SYNTHESIS OF CROSPOVIDONE DIFFERENT PROCESS
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ABSTRACT
Crospovidone is a super-disintegrant and is a thermal polymer; crospovidone is a homopolymer of N-Vinyl-2-pyrrolidone; it is a random polymer of N-Vinyl-2-pyrrolidone cross-linked with (Z)-3-ethylidene-1-vinylpyrrolidone-2-one. In this article, the overview is how to synthesise crospovidone by different processes like the main theme, is direct heating of N-Vinyl-2-pyrrolidone with alkali metal hydroxides in the presence of water.

Key Words: Crospovidone, Thermal Polymer

ABOUT AUTHOR

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INTRODUCTION

Name of the product                     : Crospovidone
Chemical Name                           : 1-ethenylpyrrolidin-2-one
CAS No.                                 : 25249-54-1
Project Code                           : CROSS
Chemical Structure                     : Polyvinylpolyprrolidone

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{H}
\end{array}
\]

Molecular Formula                      : \((C6H9NO)_n\)
Molecular weight                       : \((111)_n\)
Category                                : Super Disintegrant
Pharmacopoeia status                   : USP/Ph.Eur.

BRIEF

Crospovidones are insoluble, cross-linked homopolymers of N-Vinyl-2-pyrrolidone. The non-ionic nature and porous particle morphology, make crospovidones disintegrants of choice for fast disintegration, enhanced rate of drug dissolution and robust tablets. Through a combination of mechanisms, crospovidones undergo rapid disintegration. Firstly, with water contact it could swell by 95% to 120% of its initial volume. Also due to their porous morphology, crospovidones rapidly absorb water via capillary action which results in expeditious tablet disintegration, Tg value 190-195°C.

The proposed process is validated in the academic research in all respects and found to be consistent. Hence based on the academic research data we are recommending for taking Trails/Validations in Commercial scale.

Crospovidone polyplasdone XL: polymer has the largest average practical size (100-130µ) and provides the fastest disintegration.

Crospovidone polyplasdone XL10: polymer has a finer average particle size (30-50µ) which enhances content uniformity in the formulation of small tablets (less than 300mg) and in intra granular applications while still providing rapid disintegration.

Corpovidone polyplasdone INF-10: polymer has the finest average particle size (5-10µ) of the polyplasdone grades and is a highly adsorptive material.

Chemical Abstract Name: Cross-linked homopolymer of 1-ethenyl-2-pyrrolidinone.

Cross-linked poly (vinyl pyrrolidinone) has been known under a variety of names. Some of those have been used as "approved names" by the regulatory authorities of different countries.

NOMENCLATURE

Chemical Abstract Name: Cross-linked homopolymer of 1-ethenyl-2-pyrrolidinone.

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POLIMERISATION

The prolific polymerisation takes place through a free radical mechanism, although the presence of a free radical initiator is not always necessary to this type of polymerisation. The radical may also develop through the rupture of polymer chains with the combined actions of polymerisation and swelling, which form a great number of active sites. As a consequence, growing chains are initiated at different sites of the polymer chains at fixed positions, which form independently growing centre unable to interact with each other. These new chains, which also contain the in situ, formed or deliberately added bi-functional cross-linking monomers, get entangled with chains already formed. The overall result of these reactions is a system having a high crosslink density.

The monomer is absorbed by the swelling of the polymer network and converted to a part of the network polymerisation. By the continuous repetition of this process, the existing polymer chains first become strained due to the swelling, and then rupture. This creates new free-radical sites that react with more monomer molecules, producing new growing chains. The straining of the polymer structure can be observed with the help of polarising microscopy. The degree of optical anisotropy depends upon the chemical character of the popcorn polymer.

METHOD OF PREPARATION (DIFFERENT ROUTES OF SYNTHESIS)

Figure – I:

First one, 1-vinylpyrrolidone-2-one (NVP) direct high heating in the presence of strong aqueous alkali metal hydroxide under pressure in an inert atmosphere, in a long time it is formed (Z)-3-ethylidene-1-vinylpyrrolidone-2-one (EVP) shown in figure-II its transform devolving the Crosslink of (NVP) monomer in the organic medium in the presence of strong base, NVP 1-vinylpyrrolidone-2-one more soluble in water, but in the presence of the base medium it’s separated from the aqueous layer. The effect most probably due to the swelling of the polymer coils to the dimensions which favour popcorn polymer formation. And water acts as a pressure developing agent in high temperature, Tg value of product 190°C.

