Exploring the Role of Poly (N-vinyl pyrrolidone) in Drug Delivery

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Review
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Polyvinylpyrrolidone (PVP) is widely recognized for its hydrophilic properties, making it essential in pharmaceutical and biomedical industries as a carrier material. This review examines PVP-enriched delivery systems, emphasizing their capacity to integrate diverse active agents from both organic and synthetic sources. The versatility of PVP is showcased through its use in different formulations, such as microparticles, nanoparticles, fibrous structures, hydrogels, and tablets, which emphasize its potential in innovative drug delivery mechanisms. The review thoroughly examines the customized morphologies for specific PVP-drug combinations, detailing the active agents, methodologies, and processing parameters used. It discusses the advantages and challenges of these systems, underscoring the polymer's significant role in novel pharmaceutical product development. Overall, this detailed analysis confirms PVP's critical position in advancing drug delivery technologies, showcasing its multifaceted applications and potential for pioneering new treatments.

Keywords

nanoparticles, hydrogels, computational modeling, polyvinylpyrrolidone (PVP), drug delivery

Introduction

Polyvinylpyrrolidone is a synthetic polymer derived from N-vinylpyrrolidone. Polyvinylpyrrolidone (PVP) easily matches with biological systems and dissolves in water. It is acclaimed for its amphiphilic traits, allowing it to dissolve readily in a variety of solvents, both aqueous and organic. This versatility contributes to its formidable binding strength and stabilizing presence in both suspensions and emulsions, and enables it to host hydrophobic drugs effectively[1]. PVP is harnessed extensively within the realms of food processing, medical products, and cosmetic formulations, with a particularly pronounced presence in pharmaceutical and biomedical contexts[2]. The polymer is distinguished by its inert nature, transparency, thermal resilience, and consistent pH stability. The molecular mass of PVP spans a spectrum, indicated by K-values signifying different weight ranges, such as K12 (3100–5700 Daltons) to K90 (900,000–1,300,000 Daltons), which dictates its suitability for various applications[3].

PVP plays a multi-faceted role in the pharmaceutical industry. It is incorporated into various delivery mechanisms designed for eye, skin, and oral applications. It also plays a part in gene therapy endeavours[4] and, through its amalgamation with metallic elements, in the cutting-edge sectors of regenerative medicine[5–7] and precision-targeted delivery mechanisms[8,9]. The adaptability of PVP is evident in its compatibility with multiple drug delivery structures. Its capabilities extend to modulating drug release, stabilizing the amorphous and nanocrystalline forms of hydrophobic drugs—which in turn can increase their solubility and bioavailability—safeguarding actives from environmental variables like pH and temperature, and concealing disagreeable scents and tastes[10]. An array of active substances has been encapsulated within PVP-based micro and nanoparticles, utilizing a range of approaches such as spray drying to avant-garde methods, including supercritical fluid-assisted processes[8,11].

The polymer's capacity to form spinnable fibres has been utilized to engineer fibres loaded with diverse active agents[2,12], with substantial progress made in the formulation of PVP-based hydrogels[13,14] and oral tablets[15–19]. Such distinct attributes underscore PVP's potential in the development of pharmaceutical formulations, especially within the evolving fields of pharmaceutical and biomedical innovation, where it contributes to meeting the pharmaceutical market's ongoing demands. Never-

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theless, the extensive research featuring PVP as a fundamental carrier lacks a cohesive consolidation within the scholarly literature.

This review attempts to synthesize PVP's contributions to drug delivery. It delves into the critical factors, including chosen active principles, applied methodologies, envisaged applications, and the corresponding merits and demerits.

Different formulations for drug delivery

Hydrogels

Polymeric networks that can absorb significant water quantities have become increasingly important in various applications, notably in drug delivery systems[20]. These networks swell due to their hydrophilic groups while maintaining structure through crosslinking. Advantages for drug encapsulation include biocompatibility, minimal toxicity, and controlled drug diffusion. Challenges exist, such as rapid drug release from continuous hydrogels or toxic residue from unreacted crosslinkers[21]. Hydrogels find use in diverse delivery systems, including oral, transdermal, topical, nasal, ocular, and implants[21–25].

Rosiak *et al.*[26] engineered hydrogel dressings by polymerizing and crosslinking blends of natural and synthetic polymers, like PVP. Various methods have produced PVP hydrogels[27], though a few focused on drug delivery[14,15,28,29]. For example, PVP K30/pectin hydrogels were made using solution casting[28], embedding salicylic acid by diffusion. Hydrogen bonds formed between PVP and pectin, enhancing hydrogel strength with PVP concentration.

Studies on hydrogels responsive to stimuli like temperature and pH are increasing[14,30]. pH-responsive hydrogels release drugs according to body pH changes. A PVP hydrogel is developed with ß-methylacrylic acid, 2-butenoic acid which exhibits a novel pH-responsive nature[14]. Ketoprofen was released less in acidic conditions and more at intestinal pH levels. Hydrogel swelling, crucial for release kinetics, rose with pH.

Another research[29] produced pH-sensitive PVP K30/chitosan hydrogels, targeting gastric antibiotic delivery for *Helicobacter pylori* treatment. Amoxicillin served as the prototype medication, and chitosan was combined with PVP for efficient stomach-targeted release. The hydrogels' swelling was pH-dependent, swelling more in acidic media. Freeze-dried hydrogels had better dissolution kinetics in acid due to increased porosity and surface area.

In summary, the development of responsive hydrogels introduces new pharmaceutical and biomedical possibilities, addressing specific drug delivery challenges.

Fogaça and Catalani[13] developed a technique to produce PVP hydrogels containing PVP K90 nanofibers through electrospinning. These nanofibers were crosslinked using ultraviolet C radiation (UVC) and the Fenton reaction. The porous structures which incorporated biomolecules showed significant swelling properties. Drug release studies indicated Fickian diffusion for BSA from fibrous hydrogels and polymer chain relaxation (Case II transport) from cast hydrogels. Collagenase-loaded hydrogels released most enzymes within 10 hours, plateauing at 48 hours, and were proposed for treating wounds and burns[13].

PVP-based hydrogel systems are one of the important concepts in tissue engineering. A hydrogel is designed with PVP, carboxymethyl cellulose and polyethylene glycol embodying silver ions[7]. Gamma irradiation produced hydrogels with silver nanoparticles, improving antimicrobial properties and accelerating wound healing[31].

The existing literature on PVP-based hydrogels, while limited, highlights their potential for a variety of applications, including pH-responsive oral administration, skin applications, and tissue engineering. These hydrogels may offer novel pharmaceutical solutions, such as medicated ocular systems[32].

Fig. 1 illustrates a hydrogel sketch with active molecules dispersed in a PVP or polymeric blend network. Table 1 consolidates the primary outcomes in PVP-based hydrogel development, specifying techniques, carriers, and active compounds. This comprehensive overview underscores the versatility and potential of PVP-based hydrogels in pharmaceutical and biomedical applications.

