60th Anniversary of Povidone

Dear reader,

In 1939 Professor Reppe did the invention of Povidone as part of the acetylene chemistry, well-known under the expression “Reppe Chemistry”. Professor Reppe together with chemists like Dr. Fikentscher, Dr. Herle, Dr. Sanner and Mr. Denzinger and generations of young chemists in polymer research continued to develop types of PVP-based polymers or at least improved the existing ones up to now.

Parallel to the research chemistry, production of Povidone underwent also an evolution process resulting in GMP-like production sites in Ludwigshafen and Geismar.

Names, which supported these efforts have been Dr. Penning, Dr. Dall, Dr. Gellrich, Dr. Schröder and on the quality control side Dr. Schmötzer, Mr. Miersch, Dr. Lamprecht and Dr. Filges support the Povidone line with new analytical methods or introduced new lab standards.

Last but not least two groups responsible for marketing and technical support were part of the success of Povidone. Mr. Zöllner, Mr. Löffler, Mr. Görgens, Mr. Jenke, Mr. Lappas in marketing and on the technical side Dr. Rutz, Dr. Seeert, Dr. Schwarz, Dr. Bühlér, Mr. Reich and Dr. Lang were part of the positive development of this product line.

At the beginning there was this brilliant idea called “Reppe chemistry”, but to develop all the different aspects of this idea, it took all the skills of chemists, salesmen, pharmacists over a long period of time to reach the status of Povidone nowadays.

Team work and dedication for a production line were responsible for the success and will also help Povidone to be a winner in the decades coming up.

Yours sincerely,

BASF Aktiengesellschaft
Marketing Pharma
Ingredients

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Great 60 Years of Polyvinylpyrrolidone

Chemistry and physicochemical properties of Povidone.
H. Witteler, M. Gotsche

Introduction

As a water-soluble polymer Polyvinylpyrrolidone, also named Povidone or PVP, has a large number of commercial uses. The polymer derives its success from its low toxicity, biocompatibility, film forming and adhesive characteristics, complexing ability to proton donors, and a low osmotic pressure. Due to this exceptional combination of properties, PVP finds diverse applications in pharmaceutical and cosmetic products, food, adhesives and textile auxiliaries.

Looking back, PVP is one of the numerous products of Reppe’s acetylene chemistry. By reaction of acetylene with formaldehyde 1,4-butine diol is formed. After hydrogenation to 1,4-butane diol, γ-butyrolactone is obtained by oxidative cyclization. The conversion with ammonia to pyrrolidone is finally followed by addition of acetylene generating N-vinylpyrrolidone (NVP) (Figure 1).

PVP typically is characterized by its $K$-Value. The $K$-Value is related to the weight average of the molecular weight and is obtained from viscometric measurements. Since the $K$-Value plays a dominant role in the properties of PVP, it is usually part of the name of PVP.
grades (e.g., Kollidon K 30; PVP with a K-Value of 30). Commercial PVP grades have K-Values as high as 90. 15 percent of PVP K 90 in aqueous solution boosts the viscosity of water from 1 mPa s to more than 5000 mPa s and consequently, this type of PVP may be used as a thickener in various types of formulations (Table 1). The most frequently used Povidone grades are Kollidon 12 PF, 17 PF, 25 and 30. The qualitative identification is provided by the infrared spectrum. At the same time the infrared spectrum allows the study of complex formation of PVP with organic and inorganic molecules (see below). Quantitative determination of soluble PVP grades may be carried out by photometry of the PVP-iodine complex. This also points into the direction of an important application.

PVP is a hygroscopic substance. When used as a binder, the hygroscopic character of PVP is of great importance and plays a role in the binding properties. Besides intrinsic physical properties, the particle size distribution has a marked effect on application properties. Pharma quality means that all Kollidon grades fulfill the requirements of the important pharmacopoeias like USP, Ph. Eur. and JPE.

**Complex Formation with soluble PVP**

Due to their chemical structure, namely the amide bond, PVP forms a variety of complexes with other chemical compounds including pharmacological actives. For these compounds, complexation results in either enhanced solubility, improved bioavailability or increased stability. Complexation is a technique to obtain formulations that dissolve quickly in water from actives that are usually difficult to formulate in water. Here, the most prominent example is the complexation of iodine in water. The solubility of the disinfectant iodine in water is poor and for this reason in the past the increased solubility of the potassium triiodide was used to overcome this hurdle. But, tincture of iodine – a mixture of potassium iodide and iodine in water and ethanol – contains considerable amounts of free iodine. Free iodine leads to unwanted side effects like strong staining and itching when used in wound disinfection. PVP provides the tool to dissolve iodine in water while maintaining an extremely low level of free iodine. Here, very small doses of iodine – as low as 1 ppm in a solution that contains 1% of iodine – are supplied from a complex of PVP with HI (Figure 3).

Typical complexes of organic molecules with PVP are much weaker than the PVP-iodine complex. Complexation is effective at a high concentration of PVP that is typical of the formulated drug. At typical gastrointestinal concentration, complexation can be neglected. Still, formulation with PVP is a versatile tool to improve solubility or dissolution rate of both liquid and solid dosage forms. This effect is based on the ability to form solid solutions with a solute, e.g., an active ingredient and thus prevent it from crystallizing. The absence of crystallinity leads to improved dissolution. (Y. Nozawa et al., Pharm. Acta Helv. 60, 175 (1985); M.M. Devilliers et al., Int. J. Pharm. 163, 219 (1998)) (Table 2).

No complexation occurs between PVP and hydrogen peroxide in aqueous solutions. Still, in dried, anhydrous form complex formation is proven by IR-spectroscopy. Powders of PVP-H2O2 offer a versatile vehicle for the application of H2O2 in many applications due to their stability and the ease in handling as compared to aqueous solutions of H2O2. Possible applications cover disinfectants, topical formulations, and many others.

**Copolymerization**

Solution polymerization in water is also used for the copolymerization of NVP with different monomers to alter or to improve the properties of the PVP. Copolymers with vinyl acetate (VA) are usually prepared in water leading to more hydrophobic polymers than PVP. In order to obtain a homogencous copolymer composition, vinyl acetate is added gradually to the reaction mixture. Kollidon VA 64 (Copolidone) is a copolymer of 60 wt. % N-vinylpyrrolidone and 40 wt. % vinyl acetate. Like PVP, it is soluble in a variety of solvents ranging from water to 1-butanol, but unlike PVP it is much less hygroscopic. For film-coating of tablets, moisture uptake is of disadvantage, and here a less hygroscopic copolymer of N-vinylpyrrolidone is of advantage. Applications of PVP/VA range from galenic (coatings, binders, polymer/excipient extrusion) to cosmetics (film former in hair spray formulations). Copovidone is listed in the European Pharmacopoeia and Japanese Pharmaceutical Excipients. A USA-NF draft monograph was published in 1998 (Figure 4).

**Crosslinked Polymers**

There are different ways used for the preparation of crosslinked PVP. Slightly crosslinked PVP is obtained by treatment of linear PVP with hydrazine or hydrogen peroxide or by γ-irradiation of the linear polymer.

