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Solubility Diagram Determination of Ibuprofen-PVP Solid Dispersions Obtained by Milling.

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ABSTRACT

The improvement of solubility and oral bioavailability of poorly water-soluble drugs by solid dispersion strategy remains as one of the major challenges to a drug development scientist. The aim of this work is not only to highlight the possibility of obtaining thermodynamically stable solid dispersions of PVP-Ibuprofen (poorly water-soluble drug) by comilling at room temperature but it aimed also the solubility diagram determination in such conditions. The milled mixtures characterization was carried out using powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR) and modulated temperature-differential scanning calorimetry (MT-DSC). Thereafter, the drug-polymer solubility was determined by depressing melting point method. Thus, the obtained results revealed the existence of intermolecular H-bonds (Ibuprofen-PVP) which correlates with the plasticizing effect of the PVP. Therefore, thanks to these results, it is evident that the formation of thermodynamically stable amorphous solid dispersions of PVP- Ibuprofen is feasible at room temperature by comilling technique.

Keywords: bioavailability, Ibuprofen, thermodynamically stable solid dispersions, poorly water-soluble drugs, comilling, depressing melting point method.

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INTRODUCTION

During the last years, the use of amorphous solids in place of crystals in pharmaceutical formulation has been considerably increased in order to improve the bioavailibility and dissolution rate of poorly soluble drugs. In fact, amorphous drugs represent different advantages over their crystalline counterparts with higher solubility, faster dissolution rate and enhanced oral bioavailability [1]. However, amorphous solids are physically unstable relative to the crystalline state, the stabilization of amorphous formulations against crystallization is crucial for pharmaceutical development because crystallization nullify the advantages of such materials [2, 3]. The compromise between physical stability and high solubility is difficult to be achieved because of their antagonist properties [4]. Thus, the solid dispersion of the drug into a polymeric matrix constitutes a powerful strategy for enhancing the solubility and preventing recrystallization of amorphous drug [5]. This is the reason for using polymer with high T_g (glass transition temperature) that increases the T_g of the blend and minimizes its molecular mobility indispensible for recrystallization under specific storage conditions [6]. Therefore, the intermolecular interactions between drug and polymer are essential for the stabilization of such system [7]. To fully benefit from a solid dispersion technique and selecting suitable polymers, the determination of drug solubility in the presence of polymer is necessary [8]. But, unfortunately, the high viscosity of polymers generates some difficulties and up to now there is no standardized strategy which makes the determination of drug-polymer solubility very easy and rapid [9, 10]. Solid dispersion can be obtained by several techniques (e.g. spray drying, hot melt extrusion.). In fact, the organic materials are often difficult to be amorphized by a conventional quench cooling method which often generates chemical transformations (thermal decomposition, mutarotation, degradation ...) during melting and make it unusable ,in some cases, for certain pharmaceuticals applications. In addition to that, the use of spray drying technique to generate solid dispersion may cause some problems because it involves solvents that can be both toxic and difficult to remove from the final product and it requires an initial dissolution step which can lead to chemical changes. Therefore, the comilling of drugs with additives offers a useful and novel alternative than conventional methods, it can facilitate amorphization and stabilizing the amorphous material [11, 12]. In this context, Ibuprofen (a non-steroidal anti-inflammatory drug (NSAID)) is categorized as a class II drug, according to the biopharmaceutics classification system (BCS), in addition to that, the ibuprofen dissolution rate hinders its oral bioavailability [13]. It appears as a racemic mixture of R (−)-Ibuprofen and S(+)-Ibuprofen (the pharmacologically active form) [14]. Racemic Ibuprofen (Fig.1 [14], 2(4-isobutylphenyl) propanoic acid, may exist under two different crystalline phases: the conventional phase I (stable, melts at 349 K), and phase II (metastable, melts at 290 K) [15]. Racemic Ibuprofen has also a low glass transition temperature (T_g ≈228 K; [15]). Some researchers have obtained a physically stable amorphous phase of Ibuprofen by solid state milling with kaolin [16]. In our work, Ibuprofen was comilled with PVP K30 (ball milling) at room temperature (≈298K), The X-ray diffraction was used to identify the amorphous mixtures, thus we have tried to highlight the presence of hydrogen bonding (PVP- Ibuprofen) by using Fourier transform infrared spectroscopy (FTIR). Therefore, as a result of thermal analysis (MT-DSC), we have determined the solubility diagram by depressing melting point method [9] and the Gordon Taylor curve [17] for the obtained mixtures.

MATERIALS AND METHODS

MATERIALS

Crystalline Ibuprofen ($C_{13}H_{18}O_2$; Mw = 206, 28 g·mol−1; purity ≥99%) and amorphous PVP K30 (average molecular weight M_w = 40,000 g·mol−1) were received as a gift samples from the National drug control Laboratory (LNCM, Tunisia) and were used without further purification.

SOLID STATE MILLING

Comilling was performed in a planetary ball mill (pulverisette 7, Fritsch) using two milling jars (45 cm3)/ 7 balls (⌀ = 1 cm) in ZrO2. The rotation rate was set to 300 rpm and the ball/ sample weight ratio was 82.5:1. The milling procedure was performed during 2 h at room temperature (≈298K) constituted by 20min milling periods with pause periods (10 min) in order to reduce the sample overheating.

