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Chapter

Multifunctional Roles of PVP as a Versatile Biomaterial in Solid State

Marouene Bejaoui, Haykel Galai, Fathi Touati and Salah Kouass

Abstract

Polyvinylpyrrolidone (PVP) has proven to be a highly versatile material, as evidenced by its long history as multifunctional biomaterial with a wide range of high-performance applications (e.g., tissue engineering, drug delivery systems, and ophthalmologic applications). PVP was frequently used in medical and pharmaceutical field due to its several interesting properties (higher glass transition temperature, water solubility, biocompatibility, biodegradability, chemical stability, very good adhesive, and emulsifying agent). This chapter highlights the multifunctional roles of PVP in pharmaceutical formulations in solid state. In fact, PVP acted as a stabilizing agent for various amorphous drug molecules by minimizing their molecular mobility. Physical stabilization resulted from the reinforcement of intermolecular interactions in binary or ternary systems due to the synergetic effect of PVP. This made it possible to overcome several challenges for drug formulations (e.g., solubility and bioavailability weakness, physical instability under stress conditions, complexation efficiency of cyclodextrin molecules). In this chapter, the effect of PVP on the binary solid dispersion (indomethacin:kaolin) is discussed. We have shown that PVP enhanced physical stability of amorphous indomethacin under stress conditions (at RH: 75% and T = 40°C for three months), leading to the improvement of drug aqueous solubility by suppressing kaolin adsorption effect.

Keywords: biomaterial, PVP, molecular mobility, physical stability, water solubility, solid dispersion, kaolin, indomethacin

1. Introduction

Polyvinylpyrrolidone (PVP) is widely employed as a multifunctional material and it was approved by the US Food and Drug Administration as a safe polymer for biological experiments due to its simple processability, biocompatibility, and non-antigenicity [1, 2]. The biomedical and pharmaceutical fields are among the most explored (**Figure 1**). Recently, PVP is considered as the most promising polymers, not only for the development of new pharmaceutical formulations [3, 4] but also for the optimization of several properties of bioactive glasses [2, 5]. This chapter highlights the link between PVP and some bioactive glasses. The multifunctional roles of PVP in pharmaceutical field were also discussed, focusing on the effect of PVP in terms of physical stabilization and solubility enhancement of various drug formulations in solid state (milling method as example).