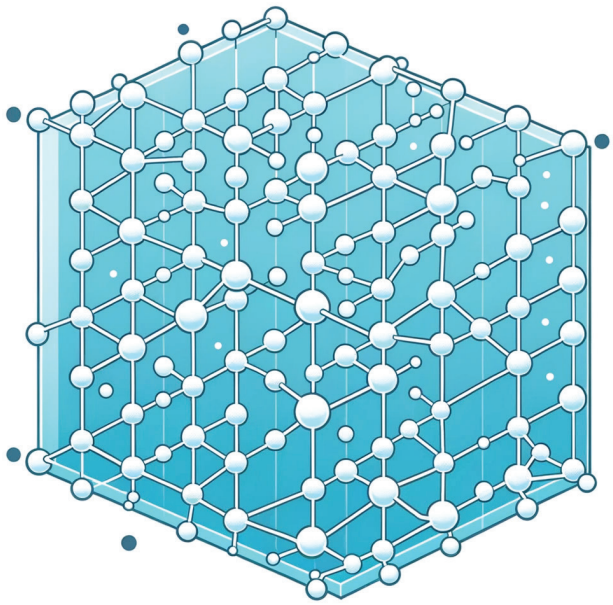

Fig. 1 – *Illustration of PVP-based hydrogels*

Table 1 – *Primary outcomes in PVP-based hydrogel development, specifying techniques, carriers, and active compounds*

Technique	Matrix material	Therapeutic agent	Observations	Reference
Gamma Radiation Synthesis	PVP/PEG**/agar/CMC***	–	Silver nanoparticle hydrogels with enhanced antimicrobial effect	7
Electrospinning and Crosslinking	PVP	BSA or collagenase	High porosity hydrogels with improved protein release rate	13
Gamma Irradiation Grafting	PVP grafted with CA	Ketoprofen	pH-targeted delivery with lower release at acidic pH	14
Casting with Radiation Crosslinking	PVP/PEG or PVP/Laponite	–	Superior water absorption and mechanical properties without active agents	15
Simple Casting	PVP/pectin	Salicylic acid	Slightly accelerated release at basic pH levels	28
Moulding with Freeze-drying	PVP*/chitosan	Amoxicillin	Optimal medication release in acidic settings	29

Tablets

The development of polymeric tablets has become a focal point in pharmaceuticals due to their efficiency in oral controlled drug release and relatively lower production costs. There are two main types of tablets: monolithic matrix systems, where the medication is uniformly distributed within a polymer matrix, and osmotic systems, that feature a core tablet encased in a semipermeable membrane.

In osmotic systems, the core usually holds the drug, referred to as the active layer, while the outer layer includes the osmotic agent, which controls the release rate of the drug.

Tablets are frequently created by compressing solid mixtures of polymers and drugs, made using various methods. For example, spray drying and ball milling were utilized to produce non-crystalline solid dispersions of PVP and vinyl acetate, which were compressed into tablets[16]. These tablets, particularly those with different tadalafil concentrations, demonstrated a significant improvement in dissolution rate compared to their crystalline forms and commercial versions. The spray-dried dispersions performed better at lower drug contents, while the ball-milled ones excelled at higher concentrations. Dissolution rates were also compared across various dosage forms, with powders dissolving faster than tablets and capsules.

Innovative methods such as solvent-free impregnation with supercritical CO_2 have also been applied to produce solid dispersions in tablet form. Researchers explored how different molecular weights of PVP affected the formulation and dissolution behaviour of piroxicam, a poorly water-soluble NSAID. They studied the polymer's impact on both the preparation process and the dissolution kinetics of this anti-inflammatory medication. The resulting tablets demonstrated that the dissolution rate markedly increased with tablets containing lower percentages of PVP K15, yet this effect diminished or reversed with higher molecular weights of PVP, possibly due to the gel layer formation in the dissolution medium. Tablets with an internal core and external coating utilizing PVP have been introduced[17].

Amorphous solid dispersions (ASDs) have gained significant attention for their ability to enhance the solubility and bioavailability of poorly water-soluble drugs, particularly those in BCS Class II. ASDs utilize polymers to stabilize the amorphous form of a drug, preventing its recrystallization and enhancing its dissolution rate. Given that more than 70 % of drugs in the pipeline suffer from poor solubility in human intestinal fluids, ASDs represent a crucial formulation strategy[33].

Several studies have demonstrated the effectiveness of ASDs in improving oral absorption. For example, formulations using polymers such as PVP, HPMC, and Eudragit have shown substantial improvements in the dissolution rates of various poorly soluble drugs. The choice of polymer and the method of preparation (e.g., hot melt extrusion, spray drying) significantly impact the stability and performance of ASDs. Hot melt extrusion has been particularly effective in producing stable ASDs with enhanced dissolution properties[34,35].

Summarizing, the ability of PVP to enhance drug dissolution rates, influence the osmotic pressure within tablet cores, and contribute to the release and durability of active ingredients illustrates the effectiveness of PVP in advancing pharmaceutical applications. Additionally, the incorporation of ASDs as a formulation strategy significantly improves the bioavailability of poorly soluble drugs, addressing a major challenge in drug development.

Fibres

The deployment of fibre structures has seen growing interest due to their versatile applications especially in drug delivery and tissue engineering[36]. Electrospinning has become a particularly notable method for producing fibres from a variety of materials, recognized for its ability to create ultrafine fibres with broad diameter ranges, from the nano to the microscale[37]. These fibres, when loaded with drugs, are particularly beneficial in enhancing the bioavailability of the active agents attributed to their expansive specific surface area and porosity which facilitate rapid drug release[38]. Nevertheless, these fibres' susceptibility to moisture can be problematic for drug delivery purposes.

PVP is frequently utilized as a base material in fabricating drug-laden fibres, leveraging its beneficial properties, yet it does encounter challenges such as moisture absorption[39]. For instance, fibres of PVP K90 infused with the NSAID indomethacin through electrospinning are produced, which reveals promising potential for use in wound care[2]. These fibres showed that altering the electrospinning solution's flow rate could influence the fibre's diameter, and showcased a high drug encapsulation efficiency with rapid dissolution rates in saline solutions, implying their effectiveness in active wound dressings. The properties of PVP, including hydrophilicity and hygroscopicity, were attributed to the accelerated drug dissolution in these fibres.

Additional studies[12] in wound healing have demonstrated that fibres made with PVP K90 and antibacterial agents such as Emodin can enhance the drug's dissolution rate, achieving full release from the PVP matrix in less than 90 minutes. Such fibres have been shown to significantly speed up the wound healing process in practical applications.

Investigations into PVP fibres have also spanned into regenerative medicine[40], with studies producing scaffolds for artificial skin tissue generation and wound healing. These studies highlight improved cell viability and accelerated healing when compared to electrosprayed PVP particles.

Oral pharmaceutical formulations have also benefitted from electrospun fibres[41,42,36]. One study[41] integrated *Garcinia mangostana* L. extract into PVP K90 fibres, resulting in fibres with increased diameter due to the active ingredient and demonstrating rapid extract release, suggesting that they are successful.

The rate of solution flow during electrospinning is a crucial factor that has been extensively analyzed across various studies[43], with slow processing times emerging as a significant challenge for scaling up production.

Yu *et al.*[42] explored the creation of ibuprofen-infused PVP fibres for the advancement of drug delivery systems which are orally dissolved. These fibres dissolved within seconds, highlighting the polymer-controlled dissolution mechanism, although a detailed analysis of the ibuprofen dissolution kinetics was not provided.

PVP is merged with other polymers to boost the attributes of electrospun fibre from the materialistic point of view[44], such as zein, a corn protein known for its hydrophobic and elastic properties[45]. These blends have been pursued for innovative drug delivery systems.

Coaxial electrospinning was employed to create core-sheath fibres designed for biphasic drug release, utilizing PVP K60 for the outer layer and zein for the inner matrix, with ketoprofen incorporated in both layers[45]. The fibres demonstrated an initial burst release followed by a prolonged release, suggesting their potential for medical applications.

