Brazilian Journal of
HEALTH AND PHARMACY

CRFMG

# Integrative performance evaluation for the development of olanzapine coated tablets

*Avaliação integrativa de desempenho para o desenvolvimento de comprimidos revestidos de olanzapina*

**Carla Giordani Testa[1,2*]; Livia Deris Prado[1,3]; Helvécio Vinícius Antunes Rocha[1,3]**

[1] Postgraduate Program in Management, Research and Development in the Pharmaceutical Industry - Farmanguinhos, Fiocruz, Rio de Janeiro, RJ, Brazil.

[2] Brazilian Navy Pharmaceutical Laboratory, Rio de Janeiro, RJ, Brazil.

[3] Laboratory of Micro and Nanotechnology, Fiocruz, Rio de Janeiro, RJ, Brazil.

***Corresponding author:** Carla Giordani Testa (ORCID: https://orcid.org/0000-0002-0785-2789)
E-mail: cgtesta22@gmail.com

*Data de Submissão: 15/10/2024; Data do Aceite: 02/07/2025.*

**Citar:** TESTA, C.G.; PRADO, L.D.; ROCHA, H.V.A. Integrative performance evaluation for the development of olanzapine coated tablets. **Brazilian Journal of Health and Pharmacy**, v. 7, n. 3, p. 23 - 47, 2025. DOI: https://doi.org/10.29327/226760.7.3-3

## ABSTRACT

Olanzapine (OLZ) is a second-generation antipsychotic drug indicated for the treatment of schizophrenia and bipolar disorder and belongs to class II of the Biopharmaceutical Classification System. The low aqueous solubility of OLZ, associated with its intricate polymorphic nature and sensitivity to certain environmental conditions such as heat and humidity, may affect bioavailability. Therefore, the objective of this study was to assess the influence of the physicochemical characteristics (particle size distribution, flow, wettability, solubility and dissolution profile) of three different raw material OLZ samples from distinct active pharmaceutical ingredient (API) manufacturers to determine their possible impacts on formulation and processability. Based on preformulation results, a direct compression formulation was proposed for the production of 10 mg olanzapine-coated tablets. The formulations were evaluated for compliance with the tests provided in official compendia, including flowability, disintegration, weight variation, friability, breaking force and assay, along with evaluating the similarity of their *in vitro* dissolution profiles to those of the reference drug product available on the national market. Notably, formulations manipulated using the API from three different manufacturers presented satisfactory results, corroborating the findings from the solubility and dissolution studies of the raw materials. The results demonstrated the equivalence of the tested formulations compared with the reference medicine in dissolution medium at pH values within the physiological range. Therefore, for olanzapine, the physicochemical properties of the drug substance, proposed formulation and manufacturing process play a determining role in the product's performance with respect to pharmaceutical equivalence assessment.

**Keywords**: Olanzapine; flowability; polymorphism; dissolution; direct compression.

## RESUMO

A olanzapina (OLZ) é um fármaco antipsicótico de segunda geração indicada no tratamento da esquizofrenia e do transtorno bipolar, pertencente à classe II do Sistema de classificação biofarmacêutica. A baixa solubilidade aquosa da OLZ, associada à sua intricada natureza polimórfica e sensibilidade a certas condições ambientais como calor e umidade pode afetar a biodisponibilidade. Portanto, o objetivo deste estudo foi avaliar a influência das

características físico-químicas (distribuição de tamanho de partícula, fluxo, molhabilidade, solubilidade e perfil de dissolução) de três diferentes amostras da matéria-prima OLZ de diferentes fabricantes de insumos farmacêuticos ativos (IFA) para determinar possíveis impactos na formulação e processabilidade. A partir dos resultados de pré-formulação, foi proposta uma formulação por compressão direta para o medicamento olanzapina 10 mg comprimido revestido. As formulações foram avaliadas quanto à conformidade com os ensaios previstos em compêndios oficiais, incluindo fluidez, desintegração, variação de peso, friabilidade, dureza e doseamento, juntamente com a avaliação da similaridade dos perfis de dissolução *in vitro* com o medicamento referência no mercado nacional. Notavelmente, a formulação manipulada com os três fabricantes diferentes apresentou resultados satisfatórios, corroborando os dados dos estudos de solubilidade e dissolução das matérias-primas. Os resultados demonstram a equivalência das formulações testadas em relação ao medicamento referência, nos meios de dissolução com pH na faixa fisiológica. Desta forma, para a olanzapina, as características físico-químicas do fármaco associadas à formulação proposta e processo produtivo apresentaram papel determinante no desempenho do produto na avaliação da equivalência farmacêutica.

**Palavras-chave**: Olanzapina; fluidez; polimorfismo; dissolução; compressão direta.

## INTRODUCTION

Schizophrenia is a severe and chronic mental disorder that, according to 2021 estimates, affects approximately 23 million people worldwide (GBD, 2024). Olanzapine (OLZ) is a second-generation atypical antipsychotic drug indicated for acute treatment (psychotic outbreak) and maintenance of schizophrenic disorders and other psychoses where positive and negative symptoms are prominent (BHANA et al., 2001; CITROME et al., 2019). OLZ is a thienobenzodiazepine analogue with affinity for numerous receptor systems: although the drug's primary pharmacological effect is attributed to its antagonism of D2 receptors, it also directly influences the serotonin system by blocking 5HT2A and 5HT2C receptors. Additionally, OLZ targets several other receptors that may contribute to both its therapeutic and adverse effects, including D1, D3 and D4 dopamine receptors; 5HT3 and 5HT6 serotonin receptors; α1 adrenergic receptors; H1 histamine receptors; and multiple muscarinic receptors (HADJOUDJ et al., 2024). OLZ is well absorbed orally but undergoes significant first-pass metabolism (KOLLI et al., 2023), with a maximum plasma concentration ($C_{max}$) occurring within 5 to –8 hours ($t_{max}$) after administration (ELI LILLY DO BRASIL, 2022). It shows linear pharmacokinetics over the clinical dosing range, and it binds extensively to plasma proteins (93%), predominantly to albumin and α1-acid-glycoprotein. The drug has an elimination half-life ranging from 21 to –54 hours (ELI LILLY DO BRASIL, 2022).

OLZ has low water solubility (DIXIT et al., 2011) and high permeability (KAMIYA et al., 2021) across biological membranes and is classified as class II (DA COSTA et al., 2022; JAWAHAR et al., 2018) according to the Biopharmaceutics Classification System (BCS). The drug is presented as a yellow crystalline solid that can be crystallized in more than 60 different forms (REUTZEL-EDENS, BHARDWAJ, 2020), eight of which are of pharmaceutical interest. Four different anhydrides (I, II, III and IV), three dihydrated forms (B, D and E), a higher hydrate and an undisclosed number of mixed solvates have been identified and characterized (ASKIN et al., 2019; KOLODZIEJSKI et al., 2011; POLLA et al., 2005; REUTZEL-EDENS et al., 2003; TESTA et al., 2019). The commercially available raw

material can contain a mixture of OLZ polymorphs (TESTA et al., 2019) depending on the manufacturing process (REUTZEL-EDENS et al., 2003; REUTZEL-EDENS, BHARDWAJ, 2020).

Pharmaceutical development aims to design a product and its manufacturing process that promote the expected therapeutic response for a particular drug, which can be produced on an industrial scale in a reproducible, safe and effective way (DHONDT et al., 2022; ICH, 2009). The clinical efficacy of a medicine is not attributed solely to the intrinsic pharmacological activity of the drug. Factors related to manufacturing processes, as well as the physicochemical properties of the drug substances and excipients, can modify the absorption of a certain API, thus altering its bioavailability (SOUSA et al., 2023; TOUKABRI et al., 2024). Exposure to solvents (PAISANA et al., 2016) and heat (TANG et al., 2021) can favour the OLZ phase transition. Anhydrous forms can hydrate differently depending on the initial polymorphic structure and moisture conditions (PAISANA et al., 2016). The conversion to hydrated forms should be avoided, as it is associated with undesirable API discolouration and may significantly affect its bioavailability due to variations in solubility (PAISANA et al., 2016), which compromises patient adherence (GALARNEUA, 2013; SELMIN et al., 2021), especially for use in patients with psychosis.

Therefore, substances sensitive to heat and humidity, such as OLZ, may benefit from being formulated via a direct compression process, as this method eliminates the use of solvents and drying steps, such as the traditional wet granulation process (YU et al., 2021). Direct compression is a preferred manufacturing technique for solid dosage forms that involves simply blending the API with suitable excipients and compressing the mixture into tablets, reducing processing time and costs and minimizing drug exposure to stress conditions (FAYED et al., 2022). Despite its advantages, the direct compression process has high requirements for the functional properties of the components of the powder, such as good flowability, compressibility and appropriate elasticity (YU et al., 2021).

However, as the Brazilian pharmaceutical market experiences a great influx of raw materials from various manufacturers (LABOISSIÈRE, 2024), each with distinct quality standards (ANVISA, 2024a), it is essential to identify and control the critical material attributes to minimize variability throughout the product life cycle. These specifications must include not only compendial analytical parameters but also internal criteria for physicochemical requirements. This is crucial to guarantee optimal performance throughout all stages of production, emphasizing the safety and efficacy of the final pharmaceutical product.

The low water solubility of olanzapine, associated with its polymorphic complexity and related susceptibility to environmental conditions, such as heat and humidity, presents some significant challenges for drug development and manufacturing. The relevant influx of raw materials from diverse manufacturers in the Brazilian pharmaceutical market introduces additional variability, reinforcing the need for stringent material characterization and process optimization. Therefore, in the present study, we aimed to determine and compare the physicochemical properties of OLZ raw materials from different suppliers to assess their impact on formulation performance. Tablets containing OLZ were produced by direct compression and evaluated using breaking force, friability, disintegration time, assay and dissolution profiles as quality control parameters.

## METHOD

Olanzapine samples were purchased from three different manufacturers, and for confidentiality reasons, they were designated OLZ A (Brazil), OLZ B

(Portugal) and OLZ C (India).