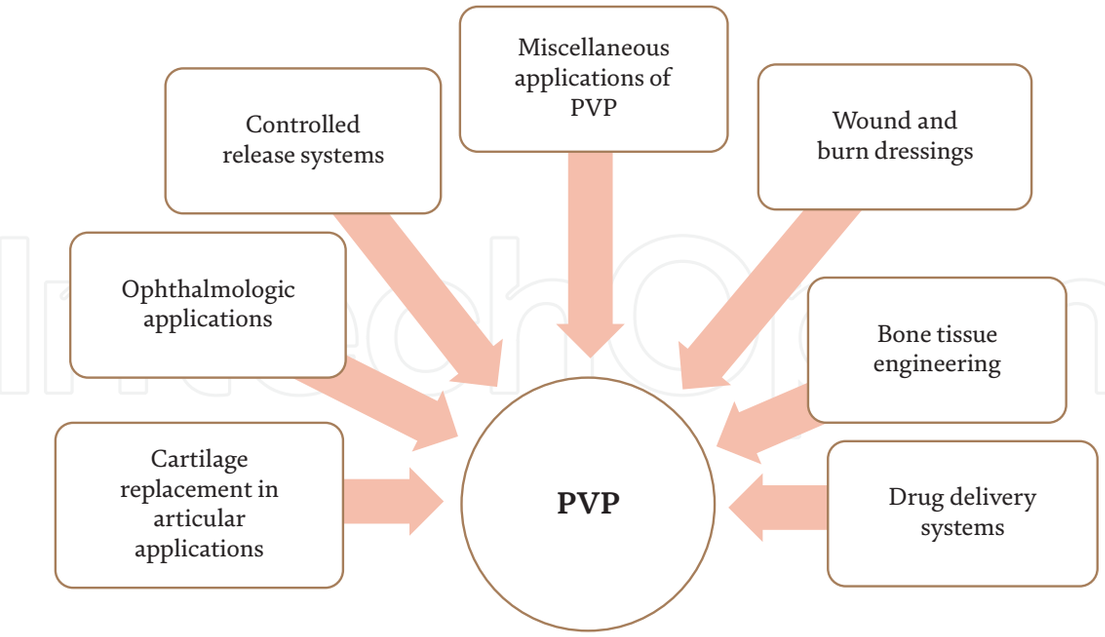


Figure 1.
Schematic representations of various PVP applications [2].

2. The usage of polyvinylpyrrolidone (PVP) in biomaterials

PVP was largely employed as a reinforcing material for biocomposites in a variety of applications, including bone tissue engineering, soft implants, biosensors, and artificial cartilage substitutes [2]. PVP can also be used in the fabrication of PVA hydrogels-based composite scaffolds for bone tissue engineering [6].

Cheng et al. have shown that, in the case of bioactive glass ceramics (BG), PVP induced faster apatite deposition and maintained the hybrid structure during electrospinning and pre-oxidation. This led to bioactivity improvement of bioactive glass [5]. For bioactive glass fibers (sol-gel synthesis), Hatcher [7] have demonstrated that PVP facilitated the synthesis process and the control of the rheological properties (more homogeneous fibrous material). PVP acted as a stabilizer by preventing gelation of the sample for 4 months. This was effective for enhancing *in vitro* bioactivity and increased proliferation of such bioactive glass fibers [7].

Moreover, Xia et al., have also shown that the addition of PVP resulted in sufficient chain entanglement and the formation of smooth bioactive glass nanofibers (electrospinning technique combined with sol-gel processing) [8]. Borate-modified bioactive glass [9] (burning-out method) was successfully achieved thanks to PVP, which greatly improved the blend's homogeneity. Ali et al. have obtained cerium-doped bioactive glass nanoparticles (scaffold fabrication) [10] by optimization of its mechanical properties using PVP. **Table 1** presents a list of published works focusing on bioactive glasses involving PVP.

Otherwise, PVP was used in some biomaterials for articular cartilage replacement because of its high hydrophilicity, which aids in the lubricating conditions of the resulting hydrogel [12]. PVP-based hydrogel was also obtained by radiation crosslinking and was effective for skin regeneration and wound dressing [13]. Multifunctional chitosan/PVP/45S5 Bioglass® scaffolds were also innovative for bone tissue engineering applications because of their outstanding bioactivity and *in situ* antibiotic-releasing capability [11]. PVP acted as stabilizer by inhibiting the enzymatic degradation of chitosan [11].

Bioactive glass	Authors
Bioactive glass-ceramics (BG)	Cheng et al. [5]
Bioactive glass fibers (sol-gel synthesis)	Hatcher [7]
Borate-modified bioactive glass (burning-out method)	Abdelghany et al. [9]
Cerium-doped bioactive glass nanoparticles (scaffold fabrication)	Ali et al. [10]
The 45S5 Bioglass® (BG)	Yao et al. [11]
Bioactive glass nanofibers (electrospinning technique combined with sol-gel processing)	Xia et al. [8]

Table 1.
List of published works on bioactive glasses involving PVP.

3. Multifunctional roles of PVP in pharmaceutical field

PVP (**Figure 2**) has several advantages in the pharmaceutical fields, and it acted as a stabilizer, a protective agent, a binder, a lubricating, a crystallization inhibitor, and a bioavailability enhancer for several active pharmaceutical ingredients (API) [4, 14]. It is widely known that PVP exhibited a higher solubility in water and polar solvents [15], and it also has a higher glass transition temperature (165 ± 1°C [16]) and was chemically stable in dry conditions [15]. Such physicochemical properties of PVP (**Table 2**) make it a versatile polymer with effective abilities in pharmaceutical field.