Other studies have explored the blending of hydrophilic PVP with hydrophobic polymers such as Polycaprolactone (PCL), creating fibres suitable for wound dressings[43] and regenerative medicine[47]. These blends showed extended release of antibacterial agents and potential for tissue engineering applications.

PVP and cyclodextrins fibres filled with meloxicam have been produced to mask the drug's taste and improve its dissolution for oral delivery, with the inclusion of flavouring and sweetening agents[48].

The collective research underscores the multifaceted nature of PVP in fibre-based drug delivery systems, highlighting its ability to be utilized with other polymers to achieve targeted release profiles, necessary mechanical characteristics, and specific therapeutic goals.

Cyclodextrins (CDs) are lauded for their capacity to conceal bitter flavours and boost the solubility of compounds with low water solubility. Their compatibility with the electrospinning technique makes them ideal candidates for crafting advanced drug delivery systems[49–51]. Samprasit *et al.*[48] research illustrates that, when β-cyclodextrin or hydroxypropyl-β-cyclodextrin are mixed with PVP, the resulting fibres display not only an enhanced structure and stability but also show a reduced hygroscopicity attributable to cyclodextrins' moisture-protective property. These PVP-CD blended fibres disintegrate swiftly, expediting the release of meloxicam, and surpass the dissolution rates of the unenhanced drug and standard market versions. Human trials further corroborated their quick disintegration and effective taste-masking capabilities.

Summing up, fibres based on PVP, predominantly synthesized through electrospinning, stand

Table 2 – *PVP-based fibres. Critical insights from PVP fibre studies, specifying the polymer matrices and active agents.*

Technique	Carrier	Active agent	Result	References
Electrospinning	PVP	Indomethacin	Complete drug release in approximately 50 minutes	2
	PVP/PCL	–	Fibres with enhanced antimicrobial activity	5
	PVP	Emodin	Wound healing accelerated over 15 days	12
	PVP/Polylactic acid	Tetracycline hydrochloride	Uniform fibre alignment, complete antibiotic release in 50 min	38
	PVP	*Garcinia mangostana* L. extracts	Full dissolution of extracts in 100 minutes	41
	PVP	Ibuprofen	Improved tablet disintegration properties	42
	PVP/PCL**	*Tecomella undulata* extract	Gradual therapeutic release over 24 hours	43
	PVP/Poly(L-lactic acid)	Benzoin	Extended release up to 24 hours	44
	PVP*/zein	Ketoprofen	Drug release initially fast, then sustained (42 %)	46
	PVP/PCL	Trans-anethole	Consistent medication delivery	47
	PVP/HP-β-CD	Meloxicam	Quick dissolution in 60 minutes	48
Sequential Electrospinning	PVP/zein blended with GO	Ketoprofen	Dual-phase release: quick initial release, followed by sustained	39
Coaxial Electrospinning	PVP/ Poly(D,L-lactide)	Naringin and Metronidazole	Two-stage release: immediate and prolonged	46

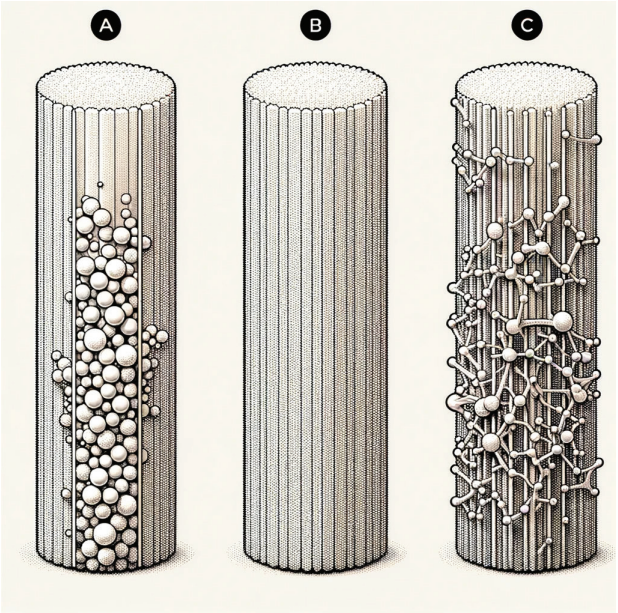

Fig. 2 – *(a) Active ingredient dispersed within the polymer matrix; (b) drug encapsulated in the centre of a form; and (c) dispersed drug in both the centre and the shell of the form*

out for their application diversity. They hold particular promise in regenerative medicine for tissue repair. Yet, the electrospinning process is hindered industrially by the extended time frames due to slow flow rates essential for achieving precise fibre properties. Overcoming this barrier—balancing swift production with fibre quality—is key for the method's widespread industrial use.

Pharmaceutically, PVP fibres' ability to enable biphasic drug release is especially advantageous for various medical treatments. Fig. 2 depicts different drug-loaded fibres that can be developed using PVP. The active ingredient might be distributed within a matrix made of PVP or its blends (Fig. 2a) or encapsulated within the core of core-shell fibres, potentially alongside a sheath that could contain the same or a different active compound (Figs. 2b and 2c). Table 2 in the associated documents compiles critical insights from PVP fibre studies, specifying the polymer matrices and active agents involved, presenting a detailed survey of the progress and potential of PVP fibre systems in drug delivery applications.

Microparticles and nanoparticles

Diminishing the drug particles dimensions to the micro and nano-scales is a critical strategy in drug delivery, directly addressing the challenge of poor water solubility that many active agents face, which can lead to suboptimal bioavailability, irregular absorption, and potential side effects due to overdosing. Minimizing particle size enhances the dissolving rate by providing a greater surface area for interaction with the dissolving medium[30]. Nonetheless, size reduction alone doesn't ensure formulation stability.

Various hydrophilic polymers are utilized to stabilize and create composite drug/polymer particles, among which PVP is particularly favoured for its distinctive characteristics[11,52,53]. PVP not only prevents the active ingredient's crystallization, enhancing dissolution in aqueous media but also acts as an odour and flavour masking agent and as a stabilizer, protecting the active ingredient from oxidation and deactivation.

PVP is integral to developing both microcapsules[52,53] and microspheres[54,55] with microcapsules featuring a core-shell structure where the active ingredient resides in the core and PVP or its blends form the shell. Microspheres, on the other hand, contain a homogeneously dispersed drug within a PVP matrix or PVP-blended matrix. Additionally, the advancement of composite nanoparticles with PVP as a carrier has been highlighted in several research projects[9], signifying PVP's role in diversifying drug delivery methods.

PVP-based nanoparticles have emerged as encouraging vehicles for selective drug delivery, especially in selectively targeting tumour cells[9,56]. In the work of Rose *et al.*[9], magnetically targeted delivery systems were crafted using PVP to coat magnetite (Fe_3O_4) nanoparticles, which were then used to adsorb epirubicin hydrochloride, a chemotherapeutic agent. The PVP coating was found to enhance the loading efficiency of the drug (78 %) and prevent nanoparticle agglomeration, subsequently achieving an 81 % inhibition rate against breast cancer cell growth. In a similar vein, a study[8] found that PVP-coated gold nanoparticles (average size of 14 nm) facilitated the targeted delivery of doxorubicin more effectively than the unprocessed drug or drug-unloaded nanoparticles, particularly against lung cancer cells.

