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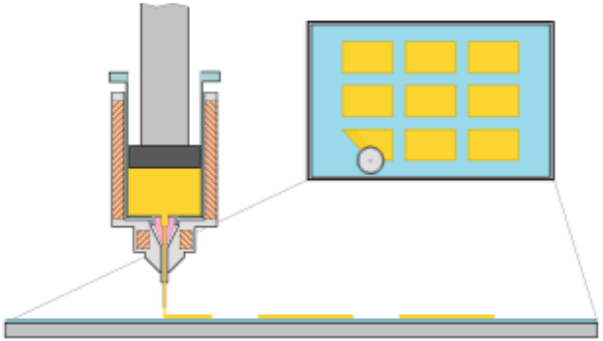
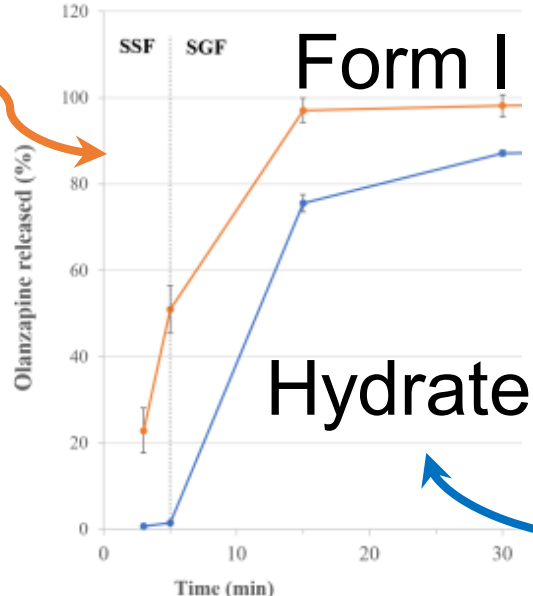
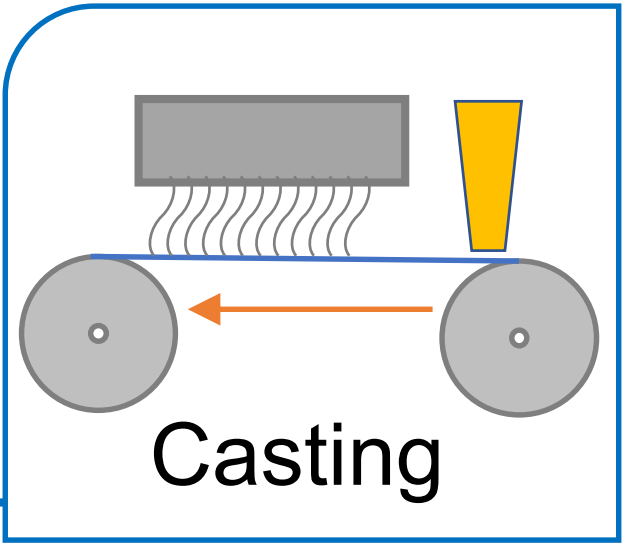
Hot-melt ram extrusion printing



Olanzapine dissolution





Relevance of production method on the physical stability and in vitro biopharmaceutical performances of olanzapine orodispersible film

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Abstract

This study assessed the relevance of the preparation process, namely solvent casting and hot-melt ram printing, on the biopharmaceutical performances of olanzapine orodispersible films (ODF) made of maltodextrin. Beside the clinical rationale, olanzapine was selected since it is subjected to polymorphism which impacts on its bioavailability. All ODF disintegrated in less than 3 min and showed content uniformity within the acceptable values. Dissolution testing in 3 mL of artificial saliva at pH=6.8 evidenced that cast and printed ODF released after 5 min about 2% and 100%, respectively; at higher volume, a yellow precipitate was formed after disintegration of the cast ODF. At pH=1.2, the $t_{85\%}$ for cast ODF was reached after about 20 min and only the 90% olanzapine was dissolved increasing the pH to 6.8. These differences were explained by DSC, TGA and X-ray diffraction data which demonstrated that the casting method, which included the preparation of an aqueous slurry, favours the conversion from Form I to a hydrated one. Since extruded ODF resulted physically stable after 30 months, this suggests the potentiality of this technique to load in ODF drugs undergoing solid-state modification after exposure to aqueous media.

Keywords

Hot-melt ram-extrusion; maltodextrins; personalize therapy; polymorphism; printing; dissolution.

1. Introduction

In recent years, new drug delivery platforms have been proposed to meet the increasing demand for dosage forms to address the specific needs of patient populations. For instance, the design of drug products to be administered to geriatric and paediatric patients should consider the presentation of the treatment to the end-user (i.e. patient, caregiver, healthcare provider) which includes the dosage form, formulation, dose, dosing frequency and packaging (Menditto et al., 2020). Patient-centric drug products would also avoid the practice of manipulating tablets or capsules which may compromise the dose accuracy, patient safety and treatment efficacy. In this context, orodispersible films (ODF) have been reported to improve ease of administration, compliance and medication adherence in patients having difficulties with swallowing (Cilurzo et al., 2018; Slavkova and Breitkreutz, 2015).

Generally speaking, the main ODF production processes can be referred to solvent-based or heating-based technologies (Musazzi et al., 2020). The first entails that the drug substance can either be suspended or dissolved in an aqueous polymeric dispersion comprising all the other excipients. Then, the slurry is subsequently cast, or jetted, onto a release liner, or edible substrate, and dried. Alternatively, in the attempt to produce small batches or to compound personalized therapies, printing technologies have been proposed. Some of them avoid the use of solvents, mainly water in the case of ODF, and can limit the risk of unintended drug phase transformations (Khalid et al., 2021), which could directly affect the dissolution rate of the loaded drug and limit its bioavailability.

