Polymorphism: an evaluation of the potential risk to the quality of drug products from the Farmácia Popular Rede Própria

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Polymorphism in solids is a common phenomenon in drugs, which can lead to compromised quality due to changes in their physicochemical properties, particularly solubility, and, therefore, reduce bioavailability. Herein, a bibliographic survey was performed based on key issues and studies related to polymorphism in active pharmaceutical ingredient (APIs) present in medications from the Farmácia Popular Rede Própria. Polymorphism must be controlled to prevent possible ineffective therapy and/or improper dosage. Few mandatory tests for the identification and control of polymorphism in medications are currently available, which can result in serious public health concerns.

Uniterms: Polymorphism. Medicines/quality control. Medicines/solubility. Medicines/bioavailability.

O polimorfismo em sólidos é um fenômeno frequente em fármacos e pode levar a problemas na qualidade dos medicamentos por alterar suas propriedades físico-químicas, em especial a solubilidade e, consequentemente, a biodisponibilidade. Nesse trabalho realizou-se levantamento bibliográfico sobre os principais estudos e problemas relacionados ao polimorismo em fármacos presentes nos medicamentos disponibilizados pela Farmácia Popular do Brasil. O polimorismo deve ser controlado a fim de evitar possível ineficácia terapêutica e/ou dosagem inapropriada dos medicamentos. Destacamos que são poucos os ensaios obrigatórios para identificação e controle desse fenômeno em medicamentos, o que pode acarretar grande problema de saúde pública.

Uniterms: Polimorfismo. Medicamentos/controle de qualidade. Medicamentos/solubilidade. Medicamentos/biodisponibilidade.

INTRODUCTION

The Brazilian Governmental Program Farmácia Popular Rede Própria was implemented to ensure access to low-cost medications that are considered essential for health for Brazilian citizens (Brasil, 2003). Some medications are manufactured and distributed through this nationwide chain. The Farmácia Popular Rede Própria is managed by Fundação Oswaldo Cruz (FIOCRUZ). The list of available medications is defined by the Ministry of Health based on epidemiological studies of the Brazilian population (Brasil, 2004). The drugs analyzed herein are all from the Farmácia Popular Rede Própria, which is hereafter referred to as FPRP.

Drug formulations provided by the FPRP are typically solid, which is consistent with the findings of a survey published in 2010 that revealed that over 80% of all medications are commercialized as tablets (Thayer, 2010). This predominance of solid drug formulations reflects the greater chemical stability of solid state compared with liquid state formulations (Nunn et al., 2005; Lee et al., 2011). Moreover, the development, manufacture, transportation, storage and supply of solid state formulations are simpler and less expensive in comparison to liquid state formulations (Nunn et al., 2005). However, solid state formulations also present challenges, such as polymorphism (Lee et al., 2011). This review focuses on the current knowledge of polymorphism in solid pharmaceuticals and the potential risk to the quality of drug products provided by the FPRP.
POLYMORPHISM

Definition and General Considerations

Polymorphism occurs when a solid compound exists in two or more crystal forms. Polymorphs are compounds with an identical chemical composition in which the molecules are arranged in at least two different ways in the crystalline state (Bilton et al., 1999; Karpinski, 2006; Desiraju, 2008; Purohit et al., 2009). In pharmaceutical science, however, the term is used to designate several solid state forms of drugs and excipients, including amorphous forms, solvates, hydrates, salts and co-crystals (Aaltonen et al., 2009).

The amorphous form does not possess a defined order in its arrangement. Although the amorphous form is the most soluble form, it exhibits the lowest stability (Haisa et al., 1974; Lowes et al., 1987; Chieng et al., 2009).

In amorphous and crystalline forms, a solid drug may be anhydrous or a solvate/hydrate. When a solid form contains a solvent, it is known as a solvate. When the solvent is water, it is termed a hydrate (European Pharmacopoeia, 2008).

Due to the frequent presence of water in the environment and its use in solvent blends during the crystallization process, the formation of hydrated drugs is common. Because the water molecule is small and able to form hydrogen bonds, it is easily incorporated into the crystalline lattice of drugs both occupying spaces and stabilizing the structure (Gillon et al., 2003).

A survey performed in 1999 on drugs described in the European Pharmacopoeia revealed that one-third of the 808 products listed therein could form hydrates (Griesser, 2006). In Brazil, drugs commercialized as hydrates include the following: amoxicillin trihydrate, ampicillin trihydrate, cephalixin monohydrate, sodium dipyromonohydrate, lidocaine hydrochloride monohydrate, meropenem trihydrate, mehyldopa sesquihydrate, pantoprazole sesquihydrate, morphine sulfate pentahydrate, and dexamethasone acetate monohydrate (Farmacopeia Brasileira, 2010).

In addition to molecular crystals, drug anhydrates or solvates/hydrates, co-crystals, and salts also occur. Co-crystals are drug solids defined as multicomponent molecular crystals in which at least one of the compounds is an active pharmaceutical ingredient (API) (Bond, 2007; Schultheiss et al., 2009). Salts are considered different from co-crystals provided that they are crystals formed by ionic multicomponents (Mohamed et al., 2009). The FDA has recently published a Regulatory Classification of Pharmaceutical Co-Crystals (FDA, 2013) in which co-crystal is defined as “Crystalline materials composed of two or more molecules within the same crystal lattice” and polymorphs as “Different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms”.