The formulation of PVP-based microparticles has utilized diverse techniques, with spray drying being particularly prevalent[57,58]. In this method, a liquid solution is atomized and dried using a stream of hot gas. For instance, Bothiraja *et al.*[11] developed spherical microparticles of PVP K30 that encapsulated andrographolide, a hydrophobic compound which has various therapeutic benefits. By varying the PVP/andrographolide ratios, they created amorphous microparticles that exhibited enhanced flow characteristics and stability over three months compared to sole drug itself. The encapsulation within PVP also notably inhibited recrystallization, as corroborated by additional research[59]. These microparticles demonstrated a quintuple rise in the dissolvent rate of andrographolide, along the release rate further augmented by a higher PVP/drug ratio, a finding consistent across various studies utilizing different micronization technologies[60,61]. Nonetheless, there were exceptions where low PVP content did not enhance dissolution[31], which was also observed with alternate techniques[62].

The morphology of drug particles encapsulated in PVP and produced by spray drying is significantly influenced by several factors. These include the rate of gas flow and the temperatures at the inlet and outlet. Elements like above also influence the consistency of prepared formulation, the dissolving of the drug and the dynamics of drug recrystallization[63,64]. For instance, Paudel *et al.*[64] investigated how the inlet temperature and airflow rate impacted certain characteristics of PVP & naproxen particles mixed at a specific ratio. They found that non-crystalline particles created under higher inlet temperatures and increased airflow rates not only dissolved faster but also exhibited enhanced stability against moisture, indicated by a slower rate of drug recrystallization.

Traditional methods like freeze-drying[65], coacervation[52,53], and co-grinding[36] have been employed for generating drug-infused PVP particles. In the study by Cavallari *et al.*[65], indomethacin was combined with PVP through freeze-drying and subsequently encased in stearic acid via ultrasonic spray-congealing. SEM analysis revealed that the freeze-dried PVP & indomethacin remained in a smaller, crystalline state.

For drug delivery systems, co-grinding is an effective method to create PVP-based dispersions. This technique can enhance drug solubility and stability by reducing particle size and increasing surface area. A multi-particulate system was developed using calcium chloride, alginate, and biopolymer chitosan microspheres to manage the targeted delivery of PVP, celecoxib, and HP-β-CD complexes[66–68]. The co-grinding process helps in the homogeneous distribution of these components, improving their interaction and effectiveness. Additionally, PVP facilitates enhanced dissolution by acting as a bridge between cyclodextrin molecules[69], thereby improving the solubility of the drug. Coacervation has been a promising method for enclosing active ingredients within PVP-based microcapsules, despite the typical use of potentially harmful organic solvents.

This encapsulation technique is important for protecting and preventing modification of dissolving rate. Studies by Dowding *et al*.[52] indicated that increasing either the thickness or molecular weight of the PVP shell could decrease the dispersion rate of the substance due to more robust interactions with lower molecular weight PVP. Additionally, pH-responsive microcapsules have been produced where PVP swelling at low pH values enhances the drug release rate[52,53].

Nonetheless, certain parameters are crucial in the coacervation process for microcapsule production. Research by Gun and Routh[53] showed that rapid evaporation (at 40 °C) could result in incomplete PVP shells or PVP granule precipitation. Conversely, slower evaporation (at 20 °C) yielded complete PVP shells, as verified by SEM imagery and dissolution experiments. Slower evaporation rates produced shells that served as more effective barriers, hence slowing the release of drugs.

Layer-by-layer encapsulation of active substances, particularly those that are poorly soluble in water, has gained traction as a novel strategy. The layer-by-layer assembly method comes with several benefits, including precise control over size, shape, composition, shell thickness, geometry flexibility, adjustable shell permeability, and substantial.

While traditional particle production techniques like spray drying are common, they come with challenges such as residual solvents, high operational temperatures, and inconsistent particle outputs[65]. In response, innovative supercritical carbon dioxide (CO_2) technologies, including supercritical assisted atomization (SAA)[60,66,70,71] and supercritical antisolvent (SAS) processes[62,72], have been introduced to overcome these limitations. In these supercritical CO_2 techniques, the CO_2 functions either as a consulate (SAA) or an antisolvent (SAS), facilitating the production of PVP-based particles that are micro to sub-micro in size with amorphous structures. These methods have significantly improved the dissolution rates of various active substances such as antioxidants[72], NSAIDs[73], vitamins[74,75], and corticosteroids[54], all the while maintaining the integrity of thermolabile substances[76].

The advantage of supercritical fluids has been presented over traditional methods by examining the production of PVP/piroxicam microspheres using SAS and spray drying techniques[77]. The SAS process yielded microspheres with a more uniform size distribution and demonstrated more rapid drug dissolution compared to the spray-dried equivalent. In mere minutes, the drug release from SAS microspheres reached completion, in stark contrast to the significantly slower release from spray-dried microspheres.

The SAS process typically results in more desirable coprecipitation, especially when forming microspheres from microdroplet drying, whereas nanoparticles or sub-microparticles may experience only partial coprecipitation[78]. Process variables like operating pressure and solution concentration crucially dictate the size of PVP-based microparticles produced via SAS, with higher pressures yielding smaller particles and greater solute concentrations resulting in larger ones[79]. Conversely, in the SAA method, the gas-to-liquid ratio is a key determinant of particle morphology and size, where higher ratios tend to produce smaller, more uniformly distributed particles.

A process innovated by Matos *et al.*[72] which combines coating and coprecipitation, utilizing PVP/curcumin particles and various polymers. A SAS has been applied in which PVP acts as the medium and other powdered polymers like microcrystalline cellulose, corn starch, or lactose pre-loaded into the chamber which resulted in diferuloylmethane and PVP being deposited on these irregular crystals. However, this method did not significantly enhance the dissolving rate measured to the standard SAS coprecipitation of PVP/curcumin, which already showed a release rate of over 95 % within minutes.

Polymeric micelles, emerging as an encouraging system, notably improve the availability of hydrophobic drugs[80]. These micelles formed from amphiphilic block copolymers in aqueous solutions.

PVP-based copolymers have been particularly effective as amphiphilic carriers for hydrophobic drugs[81]. Amphiphilic PVP derivatives with a hydrophobic end-segment have been synthesized to produce nanoparticles in solutions. For instance, an amphiphilic PVP carrier has been utilized to provide indomethacin[81] and proteins[82] with the particles formed through solvent evaporation demonstrating sizes between 50–80 nm and enabling sustained drug release.

Extensive research has been devoted to developing PVP-based microspheres. The potential of PVP in microcapsule development, especially pH-responsive ones for targeted release, remains an exciting but underexplored area.

In terms of production technologies, supercritical fluids-based methods stand out for their ability to produce solvent-free products with optimal morphology and particle size distributions. However, the cost implications of these advanced technologies compared to traditional methods must be taken into account.

For a detailed synopsis, Table 3 in the cited literature presents a compiled summary of various PVP-based particles tailored for drug delivery, outlining the techniques used, carriers selected, active principles involved.

