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Review Article

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PHARMACEUTICAL APPLICATIONS OF CROSPOVIDONE: A REVIEW.

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ABSTRACT
Crospovidone is one of the widely used excipients in the field of pharmaceutical sciences. In this review article, starting from the physicochemical properties, the various pharmaceutical applications such as solubility enhancer, adsorbent, coating material, carrier, disintegrant, extrusion spheronization aid, recrystallization inhibitor are extensively discussed. The adverse effects of crospovidone are also highlighted.
KEYWORDS Crospovidone, disintegrant, solubility enhancer, recrystallization inhibitor, coating material

INTRODUCTION

Crospovidone (CPVP) is a synthetic, water-insoluble, cross-linked homopolymer N-vinyl-2-pyrrolidone [1]. It was prepared from the monomer vinyl-pyrrolidone by popcorn polymerization technique [2] using a catalyst [3]. There are other several names for crospovidone such as cross-linked polyvinylpyrrolidone, polyvinyl polypyrrolidone, crospolividone, povidone and 1-vinyl-2-pyrrolidone[4]. From years ago, crospovidone has been developed as a drug carrier and widely used as a disintegrant agent [1], tablet excipient (disintegrant and binder) and solubilising excipient [5] in oral solid dosage pharmaceutical formulations [1]. All of these characteristics are to improve drug bioavailability [5]. The compatibility studies of most of the excipients such as dried lactose, croscarmellose sodium, starch and crospovidone are performed early in the development of a new drug product formulation. It is important to assess the instability of the active pharmaceutical ingredient (API) in the presence of the potential excipients and to characterize the degradation products formed by their interaction, and at the same time to understand how to adequately stabilize the formulation [1]. It is also used as a super-disintegrant which does not irritate the gastrointestinal tract and can be used at low amounts in the formulations [6]. Besides, crospovidone is an excipient that has the ability to stabilize the amorphous state of drugs due to inhibition of drug recrystallization [7] and a rapid solidification rate [8].

PHYSICOCHEMICAL PROPERTIES

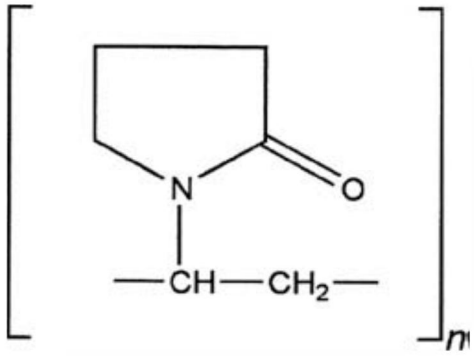


Figure 1: Chemical structure of crospovidone

Crospovidone is provided as an amorphous form [9**],** white or almost white powders with a large surface area [10]. Its molecular weight is about $(111.1)_n$ and having bulk density in the range of 0.2-0.45 g/ml [10]. It has practically no taste or odour, and has good fluidity [9, 11], compression compatibility and possessed a 'popcorn' shape containing many cavities [12] which does not melt upon heating [13]. Moreover, it is difficult to crush using a mortar or pestle [11]. The chemical structure of crospovidone is shown in Figure 1. Crospovidone is insoluble in all the usual solvents and it was found to be an insoluble excipient by American Material Safety Data Sheet [14, 15]. Since crospovidone is insoluble, it can be thoroughly washed with water to achieve a very high degree of purity [10]. Even if crospovidone is insoluble in water, it can increase the solubility of amorphous state drugs such as fulfenamic acid, griseofulvin [11] and furosemide [16**]** in water.

Crospovidone is available from different suppliers such as BASF (Germany) and ISP (Japan) [17] in different grades concerning the particle size [18]. Liew et al. reported its classification in to three grades e.g. coarse, medium (32 μm) and small (20 μm) [19]. These are two types particle structure, Type A - particle structure of normal crospovidone and Type B - particle structure of micronized crospovidone [10]. Differences in particle size distribution played a very important role on the flow and swelling properties of crospovidone [10].

Tallon et al. reported that the reaction processes for manufacturing of crospovidone such as Polyplasdone XL (XL) and Kollidon CL (CL) are different [20]. XL is made using alkali metal hydroxide and a small amount of added water, whereas CL is produced using *N,N'*-divinylimidazolidone as a cross-linker [17]. Different ways of manufacturing of crospovidone give a little bit difference in some of its characteristic such as particle size, strength as a disintegrant and its swelling properties.