**Particle size analysis**

The particle size distribution was determined by laser diffraction using a Beckman Coulter LS 13320 particle size analyser (Beckman Coulter, USA) equipped with a dry powder module (Tornado). The level of obscuration was maintained between 8% and 12%, and the vacuum pressure was set to 20" $H_2O$ (BECKMAN COULTER, 2019). Sample amounts were used for a minimum acquisition time of 30 seconds. There was no need for sample preparation. The Fraunhofer model was used for deconvolution of the diffraction data. Each sample was measured in triplicate.

The results are presented as particle diameters corresponding to 10% ($d_{10}$), 50% ($d_{50}$), and 90% ($d_{90}$) of the cumulative undersize distribution (volume), average and span index. The span index is related to the width of the particle size distribution of a specific sample (DAI et al., 2019; WANG et al., 2024) and is calculated according to Equation 1:

$$Span\ index = \frac{d_{90} - d_{10}}{d_{50}}$$

(1)

The closer the calculated index is to 1, the more uniform the particle size distribution of the sample.

**Density and powder flow**

The bulk and tapped densities of the powder samples were determined in accordance with the methods of the United States Pharmacopeia (USPNF, 2024) using a 100 mL graduated measuring cylinder mounted on autotap equipment (Nova Ética 303D, Brazil). The cylinder was carefully filled with the desired mass of powder. The initial volume (V0) was recorded, and the bulk density was calculated as the ratio of mass (grams) to volume. The measuring cylinder was subsequently mechanically tapped (10, 500 and 1250 taps), and the corresponding volume was read to the nearest millilitre. When the difference between the two volumes was smaller than 1 mL, the tapped volume (Vf) was recorded. The tap density was calculated as the ratio of mass to final volume. The Hausner ratio (Equation 2) and Carr's (compressibility) index (Equation 3) were calculated as follows:

$$Hausner\ ratio = \frac{V_0}{V_f}$$

(2)

$$Compressibility\ index = 100 \times \left[\left(\frac{V_0 - V_f}{V_0}\right)\right]$$

(3)

The flow properties of the powder samples were assessed (in triplicate) by measuring the angle of repose and the flow rate (flow through an orifice) using a granulate flow tester (Erweka GTB, Germany). To determine the angle of repose, the powder was poured into the funnel of the flow tester and allowed to flow through the hopper orifice, forming a cone of powder. The sidewall of the built-up cone was measured using an automatic laser, and the actual angle of repose was calculated. For the flow rate measurements, the powder sample was poured into the hopper and allowed to flow through the funnel orifice. The flow rate was determined as the ratio of weight (g) to time (seconds).

To develop a specific methodology for the evaluation of the OLZ batches, different nozzles (6, 8, 10, 11.3, 15 and 25 mm) and stirring device speeds (speeds 1, 2, 3 and 4) were tested to identify the minimum diameter orifice and speed at which the powder flows.

**Wettability**

Wettability studies were performed using the sessile

drop method with a drop shape analyser (Krüss DSA 100, Germany) (LA ZARA et al., 2021). Approximately 300 mg of each OLZ sample was compacted in disks at 800 psi for 1 minute with the aid of a hydraulic press. A drop of liquid (water or buffers saturated with OLZ) was dispensed on the disc surface, and images were captured immediately after. The contact angle was measured by the equipment and calculated using a mathematical expression suitable for determining the shape of the drop. The tests were performed in triplicate at room temperature (between 20 °C and 25 °C).

**Solubility**

The equilibrium solubility was determined using the shake flask method (DIXIT et al., 2011). The solubility was evaluated in 0.1 M hydrochloric acid (HCl), 0.05 M acetate buffer (pH 4.5) and 0.05 M phosphate buffer (pH 6.8), which were prepared according to the methods of the United States Pharmacopeia (USPNF, 2024). A known excess amount of sample was added to a flask filled with 100 mL of medium and shaken at 150 rpm at 37 ± 0.5 °C for 48 hours in an orbital shaking incubator (Nova Ética 430/RSBPE, Brazil). Clear supernatant was withdrawn at 1, 6, 24 and 48 hours, immediately filtered through a 0.45 µm syringe filter, diluted and analysed using an ultraviolet visible (UV–Vis) spectrophotometer (Varian Cary 50, USA) at 259 nm (maximum absorbance), with each pure medium used as a blank (DIXIT et al., 2011). The solubility measurements were performed in triplicate. In parallel, a stock solution of the drug in each medium at a concentration of 0.10 mg/mL was maintained under the same conditions as the samples to evaluate the stability of the drug in solution during the study.

The residual solids obtained from the suspensions after the 48-hour period were evaluated by differential scanning calorimetry (DSC) with a DSC 60 instrument (Shimadzu, Japan) to evaluate the potential phase transitions of olanzapine in solution. Approximately 2 mg of each sample was hermetically sealed in an aluminium pan and heated from 30 °C to 250 °C at a scan rate of 10 °C/minute under a nitrogen atmosphere (50 mL/minute).

**Powder dissolution profile**

A common method for investigating the dissolution kinetics of powders follows a "bulk approach," where dissolution is studied using a substantial amount of powder. This approach typically relies on standard methodologies, such as measuring dissolution kinetics with a USPNF dissolution apparatus (MARABI et al., 2008; PATEL et al., 2025). In these studies, both the physical and chemical properties of the liquid medium (e.g., surface tension, viscosity, density, and temperature) and the powder itself (e.g., particle size, density, porosity, and chemical composition) play significant roles in influencing dissolution kinetics (MARABI et al., 2008). The tendency of particles to agglomerate may also influence the dissolution of poorly water-soluble drugs, as once particles form cohesive masses within the dissolution medium, the available surface area decreases, directly affecting dissolution rates (DE VILLIERS et al., 1996). Therefore, the objective of this test was to evaluate the dissolution profiles of OLZ powders to determine the effects of polymorphism, particle size distribution and agglomeration on the dissolution results.

Dissolution profiles of the raw materials were evaluated using a USP type II (paddle) apparatus (Pharmatest PTWS 3CE, Germany) (ELSHAHAT et al., 2024; RUDRANGI et al., 2015). Approximately 25 mg of OLZ was accurately weighed and transferred to a dissolution vessel containing 900 mL of dissolution medium (27.78 µg/mL of the analyte) at 37 ± 0.5 °C under a rotation speed of 50 rpm. Aliquots were withdrawn at predetermined time intervals (3, 5, 7, 10, 12, 15, 30 and 60 minutes), filtered, diluted to the final concentration (8.33 µg/mL) and quantified using a UV–Vis spectrophotometer (Varian Cary 50, USA) at 259 nm as previously described (ELSHAHAT et al., 2024; RUDRANGI et al., 2015).

The analytical curves for the UV method were constructed by diluting aliquots taken from OLZ working standard solutions (100 µg/mL) with dissolution medium in 100 mL volumetric flasks, resulting in a linear concentration range of 2.5, 5, 8, 10 and 15 µg/mL. Each concentration was analysed in duplicate, and the average values were used to calculate the regression equation and correlation coefficient ($r2 > 0.999$).

Considering that OLZ is a drug with pH-dependent solubility (ELSHAHAT et al., 2024), several solvents were selected to evaluate the drug dissolution profiles when exposed to different pH values in gastrointestinal tract fluids (TASEVSKA et al., 2025). The experiments were conducted in 0.1 M HCl, 0.05 M acetate buffer (pH 4.5), 0.05 M phosphate buffer (pH 6.8), 0.05 M acetate buffer (pH 4.5) with 0.5% sodium lauryl sulfate (SLS) and 0.05 M phosphate buffer (pH 6.8) with 0.5% SLS. Six samples of each API were evaluated in each proposed medium (n=6).

**Preparation of OLZ formulations**

The tablets were prepared by direct compression. Three different batches were manipulated, which consisted of OLZ (here called L1, the batch produced with OLZ A, L2 with OLZ B, and L3 with OLZ C), spray-dried lactose monohydrate (Foremost Farmus, United States of America) as the diluent, microcrystalline cellulose 102 (Blanver, Brazil) as the diluent, crospovidone (Nanhang Industrial, China) as the disintegrant, hyprolose (Ashland, United States of America) as the tablet binder, magnesium stearate (Magnesia, Germany) as the lubricant and Opadry® 03F (Colorcon, United States of America), containing hypromellose, titanium dioxide, macrogol and propylene glycol, as the coating agent. The formulation proposed was qualitatively similar to a reference medicine (Zyprexa®). The qualitative and quantitative compositions and the process (direct compression) were the same for all three batches; therefore, the physicochemical properties of the different APIs were assumed to be the only factors influencing the tablet results.

All formulation components, except the lubricant magnesium stearate, were manually sieved through a 1 mm mesh and mixed in a V blender (Lawes, Brazil) in different stages for a total of 35 minutes. Magnesium stearate was then added to the blend and mixed for an additional 4 minutes. The density and flowability of the powder mixtures were evaluated according to methods described previously (USPNF, 2024).

Using a tablet press (Lawes, Brazil) equipped with 10 mm round punches with biconcave faces, the produced mixtures were compressed directly into tablets with an average weight of 400 mg, which is equivalent to a 10 mg dose of OLZ. During compression, the disintegration time, weight variation, friability and tablet breaking force were determined in tablet cores, according to general chapters described in the Brazilian Pharmacopeia (ANVISA, 2024b). The tablets were subsequently coated with a WG 3.5 Coater lab drum (WS Usinagem, Brazil). The coated tablet evaluation included disintegration time, weight variation (ANVISA, 2024b), OLZ content (USPNF, 2024) and dissolution profile (ANUP et al., 2018; DA COSTA et al., 2022).

**Disintegration**

Six tablets were placed in the basket rack assembly of the disintegration apparatus (Nova Ética, Brazil), and water at 37 °C ± 2 °C was used as the immersion fluid. The time at which all the tablets were completely disintegrated was determined (ANVISA, 2024b).

**Weight variation**

Twenty tablets were weighed individually, and the average weight was calculated. The requirements were met if the weights of no more than two tablets differed from the average by more than 5% and no tablet differed in weight by more than double that percentage (ANVISA, 2024b).

