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Review

# Critical comparison of pharmacopeial content in relation to solid-state characterization methods

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The pharmaceutical industry is mostly dedicated to the production of drugs in solid forms such as tablets and capsules with active ingredients and excipients in the same physical state. Regarding the regulatory requirements for the analytical development and implementation of solid-state analyses, internationally recognized pharmaceutical compendia play an important role. However, the information contained in the various general chapters and monographs differs from each other, especially in countries that have national pharmacopeias, such as Brazil. Thus, the main objective of this work is to critically evaluate, based on the technical-scientific literature, the harmonization of the United States, European, British, Japanese and Brazilian pharmacopeias with respect to the following analytical techniques used for solid-state characterization: X-ray powder diffraction, differential scanning calorimetry, thermogravimetric analysis, and infrared and Raman spectroscopies. The working principle of each analytical technique, as well as the methodological parameters that impact the implementation of the analyses, are detailed. The results indicate that, in terms of solid-state characterization analysis, the adoption of unified scientific standards and principles is not yet a reality for all compendia. Additionally, the lack of harmonization between BrazP and the other compendia is especially significant, considering that ANVISA is an ICH member, the main entity responsible for promoting harmonization.

**Keywords:** Solid-state characterization. Analytical techniques. Harmonization. Pharmacopeias.

## INTRODUCTION

Considering that most pharmaceutical products, whether active pharmaceutical ingredients (APIs), excipients or drugs, are found in solid-state or solid dosage forms, the understanding of this physical phase seems to be relevant (Cui, 2007). Based on the molecular arrangement, the solid phase can be classified into two main subphases: the crystalline solid-state and the amorphous solid-state (Byrn, Zografi, Chen, 2017). Crystalline solids can exist in multiple phases, such as polymorphs, salts, solvates, hydrates and cocrystals (Vippagunta, Brittain, Grant, 2001).

This structural arrangement of solids determines the physicochemical properties of APIs, impacting the stability, processability and bioavailability of drugs (Aaltonen *et al*., 2009; Chieng, Rades, Aaltonen, 2011). Therefore, choosing solids with adequate physical and chemical characteristics is considered a fundamental factor in pharmaceutical development strategies (Pasquali, Bettini, Giordano, 2006).

In this way, specific characteristics of the particles, such as size, shape, surface, morphology and crystalline structure, are among the main factors used to control technological and biopharmaceutical drug properties (Pasquali, Bettini, Giordano, 2006), and the establishment of reliable analytical methods for the identification of

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solid forms has become an important issue in the pharmaceutical field (Auer, Griesser, Sawatzki, 2003).

Due to the impact of solid-state characteristics on drug efficacy and safety, there has been a growing increase in academic, industrial and regulatory discussions, with the objective of promoting knowledge about crystallinity, polymorphism and amorphism, as well as their applications and implications in the pharmaceutical field (Prado, Rocha, 2015). Therefore, world regulatory agencies have started publishing guidelines to encourage solid-state monitoring of pharmaceutical products through various development stages as a new drug registration requirement (EMA, 2015; FDA, 2018; FDA, 2007).

In addition, the process of registering new drugs is complex and expensive since different countries have distinct regulatory requirements (Lakkis, 2010). Such regulatory divergences are based on the degree of risk and benefits considered acceptable for medicinal use, the burden of prevalent diseases, vulnerable populations, privacy concerns and the social and economic costs faced by each country (Zerhouni, Hamburg, 2016).

On the other hand, in a globalized world, public health and innovation are no longer considered purely national issues since it is difficult to distinguish between local and foreign pharmaceutical products (Zerhouni, Hamburg, 2016). Thus, the globalization of pharmaceutical regulatory standards is a relevant strategy for reducing unnecessary requirements, rationalizing time and costs and creating a transparent regulatory process (Lakkis, 2010).

During the harmonization process, regulatory requirements and approaches adopted across countries and regions become aligned over time, the same technical guidance documents are cited, unified scientific principles and standards are adopted, and similar regulatory practices and procedures are introduced (Mike Ward, 2014). In this way, the collaboration and coordination of efforts to promote regulatory harmonization would benefit patients, ensuring safety, innovation and access to medicines produced based on science and standard procedures (Zerhouni, Hamburg, 2016).

With respect to technical and scientific requirements, while procedures and policies presented in various pharmacopeias are recognized worldwide, they sometimes diverge from each other (Sheinin, 2020). Therefore, international harmonization works to allow for the correspondence of policies, specifications contained in monographs, analytical methods and acceptance criteria for general methods among compendia (Chowhan, 2000).

The present work proposes to contribute to the regulated sector regarding the understanding and implementation of analytical techniques used in solid-state characterization: X-ray powder diffraction (XRPD), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), infrared spectroscopy (FT-IR) and Raman spectroscopy. This contribution will take place through the comparative evaluation of the content described in the general chapters of the different pharmacopeias recognized in Brazil, signaling possible aspects of methodological misalignment. The study herein has applications in the context of industrial globalization, in which the harmonization of pharmaceutical regulatory requirements and the unification of technical practices and scientific guidelines adopted worldwide are sought.

Additionally, despite the importance of the topic and the growth of regulatory requirements for monitoring and controlling the solid form of pharmaceutical ingredients and medicines, there is a mismatch between the knowledge generated in the literature and in pharmaceutical industrial practice. Considering that the adoption of outdated analytical practices can compromise the quality, efficacy and safety of commercialized drugs, this work is relevant since it promotes the critical assessment of conformity between technical-scientific and pharmacopeial publications and discusses the need for updating the compendial approach.

## DISCUSSION

### Pharmacopeial approach

Although the harmonization of pharmacopeial requirements is a current trend and encouraged by global initiatives, much remains to be done on the analytical techniques used in solid-state characterization. The analytical techniques are supported by the general chapters of the United States Pharmacopeia (USP), the European Pharmacopeia (EP), the British Pharmacopeia

(BP), the Japanese Pharmacopeia (JP) and the Brazilian Pharmacopeia (BrazP), except for Raman spectroscopy, which is not addressed by BrazP or JP. Nevertheless, only BP and EP address crystallinity and polymorphism topics in general chapters dedicated to the subject.

Chapter 5.16 (Crystallinity) of the EP and Appendix XVII U (Crystallinity) of the BP present, in a harmonized way, general information on crystallinity. Superficially, they describe the main analytical techniques used in solid-state characterization as well as in which other general chapters the methodological principles can be consulted.

Chapter 5.9 (Polymorphism), published in EP, presents the definition of polymorphism, addresses the particularities of hydrates and solvates and highlights the different physicochemical properties and bioavailability characteristics of polymorphs. On the other hand, there is no information related to cocrystals. Like Chapter 5.16 Crystallinity of EP, it recommends analytical techniques applicable to polymorphs evaluation and it indicates in which general chapters methodological details can be found.

However, BP presents a different approach to the polymorphism theme. In chapter SC I B. The importance of the correct characterization of polymorphs in pharmaceutical ingredients and formulated products is highlighted. This chapter not only briefly describes how the topic should be addressed in individual monographs but also shows the compendium's interest in receiving user contributions, such as previously developed and validated analytical methods for the proper control of undesirable polymorphic forms in pharmaceutical products.

On the other hand, each analytical technique (XRPD, TGA, DSC, FT-IR and Raman) is addressed individually in general chapters, in which the applicability and limitations of the methodology, the equipment operating principles and the analysis parameters are discussed. Since those chapters related to solid-state characterization methodologies have not yet been harmonized, different procedures can be identified. In general, regardless of the technique evaluated, there is a lack of information in the official compendia on the implications of the brand and model of the equipment used in the analysis and the software applied to process the data.

