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Research paper

pH-independent drug release of an extremely poorly soluble weakly acidic drug from multiparticulate extended release formulations

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Abstract

Extended release mini matrix tablets for 8-Prenylnaringenin (8-PN), an extremely poorly soluble weakly acidic drug, were developed by using polyvinylacetate/polyvinylpyrrolidone as matrix former. Mini matrix tablets were manufactured by direct compression or wet granulation technique. With conventional modified release formulations, the drug demonstrated pH-dependent release due to pH-dependent solubility of the drug substance (i.e., increasing solubility at higher pH-values). In order to achieve pH-independent drug release two classes of pH-modifying agents (water-soluble vs. water-insoluble) were studied with respect to their effect on the dissolution of 8-PN. Addition of water-soluble salts of weak acids (sodium carbonate and sodium citrate) failed in order to achieve pH-independent 8-PN release. In contrast, addition of water insoluble salts of a strong base (magnesium hydroxide and magnesium oxide) was found to maintain high pH-values within the mini matrix tablets during release of 8-PN at pH 1 over a period of 10 h. The micro-environmental conditions for the dissolution of the weakly acidic drug were kept almost constant, thus resulting in pH-independent drug release. Compound release from mini matrix tablets prepared by wet granulation was faster compared to the drug release from tablets prepared by direct compression.

Keywords: pH-independence; Weakly acidic drug; Controlled release; Extended release; Basic excipients; Matrix tablets

1. Introduction

The oral route is the most common route of drug application because of its advantages in terms of convenient administration, thus leading to increased patient compliance. Extended release (ER) formulations in many cases provide further significant advantages, including improved therapeutic effect, increased patient compliance by reducing dosing frequency, and a decrease in the incidence and/or intensity of adverse effects by a constant blood concentration level [1]. Matrix tablets are one of the most common ER forms because of two main reasons: they can be made by cost-effective methods (e.g., direct compression) and the risk of dose dumping is low.

Oral tablets can be provided as single-unit or multiparticulate dosage forms. The main advantage of multiple unit dosage forms is related to their in vivo behavior, e.g., increased uniformity of plasma levels and better reproducible bioavailability [2]. Mini matrix tablets combine the advantages of a multiple unit dosage form with the advantages of matrix tablets as their manufacturing technique is well established and includes less constraints than for example extrusion/spheronization [3]. In addition, with mini matrix tablets administered drug doses can be varied easily.

Polyvinylacetate/polyvinylpyrrolidone (PVA/PVP) is a commercially available tableting excipient in the form of a physical mixture of eight parts of PVA and two parts of PVP [4]. PVA/PVP shows excellent flow properties and high compressibility, thus being a good candidate for tableting using the direct compression method [5–7]. Moreover, in mini tableting small particle sizes are necessary for

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reproducible die filling [8]. PVA/PVP has an average particle size of 100 μm indicating its possible suitability for the compression of mini-tablets.

With extended release dosage forms drug release in vitro should preferably be independent of the pH of the release medium in order to achieve as little biopharmaceutical variability as possible [9]. This has been shown to be an important parameter for weakly basic or acidic drugs [1]. Depending on the pH of the release medium or intestinal fluid they exist in their dissociated or non-dissociated form, thus showing pH-dependent solubility. 8-Prenylnaringenin (8-PN) is an extremely poorly soluble, weakly acidic estrogen that has recently been found in plants (Fig. 1). The compound seems to be a potent candidate for the treatment of postmenopausal symptoms, especially when administered in an extended release dosage form.

Several attempts to overcome pH-dependent solubility of weakly basic drugs have been published. Some authors used blends of enteric and extended release polymers as film coating materials [10,11]. Most approaches for pH-independent drug delivery of weakly basic drugs are based on the presence of acidic excipients such as organic acids within the drug formulation [9,12–14]. These organic acids keep the pH within the drug formulation in the intestinal pH-range low and thus the solubility of the drug high.

