Stability Studies of Hot-Melt Extruded Ternary Solid Dispersions of Poorly-Water Soluble Indomethacin with Poly(vinyl pyrrolidone-co-vinyl acetate) and Polyethylene Oxide

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Abstract

This investigation aims to evaluate the effect of moisture and temperature on the physical stability and dissolution behaviour of hot-melt extruded binary and plasticised ternary solid dispersions. Poorly water-soluble indomethacin (IND), poly(vinyl pyrrolidone-co-vinyl acetate) (PVPVA) and plasticiser polyethylene oxide (PEO) were selected as model compounds. Extruded samples were stored with 40 °C, at 0 % and 75 % relative humidity (RH) for 12 weeks. Results confirmed that binary solid dispersions of PVPVA-IND were successfully prepared by twin-screw hot-melt extrusion producing amorphous single-phase systems. The inclusion of semi-crystalline PEO reduced the melt viscosity of the system acting as a processing aid during extrusion without modifying the glass transition temperature (T_g) of the final doses. Samples stored at low humidity levels exhibited a dissolution profile similar to the unannealed dispersions. Samples annealed at 75 % RH showed a decrease in the dissolution rate, likely related to phase separation due to the increase in molecular mobility after the water sorption. However, all the annealed samples showed a total release of IND, indicating that the dispersions were relatively stable up to 12 weeks.

Keywords:

Amorphous Solid Dispersions

Poly(vinyl pyrrolidone-co-vinyl acetate)

Polyethylene oxide

Indomethacin

Stability

Hot-melt extrusion

1. Introduction

One of the most accepted and popular strategies to improve the solubility of non-water soluble active pharmaceutical ingredients (APIs) is the formulation of amorphous solid dispersions (ASDs) using hydrophilic polymers as carriers and drug stabilisers. The transformation of the API to the amorphous state increases its apparent solubility and dissolution rate as solvent penetration is not prevented by an endothermic barrier attributed to the disruption of crystalline lattices. During dissolution, the carrier acts as a vehicle trapping the dispersed API in a high energy state, inhibiting its crystallisation and therefore maintaining the supersaturation in the medium for prolonged times (Guzmán et al., 2004; Hancock and Parks, 2000; Van Den Mooter, 2012).

Given the enormous potential of the use of ASDs, a full understanding of the physicochemical factors ruling the stability during storage and dissolution of these systems is still needed. Undesirable behaviours are often observed and have proven to be hard to control, e.g. phase separation, nucleation and drug recrystallisation during storage and when exposed to solvents (Jackson et al., 2015; Janssens and Van den Mooter, 2009; Lust et al., 2015; Serajuddln, 1999). Besides, not only there is a lack of understanding about the properties to control the stability of these systems; the relationship between the dissolution mechanisms with the properties of the carriers and drug is still being discussed (Chen et al., 2016; Punčochová et al., 2016).

Hot-melt extrusion (HME) is an attractive technique for the manufacturing of ASDs because of the continuous nature of the process and the elimination of the use of solvents (Vasconcelos et al., 2016). However, the application of temperature and high shear inherent to the process may represent a challenge when dealing with temperature-sensitive drugs. As an alternative to expanding the extrusion processing window, the inclusion of secondary excipients to act as plasticisers have been introduced. Including plasticisers into a HME system is often investigated to improve the processing of the doses and to modify their physicochemical properties, mechanical behaviour and dissolution profile (Hanada et al., 2018; Janssens et al., 2008a; LaFountaine et al., 2016; McGinity and Zhang, 2003). However, the stability of these multiphase systems may represent a disadvantage as phase separation and drug migration from one carrier to the other have been reported (Bley et al., 2010; Janssens et al., 2008b; Wang et al., 2005).

One of the elements that plays an essential role in the investigation of the stability of the ASDs is the hygroscopicity of the systems. The sorption of water, which may act as a plasticiser of the amorphous system, increases the molecular mobility allowing the agglomeration and recrystallisation of the API, losing the dissolution advantage of its amorphous configuration (Fung and Suryanarayanan, 2017; Liu et al., 2013).

This work investigates the stability of hot-melt extruded binary solid dispersions of poly(vinyl pyrrolidone-co-vinyl acetate) (PVPVA) and indomethacin (IND). IND is an acidic compound with a pKa of 4.5 and a poor aqueous solubility (2.5 –4 µg/ml). It is classified, according to the biopharmaceutical classification system (BCS), as a class II compound (low solubility and high permeability), being its poor solubility its only barrier for bioavailability. In addition, the API exhibits a high melting temperature, which favours the melt processing. The inclusion of polyethylene oxide (PEO) in the binary system was investigated to determine the effect of the addition of the semi-crystalline plasticiser on the processing and physical properties. Accelerated stability studies were conducted to investigate the effect of temperature and moisture on the phase behaviour and dissolution profile of the dispersions.

2. Materials and Methods

2.1. Materials

Copolymer Poly(vinylpyrrolidone-co-vinyl acetate) (PVPVA) in a ratio of 6:4 by mass, was purchased from BTC Chemical Distribution. Polyethylene oxide (PEO), molecular weight 600,000 was sourced by Sigma Aldrich. Poorly water-soluble indomethacin (IND), 1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid, was purchased from Tokyo Chemical Industry UK Ltd. Phosphorus (V) pentoxide (P_2O_5) and sodium chloride (NaCl) was purchased from Fluorochem and Sigma Aldrich respectively.

2.2. Methods

2.2.1. Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) analysis was carried out using a Perkin Elmer Pyris 6 DSC. Samples between 4 and 6 mg were accurately measured and placed into open aluminium pans. The samples were heated from room temperature to 200 °C using a heating rate of 10 °C/min. Calorimetry scans were performed under a nitrogen atmosphere with a steady flow of 20 ml/min to prevent oxidation. Samples were tested in triplicates.

The degree of crystallinity of the PEO was calculated using the Equation 1 where χ_c is the degree of crystallinity, ΔH_m^o the heat of fusion of the 100 % crystalline material, ΔH_m the heat of fusion of the sample and *w* the weigh fraction.

$$\chi_c = \frac{\Delta H_m}{\Delta H_m^o w} 100\% \qquad \text{Equation 1}$$

2.2.2. Hot-Melt Extrusion (HME)

Hot-melt extrusion was performed on a bench-top Prism™ twin screw co-rotating extruder with 16 mm diameter screws and a 25:1 length to diameter ratio. Physical mixtures were fed at a rate of 13 g/min using an automatic feeder. The temperature profile from the feeding zone to die was 95 °C / 115 °C / 140 °C / 160 °C for the processing of the binary amorphous dispersions. With the inclusion of the plasticiser, the temperature profile was reduced by 10 °C. The composition of the ASD formulations is presented in Table 1.