Olanzapine (OLZ), an anti-psychotic drug available on the market as orodispersible tablets to improve the patient's adherence in the treatment of schizophrenia, could represent one of these cases. OLZ is a dibasic drug (pK_{a1} = 5.0 and pK_{a2} = 7.4) practically insoluble in water (~

43 µg/mL) (Thakuria and Nangia, 2011) which presents an intricate polymorphism since it can crystallize in several forms, including various four different anhydrates, and more than 60 solvates and hydrates (Paisana et al., 2017; Reutzel-Edens et al., 2003). The conversion towards the hydrate forms is mainly triggered by humidity and it should be avoided since it has caused problems in bioavailability due to the variation in its solubility (Galarneau, 2013; Samuel et al., 2013). Solvents and temperature process can also favour OLZ amorphization, or crystallization, or a mixture thereof (Askin et al., 2020). As an example, after spray-drying a poly(lactide)/drug solution in dichloromethane, OLZ underwent several molecular rearrangements driven by temperature (Askin et al., 2020). And again, the OLZ structure in extruded systems was attributed to the drug loading and the processing temperature (Pina et al., 2014), even if, no clear relationship between dissolution and drug crystallinity or indeed with processing temperature was found (Pina et al., 2014). Paisana et al. provided some criteria to choose excipients helping on avoiding the formation of metastable phases (Paisana et al., 2017). Among them, thanks to the ability to form specific interactions with drugs, poly(vinyl pyrrolidone) (PVP) was able to protect OLZ from undergoing hydrate transformation both in the environment at different levels of residual humidity and in solution (Paisana et al., 2017). At the same time, a low-molecular-weight grade of PVP was exploited to isolate and solve the structure of a new polymorph, namely form IV, from an amorphous dispersion obtained by spray-drying (Askin et al., 2020). Further, a PVP derivative (i.e. PVP VA64) in association with PEO, P188 and P407 was proposed as a matrix-forming material to load an amorphous dispersion of OLZ by hot-melt pneumatic extrusion at 160 °C (Cho et al., 2020).

In this context, the in vitro biopharmaceutical performances of OLZ loaded ODF prepared by two different methods, namely solvent casting and hot-melt ram printing, were compared.

2. Materials and methods

2.1. Materials

Maltodextrin, with a dextrose equivalent equal to 6 (MDX, Glucidex® IT6), was obtained from Roquette (France). Olanzapine (OLZ) was a courtesy gift from Deafarma (Azelis, Italy). Glycerol was purchased from VWR International, (Italy), Span® 80 (Croda, Spain). All solvents were of analytical grade unless otherwise specified.

2.2. ODF preparation

ODF were prepared by hot-melt ram printing and solvent casting according to the composition reported in **Table 1**. Regarding the printing, a paste made of all components was transferred into the extruding chamber heated at 95±1 °C for 10 min. The melt was extruded to print the ODF of the desired dimensions (2×3 cm) on a 20×20 cm aluminium primary packaging foil kindly provided by IBSA Spa (Italy). The printed ODF were sealed with another packaging aluminium foil without further manipulations. The ram speed (12 mm/min) and the chamber temperature were controlled by Repetier-Host 2.0.1 software (Hotword, Germany); the film dimension and number per print were designed by 3D Builder® (Microsoft, USA) and converted in G-code.
For ODF prepared by solvent casting, the aqueous dispersion was prepared by dissolving MDX, glycerol and Span® 80 to avoid shrinkage (**Table 1**) in distilled water maintained at 80 °C and stirred with a magnetic stirrer. The obtained dispersion was cooled down to 40 °C and stirred overnight and cooled down to room temperature. OLZ was added to the slurry and stirred for 90 min after a rest period to remove the air bubbles. The aqueous dispersion was cast onto a polyester release liner with a thickness selected to obtain films with a thickness of about 120 μm. The coating rate was fixed at 1 m/min, and the cast dispersion was dried in the oven at 60 °C for

15 min with horizontal air circulation of 1200 rpm using a laboratory-coating unit Mathis LTE-S(M) (Switzerland). Then, films were cut into desired shape and size and packaged individually in an airtight seal and stored at 25 ± 1 °C until use.

2.3. Film thickness

The ODF thickness was measured by using a micrometer MI 1000 μm (ChemInstruments, USA). The accuracy of the instrument was 2.5 μm ± 0.5%.

2.4. ODF water content

Loss on drying (LOD): the LOD was assayed gravimetrically using a thermobalance (Gibertini, Italy). Film samples were kept at 100 ± 2 °C until constant weight, and the percentage of moisture loss was calculated.

Water content: An ODF exactly weighted was transferred into an empty glass vial of a Karl-Fisher apparatus (Mettler Toledo, Switzerland). After adding 1.5 mL anhydrous methanol, the sample was sonicated for 30 min and a portion of 0.5 mL was injected into the titration chamber. The water content was calculated according to Equation (1):

$$\text{water content (\%)} = \frac{Ms - Mm}{Mo} \times 100 \quad (1)$$

where:

M_s is the mass of water in the sample introduced into the titration chamber;

M_m is the mass of water in the anhydrous methanol;

M_0 is the initial mass of the ODF.

Furthermore, the water activity of the formulation was also assessed by a dew point water activity meter (WaterLab, Steroglass SrL, Italy).

2.5. Drug content

ODF specimen of 2×3 cm was dissolved in the mobile phase containing a mixture of phosphate buffer at pH=6.7 and acetonitrile (60/40 %v/v). The drug concentrations were quantified by HPLC analysis (Agilent HP 1100, Chemstation, Hewlett Packard, USA). The following chromatographic isocratic conditions were used: column: InterClone™ (5 µm ODS, 100 Å, 150×4.6 mm, Phenomenex®, USA); flow rate: 1.5 mL/min; wavelength: 258 nm; temperature: 40 ºC; injection volume: 20 µm. The drug concentrations were determined from a known standard curve in the 6–600 µg/mL range (R^2 = 0.999).

2.6. Thermal analysis

Differential scanning calorimetry (DSC): DSC analysis was performed using a DSC 1 Star^e system (Mettler Toledo, Switzerland) operating with a Star^e software using (4–6 mg) samples in 40 µL aluminium pans with pierced lids at a heating rate of 10 °C min^{-1} and nitrogen purge at 80 mL min^{-1}. The system was calibrated using an indium standard.

Thermogravimetric analysis (TGA). The mass loss of the sample as a function of temperature was determined using a Mettler Toledo 851e TGA/SDTA (Mettler Toledo, Switzerland). Samples were placed in open alumina crucibles and heated at a rate of 10 °C min^{-1} under a nitrogen purge (80 mL min^{-1}).

2.7. X-ray powder diffraction (XRPD)

X-ray powder diffraction data were collected using a Bruker D8 diffractometer (Italy) with graphite monochromatized CuKα radiation source (λ = 1.541874 Å), operating at 40 kV and 40 mA up to 2θ = 60° for OLZ Form I raw material and 2θ = 50° for OLZ loaded ODF made by casting and 3D printing, respectively because no significant reflections are detectable above these limits (**Figure 1**).

2.8. Disintegration test

The disintegration test was carried out in deionized water according to the Ph. Eur. monograph on the "Disintegration of tablets and capsules" (04/2011:20901). The result was considered satisfactory if the disintegration time was lower than 3 min according to Ph. Eur. requirement for orodispersible tablets.

