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Development of a Novel Amorphous Agomelatine Formulation With Improved Storage Stability and Enhanced Bioavailability

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ABSTRACT

The present work describes the development of a novel formulation of amorphous agomelatine (AGM) that exhibits enhanced *in vitro* dissolution rate and bioavailability, as well as improved storage stability. AGM was loaded on a mixture of microcrystalline cellulose with a high specific surface area excipient, namely colloidal silicon dioxide, employing a wet granulation method, and the resultant AGM granules were subsequently formulated into immediate release film-coated tablets. Modulated temperature differential scanning calorimetry, hot-state light microscopy, powder X-ray diffraction, attenuated total reflectance FTIR, and micro-Raman spectroscopy revealed that the active pharmaceutical ingredient existed primarily in the amorphous state within the prepared formulations, with some crystals of polymorph I also present. Accelerated stability studies for up to 6 months in alu-alu blisters showed good physicochemical stability during storage. Finally, *in vitro* dissolution studies and clinical trials in healthy human volunteers showed a remarkable increase in the *in vitro* dissolution rate and a ~1.5-fold increase in bioavailability, respectively, compared to the marketed product.

Introduction

Agomelatine (AGM; N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide) is a potent melatonergic agonist (MT1 and MT2) having also 5-hydrotryptamine 2C (5-HT2c) antagonist properties.[1] It shows comparable antidepressant efficacy with better tolerability, reduced level of sexual side effects, and improved sleep quality (accompanied with reduced waking after sleep onset) compared to other antidepressants.[2-4] AGM's unique pharmacological properties may lead to simultaneous resynchronization of circadian rhythms and antidepressant action in humans. Therefore, AGM was granted marketing authorization in 2009 for the treatment of major depression in Europe while to our knowledge it is the first approved antidepressant to incorporate a nonmonoaminergic mechanism of action.[1-4]

AGM is a Biopharmaceutics Classification System Class II drug (low aqueous solubility—high permeability), consisting of a white to almost white crystalline powder that exists in 6 crystal forms (named I-VI).[5] Forms I, II, and III possess similar hydrogen-bond motifs forming 1D chains with different packing arrangements.[6] Form II is the thermodynamically stable form, marketed in the innovator product. However, it exhibits poor water solubility and low intrinsic dissolution characteristics compared to the metastable forms I and III, which possess superior intrinsic dissolution properties but poor polymorphic stability, transforming to form II *in situ* and during storage.[7] Generally, AGM form II is rapidly and almost completely absorbed, but with a low absolute bioavailability (7% and 0.2% in rat and monkey, respectively) caused partly by its poor solubility and the high level of first-pass metabolism.[1] After oral administration of 25-50 mg (therapeutic dosing), form II achieves a median time taken to reach the maximum plasma concentration (t_{max}) between 0.75-1.5 h with a dose-dependent total plasma clearance (about 1100 mL/min after intravenous doses of 1.5, 7.5, or 37.5 mg) and undergoes extensive metabolism with a very low urinary excretion of intact drug (0.01% of the dose in the 37.5 mg group).[1,8]

In order to overcome this drawback and enhance the active pharmaceutical ingredients (API's) poor solubility, besides the chemical modification by prodrug formation, several attempts have been made employing solid-state modifications, such as the use of new polymorphs,[6,7,9-11] salts,[12] cocrystals,[5,6,13] and inclusion compounds with cyclodextrins.[14] Moreover, formulation approaches have been applied, including the addition of wetting agents,

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amorphization, emulsification and micro/nanoemulsification, formation of lipid-based and micellar drug delivery systems, nanonization and so forth, all of which possess several advantages and limitations.[15] Of all the aforementioned approaches, amorphization of the API with the aid of high specific surface area excipients seems to be the most promising, since it is a commonly used technique with several successful applications.[16-22] Therefore, the present study aims to develop a novel AGM formulation with enhanced *in vitro* dissolution characteristics, storage stability, and oral bioavailability, which would enable the reduction of *per os* administrated dose and adverse effects (i.e., hepatotoxicity), containing amorphous AGM. Amorphization of the API is achieved by adsorption on a high specific surface area excipient, which is subsequently granulated and compressed into film-coated immediate release tablets. The API's physical state is characterized by differential scanning calorimetry (DSC), hot-state light microscopy, powder X-ray diffraction (pXRD), attenuated total reflectance (ATR) FTIR, and micro-Raman analysis, and the performance of the novel formulation is evaluated in terms of the *in vitro* dissolution rate and *in vivo* bioavailability in healthy human volunteers in comparison to the innovator's marketed products.