**Friability**

Twenty accurately weighed tablets were placed into the friability test apparatus (Sotax, Switzerland) and then rotated 100 times (4 minutes at 25 rpm). Afterwards, the tablets were weighed again. The percentage difference between the initial and final weights represents powder loss and is a measure of tablet friability (ANVISA, 2024b).

**Tablet breaking force**

Tests were carried out on a breaking force tester (Nova Ética, Brazil). The average breaking force of twenty tablets was determined, with the results expressed in Newtons (N) (ANVISA, 2024b).

**Assay**

OLZ content in the tablets was determined using a high-performance liquid chromatography (HPLC) system (Shimadzu, Japan) equipped with a diode array detector at 260 nm (USPNF, 2024). Separation was carried out isocratically on an L7 (150 × 4.6 mm, 5µm) HPLC column. A mixture (1:1) of sodium phosphate solution (pH 2.5) with sodium lauryl sulfate and acetonitrile was used as the mobile phase and delivered at a flow rate of 1.5 mL/minute. The column was maintained at room temperature, and the injection volume was 20 µL. For sample preparation, five tablets were transferred into a 100 mL volumetric flask and diluted with the mobile phase to volume. The flasks were mixed and sonicated for 10 minutes. A portion of the obtained solution was centrifuged, and the clear supernatant was diluted with the mobile phase to a 0.1 mg/mL OLZ solution. The standard solutions were prepared at the same concentration (0.1 mg/mL OLZ).

**Dissolution profile of the OLZ formulations**

The dissolution profiles of the OLZ formulations were obtained using a dissolution testing instrument (Pharma Test, Germany) equipped with a USPNF II apparatus (paddle) (ANUP et al., 2018; DA COSTA et al., 2022). The dissolution medium was 900 mL of 0.1 M HCl, 0.05 M acetate buffer (pH 4.5) or 0.05 M phosphate buffer (pH 6.8), all of which were prepared according to USP specifications, at 37 ± 0.5 °C with a rotation speed of 50 rpm for 30 minutes. Six tablets from each batch were evaluated in each medium. At predetermined time intervals (5, 7, 10, 12, 15 and 30 minutes), 10 mL samples were collected and filtered immediately (0.45 µm syringe filter). The concentration of OLZ in solution was measured using a UV spectrophotometer (Varian Cary 50, USA) at a wavelength of 259 nm. The dissolution data obtained were plotted as cumulative drug release versus time. Calibration curves were constructed by diluting aliquots taken from OLZ working standard solutions (100 µg/mL) with dissolution medium in 100 mL volumetric flasks, resulting in a linear concentration range of 2.5, 5, 8, 10 and 12 µg/mL in each dissolution medium examined. Each concentration was analysed in duplicate, and the average values were used to calculate the regression equation and correlation coefficient ($r2 > 0.999$).

The results obtained are expressed as percentages of dissolution and represent the averages ± standard deviations of 6 repetitions (n =6). Two batches of the reference product (Zyprexa®), named R1 and R2, were also evaluated for comparative reasons.

Different dissolution profiles were compared in terms of the mean dissolution time (MDT) (ZHANG et al., 2010) and dissolution efficiency (DE) (KHAN, 1975) (Equation 4):

$$DE = \frac{\int_{t1}^{t2} y \, . \, dt}{y_{100} \cdot (t_2 - t_1)} \times 100\% \quad (4)$$

DE is the area under the curve between time points t1 and t2 and is expressed as a percentage of the curve at maximum dissolution $y_{100}$ over the same time period. In addition, the dissolution profile similarity assessment

was calculated using the similarity factor (f2) according to Equation 5:

$$f2 = 50 \times \left\{ \log \left[ 1 + \left( \frac{1}{n} \right) \times \sum_{t=1}^{n} . (Rt - Tt)^2 \right]^{-0.5} \times 100 \right\}$$

(5)

where *n* is the number of dissolution time points and **R(t)** and **T(t)** are the reference and test percentages of the dissolved products, respectively, at time (t).

The OLZ release kinetics were evaluated according to the following models: zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas. The model that gave the highest coefficient of determination (R2) was considered the most suitable model for describing the release of OLZ from tablets (ANDERSON et al., 1998; MOURÃO et al., 2010).

All the parameters were calculated using DDSolver Excel add-in software (ZHANG et al., 2010).

## RESULTS AND DISCUSSION

Considering that the original properties of raw materials are not significantly modified during the direct compression process, their intrinsic flow and compressibility can be limiting properties (SOUSA et al., 2023). Therefore, the OLZ API powders were characterized according to their particle size distributions, density and flow properties. Table 1 and Figure 1 show the results of the particle size distributions of the API OLZ from Manufacturers A, B and C.

**Table 1:** Particle size distributions of the olanzapine samples.

| Samples | Particle size (μm) | | | | |
|---|---|---|---|---|---|
| | $d_{10}$ | $d_{50}$ | $d_{90}$ | $d_{mean}$ | Span |
| A | 0.91 ± 0.02 | 11.77 ± 0.46 | 18.89 ± 0.69 | 9.18 ± 0.69 | 2.75 ± 0.11 |
| B | 0.06 ± 0.00 | 1.94 ± 0.07 | 7.08 ± 0.18 | 3.42 ± 0.09 | 3.34 ± 0.03 |
| C | 1.22 ± 0.11 | 10.35 ± 0.97 | 29.23 ± 0.36 | 13.39 ± 1.14 | 2.71 ± 0.24 |

The results are expressed as the averages ± standard deviations (SDs) (n=3).

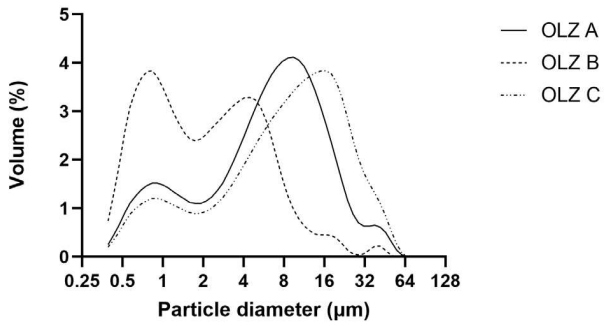


**Figure 1:** Comparative profiles of particle size distribution of olanzapine.

According to the results, OLZ B presents a particle size distribution with smaller particle diameters. The samples from Manufacturers A and C have particle sizes closest to each other, with OLZ C presenting larger ones. The three batches evaluated present high span values, indicating a large variation in the particle size distribution of these samples. Powder flow is related not only to the particle size but also to the particle size distribution: for powders with narrow particle distributions, the flow increases significantly with increasing particle size (GOH et al., 2018; LIU et al., 2008). For powders with the same average size, the more uniform this distribution is, the better the flow properties of these powders are. These data contradict the flow results obtained for the OLZ through the indirect methods (Hausner ratio, Carr's index and angle of repose) presented later. The batch of Manufacturer B, classified as good flow, has the smallest particle size and the highest span index among the three samples evaluated. Thus, as observed in practice (and presented later in this paper), the flow problems encountered for these samples are justified.

Figure 1 shows that the three lots present bimodal distributions (although in different patterns), suggesting the presence of two frequencies of different sizes for each of the evaluated samples. This type of distribution can be attributed to a series of characteristics of the samples under analysis, related to the micronization process and the presence of agglomerates (MARUSHKA et al., 2022), particle shape or even issues related to the analytical technique (CHENDO et al., 2023; SHEKUNOV et al., 2007; TINKE et al., 2008).

The density results obtained for the OLZ samples and the resulting Hausner ratio and compressibility index are shown in Table 2.

**Table 2:** Density, Hausner ratio and Carr´s index of olanzapine samples.

| Sample | Bulk density (mg/ml) | Tapped density (mg/ml) | Hausner ratio | Carr´s index | Flow character |
|---|---|---|---|---|---|
| A | 0.25 ± 0.01 | 0.32 ± 0.01 | 1.30 ± 0.03 | 22.79 ± 1.93 | Passable |
| B | 0.26 ± 0.01 | 0.31 ± 0.01 | 1.17 ± 0.02 | 14.78 ± 1.42 | Good |
| C | 0.33 ± 0.01 | 0.41 ± 0.01 | 1.28 ± 0.07 | 21.42 ± 4.29 | Passable |

Data express as average ± standard deviation (n=3).

OLZ C has bulk and tapped densities higher than those of OLZ A and OLZ B. This fact can be explained as a function of the larger particle size of this sample in relation to the other samples. The bulk density of a powder is related to several factors, such as size, shape and cohesion among particles (ABDULLAH, GELDART, 1999; GOH et al., 2018). As a rule, an increase in particle size reduces the interaction and cohesiveness among them, favouring packaging in a denser form and generating higher density results, which justifies the higher value found for the sample of Manufacturer C.

According to the laser diffraction results, OLZ B has a much smaller particle size than the other two samples evaluated. The density values would also be expected to be lower for this manufacturer. However, sample B presented density results close to those of OLZ A, with even greater bulk density. This fact can be

justified since, during manipulation of the samples, the formation of agglomerates was observed in the raw material from Manufacturer B, which was probably related to the electrostatic charge originating during the micronization process of the batch. Additionally, this batch presented a moisture value close to the maximum limit specified by the USPNF (2024) (results not shown). Water adsorption may enhance the interactions among particles (primarily van der Waals forces), increasing the contact area and facilitating the formation of agglomerates (SHAH et al., 2023). These agglomerates behave as larger particles, making technical execution difficult and causing deviations from the expected results during the determination of powder density.

For the same reasons, the Carr's index and Hausner ratio obtained for the three batches indicated that the sample from Manufacturer B presented good flow compared with OLZ A and OLZ C, which were classified only as passable flow (Table 2).

Direct (flow rate) and indirect (angle of repose) methods were used to characterize the flow of olanzapine powders. The results are presented in Table 3.

