablet by compression and compared with a marketed rutin tablet regarding solubility of the active and dissolution velocity, both determining oral bioavailability.

2. Materials and methods

2.1. Materials

Rutin was purchased from Sigma-Aldrich (Germany), Tween® 80 from Pharma Uniqema GmbH & Co. KG (Emmerich, Germany), and dimethyl sulfoxide (DMSO) from Merck Schuchardt OHG (Hohenbrunn, Germany). AEROPERL® 300 Pharma was obtained as a gift from Evonik Industries AG (Essen, Germany).

2.2. Methods

2.2.1. Production of amorphous rutin CapsMorph® powder

In a beaker, rutin was dissolved in the mixture of Tween 80 and DMSO, at a ratio of 2:1:10. Then 13 g this drug solution was added drop-wise to 10 g AEROPERL® 300 Pharma in an ointment bowl. With a continuous gentle stirring by a pestle, a uniform mixture was obtained. The added solvent (DMSO) was removed via evaporation in a compartment dryer. The evaporation was controlled by weighing. The obtained rutin loaded product powder was named as "rutin CapsMorph®". Theoretically, after two steps of drug loading processes, CapsMorph® with 28.6 wt.% rutin was obtained. The loading was expressed as weight percentage of rutin/CapsMorph®, e.g., 28.6 wt.% means that 4 g rutin is loaded in solution onto 10 g AEROPERL® 300 Pharma, the total weight being 14 g CapsMorph® powder. Verification of the practically achieved loading by high performance liquid chromatography (HPLC) revealed a loading of 20.6 wt.% in this lab-scale process.

2.2.2. X-ray diffraction (XRD)

The diffraction studies were performed by using a PW 1830 X-ray diffractometer (Philips, The Netherlands). The samples were exposed to Cu Kα (40 kV, 25 mA) and scanned between 0.6° and 40°.

2.2.3. Differential scanning calorimetry (DSC)

A computer-interfaced differential scanning calorimeter (DSC 821e, Mettler-Toledo, Germany) was employed to perform thermal analysis. The samples (about 3 mg) were accurately weighed in the pans with a hole and heated from 25 to 250 °C with a heating rate of 10 °C/min. Nitrogen was used as the purge gas with a flow rate of 20 ml/min.

2.2.4. Light microscopy

The dry powder images of pure AEROPERL® 300 Pharma, rutin raw material, rutin physical mixture with AEROPERL® 300 Pharma and rutin CapsMorph® were taken by using a light microscope (Leitz Ortoplan, Wetzlar, Germany) to demonstrate the impregnation of rutin in CapsMorph®. The light microscope was connected to a CMEX-1 digital camera (Euromex Microscopen BV, Arnhem, Netherlands). The powders of samples were spread gently between the glass slide and cover slide and analyzed at a magnification of 160×.

2.2.5. Scanning electron microscopy (SEM)

The morphology changes of rutin and AEROPERL® 300 Pharma during the loading process were observed using a scanning electron microscope (Zeiss DSM 982, Field Emission Gun Scanning Electron Microscopy, Carl Zeiss AG, Germany). A 2 kV-accelerating voltage in the secondary electron mode was employed.

2.2.6. Kinetic saturation solubility of CapsMorph® powder and raw material

To determine the kinetic saturation solubility, 0.1 M hydrochloric acid (HCl), water and pH 6.8 phosphate buffer saline (PBS) were selected as the dissolution media. The excess rutin raw material and CapsMorph® powder were put in vials, respectively, and placed in an Innova 4230 refrigerated incubator shaker (New Brunswick Scientific GmbH, Nürtingen, Germany). 20 ml of media was added into each vial to start the measurement. Samples were agitated at 100 rpm and the temperature was kept at 37 °C to achieve a uniform mixing. The time points were fixed at 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 24 h and 48 h to collect the samples. 2 ml samples from the supernatant were collected at specific time points. To obtain clear samples, all samples were filtered through 0.1 μm cellulose acetate membrane filters followed by a centrifugation at 23,000*g* for 40 min at 37 °C with a Heraeus Biofuge Stratos centrifuge (Thermo Electron Corporation, USA). After that, HPLC was applied to measure the drug concentration of each sample. The saturation solubility tests of all samples were performed in triplicate in all three media respectively to calculate the means and standard deviations.

2.2.7. In-vitro release study of CapsMorph® powder, raw material and tablets

A USP XXIII rotating paddle apparatus with a Pharmatest PTW SIII (Pharma Test, Germany) was used to obtain the dissolution profiles of rutin CapsMorph® powder, raw material and tablets in 0.1 M hydrochloric acid (HCl), water (pH 6.7) and pH 6.8 phosphate