## Thermal techniques

The main analytical techniques used in thermal analyses are described by pharmacopeias and presented in a unified manner in the form of general chapters (Table I).

**TABLE I -** Pharmacopeial approach to thermal analysis, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)

| Pharmacopeia | Consulted Edition/Year | General Chapter | First Publication Edition/Year |
|---|---|---|---|
| BrazP | 6th edition/2019 | 5.2.27 Thermal analysis | 5th edition/2010 |
| USP | USP44–NF39/2021 | ⟨891⟩ Thermal analysis | Official before 2013 |
| BP | 2021 | Appendix V M. Thermal analysis | Official in 2014 |
| EP | 10th edition/2021 | 2.2.34 - Thermal analysis | Official before 2008 (8th edition) supplement-8.6/2016 |
| JP | XVII/2016 | 2.52 Thermal analysis | JP XV/2006 |

In general, pharmacopeias are limited to presenting the working principles of TGA and DSC techniques. However, the general chapter of the USP complements the subject by superficially covering hot-stage microscopy and eutectic impurity analysis. Additionally, general chapters from BP (Appendix XVII V. Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry) and EP (Chapter 2.2.61 - Characterization of Crystalline solids by Microcalorimetry and Solution Calorimetry) present specific information on microcalorimetry and solution calorimetry.

For thermal techniques, EP, BP and JP are harmonized; however, the general chapter of USP presents content that is more complete, although with limitations compared to the knowledge published in the scientific literature.

*Thermogravimetric analysis (TGA)*

In the context of solid-state characterization, TGA is essential for identifying solvates and hydrates since the loss of volatiles occurs in a characteristic way (Gobardhan *et al*., 2023). As the sample is heated, the gradual weight loss helps to define the stoichiometry of the hydrates based on the percentage of loss obtained at each stage of the process (Jurczak *et al*., 2020; Liu, Tong, Zhou, 2022).

In most pharmaceutical laboratories, thermogravimetric analysis is a complementary technique to differential scanning calorimetry analysis, especially with regard to the interpretation of endothermic traces. For example, in a DSC scan, the loss of solvents or water may resemble the melting peak. This fact can be easily distinguished by TGA (Jurczak *et al*., 2020; Liu, Tong, Zhou, 2022).

Although the applicability of thermogravimetry has been presented in all compendia, the importance of thermal analysis in solid-state characterization has not been emphasized. The general chapters published are not fully harmonized, and therefore, the information presented varies between the different publications (Table II and Table III).

**TABLE II -** Comparison of pharmacopeial approaches for the applicability of TGA and the principles of equipment operation and calibration

| **Analytical Parameters** | | **BrazP** | **USP** | **EP** | **BP** | **JP** |
|---|---|---|---|---|---|---|
| Technique applicability | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Basic operating principle of the equipment | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Thermal calibration | Fusible metal hook technique (In, Pb, Zn, Al, Ag e Au) | ✓ | ✗ | ✗ | ✗ | ✗ |
| | Currie temperature of ferromagnetic substances (Ni) | ✗ | ✓ | ✓ | ✓ | ✓ |
| Thermobalance calibration | Reference standard | ✓ | ✗ | ✓ | ✓ | ✓ |
| | Weight standard | ✗ | ✓ | ✗ | ✗ | ✗ |
| | Range and heating ratio | ✓ | ✗ | ✓ | ✓ | ✓ |

As shown in Table II, all pharmacopeias describe the basic operating principle of the equipment used in thermogravimetric analysis and indicate the importance of thermobalance calibration. However, the calibration procedure is not harmonized.

Except for USP, which indicates the use of certified weight standards in the thermobalance weight calibration procedure, the other pharmacopeias point to the use of calcium oxalate monohydrate as a reference standard. Regarding thermal calibration, unlike other compendia, BrazP recommends the use of the hook of the hang-down wire technique. In the literature, there are few papers that present details on the equipment calibration procedure (Van Gyseghem *et al*., 2009; Schmidt, Schwarz, 2005)

The operation of a TGA instrument initially requires the establishment of several experimental parameters, including sample weight, temperature range, heating rate and atmosphere, which are used in the experiment (Byrn, Zografi, Chen, 2017). According to the scientific literature, a sample of approximately 10 mg, packed in aluminum or platinum crucibles, is commonly used in TGA analyses (Delaney *et al*., 2017; Mura *et al*., 2005; Qi *et al*., 2020; Salazar-Rojas, Maggio, Kaufman, 2020; Sheikhzadeh *et al*., 2006; Shete *et al*., 2010; Da Silva *et al*., 2020; Simões *et al*., 2020; Zoppi *et al*., 2011).

Nitrogen is preferably used as a purge gas, commonly at a flow rate of 50 mL/min. Although the temperature range applied in the test varies according to the substance under study, the heating rate is usually maintained below 20 °C/min (Chawla *et al*., 2003; Darwish *et al*., 2018; Qi *et al*., 2020; Salazar-Rojas, Maggio, Kaufman, 2020; Shete *et al*., 2010; Xu *et al*., 2014).

The selection of TGA parameters should be based on the impact on the analysis. For example, the atmosphere can be inert because nitrogen, helium or argon are inexpensive and readily available. An inert atmosphere allows the evaluation of thermal events exclusively in the sample, which is why it is commonly used for the solid-state evaluation of APIs. For the evaluation of oxidative processes, for example, air and oxygen can be used. An increase in the heating ratio increases the observed temperature at which mass loss or gain occurs.

In general, all pharmacopeias point out the importance of defining the experimental parameters previously presented. However, they do not provide guidance on how these parameters should be established (Table III). The general chapter of the USP recommends that the conditions specified in the individual product monograph be followed. Alternatively, in the absence of such information, a preliminary assessment of the TGA curve should be performed. In this case, the experiment can be conducted in a temperature range from room temperature to the degradation temperature of the material or just above the melting temperature of the compound, with a heating rate of 1 to 20 °C/min. This information is supported by the literature, which suggests that the selected temperature range should be capable of covering the phase transition of the material under study. If the transition temperature is not known, an exploratory scan can be performed using a heating rate of approximately 20 °C/min (Byrn, Zografi, Chen, 2017).

**TABLE III -** Comparison of recommended parameters for performing the TGA test

| **Analytical Parameters** | | **BrazP** | **USP** | **EP** | **BP** | **JP** |
|---|---|---|---|---|---|---|
| Thermobalance calibration | Heating rate | 10 °C/min* | ✕ | 5 °C/min** | 5 °C/min** | 5 °C/min** |
| | Temperature range | Up to 900 °C* | ✕ | Up to 250 °C* | Up to 250 °C* | Up to 250 °C* |

**TABLE III -** Comparison of recommended parameters for performing the TGA test

| Analytical Parameters | | BrazP | USP | EP | BP | JP |
|---|---|---|---|---|---|---|
| Analysis execution | Sample weight | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Sample pretreatment | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Temperature range | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Heating rate | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Purge gas composition | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Purge gas pressure and/or flow | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Blank test | ✓ | ✗ | ✗ | ✗ | ✗ |

* Recommended parameters for thermobalance calibration

** Heating rate should be defined according to the equipment manufacturer's instructions; 5 °C/minute is shown as an example.

Unlike other compendia, BrazP warns of the importance of obtaining a blank test curve. This corresponds to the heating of an empty sample holder under the same experimental conditions for equipment baseline subtraction. However, little is known about this practice in the scientific literature, and only one article that cited this recommendation was found (Salazar-Rojas, Maggio, Kaufman, 2020).