**Table 3:** Powder flowability results of olanzapine samples.

| Sample | Flow rate (seconds/100 g) | Angle of repose (°) | Flow character |
|---|---|---|---|
| A | 33.2 (14.9 - 42.8) | 38.1 | Fair |
| B | 20.9 (17.1 - 24.0) | 35.3 | Good |
| C | 23.7 (22.2 - 25.8) | 33.4 | Good |

Unlike indirect methods for flowability assessment, there is no general scale in the literature for classifying powders based on the flow values obtained, as these methods are extremely dependent on the equipment parameters configured for each product (USPNF, 2024). However, the method allows comparison of the relative values obtained for each of the OLZ batches, evaluated according to the same experimental conditions (25 mm nozzle and use of a stirring device at speed 4; other parameters were evaluated, but the best ones are those cited here).

The results revealed increasing flowability in the following order: B> C> A. This trend was relatively similar to that observed with the other method (Table 3). In both cases, sample B presented the best flow characteristics.

According to the behaviour observed during the analysis, powders that do not flow freely may have funnel-like flow, in which the particles of the upper surface of the powder bed are the first to flow, forming the so-called "rat hole" in the centre of the sample. The residual powder, however, remains adhered to the funnel wall due to the cohesive/adhesive properties of the particles. A challenge associated with this type of flow pattern is the potential collapse of the structure, leading to periods of excessive flow alternating with other periods of slow or zero flow, making the flow uneven. This erratic flow profile was observed for the three samples, accounting for the substantial variation among the replicates within each batch (Table 3).

Powder flow is influenced by multiple factors. The samples evaluated here present a series of variable parameters, such as the crystalline phase composition,

particle size and density. In any case, the performance of each sample was quite different, with sample A showing an irregular and nonreproducible flow; sample B had a more accelerated, uniform and reproducible course, with the flow of all material being observed throughout the test; and sample C demonstrated relatively regular and reproducible flow. However, none of them demonstrated a continuous and regular flow throughout the entire test.

Wettability is an important mechanism that contributes to the rate of drug dissolution. This parameter is more critical in the case of poorly soluble drugs. In these cases, the choice of dissolution medium has a direct influence on the results obtained (PURI et al., 2010). Thus, the wettability of the OLZ samples was evaluated in different dissolution media, according to the dissolution studies described later. The wettability results of the OLZ samples in water, 0.1 M HCl, and 0.5% (w/v) sodium acetate buffer with SLS and pH 6.8 sodium phosphate buffer with 0.5% (w/v) SLS are shown in Figure 2.

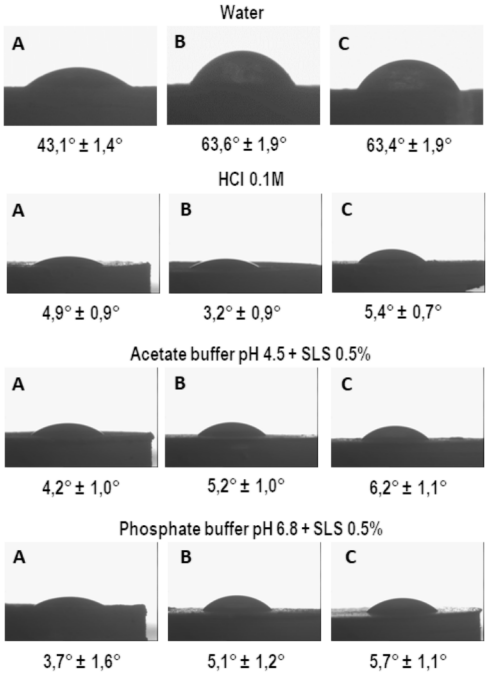


**Figure 2:** Wettability analysis for olanzapine samples in different medium.

OLZ A had a lower contact angle when water was used, indicating increased wettability compared with those of batches B and C, which had contact angle values very similar to each other (Figure 2).

The contact angles in the media tested were much smaller than those obtained in water, indicating greater wettability of the materials in these media. In 0.1 M HCl and buffered media, however, it was not possible to observe differences among the contact angles obtained for the three samples.

The solubility results of the OLZ samples in different media are presented in Table 4. Our results demonstrated that OLZ presents pH-dependent solubility: there is a reduction in the solubilized drug concentrations with increasing pH of the dissolution medium (Table 4), as expected considering the basic nature of the drug (SELMIN et al., 2021). In acidic medium (similar to gastric pH), it was not possible to

observe differences among the solubility data for the three manufacturers. However, in phosphate buffer at pH 6.8 (similar to the intestinal pH), greater solubility was observed for OLZ A than for the OLZ preparations from the other two manufacturers.

**Table 4:** Solubility results (mg/ml) of olanzapine samples in different media after 48 hours.

| Sample | HCl 0.1M | Acetate buffer pH 4.5 | Phosphate buffer pH 6.8 |
|---|---|---|---|
| A | 21.72 (0.5%) | 5.85 (0.6%) | 0.44 (1.4%) |
| B | 21.24 (0.1%) | 4.69 (0.7%) | 0.22 (1.6%) |
| C | 21.49 (0.4%) | 5.10 (0.6%) | 0.20 (1.3%) |

Data expressed as average ± standard deviation (SD) (n=3).

OLZ A and C solutions remained stable throughout the study. OLZ B, however, presented the greatest decrease in content, with reductions of 6% and 5% in the 0.1 M HCl and acetate buffer pH 4.5 media, respectively.

Another important factor to be evaluated during equilibrium solubility is related to the phase transition in the suspension. Thus, it is important to isolate the solid in suspension to ensure that the same form of the compound initially used is present at the end of the study (BRAGA et al., 2022). Figure 3 shows the DSC curves obtained for samples from batches A, B and C collected after 48 hours of solubility study in 0.1 M HCl and phosphate buffer, pH 6.8. Under both conditions, all samples presented an endotherm at temperatures close to 100 °C, which can be related to the formation of hydrates during the solubility test.

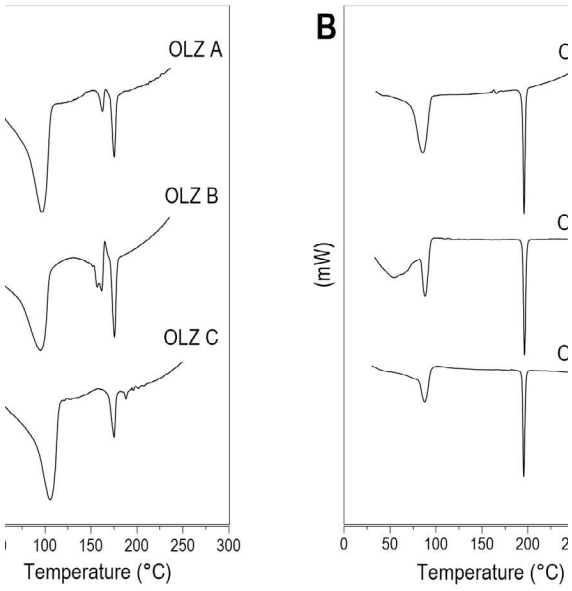


**Figure 3:** DSC curves of olanzapine samples after 48 hours of equilibrium solubility study in HCl 0.1 mol.l$^{-1}$ (A) and in phosphate buffer pH 6.8 (B).

As presented by Testa et al. (2019), the three batches evaluated here were characterized by different techniques, and polymorphs II and III were present in the three batches, whereas polymorph I was detected in samples A and B (TESTA et al., 2019).

Owing to the differences in the composition of the crystalline phases, the samples had dissimilar thermal behaviours. Samples A, B and C presented endothermic peaks close to 190°C. However, sample C presented a second endothermic peak close to 180°C, quickly followed by an exothermic signal (TESTA et al., 2019). After the solubility tests, the thermal behaviours observed in this study were different from those previously reported for all samples, especially in 0.1 M HCl. As such, during the solubility tests, the samples, with different polymorphic compositions, transitioned to hydrated forms, possibly of different types. Paisana et al. (2016) reported the hydrate transformations of anhydrous OLZ polymorphs I and II upon exposure to moisture conditions and direct contact with water, such as in solubility experiments. In aqueous medium, both polymorphs transform into the same two hydrates (higher hydrate and dihydrate B); these transitions occur within minutes to few hours. Therefore, the solubility may not be related to the initial crystal form, and the difference observed for sample A may be due to the composition of the crystal forms in the raw material, which can change the transition rate and consequently the solubility.

Extensive research has been dedicated to understanding the dissolution kinetics of powders (DA COSTA et al., 2013; DE VILLIERS et al., 1996; MARABI et al., 2008; PATEL et al., 2025). Because dissolution is a prerequisite for absorption (ZHANG et al., 2018), any alteration in the former can significantly affect the latter. Therefore, studying the dissolution behaviour of drug substances—particularly those with moderate or poor solubility—is crucial. Additionally, understanding the comparative dissolution rates of various chemical (e.g., salt, ester, prodrug) (FANDIÑO et al., 2021; GONG et al., 2021) and physical (e.g., polymorph, solvate, particle size) (BAHL, BOGNER, 2008; DA COSTA et al., 2022; ELSHAHAT et al., 2024) forms of a drug is essential for selecting the optimal form for further development.

Owing to the high solubility of OLZ in 0.1 M HCl, it was not possible to observe differences in the dissolution profiles obtained for the three samples (Figure 4). The high solubility in acid medium minimizes the impact that differences in particle size distribution, wettability and crystallinity could have on the dissolution of these materials.