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CRYSTALLINITY EVALUATION

The milled mixtures were assessed for crystallinity using powder X-ray diffraction (PXRD). The experimental procedure was performed by placing samples into Lindemann glass capillaries (⌀ = 0.7 mm) using an XPERT PRO MPD diffractometer (λCuKα =1.540 Å) equipped with an X'celerator detector.

DRUG–PVP INTERACTION STUDIES

FTIR spectra of pure crystalline and milled samples were measured for comparison. A minimum average of 32 scans for each sample was taken over a wave number region varying between 4000 and 400 cm^{-1} (ATR Bruker Diamant, FTIR 200, Nicolet Instrument).

THERMAL ANALYSIS

The thermal analysis was carried out by using the MT-DSC Q2000 (TA Instruments). For all the samples, we have used an open aluminum pan and we have calibrated enthalpy and temperature readings by using pure indium at the same scan rates used before.

DETERMINATION OF SOLUBILITY DIAGRAM

The drug/polymer solubilities determination is generally achieved by "depressed melting points" method [9]. In this procedure, physical mixtures of Ibuprofen and PVP K30 were cryomilled (15min) in a mixer mill (MM400, Retsch) using 1/2 gram of powder by bowl and the milling frequency was set to 30 Hz. In a typical heating MT-DSC scan, the ibuprofen dissolution in PVP matrix generates the appearance of an endothermic signal which has similarities to that of a melting process. The temperature (Tend) which defines the endothermic event completion represents the end of dissolution process and thus the initial ibuprofen concentration constitutes the equilibrium solubility at Tend [9]. Therefore, the solubility curve determination of Ibuprofen/PVP system will be possible by varying the initial concentration of ibuprofen.

DETERMINATION OF GORDON-TAYLOR PLOT

Gordon-Taylor plot describes the evolution of the glass transition temperature as a function of the blend composition based on a semi-empirical equation [17]:

$$\mathbf{Tg\,(Xibup) = \frac{Xibup\ Tg\,(ibup) + K\,(1 - Xibup)Tg\,(PVP)}{(Xibup + k\,(1 - Xibup))}} \qquad \mathbf{(eq.1)}$$

In this expression, Tg (ibup) and Tg (PVP) represent, respectively, the glass transition temperature of pure ibuprofen and pure PVP, Xibup is the ibuprofen proportion in the blend, and K is a fitting parameter which characterizes the curvature of the evolution.

RESULTS AND DISCUSSION

In our work, ball milling was treated at room temperature (≈25°C) because if ibuprofen amorphisation by comilling with PVP was possible, the procedure would be economic and very simple. Ibuprofen was milled in the absence and presence of PVP at different weight ratios (Table 1). The physical and thermal characterization of the obtained samples was carried out using XRD, FTIR and MT-DSC.

X-ray diffraction

The X-ray powder diffraction pattern of the crystalline Ibuprofen is reported on Figure 1. These results are in accordance with the diffraction pattern of the Phase I [15] whose crystallographic structure was assigned to the monoclinic P21/c space group [18]. Ibuprofen milled alone (Ibm) for 15 h without PVP showed no considerable change in the characteristics of the peaks (Fig.1) as compared with unmilled ibuprofen (Ibc). As well, some researchers have not found a change of crystallinity after milling of Ketoprofen for 48 h (25°C) without additives [19]. The broadenning of the Bragg peaks (Fig. 2 and 3) which distinguishes the milled sample

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is owing to the reduction of the crystallite size and slight lattice distortions generated by ball milling. It can be noted that phase II (metastable form; [15]) is absent in all samples and Bragg peaks are still present in Ib0.6P0.4 and Ib0.9P0.1 mixtures. However, the diffraction pattern of the milled sample (Ib0.1P0.9) does not show any Bragg peak indicating a complete conversion to amorphous state. It is worth noting that the milled mixture became completely amorphous for a blend composition containing 70% of PVP. Thus, we can clearly consider that the formation of amorphous ibuprofen was realizable by comilling with PVP, but milling the ibuprofen alone at ambient temperature (≈25°C) did not generate an amorphization.

Table 1: Formulation code of powdered samples of ibuprofen crystalline and milled with PVP.

Powder code	Operations	Ibuprofen (g)	PVP (g)
Ibc	Crystalline (unmilled)	1	None
Ibm	Milled (15 h)	1	None
$Ib_{0.1}P_{0.9}$	Milled (02 h)	0.1	0.9
$Ib_{0.2}P_{0.8}$	Milled (02 h)	0.2	0.8
$Ib_{0.3}P_{0.7}$	Milled (02 h)	0.3	0.7
$Ib_{0.5}$ $P_{0.5}$	Milled (02 h)	0.5	0.5
$Ib_{0.55}$ $P_{0.45}$	Cryomilled (15min)	0.55	0.45
$Ib_{0.6}$ $P_{0.4}$	Cryomilled (15min)	0.6	0.4
$Ib_{0.8}$ $P_{0.2}$	Cryomilled (15min)	0.8	0.2
$Ib_{0.9}$ $P_{0.1}$	Cryomilled (15min)	0.9	0.1

