



## Inclusion complex of methyl- $\beta$ -cyclodextrin and olanzapine as potential drug delivery system for schizophrenia

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### ABSTRACT

Olanzapine (OLP), the most important atypical antipsychotic drug of the new generation, a high cost drug, has low aqueous solubility, affecting its dissolution and absorption. Its complexation with modified cyclodextrins (CDs) is designed to achieve novel vectorization systems with higher solubility, consequently higher bioavailability. From the CD selection, among  $\beta$ -CD, methyl- $\beta$ -CD (M $\beta$ CD) and hydroxypropyl- $\beta$ -CD, it was obtained a phase solubility diagram suggesting a 1:1 (mol:mol) OLP-CD stoichiometry and complexation constants of 966.9, 149.4 and 91.1 L/mol, respectively. The M $\beta$ CD was selected for the inclusion complexes (IC) attainment, a physical mixture (PM) and a rotatory evaporator product (ROE). The analysis showed differences in the structure, morphology and performance of OLP, M $\beta$ CD, PM and ROE, revealing the occurrence of interactions between drug and CD. The ROE presented the higher dissolution efficiency and stability. The results suggest that the IC was formation, being a technological resource efficient and profitable for drug delivery.

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### 1. Introduction

Olanzapine (OLP) drug, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno(2,3 b)(1,5) benzodiazepine, is a psychotropic agent belonging to the thienobenzodiazepines class, obtained from the modification of clozapine chemical structure. The OLP is the most important atypical antipsychotic drug of the new generation. It has the reduction of extrapyramidal side effects as advantage over the previous therapy, besides being an alternative to treat patients with refractory to other medications (Rajendraprasad & Basavaiah, 2009).

The OLP drug has high costs and low water solubility, being the hydrophobic parameter an obstacle to the schizophrenia treatment. Thus, it is necessary to develop a pharmaceutical formulation which allows better dissolution and absorption and, consequently, more uniform drug bioavailability (Wawrzycka-Gorczyca, Borowski, Osypiuk-Tomasik, Mazur, & Koziol, 2007).

The drug improved solubility may lead to the development of pharmaceuticals formulations with lower doses, because the higher dissolution efficiency leads to a higher percentage of absorbed drug. With this, they would obtain formulations with reduced

costs, allowing greater access to medication, lower investments in additional medication to treat side effects, better adherence to treatment because the side effects would be reduced, and greater investments in improving mental health care services (Soares-Sobrinho, Soares, Rolim-Neto, & Labandeira, 2011).

A plausible alternative to increase drug solubility is its complexation with cyclodextrins (CDs), molecules capable of changing the drug physicochemical properties, thus favoring its dissolution and bioavailability (Serafini et al., 2012). These compounds have hydrophilic exterior, responsible for interaction with water molecules and hydrophobic internal cavity which is responsible for compatible drugs complexation (Lyra et al., 2012). This molecular aspect has allowed the use of CDs in different areas of science and technology, being the pharmaceutical industry one of the main application areas, because of the possibility of obtaining new drugs with physical and chemical properties different from the isolated active ingredient, such as increased solubility (Soares-Sobrinho, Soares, Labandeira, Alves, & Rolim-Neto, 2011).

Changes in the drug physicochemical properties after its complexation serve as parameter for the test to confirm the inclusion complexes (IC) formation, since the products obtained by mixing the drug and cyclodextrin are not necessarily leads to the formation of a IC with increased solubility. Resorted to, therefore, the techniques of differential scanning calorimeter (DSC), thermogravimetry (TG), X-ray diffraction (XRD), infrared spectroscopy (IR),

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scanning electron microscopy (SEM) (Lyra et al., 2012; Serafini et al., 2012; Soares-Sobrinho, Soares, Labandeira, et al., 2011; Soares-Sobrinho, Soares, Rolim-Neto, et al., 2011).

The present work aimed the development and characterization of a more stable and effective drug delivery system by obtaining a inclusion complex of drug-CD.