Crospovidone has the ability to enhance the wettability of the hydrophobic drugs and can exhibit 'microenvironment effect'. There was a report where the wetting time was rapid in crospovidone followed by croscarmellose sodium, pre-gelatinized starch and TAG [21]. The role of crospovidone is different for different drugs in the dissolution rate enhancement. It is confirmed by Lim et al [22] that furosemide and crospovidone act independently in the physical mixture, while in the ground mixture crospovidone alters the physical characteristic of furosemide [22].

Formulation of hydrophobic drugs into solid dispersion has also been employed to improve their dissolution and bioavailability. Solid dispersions consist of a water-soluble carrier and a hydrophobic drug dispersed in the carrier system. The hydrophilic carriers commonly used to formulate solid dispersions include crospovidone, PEG [23] and hydroxypropylmethyl cellulose (HPMC) [24]. Crospovidone has been used to formulate solid dispersions with many types of drugs including naproxen [25], indomethacin [22], nifedipine [13**]** and nifedipine analog, nitrendipine [26]. In all these cases, there is increase in dissolution and bioavailability of the drug

The choice of solvents also plays a crucial role in the interaction of crospovidone with the drugs. It is interesting to note that crospovidone not only interacts with drugs but also does so with solvents like methanol, ethanol, chloroform and water in the case of poor dissolution rate of drugs. It is believed that the carbonyl group of crospovidone takes part in the interactions with the drugs and solvent, but in the case of ethyl acetate as a solvent, there is no interaction between ethyl acetate and crospovidone because both of having the H-acceptor capability [27]. Desai [28] in his work pointed out that the interaction between povidone and Stearic acid (lubricant) forming a solid dispersion might be the plausible cause for the slowdown of the dissolution of capsule of the drugs. Hops and Mueller (1999) suggested a similar type of interaction between povidone and ibuprofen, indicating the characterization of a solid dispersion [29].

Watanabe et al. (2003) also reported the interaction between indomethacin and povidone through a C-CP/Mass-NMR study [30]. Since crospovidone has the same chemical structure as that of povidone, it may be concluded that an interaction between the carboxyl group of indomethacin and the amide carbonyl group of crospovidone, takes place as in the case of indomethacin and povidone [11].

PHARMACEUTICAL APPLICATIONS

Many pharmaceutical systems are essentially made up of a polymeric carrier hosting the active agent (drug) inside its three-dimensional network [31]. Crospovidone possesses adequate properties that are used in the manufacture of different pharmaceutical products and dosage forms.

The most important property of crospovidone as an auxiliary is its disintegration and dissolution enhancing effect, which is usually used in the preparation of tablets, granules and capsules. The use of micronized

crospovidone as an active substance against diarrhea depends on its ability to form complexes. The hygroscopicity of crospovidone can be used to adsorb water in the preparations of moisture-sensitive drugs to improve their stability. In addition, the potential inclusion of crospovidone as a disintegrant agent [32] and carbamazepine dissolution enhancer were of much importance [33].

Solubility enhancer

It is well established that the active ingredients in a solid dosage form must undergo dissolution before they are available for adsorption from the gastrointestinal tract [34] or transported into the systematic circulation. However, most of the drugs are poorly water soluble and they need another substance such as excipient or carrier to bind together to improve their solubility. Generally, the pharmaceutical excipients used with the drugs include various types of starch, croscarmellose sodium and crospovidone [35]. It is interesting to note that although crospovidone is insoluble, it can be used in solid pharmaceutical preparations to improve the dissolution rate of an active substance like drugs [10].

Previous studies [36, 37] made on crospovidone, an insoluble swellable homopolymer of N-vinyl-2-pyrrolidone suggested the use of swellable polymers as enhancers for the improvement of the dissolution rate.

