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Chapter

Ternary Solid Dispersion Strategy for Solubility Enhancement of Poorly Soluble Drugs by Co-Milling Technique

Marouene Bejaoui, Hanen Oueslati and Haykel Galai

Abstract

Amorphous ternary solid dispersion has become one of the strategies commonly used for improving the solubility and bioavailability of poorly water soluble drugs. Such multicomponent solid dispersion can be obtained by different techniques, this chapter provides an overview of ternary solid dispersion by co-milling method from the perspectives of physico-chemical characteristics in vitro and in vivo performance. A considerable improvement of solubility was obtained for many active pharmaceutical ingredients (e.g., Ibuprofen, Probucol, Gliclazid, Fenofibrate, Ibrutinib and Naproxen) and this was correlated to the synergy of multiple factors (hydrophilicity enhancement, particle size reduction, drug-carrier interactions, anti-plasticizing effect and complexation efficiency). This enhanced pharmacokinetic properties and bioavailability of these drug molecules (1.49 to 15-folds increase in plasma drug concentration). A particular focus was accorded to compare the ternary and binary system including Ibuprofen and highlighting the contribution of thermal and spectral characterization techniques. The addition of polyvinylpyrrolidone (PVP K30), a low molecular weight molecule, into the binary solid dispersion (Ibuprofen/β-cyclodextrin), leads to a 1.5–2 folds increase in the drug intrinsic dissolution rate only after 10 min. This resulted from physical stabilization of amorphous Ibuprofen by reducing its molecular mobility and inhibiting its recristallization even under stress conditions (75% RH and T = 40°C for six months).

Keywords: amorphous ternary solid dispersion, co-milling, PVP, physical stability, aqueous solubility, bioavailability, Ibuprofen

1. Introduction

In recent years, solid dispersion technology by milling technique was largely utilized by researchers in order to enhance dissolution rate, bioavailability and thus therapeutic efficiency of several poorly water-soluble drugs (**Table 1**), as it represents a simple, economic and environmental process without using solvents [1–9]. In fact, millings enable particle size reduction and promote the formation of drug nanoparticles, which enhance solubility, flow properties and content uniformities of pharmaceutical dosage forms [10]. However, this process might induced

Drug molecules	Authors
Piroxicam	Anna Penkina et al. [1]
Praziquantel	Alessio Gaggero et al. [2]
Telaprevir	Xinnuo Xiong et al. [3]
Hydrochlorothiazide	Sakib M. Moinuddin et al. [4]
Indomethacin	Georgia Kasten et al. [5]
Nifedipine	Pooja J. Patel et al. [6]
Ibuprofen	Amjad Hussain et al. [7]
Bicalutamide	Joanna Szafraniec et al. [8]
Celecoxib	Zhuang Ding et al. [9]

Table 1.
Some examples of drug molecules exhibiting solubility enhancement by binary solid dispersion using co-milling technique [1–9].

drug transition from crystalline to amorphous state which is more soluble in water but physically unstable in some cases [11]. Physical stabilization of such unstable amorphous material required an optimization strategy using additives (milling time and rate, compatible carriers with optimized proportion) in order to preserve its chemical integrity (absence of degradation) and inhibiting phase transformations or polymorphic conversion towards unstable forms [11]. In some cases, the stabilization and solubilization efficiency of binary solid dispersion is weak by exhibiting limited bioavailability enhancement [12] and required a large amount of carriers. In order to further enhance drug dissolution rate, several researchers have introduced third compound in drug formulations, this led to simultaneous enhancement of drug solubility and physical stability [13–19]. In this chapter, the challenges and strategies in developing robust ternary solid dispersion of high stability and performance are briefly discussed.

2. Ternary solid dispersion: a new alternative to promote drug dissolution rate

Solubility and stability enhancement of drug molecules in ternary solid dispersion resulted from various mechanisms (**Table 2**) including intermolecular interactions (drug/carrier, carrier/carrier) and synergetic effects of excipients. This required the use of appropriate carrier showing compatibility in ternary mixtures (e.g. polymer, surfactant, crosslinked polymer, adsorbent, aminoacids, cyclodextrin molecules) and reinforcing stabilization of amorphous drug by preventing its recristallization or chemical degradation.