## 2. Materials and methods

### 2.1. Materials

OLP was purchased from Gamma Trade, Import & Export LTD (internal batch No. 750) originated from India (batch 90L003). The cyclodextrins tested,  $\beta$ -cyclodextrin ( $\beta$ -CD) (MW 1135 g/mol), methyl- $\beta$ -cyclodextrin (M $\beta$ CD) (MW 1191 g/mol) and hydroxypropyl- $\beta$ -cyclodextrin (HP $\beta$ CD) (MW 1390 g/mol) were supplied by Roquette® (Barcelona, Spain). The solutions were prepared using ultrapure water (MILLI Q) and filtered through a 0.22  $\mu$ m Millipore® (Millipore Corp, Billerica, MA). Other reagents and chemicals were of analytical reagent grade.

### 2.2. Experimental

#### 2.2.1. Phase solubility diagram

Phase solubility studies were performed according to the method reported by Higuchi and Connors (1965). Excess quantities of OLP (~30 mg) were added to aqueous solutions containing increasing concentrations of CDs, being 0, 1, 2, 2.5, 3, 4 and 5 mmol/L for  $\beta$ CD and 0, 5, 10, 15, 20, 25 and 50 mmol/L for M $\beta$ CD and HP $\beta$ CD (Lima, Soares-Sobrinho, Correa, & Rolim-Neto, 2008). Suspensions were placed in an ultrasound bath for 15 min and shaken in an oscillating water bath thermostatically controlled at 25 °C for 7 days, which previous studies have shown to be sufficient time to ensure equilibrium. Samples were filtered and appropriately diluted. The OLP concentration was determined using a spectrophotometer in 228 nm (Rêgo, Moura, & Moita, 2010). Experiments were performed in triplicate. The drug-CD association constants (K1:1) were calculated using the linear portion of the phase solubility diagrams, assuming 1:1 stoichiometry, according to Eq. (1), where  $S_0$  is OLP water solubility in the absence of CD.

$$K = \frac{\text{slope}}{S_0 \cdot (1 - \text{slope})} \quad (1)$$

#### 2.2.2. Preparation of solid-state complexes

**2.2.2.1. Preparation of physical mixture.** The physical mixtures (PMs) of the OLP and M $\beta$ CD, molar ratio 1:1 (OLP-CD) using a OLP concentration of 5 mmol/L, were prepared to perform the comparative study between them and the rotatory evaporator product (ROE). The geometric dilution method was used to ensure the homogeneity of the product handled in porcelain mortar with the aid of a pistil, packaged in vials protected from light (Kim et al., 2006).

**2.2.2.2. Rotatory evaporator product.** For ROE preparation, amounts of OLP and M $\beta$ CD were dissolved in equimolar concentrations in methanol. The obtained solution was subjected to sonication in ultrasonic bath for 15 min. After an equilibration period of 72 h at room temperature, the solution was evaporated under vacuum at 50 °C in a rotary evaporator (Büchi Rotavapor R-200). The obtained product was placed in vials protected from light.

#### 2.2.3. Characterization of the solid-state complexes

The real obtaining of IC can only be confirmed by accurate characterization of them through various techniques of physical-chemical analysis. This assessment is very important

since it is designed to evaluate the complexation efficiency of the different preparation methods used and different types of CD employees (Zeng, Ren, Zhou, Yu, & Chen, 2011). In this study the binary systems were evaluated by several methods of characterization, including IR, DSC, TG, SEM and dissolution tests.

**2.2.3.1. Infrared spectroscopy.** The spectra acquisition was performed directly on solid samples of OLP, M $\beta$ CD, PM and ROE. It was carried out an average of 10 sweeps in the range 650–4000  $\text{cm}^{-1}$  with resolution of 4  $\text{cm}^{-1}$  in Shimadzu® Spectrophotometer Model UV/VIS-1603.

**2.2.3.2. Differential scanning calorimetry.** Samples of OLP, M $\beta$ CD, PM and ROE; with approximately 3 mg of weight were placed in aluminum pans and heated from 30 to 250 °C at a rate of 10 °C  $\text{min}^{-1}$  under a nitrogen flow of 50  $\text{mL min}^{-1}$  in a Shimadzu® Scanning Calorimeter DSC-60H.