Studies by Carli et al. [38] suggested that drugs loading into crospovidone represent a profitable tool to increase the drug dissolution rate in aqueous media and hence, the bioavailability of slightly water soluble crystalline drugs [31]. A lack in well-defined peaks and intense scattering detected by XRD indicated the characteristic of amorphous materials of crospovidone. Crospovidone showed a broad endotherm with a maximum at 90.3 °C due to the water adsorbed by the hygroscopic cross-linked polymer [39] in the DSC thermogram. It was reported that the mechanical force provided by mixing using a theta-composer leads to smaller drug particles to get adsorbed on the crospovidone particles [11]. The results indicate that the increase in the surface area, as a result of reduced particle size provides an increased contact area between the drug particles and crospovidone particles thereby enhancing drug's solubility [13].

Even though crospovidone is not soluble in water, it can also be used as a carrier to improve drug release rates. For example, a 1:2 ratio of furosemide to crospovidone led to an increase in the dissolution rate by a factor of 5.8 [16] in comparison with either the drug powder or a physical mixture of furosemide with crospovidone. The mechanism of the increase in the release rate of furosemide proved the existence of the drug in the amorphous form in the dispersion, as shown by X-ray diffraction studies [40].

The technique of coprecipitation has been adopted for crospovidone from povidone. Coprecipitates of furosemide and crospovidone markedly enhanced dissolution rate of furosemide. Figure 1 shows the dissolution of furosemide from coprecipating with crospovidone. The dissolution rate increases about 5.8-fold for furosemide:crospovidone ratio of 1:2 compared with that of pure furosemide alone [16].

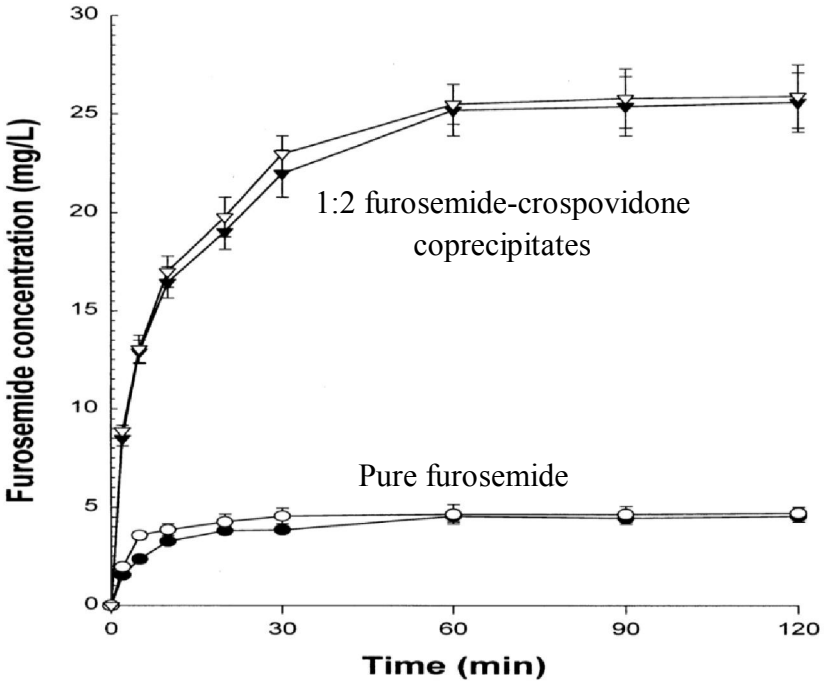


Figure 2: Dissolution rate of furosemide from coprecipating with crospovidone

Source: Shin *et al.* (1998)

Several mechanisms have been suggested for an increase in the dissolution rate of drugs from co-grinds containing carriers such as Avicel, crospovidone and microcrystalline cellulose [34]. Some of the suggested mechanisms include micronization [41], an increased wettability of the drug particles [41, 42] and an increase in the solubility of the drug [42, 43]. Although most of the studies give a positive characteristic of the crospovidone in enhancing drug's solubility, the suggested mechanisms by Betageri et al. (1999) for an increase in the solubility of the drug in the presence of the carriers, did not support this mechanism in enhancing dissolution rate of the drugs as because of its being insoluble in water [41]. Unfortunately no reference is available till now that could support these carriers having capability of improving the solubility of the drugs [34].