Watanabe et al. (2002) have reported the physical stabilization of amorphous Indomethacin (IM) by ternary solid dispersion using Mg $(OH)_2$ and SiO_2 as carriers [13]. DRIFT (Diffuse Reflectance Infrared Fourier Transform Spectroscopy) results have shown the disappearance of the OH group (carboxylic group) band of IM (**Table 3**) in ternary system and this was attributed to mechanical dehydration generated by ball milling in presence of Mg $(OH)_2$ and SiO_2. Such dehydration leads to the increase in the acidity of the carriers and enhances the acid–base interaction which ensures the rapid amorphization of IM (**Table 3**). The presence of these two carriers has increased the glass transition temperature of Indomethacin, the Tg of ternary system was higher than that of binary ground mixtures (IM-SiO_2,

Drug molecules	Carriers	Mechanisms	Pharmacokinetic properties (plasma drug concentration)	Physical stability	Drug release (at 37.0 ± 0.5°C)	Authors
Indomethacin	$Mg(OH)_2/SiO_2$	Acid–base interaction and formation of C - O -Si bridging bond	—	At 30°C and 11% RH for 2 months	—	[13]
Ibrutinib	Oxalic acid (OXA)/ microcrystalline cellulose (MCC)	Ionic Interactions	1.49-fold greater than crystalline Ibrutinib	At 75% RH and T-40°C for 6 months	5.33-folds higher than crystalline Ibrutinib	[14]
Probucol	HPC, pluronic P6g and SDS	Micelle solubilization, increase in hydrophilicity	15-folds higher than that of coarse Probucal suspension	7 days at 4 °C or 25 °C	About 40% at 2 h	[15]
	Kollidon® VA64, Cremophor® RH40	Hydrophilicity, wettability and particle size reduction	6.0-folds higher than commercial tablet	—	30% at 2 h (commercial tablets was only 0.68% at 2 h)	[16]
Naproxen	Hydroxypropyl-β-cyclodextrin, arginine	Hydrogen bond formation, Electrostatic interactions	—	—	—	[17]
Fenofibrate	Hydroxypropyl-β-cyclodextrin, hydroxypropyl methylcellulose (HPMC)	Formation of inclusion complexes	—		90% in 20 min	[18]
Gliclazid	Sodium lauryl sulfate, crosslinked polyvinylpyrrolidone	Prevention of drug agglomeration, wettability and hydrophilicity enhancement	—	—	90% in 2 h	[19]

Table 2.
Specificities of several ternary systems involving poorly water soluble drugs (Indomethacin, Ibrutinib, Probucol, Naproxen, Fenofibrate, and Gliclazid).

		IM + $Mg(OH)_2$	IM + $Si(O)_2$	IM + $Si(O)_2$ + $Mg(OH)_2$
Amorphization time		60 min	60 min	10 min
DRIFT	OH (IM)/at 3377 cm^{-1}	Decreased	Decreased	Disappeared
Bands	Silanol group/at 3747 cm^{-1}	—	Disappeared	Disappeared
	OH (Mg $(OH)_2$)/at 3377 cm^{-1}	Unchanged	—	Unchanged

Table 3.
Observed changes for Indomethacin ternary solid dispersion compared to binary mixtures [13].

IM-$Mg(OH)_2$). After storage at 30°C and 11% of RH, IM-SiO_2 ground mixtures have shown rapid crystallization of amorphous Indomethacin. However, in the ternary co-grinding system, no crystallization was observed and this was attributed to higher acid–base interaction between Indomethacin and SiO_2 -Mg $(OH)_2$ interface that promotes the formation of bridging bonds (Si-O-C or Mg-O-C) which inhibited the molecular mobility of amorphous drug.