![Structure of the PVP-HI complex. (Figure 3)](image)

![Formation of aldehyde end groups in NVP-polymerization in water. (Figure 2)](image)

![Synthesis of N-vinylpyrrolidone. (Figure 1)](image)
More densely crosslinked PVP is prepared by copolymerization of N-vinylpyrrolidone with bifunctional monomers. Because of the combination of high water uptake and insolubility, swelling is observed with crosslinked PVP when exposed to water while soluble PVP simply dissolves. The popcorn polymerization – bulk polymerization of N-vinylpyrrolidone either in presence of alkali metal hydroxide above 100°C or in presence of small amounts of bifunctional monomers at 100°C – leads to highly crosslinked PVP particles with a specific surface area of a few square meters per gram. This popcorn PVP, Crospovidone, finds important use as tablet disintegrant, as an agent for clarifying beverages and as active ingredient for stomach and gastrointestinal diseases. In contrast to soluble PVP, complexes of crosslinked PVP with high complexation constants enable the extraction of the complexed molecule. The usefulness of crosslinked PVP for gastrointestinal diseases is based on the following properties:

- formation of a protective layer on the mucous membranes
- adsorption of gas
- adsorption of water, swellability
- complexation of toxins of microbial origin

Complex formation of crosslinked PVP with tannin is of interest both in pharmacology and in beverage technology (K. J. Siebert, P. Y. Lynn, J. Am. Soc. Brew. Chem. 56, 24 (1998); D. Horn, W. Ditter, J. Pharm. Sci. 71, 1021 (1982)). Tannin is a biopolymer with polyphenol structures. The complexation constant of tannin with Kollidon CL is >1000 L mol⁻¹ (in 0.1 N hydrochloric acid).

Particle size distribution plays a more crucial role for the application properties of crosslinked PVP as compared to soluble grades. The properties of Kollidon CL grades as a disintegrant for tablets vary with particle size (Table 3) (V. Bühler, Polyvinylpyrrolidone for the pharmaceutical industry, BASF, Ludwigshafen 1996). In tablets obtained from Kollidon by compression the disintegration time decreases with the particle size of the PVP used for the formulation. Like soluble PVP, Kollidon CL-M is capable of stabilizing suspensions, such as antibiotics, antacids, vitamin preparations and topical formulations. 

Lately, it has been demonstrated, that pH-controlled drug release is possible from PVP/Polyacrylic acid interpenetrating networks (J. F. Yang, T. K. Kwei, J. Appl. Polym. Sci. 69, 921 (1998)). Radiation cured hydrogels of PVP, polyethylene glycol, and agar have many desirable properties for using as wound dressings (A. B. Lugao et al., Radiat. Phys. Chem. 52, 319 (1998)).

Polymer/Drug Melt Extrusion

As a result of close collaboration over the past ten years, Knoll AG and its parent company BASF have developed a patent-protected novel pharmaceutical manufacturing technology; drug is incorporated by melt extrusion in a matrix consisting of a pharmaceutical polymer. Due to its thermoplasticity and balanced aqueous solubility properties, Kollidon grades have been found to provide a comprehensive and universal base for various types of drugs. After melt extrusion, the active drug can be present in the extrudate in one or two forms: as a crystal suspended in the hardened Kollidon matrix, or as a molecule dissolved in the polymer during the melting phase and remaining dissolved in the finished product – a “solid solution”. Melt extrusion technology paves the way for benefits in therapy (Figure 5):

- specifically designed controlled-release formulations (both instant and sustained release)
- formulation with improved bioavailability for compounds with low aqueous solubility

Miscellaneous Applications


<table>
<thead>
<tr>
<th>Property</th>
<th>Kollidon CL</th>
<th>Kollidon CL-M</th>
<th>Crospovidone M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size (air jet screen, 5 min, 20mbar)</td>
<td>&lt; 15 µm</td>
<td>&lt; 60%</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Bulk density</td>
<td>g cm⁻³</td>
<td>0.30–0.40</td>
<td>0.15–0.25</td>
</tr>
<tr>
<td>Specific surface area (det. according Ph. Eur. 2, V 5.5.3)</td>
<td>m²·g⁻¹</td>
<td>app. 1</td>
<td>3–6</td>
</tr>
<tr>
<td>Swelling pressure of lightly compacted PVP in water</td>
<td>kPa</td>
<td>app. 55</td>
<td>app. 30</td>
</tr>
</tbody>
</table>

Properties of insoluble PVP grades. (Table 3)
Kollidon® (Polyvinylpyrrolidone)

A Review on its Use in Granulation
Prof. Dr. Peter C. Schmidt, Dept. of Pharmaceutical Technology, Eberhard-Karls-Universität Tübingen

Historical Background

Polyvinylpyrrolidone (Povidone), which is one of the products resulting from Reppe’s studies of acetylene chemistry, was patented in 1939. Originally it was introduced as a blood plasma expander and was widely used during the second world war. This application was cancelled later on due to the fact that medium molecular weight Povidone (K-25 - K-30) is not able to pass the kidney barrier completely. But nevertheless the unique properties of Povidone like high solubility in solvents of differing polarity, solubilizing and film forming ability, suspension and emulsion stabilizing effects and last but not least its binding properties make it one of the most important excipients in pharmaceutical technology.

Besides the parenteral application early reviews (Lesser 1954, Greenfield 1956, Ferraris 1959) deal with uses like complexation, sustained release action, emulsion and foam stabilizer, applications in cosmetic (Greenfield 1957) and printing industry as well as a water removable adhesive. Although a hint on tablet binding properties is given by Lesser (Lesser 1954), the first paper about the use in tablet formulations was published by Lehman (Lehman 1953) who found that aqueous Povidone solutions in a concentration range from 5 to 25% were in comparison to acacia mucilage, starch paste and syrup an “acceptable” binding agent. The amount of binder used was described as “quantum satis” to reach granular consistency, no absolute figures were presented. Next a German pharmacist described the use of Povidone to prepare charcoal tablets (Köhler 1961), lozenges (Köhler 1962 a) and its application in sugar coating of tablets (Köhler 1962). Later on the use of Povidone as a constituent for pills (Kálmán 1963) was recommended. A review by Prescott (Prescott 1965) states that Povidone can be used with success as a dry binder in direct compression, in aqueous and non aqueous binding solutions for granulation as a film forming substance, a stabilizer for aspirin and as a clarifier for wine.

Today Povidone is the most commonly used binder in tableting and has replaced natural materials like gum acacia, gelatin, tragant and others as well as many of the semisynthetic cellulose derivatives. It is available in different grades making an optimum choice possible. For further details of Povidone properties see the extensive review of Bühler (Bühler 1993).

Basic considerations
Granulation is done for a number of purposes: to enhance compressibility and compactability, to increase flowability of the bulk and to reduce dust in the tableting mixture. According to Rumpf (Rumpf 1974) the following forces of increasing order can be involved in the binding between particles: van der Waals forces, electrostatic forces, liquid bridges, binder containing bridges, salt and solid bridges. Van der Waals and electrostatic forces as well as solid bridges act mainly in dry powder compaction while liquid bridges with or without a polymer as a binder are the dominating mechanisms in conventional and fluidized bed granulation. The parameters influencing the formation of a bridge between two particles are presented in figure 1.

In the first step the solvent or the binder containing solution has to wet the surface of the solids to be granulated. The wetting depends on the surface tension of the solid and the liquid and on the interfacial tension between solid and liquid. The amount of liquid necessary to wet the whole surface of the solids depends on the surface area and porosity of the material. Finally the solubility of the solids in the solvent or the binder solution will influence the formation of liquid bridges. When the binder, in most cases an organic polymer, is mixed together with the other ingredients as a powder and moistened afterwards by the solvent, the dissolution rate of the binder in the solvent during the granulation process will also influence the properties of the resulting granules. In these cases the type of equipment used for granulation will become very important.

