

## Accepted Manuscript

Title: Solid Microcrystalline Dispersion Films as a New Strategy to Improve the Dissolution Rate of Poorly Water Soluble Drugs: A Case Study Using Olanzapine

Author: Laura Modica de Mohac Maria de Fátima Pina Bahijja Tolulope Raimi-Abraham



PII: S0378-5173(16)30378-7  
DOI: <http://dx.doi.org/doi:10.1016/j.ijpharm.2016.05.012>  
Reference: IJP 15748

To appear in: *International Journal of Pharmaceutics*

Received date: 18-1-2016  
Revised date: 28-4-2016  
Accepted date: 2-5-2016

Please cite this article as: de Mohac, Laura Modica, de Fátima Pina, Maria, Raimi-Abraham, Bahijja Tolulope, Solid Microcrystalline Dispersion Films as a New Strategy to Improve the Dissolution Rate of Poorly Water Soluble Drugs: A Case Study Using Olanzapine. *International Journal of Pharmaceutics* <http://dx.doi.org/10.1016/j.ijpharm.2016.05.012>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

# **Solid Microcrystalline Dispersion Films as a New Strategy to Improve the Dissolution Rate of Poorly Water Soluble Drugs: A Case Study Using Olanzapine**

- Order of authors: Laura Modica de Mohac, Maria de Fátima Pina, Bahijja Tolulope Raimi-Abraham

- Laura Modica de Mohac

Faculty of Pharmacy, University of Study of Palermo, Palermo, Italy

[laly0692@hotmail.it](mailto:laly0692@hotmail.it)

- Maria de Fátima Pina

UCL School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX

[m.pina@ucl.ac.uk](mailto:m.pina@ucl.ac.uk)

- Bahijja Tolulope Raimi-Abraham

UCL School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX

[b.raimi-abraham@ucl.ac.uk](mailto:b.raimi-abraham@ucl.ac.uk)

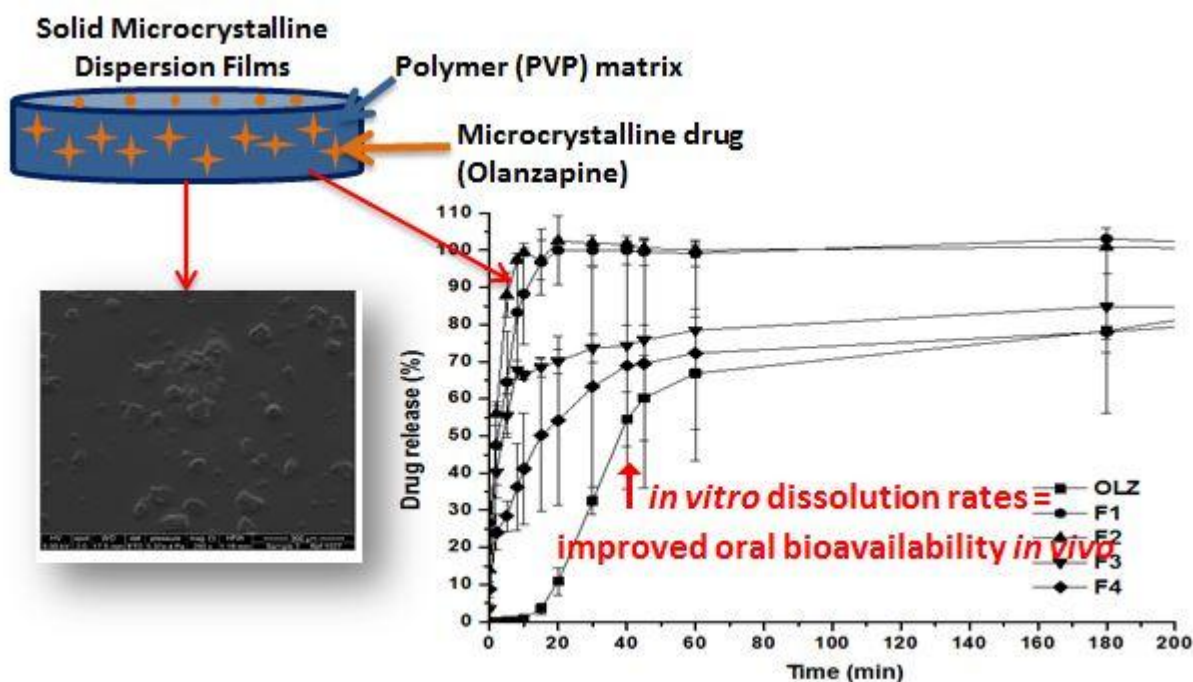
\*Corresponding Author: Bahijja Tolulope Raimi-Abraham

Full Postal Address University College London, School of Pharmacy, Department of Pharmaceutics, 29-39 Brunswick Square, London, WC1N 1AX, UK

Phone 0044 20 7753 5811

Email: [B.Raimi-Abraham@ucl.ac.uk](mailto:B.Raimi-Abraham@ucl.ac.uk)

## Graphical Abstract

**ABSTRACT (200 words):**

In this study, we evaluate the dissolution rate enhancement of solid microcrystalline dispersion (SMD) films of olanzapine (OLZ) formulated with four water-soluble polymers namely poly(N-vinylpyrrolidone) (PVP), poloxamer 188 (P188), poloxamer 407 (P407) and Soluplus® (SLP). Prepared formulations were characterised to determine particle size, morphology, hydrogen bonding interactions, thermal characteristics as well as *in vitro* dissolution studies conducted under sink conditions (pH 6.8). Particle size of OLZ in all formulations ranged between 42-58  $\mu\text{m}$ . Attenuated Total Reflectance Fourier Transform Infrared spectroscopy (ATR-FTIR), Differential Scanning Calorimetry (DSC) and Hot-Stage Microscopy (HSM) studies confirmed OLZ was well maintained in its crystalline state during the formulation process. *In vitro* dissolution studies showed immediate drug release from all formulation when compared to the drug alone. The greatest increase in *in vitro* dissolution rate was observed in formulations containing P188 most likely due to its enhanced hydrophilic and surfactant properties compared to the other agents used. Overall, this study successfully generated OLZ loaded SMD films with improved *in vitro* dissolution rates which is highly likely to result in improved oral bioavailability *in vivo*.

**Keywords (max 6 words):** solid microcrystalline dispersion; pharmaceutical film; crystalline; olanzapine; polymer, PVP

**Chemical compounds studied in this article:** Olanzapine (PubChem CID: 4585); Poly(N-vinylpyrrolidone) (PubChem CID: 6917); Poloxamer 188 (PubChem CID: 24751); Poloxamer 407 (PubChem CID: 24751)

## 1. INTRODUCTION

Olanzapine (OLZ) is an atypical antipsychotic drug used to treat schizophrenia and other mental health disorders (Maria Fátima Pina et al., 2014; Roo, 1913). It is a poorly water-soluble drug classified accordingly to the Biopharmaceutics Classification System (BCS), as a class II drug. BCS class II and IV drugs represent a significant challenge in the pharmaceutical industry due to their poor oral bioavailability as a result of their low aqueous solubility (Ku, 2008). Different formulation strategies such as co-crystal (Good and Rodríguez-Hornedo, 2009), salt formation (Serajuddln, 1999), micronization (Carr et al., 2010; Khadka et al., 2014) and most commonly, solid dispersion (SD) approaches (Chiou and Riegelman, 1971; Craig, 2002; G. Van Den Mooter, 2009; Raimi-Abraham et al., 2015) have been employed to increase BCS II and IV aqueous solubility and consequently enhance their oral bioavailability. A SD can be described as a delivery system whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhance oral bioavailability (Craig, 2002). There are different types of SDs with the difference between them being the solid state of the polymer-matrix and the active pharmaceutical ingredient (API) (Reintjes, 2011). A ‘glass suspension’, as defined by Kolter et al. (2012), is a SD where the drug remains in the crystalline state after being dispersed in an amorphous polymer. More commonly, this term is used to describe a SD where the drug is molecularly dispersed within an amorphous matrix (usually a polymer). Eutectic formulations contain both drug and polymer in the crystalline state (Bikiaris et al., 2005; Kolter K, Karl M, 2012; Leuner and Dressman, 2000; Reintjes, 2011; Vasanthavada et al., 2005). It is well-known that amorphous materials possess short range molecular order and high kinetic energy. Their weaker attractive intermolecular forces result in bonds which are easily broken that allow molecules to be lost from its surface (in the solid state) into a liquid medium easier compared to their crystalline counterparts, therefore they are more soluble and have faster dissolution rate (Shah, N.; Sandhu, H.; Choi, D.S.; Cholkshu, H.; Malick, 2014). However, amorphous materials have low stability and high

tendency to recrystallize within pharmaceutically relevant timescales (Michael, 2007; Sinko, 2011). The crystalline state (where molecules possess long range molecular order) is a low energy state which defines its higher stability allowing an adequate physical form control during formulation and storage processes (Michael, 2007; Reintjes, 2011; Sinko, 2011).