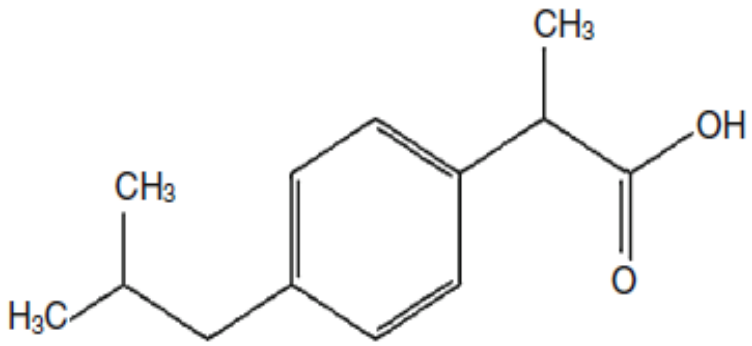

Fig.1: Ibuprofen molecular structure.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

The infrared spectrum of solid dispersion mixture ($Ib_{0.2}P_{0.8}$) was subjected to a comparison with FTIR spectra of ibuprofen (Ibc), pure PVP and physical mixtures ($Ib_{0.8}P_{0.2}$/$Ib_{0.6}P_{0.4}$). In the carbonyl frequency region (Fig.4) the ibuprofen showed a narrow strong band at 1719 cm^{-1} attributed to carboxylic C=O stretching whereas the PVP gave a broad band at 1661 cm^{-1} attributed to the cyclic amide C=O stretching. As the proportion of the PVP in the blend increases, both the C=O stretching shifted to higher wave number and the carbonyl peak of the drug decreases in intensity. Moreover, in the solid dispersion ($Ib_{0.2}P_{0.8}$) appeared a strong broad band at 1673 cm^{-1}. Thus, these results prove that a proportion of unassociated ibuprofen established hydrogen bonds with PVP. It should be noted that although the peak (observed at 1673 cm^{-1}/Fig.4) occurred at a higher frequency compared to the C=O of polymer, the presence of hydrogen bonds will not always generate a decrease in the C=O wave number, the observed changes are dependent on the degree of self-association in the pure components with respect to their mixtures [20]. Moreover, both the unmilled ibuprofen and PVP showed a peak at 2971 cm^{-1}(Fig. 5) attributed to O-H stretching for pure drug and polymer. In the solid dispersion ($Ib_{0.2}P_{0.8}$) the O-H stretching appeared in the same wave number as a broad band with a base line covering the range of 2800-3020 cm^{-1} confirming the existence of pronounced hydrogen bonds between the two chemical components in glass solution. In the frequency region of 500-1600 cm^{-1} the bands observed in the mixture, were almost the same for both ibuprofen and PVP, this might indicate that though the ibuprofen

molecule has established hydrogen bonds with the PVP via the carboxylic acid group (OH), the ibuprofen global symmetry was not significantly modified.

THERMAL ANALYSIS (MT-DSC)

For crystalline solid, the ratio of T_m (melting temperature) to T_g is a crucial parameter which indicates it's capability to form glass solution. As greater the ratio of T_m to T_g, higher the risk of recrystallization [21]. In our case, the ibuprofen which has a very low T_g (Fig.6) will have higher mobility and very rapid crystallization at room temperature (≈25°C). Thus, the solid dispersion into a polymeric matrix constitutes the best strategy to modify the thermodynamics properties and recrystallization kinetics of ibuprofen. Therefore, physical properties and thermal stability of milled mixtures were the subject of a MT-DSC study.

A/ GORDON–TAYLOR PLOT OF PVP- IBUPROFEN GLASS SOLUTIONS

By using the modulated temperature-differential scanning calorimetry (MT-DSC) for amorphous mixtures, the overlap between reversible (e.g. glass transition) and irreversible events (e.g. crystallization) can be easily avoided. Firstly, we have localized the glass transition temperatures of PVP/Ibuprofen mixtures by examining the signal of the reversible heat flow which improves the clarity of small (i.e., T_g) and avoids the overlapping of thermal events (Fig.9 and 7). At higher polymer concentrations, the onset temperature is hard to define, therefore, T_g is determined from the inflection point. The glass transition temperatures of the milled mixtures are reported in Table 2. The existence of a single T_g for all the ibuprofen–PVP mixtures prepared in this study argues for a complete miscibility between PVP and ibuprofen within the concentration range studied. The evolution of glass transitions has been adjusted by the law of Gordon-Taylor (eq.1). The best adjustment was achieved for K close to 1 (K ≈ 0.99) in accordance with the linear evolution of T_g which depends on the blend composition. As shown in figure 8, some measured *T*g values are lower compared to those estimated by Gordon Taylor law, showing a negative deviation from ideal behavior. This negative deviation as well as the K value could make us believe that the interactions between ibuprofen and PVP are very weak. This can be explained by the fact that hydrogen bonds involved in the dimers of ibuprofen are very intense, only a certain proportion of the non-associated ibuprofen formed hydrogen bonds with the PVP. On the other hand, figure 8 illustrates the effect of PVP on the Tg of the blend. In fact, increasing the PVP proportion induced an increase in T_g of the blend, this is an indicator of the plasticizing effect of PVP.