Table 1: Drug/Carriers percentages of the HME processed formulations.

Formulation	Content % (w/w)		
	PVPVA	PEO	IND
PVPVA-7.5IND	92.5	-	7.5
PVPVA-15IND	85.0	-	15.0
PVPVA-10PEO-7.5IND	82.5	10.0	7.5
PVPVA-10PEO-15IND	75.0	10.0	15.0

2.2.3. Rheology Studies

An oscillatory rheometer TA Discovery Hybrid Rheometer 2 was used for the rheology studies. The instrument was calibrated to a geometry of 25 mm diameter steel plate. An amplitude of 5 % was applied and previously verified by an amplitude sweep at a frequency of 1.0 Hz. Oscillation temperature ramps were conducted from 120 °C to 200 °C with a heating rate of 5 °C/min. Samples were loaded on the hot plate and soaked at the initial temperature for 120 s. Tests were conducted with a gap height of 1 mm.

2.2.4. Temperature and Humidity Stability Studies

Accelerated stability studies were performed following the guideline set by the European Agency for the Evaluation of Medical Products (EMEA, 2003). Sealed containers with P_2O_5 and a saturated solution of NaCl for 0 % and 75 % relative humidity (RH) levels respectively

were prepared (Rockland, 1960). Extruded solid dispersions were placed inside the containers and stored in an oven at 40 °C for 12 weeks. The collected samples were dried in a desiccator at 20 °C and 0 % RH for one week before testing.

2.2.5. High-Performance Liquid Chromatography (HPLC)

The concentration and chemical purity of indomethacin in the extruded doses was determined using HPLC. Analysis were carried out using a system consisting of a Waters Alliance e2695 separations module combined with a Waters 2487 dual λ absorbance detector and a A 150 mm x 4.6 mm Thermo Scientific ODS Hypersil column with a particle size of 5 μm. The mobile phase was a solution of 0.01 M monobasic sodium phosphate and 0.01 M dibasic sodium phosphate in HPLC grade acetonitrile (Romil) and distilled water 1:1. Both salts were obtained from Sigma Aldrich. A flow rate of 1 mL/min was maintained during the procedure, the detector was set at 254 nm, and the samples injection volume was 20 μm. A filtered solution of acetonitrile and water 1:1 was used to wash the needled between injections. Before testing, samples were diluted in the mobile phase to inhibit the precipitation of the drug and filtered using 0.20 mm syringe filters. Samples taken from five different points of the total of specimens were accurately weighted and dissolved in a known volume of the mobile phase. Before testing, solutions were filtered using 0.20 mm syringe filters.

2.2.6. *In-vitro* Dissolution Studies

In-vitro drug dissolution studies were performed using a Distek 50947 dissolution apparatus I (basket method). Tests were carried out in 900 mL of dissolution medium at 37.0 ± 0.5 °C with baskets rotating at 50 rpm. The dissolution behaviour of the samples was evaluated in pH 1.2 hydrochloric acid buffer and pH 6.8 phosphate buffer media to simulate the digestive tract. Samples of a volume of 2 ml were taken from the dissolution vessels at predetermined time intervals and immediately replaced with fresh dissolution medium. IND concentration was measured using Shimadzu UV-Visible Spectrophotometer, model UV-1280 at 320 nm.

3. Results

3.1. Thermal Characterisation

Characterisation of the solid state of the binary and ternary ASDs of PVPVA, IND and PEO were performed using DSC. Thermograms of the pure components and the hot-melt extruded

solid dispersions are presented in Figure 1. The thermogram of crystalline IND showed an endothermic peak at 164 ± 1 °C corresponding to the melting endotherm of the stable ϒ-form (Hancock and Parks, 2000; Shamblin et al., 1999). Thermograms of all the solid dispersions analysed showed the complete disappearance of this melting endotherm indicating the apparent complete transformation of IND from the crystalline to the amorphous state (Hanada et al., 2018). In the low-temperature region of the thermograms, the glass transition temperature (T_g) of the amorphous IND was recorded at 45.5 ± 0.4 °C. A separated T_g attributable to IND was not detected in the thermograms of the solid dispersions suggesting a good level of mixing and the absence of a separated phase rich in amorphous IND (Purohit and Taylor, 2015).

The thermogram of pure PEO showed an endothermic peak at 71 ± 1 °C with an enthalpy of fusion (ΔH_m) of 186 ± 26 J/g corresponding to the melting of its crystalline fraction. Assuming an enthalpy of fusion of the 100% crystalline PEO of 210 J/g, the material exhibits a degree of crystallinity of 70 ± 10 % (Apicella et al., 1993). The same endotherm attributed to the melting of the PEO crystalline fraction was detected in the thermograms of the ternary dispersions at 63.4 ± 0.4 °C and with an average ΔH_m of 9 ± 1 J/g. Considering the concentration of PEO in the dispersions, it is estimated that 43 ± 5 % of the plasticiser present is in the crystalline form. These results confirm that in the ternary solid dispersions, the PEO is in the semicrystalline state with some level of compatibility either with the PVPVA-IND system or between the drug and the plasticiser due to the reduction of the melting temperature and enthalpy of fusion.

Thermal characterisation of the binary ASDs showed a single glass transition temperature in between the T_g's of the drug and the pure main carrier PVPVA, suggesting the existence of a single phase amorphous system (see Figure 1b). In the case of the ternary dispersions, this miscible system coexists with a small fraction of crystalline PEO as shown in their thermograms (Figure 1). The values of the glass transition temperature of the solid dispersions are presented in Table 2. It can be noted that the inclusion of the plasticiser to the PVPVA-IND system did not decrease the glass transition temperature of the solid dispersions. This may be due to the relatively high molecular weight of the PEO, the low percentage dose in the formulations, and possibly to the presence of crystallites, which could contribute to the restriction of molecular motions (Struik, 1987a, 1987b).

Table 2: Glass transition temperature of binary and ternary solid dispersions of PVPVA-IND and PEO, n=3.

Formulation	T_g (°C)
PVPVA	108.3 ± 0.5
PVPVA-7.5IND	85 ± 2
PVPVA-15IND	81 ± 1
PVPVA-10PEO-7.5IND	85 ± 1
PVPVA-10PEO-15IND	81 ± 2
Amorphous IND	45.5 ± 0.4

Nevertheless, despite the unmodified glass transition temperature values, the inclusion of PEO improved the processability of the dispersions, lowering the processing temperatures and lowering the fragility of the extrudates. The improvement in the processability achieved with the inclusion of the plasticiser is represented by the change of complex viscosity reported in Figure 2. The complex viscosity curves showed a significant drop in the melt viscosity at 120 °C from 181 kPa.s for the binary dispersion with 7.5 % of IND to 121 kPa.s for the plasticised one. The same behaviour was observed for the formulations with 15 % IND passing from a viscosity value of 94 kPa.s for the unplasticised dispersion to 49 kPa.s of the ternary one. It is also important to note that the lager drop in complex viscosity is achieved with the inclusion of IND, showing that the smaller molecule acts as the main plasticiser and processing aid during processing (De Brabander et al., 2002; Lyons et al., 2007).