Mura et al. (2003), have shown that aqueous dissolution of Naproxen (a poorly water-soluble anti-inflammatory drug) can be considerably enhanced by combination with hydroxypropyl- β-cyclodextrin and some aminoacids (Arginine) [14]. Such ternary system exhibited higher stability constant and drug solubility (at pH ≈ 7and T = 25°C) than binary system (Naproxen/Arginine). The synergetic effect in Naproxen solubility (a 13.4-fold increase compared to pure drug) can be attributed to the establishment of electrostatic interactions between Arginine and the carboxylic group of Naproxen, as well as hydrogen bond formation between Arginine and the hydroxyl groups of HPβCD [14].

Lauretta et al. (2015) have shown that amorphous ternary solid dispersion of Gliclazid (poorly soluble drug used in the treatment of patients with type 2 diabetes) with crosslinked polyvinylpyrrolidone and SLS (Sodium Lauryl Sulfate) by co-milling method exhibited higher dissolution rate compared to the commercial product "Diabrezide" (Drug release of Gliclazid reached 90% in 2 h) [15]. Such solubility enhancement resulted from prevention of drug agglomeration in solution and improvement in wettability and hydrophilicity of co-milled particles.

In the case of Fenofibrate (FNB), a lipid-lowering drug (Class II) used in the treatment of hypertriglyceridemia and mixed hyperlipidemia, Xizhao Ding et al. (2018) have shown that the addition of Hydroxypropyl methylcellulose (HPMC) to the binary solid dispersion of Fenofibrate and Hydroxypropyl-β-cyclodextrin (molar ratio of 1:1), has shown a considerable enhancement of drug dissolution rate [16]. This ternary system has shown a percentage of 90% of drug release in 20 min (at 37 ± 0.5°C/pH = 7) which is higher than pure drug (24%) or binary system (60%). Such ternary solid dispersion was obtained by ball milling and led to the formation of inclusion complexes (increase in stability constants and complexation efficiency). This was attributed to the strong interactions established between FNB and HP-β-CD in presence of HPMC such as Van Der Waals dispersion forces, hydrophobic and hydrogen bonds, following the release of high-energy water molecules from HP-β-CD cavity [16].

Co-milling Ibrutinib (poorly water soluble antitumor drug) with oxalic acid (OXA) and microcrystalline cellulose (MCC) for six hours (Man Zhang et al. 2019) led to a simultaneous improvement in drug dissolution rate (5.33-fold higher than crystalline Ibrutinib) and physical stability of amorphous drug under stress conditions (75% RH and T = 40°C for six months) [17]. Plasma drug concentration of the ternary system (Ibrutinib, OXA, and MMC) exhibited also an increase of

1.49-fold compared with crystalline Ibrutinib. This was attributed to wettability and hydrophilicity enhancement, as well as the presence of ionic interactions between drug and carriers as suggested by XPS (X-ray photoelectron spectroscopy) analysis showing the appearance of protonated amines (N^+) and high binding energy (+2.75 eV) in the ternary system (Ibrutinib/OXA/MCC) [17].

The combination of polymer (Kollidon® VA64) and surfactant (Cremophor®RH40) was effective for Probucol (poorly water soluble antioxidative drug/BCS II) solubility enhancement by ball milling technique (Lijia et al. 2017) [18]. This considerably enhanced in vitro dissolution and in vivo bioavailability in rats. Such enhancement was attributed to the greater hydrophilicity, increased wettability and particle size reduction. The local solubilization effect of surfactant contributed also for preventing the aggregation of drug particles during dissolution. Otherwise, pharmacokinetic study has shown an increase of maximum plasma drug concentration for the ternary co-milled system which was 6.0-folds greater than that of Probucol commercial tablets [18].