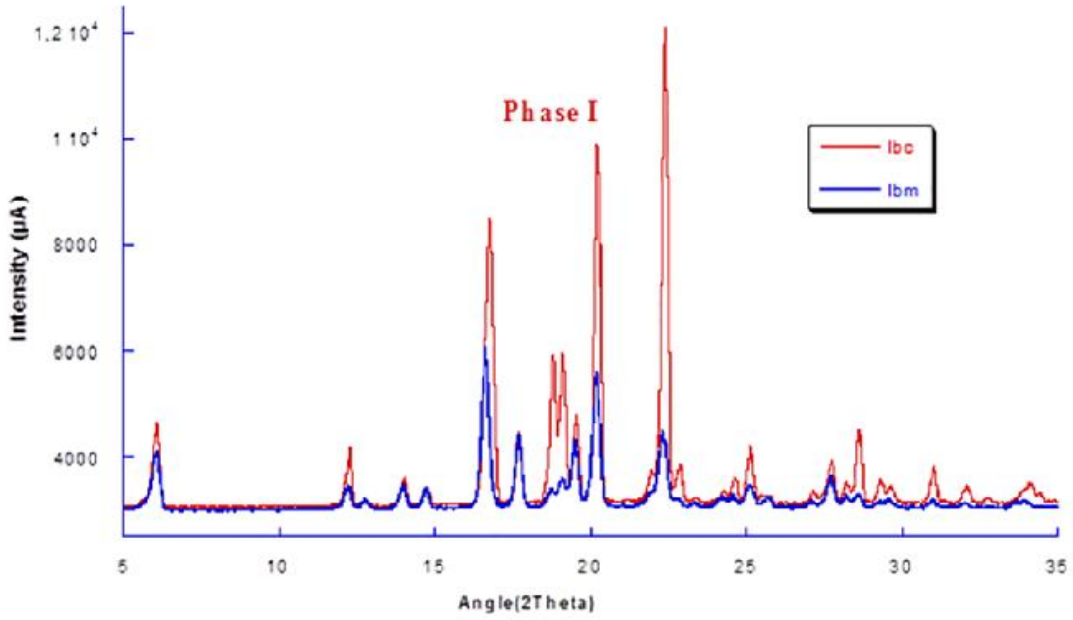

Fig.2: X-ray powder diffraction patterns of samples of ibuprofen crystal and milled for 15 h without PVP.

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Table 2: Glass transition temperatures of PVP/ Ibuprofen mixtures determined by MT-DSC.

Samples	Tg (°C)
Ibc (Quenched)	-42 ±1°C
PVP	165 ±1°C
$Ib_{0.1}P_{0.9}$	137 ±1°C
$Ib_{0.2}P_{0.8}$	107 ±1°C
$Ib_{0.3}P_{0.7}$	94 ±1°C
$Ib_{0.5}$ $P_{0.5}$	44 ±1°C
$Ib_{0.8}$ $P_{0.2}$(Quenched)	-28 ±1°C
$Ib_{0.9}$ $P_{0.1}$(Quenched)	-35 ±1°C

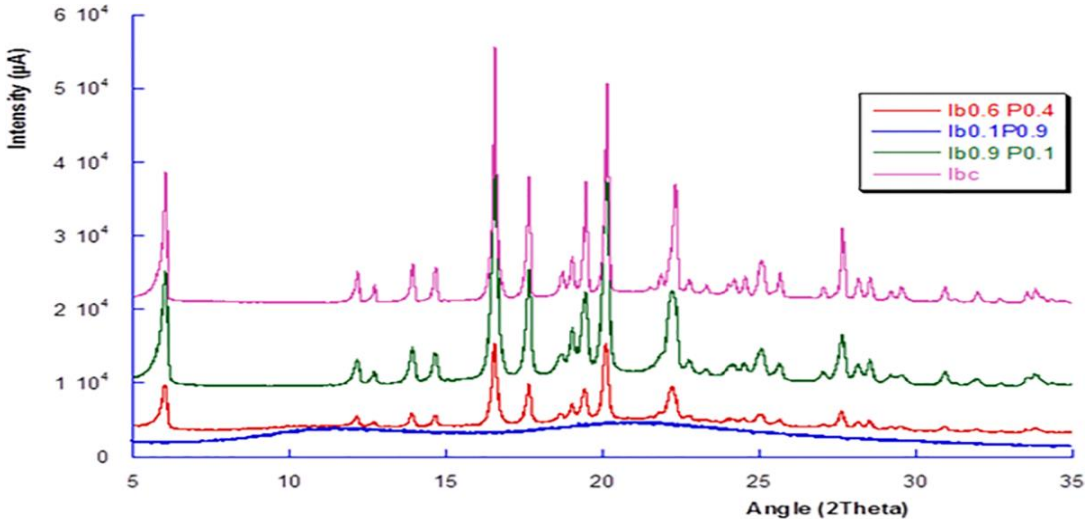

Fig. 3: X-ray powder diffraction patterns of samples of ibuprofen crystal and milled with PVP at different proportions.