3.2. Dissolution Studies

Prior to the evaluation of the dissolution profile of the dispersions, the content of indomethacin and its chemical purity was confirmed using HPLC. During the manufacture of the ASDs using HME, due to the high shears and temperatures applied to the systems, the drug is prone to degradation. It is then important to determine the effect of the extrusion step on the distribution and stability of the drug. The IND chromatographs obtained from the extruded solid dispersions showed a single peak with an elution time equal to the standard solutions at 1.772 ± 0.007 min (see Figure 3). The results corroborate the chemical integrity of the active ingredient after the thermal and mechanical treatment applied during processing. The concentration of IND on the different dispersions was quantified to evaluate the drug uniformity of content on the extrudates. The results are presented in Table 3 and these values

obtained for the real content of indomethacin were used for the calculation of the dissolution studies.

Table 3: Uniformity of indomethacin content of hot-melt extruded solid dispersions of PVPVA-PEO-IND, n=5.

Formulation	Nominal IND (%)	Real IND (%)
PVPVA-7.5IND	7.5	8.1 ± 0.4
PVPVA-15IND	15	16 ± 2
PVPVA-PEO-7.5IND	7.5	8.0 ± 0.4
PVPVA-PEO-15IND	15	16 ± 2

IND is an ionisable weekly acidic compound with a pKa of 4.5 whose aqueous solubility increases from acidic to basic media. The dissolution behaviour of IND was evaluated in an acidic (pH 1.2) and a neutral (pH 6.8) medium to simulate the digestive tract and to assess the impact of the pH on the solubility enhancement of the formulated dispersions (Varma et al., 2011; Zelenák et al., 2018).

The dissolution behaviour of ASDs depends on the drug concentration. Typically, for low drug loads, dissolution occurs quickly, and a highly supersaturated solution is generated in which drug nano-precipitates, in the amorphous or crystalline form, may coexist and be stabilised by the polymer. The dissolution mechanism is then controlled by the water-soluble carrier (Craig, 2002). A second scenario involves a slower dissolution due to higher drug loads resulting in a more sustained release. Water continuously penetrates the solid dispersion particles, mobility increases and phase separation occurs. If in the surface of the undissolved particles the drug remains amorphous due to the stabilisation effect of the polymer, the drug concentration in the media would be equal to the solubility of the amorphous drug (Huang and Dai, 2014).

The results of the dissolution studies of the unannealed solid dispersions in pH 1.2 are shown in Figure 4. In general, dispersions with a content of 7.5 % of IND exhibited a fast and complete drug release which may be related to the low drug concentration. The formulation with PEO presented a slightly slower dissolution rate (50 % at 10 min) when compared with the binary dispersion (75 % at 10 min). This slower dissolution rate, characteristic of high molecular weight PEO's, is related to its semi-crystalline state which provides a more controlled release due to the mechanism of crystals' dissolution (Cantin et al., 2016; Ma et

al., 2014; Mallapragada and Peppas, 1997). After the first 30 min, the precipitation of the drug from the dissolution solution was recorded for both binary and ternary dispersions. This behaviour has been reported for other IND systems (Chokshi et al., 2008; Liu et al., 2010). It is presumed to be caused by the transformation of the metastable amorphous IND in the supersaturated solution, where the drug molecules are prone to aggregate and nucleate. In the acidic solution, IND is not ionised due to its higher pKa, favouring the self-association and subsequent precipitation of the IND molecules.

During the dissolution in acidic conditions, dispersions with higher content of IND failed to disintegrate, forming solid rich in amorphous drug, a phenomenon linked to the drug pH controlled dissolution mechanism. It has been reported that, in acidic conditions and concentrations of at least 15 % of IND and higher, the doses form a hydrophobic shell, rich in amorphous drug, which prevents the drug release from the inside of the dose (Ewing et al., 2014; Tres et al., 2016). It is presumed that at lower IND contents, the drug-polymer interactions contributed to the stabilisation of the drug and the polymer acted as a vehicle for its dissolution, therefore, the dissolution mechanism is controlled by the carrier. At higher IND concentrations, hetero-interactions formed between IND molecules are favoured, preventing the disintegration of the dose. The dissolution mechanism is then drug controlled and, as the pH is lower than the pKa of IND, no drug dissolution was detected.

The dissolution behaviour of the dispersions in the pH 6.8 medium is shown in Figure 5. The binary dispersions showed an instant release of IND for both drug concentrations reaching and maintaining a release >90 % after 15 minutes. In opposition to the dissolution in pH 1.2 medium, the dispersions with 15 % IND showed a complete disintegration due to the neutral pH, higher than the pKa of the drug. Ternary dispersions showed a slower drug release due to the semi-crystalline state of the plasticiser, which represents a possibility for the design of controlled release doses while improving its melt processability at the manufacturing stage.

3.3. Humidity and Temperature Stability

To investigate the effect of temperature and humidity on the stability of the extruded solid dispersions, samples were stored at controlled conditions of 40 °C and 0 % and 75 % RH levels for 12 weeks. The change of the physical appearance of the extrudates is shown in Figure 6. It is observed that after 12 weeks, samples stored at 0 % RH did not change their physical appearance. In contrast, samples stored at 75 % RH softened and flowed, forming a

translucent shiny malleable solid. This transformation has been reported before for PVPVA after equilibration under similar conditions (Liu et al., 2013). It seems apparent that high levels of RH, due to the hygroscopic character of the carriers, increased the mobility of the system and compromised their physical stability. Phase separation, a behaviour reported for a similar system of PVPVA and PEG, was not visually detected as the materials maintained their homogeneity at the macroscopic level probably due to the high molecular weight of PEO in comparison with PEG (Bley et al., 2010).

3.3.1. Thermal Analysis of Annealed Dispersions

The thermal analysis of the stability samples was performed to investigate the physical state of the dispersions and their ability to maintain IND in the amorphous state over time, humidity and temperature. The DSC thermograms of the binary solid dispersions unannealed and stored under different conditions are shown in Figure 7. Systems stored at 0 % RH levels showed to be effective in the stabilisation of the amorphous IND as no sign of crystallisation could be detected for either of the drug concentrations. With the increase of the RH levels, a small endothermic indentation was noted around 175 °C attributed to the possible formation of a small fraction of oriented IND molecules. It seems apparent that the moisture absorption, due to the hygroscopic character of PVPVA, favours the molecular mobility of the system and increases the risk of drug precipitation (Weuts et al., 2005). However, the reconversion to the crystalline state is minimal, possibly due to the high miscibility between PVPVA and IND and the presence of intermolecular interactions that are also responsible for the stabilisation of the IND in the amorphous state (Chauhan et al., 2014; Pezzoli et al., 2018; Van Duong and Van den Mooter, 2016).