2.9. In vitro dissolution test

To mimic the exposure of the drug liberated from an orodispersible dosage form to biological fluids, the buffers mimicking pH values of different GI districts listed in **Table 2** were used. All media were selected without enzymes since needed enzymes should be evaluated on a case-by-case basis with adequate justification (U.S. Food and Drug Administration, 1997). Moreover, the use of surfactants (e.g. sodium taurocholate) was avoided to better understand the possible impact of the preparation method on the biopharmaceutical performances. ODF, cast or extruded, equivalent to 10 mg of OLZ (based on the drug loading of each formulation) were used. Considering that the OLZ solubility in 0.1 N HCl and pH 6.8 phosphate buffer was 90.3±2.3 mg/mL and 173±1.7 μg/mL, respectively (Suresh Kumar et al., 2013), sink conditions were maintained in all experiments. The OLZ dissolution pattern was determined in three different experimental set-ups:

Condition 1. First, the dissolution test was run in 3 mL of artificial saliva at pH=6.8 horizontally shaken at 50 rpm in a thermostated incubator (Sartorius Certomat® IS, Sartorius, USA). After 3 and 5 min, 0.1 mL was withdrawn and diluted 1:50 before HPLC analysis. The interval of 5 min was considered a suitable time to simulate the residence time of a drug in the pregastric tract after administration of an orodispersible dosage form (Seager, 1998). Immediately after removing the 5 min samples, the remaining volume was transferred to the dissolution vessel of a

Ph. Eur. dissolution apparatus (SR8 PLUS dissolution test station (Hanson Research, USA) and pre-warmed buffer at pH=1.2 simulating the gastric fluid was added to reach the total volume of 200 mL (Vertzoni et al., 2005). The dissolution medium was maintained at 37±1 °C and stirred by a paddle at 25±1 rpm. Aliquots of 1 mL were withdrawn after 15, 30, 60 e 120 min and directly assayed by HPLC to determine the OLZ content. Finally, pre-heated simulated intestinal fluid (SIF) was added to achieve the final volume of 300 mL (Marques et al., 2011) and the composition reported in **Table 2**. Samples at 180, 240 and 300 min were withdrawn and directly assayed to determine the OLZ content.

Furthermore, other two experiments were repeated only by using the compendial dissolution apparatus using 900 mL of dissolution medium thermostated at 37.0±0.5 °C and stirred at 25±1 rpm. In this case, the use of the basket apparatus was preferred to make the dissolution condition reproducible since ODF can easily float, stick on the paddle or vessel (Preis et al., 2013).

Condition 2. Preliminarily, the dissolution test was carried out in artificial saliva for 6 min; afterwards, 1N hydrochloric acid was added to decrease the pH value to 1.2.

Condition 3. The dissolution behaviour was also tested in both artificial saliva and pH=1.2 buffer for 30 min. Aliquots of 3 mL of solution were withdrawn at predetermined intervals (1, 2, 3, 6, 9, 12, 18, 24 and 30 min), immediately replaced with fresh buffers and OLZ was analysed spectrophotometrically at 257 nm (UV-Vis spectrometer, Lambda 25, Perkin Elmer, Italy). The calibration curves were in the range of 0.4–45 μg/mL (R^2 = 0.999).

Dissolution testing was carried out also after 30 months of storage at 25±1 °C (Memmert Climate Chamber ICH110, Germany).

3. Results

The operative conditions adopted for the placebo formulations permitted to obtain OLZ loaded ODF without visual defects and with sufficient quality to allow handling, independently of the adopted preparation methods, suggesting that OLZ did not significantly alter the mechanical properties of MDX films. As expected from our previous experiences, the cast films were thinner than the printed ones, even if the drug content in the superficial area of 6 cm^2 was similar (**Table 1**). The LOD was acceptable for this type of dosage form. The water activity, which is related to the unbound water and thus available to microorganisms to use for growth was about 0.3 independently of the preparation method. As microorganisms and molds show a tendency to proliferate at water activity value up to 0.60 and 0.70, respectively, this result was acceptable to assure the ODF microbiological stability.

Some differences were evident in the disintegration time which, in all cases, complied with the Ph. Eur. specifications (**Table 1**). The drug content was uniform and the HPLC analyses did not evidence any degradation peaks.

Generally speaking, the overall drug dissolution of orodispersible dosage forms is considered substantially similar to those of immediate-release oral dosage forms. Even if, after disintegration in the buccal cavity, the insoluble drug substance is dispersed in the saliva and removed from the pre-gastric tract in about 5-10 min by swallowing (Seager, 1998). Based on this consideration, the dissolution test on cast and printed ODF was carried out in artificial saliva at pH 6.8, simulating the pre-gastric tract (i.e. oral cavity and oesophagus), for 6 min which corresponds to the transit time from the buccal cavity to the stomach. Afterwards, the pH value was dropped down to 1.2 and the volume increased to 200 mL to mimic the gastric transit and then increased again to 6.8, as in the small intestine. The dissolution profile of OLZ in artificial

saliva (insert in **Figure 2**) evidenced an unexpected difference between ODF obtained by the two preparation methods since the OLZ dissolved amount was 2% and 50% from cast and extruded ODF, respectively. Considering the differences in film thickness, a slower dissolution from extruded ODF could be expected. At pH=1.2, about 90% of the drug was dissolved from cast ODF; meanwhile, the release from extruded ODF was completed in about 10 min (insert in **Figure 2**) without being further affected by variation in pH (**Figure 2**).

To deepener the effect of the pH on the dissolution behaviour of OLZ, the experiments were repeated using higher volumes of dissolution media to assure the sink condition due to the low solubility of OLZ (*Condition 2*). As shown in **Figure 3a**, only OLZ ODF made by casting formed a precipitate in artificial saliva which was readily re-dissolved at lower pH. The pH dependence in the dissolution profile of OLZ was expected considering the basic nature of this drug (dissociation constants: pK_{a1} = 4.01 and pK_{a2} = 7.24). Indeed, when the pH was shifted from 6.8 to 1.2, OLZ was completely dissolved (**Figure 3a**). The results of dissolution tests at pH 6.8 and 1.2 (*Condition 3)* agreed with the previous results since extruded ODF promptly released OLZ independently on the dissolution media, but a yellow precipitate was evident for cast ODF only in artificial saliva after 3 min (**Figure 4**).

Since excipients are basically the same, differences in the dissolution behaviour were attributed to the process production. Considering the possible polymorphic transformations of OLZ, an investigation in the drug solid-state was carried out by DSC and XRD. The DSC curve of raw material evidenced a single endothermic event with the onset at about 194 °C (ΔH=128±9 J/g) (**Figure 5**) which was attributed to the melting of Form I (**Figure 1a**) according to the XRD pattern (Polla et al., 2005). This structure was found to be anhydrous as the baseline of the thermogram is perfectly horizontal at a lower temperature. MDX DE6 presents glass transition

temperature (T_g) at about 103 °C (Selmin et al., 2015) and the mixing with plasticizer(s), i.e. water or glycerol, caused a massive drop in its value (Roussenova et al., 2010). The binary mixture of OLZ and MDX presented a broad endothermic peak at about 90-100 °C, meanwhile the melting event of Form I was preserved in terms of temperature indicating the maintenance of the crystalline phase (**Figure 5**). Hence, these preliminary results suggest that 95 °C might be a suitable temperature for the ram-extrusion of the OLZ-MDX formulation.