The correlations between the solid, the solvent and the binder can be visualized as a triangular phase diagram as shown in figure 2.

The corners of the triangle represent the solids, the solvent and the binder respectively. Along the line solids/dry binder, where the solvent content is zero, roller compaction and direct compression are located. A solvent granulation without using a binder takes place along the line solids/solvent. At any place within the triangle a ternary system comprising of solids, solvent and binder is existing. The working area for practical purposes is marked in the upper region of the triangle. The aim of a granulation process is to granulate the material with a minimum of binder. In a conventional granulation process the amount of solvent is limited by the solubility of both the binder and the solids, because an over-moistening effect leading to a suspension has to be avoided. In fluidized bed granulation, where the solvent is continuously removed, it is possible to incorporate more binder especially when the binder forms high viscous solutions. These two situations are depicted in figure 3.

The conventional granulation is a “closed system” where the addition of liquid is limited. In a fluidized bed granulator an unlimited solvent supply is possible and therefore a high amount of binder could be incorporated by the addition of a binder solution. In conventional granulation normally less than 30% of a

The formation of a binder bridge between two particles depends on: the particle’s surface, its porosity and wettability; the solubility of the ingredients being granulated in the solvent or binder solution and on the dissolution rate of the binder. (Figure 1)

Phase triangle showing the relations between the solids, the solvent and the binder in a conventional granulation process. As an example working point representing 60% solids, 32% solvent and 8% binder is given. (Figure 2)
as shown in sodium alginate, can therefore be incorporated only in
ders forming high viscous solutions, e.g. tragacanth or
be added before over-moistening takes place. Bin-
liquid depending on the properties of the solids could
but is now replaced by Kollidon 30 and Kollidon 90 F.
times the main product in granulation was Kollidon 25,
the fact, that they pass the kidney barrier. In earlier
weight types are designed for parenteral use due to
measurements shows for all types a range according
(Bühler 1993, p.36).

The molecular weight $M_w$ which is taken from viscosity
measurements shows for all types a range according to
the European Pharmacopoeia. The low molecular
weight types are designed for parenteral use due to
the fact, that they pass the kidney barrier. In earlier
times the main product in granulation was Kollidon 25,
but is now replaced by Kollidon 30 and Kollidon 90 F.
Several attempts were made to differentiate between
the binding behaviour of different types of Povidone
and to compare Povidone with other binders used in
granulation. Cuit et al. (Cuit et al. 1986) investigated
the binding efficiency of Povidone, Methocel E 15 , a
hydroxypropyl methylcellulose (HPMC) and Byco C
gelatin, a hydrolyzed gelatin, in a model system com-
prised of glass beads of a mean diameter of 26 and
40 $\mu$m respectively. They found a uniform binder dis-
tribution throughout all granulations. Povidone show-
ed the lowest granule friability, formed stronger gra-
ules compared to HPMC but not as strong as Byco
gelatin. The granule strength was slightly lower when
the binding solution: 10% (w/w) for polymers, saturated solution for lactose. Sample: un-
treated glass beads. (Figure 3)

For agglomerates and for molds Povidone K-90
showed the highest strength values followed by
Povidone K-30, the cellulose derivatives and lactose
indicating the high binding efficiency of Povidone.
When silicon treated glass beads were used the
strength values were in general lower but of the same
order showing the importance of wetting as a first step
in granulation. These findings are supported by Danjo
(Danjo 1993) who found a similar ranking when using
lactose as an excipient and preparing granules by
extrusion, fluidized bed and conventional granulation.
Jäger and Bauer (Jäger and Bauer 1984) found
coarser granules with high molecular Povidone. The
authors recommend polymer blends to adapt the
particle size distribution to a desired value.

Agglomerate strength and strength of molds
as a function of binder solution added (ml/g
powder). Concentration of binder solution: 10%
(w/w) for polymers, saturated solution for lactose. Sample: un-
treated glass beads. (Figure 4)

Dry granulation does not require any solvent and is
advantageous whenever stability problems arise with
a drug in contact with water or other solvents. No
drying operation is necessary, therefore the product is
not stressed by higher temperatures. It is a simple
process of high capacity. Nevertheless it is not fre-
quently used in pharmacy for several reasons. The
granules produced by a compaction process are
irregular in shape, show a high friability and contain
often quite a high amount of fines. Povidone, although
recommended as a dry binder has in the dry state less
binding properties compared to e.g. Kollidon VA 64,
a copolymer of vinyl pyrrolidone and vinyl acetate
(Bühler 1993, pp. 129-222). In wet granulation the
powders are normally granulated using a binder
solution. This process involves a lot of parameters, the
most important are:

- properties of the powder mass like wetting
  behaviour, solubility and tendency to rapid
  “over-moistening”.
- amount of binder solution
- concentration of binder in the solution
- mode of application of the binder solution
  like pouring or spraying
- type of granulating equipment
- time of kneading the moistened powder mass
  in conventional granulation processes

The advantage of this type of process is that the binder
is used in solution and the polymer is present in a

### Differences between a conventional and a fluidized bed granulation process. In both
cases the binder content in the final granules can easily keep constant when granulating with
the pure solvent. When using binder solutions the binder content varies depending on
the amount of fluid and is nearly unlimited in the case of fluidized bed granulation. 
(Figure 4)

**Mode of incorporation of Povidone in granules**
The binder can be incorporated into granules by three different methods:

- by dry granulation using a roller compactor
- by mixing the binder with the actives and
  excipients and subsequent moistening with a
  solvent preferably water
- by granulating the powder mass using a binder
  solution

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**Table 1: Viscosity-average values of the molecular weight, $M_w$ for the soluble Kollidon grades, calculated from the K-value.**

<table>
<thead>
<tr>
<th>Kollidon</th>
<th>$M_w$ calculated from the nominal K-Value</th>
<th>$M_w$ calculated from the K-value range given in Ph. Eur.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollidon 12 PF</td>
<td>3900</td>
<td>2600–5500</td>
</tr>
<tr>
<td>Kollidon 17 PF</td>
<td>9300</td>
<td>7100–11000</td>
</tr>
<tr>
<td>Kollidon 25</td>
<td>25700</td>
<td>19300–31100</td>
</tr>
<tr>
<td>Kollidon 30</td>
<td>42500</td>
<td>31700–51400</td>
</tr>
<tr>
<td>Kollidon 90 F</td>
<td>1100000</td>
<td>790000–1350000</td>
</tr>
</tbody>
</table>

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**Flow chart**

**Figure 3**

**Figure 4**
D’Alonzo et al. (D’Alonzo et al. 1990) used a model of binder addition. Therefore it is of interest to compare the two methods completely dissolved during the granulation process. The dissolution rate is high enough to be partially or even completely dissolved during the granulation process. Therefore it is of interest to compare the two methods of binder addition.

D’Alonzo et al. (D’Alonzo et al. 1990) used a model system consisting of microcrystalline cellulose and Povidone as binder to study the effect of binder concentration and the method of addition on granule growth in a high shear mixer. The concentration range of Povidone was 1 to 5% which is recommended for tablet formulations, the amount of water to moisten 1 kg of microcrystalline cellulose was 1 litre. The granulation time was kept constant for all experiments and the process was followed by a resistance measurement at the impeller blade of the mixer, which was also used for end point detection. The mean particle diameter of the resulting granules for both methods is shown in figure 5.