Analysis of the ternary solid dispersions equilibrated at 0 % RH levels showed a similar stabilising effect of IND to the binary systems. In Figure 8, it is observed that in the high-temperature region of the thermograms there is no sign of the recrystallisation of the drug. Similarly, dispersions stored at high humidity levels exhibited a remarked stabilisation ability as only the dispersions with 15 % IND showed a small endothermic disruption around 177 °C. For both of the systems evaluated, a progressive increase of the melting temperature and enthalpy of fusion of the PEO semi-crystalline fraction was detected from the unannealed samples to the annealed ones at 0 % and 75 % RH. At 40 °C, the amorphous fraction of the plasticiser is in the rubbery state (above its T_g but below its melting point) allowing the occurrence of cooperative movements of the polymer chains leading to their reorientation. As

a consequence, the structure of the PEO phase may become more ordered. This process, evidenced by the increase of the melting endotherm, has been previously reported for PEO at similar annealing conditions (Kiss et al., 2006). It is then proposed that the equilibration at temperatures higher than the T_g of PEO, caused the reorientation of the PEO amorphous fraction causing crystal growth. This effect was intensified in the high humidity environment due to the high hygroscopicity of both PVPVA and PEO which increased their mobility.

3.3.2. Dissolution Studies of Annealed Dispersions

The dissolution studies of the solid dispersions stored at 40 °C and 0 % RH for 12 weeks are presented in Figure 9. The results exhibited similar dissolution profiles to the results reported for the same unannealed formulations in the neutral pH medium (Figure 5). The results obtained confirmed the thermal analysis (Figure 7 and 8), suggesting that the dispersions are entirely stable for temperatures up to 40 °C in dry conditions.

Evaluation of the dissolution profiles of the binary solid dispersions stored at the high humidity level (Figure 10) revealed a slower dissolution compared to the unannealed samples reaching a drug release of 55 % and 70 % for the formulations with 7.5 and 15 % IND respectively after 15 minutes. The slower release observed may be due to the agglomeration of amorphous IND due to the increased molecular mobility promoted by the water absorption. Nevertheless, the extent of drug dissolution reached was higher than 90 % after 35 minutes. This suggests that even when small changes in the conformation of the system may occur, overall the formulation is effective in the stabilisation of IND in the amorphous state. This result correlates with the thermal analysis (Figure 7) where the samples showed to be mainly amorphous. If phase separation occurred, this nano-agglomerations would be smaller than 30 nm as this is the limit for its detection using DSC (Qian et al., 2010).

Ternary solid dispersions, due to the presence of semi-crystalline PEO, exhibited a slower drug release compared to the binary dispersions as observed for the two previous dissolution behaviours in pH 6.8. Due to the increase in the crystalline fraction induced by annealing, the dissolution profile is slower when compared to the unannealed samples. However, no significant differences were found between the dissolution rate of the samples stored at 0 % and 75 % RH levels indicating that the main factor for the orientation of the PEO phase is the temperature and not the humidity.

4. Conclusions

In this study, the influence of temperature and moisture on the stability of plasticised and un-plasticised extruded solid dispersions of PVPVA and IND was evaluated regarding their solid state and dissolution behaviour. It was observed that the presence of PEO favoured the processing conditions without affecting the stability of the system. Also, the presence of the semi-crystalline plasticiser acted as a dissolution profile modifier revealing a potential application for the development of controlled release dissolution doses. Moisture appeared to be the main factor affecting the stability of all the systems evaluated, causing an apparent phase separation leading to a slower dissolution profiles.

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6. References

Apicella, A., Cappello, B., Nobile, M.A. Del, Rotonda, M.I. La, Mensitieri, G., Nicolais, L., 1993. Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release. Biomaterials 14.

Bekiranov, S., Bruinsma, R., Pincus, P., 1996. Solution behavior of polyethylene oxide in water as a function of temperature and pressure. Phys. Rev. E - Stat. Physics, Plasmas, Fluids, Relat. Interdiscip. Top. 55, 577–585. https://doi.org/10.1103/PhysRevE.55.577

Bley, H., Fussnegger, B., Bodmeier, R., 2010. Characterization and stability of solid dispersions based on PEG/polymer blends. Int. J. Pharm. 390, 165–173.

Cantin, O., Siepmann, F., Danede, F., Willart, J.F., Karrout, Y., Siepmann, J., 2016. PEO hot melt extrudates for controlled drug delivery: Importance of the molecular weight. J. Drug Deliv. Sci. Technol. 36, 130–140. https://doi.org/10.1016/j.jddst.2016.09.003

Chauhan, H., Kuldipkumar, A., Barder, T., Medek, A., Gu, C.H., Atef, E., 2014. Correlation of inhibitory effects of polymers on indomethacin precipitation in solution and amorphous solid crystallization based on molecular interaction. Pharm. Res. 31, 500–515. https://doi.org/10.1007/s11095-013-1178-1

Chen, Y., Wang, S., Wang, S., Liu, C., Su, C., Hageman, M., Hussain, M., Haskell, R., Stefanski, K., Qian, F., 2016. Initial Drug Dissolution from Amorphous Solid Dispersions Controlled by Polymer Dissolution and Drug-Polymer Interaction. Pharm. Res. 33, 2445–2458. https://doi.org/10.1007/s11095-016-1969-2

Chokshi, R.J., Shah, N.H., Sandhu, H.K., Malick, A.W., Zia, H., 2008. Stabilization of Low Glass Trasition Temperature Indomethacin Formulations: Impact of Polymer-Type and

Its Concentration. J. Pharm. Sci. 97, 2286–2298. https://doi.org/10.1002/jps

Craig, D.Q.., 2002. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm. 231, 131–144. https://doi.org/https://doi.org/10.1016/S0378-5173(01)00891-2

De Brabander, C., Van Den Mooter, G., Vervaet, C., Remon, J.P., 2002. Characterization of ibuprofen as a nontraditional plasticizer of ethyl cellulose. J. Pharm. Sci. 91, 1678–1685. https://doi.org/10.1002/jps.10159

EMEA, 2003. Committee for Proprietary Medicinal Products. Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products, European Medicines Agency Inspections. London, UK. https://doi.org/10.3833/pdr.v2005i55.743

Ewing, A. V, Clarke, G.S., Kazarian, S.G., 2014. Stability of indomethacin with relevance to the release from amorphous solid dispersions studied with ATR-FTIR spectroscopic imaging. Eur. J. Pharm. Sci. 60, 64–71. https://doi.org/10.1016/j.ejps.2014.05.001

Fung, M.H., Suryanarayanan, R., 2017. Use of a Plasticizer for Physical Stability Prediction of Amorphous Solid Dispersions. Cryst. Growth Des. 17, 4315–4325. https://doi.org/10.1021/acs.cgd.7b00625

Guzmán, H., Tawa, M., Zhang, Z., Ratanabanangkoon, P., Shaw, P., Mustonen, P., Gardner, C., Chen, H., Moreau, J., Almarsson, O., Remenar, J., 2004. A “spring and parachute” approach to designing solid celecoxib formulations having enhanced oral absorption. AAPS J 6, T2189.