Table 3 – *Compiled summary of various PVP-derived particles tailored for drug delivery*

Technique	Carrier	Active agent	Result	References
Dynamic Stirring/ Quenching	PVP	Anticancer drugs	Nanoparticles with size about 14 nm	8
Wet Chemical Synthesis	PVP	Epinephrine and Iron Oxide	Coated nanoparticles, size between 60–113 nm	9
Spray Drying	PVP	Antioxidants	Microparticles with size 2.8–3.6 μm	11
Freeze-drying	PVP/stearic acid	Indomethacin	Rough microcapsules, with partial crystallinity	30
Coacervation	PVP	Dyes and Pyridine	No image data provided	52
Spray Drying	PVP	Antihypertensive	Microparticles, size range 1.82–2.51 μm	54
Supercritical Fluid	PVP	Anti-inflammatory drugs	Slightly rough microparticles, size 3–5 μm	57
Wet Chemical Method	PVP	Anti-inflammatory drugs	Collapsed microparticles with size < 9.0 μm	59
Emulsion Polymerization	PVP/Polymethyl methacrylate	Antibiotics	PVP-coated microspheres, 200–300 nm	61
Spray Drying	PVP	Herbal Extract	Rough spherical microparticles	63
Co-grinding	PVP/β-cyclodextrin	Celecoxib	Microparticles, stable colloidal particles	66
Freeze-drying	PVP/β-cyclodextrin	Collapsed and slightly coalescent microparticles	Collapsed and slightly coalescent microparticles	67
Supercritical Antisolvent (SAA)	PVP	Curcumin	Collapsed microparticles, size range 0.54–0.76 μm	70
Solvent Evaporation	Amphiphilic PVP	Protein-based drugs	Protein-loaded particles, around 50–80 nm	82

Conclusion

This comprehensive review has emphasized the crucial function of polyvinylpyrrolidone in the realm of active agent delivery systems. PVP is chosen in the pharmaceutical and biomedical arenas for its multiple roles—it acts as a stabilizer, a protector, an inhibitor of crystallization, and an enhancer of dissolution. However, PVP's propensity for moisture absorption presents a challenge that necessitates careful control. PVP is versatile, used either independently or synergistically with other polymers to create a variety of composite systems with diverse structures, such as core-shell designs and coatings.

Different morphologies and formulations have been synthesized using distinct technological approaches, each tailored for a particular mode of drug administration. PVP's application spans from oral tablets to microparticles and nanoparticles, enhancing the dissolution of hydrophobic active substances through size reduction and its hydrophilic matrix function. With tablets, the development of both monolithic and osmotic systems allows for varied drug release dynamics.

PVP-based fibres are notably versatile, serving purposes in topical applications, tissue engineering, and oral routes, enabling a spectrum from swift to modulated release and even offering dual-phase release in core-shell constructs. Hydrogels formulated with PVP have been employed for multiple administration methods, including transdermal, topical and oral with pH-sensitive variants designed to respond to the body's varying pH levels. Thin films based on PVP have been innovated for buccal, sublingual, and cutaneous applications, providing non-invasive systems favoured by patients for targeted release.

In practical applications, PVP of low to medium molecular weights (from PVP K10 to K30) is typically chosen for microparticle production, whereas PVP of medium to high molecular weights (from PVP K30 to K90) is selected for other formulations.

While the research corpus extensively discusses PVP-based particles and their production methods, predominantly focusing on PVP in isolation, investigations into PVP combined with other polymers are less common. The body of work on PVP-

based fibres and tablets is significant, with fibres highlighted for their adaptability. Nonetheless, these fibres are particularly susceptible to moisture, suggesting that blending with other polymers could improve their resistance to moisture. Research on hydrogel production using PVP is limited but points to the exciting potential for creating pH-sensitive systems. PVP-based hydrogels usage for ocular drug delivery has yet to be fully explored. Emerging areas such as regenerative medicine also present innovative applications for PVP-based fibres and hydrogels.

References

1. *Yagolovich, A., Kuskov, A., Kulikov, P., Kurbanova, L., Bagrov, D., Artykov, A., Gasparian, M., Sizova, S., Oleinikov, V., Gileva, A., Kirpichnikov, M., Dolgikh, D., Markvicheva, E.*, Amphiphilic poly(N-vinylpyrrolidone) nanoparticles conjugated with DR5-specific antitumor cytokine DR5-B for targeted delivery to cancer cells, Pharm. **9** (2021) 1413. doi: https://doi.org/10.3390/pharmaceutics13091413
2. *Rasekh, M., Karavasili, C., Soong, Y. L., Bouropoulos, N., Morris, M., Armitage, D., Li, X., Fatouros, D. G., Ahmad, Z.,* Electrospun PVP–indomethacin constituents for transdermal dressings and drug delivery devices, Int. J. Pharm. **473** (2014) 95. doi: https://doi.org/10.1016/j.ijpharm.2014.06.059
3. *Robinson, B., Sullivan, F., Borzelleca, J., Schwartz, S.,* PVP: A critical review of the kinetics and toxicology of polyvinylpyrrolidone (povidone), Lewis Publisher: Chelsea, MI, USA **1** (2020) 232. doi: https://doi.org/10.1201/9780203741672
4. *Song, Y., Zhang, T., Song, X., Zhang, L., Zhang, C., Xing, J., Liang, X.-J.,* Polycations with excellent gene transfection ability based on PVP-g-PDMAEMA with random coil and micelle structures as non-viral gene vectors, J. Mater. Chem. B **3** (2015) 911. doi: https://doi.org/10.1039/C4TB01754D
5. *Hu, M., Li, C., Li, X., Zhou, M., Sun, J., Sheng, F., Shi, S., Lu, L.*, Zinc oxide/silver bimetallic nanoencapsulated in PVP/PCL nanofibres for improved antibacterial activity, Artif. Cells Nanomed. Biotechnol. **6** (2018) 1248. doi: https://doi.org/10.1080/21691401.2017.1366339
6. *Hecold, M., Buczkowska, R., Mucha, A., Grzesiak, J., Rac-Rumijowska, O., Teterycz, H., Marycz, K.,* The effect of PEI and PVP-stabilized gold nanoparticles on equine platelets activation: Potential application in equine regenerative medicine, J. Nanomater. **2017** (2017) 29. doi: https://doi.org/10.1155/2017/8706921
7. *Goetten de Lima, G., de Lima, D. W., de Oliveira, M. J., Lugão, A. B., Alcántara, M. S., Devine, D. M., de Sá, M. J.,* Synthesis and in vivo behaviour of PVP/CMC/Agar hydrogel membranes impregnated with silver nanoparticles for wound healing applications, ACS Appl. Bio Mater. **1** (2018) 1842. doi: https://doi.org/10.1021/acsabm.8b00369
8. *Ramalingam, V., Varunkumar, K., Ravikumar, V., Rajaram, R.,* Target delivery of doxorubicin tethered with PVP stabilized gold nanoparticles for effective treatment of lung cancer, Sci. Rep. **8** (2018) 3815. doi: https://doi.org/10.1038/s41598-018-22172-5
9. *Rose, P. A., Praseetha, P., Bhagat, M., Alexander, P., Abdeen, S., Chavali, M.,* Drug embedded PVP coated magnetic nanoparticles for targeted killing of breast cancer cells, Technol. Cancer Res. Treat. **5** (2013) 463. doi: https://doi.org/10.7785/tcrt.2012.500333
10. *Hasa, D., Voinovich, D., Perissutti, B., Bonifacio, A., Grassi, M., Franceschinis, E., Dall'Acqua, S., Speh, M., Plavec, J., Invernizzi, S.,* Multidisciplinary approach on characterizing a mechanochemically activated composite of vinpocetine and crospovidone, J. Pharm. Sci. **100** (2011) 915. doi: https://doi.org/10.1002/jps.22331
11. *Bothiraja, C., Shinde, M. B., Rajalakshmi, S., Pawar, A. P.,* Evaluation of molecular pharmaceutical and in—Vivo properties of spray—Dried isolated andrographolide—PVP, J. Pharm. Pharmacol. **61** (2009) 1465. doi: https://doi.org/10.1211/jpp.61.11.0005
12. *Dai, X.-Y., Nie, W., Wang, Y.-C., Shen, Y., Li, Y., Gan, S.-J.,* Electrospun emodin polyvinylpyrrolidone blended nanofibrous membrane: A novel medicated biomaterial for drug delivery and accelerated wound healing, J. Mater. Sci. Mater. **23** (2012) 2709. doi: https://doi.org/10.1007/s10856-012-4728-x
13. *Fogaça, R., Catalani, L. H.,* PVP hydrogel membranes produced by electrospinning for protein release devices, Soft Mater. **11** (2013) 61. doi: https://doi.org/10.1080/1539445X.2011.580411
14. *Ajji, Z., Maarouf, M., Khattab, A., Ghazal, H.,* Synthesis of pH-responsive hydrogel based on PVP grafted with crotonic acid for controlled drug delivery, Radiat. Phys. Chem. **170** (2020) 108612. doi: https://doi.org/10.1016/j.radphyschem.2019.108612
15. *Rapado Raneque, M., Rodríguez Rodríguez, A., Peniche Covas, C.,* Hydrogel wound dressing preparation at laboratory scale by using electron beam and gamma radiation, Nucleus **53** (2013) 24.
16. *Wlodarski, K., Tajber, L., Sawicki, W.,* Physicochemical properties of direct compression tablets with spray dried and ball milled solid dispersions of tadalafil in PVP-VA, Eur. J. Pharm. Biopharm. **109** (2016) 14. doi: https://doi.org/10.1016/j.ejpb.2016.09.011
17. *Janugade, B., Patil, S., Patil, S., Lade, P.,* Effect of PVP concentration on lag time of press-coated montelukast sodium tablet, J. Pharm. Res. **2** (2009) 502.
18. *Karavas, E., Georgarakis, E., Bikiaris, D.,* Application of PVP/HPMC miscible blends with enhanced mucoadhesive properties for adjusting drug release in predictable pulsatile chronotherapeutics, Eur. J. Pharm. Biopharm. **64** (2006) 115. doi: https://doi.org/10.1016/j.ejpb.2005.12.013
19. *Sadashivaiah, R., Dinesh, B., Patil, U. A., Raghu, K.,* Design and in vitro evaluation of haloperidol lactate transdermal patches containing ethyl cellulose-povidone as film formers, Asian J. Pharm. **2** (2014) 2. doi: https://doi.org/10.22377/ajp.v2i1.173
20. *Hoffman, A. S.,* Hydrogels for biomedical applications, Adv. Drug Del.Rev. **64** (2012) 18. doi: https://doi.org/10.1016/j.addr.2012.09.010
21. *Ghasemiyeh, P., Mohammadi-Samani, S.,* Hydrogels as drug delivery systems; Pros and Cons, Trends Pharm. Sci. **5** (2019) 7.
22. *Mammadova, S. M., Tapdigov, Sh. Z., Humbatova, S. F., Aliyeva, S. A., Zeynalov, N. A., Soltanov, Ch. A., Cavadzadeh, A. A.*, Synthesis, structure and swelling properties of hydrogels based on polyacrylic acid. Asian J.Chem. **29** (2017) 576. doi: https://doi.org/10.14233/ajchem.2017.20262