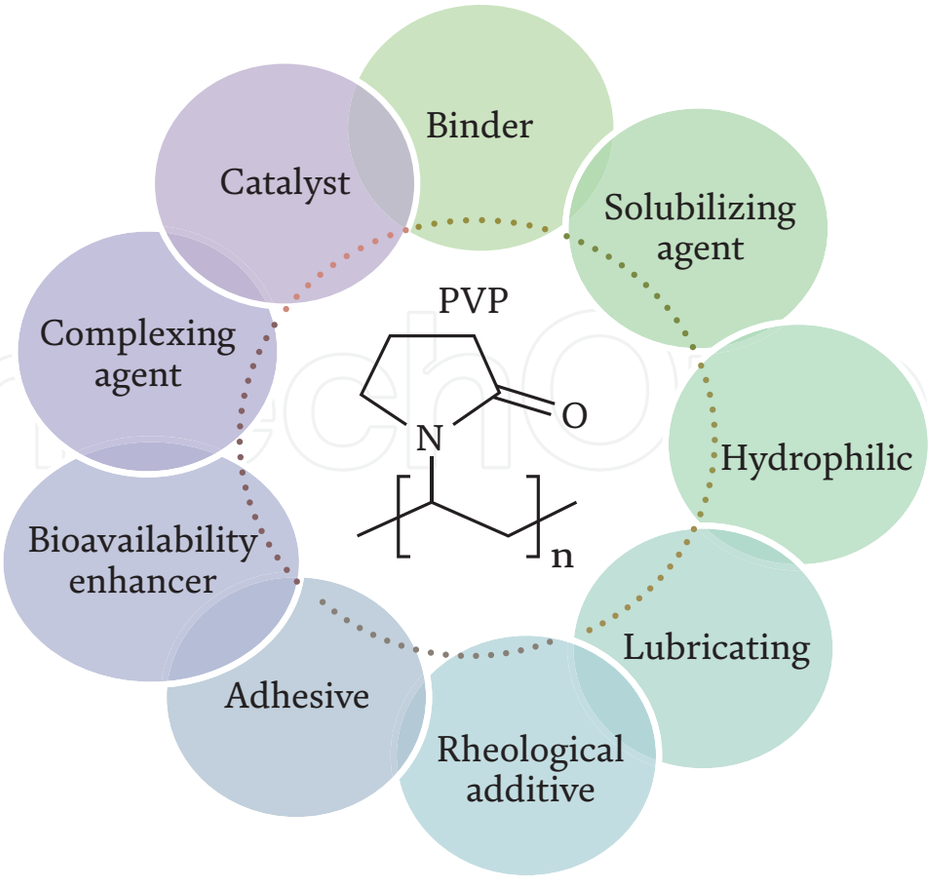


Figure 2.
Various pharmaceutical applications of PVP [14].

Properties	Details
Cas number	9003-39-8 [15]
Description	Hygroscopic amorphous white powder [15]
Formula	$(C_6 H_9 NO)_n$ [15]
Molecular weight	2500–30,00,000 D [15]
IUPAC name	l-ethenylpyirolidin-2-one [15]
Other names	Povidone, PVP, polyvidone, plasdone, Kollidon, poly [l-(2-oxo-pyrrolidinyl)ethylene], 1-vinyl-2-pyrroli-dinone polymer, 2-pyrrolidinone-l-ethenyl-homopolymer [15]
Solubility	Soluble in water, polar solvents, acids, and amines. Insoluble in ethers, hydrocarbons, mineral oil, and some esters [15]
Glass transition temperature	165 ± 1°C [16]
Stability	Chemically stable in dry form [15]
K value	Range 10–120 [15]

Table 2.
Physicochemical properties of PVP [15].

Many published works have shown the ability of PVP to enhance complexation, thus influencing drug solubility and stability [17]. Valero et al. have already shown that PVP enhanced the inclusion complex formation in the presence of β-cyclodextrin and naproxen molecules [18]. PVP has been proven to be an effective solubilizer for various β-cyclodextrin complexes [19]. Chemical stability can be also enhanced by PVP in solid state, and the chemical degradation of cilazapril was considerably inhibited by solid dispersion within PVP [20].