Hanada, M., Jermain, S. V., Williams, R.O., 2018. Enhanced Dissolution of a Porous Carrier–Containing Ternary Amorphous Solid Dispersion System Prepared by a Hot Melt Method. J. Pharm. Sci. 107, 362–371. https://doi.org/10.1016/j.xphs.2017.09.025

Hancock, B.C., Parks, M., 2000. What is the True Solubility Advantage for Amorphous Pharmaceuticals? Pharm. Res. 17, 397–404.

Huang, Y., Dai, W.-G., 2014. Fundamental aspects of solid dispersion technology for poorly soluble drugs. Acta Pharm. Sin. B 4, 18–25. https://doi.org/10.1016/j.apsb.2013.11.001

Jackson, M.J., Kestur, U.S., Hussain, M.A., Taylor, L.S., 2015. Dissolution of Danazol Amorphous Solid Dispersions: Supersaturation and Phase Behavior as a Function of Drug Loading and Polymer Type. Mol. Pharm. 13, 223–231. https://doi.org/10.1021/acs.molpharmaceut.5b00652

Janssens, S., de Armas, H.N., D’Autry, W., Van Schepdael, A., Van den Mooter, G., 2008a. Characterization of ternary solid dispersions of Itraconazole in polyethylene glycol 6000/polyvidone-vinylacetate 64 blends. Eur. J. Pharm. Biopharm. 69, 1114–1120. https://doi.org/10.1016/j.ejpb.2008.02.007

Janssens, S., Nagels, S., Armas, H.N. de, D’Autry, W., Van Schepdael, A., Van den Mooter, G., 2008b. Formulation and characterization of ternary solid dispersions made up of Itraconazole and two excipients, TPGS 1000 and PVPVA 64, that were selected based on a supersaturation screening study. Eur. J. Pharm. Biopharm. 69, 158–166. https://doi.org/10.1016/j.ejpb.2007.11.004

Janssens, S., Van den Mooter, G., 2009. Review: physical chemistry of solid dispersions. J. Pharm. Pharmacol. https://doi.org/10.1211/jpp/61.12.0001

Kiss, D., Süvegh, K., Marek, T., Dévényi, L., Novák, C., Zelkó, R., 2006. Tracking the Physical Aging of Poly(ethylene oxide): A Technical Note. AAPS PharmSciTech 7, 1–4. https://doi.org/10.1208/pt070495

LaFountaine, J.S., McGinity, J.W., Williams III, R.O., 2016. Challenges and Strategies in Thermal Processing of Amorphous Solid Dispersions : A Review. AAPS PharmSciTech 17, 43–55. https://doi.org/10.1208/s12249-015-0393-y

Liu, H., Wang, P., Zhang, X., Shen, F., Gogos, C.G., 2010. Effects of extrusion process parameters on the dissolution behavior of indomethacin in Eudragit ® E PO solid dispersions. Int. J. Pharm. 383, 161–169. https://doi.org/10.1016/j.ijpharm.2009.09.003

Liu, J., Cao, F., Zhang, C., Ping, Q., 2013. Use of polymer combinations in the preparation of solid dispersions of a thermally unstable drug by hot-melt extrusion. Acta Pharm. Sin. B 3, 263–272. https://doi.org/10.1016/j.apsb.2013.06.007

Lust, A., Strachan, C.J., Veski, P., Aaltonen, J., Heinämäki, J., Yliruusi, J., Kogermann, K., 2015. Amorphous solid dispersions of piroxicam and Soluplus®: Qualitative and quantitative analysis of piroxicam recrystallization during storage. Int. J. Pharm. 486, 306–314. https://doi.org/10.1016/j.ijpharm.2015.03.079

Lyons, J.G., Hallinan, M., Kennedy, J.E., Devine, D.M., Geever, L.M., Blackie, P., Higginbotham, C.L., 2007. Preparation of monolithic matrices for oral drug delivery using a supercritical fluid assisted hot melt extrusion process. Int. J. Pharm. 329, 62–71. https://doi.org/10.1016/j.ijpharm.2006.08.028

Ma, L., Deng, L., Chen, J., 2014. Applications of poly(ethylene oxide) in controlled release tablet systems: A review. Drug Dev. Ind. Pharm. 40, 845–851. https://doi.org/10.3109/03639045.2013.831438

Mallapragada, S.K., Peppas, N.A., 1997. Crystal dissolution-controlled release systems: I. Physical characteristics and modeling analysis. J. Control. Release 45, 87–94. https://doi.org/https://doi.org/10.1016/S0168-3659(96)01549-0

McGinity, J.W., Zhang, F., 2003. Pharmaceutical Extrusion Technology, in: Ghebre-Sellassie, I., Martin, C. (Eds.), Pharmaceutical Extrusion Technology. Marcel Dekker, Inc., New York, pp. 169–189.

Pezzoli, R., Lyons, J.G., Gately, N., Higginbotham, C.L., 2018. Investigation of miscibility estimation methods between indomethacin and poly (vinylpyrrolidone-co-vinyl acetate). Int. J. Pharm. 549, 50–57. https://doi.org/10.1016/j.ijpharm.2018.07.039

Punčochová, K., Vukosavljevic, B., Hanuš, J., Beránek, J., Windbergs, M., Štěpánek, F., 2016. Non-invasive insight into the release mechanisms of a poorly soluble drug from amorphous solid dispersions by confocal Raman microscopy. Eur. J. Pharm. Biopharm. 101, 119–125. https://doi.org/10.1016/j.ejpb.2016.02.001

Purohit, H.S., Taylor, L.S., 2015. Phase separation kinetics in amorphous solid dispersions upon exposure to water. Mol. Pharm. 12, 1623–1635. https://doi.org/10.1021/acs.molpharmaceut.5b00041

Qian, F., Huang, J., Zhu, Q., Haddadin, R., Gawel, J., Garmise, R., Hussain, M., 2010. Is a distinctive single Tg a reliable indicator for the homogeneity of amorphous solid dispersion? Int. J. Pharm. 395, 232–235. https://doi.org/https://doi.org/10.1016/j.ijpharm.2010.05.033

Rockland, L., 1960. Saturated Salt Solutions for Static Control of Relative Humidity between 5 and 40 C. Anal. Chem. 32, 1375–1376. https://doi.org/10.1021/ac60166a055

Serajuddln, a. T.M., 1999. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci. 88, 1058–1066. https://doi.org/10.1021/js980403l

Shamblin, S.L., Tang, X., Chang, L., Hancock, B.C., Pikal, M.J., 1999. Characterization of the Time Scales of Molecular Motion in Pharmaceutically Important Glasses. J. Phys. Chem. 103, 4113–4121.