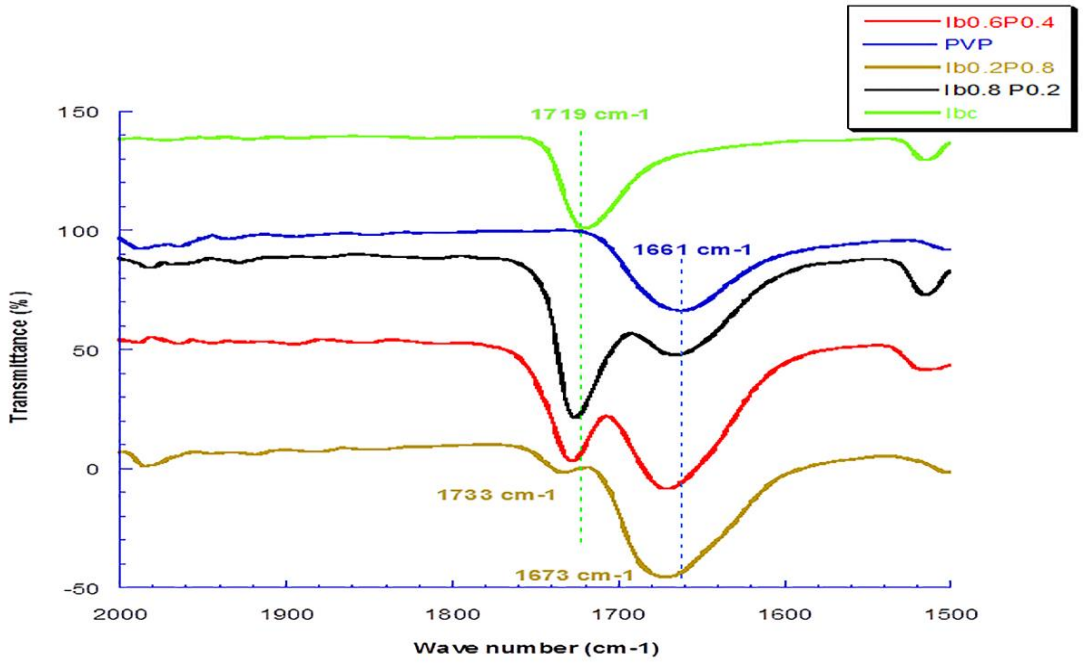

Fig.4: Evolution of C-O stretching bands.

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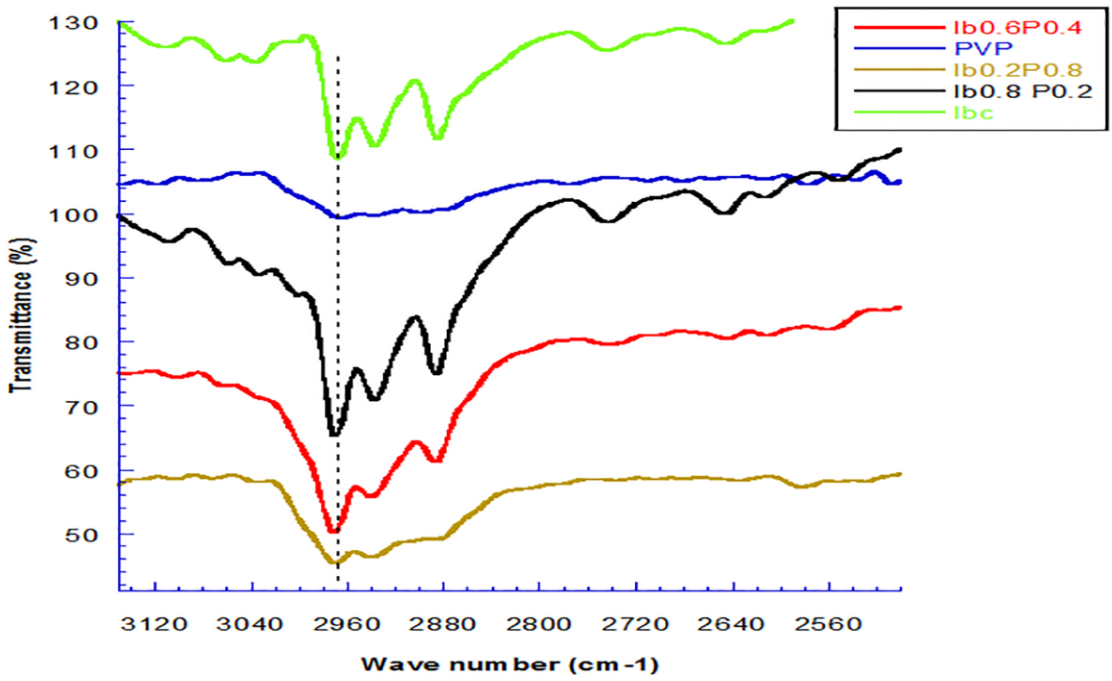

Fig.5: Evolution of OH stretching bands.

