Volker Bühler

Kollidon®

Polyvinylpyrrolidone excipients for the pharmaceutical industry

9th revised edition

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Pharma Ingredients & Services
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The Chemical Company

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Contents

Preface

Among synthetic excipients, polyvinylpyrrolidone (povidone), marketed under the brand name Kollidon®, is one of the most important substances in the pharmaceutical and cosmetic industries. Starting from the soluble Kollidon® grades which were synthesized by W. Reppe in 1939, a number of products followed, including insoluble grades, copolymerisates and sustained release preparations for numerous applications. The insoluble grades (Kollidon® CL) are prepared using a physical cross-linking process as popcorn polymers of vinylpyrrolidone. Kollidon® VA 64 (copovidone) is a water-soluble copolymerisate of vinylpyrrolidone and vinyl acetate and is mainly used as a binder in tablets, granules, capsules and in coating processes. For sustained release purposes, a mixture of polyvinyl acetate and povidone in a ratio of 8 : 2 is available under the name Kollidon® SR. "The Kollidon® family" is thus nowadays a set of modern excipients based on polyvinylpyrrolidone for use in the pharmaceutical industry.

Although the products are included in all relevant pharmacopoeias, there is a need for a detailed description with special emphasis on their technological properties and applications. This 9th edition of the "Kollidon®-Book" provides answers to all questions relevant to product properties, stability, analytical methods and applications of Kollidon®. It includes three new products: **Kollidon® CL-F** and **Kollidon® CL-SF**, both insoluble and differing in their mean particle diameter and particle size distribution, and **Kollidon® VA 64 Fine**, a water-soluble fine powder, developed as a dry binder for direct compression formulations in tableting and for dry granulation purposes.

The book is divided into 7 main chapters:
1. General notes on synthesis and applications, 2. Soluble Kollidon® grades (povidone), 3. Insoluble Kollidon® grades (crospovidone), 4. Kollidon® VA 64 grades (copovidone), 5. Kollidon® SR, 6. Registration in pharmaceuticals and food, and 7. Toxicological data. It is completed by a current list of references and an alphabetic index. Chapters 2 to 5 are constructed in an identical way, starting with the structure of the product, going on to its physical, physicochemical and chemical properties, methods of analysis, including pharmacopoeial and non-pharmacopoeial methods, and applications. Data are presented in a clear and informative way, often with the help of tables and figures. More than 600 literature citations, including the latest relevant publications, present a complete overview of povidone and related compounds.
The alphabetic index is of high quality and serves as a quick reference guide. I do not know of any other book about excipients that presents such highly concentrated scientific information with valuable practical help.

Any book going to a 9^{th} edition must be a good one. This reflects on the author, Dr. Volker Bühler. He is a pharmacist and spent nearly 30 years with BASF in the application department. Although officially retired, he is still consulting for BASF and writing books. His "Kollidon® Book" started off as a German version in 1992 and was immediately translated into English. The first Japanese edition was published in 1996. Besides this, he has written books on vitamins, on generic drug formulations, on BASF excipients for pharmaceutical technology, on polyvinylpyrrolidone and on the Kollicoat® grades, the coating excipients of BASF. I am convinced that this 9^{th} edition of the "Kollidon® Book" will be equally successful and I wish him many more editions.

Tübingen and Nürnberg, September 2007

Dr. Peter C. Schmidt
Prof. em. of Pharmaceutical Technology
Institute for Pharmacy
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BASF
Kollidon® VA 64
BASF
Kollidon® 12 PF
BASF
Kollidon® CL
40 kg net
BASF
Kollidon® 30
25 kg net

1 General notes on synthesis and applications

1.1 Soluble polyvinylpyrrolidone (soluble Kollidon® grades)

Modern acetylene chemistry is based on the work of Reppe at BASF. One of the many products of this work is N-vinylpyrrolidone (Fig. 1.1).

