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Phase quantification of antihypertensive drugs – Chlorthalidone, Hydrochlorothiazide, Losartan and combinations, Losartan/Chlorthalidone and Losartan/Hydrochlorothiazide – by the Rietveld method

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ABSTRACT

The identification and quantification of crystalline phases of antihypertensive drugs – Losartan potassium (LOS-K), Hydrochlorothiazide (HCTZ) and Chlorthalidone (CTD) were carried out by means of X-ray powder diffraction data and the Rietveld method. Quantitative phase analyses of Losartan potassium/Chlorthalidone (LOS-K/CTD) and Losartan potassium/Hydrochlorothiazide (LOS-K/HCTZ) combinations were also evaluated. The results indicated that for diuretics (HCTZ and CTD) only one crystalline phase was found in samples, and for LOS-K the crystal structure showed similarity between the Bragg peaks to the phase described as monoclinic and space group $P2_1/c$. After one year storage, the orthorhombic one was also observed in this sample.

1. Introduction

The main objectives of medication treatment of hypertension, a public health problem affecting millions of people worldwide are reducing morbidity and cardiovascular mortality. Several classes of drugs are used for this purpose, as for example; diuretics, beta blockers, non-peptide angiotensin II receptor (AT1), angiotensin-converting enzyme inhibitors, direct renin inhibitors, direct vasodilators and calcium channel blockers. Combinations of antihypertensive drugs such as mix of diuretics, diuretics and beta blockers, diuretics and AT1 receptor blockers, are also provided by the pharmaceutical industry in different proportions. For example, evaluation of antihypertensive efficacy for combinations LOS-K/CTD and LOS-K/HCTZ with two different proportions, specifically 25.0 mg of LOS-K for 12.5 mg diuretics and 25.0 mg LOS-K for 6.25 mg diuretics in Indian patients is described [1].

CTD and HCTZ (Fig. 1a and b) are representatives of the thiazide diuretics. These drugs are widely used in the treatment of hypertension due to their therapeutic efficiency and low cost. These drugs have a prolonged but weak pharmacological action. For this reason they are recommended just in mild and moderate cases [2]. The main differences between these compounds are the duration and site of action on the nephron [3]. LOS-K (Fig. 1c) is orally active and it was the first representative of a new class of non-peptide angiotensin II receptor (type AT1) for hypertension treatment [4–6].

These drugs are orally administered in solid form. In this kind of drugs the polymorphism phenomenon, i.e. the ability of a molecule to crystallise in more than one crystalline phase is relatively common. Polymorphism in drugs is a topic of great interest for the scientific community presenting a great challenge for the pharmaceutical industry, since changes in the crystalline arrangement can modify the physicochemical properties of drugs, and consequently may affect their development, security and effectiveness.

A classical example is the Ritonavir drug, which is used for the HIV (human immunodeficiency virus) treatment. This drug showed difference in solubility between two polymorphic forms, called forms I and II. It was commercialized in the crystalline phase known today as form I, described as monoclinic and space group $P2_1$. However, during the production of this form, a thermodynamically

Abbreviations: AT1, angiotensin II receptor type 1; HIV, human immunodeficiency virus; GSAS, general structure analysis system; EXPGUI, A graphical user interface for GSAS; pV-TCHZ, Thompson-Cox-Hastings pseudo-Voigt; U_{iso}, isotropic atomic displacements; XRD, X-ray diffraction; SHO, spherical harmonic order; Bck, background; LOS-K, Losartan potassium; CTD, Chlorthalidone; HCTZ, Hydrochlorothiazide.

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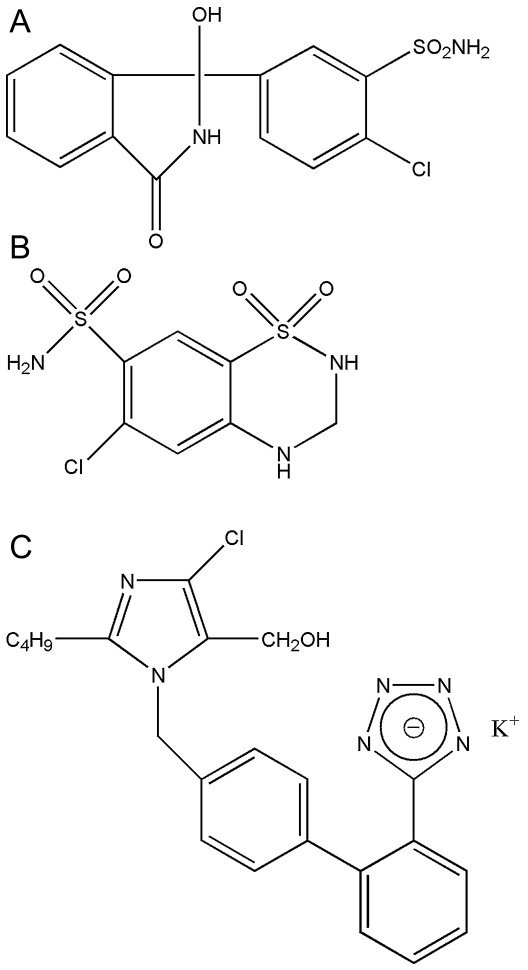

Fig. 1. Chemical structures of (a) Chlorthalidone, (b) Hydrochlorothiazide and (c) Losartan potassium.

more stable phase, known as form II, described as orthorhombic and space group $P2_12_12_1$ [7], unexpectedly appeared during the production process causing serious solubility problems [8].