On the other hand, PVP was largely used to develop various drug delivery systems, including oral, topical, transdermal, and ophthalmic administration [2, 4, 19]. PVP-based fibers composed of several active substances were successfully achieved [21]. PVP hydrogels [22], oral tablets [23], PVP films [24], composite nanoparticles [25], microcapsules [26], and microspheres [27] were also developed. **Table 3** [3, 22, 24, 28–43] shows a summary of PVP-based drug delivery systems. Gamma irradiation, crosslinking, casting, electrospinning, and grafting were the most used techniques to produce PVP-based hydrogels [22, 31, 32]. PVP-based fibers were prepared by electrospinning, coaxial, and sequential electrospinning [33, 34]. PVP-based tablets were also produced by different techniques: 3D Printing [35, 36], spray drying or ball

Drug delivery systems	Active compound involved	Authors
Nanoparticles	Ciprofloxacin, paclitaxel, curcumin	[28–30]
Hydrogels	Salicylic acid, ketoprofen, amoxicillin	[22, 31, 32]
Fibers	Indomethacin, emodin, ibuprofen	[3, 33, 34]
Tablets (3D printing)	Dipyridamole, theophylline, pantoprazole sodium	[3, 35, 36]
Films	Fentanyl, ibuprofen haloperidol. Diltiazem hydrochloride & indomethacin	[24, 37–39]
Microparticles	Andrographolide, celecoxib, cefuroxime axetil, nimesulide	[40–43]

Table 3.
Examples of PVP-based drug delivery systems [3, 22, 24, 28–43].

milling followed by compression, direct or double compression, solvent evaporation or wet granulation followed by compression and supercritical impregnation [3]. Up to now, solution casting was frequently used to obtain PVP-based films [24, 37–39]. Drug-loaded PVP particles can be prepared by several techniques including spray drying, co-grinding, supercritical-assisted atomization (SAA), supercritical antisolvent (SAS) process, coacervation, freeze drying, and wet chemical method [40–42].

Regardless of preparation method, PVP-based solid dispersions were widely employed for several poorly soluble drug molecules in order to enhance their dissolution rate, for example, indomethacin (IND), sulfisoxazole, sulfathiazole, phenytoin, chloramphenicol, furosemide, tadalafil, nifedipine, naproxen, carbamazepine, ibuprofen, celecoxib, silymarin, nimodipine, β-lapachone, gliclazide, carvedilol [2, 4, 18, 19, 44–47]. Actually, solid dispersion technology by milling is one of the most attractive techniques for PVP-drug formulations [48]. Such technique was considered as environmental, scalable, economic, and simpler than other conventional methods [49]. In fact, solubility enhancement and physical stability of amorphous ibuprofen (at RH: 75%/T = 40°C for 6 months) can be achieved by ternary system formation (ibuprofen/β-cyclodextrin/PVP K30) in the ratio (1:1:0.5 w/w) [50]. This led to a 1.5–2-fold increase in the ibuprofen dissolution rate only after 10 min [50]. Such system was obtained by milling the drug in solid state at room temperature (25°C). PVP has undoubtedly reinforced synergy between compounds by establishing intermolecular H-bonds and electrostatic interactions between ibuprofen and β-cyclodextrin molecules [50]. Gupta et al. have shown that the antiplasticizing effect of PVP plays an important role in the stabilization of amorphous celecoxib (CLX) obtained by mechanical grinding, and this effect reduces the molecular mobility of the API and inhibits its recrystallization [51]. It has also been shown that ternary mixtures containing two excipients (PVP/MEG) have a greater CLX-solubilizing effect than that obtained by binary mixtures (PVP/CLX) [52]. Dissolution rate of bicalutamide was also enhanced by physical stabilization of its amorphous state using PVP [53].

Furthermore, several pharmaceutical products are formulated with PVP, for example, Betadine®, Inadine®, Prevail-FX®, ScrubCare®, and DuraPrep® [4]. Various studies have recently reported that PVP-iodine could be explored as a preventive aid against COVID-19 thanks to its antibacterial, antifungal, and antiviral properties [54].