The granules prepared by the dry method indicate a more consistent behaviour in dependence of the amount of Povidone. Furthermore the authors state that the percentage of fines was reduced. The resistance at the impeller blade was lower for the binder solution compared to water indicating a lubrication effect of the aqueous binder solution. In a second paper (Alkan and Ulusoy 1983) granulations of lactose, starch and Povidone are described. Again the dry addition method was compared to a binder solution. The composition of the mixture was 80% lactose, 12% starch and 8% Povidone. Granulation was done in a fluidized bed dryer. To granulate 400 g of powder 200 ml of ethanol were used leading to a Povidone concentration of 16% when used as a binder solution. The particle size distribution of the resulting granules was log-normal, the mean particle diameter for the dry method was 680 µm and for the granules prepared using a binder solution 330 µm. Flowability was similar for both granulations, friability was lower for the granules prepared with Povidon in solution. A more uniform distribution of Povidon in the granules was found for the binder added in solution. The authors come to the conclusion that it is advantageous to add the binder in solution. Comparing the two papers the results seem not to be in agreement. For the system microcrystalline cellulose/Povidone/water the dry method was recommended while for lactose plus starch/Povidone/ethanol the solution method was superior. But two aspects were not considered in both papers: the properties of the excipients and the equipment. Microcrystalline cellulose absorbs high amounts of water before agglomeration starts while a mixture containing 80% of lactose and 12% of starch immediately starts agglomeration. The granulation behaviour of the substances is completely different. In addition the methods used were not directly comparable. The mechanical stress in a kneader is high compared to a fluidized bed unit. Therefore the contact between binder, excipients and water is more intensive in a mixer granulator leading to a dense packaging of the material and a better distribution of the liquid.

Voigt and Richter (Voigt and Richter 1988) and Richter et al. (Richter et al. 1989) compared the dry and the solution method using the binders gelatin, Povidone, polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC) and a hydrogelized potato starch (SHP) to granulate a starch/lactose (2:1) mixture in a fluidized bed granulator. The mean particle diameter of the granules was smaller in all cases, when the dry method was used and was nearly concentration independent, while with the solution method an increase of the mean particle diameter with increasing amount of binder was observed. Gelatin and PVA gave harder tablets after solution granulation while Povidone showed no differences. This was explained by the high dissolution rate of Povidone during granulation. Again Povidone was recommended for the method of dry binder addition and subsequent moistening.

Wan and Lim (Wan and Lim 1989) used the dry and the solution method to granulate lactose and starch respectively using 25 g of Povidone per 400 g of material in a fluidized bed dryer. They found larger particle diameters for the dry method for lactose and no significant differences for starch. The higher water absorption of starch should again be responsible for the differences between both substances.

To summarize these findings: Povidone is a valuable binder when incorporated in a powder mixture as a dry substance being granulated by the addition of water or an organic solvent. Due to its high dissolution rate it is superior to other polymers like gelatin. The experimental conditions depend on the type of material to be granulated and on the equipment used.

Povidone as a binder in model systems

Basic investigations of the granulation process are quite often carried out using model formulations. Frequently used excipients in this field are lactose, starch, mixtures thereof, microcrystalline cellulose and dicalcium phosphate. Most of the work published in the past was done with lactose or mixtures thereof with starch. The following tables summarize work which was done with Povidone alone or in comparison to other binders. Investigations dealing with lactose are summarized in tables 2 and 3, those with mixtures of lactose and starch are presented in table 4.

The results from fluidized bed granulation of lactose can be summarized as follows:

- Higher molecular weights of Povidone lead to larger and stronger granules
- The granule size is increased and the granule friability is decreased with increasing concentration, spray rate and volume of the binder solution
- Tablet hardness is increased with increasing binder concentration

Table 3 presents the results with the lactose/Povidone system granulated in high shear mixers of different types.

Due to the limited amount of liquid being used in this type of granulation the binder concentration in the solution is in general much higher compared to fluidized bed granulation. Concentrations ranging from 10 to 45% are usual. The amount of liquid should
Model granulations of lactose/Povidone using a fluidized bed granulator

(Aeronomic-Strea 1, Aeronomic-Fielder, Rubendorf, Switzerland). (Table 2)

<table>
<thead>
<tr>
<th>Lactose</th>
<th>Povidone</th>
<th>Apparatus</th>
<th>Parameters investigated</th>
<th>Results</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>lactose BP</td>
<td>solution</td>
<td>VA-64</td>
<td>high speed mixer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lactose Ph. Eur.</td>
<td>X = 52</td>
<td>35%</td>
<td>high speed mixer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lactose Ph. Eur.</td>
<td>X = 52</td>
<td>35%</td>
<td>high speed mixer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lactose 100 mesh</td>
<td>Xₜ = 90</td>
<td>30%</td>
<td>planetary mixer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lactose 350 mesh</td>
<td>Xₜ = 92</td>
<td>Povidone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lactose-monohydrate</td>
<td>1000 g</td>
<td>10%</td>
<td>planetary mixer</td>
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<td></td>
</tr>
</tbody>
</table>

Model granulations of lactose/Povidone using conventional mixing equipment. (Table 3)

<table>
<thead>
<tr>
<th>Lactose</th>
<th>Povidone</th>
<th>Apparatus</th>
<th>Parameters investigated</th>
<th>Results</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>lactose BP</td>
<td>solution</td>
<td>A: Glatt-WSG 5</td>
<td>ratio of lactose starch binder conc. in solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lactose</td>
<td></td>
<td></td>
<td>impeller speed</td>
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<td></td>
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<tr>
<td>lactose BP</td>
<td>solution</td>
<td>A: Glatt-WSG 5</td>
<td>granule properties</td>
<td></td>
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<tr>
<td>lactose</td>
<td></td>
<td></td>
<td>humidity, apparent</td>
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<tr>
<td>lactose</td>
<td></td>
<td></td>
<td>density, porosity,</td>
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<td>lactose</td>
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<td>angle of repose</td>
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<tr>
<td>lactose</td>
<td></td>
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<td>tablet properties</td>
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<tr>
<td>lactose</td>
<td></td>
<td></td>
<td>(hardness, friability,</td>
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<tr>
<td>lactose</td>
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<td>disintegration)</td>
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<tr>
<td>lactose</td>
<td></td>
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<td>tablet strength</td>
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<tr>
<td>lactose</td>
<td></td>
<td></td>
<td>increased with increasing amount of liquid in granulation</td>
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<tr>
<td>lactose</td>
<td></td>
<td></td>
<td>tablets compressed from granules prepared by method D were superior</td>
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<tr>
<td>lactose</td>
<td></td>
<td></td>
<td>ratio of 3.1:1:13 with respect to larger granule size and better flow properties</td>
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<tr>
<td>lactose</td>
<td></td>
<td></td>
<td>tablets compressed from granules prepared by method D were superior</td>
<td></td>
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</tr>
<tr>
<td>lactose</td>
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</tr>
</tbody>
</table>

In a series of papers Vojnović et al. (Vojnović et al. 1992, 1993 and 1995) optimized the operating conditions of two high shear mixers Roto J and Roto P from Zanchetta, Italy. They used a powder mix containing 68.2% of lactose and 31.8% of corn starch which was granulated with a Povidone solution. First a central composite design using a Roto J granulator was carried out leading to the following optimum conditions for the granulation process:

- moisture level: 174.5%
- impeller speed: 426.5 rpm
- granulation time: 8.01 min.