Although the sample weight, temperature range, heating ratio and atmosphere used in the experiment are covered, the compendia do not provide details on how to define these parameters. Thus, in the absence of tests involving specific APIs and/or drug product monographs, analysis becomes a challenge.

*Differential scanning calorimetry (DSC)*

Differential scanning calorimetry is considered the thermal analytical technique of choice due to its ability to provide detailed information about the physical and energetic properties of a substance (Wesolowski, Leyk, 2023). This method involves indirect measurement of the heat flow that occurs during a thermal event, which may be endothermic (such as melting and dehydration), exothermic (such as crystallization), or may involve a change in the heat capacity of a sample (glass transition phenomena) (Moura Ramos, Diogo, 2021).

DSC is addressed by pharmacopeias as an integral part of the general chapters dealing with thermal analysis. Generally, all of them define DSC as a technique capable of evaluating the energetic phenomena produced by a sample when exposed to temperature variations, either through heating or cooling. The enthalpy changes, the specific heat, and the temperature at which these events occur are defined.

The basic operating principle of the equipment, as well as the types of equipment available (energy compensation and heat flow), are succinctly presented by all compendia (Table IV). They reported that the equipment consists of a temperature programming device, thermal detectors (there may be more than 1), and a recording system that may be associated with a data processing system and a controlled atmosphere.

The importance of performing thermal and heat flow calibrations of the equipment before carrying out the

analyses is indicated by all compendia (Table IV). The use of suitable certified materials or reference standards is recommended, and pure metals such as indium, zinc and tin are indicated. Calibration records are usually not included in academic publications; however, calibration is commonly performed using indium metal as a reference standard (Daniel *et al*., 2013; Figueiras *et al*., 2007; Vippagunta *et al*., 2002; Wang *et al*., 2016).

**TABLE IV -** Comparison of pharmacopeial approaches for the applicability of DSC and the principles of operation and calibration of the equipment

| Analytical Parameters | | BrazP | USP | EP | BP | JP |
|---|---|---|---|---|---|---|
| Technique applicability | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Basic operating principle of the equipment | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Instrument | Power-compensated DSC | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Heat flux DSC | ✓ | ✓ | ✓ | ✓ | ✓ |
| Thermal calibration | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Heat flow calibration | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Procedure | | ✓ | ✓ | ✓ | ✓ | ✓ |

According to Lever (2007), temperature calibration should be performed in the temperature range of interest; nevertheless, some published articles perform calibration at a single point (normally at the melting point of indium, 156.6 °C), assuming that it is a linear process (Cirri *et al*., 2004; Figueiras *et al*., 2007; Kushida, Ashizawa, 2002; Mukharya *et al*., 2012; Wang *et al*., 2016). Unlike other compendia, when dealing with equipment thermal calibration, BrazP specifies the importance of performing linearity adjustment using a combination of indium and metallic zinc to measure the temperature axis. In some academic publications, it is possible to verify the use of two different standards in equipment temperature calibration (Jug *et al*., 2010; Rocco, Winthrop, 1994).

The analytical parameters used in the evaluation of a material by DSC are considered relevant for obtaining thermal analysis curves. Thus, according to the recommendation of the official compendia, a complete description of the conditions used in the analysis must be made available. BP, EP and JP are harmonized, and in this case, no variation in content is observed. However, the BrazP and USP compendia differ in terms of their analytical parameters (Table V).

**TABLE V -** Comparison of recommended parameters for performing the DSC analysis

| Analytical Parameters | | BrazP | USP | EP | BP | JP |
|---|---|---|---|---|---|---|
| Equipment | Brand and model | ✗ | ✓ | ✗ | ✗ | ✗ |
| | Instrument and recorder sensitivity | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Last calibration record | ✓ | ✓ | ✓ | ✓ | ✓ |
| Sample | Identification | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Weight | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Thermal history | ✗ | ✓ | ✓ | ✓ | ✓ |
| Sample holder type | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Atmosphere | Gas composition | ✓ | ✓ | ✓ | ✓ | ✓ |
| | gas flow | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Pressure | ✗ | ✓ | ✓ | ✓ | ✓ |
| Temperature | Temperature range | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Heating rate | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Temperature change direction | ✗ | ✓ | ✓ | ✓ | ✓ |

The importance of indicating the brand and model of the equipment used in the analysis is only found in the USP, although it is the first information provided in academic articles when addressing DCS analyses (Mukharya *et al*., 2012; Mura *et al*., 2005; Rocco, Winthrop, 1994). Additionally, some publications include an indication of the software used for data processing; however, clear information on the instrument and recorder sensitivity was not found (Alkhamis, Obaidat, Nuseirat, 2002; Figueiras *et al*., 2007; Panchagnula *et al*., 2003; Saerens *et al*., 2011; Shete *et al*., 2010).

The procedure required for performing the analyses is also presented in all the chapters (Table IV); however, the analytical details are omitted. The need to use an appropriate and rigorously known amount of sample is known (Talle V), but no additional information about the ideal weight or how to define it is presented. Based on the scientific literature, it can be concluded that sample amounts ranging from 2 mg (Figueiras *et al*., 2007; Jug *et al*., 2010; Kushida, Ashizawa 2002) to 10 mg are routinely used (Alkhamis, Obaidat, Nuseirat, 2002; Cirri *et al*., 2004; Jia *et al*., 2019)

In regard to the evaluation of powders, it is known that the lack of uniformity in the particle size distribution can impact the results obtained in the DSC analysis, causing distortions in the thermal analysis curve baseline during phase transitions (Lever, 2007). However, sample preparation is not addressed by pharmacopeias, and it was not found in the consulted publications.

In terms of defining the temperature range and heating rate to be used in the experiment (Table V), it is recommended that the information should be taken

from the monograph, although most of them still do not include DSC analysis. In the absence of this information, only USP advises performing a preliminary evaluation using a wide temperature range (from room temperature to the decomposition temperature of the material or just beyond the melting point, from 10 to 20 °C above the predicted value) and a wide heating rate (from 1 to 20 °C/min). However, to minimize the decomposition of the test substance and to avoid compromising the transition temperature, a lower heating rate can be applied.

In many papers, the temperature range is shown in the thermal analysis curve, with no mention throughout the text (Rocco, Winthrop, 1994; Saerens *et al*., 2011; Wang *et al*., 2016). A heating rate of 10 °C/min is commonly used (Daniel *et al*., 2013; Saerens *et al*., 2011; Vippagunta *et al*., 2002; Wang *et al*., 2016).

Despite being recommended by the official compendia, the thermal history of the sample is not normally mentioned in the academic publication. The history of previous thermal exposures to the sample prior to the current analysis can impact the analytical results, as thermal exposures can promote the phase transition. However, some experiments use heating-cooling-heating cycles (heat-cool-heat) that minimize the effect of this history on the results obtained in the analysis (Liggins, Hunter, Burt, 1997; Shete *et al*., 2010).

Regarding the equipment atmosphere, the composition and flow of the carrier gas are important analytical parameters. Nitrogen is the most commonly used gas in the pharmaceutical industry; however, the flow rate is highly variable, ranging from 20 to 100 mL/min (Daniel *et al*., 2013; Figueiras *et al*., 2007; Kushida, Ashizawa, 2002; Mukharya *et al*., 2012). Helium gas, which has a high thermal conductivity, can be used when the thermal resistance of DSCs needs to be reduced (Lever, 2007).