Only few studies have been carried out in order to achieve pH-independent release of weakly acidic drugs. Doherty and York [15] used a buffer system of disodium hydrogen orthophosphate and citric acid to achieve pH-independent release of the weakly acidic frusemide from PVP solid dispersions. The system was successful by increasing frusemide release in acidic media and decreasing release rates at higher pH. Rao et al. [16] developed controlled release matrix tablets for the weakly acidic drug divalproex sodium by compression of drug substance, hydroxypropyl methylcellulose and Eudragit E or dibasic calcium phosphate. Incorporation of Eudragit E which is soluble at low pH and insoluble at higher pH provided pH-independent drug release. In contrast, dibasic calcium phosphate was less effective in order to achieve pH-independent drug release which was attributed to the relative inability to elevate the pH and shorter residence time of dibasic calcium phosphate in the matrix relative to Eudragit E.

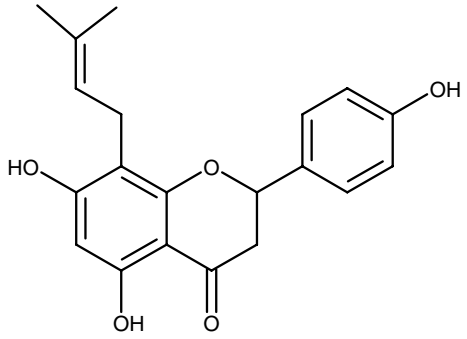

Fig. 1. Structure of 8-PN.

The objective of the present study was to achieve pH-independent release of the extremely poorly soluble but weakly acidic 8-PN from mini matrix tablets. According to pharmacokinetic modeling the desired in vitro drug release profile should demonstrate approximately 50–60% drug release within 6 h (complete drug release within 15–20 h). In a first series of experiments, several buffering excipients were evaluated in order to achieve pH-independent drug release profiles. In a second series, different formulation and process parameters were evaluated to vary the in vitro drug release rates.

2. Experimental section

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: 8-Prenylnaringenin (8-PN; 5,7-Dihydroxy-2-(4-hydroxyphenyl)-8-(3-methyl-but-2-enyl)-chroman-4-on; $pK_a = 6.2$; Schering AG, Berlin, Germany), PVA/PVP (Kollidon® SR; BASF, Ludwigshafen, Germany), magnesium hydroxide, magnesium oxide, magnesium trisilicate (Fluka, Buchs, Switzerland), acetonitrile, ammonium dihydrogen phosphate, calcium phosphate, potassium dihydrogen phosphate, sodium carbonate, sodium citrate, sodium hydroxide, triethylamine (Merck KGaA, Darmstadt, Germany), lactose (Danone GmbH, München, Germany), microcrystalline cellulose (Avicel PH 101; FMC, Philadelphia, USA), maize starch, hydroxypropyl-β-cyclodextrine (HP-β-CD; Roquette Services Techniques Laboratoires, Lestrem, France), colloidal silicon dioxide, and magnesium stearate (Herwe Chemisch-technische Erzeugnisse, Sinsheim-Dühren, Germany). All chemicals were of reagent grade or higher.

2.2. Methods

2.2.1. Mini matrix tablet preparation

Mini matrix tablets containing 1.5% (w/w) magnesium stearate as lubricant and 1% (w/w) colloidal silicon dioxide as flow promoter were prepared by direct compression if not otherwise mentioned. The respective powders (drug, polymer, and additives, for compositions see Table 1) were passed through a 0.8 mm sieve (Haver and Böcker, Celle, Germany) and blended with a turbula mixer (W. A. Bachofen AG, Basel, Switzerland). The tablets were prepared by using a single punch tableting machine (EK 0, Korsch, Berlin, Germany), equipped with 2.0 mm punches. The tablet weight was kept constant at 7 mg and the hardness of the mini matrix tablets was kept constant at 22–28 N (Schleuniger hardness tester 6 D, Schleuniger Pharmatron AG, Solothurn, Switzerland). For wet granulation the blend (Table 1, formulation No. 5) was granulated in a planetary mixer (MTI, MTI-Mischtechnik Industrieanlagen GmbH, Lage, Germany) by using distilled water.