3.1 The effect of PVP on indomethacin: kaolin solid dispersion

In our recent published work [55], we have studied the solid dispersion of binary system (indomethacin/kaolin) in the presence of PVP K30 by co-milling technique [55]. The milling procedure was carried out in a high-energy planetary ball mill (Pulverisette 7, Fritsch), using the stable γ form of indomethacin (IND, **Figure 3**). The milling parameters were optimized in order to avoid polymorphic transformations or chemical degradation of drug molecules [55].

Main results of characterization techniques are summarized in **Table 4** (curves not shown, [55]). According to XRD results [55], the addition of variable amount of PVP to the binary mixture (IND:kaolin, in 1:1 ratio) led to the loss of drug crystallinity. IND particles were totally coated by amorphous films of the polymer as shown by SEM micrographs (**Table 4**), and this was completely different to that observed in the binary mixture (IND:kaolin, in 1:1 ratio) [55]. Amorphous drug molecules maintain its physical stability even after exposure to stress conditions (RH: 75% and T = 40°C) for 6 months [55]. The stabilization of amorphous Indomethacin dispersed within kaolin was explained by different factors.

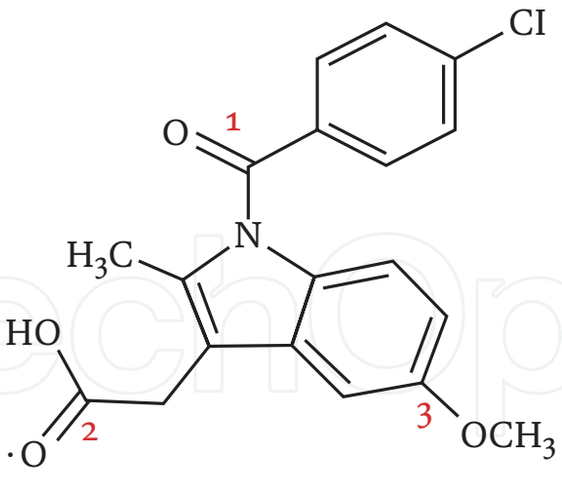


Figure 3.
Indomethacin molecule.

On the one hand, FTIR results have shown that C=O band (cyclic dimer) of IND shifted toward higher frequencies; however, the C=O (benzoyl) band shifted to lower frequencies and merged with the (C=O) band of PVP [55]. ^{13}C NMR spectroscopy has also indicated an upfield shift of IND carbon peak bound to methoxy groups and carbonyl group (2), which disappeared in the presence of 75% of PVP, while the C=O peak of PVP shifted toward higher values (from 176 ppm to 161 ppm) and merged with indomethacin peak [55]. The same behavior was already reported for IND: SiO_2 solid dispersion obtained by co-milling and this is due to intermolecular interactions between siloxane bonds and the oxygen of methoxy or carbonyl groups in IND molecules [56]. Therefore, FTIR and NMR results suggested the establishment of hydrogen bonds between carbonyl group of PVP and carboxylic group of indomethacin [55].

On the other hand, DSC curves have shown the appearance of a single transition event (Tg) that suggests the miscibility of the components in such mixture, and melting event of IND disappeared indicating complete conversion from crystalline to amorphous state [55]. The antiplasticizing effect of PVP has undoubtedly reduced the molecular mobility of amorphous drug molecules leading to its physical stability as shown by the XRD results [55].

According to previous results, the synergy of different factors could explain the stabilization of amorphous IND under stress conditions: hydrogen bonds formation between PVP and drug molecules, antiplasticizing effect of PVP, and hydrophilicity enhancement. This resulted in suppressed recrystallization of amorphous IND by inhibiting its molecular mobility [55].

