SYNTHESIS OF CROSPVIDONE DIFFERENT PROCESS

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DOI: <http://doi.org/10.47211/idcij.2020.v07iws01.003>Received 30th June 2020, Accepted 20th July 2020, Available online 30th July 2020.**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

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INTRODUCTION

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

Molecular Formula	: (C ₆ H ₉ NO) _n
Molecular weight	: (111) _n
Category	: Super Disintegrant
Pharmacopoeia status	: USP/Ph.Eur.

BRIEF

Crespovidones are insoluble, cross-linked homopolymers of N-Vinyl-2-pyrrolidone. The non-ionic nature and porous particle morphology, make crespovidones disintegrants of choice for fast disintegration, enhanced rate of drug dissolution and robust tablets. Through a combination of mechanisms, crespovidones undergo rapid disintegration. Firstly, with water contact it could swell by 95% to 120% of its initial volume. Also due to their porous morphology, crespovidones 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.

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

Crespovidone 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 Services Registration number: 9003-39-8.

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

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NOMENCLATURE

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POLIMERISATION

The proliferous 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 190⁰C.

Figure – II:

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

The second one, this also like the first method but the satin 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 crosopovidone. 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-vinylpyrrolidone-2-one (VEP) shown in figure-III this not a random polymer like crosopovidone, 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:

(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 Crosopovidone 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, Crosopovidone 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:

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 reverse of the 1 Mole of NVP add into the aqueous layer followed by a little catalytic amount of 0.01% tert dodecyl mercaptan and 0.1% potassium persulfate with respect to NVP. then Reaction mass heated to 140-160°C 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 bulk density 0.29g/mL material milled according to XL and XL-10 specifications.

Example - 2

Taken 1 mole of NVP and prepared 0.1 moles of KOH in 3 moles 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 1 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 1 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 catalytic 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 remaining residue 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 140-160°C 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 120°C under 1mm Hg vacuumed colourless 10-12% EVP contained NVP, then reaming residue 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 100-120°C 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-195°C.

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 100-140°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. having 10-15% EVP then this reaction mixture pass through the column through resin AMBERlyst 15-wet/ indion 790 ion exchange (Strongly acidic Macoreticular, 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 100-120°C for 2-5 hrs. mix well and heated 100-120°C in 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.

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 convents 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

Current Data Parameters
NAME QC11190128032
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20190128
Time 17.24 h
INSTRUM spect
PROBHD Z108618_0828 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 22.39
DW 62.400 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
SFO1 400.1324708 MHz
NUC1 1H
P1 14.00 usec
PLW1 14.94099998 W

F2 - Processing parameters
SI 65536
SF 400.1300102 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

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

TEST NAME	SPECIFICATION
Description	White or yellowish-white powder or flakes, hygroscopic.
Solubility	Practically insoluble in water, in ethanol 96 present and in methylene chloride.
Identification	
By IR	The IR Spectrum of the sample must exhibit maxima at the same wave number as exhibited in Crospovidone standard spectrum.
By Chemical Test	No blue colour should develop within 30 seconds.
By Chemical Test	A suspension should be formed, and no clear solution is obtained within 15 minutes.
By particle size (Retention on 63 μm)	More than 15% m/m
Peroxides (as H_2O_2)	Not more than 400 ppm
Water-Soluble Substances (Dry at 105-110°C for 3 hrs.)	Not more than 1.0% w/w
Impurity A (By HPLC)	Not more than 5 ppm
Loss on drying (Determined on 0.500g at 105°C)	Not more than 5.0% w/w
Sulphated Ash(Determined on 1g)	Not more than 0.1% w/w
Assay(By Titrimetry as Nitrogen content, on dried basis)	Between 11.0% w/w and 12.8% w/w
Microbial Contamination	Not more than 100 cfc/g
Total aerobic microbial count-TAMC	Not more than 100 cfc/g
Total combined Yeasts and Mould count – TYMC	Must be absent
Escherichia coli	Must be absent
Staphylococcus aureus	Must be absent
Pseudomonas aeruginosa	Must be absent
Salmonella	Must be absent
pH	5.0-8.0
Particle Size (By Air jet) Passed Through 38 μm Sieve (ASTM No. 400 mesh)	Not more than 50% w/w

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