Micronization is a well-known technique for particle size reduction. The reduction of the particle size of an API increases its surface area, contact regions with the external aqueous environment and consequently its dissolution rate (according to the Noyes-Whitney equation). Decreasing the particle size will increase the saturation solubility (Ostwald-Freundlich) and will also result in a thinned hydrodynamic layer surrounding the particle therefore, increasing its surface-specific dissolution rate (Prandtl equation) (Da Fonseca Antunes et al., 2013). A growing method to improve solubility of poorly water soluble drugs includes the preparation of crystalline SD where the particle size of the drug has been reduced (Michael, 2007; Sinko, 2011) to increase its dissolution rate.

Several methods have been used to prepare SDs (both amorphous and crystalline) such as spray drying (Taylor et al., 2010), freeze-drying (Naik and Mokale, 2014), hot melt extrusion (Djuris et al., 2014; Maria Fatima Pina et al., 2014) , pressurised gyration (Raimi-Abraham et al., 2015) and solvent casting method (commonly used to prepare pharmaceutical thin films) (Lan et al., 2010). Solvent casting method is an easy and manageable technique in which the API can either be suspended or dissolved in a polymer solution and with or without stabilizers. This method is ideal for heat-sensitive APIs as it can be conducted at room temperature (Qi et al., 2013; Brief, 2010).

Pharmaceutical films offer several advantages for oral drug delivery over other dosage forms. Upon direct contact with saliva (in the oral cavity), they instantly dissolve allowing the release of the API. Drug-loaded polymeric thin films (with a few micrometres thickness) have attracted attention for a variety of applications including oromucosal drug delivery, bio-adhesive formulations, skin delivery, and wound management (Qi et al., 2013). Pharmaceutical films are known to improve patient compliance especially in those who have difficulty or aversion to swallowing conventional oral dosage forms (Kianfar et al., 2011). These advantages make pharmaceutical thin films one of the

most portable and convenient oral dosage forms of any available today (Brief, 2010; Ghodake et al., 2013; Koland et al., 2010).

This study highlights the use of solid microcrystalline dispersion (SMD) films as an alternative strategy to improve the dissolution rate (and in turn oral bioavailability) of poorly water soluble drugs. SMD films are prepared where the drug firstly undergoes gentle micronization resulting in uniform microcrystalline drug particles. Films are then generated using the solvent cast method from an aqueous polymeric base.

The aims of the work detailed here were two-fold. Firstly, to prepare poly(N-vinylpyrrolidone) (PVP, Kollidon 90F) based SMD films (using OLZ as a model API) offering enhanced dissolution rate compared to the API alone. Secondly, to explore the use of poloxamers (poloxamer 188 (P188), poloxamer 407 (P407)) and solubilizing agents (Soluplus® (SLP)) commonly used in the generation of amorphous SDs in melt methods (such as HME) to further improve the dissolution rate of OLZ.

## 2. MATERIALS AND METHODS

### 2.1 Materials

OLZ [molecular weight (Mw) = 312.43 g/mol] was purchased from Myjoy Ltd (Hangzhou, China). P188 [Mw = 7680 - 9510 g/mol], P407 [Mw = 9840 - 14600 g/mol]; PVP [Mw = 1000000 – 1500000 g/mol] and SLP [Mw = 90000 - 140000 g/mol] were kindly donated by BASF® (Ludwigshafen, Germany). Methanol, potassium dihydrogen phosphate, dipotassium phosphate and sodium chloride were obtained from Sigma-Aldrich (Gillingham, Dorset; UK). Figure 1 shows the chemical structures of OLZ, SLP, PVP, P188 and P407.

### 2.2 Solid Microcrystalline Dispersions Preparation

SMD films containing OLZ as microcrystalline structures were prepared using the solvent casting method from an aqueous polymeric base. To ensure a homogeneous particle size distribution of OLZ, prior to film preparation, OLZ was gently milled using a Ball Mill (Ballmill M/C number 2; Christison Ltd.; Gateshead) for 10 minutes (repeated three times with a cool-down period time of 15 min in between milling) at 150 rpm. The obtained powder was passed through a 63  $\mu\text{m}$  sieve. PVP powders were dissolved in distilled water (in house system) and the poloxamers and solubilizing agents (i.e. P188, P407 and SLP) and OLZ were then added under stirring according to the formulation requirements as summarized in Table 1. Formulations were dried in a fume cupboard for 24 hours to ensure evaporation of the solvent and allow film formation.

### *2.3 Film morphology and particle size analysis*

Scanning electron microscopy (SEM) (JSM 4900LV; JEOL Ltd., Japan) images were collected on freshly prepared films to investigate SMD film morphology and particle size analysis. To improve conductivity prior to examination, samples were coated with 20 nm of gold under vacuum using a PolaronSC7640 sputter gold coater (Quorum Technologies, UK). The average diameter of the drug was determined from the mean value of 100 measurements using ImageJ (USA, version 1.46v).

The particle size of formulated OLZ in SMD films was measured. Prior to the analysis a weighed amount of film was dissolved in distilled water (120 mL) using a Hydro MV Mastersizer 3000 (Malvern; Grovewood Road, UK) at a rotational speed of 2800 rpm.

### *2.4 Attenuated Total Reflection-Fourier Transform Infrared (ATR-FTIR)*

ATR-FTIR studies were conducted to identify any molecular interaction between OLZ and polymers. Samples were placed on the ATR crystal, sufficient pressure was applied to the sample so as to enable good contact with the ATR crystal, and spectra were collected using a Bruker Vertex 90 spectrometer, from 4000 to 550  $\text{cm}^{-1}$  with 64 scans (same as background) at resolution of 2  $\text{cm}^{-1}$  for

each sample. Experiments were conducted under ambient conditions and each sample was examined in triplicate.

### 2.5 Differential Scanning Calorimetry (DSC)

DSC studies were performed using a Thermal Analysis Q1000 differential scanning calorimeter (DSC) equipped with an auto-sampler (TA Instruments, New Castle, DE). Samples were characterised using conventional DSC and modulated temperature DSC (MTDSC) mode. Conventional DSC studies were conducted at heating rates of 10, 20 and 50 °C/min. MTDSC studies were conducted at a heating rate of 2 °C/min, amplitude of  $\pm 0.318$  °C over a period of 60 seconds. Experiments were performed between 0 °C – 200 °C and TA standard crimped pans with holes in the lid were used in all experiments. Nitrogen purge gas was used with a flow rate of 50 mL/min. Calibration was performed using *n*-octadecane, indium and tin. Heat capacity was calibrated using a sapphire disk (TA Instruments, New Castle, DE). Measurements were repeated at least in triplicate.

### 2.6 Thermogravimetric Analysis (TGA)

TGA (Hi-Res TGA 2950, TA Instruments) studies were conducted to measure the water content of the prepared films. Experiments were conducted at 10 °C/min from ambient temperature to 200 °C. TA Standard crimped aluminium pans with accompanying pin holed lids were used.

### 2.7 Hot-Stage Microscopy (HSM)

HSM studies were conducted using a LeicaDM72M (Leica, Germany) with a 10 $\times$  magnification lens connected to a FP5/FP52 (Mettler Toledo, UK) heating stage unit and a FP90 (Mettler Toledo, UK) central processor unit. Samples were heated from ambient to 200 °C at 10 °C/min. Studio86 Design Capture Software was used to record and capture thermal events in real time.



### 2.8 Determination of OLZ equilibrium solubility in polymer solutions

The effect of PVP, SLP, P188 and P407 on the aqueous solubility of OLZ was investigated (in ratios presented in Table 1). Excess amounts of OLZ powders were dispersed in aqueous polymer solutions for 72 hours and stirred with 150 rpm at 37 °C using a shake incubator (SciQuip, UK). The polymer solutions were then filtered through a 0.22 µm Millex-GP filter (Merck Millipore, UK) and the concentration of OLZ was determined spectrophotometrically at 253 nm.

### 2.9 Drug loading studies

Film samples were dissolved in 10 mL of methanol, filtered through a 0.22 µm Millex-GP filter (Merck Millipore, UK) and the drug content of each sample was determined spectrophotometrically at 253 nm after suitable dilution.