Figure – II:

(Z)-3-ethylidene-1-vinylpyrrolidin-2-one
The second one, this also like the first method but the second time of forming the EVP distilled out around half
volume of water, its use instant rapid formation of EVP followed by with cross-linking of NVP easily formation
of crospovidone. In this case very carefully because if water completely distilled out, in the presences of alkali
metal hydroxide formation of a linear polymer of 3-(1-{2-oxo-1-vinylpyrrolidone-3-yl}-ethyl)-1-
vinylpyrrolidione-2-one (VEP) shown in figure-III this not a random polymer like crospovidone, this highly
soluble in aqueous solution in basic media. This also a solid form and this VEP treated with acidic it’s become
robber form. In-between reaction VEP formation but very low quantity such as very low, so half amount water
distillation is very important after that again closed and maintained the pressure in high temperature in an
inert atmosphere, maybe the water distorted VEP it helps more formation of EVP cross-linking with NVP.

Figure – III:

![Chemical structure](image)

(Z)-3-ethylidene-1-vinylpyrrolidin-2-one

The third one is different from the first 2 methods. Those were of single step but this is a 2 step process, first
develop the EVP 15-20% in strong aqueous alkali metal hydroxide after the separation of the organic layer into
the mixture. then the organic layer distilled the EVP with a combination of NVP at 120°C under vacuumed
@720mmHg fraction we getting 7-10% EVP in NVP after that polymerization reaction makes the composition
of 1.5% EVP, 78.5% NVP, and 15% water in pressure reactor in nitrogen/inert atmosphere.

MECHANISM
The first one-mole NVP converts in one mole of NVP carbanion which is developed cis form of EVP followed by
base isomerisation forms Trans EVP which is cross-linked with NVP formation of Crospovidone shown figure-IV.

IMPORTANT OR CRITICAL PARAMETERS
Any examples like 2 steps and single step, it should not use any organic solvents and acids it’s affected on
random polymerization, Crospovidone is a thermal polymerization so any step maintained reaction 100-120°C
in pressure conditions pressure should be 1-2 mm Hg an inert atmosphere. This bulk polymerisation polymer
formation time is highly exothermic so exothermic controlled by outside cooling only no pressure releasing or
nothing, that time pressure also incising depending on temperature. The main reason to pressure incising
water is not to polymerize the NVP so water has made the pressure atmosphere.
Figure – IV:

Step-I

\[
\text{NVP Monomer} + \text{NaOH/KOH} \rightarrow \text{NVP Carbanion}
\]

Step-II

\[
\text{NVP Carbanion} \xrightarrow{\text{base isomerization}} \text{EVP}
\]

Step-III

\[
\text{EVP} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{N}-\text{CH}_2\text{CH}_2\text{ONa}
\]

Reaction mechanism

**TYPES OF EXAMPLES**

**Example - 1**

Take the 0.027 to 0.17 moles of NaOH/KOH in 3.8 moles of water dissolved completely. After that reversing of the 1 Mole of NVP add into the aqueous layer followed by a little catolic amount of 0.01% tert dodecyl mercaptan and 0.1% potassium persulfate with respect to NVP. then Reaction mass heated to 140-160ºC in pressure condition in an inert atmosphere for 10-15hr. in this reaction base act as an NVP carbanion followed by EVP shown figure-IV after a long time EVP cross-linked with the monomer of NVP, the effect of the water
most probably due to the swelling of the polymer coils to the dimensions which favour popcorn polymer formation. And potassium persulfate as radical initiator and tert dodecyl mercaptan act as a surface chain transforms agent. in this Example 10-15hrs liquid NVP in thermal conditions formation of the white colour solid of crospovidone, after crospovidone formed releasing the pressure and wash with 1% sulphuric acid solution to removing of the excess of free NVP un-reacted liner polymers, sulphuric acid acts pH neutralization as well acid hydrolysis removing of free NVP, if as such reaction mass like 1000ppm by HPLC method so given to acid wash its 1 ppm or nil. Then material dried at 80°C in a hot air oven for 5-10 hrs, popcorn polymer with bulkdensity0.29g/mL martial milled according to XL and XL-10 specifications.

Example - 2
Taken 1 mole of NVP and prepared 0.1 moles of KOH in 3moles of water solution into the pressure reactor in an inert atmosphere, then heated to 130°C maintained for 3 hrs 2bar pressure, after that by the vacuumed distilled the aqueous medium half part about 1.5 moles at 120°C. distillation should be very fast, then again close the pressure reactor and heated to 130°C for 2 hrs, after distillation initiation starts and slowly propagation followed by complete solid formation reaction body as discussed at the second method, in this thermal polymerisation white colour solid obtained then material washed with 1% sulphuric acid followed by hot water washes and material dried at 80°C in a hot air oven.