However, the definitions for these solid forms are matters of debate among the scientific community, regulatory agencies, and industrial groups, without a clear consensus (Schultheiss et al., 2009; Aitipamula et al., 2012).

Moreover, a nomenclature for polymorphs has not been established. Generally, different polymorphic forms of identical molecules are denoted by numerical (Carstensen, 2001) or alphabetical sequences; they can also be differentiated by means of hydration or solvation levels. In general, polymorphs are designated by the chronological order in which they have been reported (Carstensen, 2001).

The occurrence of polymorphism and its effects on solid products are attributed to existing intermolecular bonds. These noncovalent bonds, such as hydrogen bonds and van der Waals, π-π, and electrostatic interactions, determine the arrangement of the molecules in a crystal (Desiraju, 1995, 2001; Moulton et al., 2001; Purohit et al., 2009). API molecules are produced by atoms connected by covalent bonds, whereas crystals consist of molecules arranged through intermolecular interactions. The differences in these interactions can lead to distinct polymorphic forms and vice-versa (Blagden et al., 2007).

Any variation in the intermolecular arrangement of solid materials will alter the physical and chemical properties because these characteristics are intrinsically determined by its crystalline form, with the possibility of affecting bioavailability and stability (Byrn et al., 1999; ICH Q6A, 1999; Bauer et al., 2001; Erk et al., 2004; Lee et al., 2011).

According to Lee et al., 2011, the properties that vary as a consequence of the polymorphic form of the active pharmaceutical ingredient are the following: a) chemical: chemical reactivity and photochemical reactivity; b) kinetic: the rate of dissolution and stability; c) mechanical: compactability, hardness, powder flow, and friability; d) physical: conductivity, density, hygroscopicity, and particle morphology; e) surface: interfacial tension, surface area, and surface free energy; and f) thermodynamic: chemical potential, free energy, and solubility; enthalpy and entropy; heat capacity; melting and sublimation; and vapor pressure.
Challenges for the Pharmaceutical Industry

One of the first reports concerning the influence of polymorphism on drugs dates back to 1967 (Aguiar et al., 1967). In this study, the bioavailability of chloramphenicol palmitate in suspension was evaluated in humans, and it was concluded that the distinct A and B polymorphic forms exhibited not only different dissolution rates but also differences in serum levels. Form A, which is more stable, did not exhibit adequate bioavailability, whereas form B, which is metastable, exhibited greater bioavailability (Aguiar et al., 1967).

Although the effects of polymorphism on drugs have been known since the 1960s, it was only until the case of Norvir® (ritonavir), which is used for the control of acquired immunodeficiency syndrome (AIDS), that highlighted polymorphism as a serious concern for the pharmaceutical industry (Aaltonen et al., 2009). During the development of Norvir®, only a single polymorphic form was identified. In 1998, several lots of capsules did not pass the dissolution test due to the appearance of a new polymorphic form (denoted form II) that had formed during the manufacturing process, which was more stable and not very soluble (Chemburkar et al., 2000; Bauer et al., 2001). Thus, the medication was removed from the market due to the inability to manufacture the desired polymorphic form (form I) (Lee et al., 2011). To resolve this issue, Abbott Laboratories was required to spend hundreds of millions of dollars with an estimated loss of US$250m in sales in 1998 alone (Goldbek et al., 2011).

The reformulation of Norvir® using the more stable form required approximately one year, in which patients were deprived of this important medication (Peterson et al., 2006). The impact on the standard of living of these patients caused by drug polymorphism highlights the serious consequences of drug polymorphism as a public health concern.

A similar situation occurred with rotigotine. Originally licensed as a polymorphism-free API, Schwarz Pharma commercialized rotigotine in 2006 as a transdermal medication to treat the signs and symptoms of Parkinson’s disease (Goldbek et al., 2011). Nevertheless, in 2008, rotigotine (Neupro®) was removed from the market due to the transformation into a less soluble polymorphic substance that had crystallized and was not absorbed by the skin (Goldbek et al., 2011; FDA, 2008).

Due to its strategic importance for public health, medications available in the ‘FPRP’ program (Brasil, 2012) were selected for this study to perform a bibliographic survey on the occurrence of polymorphism, its possible influence on the physicochemical properties of the API and, consequently, on the final quality of the pharmaceutical formulations.

Bioequivalence and Bioavailability

To reach an expected therapeutic aim, it is imperative that pharmaceuticals exist at the expected concentration. Considering solid formulations, the medications must release the appropriate amount of API at a suitable rate for the desired therapeutic effect and be bioequivalent to the reference product. Moreover, these formulations must exhibit physicochemical stability within their shelf life (Aulton, 2005).

The Biopharmaceutical Classification System (BCS) may provide useful information to develop strategies to control polymorphism because the solubility, dissolution, and permeability of an API are determinants of its bioavailability. According to the BCS, drugs are subdivided into the following four categories: I, high solubility and high permeability; II, low solubility and high permeability; III, high solubility and low permeability; and IV, low solubility and low permeability. A drug is considered to have high solubility when its highest recommended dose is soluble in 250 mL of aqueous medium in a pH range of 1-7.5 (Amidon et al., 1995).

Considering that polymorphic forms of an API can exhibit different solubility levels, choosing the incorrect polymorphic form or the occurrence of a phase transition during the manufacture and storage may affect the bioavailability and, consequently, the efficacy and safety, particularly for drugs for which dissolution is the absorption-limiting factor (classes II and IV) (FDA, 2007; Llinàs et al., 2008).