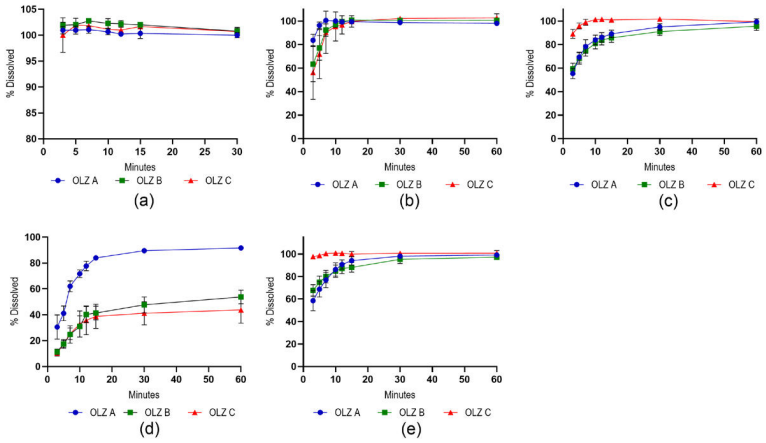


**Figure 4:** Dissolution profiles of olanzapine samples in (a) HCl 0.1 mol.l$^{-1}$ (b) acetate buffer pH 4.5, (c) acetate buffer pH 4.5 with SLS 0.5%, (d) phosphate buffer pH 6.8 (w/v), (e) phosphate buffer pH 6.8 with SLS 0.5% (w/v).

In phosphate buffer at pH 6.8, it was difficult to disperse the samples in the dissolution medium, especially for OLZ B and C. When the samples were transferred to a vessel with heated dissolution medium, particle aggregation (including drug floating and sticking to the vessel and paddle shaft) was visually observed. This behaviour is related to the lower wettability of samples B and C, as reported, and is reflected in the high standard deviation values. Additionally, after 60 minutes of testing, it was possible to achieve only approximately 50% dissolution of samples B and C relative to the initially weighed mass, whereas 90% of sample A dissolved (Figure 4).

The low final dissolution results obtained for samples B and C and the high RSD values indicate that the methodology used was not adequate to comparatively determine the dissolution profiles among the three batches of OLZ. Thus, the impact of the addition of 0.5% (w/v) SLS to the dissolution medium was evaluated. Unlike the dissolution pattern observed among the batches of OLZ before the addition of SLS to the medium, the presence of the surfactant favoured the dispersion of the sample from batch C, which presented a dissolution value close to 100% in the first few minutes of the test. Samples A and B presented dissolution profiles that were very similar to each other but lower than the profile obtained for Manufacturer C (Figure 4). In acetate buffer at pH 4.5, the behaviour of the samples was similar to that observed in buffer at pH 6.8. With the addition of SLS to the medium, sample C presented the highest values of dissolution, whereas samples A and B presented lower dissolution results but with similar profiles (Figure 4). As previously described, sample C was the only one that did not have polymorph I in its composition (TESTA et al., 2019). The SLS used in the dissolution tests contributed to the increasing wettability of sample C and possibly changed the transition rate of the polymorphs to hydrated forms, modifying the order of the samples in relation to the greater dissolution observed.

Based on the physicochemical properties of the OLZ samples, the drug proved to be a candidate with poor flowability, which may affect its manufacturability by direct compression. Therefore, selecting suitable excipients is crucial, as they should exhibit good flowability and a low tendency to segregate (GULSUN et al., 2018). The flow characteristics of the powder mixtures prepared for the direct compression process were evaluated by measuring the bulk and tapped densities, Carr's index, the Hausner ratio and the angle of repose.

The bulk density values obtained for the powder mixtures of batches L1, L2 and L3 produced with samples A, B and C of OLZ, respectively, are shown in Table 5.

**Table 5:** Density, Hausner ratio and Carr´s index of olanzapine mixture batches.

| Sample | Bulk density (mg/ml) | Tapped density (mg/ml) | Hausner ratio | Carr´s index | Flow character |
|---|---|---|---|---|---|
| L1 | 0,57 ± 0.01 | 0.73 ± 0.00 | 1.29 ± 0.02 | 22.62 ± 1.46 | Passable |
| L2 | 0.54 ± 0.02 | 0.70 ± 0.01 | 1.29 ± 0.06 | 22.55 ± 3.49 | Passable |
| L3 | 0.59 ± 0.00 | 0.75 ± 0.00 | 1.28 ± 0.00 | 21.57 ± 0.00 | Passable |

Data expressed as average ± standard deviation (SD) (n=3).

The density results were ranked as L2 <L1 <L3. The three formulations contained the same qualitative and quantitative composition, differing only by the OLZ in each sample. Although OLZ was present at small concentrations in the formulations, it was possible to observe a correlation between the particle size distribution of the API and the final density of the powder mixtures (particle size OLZ B < OLZ A < OLZ C).

Powder mixture L2, produced with OLZ B, presented lower values of bulk and tapped density. As previously reported, agglomerate formation was observed in sample B, making it difficult to perform the tests and interpret the results. However, the mixing of this raw material with the excipients and the sieving of the powders during the manipulation process of the test batch allowed the dispersion of the agglomerates, making L2 more uniform. Consequently, the density results could be correlated with the particle size of the API samples.

Because there is no standardized methodology for evaluating the products, different nozzle sizes and stirring device speeds were tested to establish the best experimental conditions for flowability evaluation. The results were more reproducible when a 6 mm nozzle was used with a stirring device at speed 1.

Sample L3 presented better flowability than the other batches did (Table 6). In accordance with the angle of repose, all batches were classified as fair flow, whereas L2 was classified as passable flow. Upon evaluating the results, it was not possible to verify differences in the flowability of the mixtures containing different batches of OLZ. Importantly, the flow properties of powder mixtures containing low percentages of the API are dictated primarily by the characteristics of the excipients. In the proposed formulation, OLZ represents only 2.5% (w/w), which would justify the similarities found among the evaluated batches.

**Table 6:** Powder flowability results of olanzapine formulations.

| Sample | Flow rate (seconds/100 g) | Angle of repose (°) | Flow character |
|---|---|---|---|
| **L1** | 65.6 (63.0 – 69.5) | 40.7 | Fair |
| **L2** | 67.6 (66.4 – 68.3) | 43.0 | Passable |
| **L3** | 56.3 (55.2 - 55.0) | 38.8 | Fair |

Disintegration time, weight variation, friability and tablet breaking force were measured for quality control of both OLZ tablet cores and coated tablets to evaluate their in vitro performance, and the results are presented in Table 7..

**Table 7:** Quality control parameters of developed olanzapine formulations.

| Sample | L1 | | L2 | | L3 | |
|---|---|---|---|---|---|---|
| | Core | Coated | Core | Coated | Core | Coated |
| Disintegration (minutes) | 2 | 6 | 2 | 6 | 2 | 7 |
| Friability (%) | 0.07 | - | 0.13 | - | 0.08 | - |
| Breaking force (N)* | 114 | - | 107 | - | 116 | - |
| Weight average (mg)* | 404.1 | 420.7 | 397.0 | 416.5 | 405.7 | 414.7 |
| Assay (%) | - | 97.8 | - | 97.3 | - | 96.9 |

* Tablet breaking force and weight variation results expressed as average.

Tablet cores prepared from the three OLZ samples exhibited low weight variation, acceptable breaking force, low friability and fast disintegration time (Table 7). The breaking forces of the tablets remained in the 107–116 N range, and their friability was low (<1%) in all the cases, indicating good tabletability and sufficient mechanical strength to withstand abrasion during the subsequent coating process. All formulations met the 30-minute limit for disintegration time of both uncoated (core) and coated tablets according to the Brazilian pharmacopeia.

The weight differences among all three batches met the pharmacopeial criteria and did not deviate more than 5% from average, indicating that the powder mixtures maintained homogeneity throughout the process (ULUHAN et al., 2023). The drug contents for all olanzapine formulations (L1, L2 and L3) were 96.9–97.8% of the expected values.

Dissolution profiling was conducted on OLZ tablets, and the results were compared with those of the reference medicine Zyprexa®, as illustrated in Figure 5. The similarity between the dissolution profiles of the test and reference products was calculated for exploratory purposes using the similarity factor (f2), as presented in Table 8.

**Table 8:** Similarity factors calculated for olanzapine tablets compared to reference product.

| Medium | R1 x Test | f2 | R2 x Test | f2 |
|---|---|---|---|---|
| HCl 0.1M | R1 x L1 | 79 | R2 x L1 | 74 |
| | R1 x L2 | 65 | R2 x L2 | 59 |
| | R1 x L3 | 67 | R2 x L3 | 60 |
| Acetate buffer pH 4.5 | R1 x L1 | 72 | R2 x L1 | 73 |
| | R1 x L2 | 42 | R2 x L2 | 43 |
| | R1 x L3 | 69 | R2 x L3 | 66 |
| Phosphate buffer pH 6.8 | R1 x L1 | 60 | R2 x L1 | 61 |
| | R1 xL2 | 39 | R2 x L2 | 56 |
| | R1 x L3 | 39 | R2 x L3 | 54 |

In 0.1 M HCl, the obtained values fell within the acceptable range of 50–100 (COSTA, SOUSA LOBO, 2001). Both the reference and test products showed very rapid dissolution, with more than 85% of the drug dissolved in 15 minutes (Figure 5).

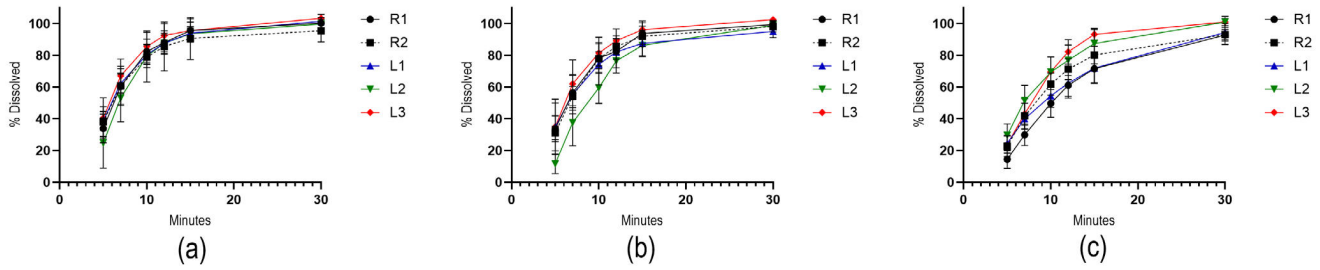


**Figure 5:** Comparative dissolution profiles of olanzapine formulations in (a) HCl 0.1 mol.l$^{-1}$ (b) acetate buffer pH 4.5, (c) phosphate buffer pH 6.8.