Example – 3
Take the l mole of NVP and add the 0.3 moles NaOH in 5.43 moles of DM water and heated to 100-140°C for 2 hrs. in a pressure reactor in presence of an inert atmosphere with high RPM about 900 rpm and separated the organic and aqueous layers into the reaction mass, then take the organic layer its having 10-15% EVP. then diluted EVP 2-2.5% by using NVP and further dilution by 1-1.5% EVP by using De-mineralized water so whole composition 2-2.5% EVP, NVP-80-80.5%, and water-17.5% the whole polymerisation composition then heated to 100-120°C to 160°C for 2hrs in a pressure reactor in an inert atmosphere, in this thermal polymerization white colour solid obtained then material washed with 1% sulphuric acid followed by hot water washes and material dried at 80°C in a hot air oven.

Example - 4
Take the l mole of NVP and add the 0.3 moles NaOH in 5.43 moles of DM water. Then reaction mass heated to 100-140°C for 2 hrs. in a pressure reactor in presence of an inert atmosphere with a high RPM about 900 rpm. After 2 hrs. separated the organic and aqueous layers into the reaction mass than take the organic layer it's having 10-15% EVP. then diluted EVP 2-2.5% by using NVP contains and further dilution of EVP 1-1.5% with NVP contains by using the De-mineralized water, so whole composition 2-2.5% EVP, NVP-80-80.5%, and water-17.5% after adding very little caticol amount of potassium persulfate 0.01% with respect to composition. The effect of the water most probably due to the swelling of the polymer coils to the dimensions which favour popcorn polymer formation and potassium persulfate as radical initiator. the whole polymerization composition then heated to 100-120°C to 160°C for 2hrs in a pressure reactor in an inert atmosphere, in this thermal polymerization white colour solid obtained then material washed with 1% sulphuric acid followed by hot water washes and material dried at 80°C in a hot air oven.

Example-5
Take the 1 mole of NVP and add the 0.55-0.83 moles of NaOH in 4.32-4.93 moles. Then heated to 140-160°C for 2 hrs with high RPM about 900 rpm after reaction 2 hrs. Maintenance separated the organic and aqueous layers into the reaction mass and then takes the organic layer. It is having 20-25% EVP then organic layer dried with sodium sulphate. Then distilled at 120°C under 1mm Hg vacuumed colourless 10-12% EVP contained NVP. Then reaming reside re-cycle the distillation by diluting of NVP up to fraction getting 1%. EVP contained NVP mix the all fraction to make the composition for polymerization reaction this ratios EVP 1-2.5% water 15-30% NVP 84-68% mix well and heated 100-120°C in a pressure reactor for 1-2 hr in an inert atmosphere in this thermal polymerization white colour solid obtained then material washed with 1% sulphuric acid followed by hot water washes and material dried at 80°C in hot air oven in this proceeds Tg value-195°C.
Example-6
Take the 1 mole of NVP and add the 0.55-0.83 moles of Noah in 4.32-4.93 moles and heated to 140-160ºC for 2 hrs with high RPM about 900 rpm after reaction 2 hours maintenance separated the organic and aqueous layers into the reaction mass than take the organic layer. It's having 20-25% EVP then organic layer dried with sodium sulphate and distilled at 120ºC under 1mm Hg vacuumed colourless 10-12% EVP contained NVP, then reaming reside re-cycle the distillation by diluting of NVP up to fraction getting 1%. EVP contained NVP, mix the all fraction to make the composition for polymerization reaction these ratios EVP 1-2.5% water 15-30% NVP 84-68% mix well and heated 100-120ºC in a pressure reactor for 1-2 hr in an inert atmosphere, in one to two hours when in-between insertions Or particle observation and propagation starts that time add hot NVP into the polymerization reaction. This is a continuous polymerization reaction or chain reaction or chain polymerization if stop the chain bulk polymerization terminate the chain, add inhibitor, or releasing the whole pressure in this reaction surface roughness low due to congested double bonds is very low so no chance to form surface smoothness incising so automatically. Incising the tablet binding as well as swellability volume and conjugation, if conjugation low, the I2 test fails test given in analytical supports. This route also Tg value-195ºC.

Example-7
Take the 1 mole of NVP and add the 0.3 moles NaOH in 5.43 moles of DM water and heated to 100-140ºC for 2 hrs in a pressure reactor in presence of an inert atmosphere with high RPM about 900 rpm and separated the organic and aqueous layers into the reaction mass, then take the organic layer. Having 10-15% EVP then this reaction mixture pass through the column through resin AMBERlyst 15-wet/ indion 790 ion exchange (Strongly acidic Macoreticilar, polymeric catalysis in hydrogen (H+) forms) water as a mobile phase for colourless fractions to make EVP 1-2.5% water 15-30% NVP 84-68%, and this ratio performed polymerization reaction at 100-120C for 2-5 hrs. Mix well and heated 100-120ºC in a pressure reactor for 1-2 hr in an inert atmosphere in this thermal polymerization white colour solid obtained then material washed with 1% sulphuric acid followed by hot water washes and material dried at 80ºC in hot air oven in this proceeds Tg value-195ºC.