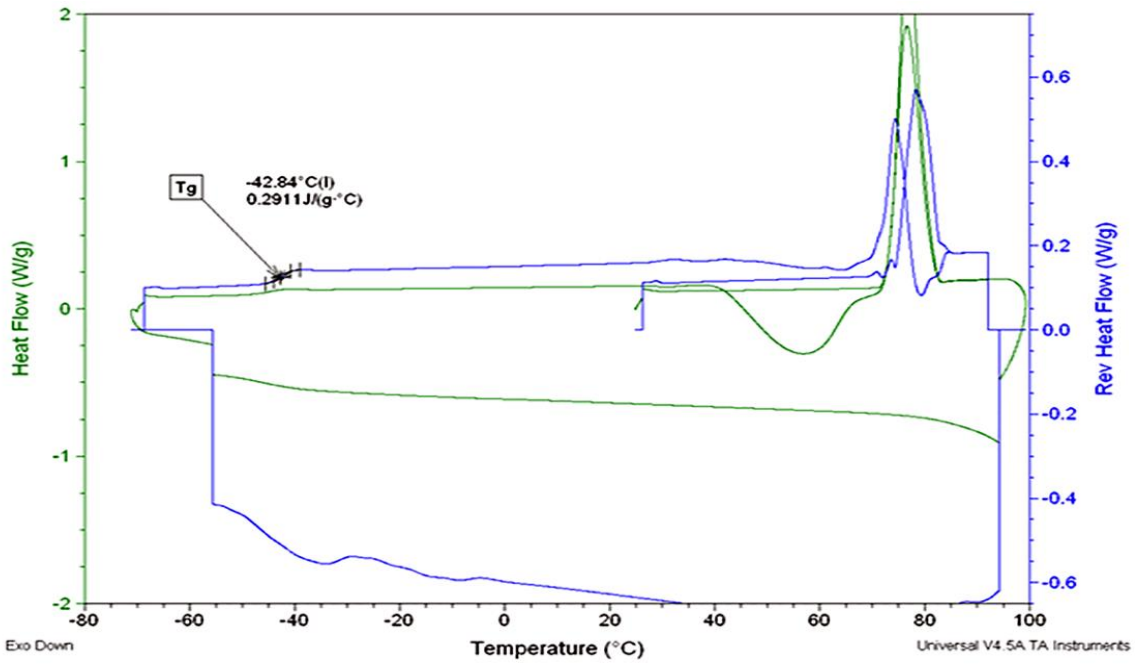

Fig.6: MT-DSC scans (unmilled crystalline ibuprofen) recorded upon 3 cycles: a/ heating at 5 K/min from 298K to 373K, b/ a quench at 20 K/min from 373 K to 203 K c/ heating at 5 K/min from 203 K to 373K.

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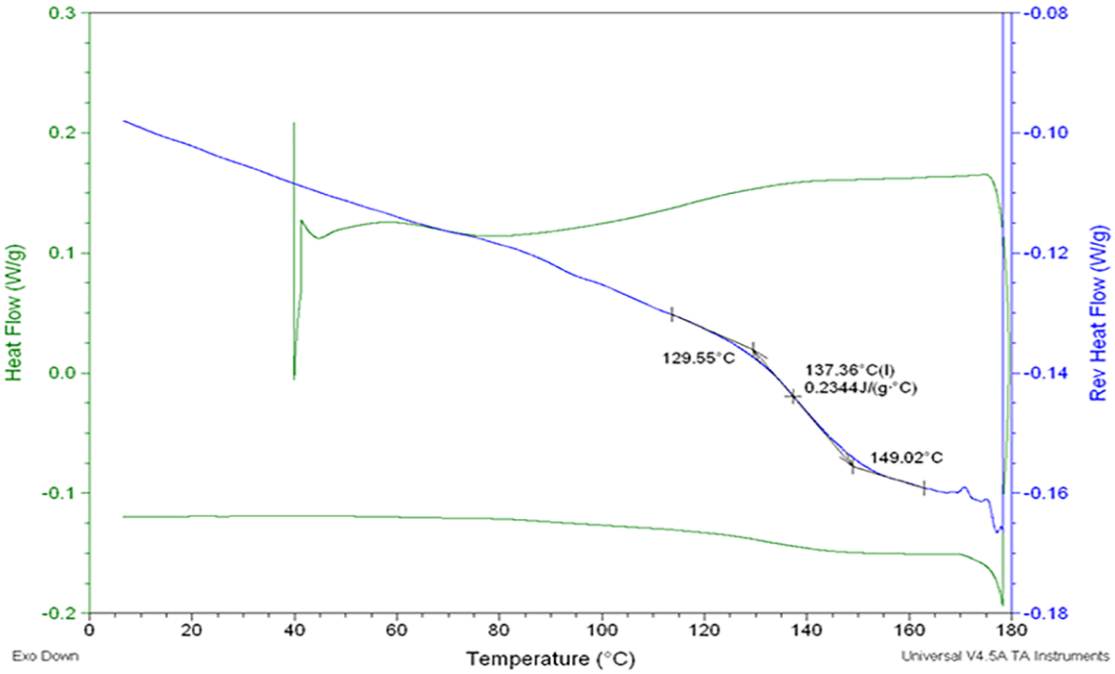

Fig.7: MT-DSC scans ($Ib_{0.1}P_{0.9}$) recorded upon 2 cycles: a/ heating at 5 K/min from 313K to 453K, b/ a quench at 5 K/min from 453 K to 273K.