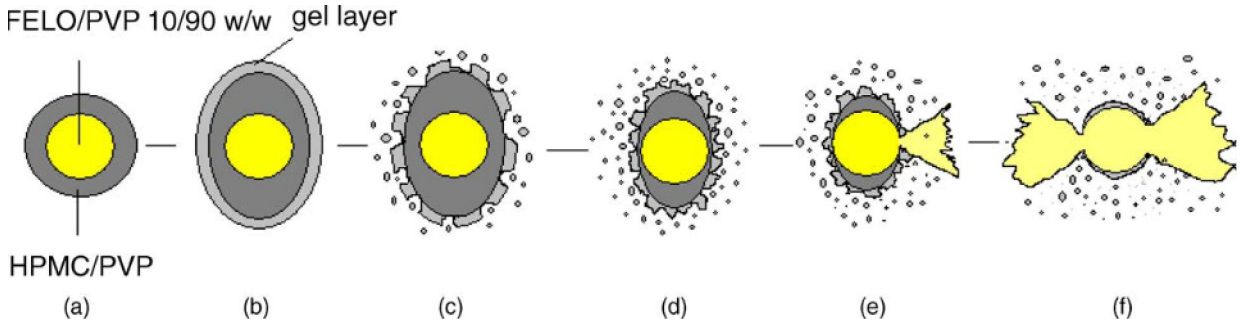
Adsorbents

Crospovidone, microcrystalline cellulose [44] and kaolin [45] serve most often as adsorbents. The adsorption of drug molecules onto the surface of excipients can reduce drug particle size and increase the surface area of drug available to the dissolution medium. Both of these effects might increase dissolution and, hence bioavailability.

Coating layer

As tablet cores that contain crospovidone or croscarmellose swell readily in the presence of water, care must be taken while coating such tablets in aqueous solutions in the coating pan. In many cases, it is advisable to subcoat the cores before applying the actual sugar or film coating [10]. Crospovidone can be used as a coating layer for several drugs. Karavas et al. (2006) used crospovidone and hydroxypropyl-methyl cellulose (HPMC) blends as coating shell. It was reported that miscibility of two polymers such as crospovidone and HPMC with strong interactions can improve tensile strength of the blends [43]. Takayama et al. [46] also described the use of crospovidone in solid dispersion prepared with solutions of drugs in organic solvents. However, the use of organic solvents in the coating of pharmaceutical dosage form has become problematic due to regulatory requirements, flammability and limits on solvent residues in the coated product. While another studies reported that a combination of 50% microcrystalline cellulose, 25% polyethylene glycol 3350 and 25% crospovidone was most suitable for minimizing the damage to the coating.

Scheme 1 below shows the rupture mechanism of double wall tablets using crospovidone and HPMC as a coating layer. The mechanism also shows the different way of dissolution rates between HPMC and crospovidone [43].



Scheme 1: Rupture mechanism of double wall tablets. (a) Initial tablet, (b) gel forming on the coating layer due to the water penetration and tablet swelling (c) erosion inception of the coating layer (d) extended erosion (e) rupture of coating layer and initiation of core dissolution and (f) extended FELO release

Recrystallization inhibitor

Crospovidone has been found to inhibit recrystallization of the drugs by restricting the mobility of the drug molecules [22] and this characteristic was proved in the work of Lipp (1998) in which the adsorption of ethinylestradiol and levonorgestrel onto the insoluble carrier crospovidone prevented the drug recrystallization [47]. They concluded that, this phenomenon was probably due to hydrogen bonds which formed between the drug molecules forming nuclei which are a precondition for crystal growth [7, 44]. However, Karmwar et al.

suggested that in cryo-milling (CM) indomethacin samples, the presence of nuclei was not the main factor influencing the resulting polymorph since the ball-milling (BM) α-form crystallized directly to the γ-form and CM α-form recrystallized to a mixture of the metastable α-form and the stable γ-form [48].

Bikiaris et al. in their DSC results showing no melting of crystalline materials [49] also proved that crospovidone macromolecules inhibited the drug crystallization in the solid dispersion.

In solid solution, the drug is molecularly dispersed in a hydrophilic carrier. These formulations will enhance dissolution characteristics because of the drug's higher internal energy. However, high energy state of the drugs will lead to spontaneous recrystallization during storage [27]. Bhugra et al. (2008) presumed that the main factors to prevent drug recrystallization in solid solutions are due to drug-carrier interactions and the viscosity of the formulation[50].