Although it is cited by pharmacopeias as a relevant analytical parameter, except for BrazP, the pressure imposed by the gaseous atmosphere on the equipment is not routinely provided by the academic literature (Liggins, Hunter, Burt, 1997; Shete *et al*., 2010; Wang *et al*., 2016).

The definition of the sample holder (crucible) can influence the result of the DSC analysis (Bhattacharya, Brittain, Suryanarayanan, 2009). The type of crucible must be selected according to the chemical reactivity of the product under analysis and the system pressure (Hilfiker *et al*., 2019). Therefore, there is a wide variety of crucibles available on the market that are produced using different materials and designed to meet the specific aspects and needs of the sample. In general, open, sealed (with nonhermetic closure) or hermetically closed crucibles can be used, in which a hole can be made in the lid to relieve system pressure (Craig, Reading, 2007).

## Crystallographic technique

Among the various experimental approaches available for the identification of solid forms, including polymorphs, solvates, salts, cocrystals and amorphous solids, X-ray powder diffraction (XRPD) stands out (Rodríguez, Gautam, Tinoco, 2021). It is a nondestructive analytical technique used to characterize crystalline materials. It is capable of providing information about structures, phases, preferred crystalline orientations and other structural parameters, such as average grain size, crystallinity, stress and crystal defects (Thakral *et al*., 2018; Chambi *et al*., 2024).

All the official compendia consulted presented a general chapter providing guidance on the crystallographic technique of powder X-ray diffraction (Table VI).

The chapter entitled "Characterization of Crystalline and Partially Crystalline Solids by X-ray Powder Diffraction" was published in the USP in 1995, modified in 2000, and then adopted and harmonized by EP and JP with minor changes (Fawcett *et al*., 2019). It should be noted that BP is also harmonized with the others.

**TABLE VI -** Pharmacopeial approach to powder X-ray diffraction (XRPD)

| Pharmacopeia | Consulted Edition/Year | General Chapter | First Publication Edition/Year |
|---|---|---|---|
| BrazP | 6th edition/2019 | 5.2.31 - Difração de raios X | 5th edition – 2nd supplement/2017 |
| USP | USP44–NF39/2021 | ⟨941⟩ Characterization of crystalline and partially crystalline solids by X-ray powder diffraction (XRPD) | Official before 2013, reviewed in 2022 for harmonization |
| BP | 2021 | Appendix XVII Q. Characterization of Crystalline and Partially Crystalline Solids by X-ray Powder Diffraction (XRPD) | Official in 2014, reviewed in 2022 for harmonization |
| EP | 10th edition/2021 | 2.9.33 - Characterization of crystalline and partially crystalline solids by X-ray powder diffraction (XRPD) | Official in 2009 and reviewed in 2022 for harmonization |
| JP | XVII/2016 | 2.58 X-ray Powder Diffraction Method | JP XV/2006 |

The general chapters evaluated are harmonized on the applicability of the technique and the basic principle of operation of the equipment, discussing the diffraction phenomenon and how it occurs in a matrix that has a long-range order, such as crystalline materials (Table VII).

**TABLE VII -** Comparison of pharmacopeial approaches for the applicability of the XRPD and the operating principles of the equipment

| Analytical Parameters | BrazP | USP | EP | BP | JP |
|---|---|---|---|---|---|
| Technique applicability | ✓ | ✓ | ✓ | ✓ | ✓ |
| Basic operating principle of the equipment | ✓ | ✓ | ✓ | ✓ | ✓ |
| Instrument | ✓ | ✓ | ✓ | ✓ | ✓ |
| X-ray radiation | ✓ | ✓ | ✓ | ✓ | ✓ |
| Procedure | ✓ | ✓ | ✓ | ✓ | ✓ |

Schematic representations of X-ray diffraction according to Bragg's law, of the equipment used in the analysis of powders and of diffractograms collected for different solid phases are presented by all pharmacopeias. In addition to USP, the other compendia also presented explanatory images of the unit cell and the crystalline plane.

According to the pharmacopeia general chapters, all crystalline phases of a substance produce characteristic X-ray diffraction patterns, which can provide 3 types of information: the angular position, the intensity, and the profile of the diffraction lines. These data are used as fingerprints to identify the solid-state of the sample.

X-rays are produced using a filament as a source of electrons (the cathode). These electrons are then accelerated by an applied voltage of 40 kV to 50 kV, striking a target (the anode), which is usually made up of metals such as copper, molybdenum, chromium, and silver. Each anode produces a characteristic X-ray spectrum (Gilmore, 2011). Thus, information on the radiation source used in the analysis is important for data collection and evaluation.

In the academic literature, there is a prevalence of the use of copper as an anode, especially through the use of monochromatic CuKα radiation (approximately 1.54 Å) (Lucier *et al*., 2014; Talukder *et al*., 2011; Wang *et al*., 2016; Yuliandra *et al*., 2018; Zhu *et al*., 2017). The operating conditions of the X-ray tube are also routinely presented. A voltage ranging from 30 kV to 45 kV and an electric current intensity ranging from 15 mA to 40 mA are commonly used (Dash, Tyle, 1996; Van Gyseghem *et al*., 2009; Leung *et al*., 1998; Liggins, Hunter, Burt, 1997; Talukder *et al*., 2011).

On the other hand, the general chapters of the pharmacopeias indicate that the choice of radiation to be used depends on the absorption characteristics of the sample and the possible fluorescence caused by the atoms present in it. Corroborating what was previously presented, they indicate that the main sources of radiation used are vacuum tubes, copper, molybdenum, iron, cobalt or chromium as anodes and that X-rays produced by copper (CuKα), molybdenum or cobalt are more commonly used for organic substances. However, no information about the operating conditions of the X-ray tubes is available (Table VIII).

**TABLE VIII -** Comparison of the parameters recommended for performing the XRD test

| **Analytical Parameters** | | **BrazP** | **USP** | **EP** | **BP** | **JP** |
|---|---|---|---|---|---|---|
| Equipment | Brand and model | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Software | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Performance evaluation | ✓ | ✓ | ✓ | ✓ | ✓ |
| X-ray radiation | Source | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Tube operating condition | ✗ | ✗ | ✗ | ✗ | ✗ |
| Sample | Weight | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Preparation | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Mounting | ✗ | ✓ | ✓ | ✓ | ✗ |
| | Particle size | ✓ | ✓ | ✓ | ✓ | ✓ |
| Procedure | Sample holder | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Temperature | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Data acquisition (transmission/reflection) | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Angular range 2θ | ✓ | ✓ | ✓ | ✓ | ✓ |

Additionally, all compendia warn about the importance of protecting equipment operators against radiation since it can be harmful to humans. According to the harmonized chapters, radiation protection practices and exposure limits defined for each country must be respected. In the absence of official regulations, the recommendations of the International Commission on Radiological Protection should be applied. BrazP does not provide details on this topic.

Powder diffraction pattern data acquisition assumes that the microcrystals are randomly and uniformly distributed in the sample. Considering that an ideal sample (isotropic particles, without composition defects or inhomogeneities, with a size of less than 1 μm) is rarely found, techniques to reduce the preferential orientation should be used, such as soft grinding with the use of grade mortar and pestle (Gilmore, 2011).

The importance of preparing the powder material and mounting the sample in a suitable support is emphasized by all pharmacopeias, as they can significantly affect the quality of the data to be collected (Table VIII). This is because the preferential orientation of the crystalline particles in the sample holder influences the intensity of the diffraction reflections, which affects the crystal identification.