Some drugs used in hypertension treatment, as CTD, HCTZ and LOS-K, present the polymorphism phenomenon. The literature describes three polymorphic forms for CTD, named forms I, II and III. Martins et al. described the crystalline forms I and III as triclinic P1 [9]. The main difference between these phases is the orientation of 2-chlorobenzenesulfonamide ring, which presents a rotation about 90° in form III when compared to form I (Fig. 1a). Form II was recently published by Martins et al., which crystallizes in monoclinic system and non-centrosymmetric space group $P2_1$ [10]. The diffraction pattern shows characteristics peaks (Cu Kα) at: 7.33; 14.36; 16.22; 16.66; 17.09; 22.33; 24.80; 27.27 and 28.99 ± 0.20° (2θ) [11].

For HCTZ, two polymorphic forms – I and II are described in literature. These forms crystallized in a monoclinic system $P2_1$ [12] and $P2_1/c$ [13], respectively, where the ring formed by C/S/N/C/N/C does not form a plane (Fig. 1b). This occurs due to the tension caused by the modification of C–S–N angle, whose values are 101.9(6)° and 100.9(1)° for forms I and II, respectively, [13].

For Losartan, several different crystalline forms were patented [14–20]. Table S1 (Supporting information) displays the characteristic peaks of these different forms. On the other hand, only three crystallographic phases are described in literature, one of them being crystallized in the acidic form under a monoclinic system, $P2_1/n$ [21]. The other two forms are potassium salts of Losartan that crystallized under a monoclinic, $P2_1/c$ [22] and orthorhombic systems, *Pbca* [23], respectively. The orthorhombic form, it is a hydrate form of LOS-K. However, these two crystalline phases are not related to any crystalline form described before.

Several analytical techniques are used in the polymorphism characterization, X-ray diffraction being most frequently and successfully employed. The main advantage over the other techniques is the ability to differentiate unequivocally one crystalline phase from the others. Thus, in this paper we use X-ray powder diffraction data in the phase identification and quantification of LOS-K, CTD, HCTZ, and combinations LOS-K/CTD and LOS-K/HCTZ in conjunction with the Rietveld method [24].

Table 1
Samples from pharmacy of Juiz de Fora, Brazil.

Samples	Lots	Codename
Losartan	0801002201	L.1
	0901017001	L.2
Chlorthalidone	027CL0606	C.1
	1008041302	C.2
Hydrochlorothiazide	050823	H.1
	10010242A	H.2
Losartan/Chlorthalidone	Req/705019[a]	LC
Losartan/Hydrochlorothiazide	Req/705020[a]	LH
Excipient	Req/705048[a]	E.1

[a] Reference to the number of request.

2. Materials and methods

The studied samples were prepared, encapsulated and available in the pharmacy shop in Juiz de Fora city, MG, Brazil. These samples were stored at room temperature and pressure.

For the X-ray analyses, these capsules containing the drugs were opened and the solid was sifted in sieves of 10 μm. For the codenames of the samples, see Table 1. The combinations LOS-K/CTD and LOS-K/HCTZ were made at ratio of 2:1, specifically, 25.0 wt% for LOS-K and 12.5 wt% for diuretics (CTD and HCTZ). Except for sample L.1, the other samples were analyzed using *Bruker D8 Advanced diffractometer* equipped with Cu Kα radiation, graphite-monochromator, NaI dynamic scintillation counter and Bragg-Brentano geometry. For these samples data were collected between 5 and 50° in 2θ with step size of 0.02° and counting time ranged for each samples varied differently. For the samples C.1, C.2 and E.1 1 s per step was used, for L.2, H.1 and H.2 20 s and for the combinations LC and LH 40 s per step. Soller slit with 2.5° of divergence, 0.6 mm divergent slit, 0.6 mm sample slit and antiscattering slit 1.0 mm were used.

For the sample L.1 the X-ray powder diffraction data were collected using *Bruker D8 Focus diffractometer*, equipped with Cu Kα radiation, LynxEye liner Position Sensitive Detector, Ni-filter and Bragg-Brentano geometry. Data was collected between 3 and 50° in 2θ with step size of 0.01° and the count time of 1 s per step, Soller slit with 2.5° of divergence, 0.2 mm divergent slit, 1.5 mm near-sample slit and antiscattering slit 8.0 mm. For all analyses a voltage of 40 kV and current of 40 mA were applied to generate the incident radiation and the measurements were performed at room temperature (298 K).

The GSAS/EXPGUI [25,26] software was used for the Rietveld refinements. The peak profiles were modeled by a modified Thompson-Cox-Hastings pseudo-Voigt (pV-TCHZ) profile function [27]. The background was fitted by a Chebyschev polynomial function [26], the preferential orientation was corrected using the spherical harmonic model [28]. The number of terms used for background fit and preferential orientation correction for each sample are listed in Table 2. Basically, the following parameters were refined: scale factor, unit cell, background, half-widths and