### 2.10 *In vitro* Dissolution Studies

*In vitro* dissolution studies were conducted (under sink conditions) using a Copley CIS 8000 dissolution bath (Copley Scientific, UK). The USP paddle method, apparatus USP type II, with a rotation speed of 50 rpm and 900 mL of phosphate buffer pH 6.8 European Pharmacopeia were used. The temperature was set to  $37.0 \pm 0.5$  °C. The weight of samples used was calculated to keep the amount of OLZ constant at 10 mg in all formulations. At predetermined intervals, 5 mL of solution was withdrawn and filtered through a 0.22 µm filter (Millex-GP filter, Merck Millipore, UK) and replaced with the same amount of fresh buffer. Subsequently, the filtrate was analysed spectrophotometrically at 253 nm. All *in vitro* dissolution studies were performed under sink conditions.

### 3. RESULTS

#### 3.1 Characterization of Raw Materials

As OLZ exists in many polymorphic forms (Maria Fátima Pina et al., 2014) it was important to confirm that the milling process had not induce any polymorphic changes. DSC studies of all raw materials are shown in Table 2 and Figure 2. Findings from DSC studies (limit of detection ~5% (Shah et al., 2006) conducted on milled and un-milled OLZ (Figure 2a) identified a melting temperature comparable to that in the literature confirming that the milling process did not induce any polymorphic changes. Thermographs of P188 and P407 (Figure 2b) showed a  $T_m$  of  $53.95 \pm 0.18^\circ\text{C}$  and  $57.02 \pm 0.07^\circ\text{C}$ , respectively. SLP (Figure 2c) showed a glass transition temperature ( $T_g$ ) of  $61.41 \pm 0.91^\circ\text{C}$  which was slightly lower than the reported value (Kolter K, Karl M, 2012). This could be due to presence of residual water lowering the  $T_g$ . DSC studies conducted on PVP raw material (Figure 2d) saw a  $T_g$  of  $172.40 \pm 1.41^\circ\text{C}$ . All findings were coherent with expected literature values (Bühler, 2008; Kolter, 2013).

ATR-FTIR studies were conducted to ascertain the effect milling had on the crystalline structure of OLZ. Further studies were conducted to identify any hydrogen bonding interactions between OLZ and the polymers used. ATR-FTIR spectra of milled and un-milled OLZ (Figure 3a), showed characteristics peaks (Silverstein M. et al., 2005) at  $3239\text{ cm}^{-1}$  (NH and OH),  $2929\text{ cm}^{-1}$  (CH stretching),  $1583\text{-}1556\text{ cm}^{-1}$  (C=C natic ring symmetric stretch),  $1468\text{-}1446\text{ cm}^{-1}$  (C=C aromatic ring asymmetric stretch),  $1411\text{ cm}^{-1}$  (CH bending),  $1288\text{ cm}^{-1}$  and  $1223\text{ cm}^{-1}$  (CN stretching). ATR-FTIR studies (in agreement with DSC studies) further confirmed that no polymorphic changes were induced during the OLZ milling process. ATR-FTIR spectra showed characteristic peaks for PVP, P188, P407 and SLP (Figure 3b) with further information on band assignment detailed in Table 3.

### *3.2 SMD Film Characterization: Particle Size and Morphology*

To successfully generate SMD films, it is necessary to ensure that the drug remains (during all formulation stages) present in its crystalline form. DSC and ATR-FTIR studies were conducted to evaluate the crystallinity of OLZ within the SMD films. SEM and LD studies were conducted to measure the mean particle size of OLZ within the formulated films results of which are provided in Table 4. Overall, particle size in all formulations (i.e. F1-4) ranged between 42-58  $\mu\text{m}$ . Differences were observed between the two sets of measurements which could be due to the irregular shape (non-spherical) of the drug crystals (Figure 4), which is known to affect particle size analysis using laser diffraction techniques (A.P. Tinke, et al., 2007; Stojanovic, 2012). In addition, SEM only allows for the analysis of a restricted portion of the sample.

### *3.3 SMD Characterization: Evaluation of drug-polymer interaction*

ATR-FTIR studies were used to confirm the presence of OLZ in the crystalline state and evaluate the existence of any interactions occurring between OLZ and the polymers used in each formulation. The region between 1700 and 1200  $\text{cm}^{-1}$  where hydrogen bonding between OLZ and polymers is likely to occur (Coleman et al., 1988) was the main focus of analysis. It is well-known that OLZ has a hydrogen bond donor group (NH) whilst PVP and SLP have one hydrogen bonding acceptor group (C=O) (Reintjes, 2011; Thakuria and Nangia, 2011). ATR-FTIR studies (Figure 5) did not show evidence of any interaction (in all formulations) at the C-N stretching region (i.e. 1288 and 1223  $\text{cm}^{-1}$ ) of OLZ. F1 (i.e. OLZ/PVP) and F4 (i.e. OLZ/PVP/SLP) showed two additional peaks at 1583 and 1556  $\text{cm}^{-1}$  which correspond to the C=C bond of OLZ (Figure 5a and 5d).

### *3.4 Thermal Properties*

DSC studies performed on the films were conducted at 10, 20 and 50  $^{\circ}\text{C}/\text{min}$  as to improve the sensitivity of detection of small thermal transitions. The best resolution of the different transitions was obtained at 10  $^{\circ}\text{C}/\text{min}$  results (shown in Figure 6). Overall, DSC studies identified three main

thermal events. F3 and F4 showed their first thermal transition at 50.98 °C and 48.34 °C which can be assigned to the  $T_m$  of P188 and P407, respectively (Figure 6a). These results suggested a possible phasic system in these formulations where the poloxamers have not bonded with other components in the formulation. The second thermal transition is a broad endothermic peak occurring at 100 °C which we attributed to water evaporation from the film matrix as confirmed by TGA studies (data not shown). TGA studies confirmed relatively high water content in all formulations around ~13% w/w, this might be due to the residual moisture content in the films, increased surface area combined with the high hygroscopic behaviour of PVP (Rumondor and Taylor, 2010). The third thermal event observed is thought to relate to the depressed  $T_m$  of OLZ however, this is difficult to assign as it also overlaps with the  $T_g$  of the PVP.

HSM studies were conducted to confirm OLZ crystalline nature within the thin film using birefringence as an indication of crystallinity. HSM images (Figure 7) showed that for each formulation the observed  $T_m$  of OLZ in fell within a similar temperature range (i.e. 173 – 183 °C) as observed in DSC studies however, some crystalline particles were still present at 190 °C. These slight variations of OLZ thermal behaviour in HSM and DSC studies is most likely due to the differences in experimental environment i.e. use of nitrogen purge gas in DSC studies and air in HSM studies.

### 3.5 Determination of OLZ solubility in the polymer solutions

Prior to *in vitro* dissolution studies, the influence of polymers used on the solubility of OLZ was investigated. Aqueous solutions of PVP, P188, P407 and SLP (at the same ratio as used in each formulation) were prepared and the results are shown in Figure S11. Aqueous solubility of OLZ was measured to be 3.33 µg/mL which is comparable to previous findings (Thakuria and Nangia, 2011). OLZ aqueous solubility increased over 3 fold (statistically significant as  $p < 0.001$  (Student  $t$  –test)) in the presence of PVP, P188, P407 and SLP at various ratios with OLZ/PVP/P188 solution (mimicking F2) improving OLZ solubility the most.

### 3.6 *In Vitro* Dissolution studies

OLZ content in all formulations was between  $8.60\% \pm 0.58$  and  $12.34\% \pm 0.29$ . Exact values are summarized in Table S11. *In vitro* dissolution studies were conducted under sink conditions in PBS pH 6.8 (Figure 8). All formulations showed immediate drug release characteristics and increased dissolution rate of formulated OLZ compared to unformulated OLZ alone. More specifically, F2 formulation (which contained OLZ, PVP and P188), showed the fastest release at the onset, reaching 100% release just after 20 min. In contrast, unformulated OLZ showed 10% drug release after 20 min reaching 100% release after 20 hours. F3 and F4 formulations had a slower drug release rate compared to F2 with ~40% and 60% OLZ release observed after 20% respectively and 100% of drug released at 20 hours for both formulations. This could be due to the low concentration of P407 within the formulation, findings in the literature (Datta et al., 2011; Lan et al., 2010; Lim et al., 1971; Reintjes, 2011) have suggested that a percentage between 25 and 95% of P407 is preferred to offer enhanced drug solubility effects. In a similar way, SLP has shown to offer improved drug dissolution at percentages 10% and above.