According to BrazP, sample preparation is generally limited to grinding the powder in an agate mortar to reduce the particle size (particle size of approximately 5 to 10 μm). Then, the pulverized sample is pressed into a sample holder made of aluminum, glass, or polymer. The harmonized compendia (USP, EP, BP and JP) points out that size reduction corresponds to the simplest and most advantageous approach to preferential orientation reduction (particle size approximately 50 μm). Although there is information that other techniques can be used, there is no further detail.

According to the harmonized chapters, excessive powder grinding can compromise data collection due to contamination of the sample by abrasive particles from grinding instruments, a reduction in the degree of crystallinity, phase transition, chemical decomposition, introduction of internal stress and solid-state reactions. Therefore, a comparison must be made between the diffraction pattern obtained for the intact sample and that of the treated sample (Bhattacharya, Brittain, Suryanarayanan, 2009).

However, most articles consulted do not mention the treatment given to the samples or the type of sample holder used (Agrawal *et al*., 2004; Liggins, Hunter, Burt, 1997; Lucier *et al*., 2014; Wang *et al*., 2016; Yuliandra *et al*., 2018; Zhu *et al*., 2017). When mentioned in the literature, the sample holder varies in material (glass or aluminum) and format (blade, support or capillary) (Alkhamis, Obaidat, Nuseirat, 2002; Dash, Tyle, 1996; Van Gyseghem *et al*., 2009; Leung *et al*., 1998; Shewale *et al*., 2015; Singh *et al*., 1998).

With respect to sample mounting in the sample holder, the harmonized chapters, except for JP, discuss the effect of sample displacement in relation to the diffractometer rotation axis and the effect of sample thickness and transparency (Table VIII). Such effects are difficult to avoid and may result in a change in the diffraction pattern; however, they can be corrected using an appropriate internal standard (Bhattacharya, Brittain, Suryanarayanan, 2009).

Despite being a good practice recommended by compendia, the evaluation of diffractometer performance using a reference standard prior to analysis (Table VIII) is rarely described in scientific articles (Van Gyseghem *et al*., 2009; Lucier *et al*., 2014; Wang *et al*., 2016).

During data collection, information such as speed, resolution, intensity and minimization of the preferred orientation must be considered (Gilmore, 2011). The need to align the goniometer and the optical system is emphasized by pharmacopeias since they directly influence the quality of XRD investigations (Table VIII). However, this information is rarely addressed in the literature (Van Gyseghem *et al*., 2009; Singh *et al*., 1998).

In general, experiments are performed on a 2θ screen, covering an angular range of 2° or 5° to 35° or 40°(Alkhamis, Obaidat, Nuseirat, 2002; Leung *et al*., 1998; Liggins, Hunter, Burt, 1997; Wang *et al*., 2016; Zhu *et al*., 2017) and sometimes 2° or 5° to 60° or 70° (Van Gyseghem *et al*., 2009; Sarkar, Perumal, Panchagnula, 2008; Shewale *et al*., 2015).

The data acquisition speed commonly ranges from 0.01° to 0.1°; however, there is no standardization for the increment of steps per unit of time (Dash, Tyle 1996;

Talukder *et al*., 2011; Wang *et al*., 2016; Yuliandra *et al*., 2018; Zhu *et al*., 2017).

The official guidelines indicate that the PXRD technique can be used for qualitative and quantitative analysis. The first is based on the visual or computer-assisted comparison of the peaks obtained for the sample under study in relation to a well-characterized reference chemical substance or to the crystalline structure deposited in certified databases. In this case, a variation of the 2θ diffraction angles up to 0.2° is accepted. However, for the comparison of diffraction angles to be performed assertively, the data collection must be performed at the same temperature. Therefore, relevant information is routinely disclosed in academic publications (Van Gyseghem *et al*., 2009; Sarkar, Perumal, Panchagnula, 2008; Shewale *et al*., 2015; Wang *et al*., 2016; Zhu *et al*., 2017).

In summary, the general chapters of USP, EP, BP and JP are harmonized. However, they do not address the operating conditions of the X-ray tube (voltage and intensity of the electric current), which are considered essential parameters for an effective analysis. On the other hand, BrazP takes a different approach from other compendia, especially in terms of sample preparation, including grinding and adequate particle size, the recommendation of using an internal standard and the definition of the extension of a 2θ scan for use in data collection.

## Spectroscopic techniques

### *Infrared spectroscopy*

The electromagnetic region in which the infrared band is located can be divided into 3 subregions: the near-infrared (from 12,500 $cm^{-1}$ to 4,000 $cm^{-1}$), mid-infrared (from 4000 $cm^{-1}$ to 400 $cm^{-1}$) and far-infrared or terahertz regions (from 400 $cm^{-1}$ to 10 $cm^{-1}$). For pharmaceutical analytical applications, medium or near-IR regions are generally used (Song *et al*., 2020). Among spectroscopic techniques, near-infrared spectroscopy is a powerful technique that provides information about the chemical (heterogeneity and humidity) and physical (particle size and crystalline environment) properties of a sample (Razuc *et al*., 2019; Yang *et al*., 2021).

Infrared spectroscopy was performed by all consulted compendia (Table IX). However, except for the chapter of BP, which is harmonized with Chapter 2.2.24 - Absorption spectrophotometry infrared of the EP, there is a variation in the other compendia content.

**TABLE IX -** Pharmacopeial approach to infrared (IR) spectroscopy

| Pharmacopeia | Consulted Edition/Year | General Chapter | First Publication Edition/Year |
|---|---|---|---|
| BrazP | 6th edition/2019 | 5.2.14 Espectrofotometria no ultravioleta, visível e infravermelho | 4th edition/1988 |
| USP | USP44–NF39/2021 | ⟨197⟩ Spectrophotometric identification tests | Official before 2013 and reviewed by USP43-NF38/2020 |
| | | ⟨854⟩ Mid-infrared spectroscopy | USP41–NF36/2018, reviewed in 2020 |
| | | ⟨1854⟩ Mid-infrared spectroscopy—theory and practice | USP38–NF33/2015 |
| | | ⟨856⟩ Near-infrared spectroscopy | USP43-NF38/2020 |
| | | ⟨1856⟩ Near-infrared spectroscopy—theory and practice | Official before 2013 and reviewed by USP43-NF38/2020 |

**TABLE IX -** Pharmacopeial approach to infrared (IR) spectroscopy

| Pharmacopeia | Consulted Edition/Year | General Chapter | First Publication Edition/Year |
|---|---|---|---|
| BP | 2021 | Appendix II A. Infrared Spectrophotometry (Absorption Spectrophotometry, Infrared) | Official in 2014, reviewed in 2021 |
| EP | 10th edition/2021 | 2.2.24 - Absorption spectrophotometry, infrared | Official before 2008 and reviewed in 2021 |
| | | 2.2.40 - Near-infrared spectroscopy | Official before 2008 and reviewed in 2014 |
| JP | XVII/2016 | 2.25 Infrared Spectrophotometry | JP XV/2006 |

Unlike other pharmacopeias, BrazP is characterized by ultraviolet, visible, and infrared spectrophotometry in the same chapter. The focus of FT-IR is on the near-infrared (NIR) region and mid-infrared (MIR) region, and there is no detailed information about the far-infrared region. The BP, in turn, only presents information on MIR spectroscopy.

In general, all consulted compendia define the wavelength bands of electromagnetic energy contained in the infrared region, but in a nonharmonized way (Table X). Additionally, there is no consensus on which region would be the best region for solid-state investigation, compromising the understanding and analysis of the technique. The only exception is JP, which does not provide a definition of the wavelength range and suggests that readings be taken from 4000 to 400 $cm^{-1}$, which corresponds to the MIR range. It should be noted that JP does not even consider the IR as an analytical tool for solid-state characterization and presents the technique in a superficial way.