Their second paper deals with the simultaneous optimization of several response variables. Using the same formulation the optimum zone of the 10-litre machine was determined and scaled up to a 50-litre high shear mixer. In the third paper the central composite design was optimized by an "a priori" approach.
Besides lactose and mixtures of lactose and starch some papers deal with other excipients like dicalcium phosphate and microcrystalline cellulose as model substances in granulation. Ritela et al. (Ritela et al. 1986 and 1988) used a high shear mixer (Fielder PMAT 25 VG) in basic investigations with dicalcium phosphate and the binders Povidone K-25, Povidone K-90, two hydroxypropyl methylcelluloses Methocel E5 and E15, a hydrozilized gelatin (Byco C or Protein S) and a poly(vinylpyrrolidone-vinylacetate) copolymer. Povidone K-90 and Protein S facilitated the granule growth leading to coarser granules. Aviel was used to study the interactions of this microcrystalline cellulose with aqueous solutions of Povidone K-25 and hydroxypropyl methylcellulose (Pharmacel 603) using a laboratory-scale, instrumented mixer torque rheometer. The authors found differences between the two binders which were explained by theories relating binder surface tension to granule properties.

Povidone in the granulation of active ingredients

In model systems containing lactose, starch, mixtures thereof, microcrystalline cellulose or dicalcium phosphate as excipients, the influence of different binders on the granule properties could be studied relatively easily. Except lactose these excipients are water-insoluble, the bonding between them and the binder depends on their wetting behaviour, water uptake, swelling, and later on during compression of the tablets on their compression and compaction properties. When adding an active ingredient the situation becomes more difficult. Wetting and solubility as well as its companssional behaviour will – depending on the dosage – more strongly influence the properties of the resulting granules and tablets. Table 5 summarizes those articles from literature which deal with Povidone as a binder. The examples chosen cover a range of pharmaceutical actives. It was not the intention to collect all papers published.

Acetaminophen is a high dosed drug which is sparingly soluble in water and poorly compressible. Therefore it is a good example to test the capability of binders in granulation. Liu et al. (Liu et al. 1994) used Povidone K-30 to develop a direct compressible acetaminophen. In preliminary trials Povidone was applied at the three levels 2, 5, and 10% in the granules via 5, 7.5 and 10% solutions using a Glatt GPCG-1 (Glatt Air Techniques Inc., Einzen, Germany) fluidized bed granulator. It was found that in minimum 5% of Povidone are required to give a free flowing granulate. In an additional factorial experiment 5% of Povidone were used in two spray concentrations of 5 and 7.5% in solution. The other factors were spray rate, spray pressure and inlet air temperature. The batch size was 500 g. The validity of the model was proven with Povidone containing one using a combination of a high shear mixer Diosna P 10 (Dierks & Söhne, Osnabrück, Germany) and a fluidized bed dryer Strea 1 (Aeromatic-Fielder, Bubendorf, Switzerland). They compared Povidone K-30, a hydroxypropyl methylcellulose (Cellulose HP-M 603), a pregelatinized starch (Lycatal PGS), a maltodextrin (Lycatal DSH) and a low substituted hydroxypropylcellulose (L-HPC, type 11). The binders were added as powders and granulation was done with water. Although they were able to detect differences between the binders there was no formulation found leading to a tablet with sufficient properties. Here the question is whether or not the mode of incorporation of the binders into the granules plays an important role. Ebube and co-workers (Ebube et al. 1996) compared the influence of acetaminophen as an example of a sparingly soluble drug and pseudoephedrine sulfate showing a high water solubility on tablet properties using a hydroxypropyl methylcellulose and Povidone K-30 as binders. The drugs were used alone and in combination in a matrix of the two binders of differing ratios. The total polymer content was between 3.5 and 19.2% in the final matrix. The presence of the water soluble pseudoephedrine significantly influenced the properties of the acetaminophen granulation by reducing the particle size distribution of the granules and the friability of the tablets.

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Povidone-type and concentration</th>
<th>Main purpose of the investigation</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>K-30; 2/5/10% in gran. 5/15/15% in sohn.</td>
<td>Development of acetaminophen for direct compression</td>
<td>Liu et al. 1994</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>K-30; 2 and 5%</td>
<td>Development of acetaminophen for direct compression</td>
<td>Chen et al. 1995</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>K-30; 0/2/6/10%</td>
<td>Comparison of Povidone with other binders</td>
<td>Becker et al. 1997</td>
</tr>
<tr>
<td>Acetaminophen/ Povidone/</td>
<td>K-28-32, blended with HPMC; 3/4 to 19.2%</td>
<td>Effect of drug, formulation and process variables on granulation, and compaction characteristics</td>
<td>Ebube et al. 1996</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>not specified; 1/3/5%</td>
<td>Comparison of Povidone with corn starch and HPC</td>
<td>Anjik et al. 1988</td>
</tr>
<tr>
<td>Aspirin</td>
<td>K-90, 6%</td>
<td>Influence of solvent type (water/ethanol on granules and tablets)</td>
<td>Wells and Walker 1963</td>
</tr>
<tr>
<td>Caffeine</td>
<td>K-12/K-17K/25/ K-90; 3%</td>
<td>Application of polymer blends in granulation</td>
<td>Jäger und Bauer 1984</td>
</tr>
<tr>
<td>Herbal drugs</td>
<td>K-30/K-90; 5%</td>
<td>Effect of binder solution on physical properties of granules</td>
<td>Seko et al. 1993</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>K-30; 5%</td>
<td>Comparative evaluation of two pharmaceutical binders</td>
<td>Symko et al. 1993</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Povidone; M. 44000</td>
<td>Comparison of Povidone, gelatin and methylcellulose as binders for metronidazole</td>
<td>Ritela and Pipel 1986</td>
</tr>
<tr>
<td>Naproxen</td>
<td>K-25; 5%</td>
<td>Comparison of wet granulation and direct compression</td>
<td>Tariq and Sabir- ul-Fattah 1995</td>
</tr>
<tr>
<td>Naproxen</td>
<td>K-29-32; 5%</td>
<td>Action of “superdisintegrants” in Povidone based granulations</td>
<td>Gordon et al. 1991</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Povidone, M. 10000; 3.78/78/10/15%</td>
<td>Influence of mode of incorporation on dissolution rate</td>
<td>Gabor et al. 1991</td>
</tr>
<tr>
<td>Piracetam</td>
<td>Povidone; 3%</td>
<td>Influence of piracetam solubility on granule properties</td>
<td>Fabregas and Cucala 1987</td>
</tr>
<tr>
<td>Ranitidine Hydrochloride</td>
<td>K-30; 5%</td>
<td>Influence of moisture and different binders on the properties of granules prepared from ranitidine</td>
<td>Uzunarslan and Atkuga 1997</td>
</tr>
<tr>
<td>Salicylic acid/ Sulfinilamide Kaolin</td>
<td>K-28-32; 5%</td>
<td>Influence of wettability of insoluble active ingredients on granule properties</td>
<td>Jayalakshmi and Spring 1990</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>K-90; 5/10/15%</td>
<td>Comparison of Povidone, acacia and gelatin as binders for sulfadiazine</td>
<td>Hooph 1986</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>not specified; 3%</td>
<td>Effect of type of binder on the properties of sulfamethoxazole tablets</td>
<td>Agrawal and Prakash 1988</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>not specified; 5%</td>
<td>Influence of solvent type and drying method on granule</td>
<td>Mandel 1995</td>
</tr>
</tbody>
</table>

Comparison of Povidone, acacia and gelatin as binders for sulfadiazine

Fluid bed granulation.
Aminophylline was granulated using Povidone, corn starch and hydroxypropyl cellulose by Anjo and co-workers (Anjo et al. 1999). Povidone showed the best dissolution rate and the lowest disintegration time at sufficient hardness values of the tablets. The influence of binder vehicle upon granule and tablet properties has been studied by Wells and Walker (Wells and Walker 1983) in a model system containing aspirin and Povidone. Water and ethanol were chosen as solvents changing the solubility of aspirin from 4.66 mg per ml in pure water gradually to 133.6 mg per ml in pure ethanol. Using mixtures containing 25, 50 and 75% ethanol besides the two pure solvents it was possible to study the influence of a change in drug solubility on the granule and tablet properties. Greater solubility of the drug increases the granule size distribution and decreases the friability of the granules. The disintegration time was prolonged when using a solvent with a higher drug solubility.