When the occurrence of two or more solid forms of an API, including polymorphs, is identified during the development of a drug, the chosen form is typically the most stable (Shingal et al., 2004; Von Raumer, Dannappel, Hilfiker, 2012). In addition to being easily controllable, the more stable polymorphic form also complies with requirements described in the Q6A Guide of the International Commission on Harmonization (ICH) for solid form selection (Grant et al., 2004).

KNOWN CRYSTAL FORMS OF APIs PROVIDED BY THE FPRP

Table I summarizes the different APIs distributed by the FPRP as solid pharmaceutical formulations, for which the therapeutic class and relevant information on polymorphism are also included. Despite 79 of 113 (69.9%) solid formulations from the FPRP, the number...
# TABLE I - Solid-state forms of Farmácia Popular drugs

| API                      | Indication   | BCS | # | Stable form* | Reference                                                                 |
|--------------------------|--------------|-----|---|--------------|---------------------------------------------------------------------------|
| Acyclovir                | Antiviral    | III | 6 | I            | (TSRL inc, 2012; Kristl et al., 1996; Sohn et al., 2008; Lutker et al., 2011; Tutughamiarso et al., 2012) |
| Acetylsalicylic Acid     | Analgesic    | IV  | 2 | I            | (TSRL inc, 2012; Klein et al., 1994; Vishweshwar et al., 2005; Bond et al., 2011) |
| Ibuprofen               | Analgesic    | II  | 2 | I            | (TSRL inc, 2012; Shankland et al., 1996; Erk et al., 2004; Stone et al., 2009; Derollez et al., 2010) |
| Acetaminophen           | Analgesic    | IV  | 6 | I            | (TSRL inc, 2012; Haisa et al., 1974; Naumov et al., 1998; McGregor et al., 2002; Parkin et al., 2002; Peterson et al., 2002; Fabbiani et al., 2004) |
| Albendazole             | Anthelmintic | II  | 2 | II           | (TSRL inc, 2012; Pranzo et al., 2010)                                    |
| Mebendazole             | Anthelmintic | II  | 3 | A            | (TSRL inc, 2012; Rodriguez-Caabeiro et al., 1987; Martins et al., 2009; Ferreira et al., 2010) |
| Loratadine              | Antiallergic | II  | 2 | ‡           | (TSRL inc, 2012; Khunt, 2008; Gala, 1999)                                 |
| Ferrous sulfate         | Antianemic   | †   | 3 | ‡           | (Wehner et al., 1976)                                                    |
| Folic acid              | Antianemic   | IV  | 1 | Dihydrate    | (TSRL inc, 2012; Mastropaolo et al., 1980)                                |
| Diazepam                | Antianxiety  | II  | 2 | ‡           | (TSRL inc, 2012; Camerman et al., 1972)                                  |
| Amiodarone hydrochloride| Antiarrhythmic| II  | 1 | ‡           | (Wu et al., 2005; Cody et al., 1989)                                     |
| Digoxin                 | Antiarrhythmic| I   | 3 | Amorphous    | (TSRL inc, 2012; Chiou et al., 1979; Go et al., 1980; Eberhard et al., 1983) |
| Verapamil hydrochloride | Antiarrhythmic, Antihypertensive| II  | 1 | ‡           | (TSRL inc, 2012; Carpy et al., 1985; Yoshida et al., 2010)                |
| Amoxicillin             | Antibiotic   | IV  | 1 | Trihydrate   | (TSRL inc, 2012; Blanco M et al., 2005; Montejo-Bernardo et al., 2009)    |
| Azithromycin            | Antibiotic   | II or IV | 3 | Dihydrate   | (TSRL inc, 2012; Turel et al., 2003; Fabbiani et al., 2008; Fabbiani et al., 2009; Fabbiani et al., 2011) |
| Benzylpenicillin        | Antibiotic   | I or III | 1 | I            | (TSRL inc, 2012; Dexter et al., 1978)                                    |
| Cephalaxin (hydrochloride or sodium salt) | Antibiotic | II  | 8 | IV (monohydrate) | (Otsuka et al., 1983; Stephenson et al., 1998; Kennedy et al., 2003; Kasim et al., 2004; Aguiar et al., 2011) |
| Ciprofloxacin           | Antibiotic   | III | 3 | II (hydrate) | (TSRL inc, 2012; Turel et al., 2003; Fabbiani et al., 2008; Fabbiani et al., 2009; Fabbiani et al., 2011) |
| Doxycycline             | Antibiotic   | IV  | 2 | ‡           | (TSRL inc, 2012; Legendre et al., 2012)                                  |
| Erythromycin            | Antibiotic   | IV  | 4 | Dihydrate    | (TSRL inc, 2012; Fukushima et al., 1983; Stephenson et al., 1997; Miroshnyky et al., 2006) |
| Sulfamethoxazole        | Antibiotic   | IV  | 4 | III (hemihydrate) | (TSRL inc, 2012; Maury et al., 1985; Hartauer et al., 1992; Takasuka et al., 2001; Price et al., 2005; Fioritto et al., 2007) |
| Sulfasalazine           | Antibiotic   | II  | 2 | ‡           | (TSRL inc, 2012; Bilton et al., 1999; Filip et al., 2001)                 |
| Trimethoprim            | Antibiotic   | IV  | 1 | ‡           | (TSRL inc, 2012; Koetzle et al., 1976)                                   |
### TABLE I - Solid-state forms of Farmácia Popular drugs (cont.)