In the case of ODF (cast and printed), the presence of glycerol determined several endothermic events up to 130 °C which were ascribed to the thermal degradation of the film and did not permit to describe the melting behaviour of OLZ (data not shown). The presence of Form I of crystalline OLZ in the films is confirmed by XRD either in the case of cast ODF (**Figure 1b**), although the peaks at 2θ values of about 9°, 14.4° and 18.7° were relatively broad and with significant background noise associated, or for printed ODF which showed only two sharp diagnostic peaks corresponding to 2θ values at about 9° and 18.5° (**Figure 1c**).

Indeed, Form I OLZ is reported to be obtained exclusively from dry non-solvate forming organic solvents; meanwhile, the hydrates usually and readily crystallize when water is present (Reutzel-Edens et al., 2003). In line with these considerations, XRD and TGA measurements were carried out on the OLZ precipitate recovered during in vitro dissolution in SSF pH 6.8 without further purification steps. First, it was noticed that the XRD pattern was not superimposable to that of OLZ Form I, but some shifts in the 2θ values of the most characteristic peaks were evident (**Figure 1d**) and during the thermal treatment a mass loss of about 2% corresponding to about 0.5 mol of water was measured. Based on this result, it can be assumed that the casting method, which included the preparation of an aqueous slurry, favours the conversion from Form I to a hydrated one.

The dissolution profile of OLZ for ODF stored at 25±1 °C for 30 months was superimposable to that of ODF after preparation. This evidence allowed us to assume that there was not a conversion of OLZ in a more stable, and less soluble form (**Figure 3b**).

4. Discussion

Independently of the technology selected to produce ODF, both the formulation and process need to be optimized in relation to the physical instability of the drug substance. For instance, ibuprofen, which undergoes sublimation, can be formulated as ion-pair complexes in cast ODF (Liu et al., 2020). In the case of loperamide, when hydroxypropyl cellulose was selected as a film-forming polymer, the transformation from polymorph I to polymorph II occurred over time (Woertz and Kleinebudde, 2015). Also, the use of solvents, mainly water in the case of ODF, can cause unintended drug phase transformations (Khalid et al., 2021), which could directly affect the dissolution rate of the loaded drug and limit its bioavailability.

In the current work, the possible impact of preparation methods, namely casting and hot-melt ram-extrusion printing, on polymorphisms and dissolution performances of OLZ was investigated, keeping constant the qualitative composition of ODF.

The comparison of results obtained by the in vitro dissolution testing buffers differing in volume and pH, as occurs in GI transit, evidenced that the transition from Form I to the hydrate one occurred only after the preparation of an aqueous slurry to be cast, and not a paste to be extruded. It was hypothesized that a variation in solid-state would be responsible for differences in drug solubility and the different amount of water present in the slurry to be cast or paste to be printed is an important factor of OLZ polymorphic conversion. Ostwald's rule of stages posits that metastable forms would crystallize first because they are closest in energy to the amorphous

form, and this will be followed by recrystallisation to the thermodynamically stable phase. Although not a universal rule, Askin et al. showed that it can be true for OLZ since the known stable form of OLZ, Form I, was not the first polymorph to crystallize in any of the dispersions (Askin et al., 2020). Therefore, it can be assumed that traces of anhydrous crystals with a different structure with respect to form I evidenced by XRD in the cast film would cause the precipitation of hydrates during the dissolution test; vice versa, the ram-extrusion printing process, despite the relatively high temperature, did not affect the OLZ physical state and therefore dissolution. It is worthy to underline that those differences evident using different dissolution media were not affected by storage time at 25 °C for 30 months.

These results on hot-melt ram extrusion agreed with recent findings on ODF loaded diclofenac (Khalid et al., 2021). Indeed, the anhydrous form diclofenac formed to a hydrate species by exposure to relative humidity even below 60% at 25 °C (e.g., storage under uncontrolled environmental conditions or contact with water vapour during manufacturing process). In the case of loaded ODF, the preparation method did not change the diclofenac solid-state (Khalid et al., 2021).

5. Conclusion

In the last years, a considerable body of work was undertaken to produce ODF in large scale or small batches. Experimentation has been mainly focused on production innovation and development of assays to determine their quality attributes. While this effort has brought to the market dosage forms enable to improve patient's adherence, there is a clear need to establish the impact of a production method on biopharmaceutical properties of ODF. The understanding of possible relation between formulation and process variable (*e.g.*, solvents, moisture and

temperature) with solid-state characteristics is deepen in large-scale manufacturing, but it needs to be addressed to make the compounding of personalized therapy a reality. Indeed, procedures covering the preparation of “not-standardized” formulations are not available and the practical aspects related to quality and safety need to be addressed.

Regarding the loading of OLZ in ODF, the main criticism is the possible conversion from the anhydrous towards hydrated forms with concomitant decrease in solubility. Although solvent casting is the most used, hot-melt ram extrusion printing seems to be promising since it limits the exposure of OLZ to stress-factors (i.e. water and temperature) which can trigger solid-state modifications. The drug solid-state was stable after preparation and over 30 months, as confirmed by dissolution testing in buffers at different pH. Hence, hot-melt ram extrusion printing can represent a valid alternative to the casting when polymorphic transition occurred.

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Table 1. Compositions (% w/w) of the placebo and olanzapine (OLZ) loaded ODF made of maltodextrin (MDX) by printing and solvent casting. ODF thickness, weight, loss on drying (LOD), moisture content (MC), disintegration time (Disint), weight, and drug content are presented as mean ± standard deviation (SD).

Technology	Components (%)					Thickness (µm)	LOD (%)	Disint (s)	ODF weight (mg)	OLZ content (mg)
	OLZ	MDX	Glycerol	Water	Span®80					
Printing	-	78.00	20.00	2.00	-	220±27	3.4±1.2	38±2	333±26	-
	6.29	73.09	18.74	1.87	-	278±13	4.4±0.6	44±2	203±5	12.6±0.2
Casting	-	46.41	10.56	41.27	1.76	126±4	7.0±0.1	76±0	101±1	-
	5.07	44.05	10.04	39.18	1.67	140±5	5.6±0.7	38±12	121±5	9.4±0.1

Table 2 – Composition of dissolution media used to carry out the *in vitro* dissolution testing.