On the other hand, Fang Li et al. (2019) have shown that dissolution rate and oral absorption of Probucol can be further improved by the formation of drug nanosuspensions (planetary beads-milling technique) using ternary stabilizers mixtures (Hydroxypropyl cellulose, an anionic surfactant (Sodium dodecylsulfate, SDS) and a nonionic surfactant (Pluronic F69)) [19]. Such Probucol nanosuspensions were physically stable after storage during 7 days at 4°C or 25°C, with highest dissolution rate (more than 60% at 2 h). The in vivo pharmacokinetic study has also shown 15-folds higher value of the plasma Probucol concentration compared to that obtained for coarse Probucol suspension. Probucol dissolution enhancement was attributed to particle size reduction and the characteristics of the polymeric chain which is dependent on the nature of polymeric stabilizer used in the mixture [19].

3. Solubility enhancement of Ibuprofen by formation of physically stable amorphous ternary system (Ibuprofen, PVP, β-cyclodextrin)

In recent years, researchers have used several techniques to improve the dissolution rate and bioavailability of Ibuprofen (IB), a non-steroidal anti-inflammatory drug (NSAID) which is poorly water soluble. The manipulation of the solid state of ibuprofen (**Figure 1**) remains a challenge for researchers because of its lower glass transition (Tg = −42 ± 1° C) and its tendency to recrystallized at room temperature [20]. The solubility improvement of ibuprofen was achieved by solid dispersion with different excipients (HPMC, Soluplus, PVP, Kaolin) [21–23], which differ in their solubilization abilities and their interactions with drug molecules. Several researchers have used complexation in the presence of βCD to improve the bioavailability of IB [24]. A water-soluble complex IB/βCD was obtained by co-precipitation or granulation (wet process) [25, 26]. Ibuprofen can also form an inclusion complex

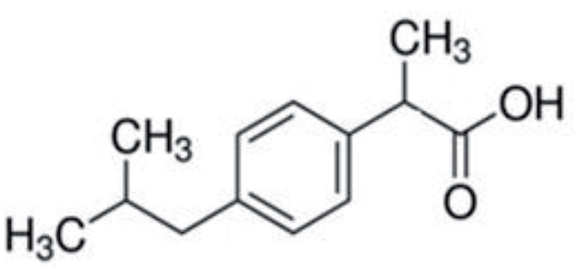

Figure 1.
Ibuprofen molecule.

with βCD mechanically [27]. It has been shown that the complexing efficiency of the IB/βCD system formed in the solid state depends on the techniques applied [28]. In our previous published work [29], binary solid dispersion of IB was achieved by co-milling the drug and βCD molecules, and then PVP was added to the binary mixture (IB/βCD) in order to evaluate physico-chemical changes in solid state.

3.1 Milling method

Ibuprofen was milled in presence of β-Cyclodextrin and then PVP at different weight ratios, physical mixtures (PM) were prepared by homogenization of pure components using ceramic mortar. Milling procedure was performed in a planetary ball mill (Pulverisette 7, Fritsch) using two milling jars (45 cm3)/7 balls (⌀ = 1 cm) in ZrO_2. The rotation rate was set to 300 rpm and the ball/sample weight ratio was 82.5:1. The milling procedure was optimized for 10 h at room temperature (≈298 K) constituted by 20 min milling periods with pause periods (10 min) in order to minimize the overheating of the sample.

3.2 Results

In the case of the binary system (IB/βCD), the X-ray diffraction results showed the complete amorphization of the βCD (**Figure 2**), while the crystallinity of the IB has been slightly modified [29]. Amorphization of βCD by milling at room temperature is predictable, as milling is carried out at a temperature sufficiently below the Tg of βCD (Tg ≈ 292°C) [30]. The enlargement of the Bragg peaks is explained by the reduction in the size of the crystallites and slight distortions of the crystal lattice generated by ball milling. As shown by SEM micrographs (**Figure 2**), the birefringence and the crystallinity of drug particles were moderately affected in the binary system (IB/βCD). By adding 20% of PVP to this binary mixture, the formation of amorphous agglomerations can be observed [29]. This aspect is similar to that obtained in the case of inclusion complexes between IB and βCD by different methods (co-precipitation, lyophilization) [31]. As shown by X-ray diffraction results (**Figure 2**), the ternary mixture (IB/βCD/PVP) was totally amorphous and showed physical stability after storage under stress conditions at RH: 75% and T = 40° C for 6 months, while the quenched IB (**Figure 2**) recrystallized at room temperature after few minutes [29].