23. *Peppas, N.,* Devices based on intelligent biopolymers for oral protein delivery, Int. J. Pharm. **277** (2004) 11. doi: https://doi.org/10.1016/j.ijpharm.2003.03.001
24. *Mozalewska, W., Czechowska-Biskup, R., Olejnik, A. K., Wach, R. A., Ulański, P., Rosiak, J. M.,* Chitosan-containing hydrogel wound dressings prepared by radiation technique, Radiat. Phys. Chem. **134** (2017) 1. doi: https://doi.org/10.1016/j.radphyschem.2017.01.003
25. *Szafulera, K., Wach, R. A., Olejnik, A. K., Rosiak, J. M., Ulański, P.,* Radiation synthesis of biocompatible hydrogels of dextran methacrylate, Radiat. Phys. Chem. **142** (2018) 115. doi: https://doi.org/10.1016/j.radphyschem.2017.01.004
26. *Demeter, M., Scărişoreanu, A., Călina, I.,* State of the art of hydrogel wound dressings developed by ionizing radiation, Gels **9** (2023) 55. doi: https://doi.org/10.3390/gels9010055
27. *Lopérgolo, L. C., Lugao, A. B., Catalani, L. H.,* Direct UV photo crosslinking of poly (N-vinyl-2-pyrrolidone) (PVP) to produce hydrogels, Polymer **44** (2003) 6217. doi: https://doi.org/10.1016/S0032-3861(03)00686-4
28. *Mishra, R. K., Datt, M., Banthia, A. K.,* Synthesis and characterization of pectin/PVP hydrogel membranes for drug delivery system, Aaps. Pharmscitech. **2** (2008) 395. doi: https://doi.org/10.1208/s12249-008-9048-6
29. *Risbud, M. V., Hardikar, A. A., Bhat, S. V., Bhonde, R. R.,* pH-sensitive freeze-dried chitosan–polyvinyl pyrrolidone hydrogels as controlled release system for antibiotic delivery, J. Control. Release **68** (2000) 23. doi: https://doi.org/10.1016/S0168-3659(00)00208-X
30. *Savjani, K. T., Gajjar, A. K., Savjani, J. K.,* Drug solubility: Importance and enhancement techniques, ISRN Pharm **2012** (2012) 195727. doi: https://doi.org/10.5402/2012/195727
31. *Humbatova, S. F., Zeynalov, N., Tagiyev, D., Tapdiqov, S., Mammedova, S. M.*, Chitosan polymer composite material containing of silver nanoparticle, DJNB **11** (2016) 39.
32. *Tapdiqov, S., Zeynalov, N., Tagiyev, D., Humbatova, S., Mammedova, S., Nasiyyati, E., Babayeva, D.,* Hydrogels for immobilization of trypsine based on poly-N-vinylpyrrolidone and arabinogalactan graft copolymers, J. Chem. Soc. Pak. **37** (2015) 1112.
33. *Zhang, J., Guo, M., Luo, M., Cai, T.,* Advances in the development of amorphous solid dispersions: The role of polymeric carriers, AJPS **18** (2023) 100834. doi: https://doi.org/10.1016/j.ajps.2023.100834
34. *Butreddy, A.,* Hydroxypropyl methylcellulose acetate succinate as an exceptional polymer for amorphous solid dispersion formulations: A review from bench to clinic, Eur. J. Pharm. Biopharm. **177** (2022) 289. doi: https://doi.org/10.1016/j.ejpb.2022.07.010
35. *Qin, Y., Xiao, C., Li, X., Huang, J., Si, L., Sun, M.,* Enteric polymer–based amorphous solid dispersions enhance oral absorption of the weakly basic drug nintedanib via stabilization of supersaturation, Pharm. **9** (2022) 1830. doi: https://doi.org/10.3390/pharmaceutics14091830
36. *Colombo, I., Grassi, G., Grassi, M.,* Drug mechanochemical activation, J. Pharm. Sci. **98** (2009) 3961. doi: https://doi.org/10.1002/jps.21733
37. *Yoshimoto, H., Shin, Y., Terai, H., Vacanti, J.,* A biodegradable nanofiber scaffold by electrospinning and its potential for bone tissue engineering, Biomaterials **24** (2003) 2077. doi: https://doi.org/10.1016/S0142-9612(02)00635-X
38. *Wang, L., Chang, M.-W., Ahmad, Z., Zheng, H., Li, J.-S.,* Mass and controlled fabrication of aligned PVP fibers for matrix type antibiotic drug delivery systems, Chem. Eng. J. **307** (2017) 661. doi: https://doi.org/10.1016/j.cej.2016.08.135
39. *Satturwar, P. M., Fulzele, S. V., Dorle, A. K.,* Evaluation of polymerized rosin for the formulation and development of transdermal drug delivery system: A technical note, AAPS PharmSciTech **6** (2005) 649. doi: https://doi.org/10.1208/pt060481
40. *Román-Doval, R., Tellez-Cruz, M., Rojas-Chávez, H., Cruz-Martínez, H., Carrasco-Torres, G., Vásquez-Garzón, V.,* Enhancing electrospun scaffolds of PVP with polypyrrole/iodine for tissue engineering of skin regeneration by coating via a plasma process, J. Mater. Sci. **54** (2019) 3342. doi: https://doi.org/10.1007/s10853-018-3024-7
41. *Sriyanti, I., Edikresnha, D., Munir, M. M., Rachmawati, H., Khairurrijal, K.,* Electrospun polyvinylpyrrolidone (PVP) nanofiber mats loaded by *Garcinia mangostana* L. extracts, Mater. Sci. Forum **880** (2017) 11. doi: https://doi.org/10.4028/www.scientific.net/MSF.880.11
42. *Yu, D. G., Zhang, X. F., Shen, X. X., Brandford—White, C., Zhu, L. M.,* Ultrafine ibuprofen-loaded polyvinylpyrrolidone fiber mats using electrospinning, Polym. Int. **9** (2009) 1010. doi: https://doi.org/10.1002/pi.2629
43. *Suganya, S., Senthil Ram, T., Lakshmi, B., Giridev, V.,* Herbal drug incorporated antibacterial nano fibrous mat fabricated by electrospinning: An excellent matrix for wound dressings, J. Appl. Pol. Sci. **121** (2011) 2893. doi: https://doi.org/10.1002/app.33915
44. *Nie, W., Yu, D., Branford-White, C., Shen, X., Zhu, L.,* Electrospun zein–PVP fibre composite and its potential medical application, Mater. Res. Innov. **16** (2012) 14. doi: https://doi.org/110.1179/1433075X11Y.0000000013
45. *Lee, H., Xu, G., Kharaghani, D., Nishino, M., Song, K. H., Lee, J. S., Kim, I. S.,* Electrospun tri-layered zein/PVP-GO/zein nanofiber mats for providing biphasic drug release profiles, Int. J. Pharm. **531** (2017) 101. doi: https://doi.org/10.1016/j.ijpharm.2017.08.081
46. *Jiang, Y.-N., Mo, H.-Y., Yu, D.-G.,* Electrospun drug-loaded core–sheath PVP/zein nanofibers for biphasic drug release, Int. J. Pharm. **438** (2012) 232. doi: https://doi.org/10.1016/j.ijpharm.2012.08.053
47. *Shadamarshan, R. P., Balaji, H., Rao, H. S., Balagangadharan, K., Chandran, S. V., Selvamurugan, N.,* Fabrication of PCL/PVP electrospun fibers loaded with trans-anethole for bone regeneration in vitro, Colloids Surf. B **171** (2018) 698. doi: https://doi.org/10.1016/j.colsurfb.2018.08.005
48. *Samprasit, W., Akkaramongkolporn, P., Ngawhirunpat, T., Rojanarata, T., Kaomongkolgit, R., Opanasopit, P.,* Fast releasing oral electrospun PVP/CD nanofiber mats of taste-masked meloxicam, Int. J. Pharm. **487** (2015) 213. doi: https://doi.org/10.1016/j.ijpharm.2015.04.044
49. *Zhang, W., Chen, M., Diao, G.,* Electrospinning β-cyclodextrin/poly (vinylalcohol) nanofibrous membrane for molecular capture, Carbohydr. Polym. **86** (2011) 1410. doi: https://doi.org/10.1016/j.carbpol.2011.06.062
50. *Uyar, T., Havelund, R., Nur, Y., Hacaloglu, J., Besenbacher, F., Kingshott, P.,* Molecular filters based on cyclodextrin functionalized electrospun fibers, J. Membr. Sci. **332** (2009) 129. doi: https://doi.org/10.1016/j.memsci.2009.01.047
51. *Bai, J., Yang, Q., Li, M., Zhang, C., Yiaoxian, L.,* Synthesis of poly (N-vinylpyrrolidone)/β-cyclodextrin composite nanofibers using electrospinning techniques, J. Mater. Process. Technol. **208** (2008) 251. doi: https://doi.org/10.1016/j.jmatprotec.2007.12.109