**TABLE X -** Wavelength bands characteristic of IR spectroscopy ($cm^{-1}$)

| Analytical Parameters | BrazP | USP | EP | BP | JP |
|---|---|---|---|---|---|
| Near-infrared (NIR) | 13300–4000 | 12821-4000 | 12800–4000 | 12500–4000 | NI* |
| Mid-infrared (MIR) | 2500–400 | 4000–400 | 4000–400 | 4000–400 | |
| Far-infrared (terahertz) | 400–33 | NI* | 400–10 | 400–10 | |

*NI = not informed

USP does not discuss the far-infrared region but contains an image that indicates that wavelengths below 500 $cm^{-1}$ are associated with this electromagnetic radiation range. The technique applicability, the basic operating principle of the equipment, details about the instrument and the analysis procedure are included in all compendia, except for JP (Table XI).

**TABLE XI -** Comparison of pharmacopeial approaches for the applicability of IR spectrophotometry and the operating principles of the equipment

| Analytical Parameters | BrazP | USP | EP | BP | JP |
|---|---|---|---|---|---|
| Technique applicability | ✓ | ✓ | ✓ | ✓ | ✓ |
| Basic operating principle of the equipment | ✓ | ✓ | ✓ | ✓ | ✗ |
| Instrument | ✓ | ✓ | ✓ | ✓ | ✗ |
| Procedure | ✓ | ✓ | ✓ | ✓ | ✗ |

NIR radiation has become widely used in the pharmaceutical industry for the quality control of raw materials, including active ingredients and excipients. It is commonly used in moisture determination and hydrate evaluation since it is especially sensitive to water. Additionally, it can be applied in the differentiation and quantification of other solvates, cocrystals and salts, as well as polymorphs (Chavan *et al*., 2017; Strachan *et al*., 2021). As NIR spectroscopy features particle size-dependent light scattering, which appears as a change in the spectrum baseline, it can be used for particle size characterization (Strachan *et al*., 2021).

MID spectra provide molecular fingerprints. Since they have defined and frequently resolved spectral bands, they are commonly used in chemical analysis. As the intensities and frequencies of the bands are also affected by the molecular arrangement, this method is widely used in solid-state characterization (Van Eerdenbrugh, Taylor 2011; Strachan *et al*., 2021).

BP Appendix II A and EP Chapter 2.2.24 indicate that MIR spectroscopy is used in chemical (such as identification and quantification of substances) and physical (such as determination of solid-state properties) analysis. According to Chapter 2.2.40 of EP, NIR spectroscopy can be used in process analyses. JP, in turn, presents only the identification and determination of substances as applicable for the technique.

USP, on the other hand, contains a specific chapter to guide the use of spectroscopic techniques in the identification of materials (197-Spectrophotometric identification tests). In this chapter, it is reported that variations between the spectra of the standard and the sample may occur due to differences in the solid form of the material. Details of the NIR and MIR spectroscopy methods used are covered in specific chapters (854, 1854, 856 and 1856) (Table IX).

On the other hand, MIR spectroscopy is characterized as an identification test for BrazP, and NIR spectroscopy is widely used in the quantification and identification of APIs and excipients, solid-state identification, particle size determination and disintegration patterns, as well as in process control analyses.

Although far-infrared spectroscopy has been used in solid-state determination, in the identification and quantification of polymorphs, solvates, cocrystals, and amorphous solids (Strachan et al., 2021), only EP and BP have been studied. In a superficial and nonorientative way, they associate the far-infrared band with the crystalline structure, hydrogen bonds, vibrations of angular deformation of heavy atoms and molecular rotations. Corroborating the lack of information in official compendia on the use of far-infrared spectroscopy in solid-state characterization, the academic literature commonly uses the MIR spectral region for this purpose (Araya-sibaja *et al*., 2019; Cuzzucoli *et al*., 2018; Kini, Patel, 2016; Lu *et al*., 2016; Mkaouar *et al*., 2015; Ogawa *et al*., 2015; Shewale *et al*., 2015; Stofella *et al*., 2019).

In general, infrared spectra are acquired through dispersive instruments or with Fourier transform infrared (FT-IR) spectroscopy (Munson, 2009).

Dispersive spectrometers consist of a radiation source, a monochromator, and a detector. Although the IR radiation sources used are similar for both types of equipment, in regard to instrumentation, the monochromator is replaced by the interferometer in the Fourier transform equipment (Van Eerdenbrugh, Taylor, 2011).

The introduction of FT-IR instrumentation revolutionized the field of mid-infrared spectroscopy and almost entirely replaced the use of dispersive instruments. As it is the most common equipment, only the Fourier transform spectrophotometer is included in EP and BP, although the other compendia cover both types of equipment.

According to previous reports, the use of FT-IR spectrometers in solid-state characterization studies has increased (Araya-sibaja *et al*., 2019; Cuzzucoli Crucitti *et al*., 2018; Kini, Patel, 2016; Mkaouar *et al*., 2015; Srivastava *et al*., 2011; Xu *et al*., 2014).

IR spectra are characterized by the number of absorptions and the wavenumbers at which they occur, as well as the intensity and sharpness of the peaks formed (O'Neil, Edwards, 2011). Given the above, the analytical parameters used in the analysis are defined with the objective of obtaining a high signal-to-noise ratio from the spectrometer, sufficient resolution between the peaks and instrument stability (Reich, 2005) (Table XII).

Although routinely cited in the academic literature, there is little information about the model of spectrometers in official compendia (Table XII). This issue is considered relevant during equipment performance evaluation, in which the general chapters indicate that the manufacturer's recommendations must be followed.

According to EP Chapter 2.2.40 and BP Appendix II, to determine the best signal-to-noise ratio for analysis execution, it is necessary to optimize the data acquisition time and the number of scans. However, there is no guidance procedure for the correct determination of these parameters. In general, the use of 32 scans per sample is common in academic studies; on the other hand, the collection time is not usually mentioned (Araya-sibaja *et al*., 2019; Daniel *et al*., 2013; Ogawa *et al*., 2015; Stofella *et al*., 2019).

**TABLE XII -** Comparison of the recommended parameters for performing the IR test

| **Analytical Parameters** | | **BrazP** | **USP** | **EP** | **BP** | **JP** |
|---|---|---|---|---|---|---|
| Equipment | Brand and model | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Software | ✗ | ✓ | ✓ | ✓ | ✗ |
| | Instrument | ✓ | ✓ | ✓ | ✓ | ✗ |
| | Resolution | ✗ | ✓ | ✓ | ✓ | ✗ |
| | Performance evaluation | ✗ | ✓ | ✓ | ✓ | ✓ |
| Spectra acquisition | Acquisition mode | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Data acquisition time | ✗ | ✗ | ✓ | ✓ | ✗ |
| | Number of scans | ✗ | ✗ | ✓ | ✓ | ✗ |
| | Temperature | ✗ | ✓ | ✓ | ✓ | ✗ |
| Sample | Weight | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Preparation | ✓ | ✓ | ✓ | ✓ | ✓ |

Regarding the resolution between peaks, nominal values between 1 $cm^{-1}$ (Kini, Patel 2016; Lu *et al*., 2016) and 4 $cm^{-1}$ (Daniel *et al*., 2013; Jiang *et al*., 2014; Srivastava *et al*., 2011; Xu *et al*., 2014) are found in the academic literature. Although BP and EP indicate the importance of resolution, only USP, in Chapter 1854, deeply presents the subject, stating that the main factor that affects the resolution of FT-IR equipment is the maximum difference in the optical path of the interferogram (Table XIII).