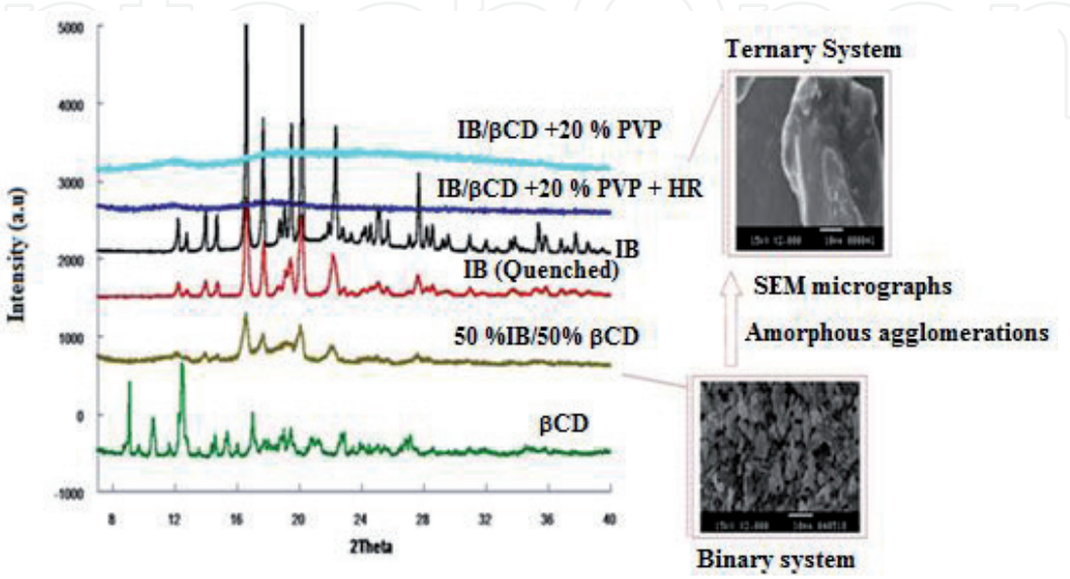

Figure 2.
X-ray diffraction results and SEM micrographs of binary and ternary system [29].

Different mechanisms were involved in the physical stabilization of amorphous IB in the ternary system, this required the use of several techniques (XRD, FTIR, SEM, DSC, and NMR) according to ICH recommendations [32]. Noticeable changes were resumed in **Tables 4** and **5**. In the case of the binary mixture (IB/βCD), the frequency shift of the carbonyl group of IB (**Table 4**) [29], could be attributed to the breaking of certain intermolecular bonds (hydrogen bonds) associated with IB dimmers, largely described in the literature [33]. The shift of the CO (primary alcohol) band and the OH (associated) band of βCD compared to physical mixtures, as well as the disappearance of the NMR proton of the carboxylic group of IB and the hydroxyls peaks of βCD (2, 3, 6) suggested the presence of hydrogen bonds between the carboxylic group of IB and hydroxyl groups of βCD [29]. DSC results (**Table 5**) have shown that the ternary mixture (IB/βCD/PVP) exhibited higher glass transition temperature (Tg>250°C). This effect contributed to the reduction of molecular mobility of amorphous drug molecules and prevented its recristallization [29]. The addition of PVP to the binary system (IB/βCD) generated higher shifts for several infrared bands of IB, PVP and βCD (**Table 4**), this was accompanied also by an upfield shift of proton peaks of IB and βCD (located inside and outside the cavity), and a downfield shift of carbonyl peaks of IB and PVP [29]. All these changes can be attributed to the formation of multiple hydrogen bonds between the carboxylic group of IB and the carbonyl group and nitrogen of the pyrrolidone ring of PVP [34], as well as intermolecular hydrogen bonds between βCD (**Figure 3**) and PVP that were frequently observed in ternary systems [29, 35].