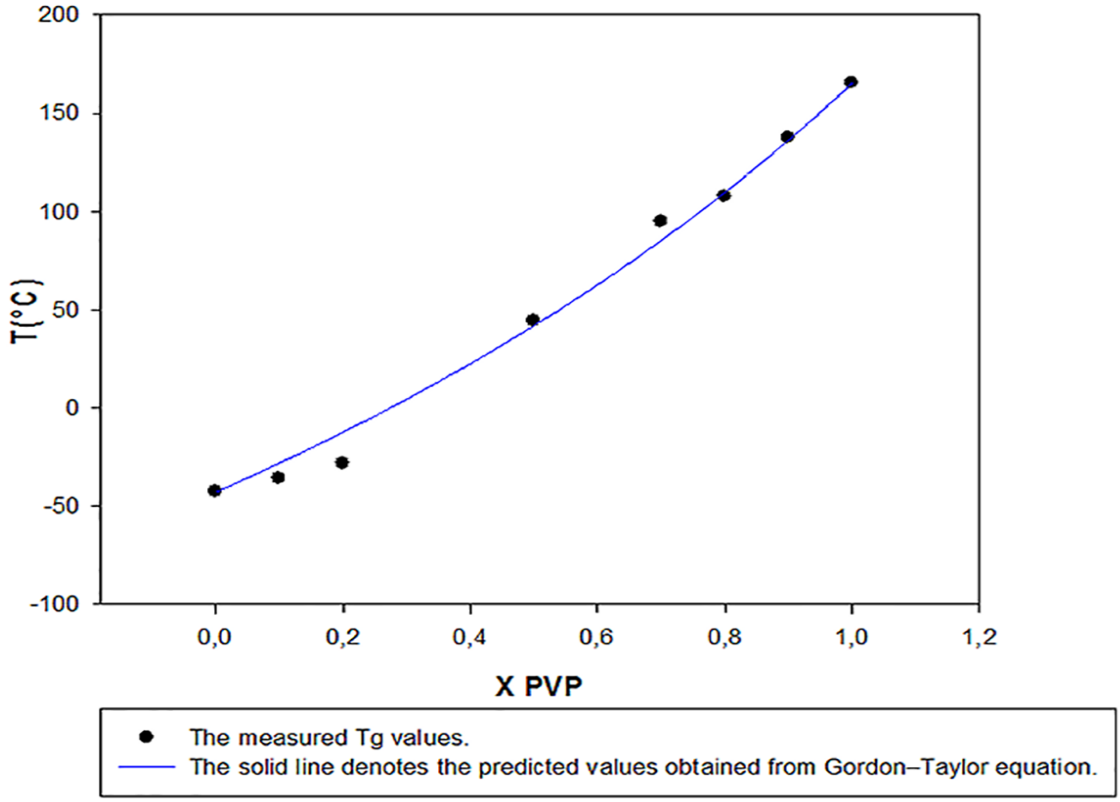

Fig.8: Effect of PVP on the T_g of the blend.

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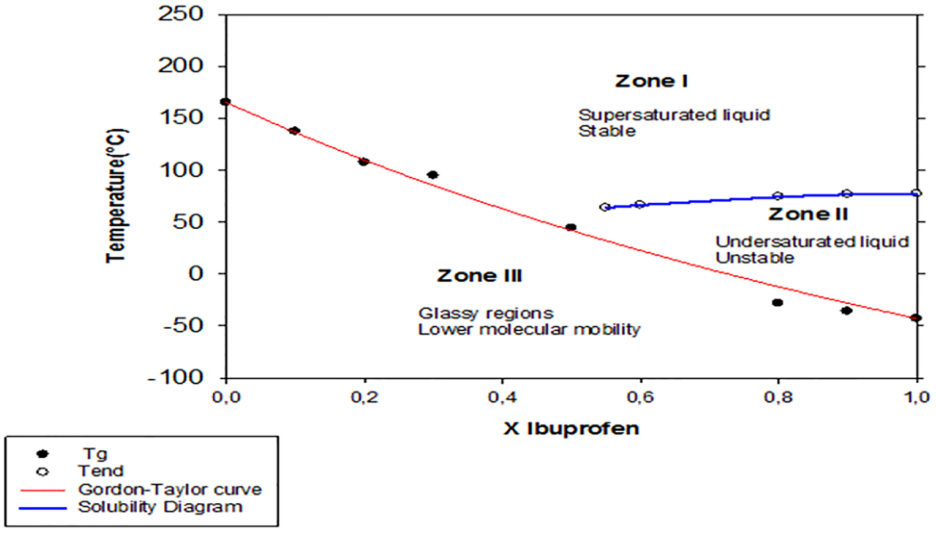

Fig.9: Binary phase diagram for Ibuprofen/ PVP system.