## 4. DISCUSSION

This study has highlighted the potential of SMD films as an alternative strategy to improving the dissolution rate (and in turn oral bioavailability) of poorly water soluble drugs such as OLZ. SMD films are generated using a relatively straightforward two-step process involving gentle API micronization followed by film formation via the solvent cast method. PVP-OLZ SMD films with poloxamers and solubilizing agents added were generated. High MW PVP (i.e. Kollidon 90F) was used as the base polymer due to its well-known capabilities in pharmaceutical film formation in particular as a strengthening polymer in the development of fast dissolving films (Ali et al., 2005; Qi et al., 2013) (Augello et al., 2004). The aims of the work detailed here, was to prepare PVP-OLZ

SMD films offering faster dissolution rates of OLZ and further enhance this effect through the addition of poloxamers and solubilizing agents.

Particle size analysis of OLZ particles within the formulated SMD films confirmed that drug particles were present in the micron range (i.e. 42 -58  $\mu\text{m}$ ). With further characterisation of the films using ATR-FTIR, DSC and HSM methods confirmed that OLZ was well maintained in its crystalline state (without the induction of polymorphic changes). Immediate drug release and increased dissolution rate of formulated OLZ compared to OLZ alone was observed. Micronization is known to increase drug dissolution rate by increasing the surface-area-to-drug ratio though this process does not increase drug equilibrium aqueous solubility (Khadka et al., 2014). Poloxamers and solubilizing agents were added to SMD films to exploit their known benefits in dissolution and solubilization enhancement commonly applied in amorphous SD melt generation methods. Their ability to act as stabilizers due to their ability to prevent crystal agglomeration and reduce the occurrence of Ostwald ripening (Ali et al., 2005; Kolter K, Karl M, 2012; Mike Evangelista et al., 2015) was also exploited. The F2 formulation (which contained OLZ, PVP and P188), showed the fastest dissolution rate (at the onset), reaching 100% release after just 20 minutes compared to the other formulations. This phenomenon observed could be due to the higher proportion of oxyethylene segments present in P188 compared to P407, giving it greater hydrophilic properties (Medarević et al., 2015). The greater hydrophilic nature of P188 is further confirmed by its higher hydrophilic–lipophilic balance (HLB) compared to P407 (Lippens et al., 2013). Overall in this study, we have used the combined influence of micronized drug particles and improvement of drug aqueous solubility (due to the influence of polymer agents used) to develop SMD films which result in enhanced dissolution rate (compared to the unformulated drug alone).

## 5. CONCLUSION

This study successfully generated PVP-OLZ SMD pharmaceutical films leading to a significant improvement in OLZ dissolution rate. Strategies were employed to ensure that OLZ was well maintained in its crystalline state (without the induction of polymorphic changes) throughout the formulation process. All formulations saw faster dissolution of OLZ compared to the drug alone. This study highlights the potential of SMD films as a strategy to increase aqueous solubility of poorly water soluble drugs as well as enhancing dissolution rate which in turn could result in enhanced oral bioavailability *in vivo*. Furthermore, as the crystalline state of the drug can be maintained, higher stability is expected over pharmaceutically relevant time frames.

## ACKNOWLEDGEMENT

The authors would like to acknowledge the ‘Erasmus Plus Programme’ for their financial support. BASF for the supply of raw materials (Kollidon 90F, Soluplus, Poloxamer 188 and 407). The authors would also like to thank Miss Stefania Marano for her assistance.

## REFERENCES

- A.P. Tinke, A. Carnicer, R. Govoreanu, G. Schektjens, L. Lauwerysen, N. Mertens, K. Vanhoutte, M.E.B., 2007. Particle shape and particle orientation in the laser diffraction and static image analysis size distribution analysis of micrometer size rectangular particles 2–57.
- Ali, S., Quadir, A., Corporation, B., Solutions, P., West, U.S.H.W.Y., 2005. BASF Polymers in Film Development Technology For Drug Delivery Applications 7852.
- BASF, 2013. Technical Information Poloxamers-Kolliphor 1–4.
- Bikiaris, D., Papageorgiou, G.Z., Stergiou, A., Pavlidou, E., Karavas, E., Kanaze, F., Georganakis, M., 2005. Physicochemical studies on solid dispersions of poorly water-soluble drugs: Evaluation of capabilities and limitations of thermal analysis techniques. *Thermochim. Acta* 439, 58–67. doi:10.1016/j.tca.2005.09.011
- Borodko, Y., Habas, S.E., Koebel, M., Yang, P., Frei, H., Somorjai, G. a., 2006. Probing the interaction of poly(vinylpyrrolidone) with platinum nanocrystals by UV - Raman and FTIR. *J. Phys. Chem. B* 110, 23052–23059. doi:10.1021/jp063338
- Brief, T., 2010. Dissolving Film, Particle Sciences.
- Bühler, V., 2008. Kollidon® Polyvinylpyrrolidone excipients for the pharmaceutical industry 9th, -.
- Carr, A.G., Mammucari, R., Foster, N.R., 2010. Solubility and micronization of griseofulvin in subcritical water. *Ind. Eng. Chem. Res.* 49, 3403–3410. doi:10.1021/ie901189r
- Chiou, W.L., Riegelman, S., 1971. Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* 60, 1281–1302. doi:10.1002/jps.2600600902
- Coleman, M.M., Skrovanek, D.J., Hu, J., Painter, P.C., 1988. Hydrogen bonding in polymer blends . 1 . FTIR studies of urethane-ether blends *Hydrogen Bonding in Polymer Blends . 1 . FTIR Studies of Urethane-Ether Blends* 21, 59–65. doi:10.1021/ma00179a014



- Craig, D.Q.M., 2002. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm.* 231, 131–144. doi:10.1016/S0378-5173(01)00891-2
- Da Fonseca Antunes, A.B., De Geest, B.G., Vervaet, C., Remon, J.P., 2013. Solvent-free drug crystal engineering for drug nano- and micro suspensions. *Eur. J. Pharm. Sci.* 48, 121–129. doi:10.1016/j.ejps.2012.10.017
- Datta, A., Saha, N., Ghosh, S., Debnath, S., 2011. Development , characterization and solubility study of solid dispersion of nifedipine hydrochloride by solvent evaporation method using poloxamer 407 2–8.
- Dell, S.M., Hope, N., Us, P.A., Tuason, D.C., Modliszewski, J.J., Us, N.J., Ruszkay, T.A., Us, D.E., Werner, D.E., Grove, W., Us, P.A., May, U.S., Lachman, L., Lieberman, H., Kanig, J., 2004. ( 12 ) United States Patent 101.
- Djuris, J., Ioannis, N., Ibric, S., Djuric, Z., Kachrimanis, K., 2014. Effect of composition in the development of carbamazepine hot-melt extruded solid dispersions by application of mixture experimental design. *J. Pharm. Pharmacol.* 66, 232–243. doi:10.1111/jphp.12199
- G. Van Den Mooter, 2009. Solid dispersions as a formulation strategy for poorly soluble compounds. *Annu. Symp. Finish Soc. Phys. Pharm.* 1, 1–37.
- Ghodake, P.P., Karande, K.M., Osmani, R.A., Bhosale, R.R., Harkare, B.R., Kale, B.B., 2013. Mouth Dissolving Films : Innovative Vehicle for Oral Drug Delivery 2, 41–47.
- Good, D.J., Rodríguez-Hornedo, N., 2009. Solubility Advantage of Pharmaceutical Cocrystals. *Cryst. Growth Des.* 9, 2252–2264.
- Khadka, P., Ro, J., Kim, H., Kim, I., Kim, J.T., Kim, H., Cho, J.M., Yun, G., Lee, J., 2014. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. *Asian J. Pharm. Sci.* 9, 1–13. doi:10.1016/j.ajps.2014.05.005
- Kianfar, F., Antonijevic, M.D., Chowdhry, B.Z., Boateng, J.S., 2011. Formulation development of a

carrageenan based delivery system for buccal drug delivery using ibuprofen as a model drug  
2011, 582–595. doi:10.4236/jbnb.2011.225070

Koland, M., Sandeep, V., Charyulu, N., 2010. Fast Dissolving Sublingual Films of Ondansetron Hydrochloride: Effect of Additives on in vitro Drug Release and Mucosal Permeation. *J. Young Pharm.* 2, 216–222. doi:10.4103/0975-1483.66790

Kolter K, Karl M, G. a, 2012. Hot-Melt Extrusion with BASF Pharma Polymers. BASF. Chem. Co. 192.

Kolter, K., 2013. Soluble Kollidon ® grades. BASF, Pharma Ingredients Serv. Extr. 1–12.

Ku, M.S., 2008. Use of the Biopharmaceutical Classification System in early drug development. *AAPS J.* 10, 208–212. doi:10.1208/s12248-008-9020-0

Lan, Y., Ali, S., Langley, N., 2010. Poloxamers as Solubilizing Agents in Solid Dispersions 500.

Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* 50, 47–60. doi:10.1016/S0939-6411(00)00076-X

Lim, H., Howland, H., Fahmy, R., Hoag, S.W., 1971. Solubility Enhancement of Poorly Water Soluble Drug using a Novel Polymeric Solubilizer ( Soluplus ). Office 60, 21201.

Lippens, E., Swennen, I., Gironès, J., Declercq, H., Vertenten, G., Vlaminck, L., Gasthuys, F., Schacht, E., Cornelissen, R., 2013. Cell survival and proliferation after encapsulation in a chemically modified Pluronic(R) F127 hydrogel. *J. Biomater. Appl.* 27, 828–39. doi:10.1177/0885328211427774

Medarević, D.P., Kachrimanis, K., Mitrić, M., Djuriš, J., Djurić, Z., Ibrić, S., 2015. Dissolution rate enhancement and physicochemical characterization of carbamazepine-poloxamer solid dispersions. *Pharm. Dev. Technol.* 1–9. doi:10.3109/10837450.2014.996899

Michael, E., 2007. Aulton ' s Pharmaceutics : The Design and Manufacture of Medicines.

- Mike Evangelista, Nathan Haden, A.J., 2015. Hydrophilic and Hydrophobic Properties of Dissolvable Thin Film 1–6.
- Naik, J.B., Mokale, V.J., 2014. Preparation of Freeze-dried Solid Dispersion Powder using Mannitol to Enhance Solubility of Lovastatin and Development of Sustained Release Tablet Dosage Form 1, 11–26.
- Pina, M.F., Zhao, M., Pinto, J.F., Sousa, J.J., Craig, D.Q.M., 2014. The influence of drug physical state on the dissolution enhancement of solid dispersions prepared via hot-melt extrusion: A case study using olanzapine. *J. Pharm. Sci.* 103, 1214–1223. doi:10.1002/jps.23894
- Pina, M.F., Zhao, M., Pinto, J.F., Sousa, J.J., Craig, D.Q.M., 2014. The influence of drug physical state on the dissolution enhancement of solid dispersions prepared via hot-melt extrusion: A case study using olanzapine. *J. Pharm. Sci.* 103, 1214–1223. doi:10.1002/jps.23894
- Qi, S., Moffat, J.G., Yang, Z., 2013. Early stage phase separation in pharmaceutical solid dispersion thin films under high humidity: improved spatial understanding using probe based thermal and spectroscopic nano-characterisation methods. *Mol. Pharm.* doi:10.1021/mp300557q
- Raimi-Abraham, B.T., Mahalingam, S., Davies, P.J., Edirisinghe, M., Craig, D.Q.M., 2015. Development and Characterization of Amorphous Nanofiber Drug Dispersions Prepared Using Pressurized Gyration. *Mol. Pharm.* acs.molpharmaceut.5b00127. doi:10.1021/acs.molpharmaceut.5b00127
- Raimi-Abraham, B.T., Mahalingam, S., Edirisinghe, M., Craig, D.Q.M., 2014. Generation of poly(N-vinylpyrrolidone) nanofibres using pressurised gyration. *Mater. Sci. Eng. C* 39, 168–176. doi:10.1016/j.msec.2014.02.016
- Reintjes, T., 2011. 10. Kolliphor™ P grades (Poloxamers). Solubility Enhanc. with BASF Pharma Polym. Solubilizer Compend. 103–111.
- Roo, D., 1913. Review Relationship between P-glycoprotein and second-generation antipsychotics

Review 1193–1211.

Rumondor, A.C., Taylor, L.S., 2010. Effect of polymer hygroscopicity on the phase behavior of amorphous solid dispersions in the presence of moisture. *Mol. Pharm.* 7, 477–490.

doi:10.1021/mp9002283

Serajuddin, A.T.M., 1999. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.* 88, 1058–1066.

doi:10.1021/js9804031

Shah, B., Kakumanu, V.K., Bansal, A.K., 2006. Analytical techniques for quantification of amorphous/crystalline phases in pharmaceutical solids. *J. Pharm. Sci.* 95, 1641–1665.

doi:10.1002/jps.20644

Shah, N.; Sandhu, H.; Choi, D.S.; Cholkshu, H.; Malick, A.W., 2014. *Amorphous Solid Dispersions Theory and Practice.*

Shamma, R.N., Basha, M., 2013. Soluplus: A novel polymeric solubilizer for optimization of Carvedilol solid dispersions: Formulation design and effect of method of preparation. *Powder Technol.* 237, 406–414. doi:10.1016/j.powtec.2012.12.038

Silverstein M.Robert, Webster X. Francis, K.J.D., 2005. *Spectrometric Identification of Organic Compounds.* Org. Chem.

Sinko, P.J., 2011. *Martin's physical pharmacy and pharmaceutical sciences Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical sciences.* Martin's Phys. Pharm. Pharm.

Sci. 182–196.

Stojanovic, Z., 2012. *Determination of Particle Size Distributions by Laser Diffraction.*

Taylor, M.J., Tanna, S., Sahota, T., 2010. In vivo study of a polymeric glucose-sensitive insulin delivery system using a rat model. *J. Pharm. Sci.* 99, 4215–4227. doi:10.1002/jps

Thakuria, R., Nangia, A., 2011. Polymorphic form IV of olanzapine. *Acta Crystallogr. Sect. C Cryst. Struct. Commun.* 67, 461–463. doi:10.1107/S0108270111043952

Vasanthavada, M., Tong, W.Q., Joshi, Y., Kislalioglu, M.S., 2005. Phase behavior of amorphous molecular dispersions II: Role of hydrogen bonding in solid solubility and phase separation kinetics. *Pharm. Res.* 22, 440–448. doi:10.1007/s11095-004-1882-y

Vyas, V., Sancheti, P., Karekar, P., Shah, M., Pore, Y., 2009. Physicochemical characterization of solid dispersion systems of tadalafil with poloxamer 407. *Acta Pharm.* 59, 453–461. doi:10.2478/v10007-009-0037-4