EP and USP emphasize that sample temperature is an important methodological aspect, especially for liquid analysis, since small changes in this analytical parameter can generate relevant changes in the spectrum. Additionally, USP states that the environmental conditions of temperature and humidity must be controlled (Table XIII). In regard to the study of solids, environmental conditions are usually used (Daniel *et al*., 2013; Jiang *et al*., 2014; Xu *et al*., 2014); however, these experimental data are not included in most academic publications (Cuzzucoli Crucitti *et al*., 2018; Kini, Patel 2016; Lu *et al*., 2016; Ogawa *et al*., 2015; Shewale *et al*., 2015).

**TABLE XIII -** Comparison of the procedures described for the preparation of solid samples, according to the spectrogram acquisition method

| Acquisition mode | BrazP | USP | EP | BP | JP |
|---|---|---|---|---|---|
| Transmission | Powder dispersion in mineral oil<br><br>Tablet preparation using potassium and sodium halides | Powder dispersion in liquid paraffin<br><br>Tablet preparation using alkali halide<br><br>Compression cells<br><br>Self-Supported Polymer Films | Powder dispersion in liquid paraffin<br><br>Tablet preparation using potassium bromide or potassium chloride | Powder dispersion in liquid paraffin<br><br>Tablet preparation using potassium bromide or potassium chloride | Preparation of the sample paste in liquid paraffin<br><br>Tablet preparation using potassium bromide |
| Diffuse reflection | Sample mixture 5% (w/w) in potassium bromide | There is no preparation | | | Sample crushed mixed with potassium bromide |
| Attenuated total reflectance | There is no preparation | | | | |
| Transflection | There is no information | There is no preparation | | | There is no information |

FT-IR spectrometers are designed to operate in different spectrum acquisition modes, including transmittance, diffuse reflectance and attenuated total reflectance (ATR) (Byrn, Zografi, Chen, 2017). This information is covered by all official compendia, including sample preparation guidance information (Table XIII).

Due to the strong radiation absorption of most organic materials in the MIR region, in terms of the transmission method, samples need to be pulverized to a fine powder (particle size ≤ 10 μm) and diluted in suitable material (liquid paraffin or alkali halide), such as KBr, for further compression into tablets (Byrn, Zografi, Chen, 2017; Strachan *et al*., 2021).

As the compression process to produce tablets can result in phase transformation and alkaline salts can be hygroscopic, reducing the signal quality in the spectrum through water interference, nondestructive

spectral acquisition methods such as diffuse reflectance and ATR may prove useful (Byrn, Zografi, Chen, 2017). In these cases, the solid under analysis is exposed through a diffuse reflectance cell or is presented directly on the crystal without any prior preparation (Munson, 2009).

The use of attenuated total reflectance as a sampling configuration for solid analysis is common in the literature (Araya-sibaja *et al*., 2019; Cuzzucoli Crucitti *et al*., 2018; Daniel *et al*., 2013; Lu *et al*., 2016; Stofella *et al*., 2019). However, KBr tablet preparation, indicating the transmittance data acquisition mode, is still routinely used (Kini, Patel, 2016; Mkaouar *et al*., 2015; Ogawa *et al*., 2015; Shete *et al*., 2018; Shewale *et al*., 2015; Srivastava *et al*., 2011).

The general chapters of pharmacopeias indicate that sample preparation and presentation procedures vary according to the physical state of the sample and the data acquisition method used (Table XIII).

According to EP (Chapter 2.2.24) and BP, IR has several limitations, such as the need for additional techniques for complete identification of the substance, the inability to distinguish between pure enantiomers and the possibility of phase change during the preparation of samples. Additionally, direct comparison between the spectra obtained for the BrazP sample and the chemical reference substance is not recommended.

*Raman spectroscopy*

As discussed for infrared spectroscopy, the Raman technique corresponds to vibrational spectroscopy. However, in this case, the inelastic scattering of monochromatic radiation caused by a sample was studied (Sun *et al*., 2023). Raman spectroscopy is used to identify pharmacologically active substances, carry out qualitative and quantitative analyses, characterize crystalline forms, perform structural determination and perform pharmacokinetic evaluations (Kashvi *et al*., 2023; Shah *et al*., 2023). It can also be used to evaluate polymorphism during the production process, including the crystallization, drying, grinding, granulation and heat treatment stages (Gao *et al*., 2021; Shah *et al*., 2023).

Unlike other analytical techniques, which are supported in all official compendia, Raman spectroscopy is not included in BrazP and JP (Table XIV).

**TABLE XIV -** Pharmacopeial approach to Raman spectroscopy

| Pharmacopeia | Consulted Edition/Year | General Chapter | First Publication Edition/Year |
|---|---|---|---|
| USP | USP44–NF39/2021 | <858> Raman spectroscopy | USP43-NF38/2020 |
| | | <1858> Raman spectroscopy - theory and practice | Official before 2013 and reviewed by USP43-NF38/2020 |
| BP | 2021 | Appendix II H. Raman Spectroscopy | Official in 2014, reviewed in 2022 |
| EP | 10th edition/2021 | 2.2.48 - Raman spectroscopy | Official in 2016, reviewed in 2022 |

The absence of a general Raman chapter in BrazP makes it difficult to implement these techniques by the regulated sector since access to other compendia is not free of charge and requires mastery of the English language. Furthermore, considering that Brazil became a member of the ICH management committee (the main organization driving the harmonization of technical and regulatory requirements) in 2019, the discrepancy between BrazP and other compendia is relevant.

The USP presents the Raman technique in two distinct general chapters: Chapter 858, entitled Raman spectroscopy, addresses the equipment qualification procedure, describes the validation and verification parameters of the analytical methods, and summarizes the analysis procedure. On the other hand, Chapter 1858, entitled Raman spectroscopy - theory and practice, describes in detail the analysis procedure.

All three compendia that cover Raman spectroscopy (USP, EP and BP) discuss the technique applicability, the operating principle of the equipment, the equipment information and the procedure used in the analysis (Table XV). It should be noted that the information contained in the BP and EP compendia are harmonized.

**TABLE XV -** Comparison of pharmacopeial approaches for the applicability of Raman spectrophotometry and the operating principles of the equipment

| Analytical Parameters | USP | EP | BP |
|---|---|---|---|
| Technique applicability | ✓ | ✓ | ✓ |
| Basic operating principle of the equipment | ✓ | ✓ | ✓ |
| Instrument | ✓ | ✓ | ✓ |
| Procedure | ✓ | ✓ | ✓ |

Raman spectroscopy is a nondestructive, noninvasive, and fast technique that requires little or no sample preparation. Therefore, some determinations can be performed through the use of packaging materials (Calvo, Maggio, Kaufman, 2017). Corroborating the above, the general chapters of the pharmacopeias indicate that Raman spectroscopy can be applied in qualitative and quantitative assessments, both in chemical and physical analysis and in process analysis.

Regarding the operating principle of the equipment, the official compendia indicates that IR and Raman spectroscopy have different sensitivities and are considered complementary techniques. While IR detects the absorption of electromagnetic energy due to the variation in the dipole moment of a molecule, Raman spectroscopy focuses on the polarization of molecular bonds during vibration.

Different excitation sources can be used in Raman spectroscopy, such as krypton ions (530.9 and 647.1 nm), He:Ne (632.8 nm), $Nd^{3+}$:YAG (1064 nm and 532 nm) (Atassi *et al*., 2010; Shete *et al*., 2018), argon ions (488.0 and 514.5 nm) (Mkaouar *et al*., 2015) and diode lasers (630 and 780 nm) (Araya-sibaja *et al*., 2019; Cuzzucoli Crucitti *et al*., 2018; Saerens *et al*., 2011).