Caffeine as a model drug was used by Kesavan and Peck (Kesavan and Peck 1996) to optimize a formula by artificial neural networks. Their basic formulation is shown in table 6.

Besides the variation of the type of binder four concentrations of Povidone ranging from 2 to 5%, the mode of addition of binder in the dry state and as a solution and a high shear mixer as well as a fluidized bed dryer were used. The granules were compressed into tablets and hardness, friability, thickness, disintegration time and average tablet weight were determined. A good correlation between predicted and observed values was found for all granule and tablet parameters. In a second paper dealing with caffeine Jäger and Bauer (Jäger and Bauer 1984) investigated the influence of different types of Povidone including K-12, K-17, K-25 and K-90 and mixtures thereof in the preparation of granules and in subsequent tableting. They came to the conclusion that the use of polymer blends containing K-25 and K-90 have superior properties compared to the single Povidone types.

Seko et al. (Seko et al. 1993) published a paper on the granulation of crude drug powders comparing hydroxypropyl cellulose, sodium carboxymethylcellulose and the Povidone types K-30 and K-90. The following powdered drugs were used: Glycyrrhiza, Senna leaf, Rhubarb, Magnolia bark, Peony root and Cedrinum rhizome. The granulation was done by two methods: fluidized bed granulation using a Glatt CPCG-1 granulator and by agitation granulation using a Multiplex granulator FM-MP-10. Different concentrations of binder solutions were applied. The results were analyzed by multiple linear regression yielding a regression equation for each response parameter and both granulators. The physical properties of the products of both, agitation and fluidized bed granulation, are closely related to the amount and the viscosity of the binder solution. Hydrochlorothiazide was granulated comparing Lycatab DSH, a maltodextrin, and Povidone K-30 (Symecko et al. 1993). The binder was added in the dry state and granulation was carried out following the scheme shown in figure 6.

This is a typical scheme to prepare granules using the binder in the dry state and moistening the powder mix during the granulation with water. In these cases the binder has to have a good water solubility combined with a high dissolution rate. The results obtained in this investigation are summarized in table 7.

The granule and tablet properties for both binders are similar. The dissolution of hydrochlorothiazide is a little bit faster for Povidone. The compression/hardness profile of the two formulations is presented in figure 7, indicating a higher binding capacity for Povidone. Naproxen, a poorly water soluble nonsteroidal anti-inflammatory agent, was compared in direct compression and granulation formulations by Tarimci and Satiroglu-Tezcan (Tarimci and Satiroglu-Tezcan 1999) using 5% Povidone K-25 as a binder. Although the mechanical tablet properties were almost the same for both preparation methods the authors detected significant differences between direct compression and granulation. All granulated formulations liberate the active ingredient completely within 10 minutes while some of the direct compression formulations showed a prolonged drug dissolution. Gordon et al. (Gordon et al. 1993) investigated the influence of three so called “super disintegrants” on the dissolution of naproxen from granulated tablets on storage under different conditions and found that crospovidone and sodium starch glycinate were superior compared to croscarmellose sodium. The way of incorporation of the disintegrants did not influence the drug dissolution. The binder used for granulation was Povidone K 29-32 in an amount of 5% in the final tablet dissolved in water.
Phenytoin was used as a model substance to investigate differences in the mode of drug incorporation into a tablet by cocrystallization during granulation, coprecipitation alone, solvent deposition and granulation using a Povidone solution. Povidone, M, 10 000, in an ethanolic solution in different concentrations was used as a binder. The disintegration times of all tablet formulations were within the USP specifications although there was an increase with increasing Povidone concentration. On the other hand the dissolution of phenytoin was increased with increasing Povidone concentration in general. Differences were found for the way of incorporation. Best results were obtained when the drug was dissolved together with Povidone in ethanol and cocrystallization occurred during granulation. The slowest disintegration rates were observed when a simple granulation with a Povidone solution was done.

The influence of the solvent used in granulation on the disintegration time of tablets during storage was investigated with piracetam as an example for a highly water soluble drug (Fábregas and Cucala 1987). The authors came to the conclusion that whenever a part of the drug is dissolved during granulation the disintegration time of the tablets is prolonged on storage especially under humid conditions. A similar influence of drug was found for propranolol hydrochloride when it was dissolved together with Povidone prior to granulation (Wan et al. 1996). Besides the drug influence the authors found an increase in crushing strength of the tablets with increasing volume and concentration of binder used. High molecular Povidone resulted in stronger tablets.

The effect of wetting ternary powder mixtures in granulation was investigated by Jaiyeoba and Spring (Jaiyeoba and Spring 1980). As a basic mixture they used a combination of lactose and boric acid in different proportions and an aqueous 5% Povidone K-29-32 solution as a binder. The third component of the ternary mixture was either kaolin, sulfanilamide or salicylic acid added in an amount of 10%. The addition of kaolin, which is very readily wetted by water, resulted in stronger granules. Sulfanilamide did not change the granule strength due to its medium wettability which lies between lactose and boric acid, while salicylic acid, which is not wetted by water, reduces the granule strength significantly.

Sulfadiazine was granulated by the fluidized bed as well as by a conventional method comparing gelatin, acacia and Povidone K-90 in concentrations of 5, 10 and 15% based on the binder content in the final tablet (Nouh 1986). It was found that in all cases fluidized bed granulation was superior compared to the traditional method and that Povidone gave better disintegration times at the same hardness level compared to gelatin and acacia. The effect of starch, ethyl cellulose, Povidone (type not specified) and acacia in an amount of 3% based on the dry basis on tablet properties of sulfamethoxazole tablets was investigated by Agrawal and Prakasham (Agrawal and Prakasham 1985). Although they obtained best flow properties and lowest angle of repose with Povidone they came to the following ranking of the binders: starch > ethyl cellulose > Povidone > acacia. In an investigation on the influence of microwave drying on granule and tablet properties Mandal (Mandal 1995) used Povidone in a concentration of 5% in water, 50% water and 50% ethanol and ethanol respectively to granulate mixtures comprising of 45% starch, 45% lactose and 10% sulfathiazole. There was no significant difference between the microwave and the conventional drying method, but water based granules showed a higher granule strength compared to 50% water/50% ethanol and pure ethanol.