In acid medium, the similarity of the dissolution profiles is consistent with the results of the solubility and powder dissolution tests, indicating no significant differences among OLZ A, OLZ B and OLZ C. Class II drugs, which exhibit weak base characteristics, such as OLZ, can dissolve at low pH values. Thus, the fasted stomach is the most favourable environment for the dissolution of these drugs, but in most cases, a small change in gastric pH can significantly alter its solubility, causing great intra- and interindividual variability and erratic drug absorption (DRESSMAN et al., 2007). Few drugs are absorbed in the stomach; generally, the dissolved drug must pass into the small intestine for absorption to occur. However, exposure of the drug to the higher pH values of intestinal fluids may lead to its precipitation before it reaches the site of absorption, compromising its bioavailability (DRESSMAN et al., 2007; KLEIN, 2010). Thus, assessing the dissolution profile of products containing class II drugs in media with different pH ranges can help to understand their in vivo behaviours (DRESSMAN et al., 1998). Therefore, the tests and reference tablets of OLZ were also evaluated for their dissolution profiles in acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) (Figure 5).

In contrast to the behaviour reported in acidic medium, at pH 4.5, L2 presented f2 values less than 50 compared with both reference batches (R1 and R2), indicating potential inequivalence. Additionally, the two batches of the reference drug showed distinct dissolution profiles in phosphate buffer at pH 6.8. Sample R1 showed drug dissolution values approximately 10% lower than those obtained for sample R2 within the first 15 minutes. The dissolution values were similar only at the end of the study (Figure 5). Among the three OLZ batches evaluated, all presented adequate f2 factors compared with R2. However, only sample L1 presented a similarity profile when both reference products were considered (Table 8).

The dissolution profiles of the OLZ tablets were also compared based on dissolution efficiency and mean dissolution time data, the results of which are presented in Table 9.

**Table 9:** Dissolution parameters of olanzapine tablets.

| Batch | DE | MDT | Coefficient of determination ($R^2$) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Zero order | First order | Higuchi | Korsmeyer Peppas | Hixson Crowell |
| **Dissolution media** | | | **HCl 0.1M** | | | | |
| **R1** | 77 | 7 | -0.7043 | 0.8612 | 0.6672 | -1.6626 | 0.9057 |
| **R2** | 74 | 7 | -1.2596 | 0.8903 | 0.6217 | 0.6449 | 0.9373 |
| **L1** | 77 | 7 | -0,9599 | 0.8442 | 0.6985 | -1.2950 | 0.9560 |
| **L2** | 74 | 8 | -0.1386 | 0.5695 | 0.6899 | 0.5011 | 0.8720 |
| **L3** | 80 | 7 | -1.2976 | 0.8661 | 0.6155 | -1.2688 | 0.9343 |
| **Dissolution media** | | | **Acetate buffer pH 4.5** | | | | |
| **R1** | 75 | 7 | -0.5049 | 0.8943 | 0.7345 | 0.6515 | 0.9062 |
| **R2** | 74 | 7 | -0.4054 | 0.8489 | 0.7123 | 0.5911 | 0.8539 |
| **L1** | 72 | 7 | -0.7297 | 0.9177 | 0.7254 | 0.6814 | 0.8842 |
| **L2** | 66 | 10 | 0.5444 | 0.5737 | 0.7386 | 0.2715 | 0.8573 |
| **L3** | 78 | 7 | -0.6871 | 0.8667 | 0.6934 | -1.6075 | 0.9121 |
| **Dissolution media** | | | **Phosphate buffer pH 6.8** | | | | |
| **R1** | 58 | 11 | 0.7353 | 0.8867 | 0.8180 | 0.8192 | 0.9344 |
| **R2** | 65 | 9 | 0.2945 | 0.9136 | 0.8244 | 0.7171 | 0.8985 |
| **L1** | 61 | 11 | 0.5470 | 0.9276 | 0,9135 | 0.8773 | 0.9827 |
| **L2** | 71 | 9 | 0.0452 | 0.8957 | 0.8477 | -1.21106 | 0.9594 |
| **L3** | 72 | 9 | 0.2520 | 0.7211 | 0.7644 | -2.0464 | 0.8608 |

Underlined values indicate the highest $R^2$ values.

Compared with the test and reference batches, the tablets presented a narrow DE range in both the 0.1 M HCl and the pH 4.5 buffer media. The differences within the ±10% limits suggest that the reference and test dissolution profiles are equivalent (ANDERSON et al., 1998). However, in buffer pH 4.5, f2 values equal to 42 and 43 (L2 formulation) corresponded to DE differences of 9 and 8%, respectively. These results are similar to the findings of Anderson et al. (1998), where f2 values ranging from 40–50 were not supported by the DE results. In buffer at pH 6.8, samples L2 and L3 presented greater rates of release than R1 did, with DE results superior to those of the reference product and in agreement with the results obtained with f2 (Table 8). In all the cases in which f2 ≤ 40, the ΔDE value was greater than 10%. The mean dissolution times were similar among all the test and reference formulations.

The dissolution data were analysed to assess the OLZ release kinetics. The coefficients of determination for each model are described in Table 9. The most suitable kinetics model for describing the release of OLZ tablets was the Hixson–Crowell model for all batches, both reference (Zyprexa®) and test formulations, in the dissolution media evaluated (HCl 0.1 M, pH 4.5 and pH 6.8). Exception were observed for formulations L1 and R2, which presented slightly higher R2 values when the first-order model was applied at pH 4.5 and pH 6.8, respectively. The Hixson Crowell model assumes that drug release is limited by the drug particle dissolution rate rather than diffusion (COSTA, SOUSA LOBO, 2001). This model applies to pharmaceutical forms such as eroding tablets (KRUEGER et al., 2023), in which the surface area and diameter of the particles or tablets change over time and gradually decrease while maintaining their geometric shape throughout the dissolution process (GERAILI, MEQUANINT, 2020). As the dosage form surface area decreases, the release rate progressively diminishes, a phenomenon especially significant for tablets containing poorly water-soluble drugs, such as OLZ (TAVESKA et al., 2025). Figure 6 shows the predicted Hixson–Crowell model compared with the observed values of the OLZ dissolution profile in 0.1 M HCl.

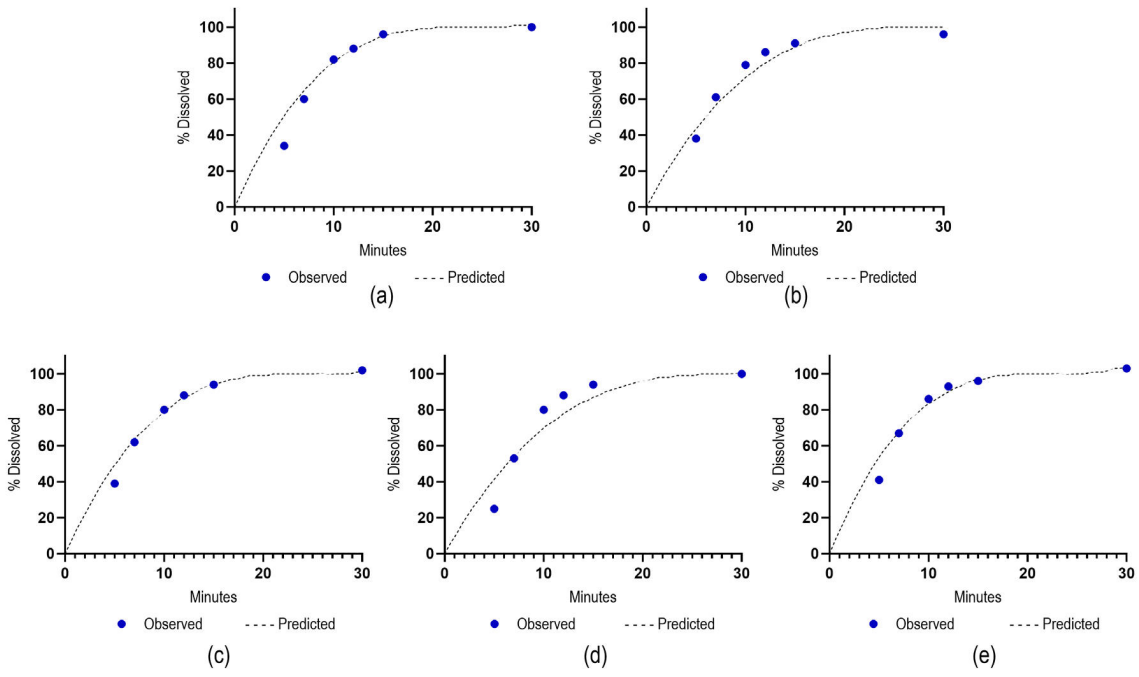


**Figure 6:** Predicted and observed dissolution kinetics of reference (a) R1 and (b) R2 and test olanzapine formulations (c) L1, (d) L2 and (e) L3 in HCl 0.1M according to Hixson-Crowell model.

The comparative dissolution profile results demonstrate that formulations L1, L2 and L3 are similar to batches of the reference product in dissolution profiles conducted in media with pH values within the physiological range. Therefore, the proposed formulations can be considered equivalent to the reference product. Thus, they can be considered prototypes for further scale-up and the future fabrication of a pilot batch to complement regulatory and industrial process development.

## CONCLUSION

In this study, an immediate-release tablet composed of olanzapine fabricated by direct compression was proposed. Three batches from distinct API manufacturers were evaluated to assess critical quality attributes. The combination of various physicochemical techniques permitted the differentiation of samples based on properties such as particle size distribution, density and solubility. Despite the observed differences in density and flowability, they did not significantly affect tablet quality, probably due to the low API percentage in the tablet composition. All three formulations showed good mechanical strength and met the pharmacopeial standards for quality control.