GI section	**Total volume (mL)***	**Composition (g/L)**	**pH**	**Total time (min)**	**Ref**
Buccal cavity	3	8 g NaCl 0.19 g KH_2PO_4 2.38 g Na_2HPO_4	6.8	5	(Marques et al., 2011)
Stomach	200	2.92 g NaCl, 1 N HCl to pH=1.2	1.2	115	(Musazzi et al., 2019)
Small intestine	300	6.8 g KH_2PO_4; NaOH to pH=6.8	6.8	180	(Musazzi et al., 2019)

* referred to Condition 1.

Caption of illustrations:

Figure 1 – XRDP of (a) OLZ form I, (b) OLZ loaded ODF obtained by casting, (c) OLZ loaded ODF obtained by printing, and (d) precipitated OLZ from cast ODF during the dissolution study at pH 6.8 SSF.

Figure 2 – Dissolution profiles of cast (full circles) and printed ODF (empty circles) in dissolution media mimicking the volume and pH of oral cavity (3 mL, artificial saliva (A) at pH 6.8), stomach (200 mL, dissolution medium at pH=1.2) and small intestine (300 mL, phosphate buffer at pH 6.8).

Figure 3 – *In vitro* dissolution profile of OLZ from printed (blue line) and cast (grey line) ODF in 900 mL of pH=6.8 simulated saliva at time 0 (a) and after 30 months of storage at 25±1 °C (b). pH was dropped down at 1.2 after 6 min.

Figure 4 – *In vitro* dissolution profile of OLZ in 900 mL of pH 1.2 buffer (empty symbols) and in pH 6.8 artificial saliva (full symbols) from cast (blue line) and extruded (grey line) ODF.

Figure 5 – DSC trace of pure OLZ (black line) and physical mixture of OLZ and MDX (grey line).

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

credit author statement

Conceptualization, F.C. and F.S.; Methodology, F.C., F.S., F.D. and U.M.M.; Investigation, U.M.M., F.S., G.M.K. and F.D.; Writing, F.C. and F.S.; Writing, F.C. and F.S.; Supervision, F.C. and P.M.

Figure 1

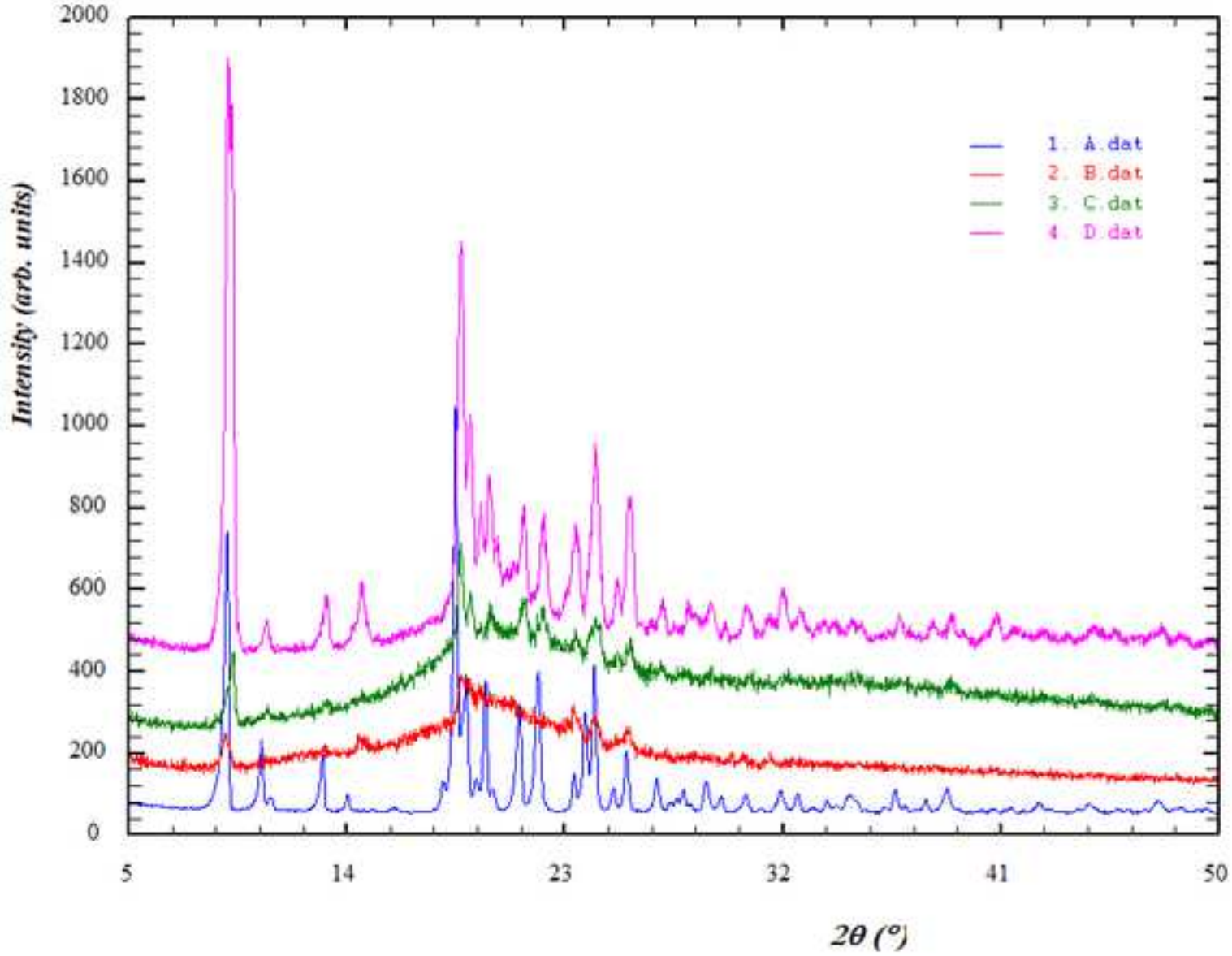

Intensity (arb. units)
2θ (°)
1. A.dat
2. B.dat
3. C.dat
4. D.dat
0
200
400
600
800
1000
1200
1400
1600
1800
2000
5
14
23
32
41
50