52. *Dowding, P. J., Atkin, R., Vincent, B., Bouillot, P.,* Oil core/polymer shell microcapsules by internal phase separation from emulsion droplets. II: Controlling the release profile of active molecules, Langmuir **21** (2005) 5278. doi: https://doi.org/10.1021/la0470838
53. *Gun, W. J., Routh, A. F.,* Formation and characterization of pH-responsive liquid core microcapsules, Langmuir **29** (2013) 12541. doi: https://doi.org/10.1021/la403175w
54. *Prosapio, V., De Marco, I., Reverchon, E.,* PVP/corticosteroid microspheres produced by supercritical antisolvent coprecipitation, Chem. Eng. J. **292** (2016) 264. doi: https://doi.org/10.1016/j.cej.2016.02.041
55. *Prosapio, V., Reverchon, E., De Marco, I.,* Formation of PVP/nimesulide microspheres by supercritical antisolvent coprecipitation, J. Supercrit. Fluids **118** (2016) 19. doi: https://doi.org/10.1016/j.supflu.2016.07.023
56. *Xu, H., Hou, Z., Zhang, H., Kong, H., Li, X., Wang, H., Xie, W.,* An efficient trojan delivery of tetrandrine by poly (N-vinylpyrrolidone)-block-poly(ε-caprolactone)(PVP-b-PCL) nanoparticles shows enhanced apoptotic induction of lung cancer cells and inhibition of its migration and invasion, Int. J. Nanomed. **9** (2014) 231. doi: https://doi.org/10.2147/IJN.S55541
57. *Gupta, P., Bansal, A. K.,* Spray drying for generation of a ternary amorphous system of celecoxib, PVP, and meglumine, Pharm. Dev. Technol. **2** (2005) 273. doi: https://doi.org/10.1081/PDT-54460
58. *Paudel, A., Van den Mooter, G.,* Influence of solvent composition on the miscibility and physical stability of naproxen/PVP K 25 solid dispersions prepared by cosolvent spray-drying, Pharm. Res. **29** (2012) 251. doi: https://doi.org/10.1007/s11095-011-0539-x
59. *Thybo, P., Pedersen, B. L., Hovgaard, L., Holm, R., Müllertz, A.,* Characterization and physical stability of spray dried solid dispersions of probucol and PVP-K30, Pharm. Dev. Technol. **13** (2008) 375. doi: https://doi.org/10.1080/10837450802244843
60. *Di Capua, A., Adami, R., Reverchon, E.,* Production of luteolin/biopolymer microspheres by supercritical assisted atomization, Ind. Eng. Chem. Res. **56** (2017) 4334. doi: https://doi.org/10.1021/acs.iecr.7b00211
61. *Sairam, M., Ramesh Babu, V., Krishna Rao, K., Aminabhavi, T.,* Poly (methylmethacrylate)-poly (vinyl pyrrolidone) microspheres as drug delivery systems: Indomethacin/cefadroxil loading and in vitro release study, J. Appl. Pol. Sci. **104** (2007) 1860. doi: https://doi.org/10.1002/app.25844
62. *Uzun, İ. N., Sipahigil, O., Dinçer, S.,* Coprecipitation of cefuroxime axetil–PVP composite microparticles by batch supercritical antisolvent process, J. Supercrit. Fluids **55** (2011) 1059. doi: https://doi.org/10.1016/j.supflu.2010.09.035
63. *Martins, R. M., Pereira, S. V., Siqueira, S., Salomão, W. F., Freitas, L. A. P.,* Curcuminoid content and antioxidant activity in spray dried microparticles containing turmeric extract, Food Res. Int. **50** (2013) 657. doi: https://doi.org/10.1016/j.foodres.2011.06.030
64. *Paudel, A., Loyson, Y., Van den Mooter, G.,* An investigation into the effect of spray drying temperature and atomizing conditions on miscibility, physical stability, and performance of naproxen–PVP K 25 solid dispersions, J. Pharm. Sci. **102** (2013) 1249. doi: https://doi.org/10.1002/jps.23459
65. *Cavallari, C., Luppi, B., Di Pietra, A. M., Rodriguez, L., Fini, A.,* Enhanced release of indomethacin from PVP/stearic acid microcapsules prepared coupling co-freeze-drying and ultrasound assisted spray-congealing process, Pharm. Res. **3** (2007) 521. doi: https://doi.org/10.1007/s11095-006-9168-1
66. *Mennini, N., Furlanetto, S., Cirri, M., Mura, P.,* Quality by design approach for developing chitosan-Ca-alginate microspheres for colon delivery of celecoxib-hydroxypropyl-β-cyclodextrin-PVP complex, Eur. J. Pharm. Biopharm. **80** (2012) 67. doi: https://doi.org/10.1016/j.ejpb.2011.08.002
67. *El-Maradny, H., Mortada, S., Kamel, O., Hikal, A.*, Characterization of ternary complexes of meloxicam-HPβCD and PVP or L-arginine prepared by the spray-drying technique, Acta Pharm. **58** (2008) 455. doi: https://doi.org/10.2478/v10007-008-0029-9
68. *Tapdigov, S. Z., Safaraliieva, S. F., Theato, P., Zeynalov, N. A., Taghiyev, D. B., Raucci, M. G., Hasanova, M. X.*, Synthesis of n,n-diethyl, n-methyl chitosan chloride with certain quaternization degree and molecular spectroscopic and thermo-morphological study of the alkylation, JBBBE **39** (2018) 77. doi: https://doi.org/10.4028/www.scientific.net/jbbbe.39.77
69. *Valero, M., Tejedor, J., Rodríguez, L. J.,* Encapsulation of nabumetone by means of-drug:(β-cyclodextrin) 2: Polyvinylpyrrolidone ternary complex formation, J. Lumin. **126** (2007) 297. doi: https://doi.org/10.1016/j.jlumin.2006.07.028
70. *Adami, R., Di Capua, A., Reverchon, E.,* Supercritical assisted atomization for the production of curcumin-biopolymer microspheres, Powder Technol. **305** (2017) 455. doi: https://doi.org/10.1016/j.powtec.2016.10.020
71. *Di Capua, A., Bejarano, A., Adami, R., Reverchon, E.,* Preparation and characterization of chilean propolis coprecipitates using supercritical assisted atomization, Chem. Eng. Res. Des. **136** (2018) 776. doi: https://doi.org/10.1016/j.cherd.2018.06.037
72. *Matos, R. L., Lu, T., Leeke, G., Prosapio, V., McConville, C., Ingram, A.,* Single-step coprecipitation and coating to prepare curcumin formulations by supercritical fluid technology, J. Supercrit. Fluids **159** (2020) 104758. doi: https://doi.org/10.1016/j.supflu.2020.104758
73. *Zahran, F., Cabañas, A., Cheda, J. A. R., Renuncio, J. A. R., Pando, C.,* Dissolution rate enhancement of the anti-inflammatory drug diflunisal by coprecipitation with a biocompatible polymer using carbon dioxide as a supercritical fluid antisolvent, J. Supercrit. Fluids **88** (2014) 56. doi: https://doi.org/10.1016/j.supflu.2014.01.015
74. *Prosapio, V., Reverchon, E., De Marco, I.,* Incorporation of liposoluble vitamins within PVP microparticles using supercritical antisolvent precipitation, J. CO_2 Util. **19** (2017) 230. doi: https://doi.org/10.1016/j.jcou.2017.04.004
75. *Prosapio, V., De Marco, I., Scognamiglio, M., Reverchon, E.,* Folic acid–PVP nanostructured composite microparticles by supercritical antisolvent precipitation, Chem. Eng. J. **277** (2015) 286. doi: https://doi.org/10.1016/j.cej.2015.04.149
76. *Di Capua, A., Adami, R., Cosenza, E., Jalaber, V., Crampon, C., Badens, E., Reverchon, E.,* β-Carotene/PVP microspheres produced by supercritical assisted atomization, Powder Technol. **346** (2019) 228. doi: https://doi.org/10.1016/j.powtec.2019.01.069
77. *Wu, K., Li, J., Wang, W., Winstead, D. A.,* Formation and characterization of solid dispersions of piroxicam and polyvinylpyrrolidone using spray drying and precipitation with compressed antisolvent, J. Pharm. Sci. **98** (2009) 2422. doi: https://doi.org/10.1002/jps.21598