Struik, L.C.E., 1987a. The mechanical and physical ageing of semicrystalline polymers: 1. Polymer (Guildf). 28, 1521–1533. https://doi.org/10.1016/0032-3861(87)90353-3

Struik, L.C.E., 1987b. The mechanical behaviour and physical ageing of semicrystalline polymers: 2. Polymer (Guildf). 28, 1534–1542. https://doi.org/10.1016/0032-3861(87)90353-3

Taylor, L.S., Langkilde, F.W., Zografi, G., 2001. Fourier transform raman spectroscopic study of the interaction of water vapor with amorphous polymers. J. Pharm. Sci. 90, 888–901. https://doi.org/Doi 10.1002/Jps.1041

Tres, F., Treacher, K., Booth, J., Hughes, L.P., Wren, S.A.C., Aylott, J.W., Burley, J.C., 2016. Indomethacin-Kollidon VA64 Extrudates : A Mechanistic Study of pH-Dependent Controlled Release. Mol. Pharm. 13, 1166–1175. https://doi.org/10.1021/acs.molpharmaceut.5b00979

Van Den Mooter, G., 2012. The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. Drug Discov. Today Technol. 9, 79–85. https://doi.org/10.1016/j.ddtec.2011.10.002

Van Duong, T., Van den Mooter, G., 2016. The role of the carrier in the formulation of pharmaceutical solid dispersions. Part II: amorphous carriers. Expert Opin. Drug Deliv. 13, 1681–1694. https://doi.org/10.1080/17425247.2016.1198769

Varma, M. V, Gardner, I., Steyn, S.J., Nkansah, P., Rotter, C.J., Whitney-Pickett, C., Zhang, H., Di, L., Cram, M., Fenner, K.S., El-Kattan, A., 2011. pH-Dependent Solubility and Permeability Criteria for Provisional Biopharmaceutics Classification (BCS and BDDCS) in Early Drug Discovery. Mol. Pharm. 9, 1199–1212. https://doi.org/10.1021/mp200103h

Vasconcelos, T., Marques, S., das Neves, J., Sarmento, B., 2016. Amorphous solid dispersions : Rational selection of a manufacturing process. Adv. Drug Deliv. Rev. 100, 85–101. https://doi.org/http://dx.doi.org/10.1016/j.addr.2016.01.012

Wang, X., Michoel, A., Van Den Mooter, G., 2005. Solid state characteristics of ternary solid dispersions composed of PVP VA64, Myrj 52 and itraconazole. Int. J. Pharm. 303, 54–61. https://doi.org/10.1016/j.ijpharm.2005.07.002

Weuts, I., Kempen, D., Decorte, A., Verreck, G., Peeters, J., Brewster, M., Van Den Mooter, G., 2005. Physical stability of the amorphous state of loperamide and two fragment molecules in solid dispersions with the polymers PVP-K30 and PVP-VA64. Eur. J. Pharm. Sci. 25, 313–320. https://doi.org/10.1016/j.ejps.2005.03.012

Zelenák, V., Halamová, D., Almási, M., Zid, L., Zelenáková, A., 2018. Ordered cubic nanoporous silica support MCM-48 for delivery of poorly soluble drug indomethacin.

Appl. Surf. Sci. 443, 525–534. https://doi.org/10.1016/j.apsusc.2018.02.260

Figure's Captions:

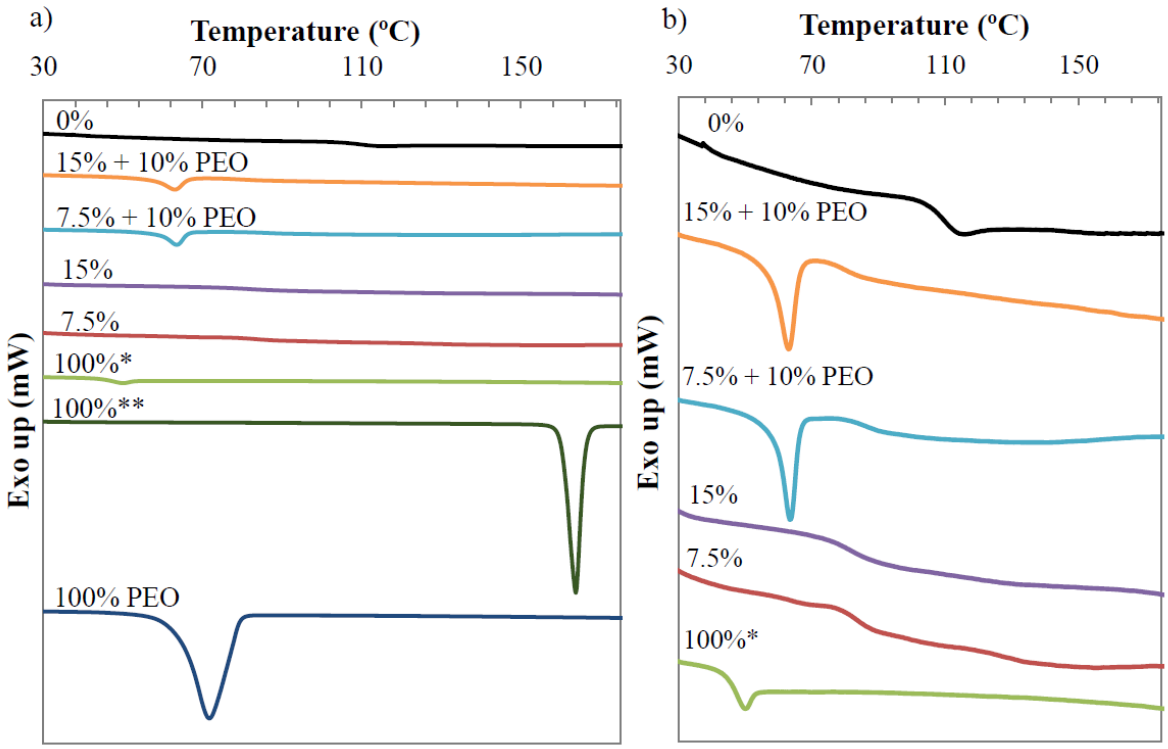

Figure 1: a) DSC thermograms of pure PVPVA, pure PEO, amorphous IND (*), crystalline IND reduced by half (**) and the PVPVA based solid dispersions. b) Zoomed view of the DSC thermograms. Numbers indicate the IND content.