Figure 2

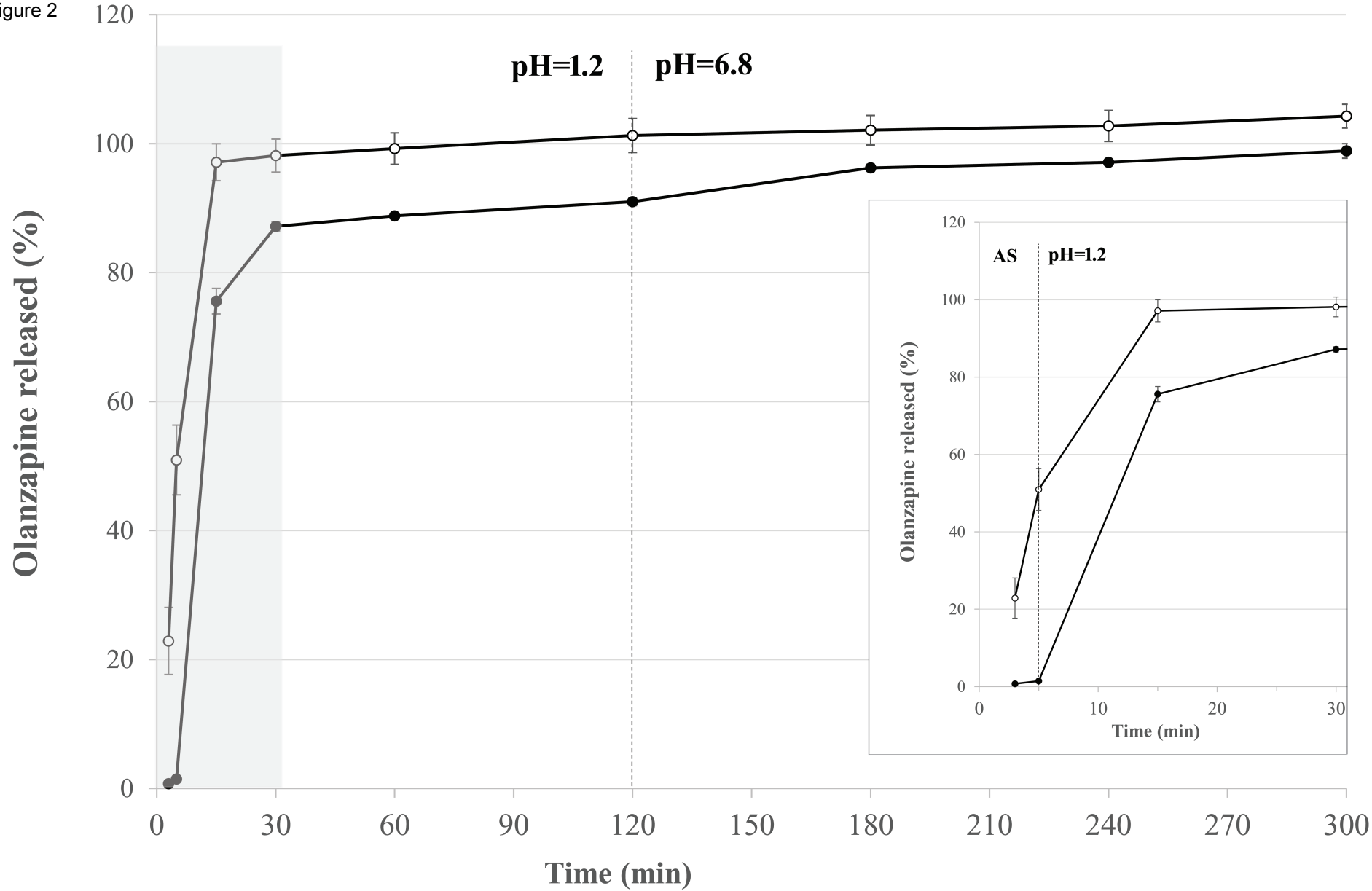
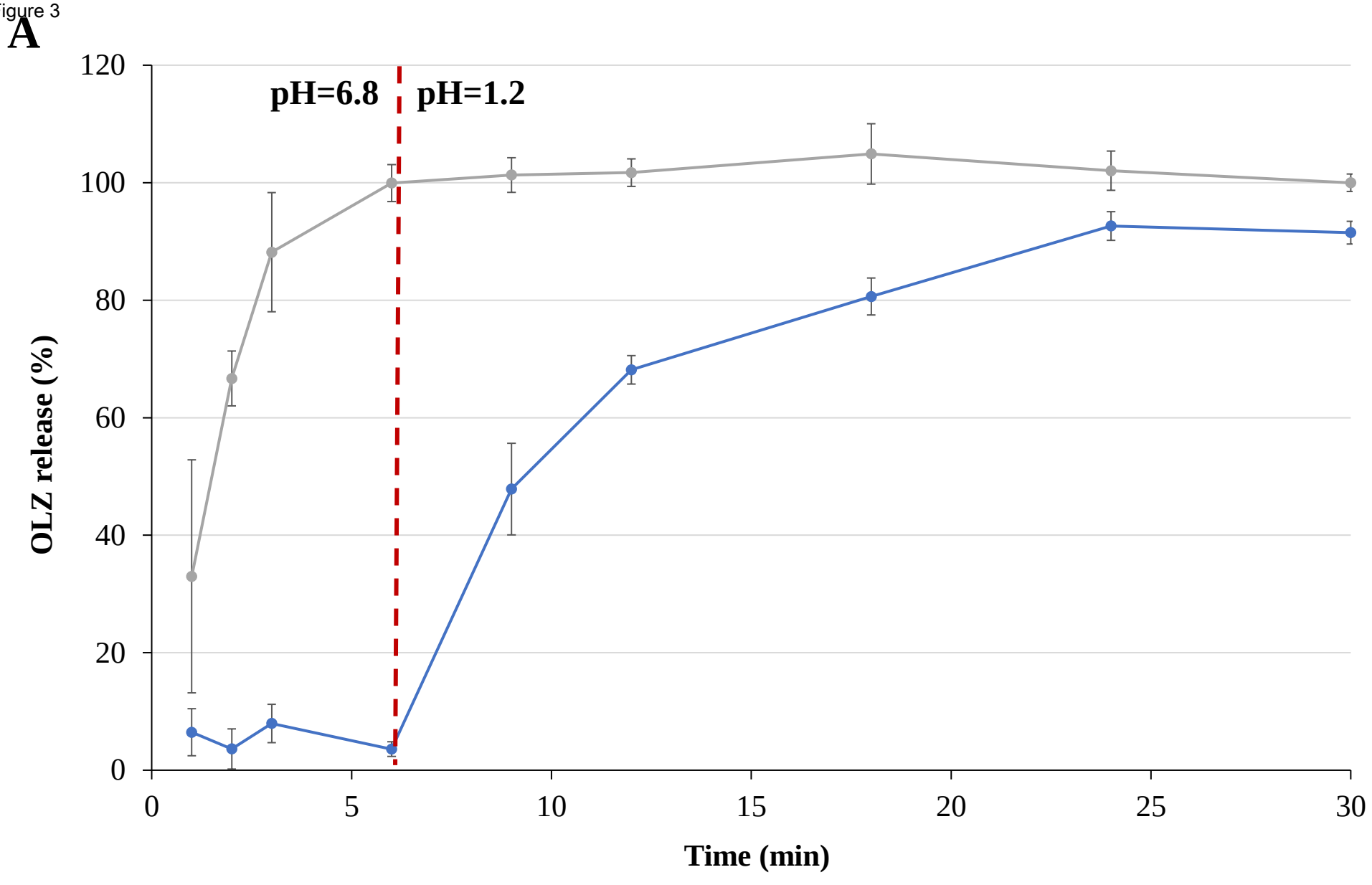

pH=1.2
pH=6.8
Olanzapine released (%)
Time (min)
0
20
40
60
80
100
120
0
30
60
90
120
150
180
210
240
270
300
AS
pH=1.2
Olanzapine released (%)
Time (min)
0
20
40
60
80
100
120
0
10
20
30