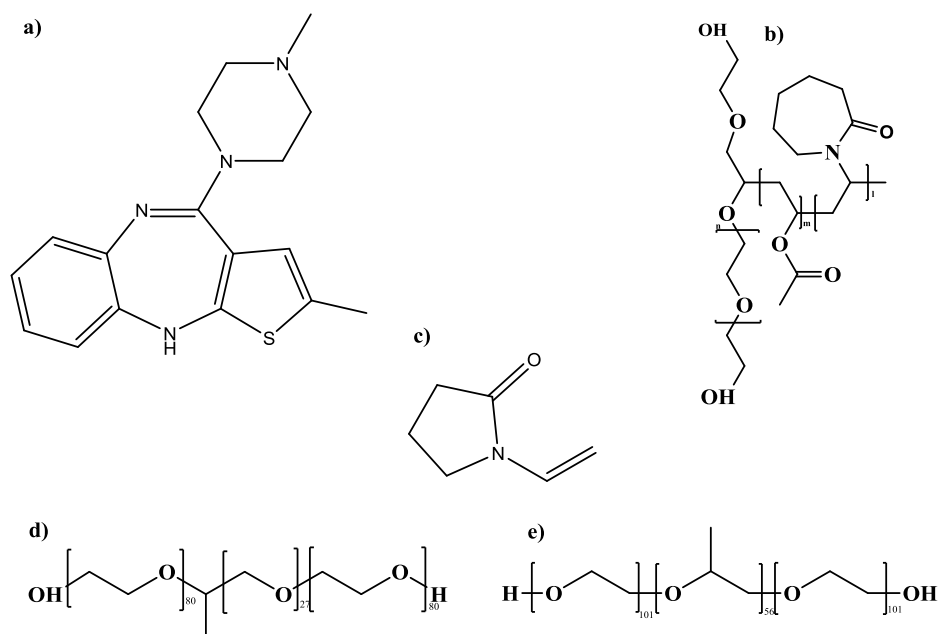
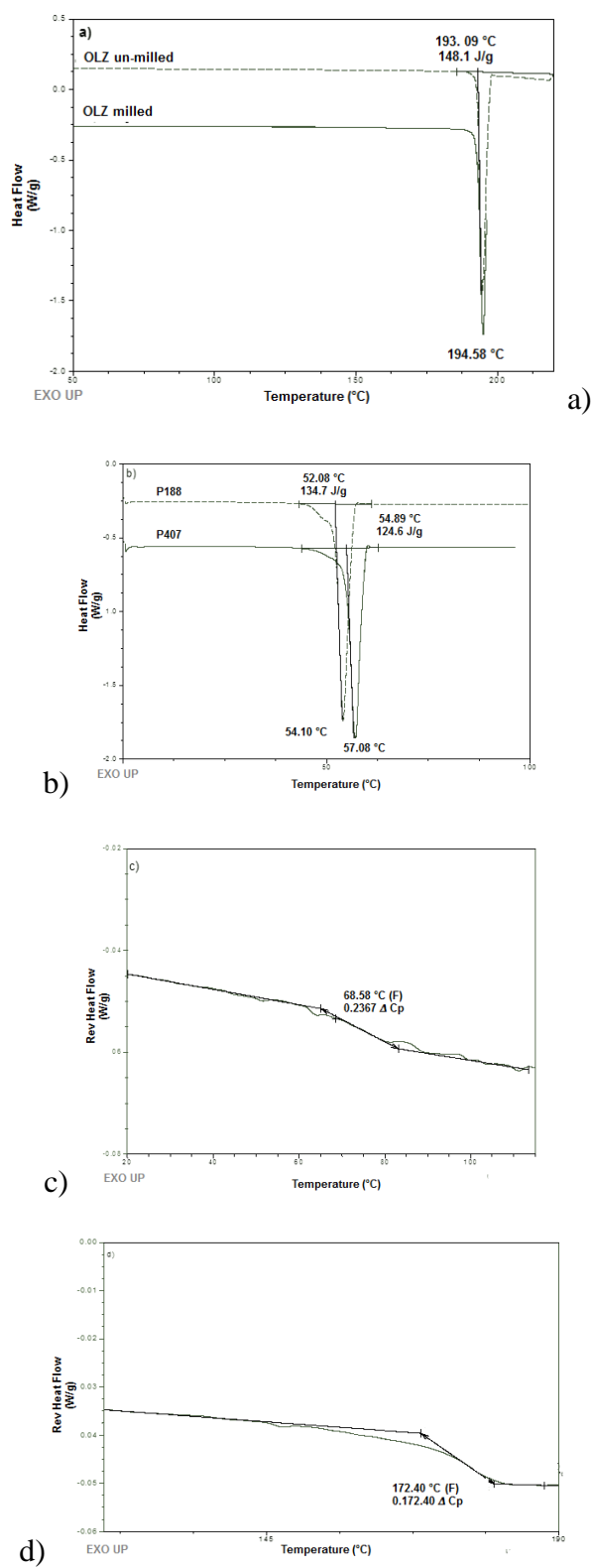
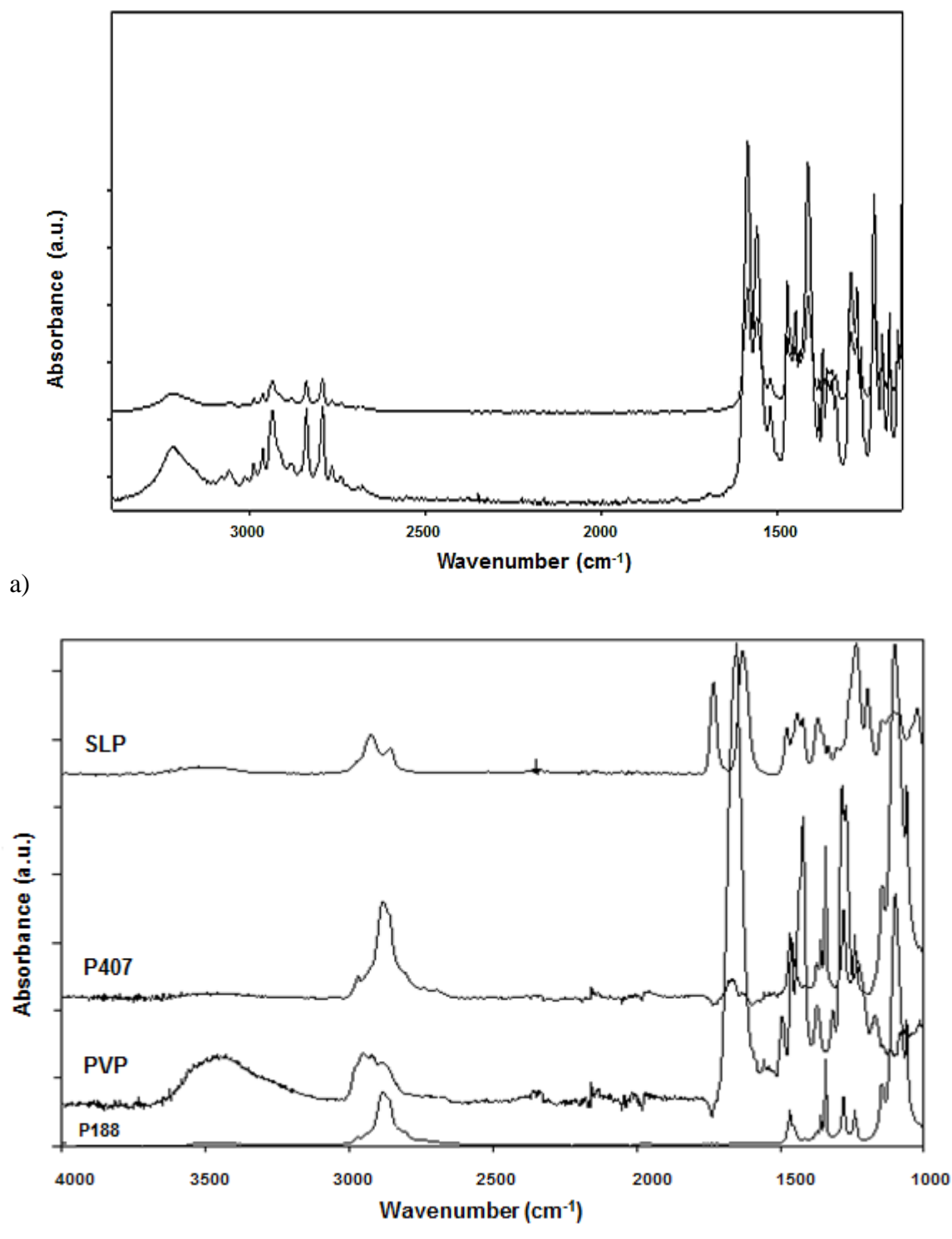


Figure 1. Chemical structure of the different materials used in this study: a) OLZ; b) SLP; c) PVP; d) P188; e) P407.