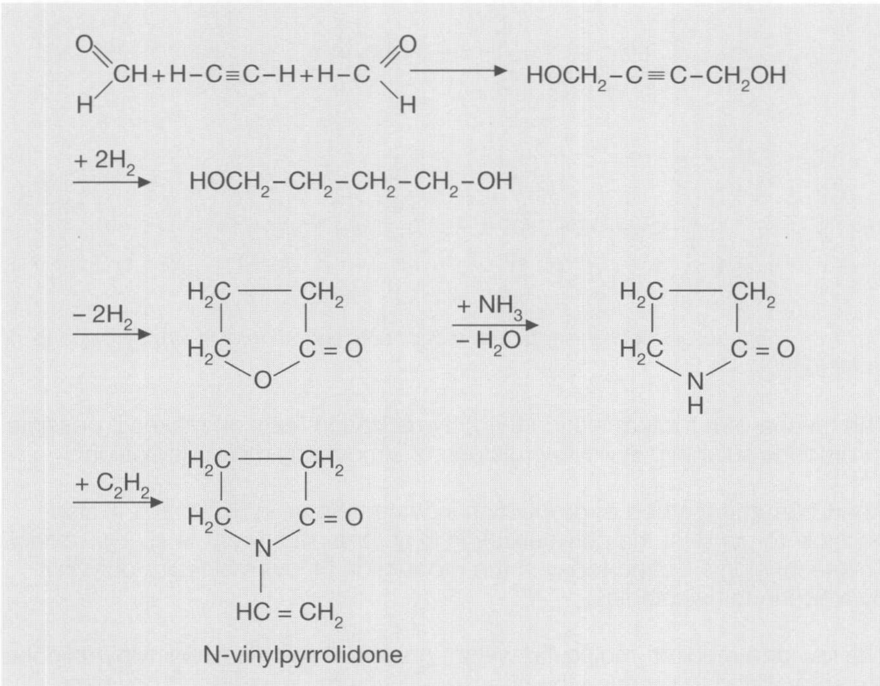

Fig. 1.1: Reppe's synthesis of N-vinylpyrrolidone (C_6H_9NO; Mr 111.1) [669]

The first polymerization product of N-vinylpyrrolidone was soluble polyvinylpyrrolidone, which was patented in 1939. Fig. 1.2 shows one of the mechanisms of polymerization: free-radical polymerization in water using hydrogen peroxide as initiator [1, 141].

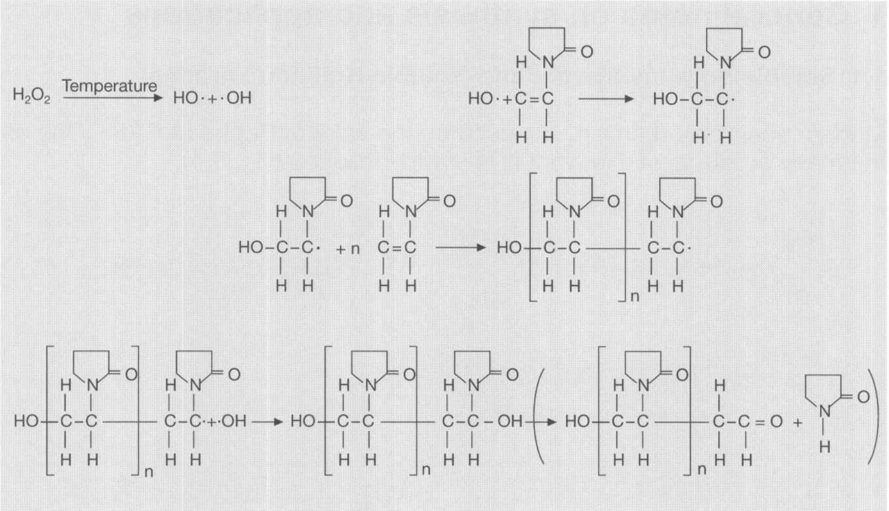

Fig. 1.2: The reaction mechanism for the radical polymerization of N-vinylpyrrolidone in water [669]

The mechanism for terminating the polymerization reaction makes it possible to produce soluble polyvinylpyrrolidone of almost any molecular weight.

Apart from the method of production in water shown in Fig. 1.2, it is also possible to conduct the polymerization in an organic solvent, e. g. 2-propanol. This technology is used today in the production of low-molecular polyvinyl-pyrrolidone for injectables.

The low and medium-molecular weight grades of soluble polyvinylpyrrolidone are spray-dried to produce the pharmaceutical-grade Kollidon® powders, while the high-molecular weight grade is roller-dried.

Soluble polyvinylpyrrolidone was first used during World War II as a blood-plasma substitute. Although it has excellent properties for this purpose, it has no longer been used for a number of decades. The organism does not metabolize the polymer, with the result that after parenteral administration, small quantities of high-molecular components may remain within the body. This problem does not exist with oral administration.

Today, soluble polyvinylpyrrolidone (e. g. Kollidon®) is one of the most versatile and widely used pharmaceutical auxiliaries.

It is also used in the production of one of the most important topical disinfectants, PVP-Iodine.

1.2 Insoluble polyvinylpyrrolidone (crospovidone, Kollidon® CL grades)

Insoluble polyvinylpyrrolidone (crospovidone) is obtained by popcorn polymerization of N-vinylpyrrolidone [2], which yields a crosslinked polymer [4–6]. The process is illustrated in Fig. 1.3 and uses either an alkali hydroxide at temperatures over 100 °C, which yields some bifunctional monomer, or a small percentage of bifunctional monomer in water to initiate crosslinking of the polymer.