| API                        | Indication           | BCS | # | Stable form* | Reference                                                                                              |
|----------------------------|----------------------|-----|---|--------------|--------------------------------------------------------------------------------------------------------|
| Carbamazepine              | Anticonvulsant       | II  | 6 | Dihydrate    | (TSRL inc, 2012; Himes et al., 1981; Rebou et al., 1981; Lowes et al., 1987; Lisgarten et al., 1989; Lang et al., 2002; Grzesiak et al., 2003; Harris et al., 2005; Gelbrich et al., 2006; Kogan et al., 2008; Arlin et al., 2011) |
| Phenytin                   | Anticonvulsant       | II  | 1 | I            | (TSRL inc, 2012; Nokhodchi et al., 2003)                                                               |
| Phenobarbital              | Anticonvulsant       | IV  | 13| A            | (TSRL inc, 2012; Otsuka et al., 1993; Platteau et al., 2005; Zencirci et al., 2009; Zencirci et al., 2010) |
| Amitriptyline hydrochloride| Antidepressant       | I   | 1 | I            | (TSRL inc, 2012; Klein et al., 1994)                                                                  |
| Fluoxetine hydrochloride   | Antidepressant       | I   | 1 | I            | (TSRL inc, 2012; Robertson et al., 1988)                                                              |
| Glibenclamide              | Antidiabetic         | II  | 1 | I            | (TSRL inc, 2012; Byrn et al., 1986)                                                                    |
| Metformin hydrochloride    | Antidiabetic         | III | 2 | A            | (TSRL inc, 2012; Childs et al., 2004)                                                                   |
| Metoclopramide hydrochloride| Antiemetic         | II or IV | 3 | †           | (TSRL inc, 2012; Pabón et al., 1996)                                                                   |
| Clonazepam                 | Antiepileptic        | †   | 1 | I            | (Chanant et al., 1979)                                                                                  |
| Ketoconazole               | Antifungal           | II  | 2 | I (enantiomer +) | (Peeters et al., 1979; Peeters et al., 2004; Wu et al., 2005)                                           |
| Fluconazole                | Antifungal           | III | 4 | I            | (TSRL inc, 2012; Alkhamis et al., 2002; Caira et al., 2004; Chandavarkar, Jindai, Kulkarni, 2011)         |
| Miconazole Nitrate         | Antifungal           | †   | 3 | ‡           | (Pedersen et al., 1993; Peeters et al., 2004)                                                           |
| Promethazine hydrochloride | Antihistamine        | I   | 2 | ‡           | (TSRL inc, 2012; Borodi et al., 2012)                                                                   |
| Atenolol                   | Antihypertensive     | III | 2 | I            | (TSRL inc, 2012; Esteves De Castro et al., 2007)                                                        |
| Captopril                  | Antihypertensive     | III | 2 | I (B)        | (TSRL inc, 2012; Haoming et al., 1985; Fekete, 1997; Zhenhong et al., 2011)                             |
| Enalapril maleate          | Antihypertensive     | I   | 2 | II           | (TSRL inc, 2012; Précigoux et al., 1986; Evjolfsson, 2003; Kiang et al., 2003)                           |
| Losartan                   | Antihypertensive     | III | 5 | I            | (TSRL inc, 2012; Campbell et al., 1997; Doltzky et al., 2004; Wu et al., 1993; Fernández et al., 2002; Tessler et al., 2004) |
| Methyldopa                 | Antihypertensive     | III | 1 | ‡           | (TSRL inc, 2012; Neuman et al., 1984)                                                                   |
| Nifedipine                 | Antihypertensive     | II  | 3 | A= I= a      | (TSRL inc, 2012; Uekama et al., 1992; Grooff et al., 1997; Gunn et al., 2012)                            |
| Propranolol hydrochloride  | Antihypertensive     | I   | 3 | II           | (TSRL inc, 2012; Bartolomei et al., 1999; Bredikhin et al., 2004)                                        |
| Simvastatin                | Antilipemic          | II  | 3 | I            | (TSRL inc, 2012; Cejka et al., 2003; Husak et al., 2010)                                               |
| Biperiden                  | Antiparkinsonian     | I   | 1 | I            | (TSRL inc, 2012; Coddington, 1986)                                                                     |
| Carbidopa                  | Antiparkinsonian     | I   | ‡ | ‡           | (Lindenberg et al., 2004)                                                                               |
TABLE I - Solid-state forms of Farmácia Popular drugs (cont.)