**2.2.3.3. Scanning electron microscopy.** Surface morphologies of samples were examined using a Jeol® JSM-5900. Particles were fixed on a brass stub using double-sided tape and vacuum-coated gold.

**2.2.3.4. Thermogravimetry.** Samples of OLP, M $\beta$ CD, PM and ROE; weighting about 8 mg were placed in alumina pan and heated from 30 to 600 °C at a rate of 10 °C  $\text{min}^{-1}$  under a nitrogen flow of 50  $\text{mL min}^{-1}$  in a Shimadzu® Thermogravimetry DTG-60H. The thermoanalytical data were analyzed using software-TA 60WS® (Therma Analysis) version 2.20 from Shimadzu®.

**2.2.3.5. X-ray diffraction.** The X-ray powder diffraction patterns were collected using copper radiation (40 kV, 20 mA), on a Ultima diffractometer (Rigaku®) with Bragg-Brentano geometry, in the  $2 < 2\theta < 60$  range with a step size of 0.02° and counting time of 2 s per step.

**2.2.3.6. Dissolution test.** The samples to be analyzed (OLP, PM and ROE) were placed in capsules with a weight equivalent to 10 mg of OLP each. The dissolution tests were carried out at a temperature of 37 °C ( $\pm 0.5$  °C), 900 mL of water as dissolution medium and an agitation speed of 75 rpm on a Varian® 7010 VK dissolutor (Soares-Sobrinho et al., in press). The drug assay was conducted by UV/VIS Spectrophotometry at 228 nm at intervals of 15, 25, 30 and 60 min. The drug concentration was determined against the initial calibration curve and the dissolution profiles were evaluated using dissolution efficiency in time of 30 min ( $\text{ED}_{30}$ ).

## 3. Results and discussion

### 3.1. Phase solubility diagrams

According to the phase solubility diagram results it was observed that the type of CD used influences greatly the OLP solubility (Chadha, Arora, Gupta, & Jain, 2011). In all cases, the solubility of OLP increased linearly as a function of CD concentration over the concentration range under study, therefore, exhibit solubility diagram phase type A<sub>L</sub> (Higuchi & Connors, 1965) to the binary systems complexing OLP- $\beta$ CD, OLP-M $\beta$ CD (Fig. 1A).

The slope value of each diagrams presented below unity, indicating complexation of first order and suggesting a 1:1 mol:mol OLP-CD stoichiometry, allowing the determination of the stability constants respective values, as evidenced in Fig. 1 (Zeng et al., 2011).

Given the CD used for the binary complexes formation, the complexation constant increased in the following order:

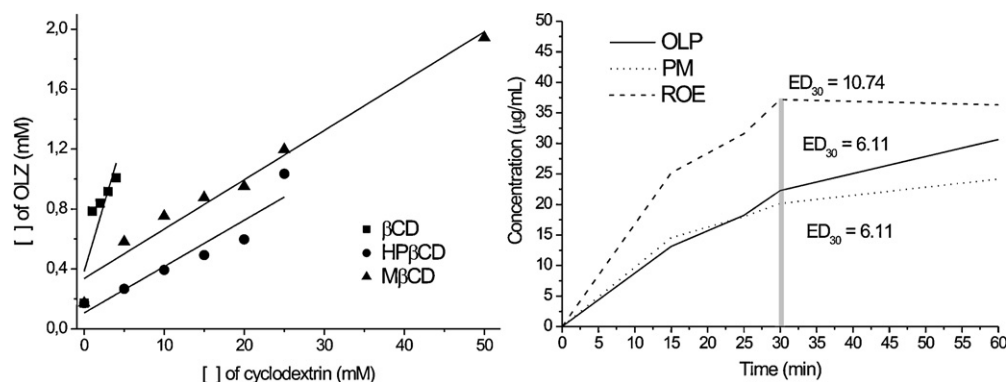


Fig. 1. (A) Phase solubility diagram of OLP in water depending on the CD concentration ( $\beta$ CD, M $\beta$ CD and HP $\beta$ CD). (B) Dissolution profiles of OLP, PM and ROE.