Mixtures/ infrared bands	**Shifts**					
	C=O(IB)	**C=O(PVP)**	**OH/associated (βCD)**	**C-O/ secondary alcohol (βCD)**	**C-O/ primary alcohol (βCD)**	**C-N (PVP)**
Binary system	8 cm^{-1}	—	11 cm^{-1}	2 cm^{-1}	3 cm^{-1}	—
Ternary system	12 cm^{-1}	5 cm^{-1}	22 cm^{-1}	5 cm^{-1}	6 cm^{-1}	12 cm^{-1}

Table 4.
Shifts of Infrared Bands compared to physical mixtures [29].

	DSC	**RMN 1H**	**RMN 13 C**
Binary system	• A decrease of melting temperature Tf (IB)	• Disappearance of the proton peaks of IB carboxylic group and hydroxyl groups of βCD (2, 3, 6)	• Upfield shirt of IB carbon peaks (Δδ [0.04:0.08] ppm)
Ternary system	• Disappearance of IB melting event	• Upfield shift of all proton peaks of βCD (located inside and outside the cavity) except hydroxyl peak (6) which downfielded	• Downfield shift of carbonyl peaks of IB and PVP
	• Tg (glass transition temperature) >250°C	• Upfield shift of IB protons (higher than binary system)	

Table 5.
NMR and DSC characterization of co-milled mixtures (IB/βCD, IB/βCD/PVP) [29].

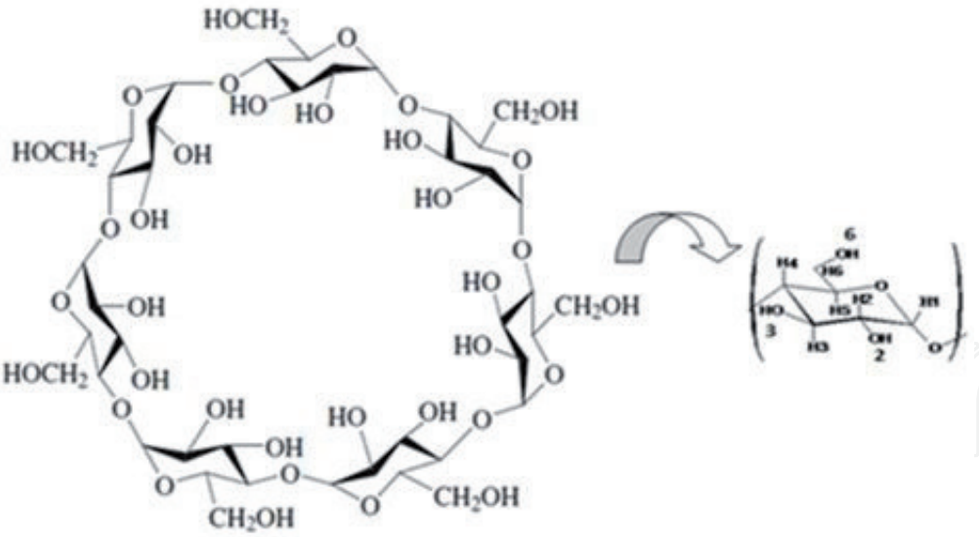

Figure 3.
βCD molecule [29].