| API                        | Indication            | BCS | # | Stable form* | Reference                                                                 |
|----------------------------|-----------------------|-----|---|--------------|---------------------------------------------------------------------------|
| Levodopa                   | Antiparkinsonian      | I   | 2 | I            | (TSRL inc, 2012; Mostad et al., 1970; Mostad et al., 1971; Howard et al., 1995) |
| Benserazide hydrochloride  | Antiparkinsonian      | †   | ‡ | ‡            | (TSRL inc, 2012; Galván-Tejada et al., 2002)                                |
| Metronidazole              | Antiprotozoal         | IV  | 1 | ‡            | (TSRL inc, 2012; McDowel, 1969; Klein et al., 1986)                        |
| Chlorpromazine             | Antipsychotic         | II  | 2 | Anhydrous    | (TSRL inc, 2012; Prasanna et al., 2001)                                    |
| Haloperidol                | Antipsychotic         | II  | 1 | I            | (TSRL inc, 2012; Prasanna et al., 2001)                                    |
| Omeprazole                 | Antiulcer             | †   | 1 | ‡            | (Ohishi et al., 1989)                                                     |
| Ranitidine hydrochloride   | Antiulcer             | III | 4 | II           | (TSRL inc, 2012; Ngooi et al., 1994, Agatonovic-Kustrin et al., 1999; Hempel et al., 2000; Chieng et al., 2006) |
| Oseltamivir phosphate      | Antiviral             | I or III | 1 | ‡            | (TSRL inc, 2012; Kang et al., 2012)                                       |
| Salbutamol sulfate         | Bronchodilator        | I   | 3 | I            | (Lindenberg et al., 2004; Lulla et al., 2011, Rao et al., 2011; Palacio et al., 2007) |
| Allopurinol                | Chronic gout treatment| IV  | 1 | I            | (TSRL inc, 2012; Prusiner et al., 1972)                                    |
| Ethinyl estradiol          | Contraceptive         | I   | 1 | Hemihydrate  | (TSRL inc, 2012; Guguta et al., 2008)                                     |
| Levonorgestrel             | Contraceptive         | I   | 2 | ‡            | (TSRL inc, 2012; Chang, Chen, 2009)                                       |
| Norethisterone             | Contraceptive         | I   | 1 | ‡            | (Linberg et al., 2004; Reisch et al., 1993; Shikii et al., 2005)            |
| Furosemide                 | Diuretic              | IV  | 3 | I            | (TSRL inc, 2012; Babu et al., 2010)                                       |
| Hydrochlorothiazide        | Diuretic              | IV  | 2 | ‡            | (TSRL inc, 2012; Leech et al., 2008)                                      |
| Prednisone                 | Glucocorticoid        | I   | 1 | ‡            | (Vogt et al., 2007; Sui cherished et al., 2008)                           |
| Azathioprine               | Immunosuppressant     | IV  | 2 | ‡            | (TSRL inc, 2012; Cook, Bugg, 1975; Acharya, 1984)                          |
| Alendronate sodium         | Inhibitor of bone resorption | III | 13 | ‡            | (TSRL inc, 2012; Kieczynski et al., 1990; Vega et al., 1996; Finkelstein et al., 2004; Asnani et al., 2009) |
| Isosorbide mononitrate     | Vasodilator           | I   | 2 | ‡            | (Fotaki, Vertzoni, 2010; Kanters et al., 1993)                             |

#: minimum number of known crystal structures; *: Room temperature; †: Unclassified; and ‡: Not reported.

Note: For the overall polymorphic forms, neither salts and solvates without pharmaceutical application nor co-crystals were considered.

The Cambridge Structural Database (CSD, 2011) and Inorganic Crystal Structure Database (ICSD, 2002) was used to analyze crystalline structures by entering the compound name, molecular form, and chemical structure. Information on patents and indexed journals in the electronic databases SciFinder© (2012) and Web of Science© (2012) were also collected. Compound structures were included as single component forms, hydrates, salts, and solvates with pharmaceutical application. Biopharmaceutical classification was obtained at the Therapeutic System Research Laboratories, which is managed by Amidon et al., 2012 (TSRL inc 2012). Furthermore, a search was performed using the aforementioned electronic databases by combining the terms “name of the compound in English” and
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“polymorph” in the free search of databases. Articles that discussed solid state chemical polymorphism were included; articles that discussed other types of polymorphism were excluded.

Table I indicates that phenobarbital and alendronate sodium are the APIs with the most reported polymorphic crystal structures (11 forms each) followed by cephalixin (8 forms) and acetaminophen/carbamazepine/acyclovir (6 forms each). A total of 168 crystal structures were found for the 65 APIs listed in Table I, which resulted in a mean value of 2.67 polymorphs per API. Figure 1a illustrates that 42 (65%) of the 65 APIs exhibit two or more polymorphs of known crystal structure. Only 21 (32%) APIs do not exhibit more than one reported crystal form. However, it is important to emphasize that in this review, only polymorphs deposited in the CSD® and ICSD® or in articles indexed in SciFinder® and Web of Science® were considered. The revision work also indicates that no crystal structure is known for 2 (3%) APIs listed in Table 1. For some APIs, the thermodynamically stable form (or preconized polymorphic form) is reported in the literature. This result is also summarized in Table I and is illustrated in Figure 1b. Noteworthy is the number of APIs (24, 37%) without studies indicating the correct crystal form, of which 13 (54%) have two or more known polymorphic crystal structures.

Figures 1c and 1d show the BCS classification of the 65 solid APIs available at the FPRP, illustrating that 31 (48%) possess low solubility (classes II and IV). Figure 2 shows the number of APIs with “unknown”, “only one”, and “two or more” crystal structures per BCS class. For 21 (68%) of the 31 class II and IV APIs (low solubility), two or more crystal structures have been reported. For 17 (68%) of the 25 class I and III APIs (high solubility), two or more polymorphic structures have been reported.