HP $\beta$ CD < M $\beta$ CD <  $\beta$ CD. The increased stability of the OLP– $\beta$ CD complex in comparison with OLP–M $\beta$ CD and OLP–HP $\beta$ CD may be due to obstruction established by methyl and propyl substituents, respectively, near the cavity of the cyclodextrin which prevent, in stoichiometric ratios, the OLP inclusion (Zeng et al., 2011).

Considering the results, the M $\beta$ CD has selected for the IC attainment because of its good solubilize capacity. The  $\beta$ CD was not chosen, despite its higher complexation constant value, because its limited solubility in water would hamper their use in pharmaceutical formulations. Therefore, it is inferred that the M $\beta$ CD, has a higher propensity to be used in solid dosage forms for oral use, as it has greater water solubility, lower toxicity compared to  $\beta$ CD and high efficiency of complexation (Yang et al., 2011).

### 3.2. Characterization of solid state complexes

#### 3.2.1. Differential scanning calorimetry

The OLP thermal behavior observed by DSC is characteristic of an anhydrous and crystalline compound, being visible an intense and well defined endothermic peak 197.92 °C, corresponding to the drug melting temperature. The M $\beta$ CD DSC curve presents an wider endothermic effect around 293 °C, which is due to the CD crystallization water loss (Fig. 2A) (Marreto et al., 2008).

The thermal analysis of the PM noticed displacement at lower temperatures and endothermic peak enlargement corresponding to the fusion of the drug. It is observed that the OLP fusion peak is at 197.92 °C, while the PM peak is seen at 193.68 °C. This displacement to lower temperature may be explained by the chemical interaction between CD and OLP during the heating process inherent of DSC test. Since the PM melting peak size reduction can be justified by the lower energy requirement for the occurrence of this physical phenomenon, since the OLP amount is lower (Serafini et al., 2012). The ROE DSC curve indicates a complete disappearance of the endothermic peak corresponding to the drug solid–liquid transition. As evidenced by Chadha et al. (2011), the disappearance of the drug melting endothermic peak may be attributed to the inclusion in the CD cavity, suggesting the formation of IC.

#### 3.2.2. Thermogravimetry

The data obtained in the thermogravimetric analysis reaffirm the data obtained from DSC analysis. Analyzing the OLP TG curve can be observed that on the temperature corresponding to the drug melting, 197.92 °C, no sample weight variation was observed, confirming that this peak refers to a physical process.

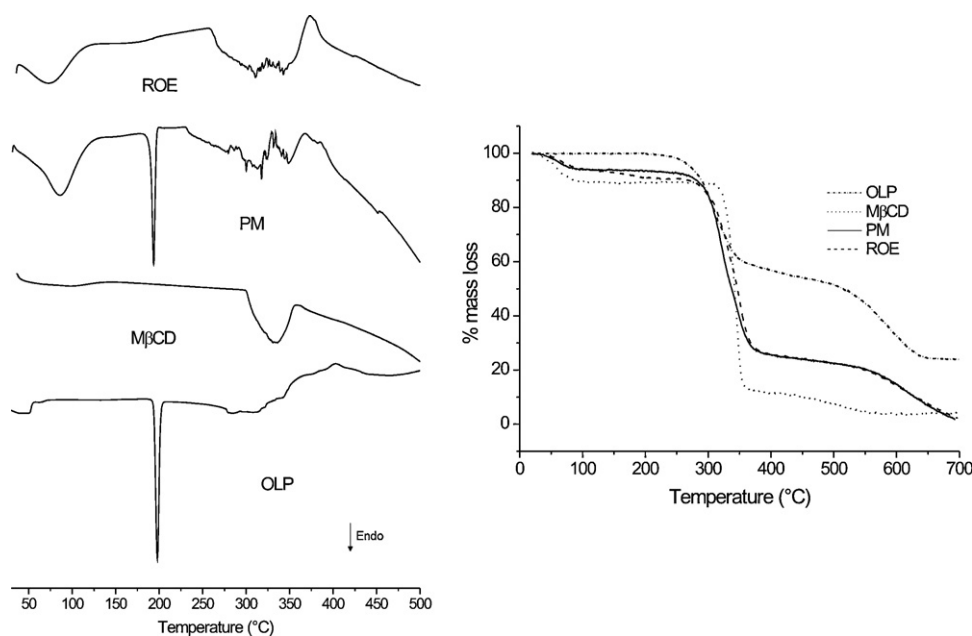


Fig. 2. (A) DSC curves of OLP, M $\beta$ CD, PM and ROE. (B) TG curves of OLP, M $\beta$ CD, PM and ROE.