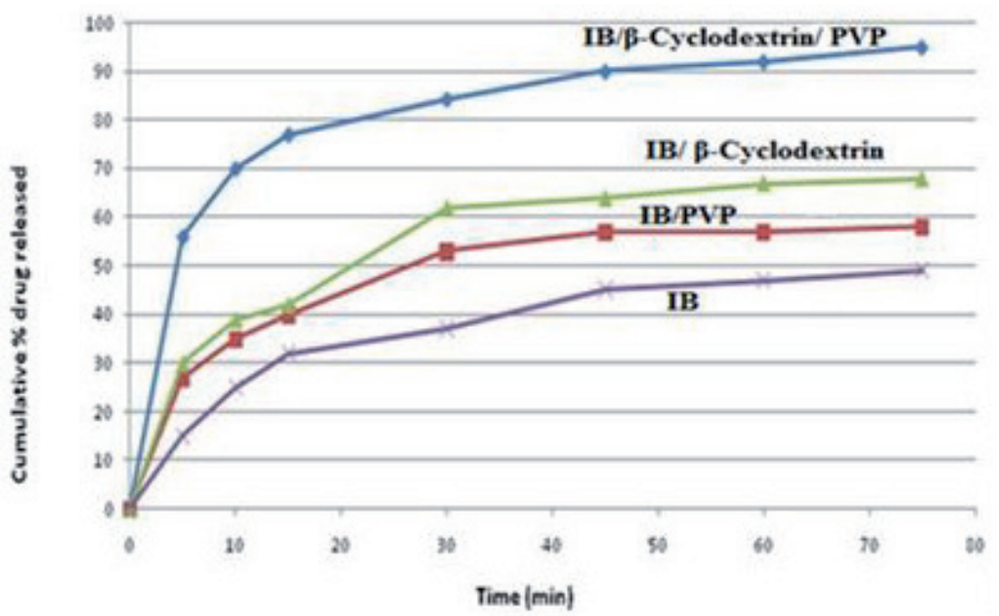

Figure 4.
Dissolution test results of co-milled mixtures (each point represents mean ± S.D., n = 3 [29]).

As a result of physical stabilization of amorphous Ibuprofen via different factors described previously, the IB dissolution rate (**Figure 4**) in the ternary mixture (IB/βCD/PVP) in 1:1:0.5 w/w ratio was greater than that obtained in the case of the binary mixture (IB/βCD) or (IB/PVP) in 1:1 w/w ratio [29]. The formation of such a water-soluble system can be explained not only by the synergistic effect of PVP and βCD via their mutual intermolecular interactions, but also by the ability of PVP to solubilize and promote formation of βCD complexes in the solid state [29]. Loftsson et al., have shown the role of PVP as a solubilizer in the case of several βCD complexes [36]. A ternary system (salt formation) was also obtained for IB and showed a considerable improvement in drug solubility and stability compared to the IB/βCD binary system [37]. Thus, the combination of PVP and β-Cyclodextrin molecules represents a scalable alternative for dissolution enhancement of IB which weakly interacted with β-Cyclodextrin by ball milling at ambient temperature [29].

4. Conclusion

In summary, the formation of physically stable ternary amorphous system by solid dispersion method using optimized ball milling technique, represents a promising alternative for drug solubility and stability enhancement. This succeeded for improving the dissolution rate of several active pharmaceutical ingredients (e.g., Probucol, Gliclazid, Fenofibrate, Ibrutinib and Naproxen). Their pharmacokinetic properties and in vivo bioavailability were considerably improved in comparison to pure drug molecules (up to 15-folds increase in plasma drug concentration). Ibuprofen dissolution rate was considerably enhanced in presence of PVP and βCD (release of 90% in 1 h), such ternary system (IB/βCD/PVP) in 1:1:0.5 w/w ratio exhibited higher drug release than binary systems (IB/PVP, IB/βCD) in 1:1 w/w ratio. This was resulted from various mechanisms (intermolecular interactions, synergetic effects of carriers, anti-plasticizing effect, hydrophilicity enhancement, particle size reduction, inclusion of IB molecules in βCD cavity) promoting stabilization of amorphous Ibuprofen even under stress conditions (75% RH and T = 40°C for six months). However, such scalable strategy requires the association of several analytical techniques in order to fully understand the solubilization and stabilization processes involved.

5. Perspectives

A development of stability assay method should be performed to evaluate the absence of drug impurities in the ternary system. Moreover, it is necessary to further investigate the nature of interactions between drug molecules and carriers in such complex system.

Acknowledgements

The authors thank Pr. Abdessalem Ben Haj Amara (Faculty of Sciences of Bizerte, Tunisia) for his considerable inputs and helpful discussions. On the other hand, the authors confirmed that this research Work did not receive any specific funding.

Conflict of interest

The authors declare that they have no conflict of interest.

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