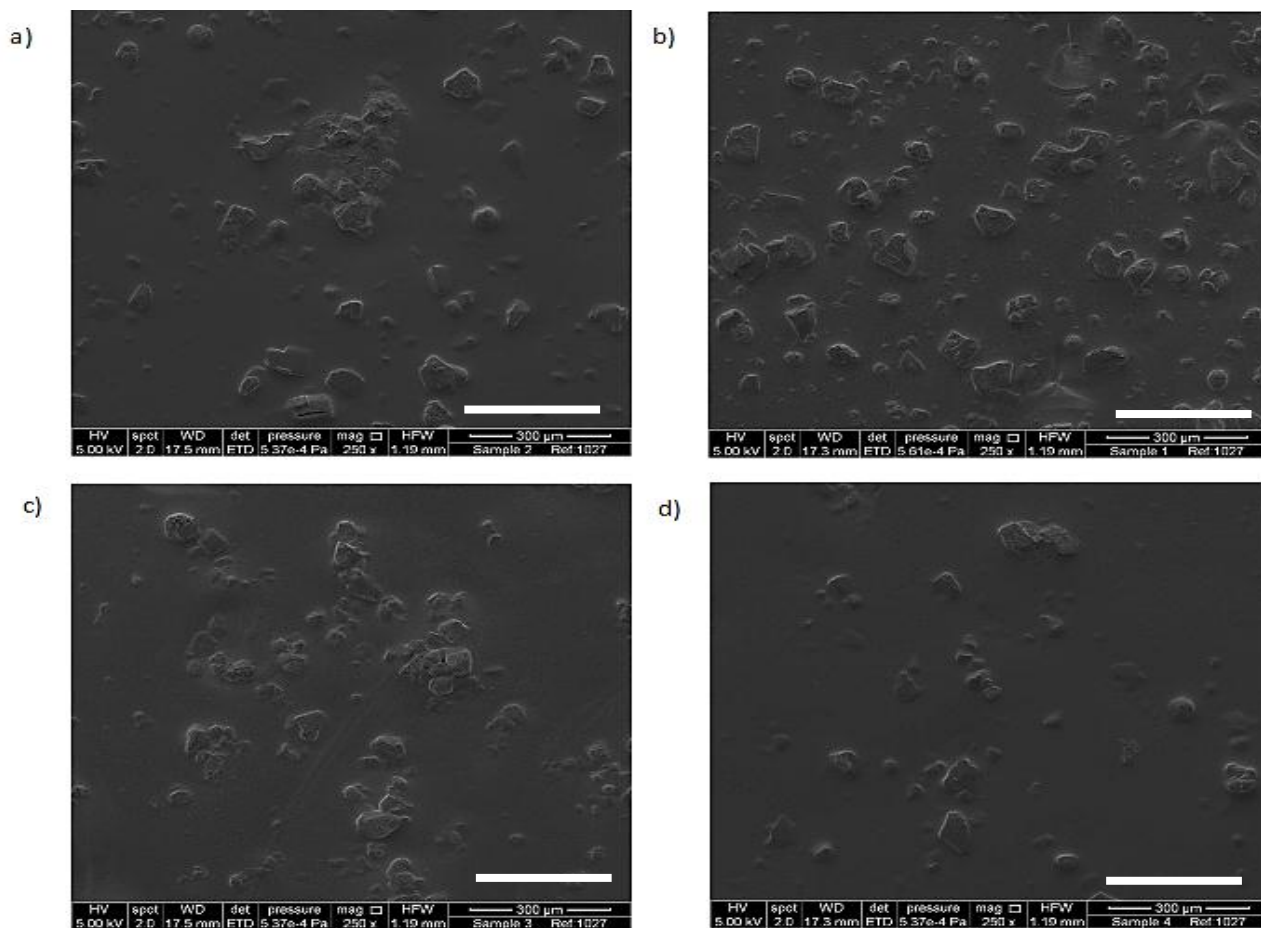


**Figure 2.** Representative DSC and MTDSC traces of a) milled and un-milled OLZ; b) P188 and P407 c) SLP and d) PVP.

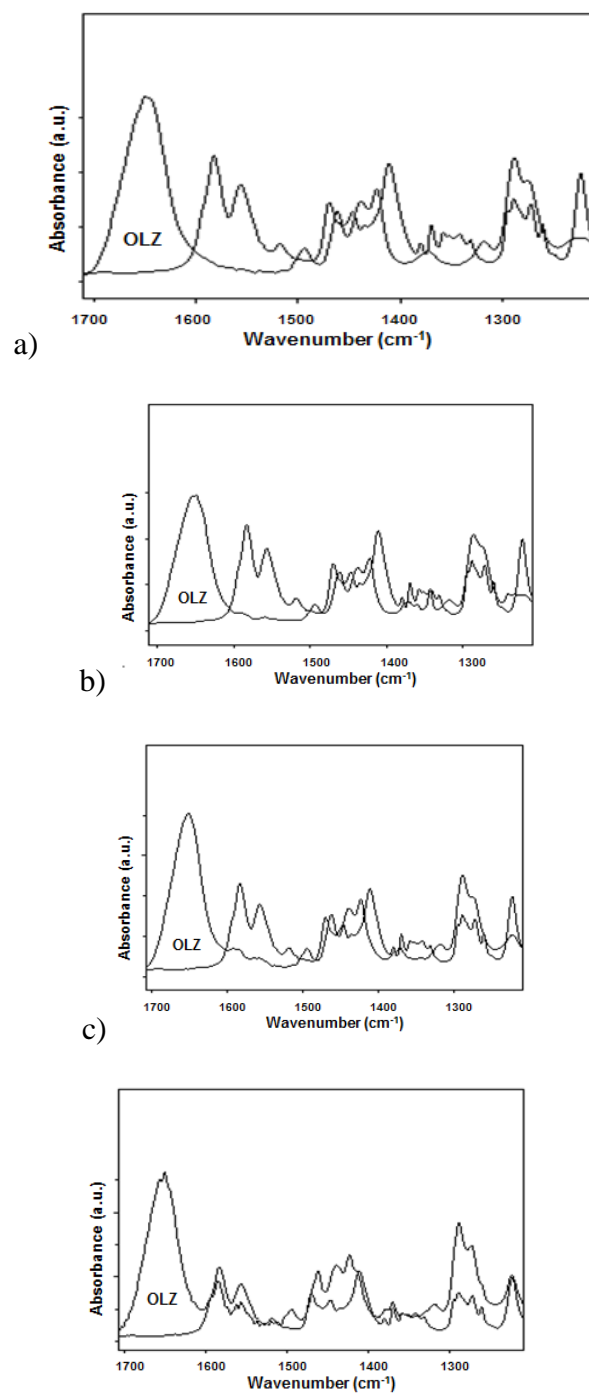


**Figure 3.** ATR-FTIR spectra of a) milled (top) and un-milled (bottom) OLZ and b) P407, SLP, P188 and PVP

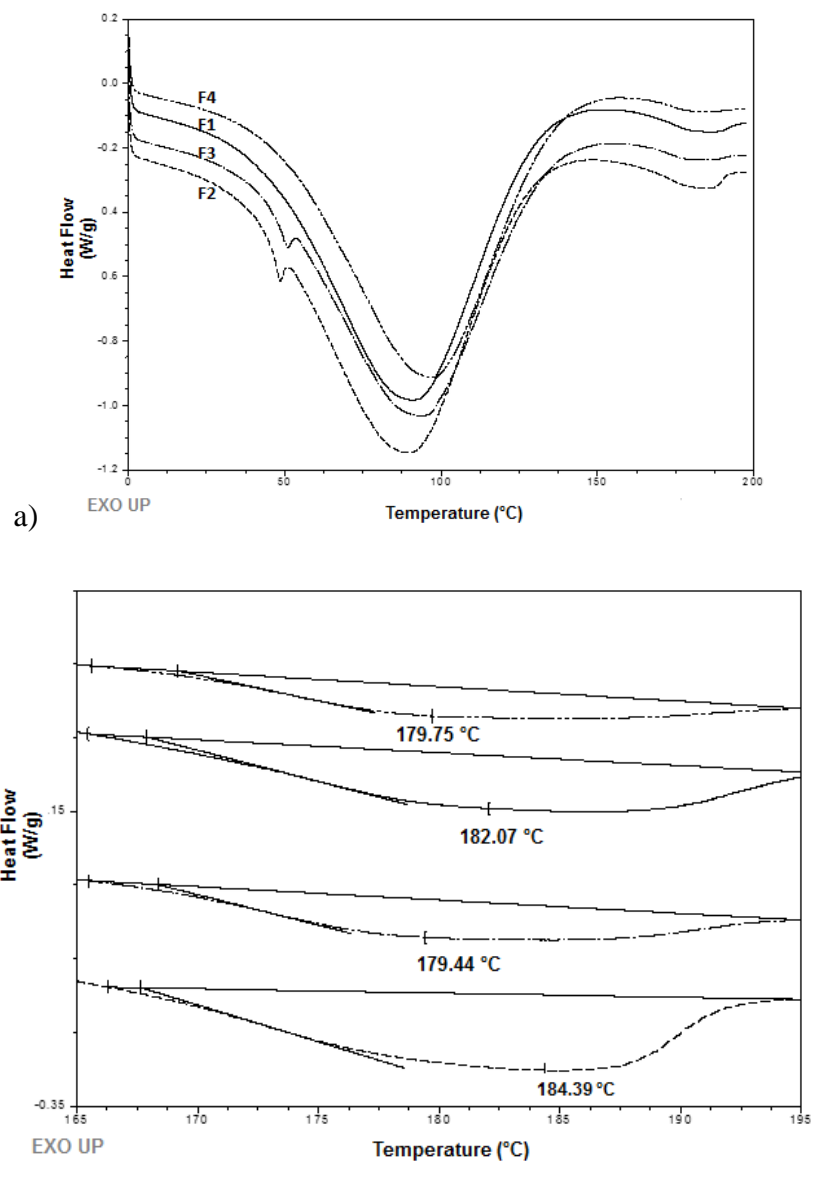




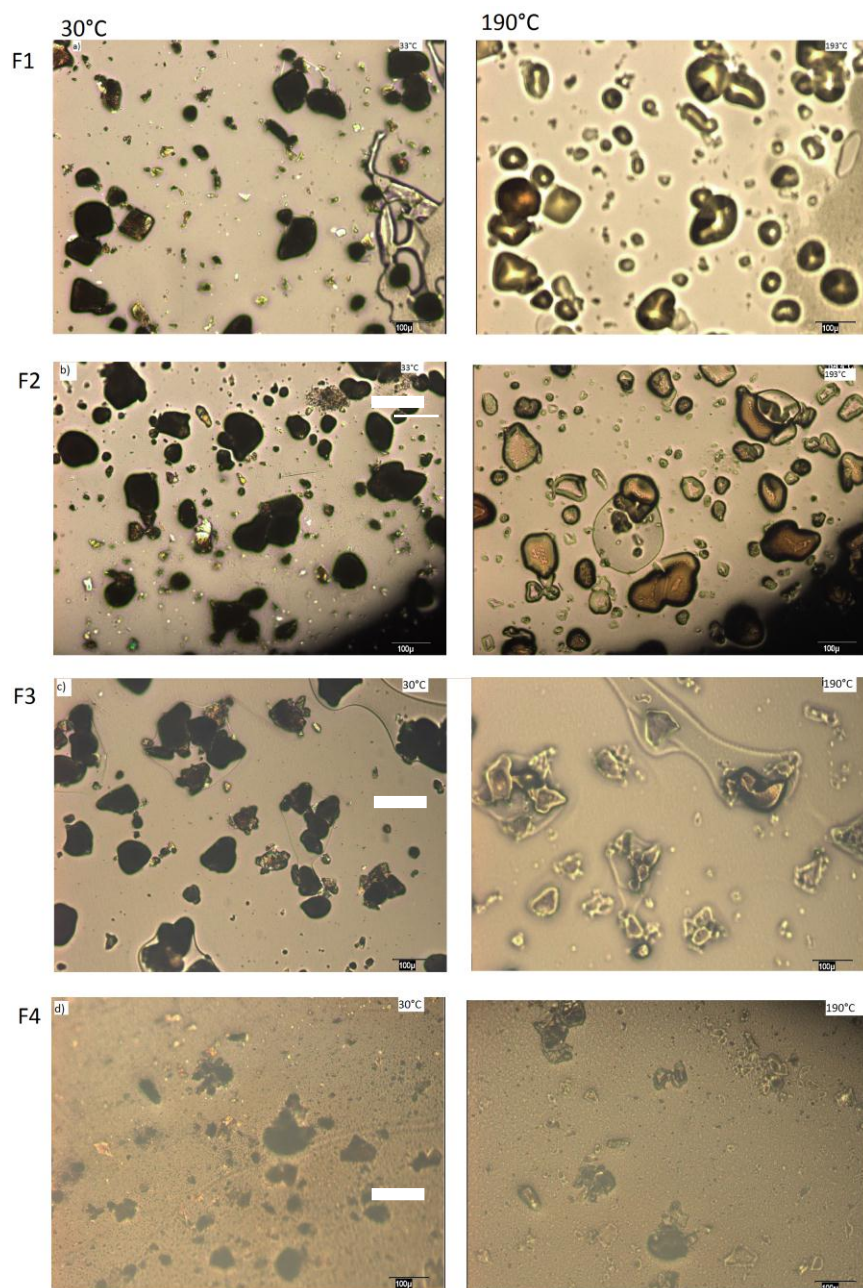
**Figure 4.** SEM microphotographs of a) F1 b) F2 c) F3 d) F4. Scale bars are shown in each image.



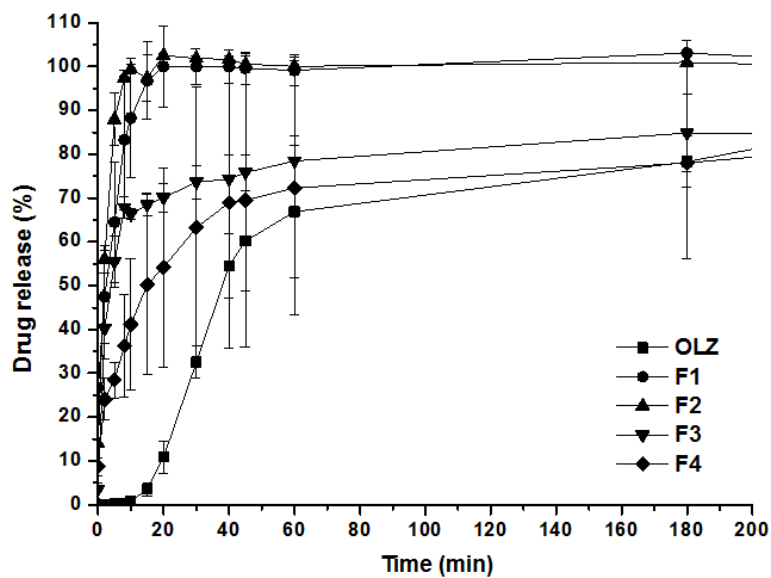
**Figure 5.** ATR-FTIR spectra of OLZ and a) F1, b) F2, c) F3 and d) F4



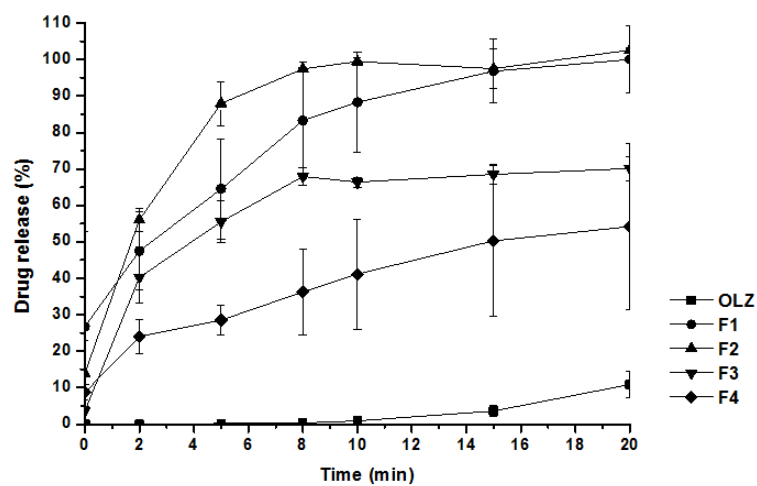
**Figure 6.** DSC heat flow signal of a) F1, F2, F3 and F4 and b) zoom-in of the thermal events occurring at high temperatures (165 – 195 °C)



**Figure 7.** Hot stage microscopy images of each formulation at room temperature (30 °C) and at 190 °C. Scale bar corresponds to 100 μm.



a)



b)

**Figure 8.** *In vitro* dissolution studies of a) OLZ, F1, F2, F3 and F4 formulations and b) enlargement of the first 20 minutes of the study.

**Table 1. Composition of OLZ, PVP, P188, P407 and SLP used to prepare SMD pharmaceutical films.**

<b>Formulation</b>	<b>Ingredient (% w/w)</b>				
	<b>OLZ</b>	<b>PVP</b>	<b>P188</b>	<b>P407</b>	<b>SLP</b>
<b>F1</b>	10%	90%	-	-	-
<b>F2</b>	10%	85%	5%	-	-
<b>F3</b>	10%	85%	-	5%	-
<b>F4</b>	10%	85%	-	-	5%