**Table 1**Data from the main thermal decomposition stage of OLP, M $\beta$ CD, PM and ROE.

Sample	Degradation initial temperature (°C)	Degradation final temperature (°C)	Mass loss (%)
OLP	263	353	39.54
M $\beta$ CD	308	355	75.88
PM	284	388	66.68
ROE	306	388	63.79

Two weight loss steps were observed in OLP TG curves, corresponding to degradation processes (Fig. 2B). In the ROE TG curve analysis only one peak of OLP chemical degradation was observed, indicating that the interaction between OLP–CD protected the antipsychotic drug of degradations, characterizing the IC formation (Marreto et al., 2008). Can be noted that in the PM TG curve was also verified the occurrence of one OLP degradation peak, however, this degradation is more pronounced, showing a mass loss of 66.68%, compared to the ROE mass loss of 63.79% (Table 1), indicating that the complexation is more efficiently in ROE. The protection of the OLP degradation presented by the PM may be associated with interaction induced by the sample heating during TG analysis.

Analyzing the initial and final degradation temperatures of the ROE, presented in Table 1, it is noted that the complexation confers stability to OLP, since with the complex formation the initial degradation temperature was displaced from 263 to 306 °C. This is a further evidence of complexing, as well as the IC also gives higher solubility give better stability to the molecule in the new drug delivery systems. In the physical mixture is also shown a physical delay of the initial degradation temperature, however, less effective as compared to ROE. This change can be associated with a slight interaction occurrence between drug and cyclodextrin provided by the heating process, inherent to decomposition test.

Another complexation evidence suggested by TG curve, presented in Table 1, is the percentage of mass loss evidenced in the binary systems. The PM showed a higher mass loss (66.68%) in

comparison to ROE (63.79%). A higher weight loss indicates less stability (Soares et al., 2011).