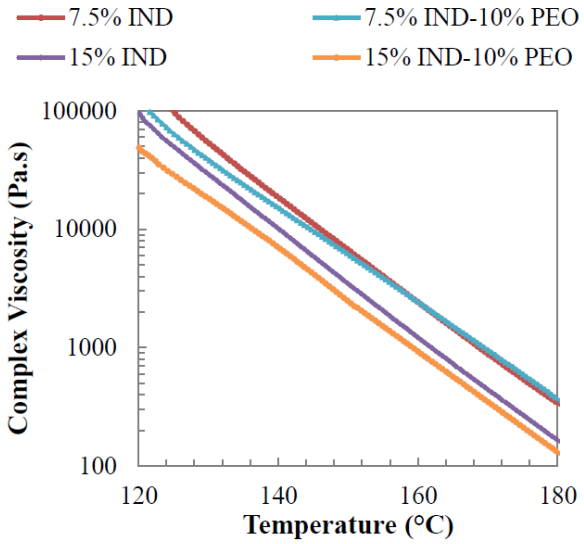

Figure 2: Change of complex viscosity vs the temperature of the binary and ternary solid dispersions.

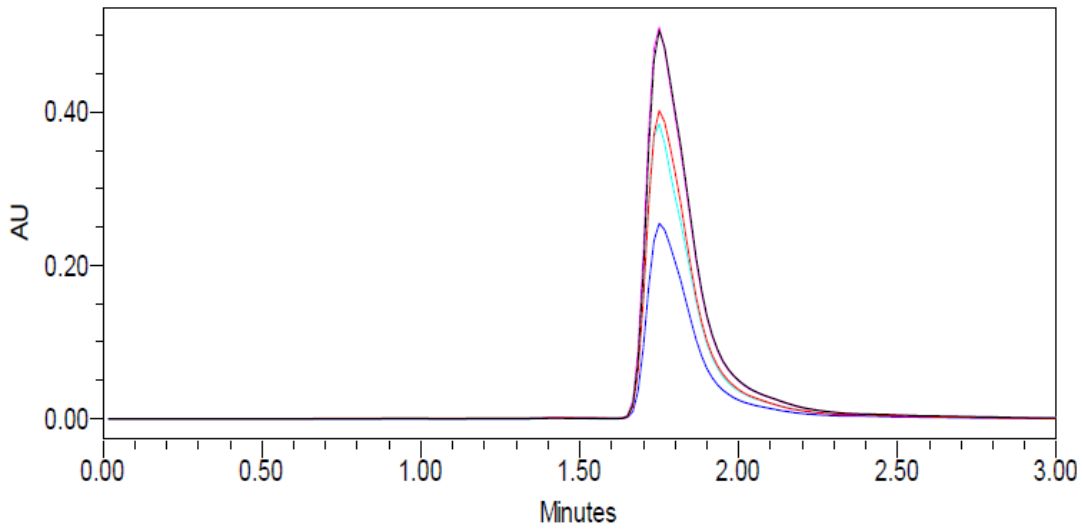

Figure 3: HPLC chromatograph of indomethacin from the standard solution (blue), binary and ternary extruded solid dispersions.

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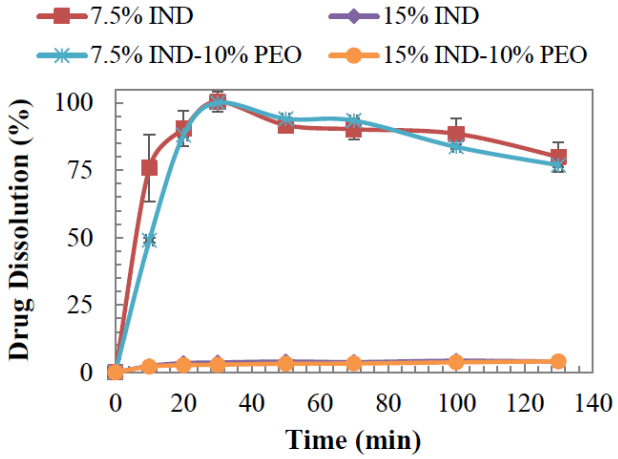

Figure 4: Dissolution of unannealed binary and ternary solid dispersions in pH 1.2 medium.

590

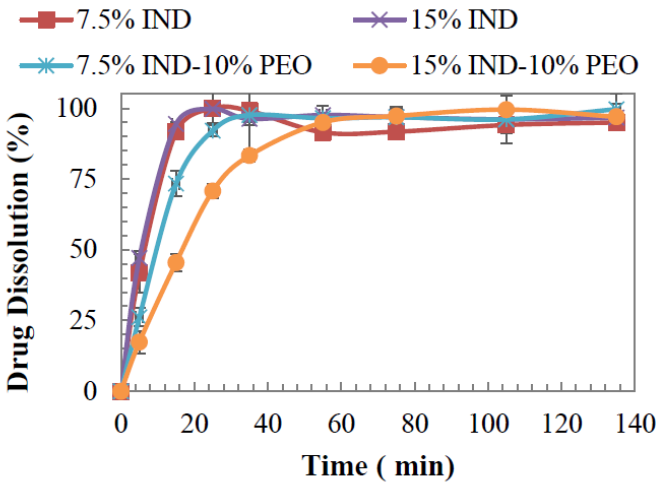

Figure 5: Dissolution of unannealed binary and ternary solid dispersions in pH 6.8 medium.

