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Investigation of physicochemical properties and in-vitro in-vivo evaluation of agomelatine polymorphs

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ABSTRACT

In the present study, Form I, Form II and Form III of agomelatine were prepared to investigate the variability of polymorphs, then the in-vitro in-vivo correlation were established. The presence of three polymorphs of agomelatine was corroborated through studies by XRPD, TGA and DSC. All the forms obtained were then subjected to the powder and intrinsic dissolution tests. The IDR ranked in the order of Form III > Form I > Form II. Form I and Form III both underwent solvent-mediated phase transformation (SMPT) to Form II during dissolution and the transition points were 62 and 45 min, respectively. Pharmacokinetic profiles were acquired after oral administration of tablets, showing that the ka and $AUC_{0-12\ h}$ of Form I, Form II, Form III were 0.58 ± 0.11, 0.34 ± 0.05, $0.74 \pm 0.07\ h^{-1}$ and 296.25 ± 49.39, 186.05 ± 45.93, 331.16 ± 54.74 ng*h/ml, respectively. Good linearities between IDR and k_a, IDR and AUC were established, suggesting that the agomelatine polymorphic forms with faster dissolution rates in-vitro would increase the rate and extent of oral absorption in-vivo. These results demonstrated that IDR was predictive in estimating the relative bioavailability of agomelatine polymorphic forms.

1. Introduction

Agomelatine (N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide), is a novel antidepressant developed by Servier Laboratories [1]. It represents the only MT_1/MT_2 melatonergic receptor agonist and 5-HT_{2C} antagonist available, shown to induce resynchronization of circadian rhythms and antidepressant action in humans [2–5]. Extensive clinical trials have established efficacy of agomelatine taken by major depression patients, with an improvement of sleep quality, preservation of sexual function, absence of weight gain and good tolerability. This overall profile compares favorably to antidepressants

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currently available. Therefore, agomelatine (Valdoxan/Thymanax; Servier) was granted marketing authorization in 2009 for the treatment of major depression in Europe and become the first approved antidepressant to incorporate a non-monoaminergic mechanism of action [1,5].

After oral administration there is rapid and high absorption of agomelatine with low absolute bioavailability (<5% at the therapeutic oral dose) and substantial interindividual variability [6]. Up to now, at least six polymorphs as well as other solvates are known for agomelatine [7]. However, little information is available about their in-vitro physicochemical properties such as the dissolution behavior. In addition, the effect of agomelatine polymorphism on its bioavailability and the relationship between the in-vitro dissolution properties and in-vivo pharmacokinetics of agomelatine polymorphs are not determined.

Polymorphism is defined as the ability of a compound to exist in two or more crystalline phases with different arrangements and/or conformations of the molecule in the crystal lattice [8]. These individual crystal phases can exhibit differences in physicochemical properties, such as stability, dissolution rate, and solubility, which may affect drug manufacturability and quality/in-vivo performance [9]. The phenomenon of polymorphism is very common among pharmaceutical substances and has been widely reported in the literature [8–13]. Thorough investigation and characterization of a polymorphic drug substance are recognized as an essential part of drug development [14].

For this reason, the following objectives were set for this study: firstly, to investigate the variability of agomelatine polymorphs by fully characterizing the physicochemical properties using a variety of approaches (XRPD, DSC, TGA, solubility, and disc intrinsic dissolution rate); Secondly, to determine the effects of physicochemical properties of Form I, Form II and Form III on the plasma level of agomelatine by performing pharmacokinetic tests on Beagle dogs; Finally, to establish the correlation between in-vitro properties and in-vivo absorption.

2. Materials and methods

2.1. Materials

Agomelatine (99.9% purity; Korey Pharm Co. Ltd., shanghai, China) was used without further purification. The original drug substance employed here was identified to be Form II exclusively. All organic solvents were HPLC grade. All other chemicals and reagents were analytical grade. All the solvents employed were commercially available and used as received without further purification.

2.2. Preparation of agomelatine polymorphs

In search of all possible polymorphs of agomelatine, a variety of preparation methods, including solvent cooling, solvent evaporation, melt crystallization, anti-solvent and spray drying method were tried in our study. Eventually, another two distinct polymorphic forms were obtained, which were identified as Form I and Form III in accordance with the findings disclosed in the US patents [7,15,16]. In order to get crystalline forms with high purity reliably and reproducibly, the following procedure was used:

- Form I: 1 g agomelatine bulk powder suspending in ethylene glycol was heated to 60 °C. The hot solution was filtered to remove undissolved nuclei and then cooled to room temperature. The filtrate was dropwise to ice-water mixture stirring with a magnetic stirrer. The precipitated crystals were collected on a filter and dried at 35 °C.
- Form III: 1 g agomelatine bulk powder was heated at 110 °C in an oven until the melting was completed, and then slowly cooled until crystallization [16].

The received crystals were all stored in a desiccator at room temperature and identified by XRPD, DSC and TGA.

2.3. Identification of agomelatine polymorphs

2.3.1. X-ray powder diffraction (XRPD)

XRPD patterns were recorded at room temperature on a Rigaku Powder X-ray diffraction system (Model D/MAX-2200 Ultima/PC, Japan) with Ni-filtered Cu-Kα radiation powered at 40 kV and 30 mA. The samples were packed into a quartz cell of 0.2 cm deep and analyzed over an angular range from 3° to 40° in continuous scan mode by using a step size of 0.02°and scan rate of 10°/min.

2.3.2. Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)

DSC analysis was performed by using a DSC Q2000 (TA Instruments, USA) with data analysis via a thermal analyzer (Universal Analysis 2000, TA Instruments, USA). TGA were determined by using the NETZSCH TGA system (STA 409 PC) operating with version 6.1 Stare software. Approximately 5 mg samples were weighed (MS105DU microbalance, Mettler Toledo, Switzerland) in loosely covered aluminum pans and scanned from 25 °C to 120 °C at the heating rate of 10 °C/min with the nitrogen gas flow rate of 50 ml/min. The calorimeter was calibrated by using ultrapure indium (99.999%, melting point 156.61 °C, enthalpy of fusion 28.54 J/g) as standard. DSC and TGA measurements were both conducted in triplicate.

2.4. Dissolution studies

2.4.1. Dissolution studies by the powder dispersed method

The dissolution behaviors of agomelatine crystalline solids in the 0.1 M HCl were carried out by using a USP type II (paddle) apparatus (ZRS-8G, Tianjin Tianda Tianfa Technology Co., Ltd, China) by the dispersed method. All crystalline powder was sieved through a 100-mesh screen to provide samples with approximate particle size ranges of 150–250 μm. Approximately 350 mg samples were added to the dissolution medium of 200 ml that maintained at 37 ± 0.5 °C and the paddle stirred at 100 rpm. Samples of 2.0 ml were withdrawn (with replacement) at predetermined time points up to 72 h and filtered through a 0.22 μm Nylon syringe filter. Subsequently they were diluted appropriately and analyzed by an HPLC system consisting of a pump (L-2130, Hitachi, Japan), an autosampler (L-2200, Hitachi, Japan) and a UV detector