In the case of binary mixtures (IND:kaolin), drug solubility decreased (**Table 5**) and this was attributed to kaolin adsorption effect [57]. Such attenuation occurred for many kaolin-based formulations [13], which constitutes an impediment for pharmaceutical use of kaolin [58]. As a result of PVP addition, water solubility of Indomethacin has been considerably improved (**Table 5**) in ternary systems [55]. By adding 75% of PVP to the binary system (in 1:1 ratio), water solubility increased about 4.5-folds [55].

It was already shown that PVP has a potential ability to enhance drug solubility, in many ternary systems [59]. Adding PVP to the binary solid dispersion (sodium lauryl sulfate/ibuprofen) was more efficacious in terms of drug dissolution enhancement [59]. Mahapatra et al. have shown that PVP has better enhanced valsartan solubility than β-cyclodextrin and hydroxypropyl β-cyclodextrin [60]. Dissolution rate enhancement

	DSC	XRD	RMN^{15}C	FTIR	SEM micrographs
BM	• A decrease of melting temperature T_f (IND)	• Partial disappearance of drug X-ray diffraction peaks	• No remarkable shifts	v(C=O)band (benzoyl) decreased	Apparition of amorphous microfibers adsorbed at the surface of kaolin [55]
TM	• Disappearance of drug melting event • Tg (IND) increased (Tg = 47 ± 1°C in the presence of 75% PVP)	• Appearance of halos and loss of drug crystallinity	• Upfield shift of IND carbon peaks (2 and 3) • Downfield shift of C=O peak of PVP	v (C=O)band (cyclic dimer) increased v (C=O)band (benzoyl) decreased	Drug particle was totally coated by amorphous films of the polymer [55]

Table 4.
Summary of characterization results for binary (BM) and ternary systems (TM) [55].

Samples	Solubility (μg/ml)
IND	9.33 ± 0.05
50% IND + 50% kaolin (BM)	8.38 ± 0.05
25% IND + 75% kaolin	6.01 ± 0.05
BM + 10% PVP	16.66 ± 0.1
BM + 25% PVP	29.05 ± 0.1
BM + 50% PVP	43.44 ± 0.1
BM + 75% PVP	44.44 ± 0.1

Table 5.
Water solubility measurement of indomethacin in binary (BM) and ternary systems [55].

of efavirenz was successfully obtained by ternary solid dispersion using PVP and polyethylene glycol 8000 [61]. In addition to aforesaid, we have recently reported that solubility enhancement of poorly soluble drugs can be achieved by co-milling the drug in the presence of multiple carriers, and this led to the formation of physically stable amorphous system and was more effective than simple binary systems [62].

4. Conclusion

In summary, the versatility of PVP comes from its multiple utilizations as multifunctional additive in biomedical and pharmaceutical fields. PVP has promoted the actual advances in bioactive glass design (optimizing mechanical properties, enhancing *in vitro* bioactivity, increasing proliferation and homogeneity of the material). The use of PVP in bone tissue engineering and scaffolds fabrication has grown considerably in recent years and constitutes a crucial element for designing new biomaterials. Pharmaceutical field has also profited from physicochemical properties of PVP that mainly acted as stabilizer, a crystallization inhibitor, and a solubility enhancer for several poorly soluble drugs in solid state. Solid dispersion in the presence of PVP was proven to be a potential strategy for improving drug solubility in binary and ternary systems. It has also enhanced complexation abilities for many β-cyclodextrin complexes in solid state. In this chapter, we have shown that PVP was able to overcome solubility challenge for indomethacin:kaolin solid dispersion by suppressing the adsorption effect of clay mineral and stabilizing amorphous drug molecules under stress conditions. Stabilization of amorphous drug formulations was correlated with the synergy of different PVP abilities: antiplasticizing effect, hydrogen bond formation between drug and carrier, and hydrophilicity enhancement. Thus, PVP can be considered as a promising material that may contribute to the development of new pharmaceutical products in order to face the current challenges in the medical field.

5. Perspectives

It is necessary to further investigate on the mechanisms and nature of interactions within bioactive glass materials containing PVP. More attention should be accorded to the role of PVP in drug formulations composed of clay minerals.

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Conflict of interest

The authors declare that they have no conflict of interest.

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