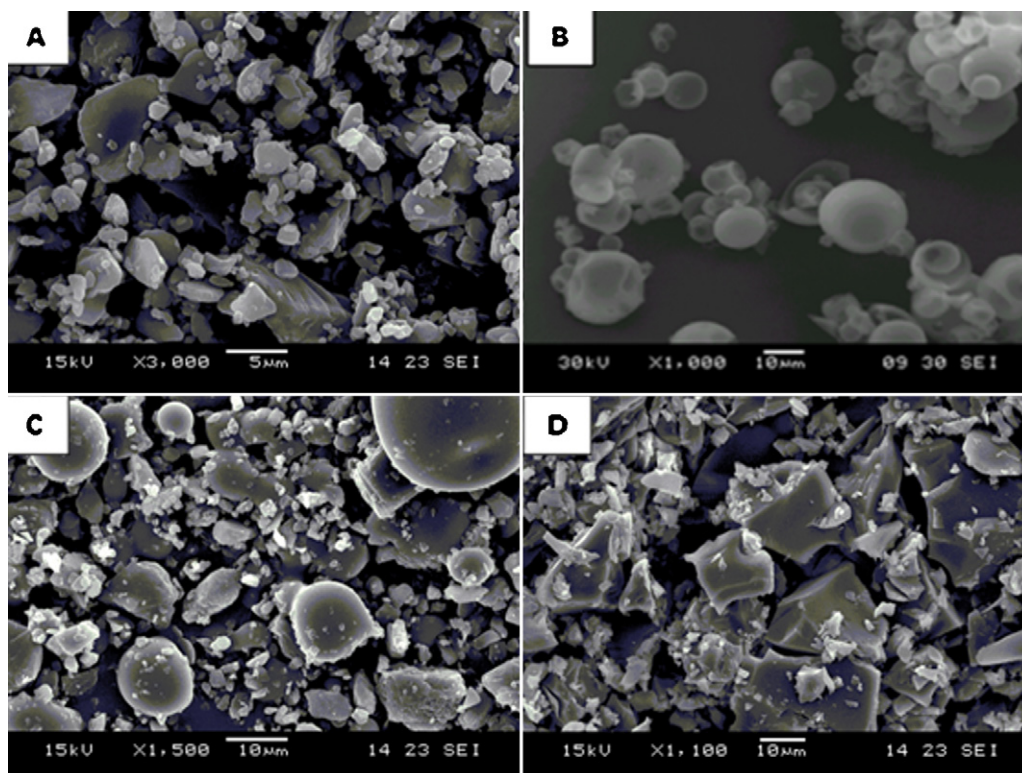
### 3.2.3. Scanning electron microscopy

The photomicrographs observation, presented in Fig. 3, revealed the presence of irregular shape crystals of OLP (Fig. 3A) and spherical forms characteristics of M $\beta$ CD (Fig. 3B). In turn, the PM microscopic observation revealed the presence of each constituents, maintaining their original morphology, with the OLP crystals adhered to the M $\beta$ CD surface (Fig. 3C), not revealing, apparently, interactions between drug and CD. However, the ROE photomicrograph (Fig. 3D) shows a change in particles morphological appearance, with loss of the M $\beta$ CD spherical shape and loss of the OLP typical shown (Fig. 3A and B). Morphological changes can be used as evidence to verify interactions between molecules (Ding, He, Huang, & Lu, 2010). Although SEM studies are inadequate to confirm the IC formation, the particle form changes in appearance and size, is a strong indication for the IC formation (Fernandes, Viera, & Veiga, 2002).

Thus, the data obtained from SEM are added to previous results, suggesting the inclusion complex formation from the processing of the OLP and CD by rotary evaporation.

### 3.2.4. Infrared spectroscopy

Analyzing Fig. 4, shows that the OLP spectrum presents a band corresponding to the amino group of the ring containing two nitrogen atoms ( $3100\text{--}3400\text{ cm}^{-1}$ ). The M $\beta$ CD spectrum presents a band characteristic of the free OH ( $3450\text{--}3700\text{ cm}^{-1}$ ). The infrared spectroscopy results reveal changes in the region between  $3000$  and  $3700\text{ cm}^{-1}$  in the PM and ROE spectra. Analyzing the PM spectrum is observed that there is a partial overlap of the two peaks mentioned previously, thus suggesting that there was no chemical interaction between these groups. In the ROE spectrum there is a displacement of this band that can be associated with a OH band covering the NH or vice versa. As the band appeared shifted



**Fig. 3.** Photographs of scanning electron microscopy of (A) OLP, (B) M $\beta$ CD, (C) PM and (D) ROE.

to the right side, when compared to the band found in the OLP spectrum, it is evident that the band overlap is the OH occurring on NH, since the values are more characteristic of OH. This suggests the CD input on the molecule on the aromatic ring side, being verified the occurrence of interactions type hydrogen bonding between the free hydroxyls of the CD ring and amino group containing two nitrogen atoms.

The reduction and extension of the C=C characteristic bands of ( $1450\text{--}1600\text{ cm}^{-1}$ ) confirm the hypothesis of the complexation occurs between the aromatic ring within the hydrophobic cavity. Another factor that enhances this hypothesis is the possibility of a hydrogen bond formation between N–H of ring containing two nitrogen atoms and the CD hydroxyl, fact supported by the reduction of N=C bands ( $570\text{--}705\text{ cm}^{-1}$ ) of the ring containing two nitrogen atoms in the ROE infrared (Fig. 4).