Figure 3


A
120
100
80
60
40
20
0
pH=6.8
pH=1.2
OLZ release (%)
0
5
10
15
20
25
30
Time (min)

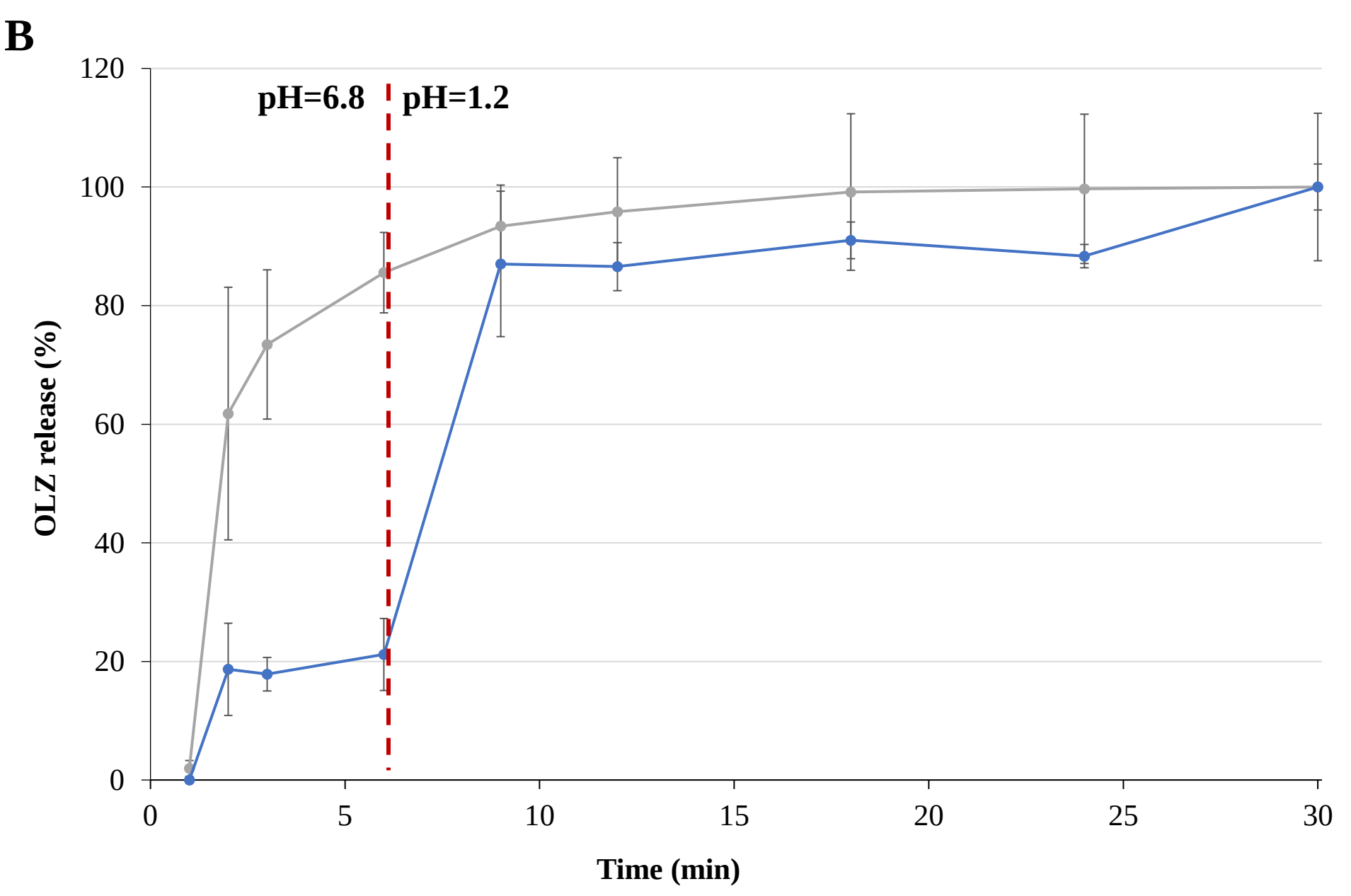

B
120
100
80
60
40
20
0
pH=6.8
pH=1.2
OLZ release (%)
0
5
10
15
20
25
30
Time (min)