**Summary**

Linear, soluble polyvinyl pyrrolidone (Povidone) was synthesized in 1939 by Reppe. Its main application was first as blood plasma expander. After the second world war other applications came up and in the field of pharmaceutical technology one of the main purposes is to now the use as a binder in granulation. At present five types K-12, K-17, K-30 and K-90, differing in their molecular weight, are available. The low molecular weight types K-12 and K-17 are used in parenterals while the higher ones are preferred in peroral medicines. The binding properties of Povidone increase with increasing molecular weight. Therefore strongest bonds between particles in granulation are formed by the high molecular weight type K-90. On the other hand this type shows the highest viscosity which could be a limiting factor. The formation of granules is mainly influenced by the factors:

- type of Povidone
- concentration of Povidone in the granulation fluid
- concentration of Povidone in the final tablet
- the mode of addition of the binder
- the equipment used in granulation
- the properties of the active ingredients being granulated.

The type of Povidone determines the granule strength together with the concentration. Higher molecular weight Povidone leads to a higher granule strength. Therefore Povidone K-90 quite often is preferred. On the other hand the use of high viscous solutions could be a limitation when only a certain amount of liquid can be used. The concentration of Povidone in the granulation fluid therefore varies between 10 and 40%.

![Granule and tablet properties of hydrochlorothiazide tablets](adapted from Symecko et al. 1993). (Table 7)

<table>
<thead>
<tr>
<th>Granule</th>
<th>Binder</th>
<th>Kollidon 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow rate (g/sec)</td>
<td>4.39</td>
<td>4.51</td>
</tr>
<tr>
<td>Granule friability (%)</td>
<td>3.87</td>
<td>4.37</td>
</tr>
<tr>
<td>Mean particle size (μm)</td>
<td>201.7</td>
<td>143.9</td>
</tr>
<tr>
<td>Density</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (mg)</td>
<td>315.5</td>
<td>313.1</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.38</td>
<td>0.51</td>
</tr>
<tr>
<td>Disintegration time (min)</td>
<td>13.42</td>
<td>13.71</td>
</tr>
<tr>
<td>Hardness (kg)</td>
<td>7.63</td>
<td>7.45</td>
</tr>
<tr>
<td>Dissolution profile: 20 min</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>30 min</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

![Comparison of tablet hardness against maximum compression force for the two binders Lycatab DSH, a maltodextrin, and Povidone K-30, both added as powders in a concentration of 5%](Symecko et al. 1993). (Figure 7)
in conventional granulation while in fluidized bed granulation the concentration normally is in a range of 5% to 10%. In the final tablet the concentration of Povidone as a binder is between 3% to 5% and 10%. The binder could be added either as a dry powder followed by the addition of a solvent or as a binder solution. The first method has the advantage that there is always a constant amount of binder in the formulation, the disadvantage is that the binder in many cases is not completely dissolved and that therefore the type of the equipment used and the processing time become very important for the result of the granulation process. In addition only could water soluble binders be used in this process.

The use of a binder solution has the advantage that there is a molecular distribution of the binder leading to the formation of the maximum number of bonds between particles. The disadvantage is that there could be a variation in the amount of binder added due to the fact that the amount of fluid necessary for granulation varies between different batches of powder. Therefore when using this method the raw materials have to be standardized with respect to particle size or surface area.

The equipment has an additional influence in granulation. Today there are two different concepts in use:

- the fluidized bed technology and the
- high shear mixer technology often combined with a fluidized bed dryer.

The fluidized bed technology is a one step process where mixing of the powders moistening of the material, granulation and drying are carried out in the same apparatus. The method has no restrictions with respect to the amount of binder added and yields highly compressible granules due to its loose structure. Disadvantages are the limited batch size and the time consuming process. The high shear technology offers a rapid method for mixing the powder, moistening and granulation within a few minutes leading to a denser material compared to the fluidized bed technology. There is equipment ranging from small scale (below 100 grams) to high capacity apparatus of several hundred kilograms available. The disadvantages are: the amount of binder added as a binder solution is limited due to the solubility and viscosity of the polymer used for granulation and drying is normally carried out in a second unit quite often a fluidized bed dryer.

The presence of active ingredients can tremendously alter the properties of the granulation mixture. In granulation the first step is the wetting of the material by the granulating fluid. This can be facilitated by wetting agents. The solubility of the actives and excipients in the granulation liquid will also influence the process and is quite often the determining factor when highly water soluble drugs have to be granulated. In addition a recrystallization during drying can occur leading to a change in hardness, disintegration and dissolution of the tablets prepared from these granules. These physical changes occur during storage over a prolonged period of time. Nevertheless today Povidone is besides many other applications the most widely used binder in granulation.

**Acknowledgements**

The author acknowledges the help of BASF in the literature search and thanks Dr. Volker Bühler and Dr. Siegfried Lang, BASF, Ludwigshafen, for helpful discussions. Thanks should also be given to Mrs. Renate Beer, University of Tübingen, for typing and revising the manuscript.

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Toxicology of Polyvinylpyrrolidone

A comprehensive summary of the toxicological properties of Povidone.

St. Schulte

General

Polyvinylpyrrolidone (Povidone) is a linear homopolymer of 1-vinyl-2-pyrrolidone monomer used in a wide range of applications in the pharmaceutical, food, and cosmetic industry. Povidone grades are available in different molecular weight ranges. The letter K and an appropriate number related to the molecular weight are used to designate the different Povidones. Numerous toxicological and kinetic studies with Povidones have been performed indicating the biological inertness of the compound.

Absorption, Metabolism, Distribution, Excretion
The absorption of Povidone from the gastrointestinal tract is very limited and proceeds primarily by fluid-phase pinocytosis. After injection, Povidone may be stored at the injection site or at distant sites (cutaneous storage syndrome). The disappearance of Povidone from the bloodstream is inversely related to the molecular weight and involves an initial rapid removal of low molecular weight materials by the kidney and a prolonged slower removal of higher molecular weight material into lymph and tissues, primarily the reticuloendothelial system tissues, including liver, spleen, bone marrow, bone and kidney. Tissue storage disease in humans occurs only following parenteral administration of large amounts of the higher molecular weight Povidones. Orally administered Povidone is eliminated almost totally in the faeces; very little is found in the bile or urine. Povidone is not metabolized in the body.

Acute toxicity studies
Studies in rodents, dogs and primates have shown that Povidone is a substance with a very low acute toxicity. It is essentially impossible to kill animals by administration of Povidone except by gross osmotic imbalance. Thus the LD50 of Povidone orally is reported to exceed 100g/kg and to be around 10g/kg or more intravenously or intraperitoneally. The only evidence of toxicity following oral administration is the production of diarrhoea with doses exceeding 0.5g/kg due to the non-absorbed osmotic load in the gut lumen.

Subchronic toxicity studies
Repeat-dose oral studies in rodents and dogs have shown that apart from diarrhoea at high doses related to the bulk purgative actions of Povidone there is no evidence of any toxicity as judged by clinical chemistry, hematology or histopathology. Occasional reductions in weight gain have been observed with 10% Povidone in the diet, but this is probably related to reduced food intake and diarrhea. There is some evidence of minimal absorption as judged by the appearance of cell inclusions in the mesenteric lymph nodes in one dog study, but this is probably not of any toxicological significance. The no-adverse-effect level in subchronic studies in rodents and dogs is around 5g/kg/day.

Chronic toxicity/carcinogenicity studies
In two well conducted chronic studies using Povidone K25 and K90 at dose levels in the diet up to 10% and 5%, respectively, over a 2 year period, there was no evidence of any substance-related toxicity in clinical chemistry, hematology, urine analysis or histopathology. There was no evidence of an carcinogenic effect or evidence of Povidone storage in any organ. In less well reported chronic oral dog studies in which Povidone K30 was administered in the diet for 1–2 years, there was no evidence of treatment-related effects other than some evidence of Povidone storage in the regional lymph nodes. There was no evidence of any cumulative damage over the 2 years.