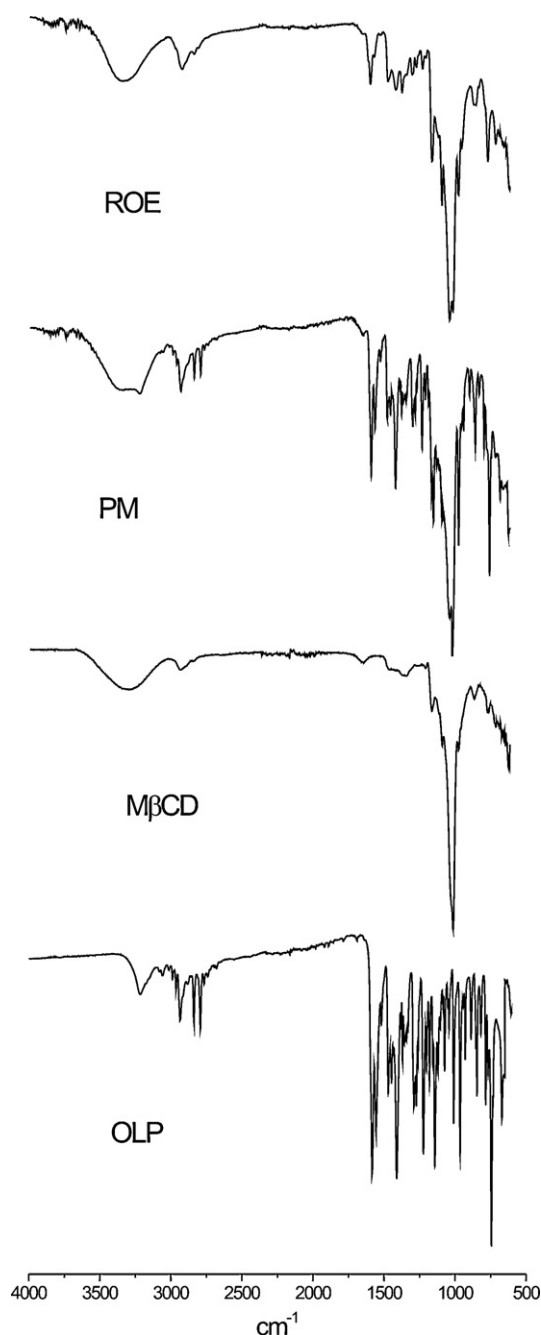


Fig. 4. Infrared spectrum of OLP, MβCD, PM and ROE.

In the OLP spectrum, around  $750\text{ cm}^{-1}$ , can be observe a characteristic C–H band of benzene compounds 1,2 substituted ( $735\text{--}770\text{ cm}^{-1}$ ). This band is reduced on the IR spectrum of ROE, indicating possible complexation of the aromatic ring within the CD. Changes of the N cyclic bands connected to  $\text{CH}_3$  ( $2760\text{--}2820\text{ cm}^{-1}$ ) are found in the ROE spectrum. Thus the N– $\text{CH}_3$  of the piperazine ring may be involved in hydrophobic interactions in the cyclodextrin cavity, assuming the complexation by the input of CD in the piperazine ring.

### 3.2.5. X-ray diffraction

The OLP diffractometric profile reveals the presence of two peaks of higher intensity between  $2\theta = 7.5\text{--}10^\circ$  and  $17.5\text{--}20^\circ$  (Fig. 5), beyond several secondary peaks, indicating the OLP crystalline behavior. The MβCD does not present the peaks characteristic to crystalline compounds, and therefore, the PM diffractometric profile is the result of the OLP and MβCD individual diffraction pattern overlapping, indicating that the drug maintained their initial crystallinity. However, in the ROE diffraction pattern is no longer possible to distinguish the OLP characteristic peaks, thus suggesting the formation of amorphous inclusion complex (Chadha et al., 2011).