While all compendia address the importance of laser selection (Table XVI), only USP has a table listing radiation source options, the nominal wavelength and range, and the typical frequency of each laser. However, guidance information regarding the proper light source and laser power choice is not available.

**TABLE XVI -** Comparison of recommended parameters for performing the Raman test

| Analytical Parameters | | USP | EP | BP |
|---|---|---|---|---|
| Equipment | Laser selection | ✓ | ✓ | ✓ |
| | Laser power | ✓ | ✓ | ✓ |
| | Detection spectral region | ✓ | ✓ | ✓ |
| | Focus and geometry of incident light | ✓ | ✓ | ✓ |
| | Detector selection | ✓ | ✗ | ✗ |
| | Software | ✗ | ✗ | ✗ |
| | Calibration | ✓ | ✓ | ✓ |
| Sample | Weight | ✓ | ✓ | ✓ |
| | Preparation | ✓ | ✓ | ✓ |
| | Size and distribution | ✓ | ✓ | ✓ |
| | Sample holder | ✓ | ✗ | ✗ |
| Spectra acquisition | Data acquisition time | ✓ | ✗ | ✗ |
| | Resolution | ✗ | ✗ | ✗ |
| | Temperature | ✗ | ✗ | ✗ |

Dispersive Raman systems show greater sensitivity and allow for shorter measurement times than FT-Raman. However, the beam diameter at the laser focus is smaller, which can cause heating of the sample and photodegradation and increase the risk of inducing fluorescence in prone materials (Strachan *et al*., 2021).

The main limitation of Raman spectroscopy lies in the native fluorescence of some samples, which can mask the signal and leave the bands completely undetectable (Calvo, Maggio, Kaufman, 2017; Strachan *et al*., 2021). All the general chapters indicate that the fluorescence of the material under study or of contaminating impurities may overlap with the Raman signal, compromising the analysis. They also state that fluorescence can be avoided by choosing a longer excitation wavelength, for example, in the near-infrared region.

According to Rostron *et al*., (2016), the use of an NIR excitation laser (1064 nm) has a smaller fluorescence effect than visible-wavelength lasers. Thus, the excitation source must be carefully defined because the correspondence between the wavelength and the electronic transition of the material increases the probability of the incidence of fluorescence (Bowie *et al*., 2000).

In addition to fluorescence, the use of very high laser power can cause thermal damage or changes in the sample (such as dehydration), compromising the analysis (Bowie

*et al*., 2000; Strachan *et al*., 2021). According to USP, the local heating of the sample by the light source and photodegradation are factors that need to be evaluated.

Although sample preparation is not required in Raman spectroscopy, the particle size is an important parameter for obtaining accurate and reproducible results (Calvo, Maggio, Kaufman, 2017). Additionally, the volume sampled affects the signal, as well as the powder surface uniformity (Strachan *et al*., 2021). USP indicates that the lack of sample homogeneity and differences in the sampling area can impact the signal intensity. Additionally, the absorption of the Raman signal and the effect of sample polarization are also important factors for the quality of the analysis.

According to EP and BP, the factors that affect the intensity of Raman bands are the polarization and intensity of the radiated light, the polarization of the scattered Raman light, the instrument response, the focus and geometry of the sample, the density of the packaging material for solid samples measured directly, the material refractive index, the particle size and distribution, and the scattering and absorption cross section (Table XVI). However, there is no guidance on how the analytical parameters should be defined to ensure the quality of the analysis. Among the analytical parameters required to perform Raman spectroscopy in solid samples, spectral resolution is one of the most important (Tuschel, 2019). Although this information is routinely presented in many publications (Araya-sibaja *et al*., 2019; Atassi *et al*., 2010; Gilmore, 2011; Lu *et al*., 2016; Ogawa *et al*., 2015; Saerens *et al*., 2011; Shete *et al*., 2018; Srivastava *et al*., 2011; Stofella *et al*., 2019), this is an analytical parameter not covered by official compendia (Table XVI).

Although the harmonization of pharmacopeial requirements is a current trend and encouraged by global initiatives, in general, with regard to analytical techniques related to solid-state characterization, there is still much to be done. As a rule, regardless of the technique in question, official compendia lack information regarding the implications of the brand and model of the equipment used in the analysis and the software used to process the data.

Regarding the XRPD, the general chapters of USP, EP, BP and JP are harmonized. However, they do not address the operating conditions of the X-ray tube (voltage and intensity of the electric current), which are essential parameters for an effective analysis. PharmB, in turn, presents a different approach from other compendia, especially with regard to sample preparation, including grinding and appropriate particle size, as well as the recommendation for the use of an internal standard and the definition of the length of the 2θ scan to be used in data collection.

For thermal techniques, EP, BP and JP are harmonized; however, the USP general chapter presents content that is more complete, although with limitations compared to the knowledge published in the scientific literature. For DSC, the general chapters say little about the preparation and definition of sample taking, as well as about the different types of sample holders available and how to select them appropriately to conduct the study. Regarding TGA, although the sample weight, temperature range, heating rate and atmosphere used in the experiment are covered, the compendia do not provide details on the procedure for defining these parameters. Therefore, in the absence of the test in specific IFA and/or medication monographs, conducting the analysis becomes difficult.

The harmonization of the general chapters that describe spectroscopic techniques is even more limited, so that only EP and BP correspond to the methods evaluated. It should be noted that PharmB and JP do not include Raman spectroscopy and present IR in a superficial manner. It was also found that the definition of the wavelength range that represents each infrared region is misaligned among the compendia consulted. Therefore, there is no consensus on which region (NIR, MIR or far IR) is best for investigating the solid state, which compromises the understanding of the technique and the conduct of the analyses. It is worth mentioning that JP does not even consider IR as an analytical tool for characterizing the solid state.

Other techniques are also highly relevant for characterizing the solid-state of pharmaceutical raw materials and formulations, such as optical and electronic microscopy, sieving, laser diffraction, and the evaluation of flow and deformation parameters. In general, the techniques discussed in this article are most commonly used to evaluate the structural aspects

of compounds. Solid-state characterization must always be carried out from a complementary perspective, in which the techniques seek to evaluate parameters that are essential for the rational planning of the formulation and manufacturing process. Therefore, other approaches may be adopted in other articles, focusing on techniques not detailed here.

## CONCLUSIONS

In the present study, the methodological approaches adopted by BrazP, USP, EP, BP and JP for the analytical techniques used in solid-state characterization (XRPD, DSC, TGA, IR and Raman) were critically confronted. The detailed comparative assessment, obtained as a result of this research, correlates the operating principle of the equipment with the parameters required for the correct performance of the analyses for each methodology. Thus, it contributes to the construction of knowledge on the subject and facilitates the understanding and implementation of these analytical techniques in pharmaceutical industrial practice. Despite the worldwide efforts applied in favor of the correspondence/equivalence of pharmaceutical technical-scientific requirements, the general chapters of the main compendia differ from each other (except for EP and BP, which are harmonized) and present gaps in relation to the knowledge established by the literature, especially regarding the details of the methodological parameters.

Considering that this misalignment can be responsible for the emergence of doubts and misunderstandings during the implementation of solid-state analysis, in the development and quality control phases, compromising the quality and effectiveness of medicines produced worldwide, the impact of the research findings is significant. Therefore, it is concluded that the compendial approach needs to be updated in the face of scientific knowledge and that the harmonization of the general chapters in question is urgent.

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