Despite 41 (63%) APIs (Table 1) with more than one reported crystal structure, as previously mentioned, there are studies concerning the influence of polymorphism on drug performance for only 22 (14.3%). Problems related to either the efficacy or the manufacture caused by polymorphism have been reported, i.e., for mebendazole, carbamazepine, estradiol, and acetaminophen.

**Albendazole and Mebendazole**

The antiparasitic albendazole and mebendazole are among the low solubility drugs with reported polymorphism. Albendazole is commercialized in form I (metastable), which is the most soluble form. Both forms I and II are stable under storage conditions; however, much care is required to control the form because of the possibility of undesirable polymorphic phase conversion in this API (Pranzo et al., 2010).

Mebendazole exhibits polymorphic forms A, B, and C, which differ in their biopharmaceutical and physicochemical properties. Polymorph C is the pharmaceutically preferred form due to its adequate aqueous solubility (Rodriguez et al., 1987; Charoenlarp et al., 1993). Form A is the most...
FIGURE 2. The number of different crystal structures distributed in the four classes of the BCS for the 65 APIs that are available as a solid formulation at the FPRP.

stable, less soluble form that is considered therapeutically ineffective (Rodriguez et al., 1987). In a clinical study with 958 children, the efficacy of polymorph A did not differ from the placebo (Charoenlarp et al., 1993). Costa et al. (1991) have shown that polymorph B is more soluble than polymorph C. Therefore, polymorph B should be avoided or a strategy to ensure the proper dosage must be developed to enable the drug to exert the desired effect. Form C, thus, recommended for oral use, is metastable and, in solution, may crystallize as the more stable form A (Rodriguez et al., 1987; Agatonovic-Kustrin et al., 2008). Moreover, regarding stability, the presence of small quantities of form A in tablets results in a rapid increase of transformation into other polymorphic forms. Four analyzed trademark drugs presented traces of form A, and, in most of them, the shelf life was reduced to less than a month. These products also failed to comply with the acceptance criteria of the United States Pharmacopoeia (USP) and the Food and Drug Administration (FDA) in dissolution assays (Brits et al., 2010). Therefore, the anthelmintic efficacy of mebendazole is highly dependent on the polymorphism (Martins et al., 2009).

Quality control routine tests that may distinguish among polymorphic forms include the dissolution assay, IR spectroscopy, thermogravimetric analyses, and primarily powder X-ray diffraction measurements (Liebenberg et al., 1998). Nevertheless, it was observed that the mebendazole dissolution assay described in USP 25 did not distinguish among the three polymorphic forms. The recommended dissolution medium was 0.1 M hydrochloride acid containing sodium lauryl sulfate (SLS). The solubility difference among the polymorphs had been masked with the inclusion of the surfactant, and the removal of SLS from the dissolution medium resolved the polymorphic forms (Swanepoel et al., 2003).

Despite this example, the USP 34 (2011) continues to recommend a dissolution medium that contains SLS. Therefore, much attention should be directed at quality control methods that are able to discriminate between polymorphic forms and that the polymorphic form present in the medication is the recommended form. In this respect, characterization using powder X-ray diffraction is very useful.

In 2005, an analysis of the raw materials and drug products containing mebendazole in the Brazilian market revealed the following alarming results: the expected form C was not found in any analyzed raw material, USP reference standard included. From the 10 analyzed medications, five contained polymorph A, three contained polymorph C, and two contained a mixture of polymorphs B and C, with B as the majority. At the time the study was published, the mebendazole reference brand (manufactured by Abbott Laboratories) was altered. Polymorph C was not detected in this new reference medication, which also contained different polymorphs in different lots (Froehlich et al., 2005).

**Furosemide**

Another low solubility drug that exhibits problems related to the dissolution assay in official compendia is the diuretic furosemide. When the solubilities of furosemide polymorphs are compared, the metastable form II is found to be the most soluble (Matsuda et al., 1990). This API has been observed to undergo photolytic degradation from which the metastable forms suffer more than the thermodynamically stable form I (Matsuda et al., 1990; Villiers et al., 1992). To differentiate furosemide polymorphic forms in pharmaceutical formulations, several dissolution mediums were tested, which resulted in a recommended medium at pH 2.2 due to its ability to differentiate the commercialized form (form I) from the other forms (II and III) (Maggio et al., 2009).

Considering the diuretic furosemide as an example, the in vitro dissolution assay is an excellent tool to differentiate polymorphic forms and identify polymorphic phase transitions. Provided the test anticipates bioavailability and physical stability, it can evaluate the quality of a medication (Yu et al., 2003; Raw et al., 2004).

Therefore, methods that are described in official compendia must be carefully considered because, as observed with mebendazole, the recommended dissolution test for furosemide does not discriminate among forms (United States Pharmacopoeia, 2011). Thus,
the development of methods that are able to differentiate polymorphic forms is essential for the quality control of medications, particularly for low solubility drugs (Bonfilio et al., 2012).

**Fluconazole**

Fluconazole confirms the high frequency of hydrate occurrence in APIs. Fluconazole exists as a mixture of forms I and II and fluconazole monohydrate (Park et al., 2007). The solubility order among the polymorphs of this API is II (metastable) > I > monohydrate (Park et al., 2010), and forms I and II convert into the monohydrate when dissolved in water (Park et al., 2010). Polymorph II has been found to absorb humidity and form the monohydrate phase from both the environment and the excipient during either the storage phase or the manufacturing phase (Chandavarkar, Jindai, Kulkarni, 2011).