Figure 4

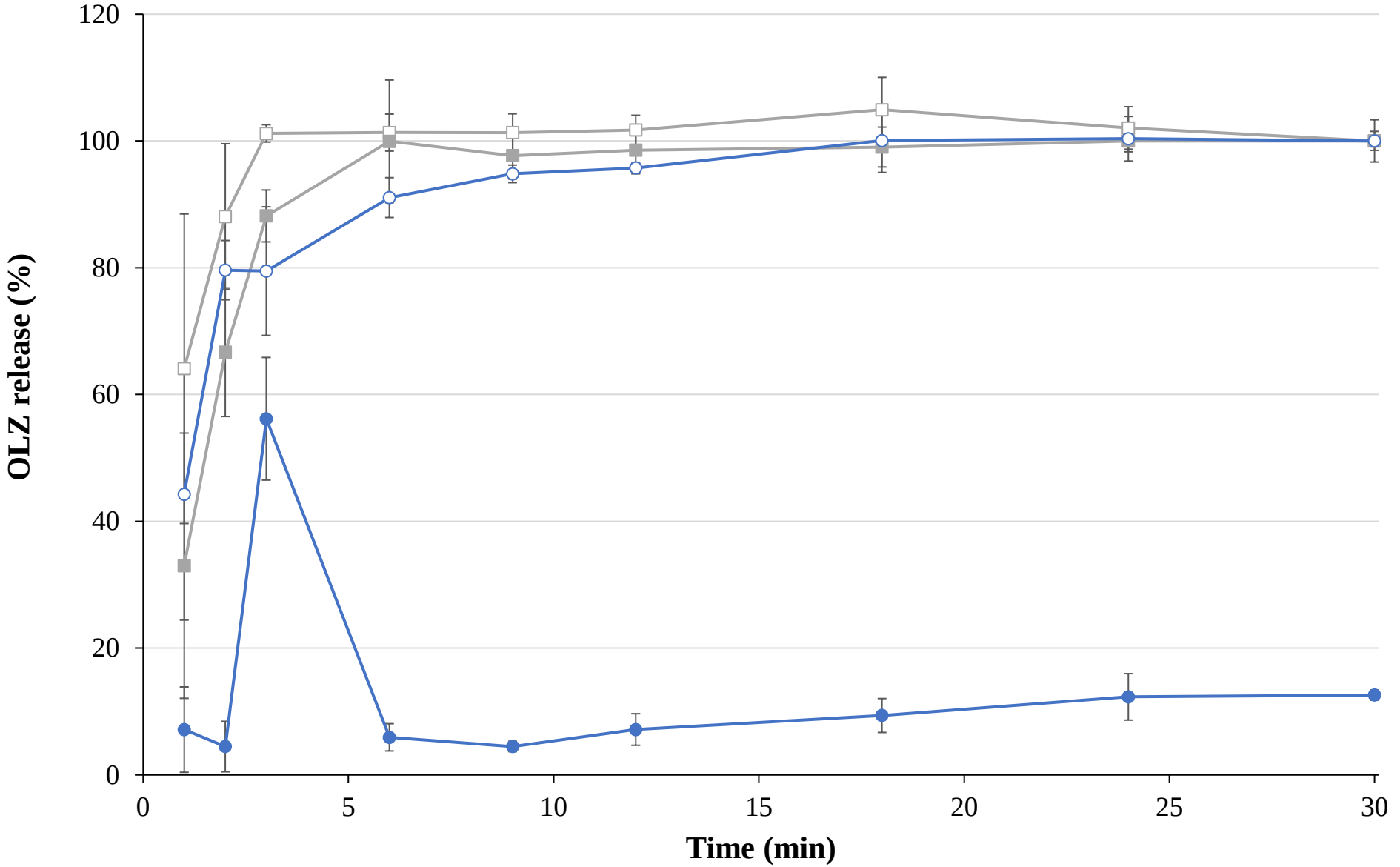
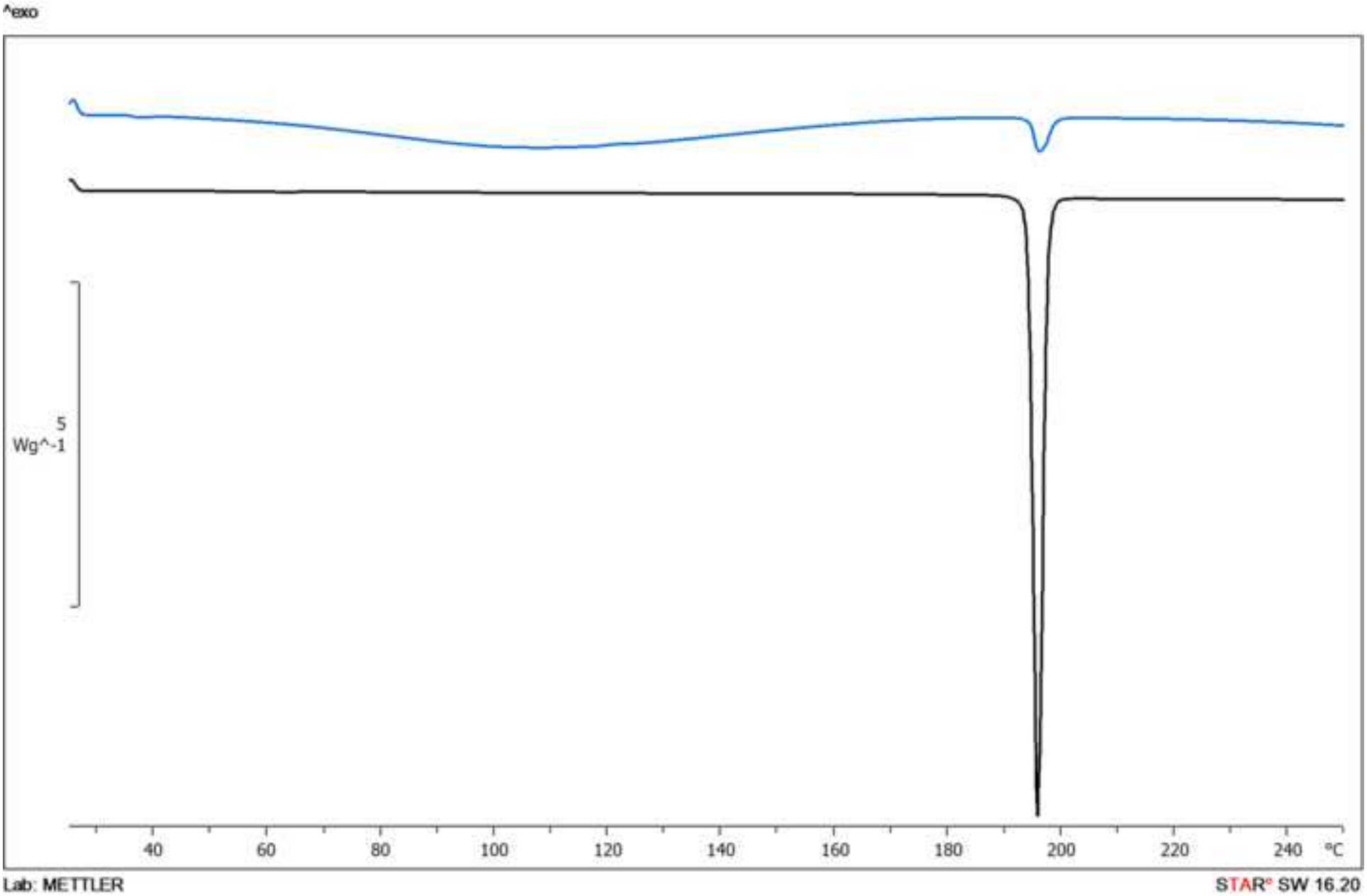


Figure 5


^exo
5
Wg^-1
40
60
80
100
120
140
160
180
200
220
240
°C
Lab: METTLER
STAR° SW 16.20

Highlights (not mandatory)

- Water can induce polymorphic transition of olanzapine during the preparation of ODF
- Aqueous solubility of olanzapine hydrate is ten times lower than form I.
- Hot-melting techniques assures olanzapine physical stability in ODF up to 30 months.