**Table 2. Experimental thermal properties of OLZ, PVP, P188, P407 and SLP**

	$T_m$ (°C) onset	$T_m$ (°C)	$\Delta C_p$ (J/g°C)	$T_g$ (°C)	$\Delta C_p$ (J/g°C)
<b>OLZ</b>	$193.13 \pm 0.05$	$194.81 \pm 0.20$	$131.46 \pm 16.89$	$70.95 \pm 0.70$	$0.39 \pm 0.06$
<b>P188</b>	$52.18 \pm 0.10$	$53.95 \pm 0.18$	$138.40 \pm 2.65$	-	-
<b>P407</b>	$54.95 \pm 0.11$	$57.02 \pm 0.07$	$137.90 \pm 22.57$	-	-
<b>PVP</b>	-	-	-	172.40	$\pm 0.24 \pm 0.01$
				1.41	
<b>SLP</b>	-	-	-	$57.85 \pm 1.25$	$0.87 \pm 0.06$

**Table 3. ATR-FTIR and assignment for OLZ, PVP, P188, P407 and SLP**

Absorption band (cm <sup>-1</sup> )	Assignment (Borodko et al., 2006)
	(BASF, 2013) (Vyas et al., 2009) (Ali et al., 2005; Shamma and Basha, 2013) (Raimi-Abraham et al., 2014)
	<b>PVP</b>
2879	CH aliphatic stretch
1463	CN stretch
2952	CH asymmetric stretch
1656	C=O
1423 and 1284	C-C stretching vibration
	<b>P188</b>
2880	CH aliphatic stretching
1341	OH bend
1101 and 1060	C=O
	<b>P407</b>
1344	OH bend
1104	C-O stretch
	<b>SLP</b>
2926	aromatic CH stretching
1732 and 1633	C=O stretch
1477	C-O-C stretch



**Table 4. Particle size measurements of OLZ crystals in each formulation using SEM and LD.**

	Particle Size ( $\mu\text{m}$ )	
	SEM	LD
<b>F1</b>	$47.50 \pm 15.23$	$48.60 \pm 0.02$
<b>F2</b>	$48.41 \pm 14.78$	$58.30 \pm 0.01$
<b>F3</b>	$37.47 \pm 11.82$	$58.00 \pm 1.20$
<b>F4</b>	$40.99 \pm 12.26$	$42.20 \pm 0.45$