Parenteral toxicity studies
After parenteral administration, Povidone is well tolerated, with little evidence of local damage after single or 5 injections. However, parenteral administration of large amounts has been reported to cause histamine release in the dog and Charolais cow, and other cardiovascular phenomena secondary to osmotic imbalance. Histamine release is well-known for the canine family. Numerous studies on the chronic effects of injection of Povidone in rats have given conflicting results, virtually all due to poorly designed and conducted studies. When well conducted studies have been carried out, there is no evidence of a carcinogenic effect from repeated parenteral administration. Repeated injection of Povidones, especially the larger molecular weight materials, e.g. K-30 and over, can result in accumulation of Povidone in the tissues. This is particularly so if the Povidone is injected into poorly perfused sites. This has been demonstrated in animals to lead to development of foreign body type sarcomas at the site of injection but with no metastases.

Mutagenicity studies
Several investigations of the mutagenic potential of Povidone have been carried out, all of which indicate that Povidone is without mutagenic activity. In the Ames test, Povidone K30 has given negative results with and without activation. Povidone K30 was also found to be non-mutagenic in the mouse lymphoma assay with and without metabolic activation. In vivo, the dominant lethal test and a cytogenetic in the bone marrow of Chinese hamsters gave no indication of a genotoxic or clastogenic activity from Povidone K30.

Developmental toxicity studies
Four studies have been performed, two in the rat and two in the rabbit, using Povidone with four different molecular weight distributions, Povidone K30 and Povidone K90 were given in the diet during the first 20 days of pregnancy. There were no indications of embryotoxicity or teratogenicity in the treated groups. In rabbits treated by intravenous injection with Povidone -K12 from days 6–18 of pregnancy, no adverse effects were observed. Povidone with an average molecular weight of 11,500 given intra-amniotically to rabbit embryos showed no evidence of embryotoxicity or teratogenicity.

Conclusion
The extensive volume of toxicological data on Povidone supports the inertness and hence the safety of Povidone. The acute, subchronic and chronic toxicity of orally administered Povidone is very low, with the only effect observed being diarrhoea at high doses due to the osmotic action of Povidone. Occasional observations of minimal absorption with storage in mesenteric lymph nodes seem to be of no toxicological importance. Povidone was found to be neither mutagenic nor developmentally toxic. The currently permitted FAO/WHO Acceptable Daily Intake (ADI) of 0–50mg/kg body weight for food use provides an adequate margin of safety.
Product Launch

Kollicoat® MAE 100 P – A new redispersable powder for enteric coating.

Since more than a year Kollicoat MAE 30 DP is marketed for enteric film-coating of pharmaceutical dosage forms. Kollicoat MAE 30 DP is an aqueous dispersion of a copolymer derived from methacrylic acid/ethyl acetate (1:1). Kollicoat MAE 30 DP complies with the requirements of the European Pharmacopoeia monograph “Polyacrylate dispersion 30%”, the USP-NF monograph “Methacrylic Acid Copolymer Dispersion” and the JPE monograph “Methacrylic Acid Copolymer LD”.

Transporting and storing aqueous dispersions, e.g. Kollicoat MAE 30 DP involve certain risks. Exposure to heat causes polymer losses as a result of skin formation on the surface, agglomeration and sometimes sedimentation. Freezing may induce coagulation. Transporting and storing redispersable powders do not involve these risks and hence are particularly suitable to be used in countries with hot and cold climates.

Kollicoat MAE 100 P is a new redispersable powder for aqueous enteric coating and available since May 1999.

Kollicoat MAE 100 P is prepared from the aqueous dispersion Kollicoat MAE 30 DP using an FSD-spraying technology. Kollicoat MAE 100 P can be easily redispersed without further auxiliaries by pouring it into water while stirring.

Redispersion of the powder into the aqueous dispersion can be performed just before the spraying process. The physical stability of the redispersion is, however, excellent, so that the latex can also be stored for some days. The technical relevant properties of the redispersion, e.g. particle size, compatibility with additives, processibility and film formation, are very similar to those of the original latex. Processing occurs in the usual manner with plasticizer, pigments and other excipients.

Films of Kollicoat MAE 30 DP and Kollicoat MAE 100 P are equal with regard to their gastric resistance and dissolution behaviour above pH 5.5.

Regulatory Affairs

Kollidon VA 64 approved for the US market.

During the last 12 month the FDA approved 3 different formulations containing Kollidon VA 64. This includes the oral application of Kollidon VA 64 and the functionality as an effective dry binder.

A monograph of “Copovidone” was prepared and published in the US Pharmacopeial Forum Vol. 24, No. 4, July/August 98, pp 6456-6459. The monograph will be included in the USP as official monograph soon.

New production plant for PVP-Iodine.

The production of PVP-Iodine will be transferred from the Ludwigshafen production site to our new and modern production plant in Geismar, US in 1999. The production plant in Geismar was designed for Pharma production and is manufacturing PVP-Iodine since 1996. Information material and PVP-Iodine samples for reapproval studies are available.

For more information please contact Dr. Folker Ruchatz, MEM/FP, Fax No. +6216094-616 or via e-mail folker.ruchatz@basf-ag.de.
Sustained release products are gaining more and more interest due to a long lasting drug action with low side effects and a better compliance related to immediate release dosage forms.

However, for the manufacturing of coated sustained release dosage forms only few polymers are applicable.

Each of these polymers has certain disadvantages, e.g. curing effects, necessity of high amounts of plasticizer, pH-dependent release characteristics, interaction with the active ingredient, high tackiness, etc. Some of the commercially available products are marketed at a very high price. In view of these facts a strong demand for a new polymer becomes obvious.

Kollicoat SR 30 D, a recently developed product for sustained release coating, represents a break-through in this application field. Besides other topics, ExAct No. 3 will deal with this innovative coating excipient.

Should you require information in advance, please contact your local BASF company or one of our regional centres.

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**BASF Fine Chemicals for the Pharmaceutical Industry.**

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**Binders, Solubilizers**
- Kollidon® 12 PF/77 PF, Kollidon® 25/30/90 F

**Disintegrants, Suspension Stabilizers**
- Kollidon® CL, Kollidon® CL-M

**(Dry) Binders, Film Formers**
- Kollidon® VA 64

**Disinfectants**
- PVP-Iodine 30/06, PVP-Iodine 30/06 M10

**Enteric Film Coatings**
- Kollicoat® MAE 30 DP, Kollicoat® MAE 30 D, Kollicoat® MAE 100 P

**Sustained Release Film Coatings**
- Kollicoat® EMM 30 D, Kollicoat® SR 30 D

**Solubilizers/Emulsifiers**
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- Propylene Glycol, Soluphor® P

**Active Ingredients**
- Crospovidone M, Tretinoin, Isotretinoin, Retinol 50P, Carotenoids, Active ingredients from Knoll

**Fat-soluble Vitamins**
- Vitamin A, Vitamin D2, D3, Vitamin E, Vitamin K

**Water-soluble Vitamins**
- Vitamin C, Vitamin B1 (Thiamin), Vitamin B2 (Riboflavin), Vitamin B3 (Nicotinamid), Vitamin B5 (Calpan), Vitamin B6, Vitamin B12, Vitamin H (Biotin)

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