78. *Franco, P., Reverchon, E., De Marco, I.,* Zein/diclofenac sodium coprecipitation at micrometric and nanometric range by supercritical antisolvent processing, J. CO_2 Util. **27** (2018) 366.
doi: https://doi.org/10.1016/j.jcou.2018.08.015

79. *Prosapio, V., De Marco, I., Reverchon, E.,* Supercritical antisolvent coprecipitation mechanisms, J. Supercrit. Fluids **138** (2018) 247.
doi: https://doi.org/10.1016/j.supflu.2018.04.021

80. *Lukyanov, A. N., Torchilin, V. P.,* Micelles from lipid derivatives of water-soluble polymers as delivery systems for poorly soluble drugs, Adv. Drug Del. Rev. **56** (2004) 1273.
doi: https://doi.org/10.1016/j.addr.2003.12.004

81. *Kuskov, A. N., Voskresenskaya, A. A., Goryachaya, A. V., Artyukhov, A. A., Shtilman, M. I., Tsatsakis, A. M.,* Preparation and characterization of amphiphilic poly-N-vinylpyrrolidone nanoparticles containing indomethacin, J. Mater. Sci. Mater. **21** (2010) 1521.
doi: https://doi.org/10.1007/s10856-010-4029-1

82. *Kuskov, A., Villemson, A., Shtilman, M., Larionova, N., Tsatsakis, A., Tsikalas, I., Rizos, A.*, Amphiphilic poly-N-vinylpyrrolidone nanocarriers with incorporated model proteins, J. Phys. **19** (2007) 205139.
doi: https://doi.org/10.1088/0953-8984/19/20/205139