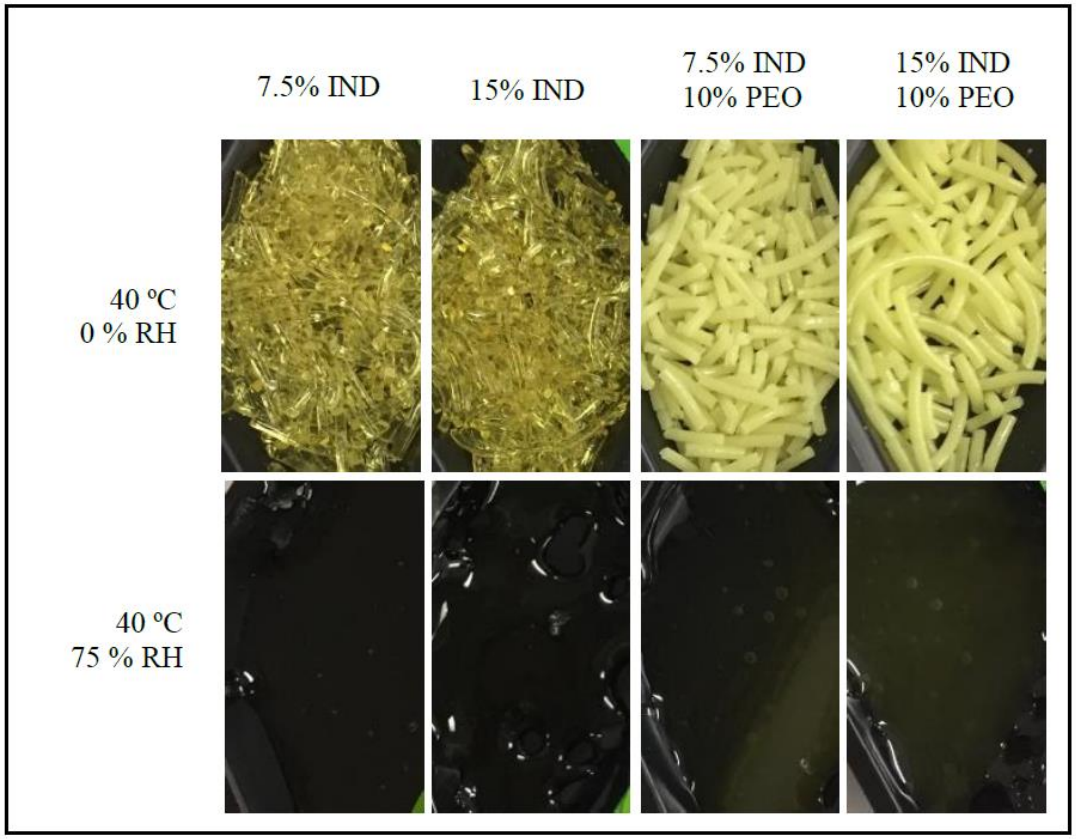

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Figure 6: Physical appearance of solid dispersions stored at 40 ºC and controlled relative humidity for 12 weeks.

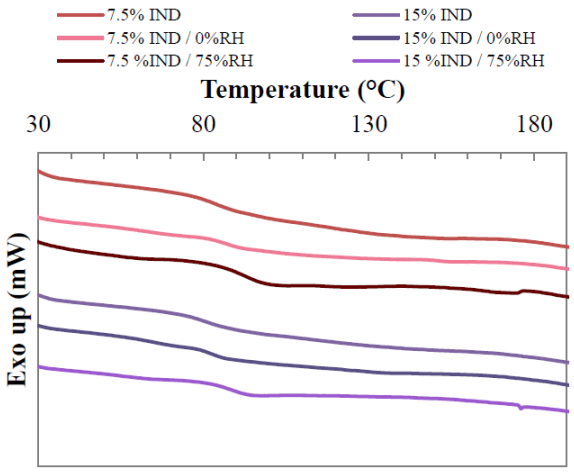

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Figure 7: DSC thermograms of unannealed PVPVA-IND binary ASD and stored at 40 ºC, 0 % and 75 % RH for 12 weeks.

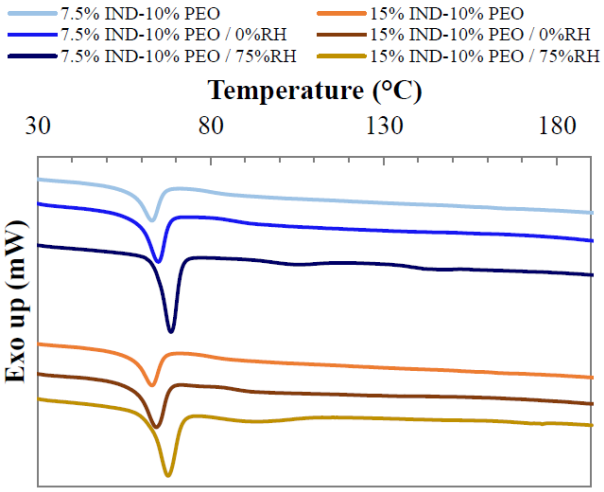

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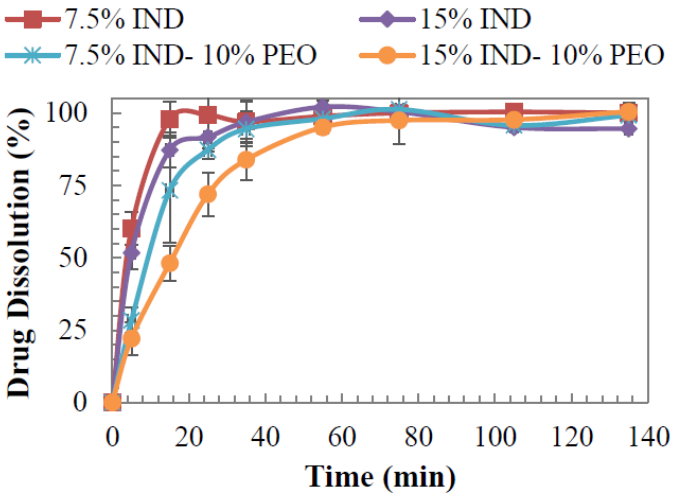
Figure 8: DSC thermograms of unannealed PVPVA-PEO-IND solid dispersions and stored at 40 ºC, 0 % and 75 % RH for 12 weeks.



610 **Figure 9:** Dissolution of PVPVA–PEO–IND solid dispersions in pH 6.8. Samples were stored at 0 % RH and 40 ºC

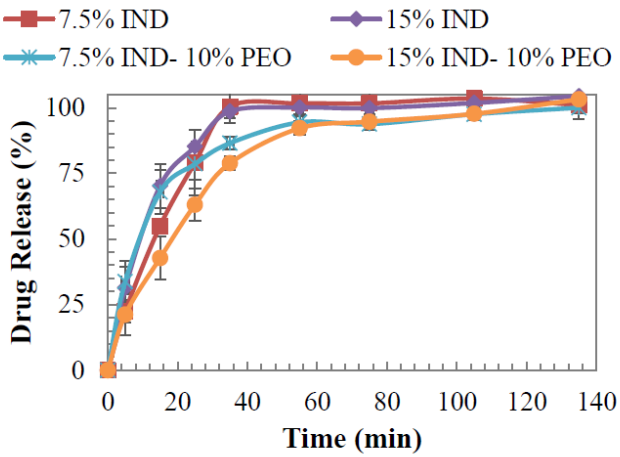


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Figure 10: Dissolution of PVPVA–PEO–IND solid dispersions in pH 6.8. Samples were stored at 75 % RH and 40 ºC