Olanzapine Solvates

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ABSTRACT: Olanzapine was crystallized from 12 organic solvents alone or in mixture, by cooling in the freezer, by slow evaporation of the solvent, or by suspending olanzapine powder for some time in the solvent. All the samples thus obtained were examined by thermal analysis (differential scanning calorimetry—DSC and thermogravimetry—TG) to certify the formation of a solvate, the presence of polymorph (form 1 or 2) in the desolvated olanzapine, comparing the different profile of the thermograms, and to calculate the stoichiometry of the possible solvate. According to the DSC thermogram, the solvents can be divided into four classes: those that do not form solvates and leave olanzapine form 1 (ethyl acetate, toluene, diethyl ether, and acetone); those that form solvate and leave form 1 of olanzapine after desolvation (methanol, 1- and 2-propanol); those that after desolvation of the solvate show a polymorph transition in the thermogram indicating the presence of form 2 of olanzapine (ethanol); other solvents (tetrahydrofuran, chloroform, acetonitrile) give solvate thermograms, where this last thermal trace is only poorly evident. With few exceptions, each solvent forms solvate both when pure and in mixture (10%, v/v, in ethyl acetate). Methanol monosolvate displays complex thermogram and thermogravimetric desolvation profiles, depending on the crystallization experimental conditions, used to prepare the solvates. Dichloromethane solvate was found by X-ray diffraction analysis to be amorphous and, on heating during DSC analysis, allowed the crystallization of both form 1 and 2, with different weight ratio, according to the experimental conditions of the solvate preparation. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:4046–4056, 2013

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INTRODUCTION

An active agent suitable for administration must be obtained at a high degree of purity and needs extensive and in-depth knowledge of its physical stability in the solid state and in aqueous solution. The contact with a crystallization solvent, for purification's safe, has important implications on the nature of the final solid state of the drug. The drug can incorporate crystallization solvent molecules into its crystal lattice forming solvates, especially if the solvent is capable of forming hydrogen bonds with the drug molecules. Moreover, for formulation reasons, related to the value of the dosage, it could be important to use the desolvated form, usually obtained by mild heating of a solvate: solvates are in fact rarely used in pharmaceutical formulations because solvents are volatile, thus making difficult the physical stabilization of the active agent. A scheduled or unforeseen (due to storage conditions) desolvation of a pharmaceutical solvate could lead to the formation of unexpected polymorph transition or the collapse of the crystal structure that originates an amorphous compound with different physical properties, batch-to-batch variability, and undesired shelf life of the active agent.[1] Olanzapine is a molecule with a certain degree of structural complexity that is reported to exist in several forms in the solid state and able to form solvate with a variety of solvents[2]; as a consequence, in defining its solid state, the physical treatments and technological processes undergone by the drug play important roles to preview its performance in terms of dissolution rate and absorption and finally of therapeutic activity and response. In fact, hydrates and solvates can be problematic during both the production and formulation of olanzapine: in the production step, desolvation can occur, originating unstable, hygroscopic, and/or amorphous material that must be controlled during storage or suitably treated to recover the normal crystallinity because of the unstable nature of the solvated/desolvated materials.

Moreover, the recommended oral olanzapine dose for schizophrenia ranges from 5 to 20 mg once daily, which is a small amount requiring a well-defined purity and assessment of the nature of the active agent; the manufacturing process of solid olanzapine for practical formulation could be complicated by its ability to form such different structures. In addition, the simple crystallization of olanzapine can produce consequences such as the dominant precipitation of one polymorphic form over another, or the selective formation of polymorphic form following the desolvation of solvates formed with different solvent molecules that display therapeutic responses different from those expected. These facts justify the number of studies concerning evaluation of anhydrous and solvated forms of olanzapine and the development of techniques especially adapted to ensure the environment for investigating the solvated species is maintained.

The objective of this paper was a systematic preparation of olanzapine solvates with common solvents, such as some alcohols, halogen solvents, and a few others and a thermal study to safely and rapidly state which solvent must be used to obtain a pure and desolvated form suitable for stable formulations or which pathway must be followed to prepare a pure solvate or a pure polymorph form or amorphous structure for different purposes. Differential scanning calorimetry (DSC) was employed to show the different situations that can be encountered crystallizing olanzapine from selected solvents, by comparison of the thermogram profiles; thermogravimetric analysis (TCA)

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allowed determination of the stoichiometry of the solvates as formed from pure solvents.

EXPERIMENTAL PART

Olanzapine was a gift from Monteresearch (Bollate–Milan, Italy). Crystallization by cooling anhydrous ethyl acetate solution gives the stable form 1 that was used throughout the experimental work.[2] The solvents (ethyl acetate, acetone, diethyl ether, toluene, methanol, absolute ethanol, 1-propanol, 2-propanol, acetonitrile, tetrahydrofuran—THF, chloroform, dichloromethane) were commercial samples of pharmaceutical purity grade (Sigma–Aldrich srl, Milan, Italy).