Materials and Methods

Materials

AGM form I ($d_{(90)} = 91.8$ μm measured with Malvern's Mastersizer 2000; Malvern, Malvern, UK) was purchased from MSN Pharmachem Pvt. Ltd. (Hyderabad, India). AGM form II was supplied by Changzhou Pharmaceutical Factory (Changzhou, China). Colloidal silicon dioxide with specific surface area of 300 m^2/g (Aerosil300; Evonik Industries AG, Essen, Germany) used as carrier during the API amorphization process, microcrystalline cellulose (MCC-102; Vivapur102, JRS Pharma, Rosenberg, Germany) and lactose monohydrate (Tablettose 100; Meggle, Wasserburg, Germany) used as diluents, pregelatinized starch (Starch 1500; Colorcon, Dartford, UK) used as binder, croscarmellose sodium (Kollidon CL; BASF Co., Ledgewood, NJ) used as disintegrant, magnesium stearate (Ligamed MF-2V; Peter Greven, Bad Münstereifel, Germany) used as lubricant, and Opadry 200F (Colorcon, Dartford, UK) used as coating agent were tested for the preparation of tablet formulations. Commercial AGM immediate release tablet formulation Valdoxan® (Product A; Les Laboratoires Servier, Suresnes, France) was purchased from a local pharmacy store. All other materials and reagents were of analytical grade and used as received.

Preparation of AGM Formulations

Preparation of Granules Containing Amorphous AGM

For the preparation of AGM amorphous granules, 3 different AGM:Aerosil 300 ratios were evaluated, namely 1/1 (a), 1/2 (b), and 1/4 (c). Granulation was performed by a standard wet granulation process. More specifically, 250.0 g of AGM form I was dissolved in 5000.0 g of isopropyl alcohol/dichlomethene (ratio 1/1 v/v) at room temperature. The prepared solution was kneaded in a high shear granulator (Mycromix; Huettlin-Bosch, Stuttgart, Germany) with 250.0 g (a), 500.0 g (b), and 1000.0 g (c) Aerosil 300 until a paste-like mass was observed. Then, several commonly used diluents were evaluated, and MCC was chosen due to its excellent wet granulation properties. Hence, 1750.0 g of MCC-102 were added in the granulator and kneaded until a well-wetted mass was observed. The wetted mass was dried in a fluid bed dryer (Solid-Lab I; Huettlin-Bosch) at 60°C for 3 h. The resultant dried granules were sieved through a 40 mesh sieve and stored in a double polyethylene bag placed in a high-density polyethylene container under low moisture conditions.

Preparation of AGM Film-Coated Tablets

The granules containing amorphous AGM (AGM:Aerosil 300 ratio of 1/4 w/w) were sieved and transferred in a double-cone bin blender and mixed with 558 g of lactose monohydrate, 1117 g of pregelatinized starch 1500, 250 g of croscarmellose sodium, and 25 g of colloidal silicon dioxide for 10 min at 15 rpm. Then 5.0 g of magnesium stearate are added and mixed for 3 min. The lubricated blend is compressed into tablets corresponding to 25 mg of AGM in a rotary compression machine (Manesty Press100; Manesty-Bosch, Stuttgart, Germany) using 16.0 × 8.0 mm oblong punches. The prepared tablets were film coated with Opadry up to a weight gain of 3.0% in a Solid-Lab 1 pan-coater (Huettlin-Bosch).

Physicochemical Characterization of AGM Crystals and Formulations

The crystallinity and polymorphic purity of AGM in granules were assessed by thermal analysis, FTIR, micro-Raman, and powder X-ray diffractometry.

DSC—Modulated Temperature DSC

DSC determinations were carried out on a DSC 204 F1 Phoenix heat-flux differential scanning calorimeter (NETZSCH, Selb, Germany). Accurately weighted amounts of samples (3-5 mg) were placed in perforated aluminum pans and scanned through a temperature range of 20°C-150°C at a heating rate of 10°C/min.

For the evaluation of AGM's glass-forming ability (GFA) according to Baird et al.,[23] a heating-cooling-reheating cycle was performed in triplicate, by heating the sample from 25°C to 130°C, equilibrated for 3 min at 130°C, followed by cooling at −60°C, equilibrated at that temperature for another 3 min, and then reheating up to 130°C, using the same heating rate of 10°C/min for all 3 cycles. The glass transition temperature was calculated from the midpoint of the step change in heat flow during the cooling and the second heating run.

Moreover, for more sensitive detection of crystallization of the amorphous phase, the granules containing amorphous AGM were subjected to modulated temperature DSC (MT-DSC) at an underlying heating rate of 2°C/min using a modulation amplitude of 1°C and a modulation period of 60 s.

The instrument was calibrated for temperature and energy using indium standards, and a nitrogen purge gas flow of 75 mL/min was used in all experiments.

Powder X-Ray Diffraction

pXRD patterns of the raw materials and the prepared formulation were measured on a Bruker D2 Phaser powder diffractometer with a nickel-filtered radiation. The patterns were recorded on a quartz plate at a tube voltage of 30 kV and a current of 10 mA applying a scan rate of 0.02° 2θ/s in the angular range of 5°-45° 2θ. The accuracy of the instrument was tested against a corundum A26-B29-S reference sample.

Attenuated Total Reflectance FTIR Spectroscopy

FT-IR spectra in the region of 600-3600 cm^{-1} for both starting materials (forms I and II), prepared amorphous granules, placebo granules, and used excipients were obtained using a Shimadzu IR-Prestige-21 FT-IR spectrometer coupled with a horizontal Golden Gate MKII single-reflection ATR system (Specac, Kent, UK) equipped with a ZnSe lens after appropriate background subtraction. Sixty-four scans over the selected wave number range at a resolution of 4 cm^{-1} were averaged for each sample. For the spectra of pure amorphous AGM, melting of powdered AGM form I on the