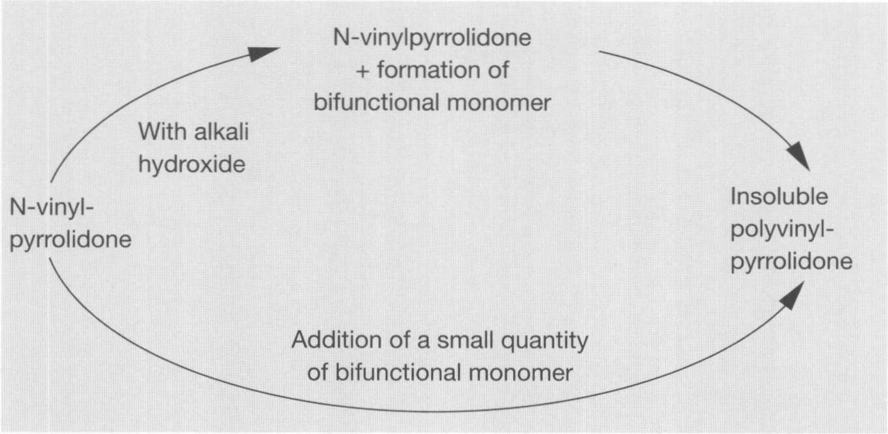

Fig. 1.3: Production processes for insoluble N-vinylpyrrolidone popcorn polymers

A comparison of the infrared spectra of the insoluble popcorn polymer obtained as shown in Fig. 1.3 and that of soluble polyvinylpyrrolidone shows practically no difference, while the infrared spectrum of chemically crosslinked insoluble polyvinylpyrrolidone polymer prepared in the laboratory is quite different, which indicates that the crosslinking in the popcorn polymer is essentially of a physical nature.

Insoluble polyvinylpyrrolidone finds extensive applications in the pharmaceutical and beverage industries as a swelling popcorn polymer with selective adsorptive properties. Its disintegration effect in tablets, its ability to hydrophylize insoluble active ingredients and to adsorb and form complexes are the main properties that make it useful as a pharmaceutical auxiliary. Today, Kollidon® CL is regarded as one of the "superdisintegrants" for tablets.

Further, micronized insoluble polyvinylpyrrolidone is of considerable significance as an active substance against diarrhoea in certain parts of the world. The high bulk density product could be obtained by micronization of normal crospovidone (e.g. Kollidon® CL) and a micronized low bulk density product is available as Kollidon® CL-M.

1.3 Vinylpyrrolidone-vinyl acetate copolymer (copovidone, Kollidon® VA 64 grades)

Water-soluble vinylpyrrolidone-vinyl acetate copolymer contains the two components in a ratio of 6 : 4. It is produced in the same way as soluble polyvinylpyrrolidone, by free-radical polymerization reaction (Fig. 1.4). As vinyl acetate is not soluble in water, the synthesis is conducted in an organic solvent such as ethanol or 2-propanol.

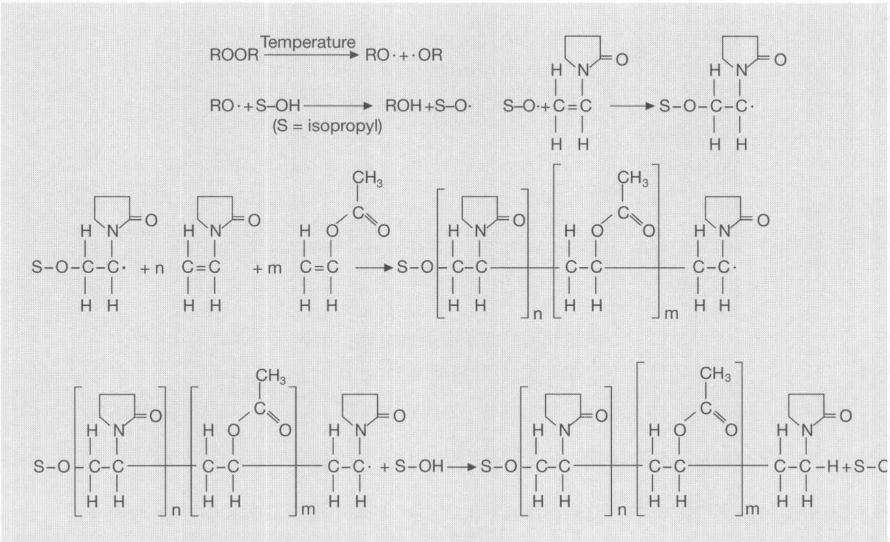

Fig. 1.4: Free-radical polymerization of vinylpyrrolidone-vinyl acetate copolymer $(n+1):m = 6:4$ [669]

Because of its vinyl acetate component, Kollidon® VA 64 grades are somewhat more hydrophobic and gives less brittle films. This gives the products their favourable properties as soluble binders or dry binders and film-forming agent, particularly for solid dosage forms.

1.4 Spray dried polyvinyl acetate containing povidone (Kollidon® SR)

Polyvinyl acetate having a average molecular weight of about 450 000 is produced by radical polymerization as aqueous dispersion in water (Kollicoat® SR 30D), addition of about 19 % of povidone (Kollidon® 30) and spray drying.
The addition of about 0.8 % sodium lauryl sulfate and about 0.6 % of silica are further auxiliaries needed as stabilizer and flowability agent to obtain the free flowing spray dried powder Kollidon® SR.