BELCHING THE POLYMER
Belching step or surface crosslink molecule depolymerisation with hydrogen peroxide.
In the first and second method colour not obtained or surface roughness incising the tablet formulation, first, it happened the only route is the coagulation double bonds are crosslink in the surface are so conjugation, low Hydrogen peroxide step uses like this. So the process is taking the 1 time of crospovidone wet or dry crospovidone powder than add to 5 volumes of 30% hydrogen peroxide with (dry base adjusted LOD) stir at RT for 15-30 followed by filtration then dried at RT for 30-60 min up to beaching will happen as material convets look like white colour changes. Then wash with water hydrogen peroxide contents fall down under limits than material dried at 80C this hydrogen peroxide is used surface smoothness of crospovidone random polymer which is acts or use reducing the hardness of tablet coating and incising the swell ability which is acts more disintegrate, so incising the smoothness of the white colour crospovidone powder.
EXPERIMENTAL SUPPORT

Figure – V: It shows in 2 step process up to distillation fraction
A study to assess the effectiveness of structured teaching programme on enhancing knowledge regarding arterial blood gas analysis among the staff nurses who are working in ICU at Vinayaka Mission Hospital at Salem.

OBJECTIVES OF THE STUDY

1. To assess the pre-test and post-test knowledge of experimental and control group of staff nurses regarding ABG analysis.
2. To compare the Pre-test and Post-test knowledge of experimental and control groups regarding ABG analysis.
3. To implement and evaluate the STP regarding ABG analysis.
4. To find out the association between the knowledge of staff nurses with their selected demographic variables.
Figure – VI: Crospovidone IR report: The IR spectrum of sample must exhibit maxima at the same wave numbers as exhibited.
Figure – VII: Malvern particle size analysis report polyplasdone – XL
Figure – VIII: Malvern particle size analysis report polyplasdone - XL-10 (Type-B)
## ANALYTICAL BACKGROUND

(Polymerization reaction) Ph. Eur. Specification

<table>
<thead>
<tr>
<th>TEST NAME</th>
<th>SPECIFICATION</th>
</tr>
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<tbody>
<tr>
<td>Description</td>
<td>White or yellowish-white powder or flakes, hygroscopic.</td>
</tr>
<tr>
<td>Solubility</td>
<td>Practically insoluble in water, in ethanol 96% present and in methylene chloride.</td>
</tr>
<tr>
<td>Identification</td>
<td></td>
</tr>
<tr>
<td>By IR</td>
<td>The IR Spectrum of the sample must exhibit maxima at the same wave number as exhibited in Crospovidone standard spectrum.</td>
</tr>
<tr>
<td>By Chemical Test</td>
<td>No blue colour should develop within 30 seconds.</td>
</tr>
<tr>
<td>By Chemical Test</td>
<td>A suspension should be formed, and no clear solution is obtained within 15 minutes.</td>
</tr>
<tr>
<td>By particle size (Retention on 63 µm)</td>
<td>More than 15% m/m</td>
</tr>
<tr>
<td>Peroxides (as H2O2)</td>
<td>Not more than 400 ppm</td>
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<tr>
<td>Water-Soluble Substances (Dry at 105-110°C for 3 hrs.)</td>
<td>Not more than 1.0% w/w</td>
</tr>
<tr>
<td>Impurity A (By HPLC)</td>
<td>Not more than 5 ppm</td>
</tr>
<tr>
<td>Loss on drying (Determined on 0.500g at 105°C)</td>
<td>Not more than 5.0% w/w</td>
</tr>
<tr>
<td>Sulphated Ash (Determined on 1g)</td>
<td>Not more than 0.1% w/w</td>
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<tr>
<td>Assay (By Titrimetry as Nitrogen content, on dried basis)</td>
<td>Between 11.0% w/w and 12.8% w/w</td>
</tr>
<tr>
<td>Microbial Contamination</td>
<td>Not more than 100 cfc/g</td>
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<tr>
<td>Total aerobic microbial count-TAMC</td>
<td>Not more than 100 cfc/g</td>
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<tr>
<td>Total combined Yeasts and Mould count – TYMC</td>
<td>Must be absent</td>
</tr>
<tr>
<td>Escherichia coli</td>
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<tr>
<td>Staphylococcus aureus</td>
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<tr>
<td>Pseudomonas aeruginosa</td>
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<tr>
<td>Salmonella</td>
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</tr>
<tr>
<td>pH</td>
<td>5.0-8.0</td>
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<tr>
<td>Particle Size (By Air jet) Passed Through 38 µm Sieve (ASTM No. 400 mesh)</td>
<td>Not more than 50% w/w</td>
</tr>
</tbody>
</table>
REFERENCES

20. Eugene S. Barabas¹ and Christianah M. Adayeye²