**Acyclovir**

The acyclovir in pharmaceutical formulations is present as a hydrate (polymorph V) (Kristl et al., 1996; Lutker et al., 2011). Unexpectedly, the hydrated form of acyclovir solubilizes more rapidly than the anhydrous form (Kristl et al., 1996; Stephenson et al., 1997), which is explained by the high thermodynamic stability and low hygroscopicity of the anhydrous form (Kristl et al., 1996).

**Cephalexin, Erythromycin, Ciprofloxacin, Sulfamethoxazole, and Digoxin**

A tendency to form hydrates is also observed in the antibiotics cephalexin, erythromycin, ciprofloxacin, and sulfamethoxazole. In pharmaceutical preparations, monohydrated cephalexin is the predominant polymorphic form (Aguiar et al., 2011). Cephalexin is also found in the dihydrated form, which, at room temperature, rapidly loses one molecule of water to form the monohydrated cephalexin (Kennedy et al., 2003). A similar phenomenon occurs with erythromycin, which is commercialized in its more stable and less soluble dihydrated form. This API loses its water molecules at relatively low temperature (71 °C) (Fukumor et al., 1983).

As for ciprofloxacin, the exposure of form I (anhydrous) to a relative humidity higher than 90% leads to the appearance of form II (hydrate), which is observed when an aqueous suspension of form I is prepared (Mafra et al., 2012).

For sulfamethoxazole, form II converts to the hemihydrate (form III) more rapidly than form I. In the solubility assay, a phase transition was not observed for form II, whereas form I converted to the hemihydrate under identical conditions (Fioritto et al., 2007).

Micronization with supercritical antisolvent has led to an increase in the sulfamethoxazole dissolution rate and has caused the phase transition of polymorph I to II, with a solubility ratio of 1.2 (Pudipeddi et al., 2005; Chang et al., 2008).

Studies revealed that for digoxin, the grinding process leads to amorphization (Florence et al., 1976). Storage of the amorphous form at room temperature results in a reduction in solubility (Chiu et al., 1979), which is a great concern considering that this antiarrhythmic has a narrow therapeutic window. Thermal stress of digoxin also results in polymorphic phase transitions (Eberhard et al., 1983).

**Carbamazepine**

The impact of polymorphism has been extensively studied on the anticonvulsant carbamazepine, highlighting its impact on product quality. In 1988, a clinical failure was reported for Tegretol® tablets (carbamazepine), likely due to the polymorphic phase transition from the anhydrous to the dihydrate form (Lee et al., 2011). Moreover, there are several reports of variability in the dissolution profile of commercially available carbamazepine tablets (Davidson, 1994; Meyer et al., 1992, 1998; Al-Zein et al., 1999; Lake et al., 1999; Mittapalli et al., 2008).

Carbamazepine is one of the few APIs for which the recommended polymorphic form is described in official compendia. Although such compendia determine form III for medical preparations, they do not define limits for the other forms (European Pharmacopeia, 2008; British Pharmacopoeia, 2009; United States Pharmacopeia, 2011), and the manufacture of this API does not always result in pure crystalline phases (Rustichelli et al., 2000; Lang et al., 2002; Grzesiak et al., 2003; Quist et al., 2008; Javadzadeh et al., 2009; Diao et al., 2012; Wang et al., 2012), which emphasizes the need to develop methods to quantify the contamination of form III with other polymorphic forms (Kipouros et al., 2005).

A mixture of polymorphic forms has been observed in commercial samples of carbamazepine raw material (Šehić et al., 2010; Flicker et al., 2011). As expected, these polymorphs exhibit different dissolution rates. Form III converts to carbamazepine dihydrate (a less soluble form) more rapidly than form I, which critically affects the solubility and bioavailability of pharmaceutical preparations (Kobayashi et al., 2000).

When pure form III samples are compared, the effect of particle size on the dissolution rate is counterintuitive,
i.e., a larger amount of small-sized particles results in a slower carbamazepine dissolution rate, which occurs because the narrow shape of these particles enables the conversion to the dehydrate (Flicker et al., 2011). Micronization of carbamazepine by expansion in supercritical solution appears to increase the solubility of the drug, although this process may lead to a phase transition (Bolten et al., 2012).

**Phenobarbital**

Six of the polymorphic forms of another anticonvulsant, phenobarbital (A, B, C (monohydrate), D (dioxane solvate), E (hemihydrate) and F), were evaluated. The order of the dissolution rate among the forms is F > B > E > C > A > D, and the order of the hardness among the tablets containing them is D > A > C > E > B = F (Otsuka et al., 1994).

Under isothermal conditions (45 °C), phenobarbital stability was as follows: A, B, and F forms were stable at 0 and 75% relative humidity, whereas C, D, and E forms underwent transformation during storage, with the transformation rate of form D as the fastest (Otsuka et al., 1993).

**Acetylsalicylic Acid**

The possibility of the occurrence of polymorphism in acetylsalicylic acid (ASA) antiinflammatory and analgesic products has been investigated since the 1960s (Tawashi, 1968). It was only in 2005 that polymorphism was verified in this API, in which it was found that form II (metastable) coexists with form I (Vishweshwar et al., 2005). Subsequently, form II was isolated, and its conversion into form I occurs at room temperature, which is accelerated by mechanical grinding (Varughese et al., 2011).