Preparation of the Solvates

The following methods were used to prepare the solvates.

Method 1

Saturated solutions of olanzapine in the different solvents were prepared by mild heating under constant stirring until most of the drug was dissolved. The final solution was filtered and left to reach room temperature until crystallization started; alternatively, crystallization was promoted by solvent evaporation or storage in the freezer at −20°C.

Method 2

Crystallization was carried out in ethyl acetate containing 10% (v/v) (or higher amount) of the selected solvent: olanzapine is known not to form solvates or different polymorphs when crystallized from ethyl acetate,[2] as a consequence, possible changes in the solid sample obtained could be driven only by the added solvent.

Method 3

Olanzapine was suspended in the selected solvent and the system stirred at room temperature for 2 weeks; the slurry was filtered, air dried for 1 day, and analyzed. The same could not be repeated with chloroform, THF, and 1-propanol because of the high solubility of olanzapine in these solvents.

The samples thus obtained were filtered and air dried at room temperature for 1 day and finally stored in a firmly closed container. Each sample was manually crushed in a mortar to reduce and, possibly, uniform the particle size for the thermal analysis.

THERMAL METHODS OF ANALYSIS

Differential Scanning Calorimetry

Differential scanning calorimetry traces were recorded with an automatic thermal analyzer system (Mettler 821^e). The data processing system (Mettler 821^e/500/847 thermo-cryostat) was connected to the thermal analyzer. Sealed aluminum pans with a pin hole were used for the experiment for all samples. Indium (melting point 156.6°C) was used to calibrate the instruments. The thermograms were run at a heating rate of 10°C/min, from 30 to 320°C under a nitrogen purge of 20 mL/min. A mass, not exceeding 5 –6 mg, was measured into aluminum pans with or without a small pinhole in the lid.

Thermogravimetric Analysis

Loss of solvent from the crystals was characterized by TGA with a Mettler Toledo automatic thermal analyzer system TGA/SDTA851^e/SF/1100). TG traces were recorded at heating rates of 10°C/min under a nitrogen purge. Samples with masses between 1 and 10 mg were analyzed using open alumina crucibles; mass loss (%) was calculated from TG curves, based on the mass of the original sample.

Scanning Electron Microscopy

A scanning electron microscope (SEM, EVO50EP ZEISS) was used to obtain photomicrographs of the olanzapine solvates. The particles were observed without coating, working in VP mode at approximately 90 Pa in chamber and using a 20 kV accelerating voltage, before taking the image.

An energy dispersion spectrometry (EDS) spectrum was taken from the surface of one particle showing the main elemental composition of the area itself.

X-Ray Diffraction

Some of the systems were analyzed by X-ray powder diffraction technique, using Philips PW 3719 diffractometer controlled by a computer. Experimental conditions: Cu Ka radiation (λ = 1.78896 Å); 40 kV and 30 mA. Scanning interval: 0°–50° 2θ; Time per step: 1 s; graphite monochromator on the diffracted beam.

RESULTS AND DISCUSSION

The Molecule of Olanzapine

Olanzapine, the generic name for (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-*b*] [1,5]benzodiazepine), is an atypical antipsychotic agent of the new generation of the thienobenzodiazepine class, of proven efficacy against the positive and negative symptoms of schizophrenia. The drug is known to crystallize in many different solid forms, including polymorphic anhydrates, hydrates, dehydrates, and a large number of solvates,[3] cocrystals,[4] and soluble salts[5]; though practically insoluble in water, the drug forms a hydrate containing two water molecules, and many single and mixed solvates have also been identified and for a few of them the crystal structure was reported.[6]

The crystallization experiments led only to formation of forms 1 and 2.[7]

The form 1, the most stable one, can be obtained from anhydrous suitable solvents (e.g., ethyl acetate); the form 2, the metastable one, can be obtained after mild desolvation of some solvate (e.g., ethanol solvate).[8] The two forms display different thermal behaviors. The DSC trace of form 1 shows an endothermic peak not related to weight loss, as checked by TGA: the melting peak was found to be centered at 197°C. This form is the stable polymorph present in common dosage forms. Form 2 shows additional peaks: an endotherm at about 177°C followed by an exothermal signal, typical of a polymorph transition (melting of the metastable form/recrystallization of the stable form); the melting peak of the stable form at 197°C is perfectly superposed on that of the form 1.[7] Form 2 can be considered the metastable one and was reported as unsuitable for commercial use as it discolors in the presence of air.[8] Other forms were not considered in the present paper.

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