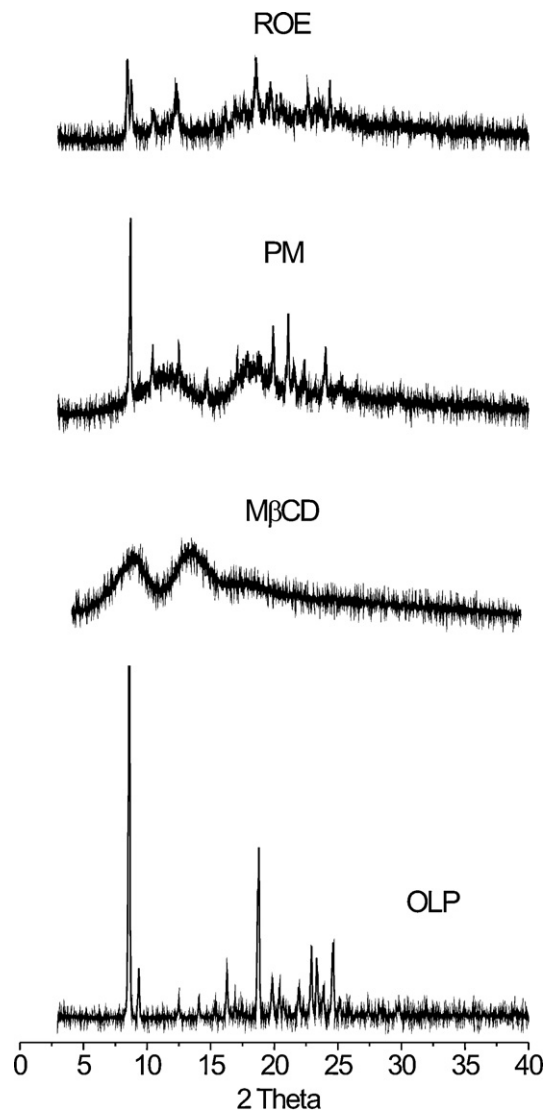


Fig. 5. X-ray diffraction pattern of OLP, MβCD, PM and ROE.

### 3.2.6. Dissolution test

Although the phase solubility studies are of great importance from the theory point of view, in practice the most informative solubility method is the dissolution test. As shown in Fig. 1B, the OLP dissolution is favored in ROE compared to the OLP isolated and PM. This result, favorable to ROE, is associated with the decreased crystallinity and increased wettability induced by the drug complexation (Bootsma et al., 1989).

The highest ROE ED<sub>30</sub> value observed, compared to OLP and PM, reflects the products crystallinity differences as observed on the SEM studies (Zeng et al., 2011). This increase can be attributed to the following reasons: properties surfactants of CD, which reduce the interfacial tension between the drug and the dissolution medium, causing an increase in the drug dissolution rate; increased solubility conferred by the complexation process, demonstrated experimentally by determining the drug solubility in the complex; formation of amorphous or low crystallinity compounds, as previously shown by SEM studies, whose solubility is favored (Mura, Faucci, & Bettinetti, 2001).

Being this drug being a weak base ( $pK_a = 7.5 \pm 0.5$ ), its dissolution is favored under acidic conditions. As the dissolution medium used was water (pH=7), it is observed that the dissolution has been hampered, thus contributing to the low ED<sub>30</sub> values found, independent of the analyte (OLP, PM and ROE). The ROE assay shows a OLP content of 94%. This reduction may be associated with drug loss or drug degradation generated by the binary system preparation procedure or by the drug photo-sensitivity. Thus, it is observed that the ED<sub>30</sub> value is presented underestimated, since 94% of OLP is generated dissolution efficiency of 10.74, then 100% of OLP would generate a higher efficiency, showing therefore more marked increase in dissolution promoted by the formation of IC.

## 4. Conclusion

A factor of great importance for obtaining IC with dissolution characteristics favorable of a good bioavailability is the nature of the CD used. Thus, the possibility of the formation of IC between the OLP,  $\beta$ CD, M $\beta$ CD and HP $\beta$ CD, was confirmed by the phase solubility test showed a linear profile with satisfactory equilibrium constants for the three CDs evaluated. The application of different analytical methods allowed the physicochemical characterization of the binary systems, PM and ROE, obtained in the solid state. The ROE obtained showed differences in morphology, thermal, structural and spectroscopic profiles when compared to the OLP and CDs free molecules, and the PM product showed a simple combination of these substances. Thus, based on the physico-chemical characterization undertaken, it was confirmed the IC formation between OLP and M $\beta$ CD. The complexing data can be used for comparison the OLP drug free and OLP complexed, aiming the attainment of formulations viable, safe, effective and more soluble and stable, this characteristic is essential for a good bioavailability of the drug, thus constitutes a new system for drug delivery to treat schizophrenia.

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