**Acetaminophen**

Acetaminophen, which is another analgesic and antithermic drug, is an example of manufacturing problems associated with polymorphism (Snider et al., 2004). Form II (metastable), in contrast to form I (stable), can be used in the manufacture of tablets, which is advantageous because the process is simpler and less expensive (Di et al., 1996; Nichols et al., 1998). To manufacture medications containing form I, commercially available agglutinant excipients are required, which increases the cost (Di et al., 1997; Nichols et al., 1998). Because the dissolution rate is similar for both form II and commercialized form I tablets, a possible transformation does not lead to problems with bioavailability (Di et al., 1996).

**Verapamil Hydrochloride, Enalapril, Losartan, and Propranolol**

For antihypertensive drugs that contain verapamil hydrochloride, studies were performed at temperatures varying from 25 °C to 750 °C using several analytical techniques, and it was found that this API did not exhibit polymorphic forms at the evaluated conditions (Yoshida et al., 2010).

In the studies on enalapril, form II was observed to be much less stable than form I in tablets containing an identical amount of sodium hydrogen carbonate (Eyjolfsson, 2002). The increased ratio of sodium hydrogen carbonate in the tablet containing form II and the presence of desiccant in the blister packaging significantly decreased its degradation (Eyjolfsson, 2003).

Losartan antihypertensive form I is thermodynamically more stable and less soluble than form II at room temperature, and form II may convert to form I during storage (Wu et al., 1993; Crocker et al., 1997).

Both forms I and II of another antihypertensive, propranolol, are stable at room temperature even after grinding and compression. Polymorph I (metastable) is 34% more soluble than form II (commercially available) (Bartolomei et al., 1999).

**Ranitidine, Glibenclamide, and Estradiol**

Ranitidine, which is prescribed for the treatment of ulcers, exhibits polymorphic forms I and II with similar solubility and bioavailability (Bawazir et al., 1998; Parkin et al., 2002). Notwithstanding, a slight difference in stability was observed between these forms, and phase transitions can occur via water absorption, mechanical strength (Carstensen et al., 1995; Foster et al., 1998; Chieng et al., 2006) and during storage (Madan et al., 1994).

Glibenclamide form I is the most stable with a melting point of 175.4 °C and that of form II of 151.0 °C. Every form (I, II, III, and IV) was found to be stable below zero or 100% relative humidity, with form III as the most soluble (Sohn et al., 1997).

A polymorphism effect was also found for estradiol. Transdermal adhesives, which contain this drug, formed crystals during storage. The crystals belonged to different estradiol polymorphs and also to the polymeric adhesive (Variankaval et al., 1999).
QUALITY CONTROL OF POLYMORPHIC SOLID FORMS

Single crystal and powder X-ray diffraction techniques are the most suitable and more utilized tools to study and characterize polymorphs in pharmaceutical solids because they provide unequivocal proof of either polymorphism existence or polymorphism occurrence (FDA, 2007). Powder X-ray diffraction is feasible for application in the quality control of polymorphism in capsules, tablets, and pastes, among others. For this purpose, the API must be crystalline and be present at a concentration greater than 5% (w/w) in the formulation, which is the commonly adopted detection limit for phase quantification using PXRD techniques. The pharmaceutical formulation can be analyzed after minimal or no pretreatment of the sample without a requirement to separate the API from the excipients because most excipients are not detected by X-rays. Moreover, it is possible to simultaneously identify more than one API in the formulation (Phadnis et al., 1997).

Others important techniques such as microscopy, thermal analysis (e.g., differential scanning calorimetry, thermal gravimetric analysis, and hot-stage microscopy), and spectroscopy (e.g., infrared [IR], Raman, and solid-state nuclear magnetic resonance [ssNMR]) are also commonly used in the quality control of polymorphism in drugs. Diffraction, spectroscopic, and thermal techniques are considered complementary in the study of polymorphs. Polymorphic transitions can also be detected using drug product dissolution testing (FDA, 2007) because the test is demonstrably able to differentiate different forms.

Despite the vast accumulated scientific knowledge on the effects of phase transitions in APIs in the solid state, crystalline form characterization assays are not included in most monographs described in official compendia. Conversely, the FDA published the Guidance for Industry of FDA - ANDAs: Pharmaceutical Solid Polymorphism Chemistry, Manufacturing, and Controls Information that provides recommendations for the monitor and control of polymorphs in drug substances and/or drug products (FDA, 2007). However, in USP 35-NT 30, assays on powder X-ray diffraction are described in only 15 monographs from the 4,500 monographs that include APIs, excipients and drug products (United States Pharmacopeia, 2012).

CONCLUSION

For many drugs present in medications that are available at the FPRP, according to the best of the authors’ knowledge, there are few studies that correlate polymorphism to possible influences on drug solubility as well as its clinical impact. Therefore, the existence of polymorphs may potentially be an important source of variation in pharmaceutical properties, which can cause problems concerning the stability, solubility and, consequently, efficacy and bioavailability of drug products. Relatively simple quality control tests allow the differentiation of polymorphs. However, the identification of the polymorphic phase is not a mandatory test for the large majority of drugs. Thus, more commitment is necessary by regulatory and quality control authorities to monitor polymorphism not only for FPRP medications but also for all commercial drugs. This monitoring includes the control of polymorphism in raw materials, manufacturing steps and finished products by the end of the shelf life of the drug. In this manner, possible public health concerns linked to polymorphism in medicines can be avoided.
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