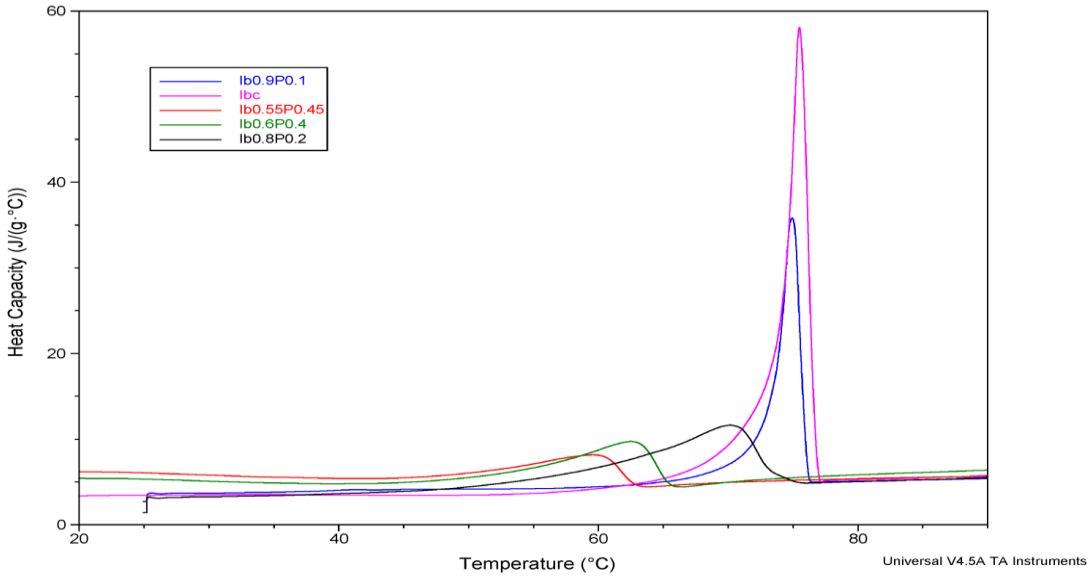

Fig.10: The dissolution equilibrium of physical mixtures heated at 1K/min.

B/ SOLUBILITY DIAGRAM OF PVP- IBUPROFEN MIXTURE

We have determined the solubility limits of the mixtures (Ibuprofen + PVP K30) by depressed melting points method. Firstly, physical mixtures ($Ib_{0.8}$ $P_{0.2}$ /$Ib_{0.6}$ $P_{0.4}$ / $Ib_{0.55}$ $P_{0.45}$ / $Ib_{0.9}$ $P_{0.1}$) heated at 1K/min until the dissolution equilibrium is reached (Fig.10). Thus we have identified an endothermic signal which corresponds to the melting of the mixture (Tend), the results are recapitulated in Table 3. Therefore, we have constructed the solubility curve of Ibuprofen/PVP system (Fig.9). It should be noted that T_{end} value cannot be determined near the Tg one (Zone III). Therefore, extrapolation method or model prediction is promising for the determination of equilibrium solubilities of ibuprofen in a PVP matrix below Tg [10]. In fact, the T_g curve delimits the kinetic boundary of molecular mobility [22]. As shown in Fig.8, the Tg curve defines the limit between Zone III (glassy regions) and Zones (I, II) representing the equilibrium liquid with higher molecular

mobility. Above T_g, drugs are hampered by the viscosity and interactions between drug and polymer, in presence of higher molecular mobility, the recrystallization probability at $T>T_g$, is certainly important [22]. Below T_g, the glassy regions are characterized by lower molecular mobility. Particularly, some authors have shown that at $T<T_g$-50°C, we can neglect the molecular mobility and amorphous materials will be stable for long periods [6]. On the other hand, the solid dispersions stability depends considerably on the kinetics of crystallization and/ or phase separation. The solubility curve (Figure 9) represents the maximum amount of ibuprofen that can be blended with the PVP with absence of crystallization risk or phase separation. Thus, it represents the borderline between the thermodynamically unstable zone (II) and stable region (zone I). Zone I is therefore the secure region, where any fluctuation of temperature in prepared mixtures or drug concentration will not cause the instability of the amorphous material. As shown by MT-DSC and FTIR results, the existence of a thermodynamically stable zone is due not only to the PVP plasticizing effect but also to the intermolecular H-bonds between ibuprofen and PVP.

Table 3: Determination of Tend.

Mixtures	Tend (°C)
Ibc	77 ±1°C
$Ib_{0.55}$ $P_{0.45}$	63 ±1°C
$Ib_{0.6}$ $P_{0.4}$	66 ±1°C
$Ib_{0.8}$ $P_{0.2}$	74 ±1°C
$Ib_{0.9}$ $P_{0.1}$	76 ±1°C

CONCLUSION

Ball milling was proven to be a powerful tool for the formation of amorphous ibuprofen only in presence of PVP in the solid state at room temperature (≈25°C). The degree of amorphisation depends on the amount of PVP in the mixtures. The MT-DSC result has clearly suggested a correlation between the two factors responsible for the stabilization of amorphous blend: the PVP plasticizing effect and intermolecular H-bonds (Ibuprofen-PVP). Thus, the solubility diagram of ibuprofen/ PVP system has shown a thermodynamically stable zone where any fluctuation of thermodynamic factors will not cause the instability of the mixtures. Given to the complexity regarding the drug–polymer solubility determination, other fundamental studies are necessary not only to estimate the solubilities near and bellow Tg but to highlight the effects of the other factors causing the instability of the amorphous solid dispersions.

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