When assessing the solubility and dissolution profiles, OLZ A, which has a moderate particle size and high wettability, exhibited superior solubility and dissolution, mainly in phosphate buffer at pH 6.8, which was the medium with the lowest drug solubility. In contrast, OLZ B, despite having the smallest particle size, demonstrated lower wettability, leading to poor dispersion, particle aggregation, and significantly lower dissolution results. These findings suggest that wettability plays a more crucial role in OLZ dissolution than does particle size alone. The impact of these raw material properties extends to tablet performance, as formulations produced with OLZ A (L1) presented the highest similarity to the reference drug Zyprexa across all pH conditions, reflecting its superior wettability and solubility. Conversely, tablets formulated with OLZ B (L2) demonstrated lower similarity factors and reduced dissolution efficiency, particularly at pH 4.5, mirroring the poor dissolution characteristics of its raw material. Hence, for olanzapine, the physicochemical properties of the drug associated with the selected formulation and manufacturing process significantly influence product performance and quality.

The proposed approach, centered on direct compression and strategic raw material selection, offers several key advantages: reduced manufacturing complexity, cost-effectiveness, and consistent product quality despite raw material variability. The systematic characterization approach demonstrated in this work establishes a robust framework for raw material qualification that pharmaceutical manufacturers can implement to ensure consistent product quality despite supplier variability. This approach is particularly valuable in markets like Brazil where multiple API sources are common. By identifying wettability as a critical quality attribute for olanzapine raw material, manufacturers can develop targeted specifications and implement appropriate control strategies to mitigate variability risks. Additionally, implementing real-time analytical tools and advanced characterization methods would refine control strategies, supporting robust scale-up and regulatory alignment.

## ACKNOWLEDGMENT

The authors acknowledge the support from CNPq (420221/2023-9) and FAPERJ (Rio Network for Innovation in Nanosystems for Health – NanoSAÚDE - E-26/010.000983/2019).

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

## REFERENCES

ABDULLAH, E.C.; GELDART, D. The use of bulk measurements as flowability indicators. **Powder Technology**, v. 102, n. 2, p. 151-165, 1999. DOI: https://doi.org/10.1016/S0032-5910(98)00208-3.

ANDERSON, N.H. et al. An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles. **Journal of Pharmaceutical and Biomedical Analysis**, v. 17, n. 4-5, p. 811-822, 1998. DOI: https://doi.org/10.1016.S0731-7085(98)00011-9.

ANUP, N.; THAKKAR, S.; MISRA, M. Formulation of olanzapine nanosuspension based orally disintegrating tablets (ODT); comparative evaluation of lyophilization and electrospraying process as solidification techniques. **Advanced Powder Technology**, v. 29, p. 1913-1924, 2018. DOI: https://doi.org/10.1016/j.apt.2018.05.003.

ANVISA. AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA. Relatório de Inspeção internacional de fabricantes de insumos farmacêuticos ativos (RIIFA_2023). Brasília: Anvisa, 2024a. 25 p. Available in: https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/certificacao-e-fiscalizacao/manuais-e-orientacoes/relatorio-de-revisao-farmoquimicas-internacionais-2023. Accessed on march 09, 2025.

ANVISA. AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA. Farmacopeia Brasileira. 7 ed. Brasília: Anvisa, 2024b. Volume I.

ASKIN, S. et al. Olanzapine form IV: discovery of a new polymorphic form enabled by computed crystal energy landscapes. **Crystal Growth & Design**, v. 19, n. 5, p. 2751-2757, 2019. DOI: https://doi.org/10.1021/acs.cgd.8b01881.

BAHL, D.; BOGNER, R.H. Amorphization Alone Does Not Account for the Enhancement of Solubility of Drug Co-ground with Silicate: The Case of Indomethacin. **AAPS PharmSciTech**, v. 9, n. 1, p. 146-152, 2008. DOI: https://doi.org/10.1208/s12249-007-9013-9.

BECKMAN COULTER INC. User´s manual: LS 13320 Laser diffraction particle size analyzer. Issue AD. 2019. 266 p.

BHANA, N. et al. Olanzapine: an updated review of its use in the management of schizophrenia. **Drugs**, v. 61, n. 1, p. 111-61, 2001. DOI: https://doi.org/10.2165/00003495-200161010-00011.

BRAGA, D.; CASALI, L.; GREPIONI, F. The relevance of crystal forms in the pharmaceutical field: Sword of Damocles or innovation tools? **International Journal of Molecular Sciences**, v. 23, n. 16, p. 9013, 2022. DOI: https://doi.org/10.3390/ijms23169013.

CHENDO, C.; PINTO, J.F.; PAISANA, M.C. Comprehensive powder flow characterization with reduced testing. **International Journal of Pharmaceutics**, v. 642, p. 123107, 2023. DOI: https://doi.org/10.1016/j.ijpharm.2023.123107.

CITROME, L. et al. A commentary on the efficacy of olanzapine for the treatment of schizophrenia: the past, present, and future. **Neuropsychiatric Disease and Treatment**, v. 15, p. 2559-2569, 2019. DOI: https://doi.org/10.2147/NDT.S209284.

COSTA, P.; LOBO, J.M.S. Modeling and comparison of dissolution profiles. **European Journal of Pharmaceutical Sciences**, v. 13, n. 2, p. 123-133, 2001. DOI: https://doi.org/10.1016/S0928-0987(01)00095-1.

DA COSTA, M.A. et al. Efavirenz Dissolution Enhancement I: Co-Micronization. **Pharmaceutics**, v. 5, p. 1-22, 2013. DOI: https://doi.org/10.3390/pharmaceutics5010001.

DA COSTA, N.F. et al. Downstream Processing of Amorphous and Co-Amorphous Olanzapine Powder Blends. **Pharmaceutics**, v. 14, p. 1535, 2022. DOI: https://doi.org/10.3390/pharmaceutics14081535.

DAI, S. et al. A compression behavior classification system of pharmaceutical powders for accelerating direct compression tablet formulation design. **International Journal of Pharmaceutics**, v.

572, 118742, 2019. DOI: https://doi.org/10.1016/j.ijpharm.2019.118742.

DE VILLIERS, M.M. Influence of agglomeration of cohesive particles on the dissolution behaviour of furosemide powder. **International Journal of Pharmaceutics**, v. 136, n. 1-2, p. 175-179, 1996. DOI: https://doi.org/10.1016/0378-5173(95)04380-2.

DHONDT, J. et al. A multivariate formulation and process development platform for direct compression. **International Journal of Pharmaceutics**, v. 623, 121962, 2022. DOI: https://doi.org/10.1016/i.ijpharm.2022.121962.

DIXIT, M.; KINI, A.G.; KULKARNI, P.K. Enhancing the aqueous solubility and dissolution of olanzapine using freeze-drying. **Brazilian Journal of Pharmaceutical Sciences**, v. 47, n. 4, p. 743-749, 2011. DOI: https://doi.org/10.1590/S1984-82502011000400011.

DRESSMAN, J.B. et al. Estimating drug solubility in the gastrointestinal tract. A**dvanced Drug Delivery Reviews**, v. 59, n. 7, p. 591-602, 2007. DOI: https://doi.org/10.1016/j.addr.2007.05.009.

DRESSMAN, J.B. et al. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. **Pharmaceutical Research**, v. 15, n. 1, p. 11-22, 1998. DOI: https://doi.org/10.1023/A:1011984216775.

ELI LILLY DO BRASIL LTDA. Zyprexa®: olanzapina. Responsável técnico: Felipe B.Z. da Silva. Porto Rico: Lilly del Caribe Inc., 2022. Bula de medicamento.

ELSHAHAT, A. et al. Formulation and optimization of olanzapine-carboxylic acid cocrystals orodispersible tablets: In-vitro/In-vivo study. **Journal of Drug Delivery Science and Technology**, v. 100, 106093, 2024. DOI: https://doi.org/10.1016/j.jddst.2024.106093.

FANDIÑO, O.E. et al. Mechanochemical synthesis of a novel eutectic of the antimicrobial nitazoxanide with improved dissolution performance. **Pharmaceutical Sciences**, v. 27, n. 4, p. 585-592, 2021. DOI: https://doi.org/10.34172/PS.2021.10.

FAYED, M.H. et al. Design-of-experiment approach to quantify the effect of nano-sized silica on tableting properties of microcrystalline cellulose to facilitate direct compression tableting of binary blend containing a low-dose drug. **Journal of Drug Delivery Science and Technology**, v. 68, 103127, 2022. DOI: https://doi.org/10.1016/j.jddst.2022.103127.

GALARNEAU, D. A Case of Teeth Discoloration Upon Transition from Zyprexa to Generic Olanzapine. **The Ochsner Journal**, v. 13, n. 4, p. 550-552, 2013.

GBD. GLOBAL BURDEN OF DISEASES, INJURIES AND RISK FACTOR STUDY. Global Health Metrics: Schizophrenia – Level 3 cause. GBD, 2024. Available in: https://www.healthdata.org/research-analysis/disease-injuries-risk/factsheets/2021-schizophrenia-level-3-disease. Accessed on february 09, 2025.

GERAILI, A.; MEQUANINT, K. Systematic studies erosion of photocrosslinked polyanhydride tablets and data correlation with release kinetics models. **Polymers**, v. 12, n. 5, 2020. DOI: https://doi.org/10.3390/polym12051105.

GOH, H.P.; HENG, P.W.S.; LIEW, C.V. Comparative evaluation of powder flow parameters with reference to particle size and shape. **International Journal of Pharmaceutics**, v. 547, n. 1-2, p. 133-141, 2018. DOI: https://doi.org/10.1016/j.ijpharm.2018.05.059.

GONG, W. et al. Cocrystals Salts and Salt-solvates of olanzapine: selection of coformers and improved solubility. **International Journal of Pharmaceutics**, v. 608, 121063, 2021. DOI: https://doi.org/10.1016/j.ijpharm.2021.121063.

GULSUN, T. et al. Development and evaluation of terbutaline sulfate orally disintegration tablets by direct compression and freeze drying methods. **Journal of Drug Delivery Science and Technology**,

v. 46, p. 251-258, 2018. DOI: https://doi.org/10.1016/j.jddst.2018.05.014.

HADJOUDJ, J. et al. Association between olanzapine plasma concentrations and treatment response: A systematic review, meta-analysis and individual participant data meta-analysis. **Biomedicine & Pharmacotherapy**, v. 172, 116236, 2024. DOI: https://doi.org/10.1016/j.biopha.2024.116236.

ICH. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Pharmaceutical Development Q8(R2), Step 4, Aug. 2009. Available in: https://www.ich.org/page/quality-guidelines. Accessed on december, 16, 2023.

JAWAHAR, N. et al. Enhanced oral bioavailability of an antipsycotic drug through nanostructured lipid carriers. **International Journal of Biological Macromolecules**, v. 110, p. 269-275, 2018. DOI: https://doi.org/10.1016/j.ijmac.2018.01.121.

KAMIYA, Y. et al. Prediction of permeability across cell monolayers for 219 disparate chemicals using in vitro experimental coefficients in a pH gradient system and in silico analyses by trivariate linear regressions and machine learning. **Biochemical Pharmacology**, v. 192, 114749, 2021. DOI: https://doi.org/10.1016/j.bcp.2021.114749.

KHAN, K.A. The concept of dissolution efficiency. Pharmaceutical Acta Helvetica, v. 41, p. 594-607, 1972. **Journal of Pharmacy and Pharmacology**, v. 27, n. 1, p. 48-49, 1975. DOI: https://doi.org/10.111/j.2042-7158.1975.tb09378.x.

KLEIN, S. The Use of Biorelevant Dissolution Media to Forecast In Vivo Performance of a Drug. **The AAPS Journal**, v. 12, n. 3, p. 397-406, 2010. DOI: hhttps://doi.org.10.1208/s12248-010-9203-3.

KOLLI, P. et al. Olanzapine Pharmacokinetics: A clinical review of current insights and remaining questions. **Pharmacogenomics and Personalized Medicine**, v. 16, p. 1097-1108, 2023. DOI: https://doi.org/10.2147/PGPM.S391401.

KOLODZIEJSKI, W. et al. Kinetics of $^{1}H \rightarrow {}^{13}C$ NMR cross-polarization in polymorphs and solvates of the antipsychotic drug olanzapine. **Solid State Nuclear Magnetic Resonance**, v. 39, n. 3-4, p. 41-6, 2011. DOI: https://doi.org/10.1016/j.ssnmr.2010.12.003.

KRUEGER, L. et al. 3D printing tablets for high-precision dose titration of caffeine. **International Journal of Pharmaceutics**, v. 642, 123132, 2023. DOI: https://doi.org/10.1016/j.ijpharm.2023.123132.

LABOISSIÈRE, P. Brasil estima déficit de R$ 20 bi com insumos farmacêuticos importados. Agência Brasil, Brasília, 01 de agosto de 2024. Economia. Available in: https://agenciabrasil.ebc.com.br/economia/noticia/2024-08/brasil-estima-deficit-de-r-20-bi-com-insumos-farmaceuticos-importados. Accessed on march 09, 2025.

LA ZARA et al. Drug powders with tunable wettability by atomic and molecular layer deposition: From highly hydrophilic to superhydrophobic. **Applied Materials Today**, v. 22, 2021. DOI: https://doi.org/10.1016/j.apmt.2021.100945.

LIU, L. et al. Effect of particle properties on the flowability of ibuprofen powders. **International Journal of Pharmaceutics**, v. 362, n. 4, p. 109-117, 2008. DOI: https://doi.org/10.1016/j.jpba.2010.10.013.

MARABI, A. et al. Assessing dissolution kinetics of powders by a single particle approach. **Chemical Engineering Journal**, v. 139, n. 1, p. 118-127, 2008. DOI: https://doi.org/10.1016/j.cej.2007.07.081.

MARUSHKA, J. et al. Milling of pharmaceutical powder carrier excipients: Application of central composite design. **Advanced Powder Technology**, v. 33, p. 103881, 2022. DOI: https://doi.org/10.1016/j.

apt.2022.103881.

MOURÃO, S.C. et al. Dissolution parameters for diclofenac-containing hypromellose matrix tablet. **International Journal of Pharmaceutics**, v. 386, n. 1-2, p. 201-207, 2010. DOI: https://doi.org/10/1016/j.ijpharm.2009.11.022.

PAISANA, M.C.; WAHL, M.A.; PINTO, J.F. Role of moisture on physical stability of polimorphic olanzapine. **International Journal of Pharmaceutics**, v. 509, p. 135–148, 2016. DOI: http://dx.doi.org/10.1016/j.ijpharm.2016.05.038.

PATEL, R.P.; NORDQUIST, E.B.; POLLI, J.E. Prediction of surfactant-mediated dissolution of poorly soluble drugs from drug powder. **European Journal of Pharmaceutical Science**, v. 208, 107052, 2025. DOI: https://doi.org/10.1016/j.ejps.2025.107052.

POLLA, G.I. et al. Thermal behaviour and stability in Olanzapine. **International Journal of Pharmaceutics**, v. 301, n. 1-2, p. 33-40, 2005. DOI: https://doi.org/10.1016/j.ijpharm.2005.05.035.

PURI, V. et al. Wettability and surface chemistry of crystalline and amorphous forms of a poorly water soluble drug. **International Journal of Pharmaceutics**, v. 40, n. 2, p. 84-93, 2010. DOI: https://doi.org/10.1016/j.ejps.2010.03.003.

REUTZEL-EDENS, S.M. et al. Anhydrates and Hydrates of Olanzapine: Crystallization, Solid-State Characterization and Structural Relantionships. **Crystal Growth & Design**, v. 3, n. 6, p. 897-907, 2003. DOI: https://doi.org/10.1590/S0100-40422010000200041.

REUTZEL-EDENS, S.M.; BHARDWAJ, R.M. Crystal forms in pharmaceutical applications: olanzapine, a gift to crystal chemistry that keeps on giving. **IUCrJ**, v. 7, p. 955-964, 2020. DOI: https://doi.org/10.1107/S2052252520012683.

RUDRANGI, S.R.S. et al. Preparation of olanzapine methyl-β-cyclodextrin complexes using a single-step, organic solvent-free supercritical fluid process: An approach to enhance the solubility and dissolution properties. **International Journal of Pharmaceutics**, v. 494, p. 408-416, 2015. DOI: https://dx.doi.org/10.1016/j.ijpharm.2015.08.062.

SELMIN, F. et al. Relevance of production method on the physical stability and in vitro biopharmaceutical performances of olanzapine orodispersible film. **International Journal of Pharmaceutics**, v. 603, 120697, 2021. DOI: https://doi.org/10.1016/j.ijpharm.2021.120697.

SHAH, D.S. et al. A concise summary of powder processing methodologies for flow enhancement. **Heliyon**, v. 9, e16498, 2023. DOI: https://doi.org/10.1016/j.heliyon.2023.e16498.

SHEKUNOV, B.Y. et al. Particle size analysis in pharmaceutics: principles, methods and applications. **Pharmaceutical Research**, v. 24, n. 2, p. 203-27, 2007. DOI: https://doi.org/10.1007/s11095-006-9146-7.

SOUSA, A.S. et al. Leveraging a multivariate approach towards enhanced development of direct compression extended release tablets. **International Journal of Pharmaceutics**, v. 646, 123432, 2023. DOI: https://doi.org/10.1016/j.ijphar.2023.123432.

TANG, J. et al. Stability and phase transition investigation of olanzapine polymorphs. **Chemical Physics Letters**, v. 767, 138384, 2021. DOI: https://doi.org/10.1016/j.cplett.2021.138384.

TASEVSKA, T. et al. 3D printed extended-release hydrochlorothiazide tablets. **European Journal of Pharmaceutical Sciences**, v. 206, 106998, 2025. DOI: https://doi.org/10.1016/j.ejps.2024.106998.

TESTA, C.G. et al. Challenging identification of polymorphic mixture: polymorphs I, II and III in olanzapine raw materials. International Journal of Pharmaceutics, v. 556, p. 125-135, 2019. DOI: https://doi.org/10.1016/j.ijpharm.2018.12.008.

TINKE, A.P. et al. Particle shape and orientation in diffraction and static image analysis size distribution analysis of micrometer sized rectangular particles. **Powder Technology**, v. 186, n. 11, p. 154-167, 2008. DOI: https://doi.org/10.1016/j.powtec.2007.11.017.

TOUKABRI, I. et al. Impact of crystal polymorphism of rifaximin on dissolution behavior. **Heliyon**, v. 10, e27131, 2024. DOI: https://doi.org/10/1016/j.heliyon.2024.e27131.

ULUHAN. O.D.; GULSUN, T.; SAHIN, S. Development and characterization of trimethobenzamide hydrochloride containing orally disintegrating tablets. **International of Drug delivery Science and Technology**, v. 88, 104980, 2023. DOI: https://doi.org/10.1016/j.jddst.2023.104980.

USPNF. UNITED STATES PHARMACOPEIA. Rockville: United States Pharmacopeial Convention: 2024.

WANG, J.; SHAO, Y.; ZHU, J. Influence of the 'Left Span" on flow and fluidization characteristics of cohesive powders. **Powder Technology**, v. 439, 119706, 2024. DOI: https://doi.org/10.1016/j.powtec.2024.119706.

YU, Y. et al. Research on the powder classification and the key parameter affecting tablet qualities for direct compaction based on powder functional properties. **Advanced Powder Technology**, v. 32, n. 2, p. 565-581, 2021. DOI: https://doi.org/10.1016/j.apt.2021.01.002.

ZHANG, Y. et al. DDSolver: An Add-In Program for Modeling and Comparison of Drug Dissolution Profiles. **The AAPS Journal**, v. 12, n. 3, p. 263-271, 2010. DOI: https://doi.org/10.1208/s12248-010-9185-1.

ZHANG, X. et al. Pharmaceutical Dispersion Techniques for Dissolution and Bioavailability Enhancement of Poorly Water-Soluble Drugs. **Pharmaceutics**, v. 10, n. 3, p.1-33, 2018. DOI: https://doi.org/10.3390/pharmaceutics10030074.