Doherty and York (1987) [51], Taylor and Zografi (1997) [52], and Bhugra and Pikal (2008) [50] agreed with the common conclusion that the inhibition of drug recrystallization is mainly due to intermolecular interactions between drug and excipient as a result of which, the excipient immobilizes the drug molecules and "poisons" the crystallization.

The loading of carbamazepine on the surface of crospovidone induces a polymorphic transformation in the recrystallization of the drug obtained in the same solvent mixture that is used for the preparation of the rv system without any structural change of the crystallinity of the drug [2].

Further Lim et al. [22], from super critical anti solvent (SAS) test reported that amorphous indomethacin in crospovidone matrix co-precipitates with crospovidone content above 50 wt.%. With no recrystallization of indomethacin and it was found to remain stable even after 7 months storage.

Carrier, excipient and disintegrant

Crospovidone is one of the main pharmaceutical carriers to modify the solubility and the dissolution of poorly soluble drugs in several solid dosage forms [53]. It was used as a carrier in solid dispersion [11], granules [39], tablets, capsules [53] and also widely used as a tablet disintegrant because of its highly hydrophilic character, rapid water uptake and good swelling properties [53]. It is commonly used as a disintegrant in concentrations ranging from 2 to 5% in solid dosage forms [54]. Different disintegrants work in different ways, involving swelling, wicking and deformation effects and also the repulsion of the charged particles. The effect of crospovidone as a disintegrant is mainly based on its predictable swelling properties as it has ability to swell without forming a gel. However, Balamuralidhara et al. claimed that wicking property of crospovidone is more effective than swelling properties compared to croscarmellose sodium which entertains the water up to a maximum extent and allows the disintegration rapidly due to the clean interaction of the particle arrangement of the super disintegrant [21]. Though the solubility of the tableting mixture (drug and filler) in water has a

definite influence to the effectiveness of disintegrants but it is more effective in insoluble mixture. Thus, calcium phosphate placebo tablets with 4% crospovidone disintegrate significantly faster than tablets with lactose [10]. This contention has been examined by Sreenivas et al. (2009) by, using various disintegrants including crospovidone, croscarmellose sodium and starch to prepare rabeprazole orodispersible tablets [35].

It may be stated here that all disintegrants do not function in the same way, but they can behave somewhat differently depending on the tablet formulations. Thus, there is no ideal disintegrant for all tablets or capsules and it is therefore necessary to compare different disintegrants for the same drug formulation. The most important is the final quality criteria of the effect of disintegrant in enhancing dissolution rate for the poor water soluble drugs [10], as shown in Table 1

1. Composition

p-Aminobenzoic acid	1.0%
Sorbitol	48.3%
Dicalcium phosphate	48.3%
Magnesium stearate	0.5%
Disintegrant	2.0%

2. Dissolution of the drug after 15 min

Disintegrant	After manufacture	After 14 months storage at 30°C (packaged)
None	27%	34%
Crospovidone (Kollidon® CL)	78%	81%
Crospovidone (Polyplasdone® XL)	79%	82%
Croscarmellose	80%	74%
Carboxymethyl starch	68%	74%

Table1: Comparison of disintegrants in p-aminobenzoic acid table before and after storage

Super disintegrant

From a survey of literatures as regards to the comparison between disintegrants in tablet and capsule formulations, it may be concluded that crospovidone is one of the super disintegrants [10]. Usually, most of the physical mixture between crospovidone and the drugs give no complete amorphization of the drugs [53]. This phenomenon might be ascribed to the super disintegrant properties of the crospovidone [53]. However, this phenomenon does not conclude that crospovidone is not good enough to use for enhancing solubility of the

drugs as evidenced from a remarkable decline in drug crystallinity, approximately 40% amorphous of ibuprofen while combining ibuprofen with crospovidone in a simple physical mixture [3].

Swelling and hydration of super disintegrants could be influenced by several physicochemical properties of the particles [55]. A larger particle size and hence, increased porosity lead to a faster wicking and swelling with different grades of crospovidone. Moreover, a sponge-like surface morphology of the particles increased the intraparticle porosity [56].

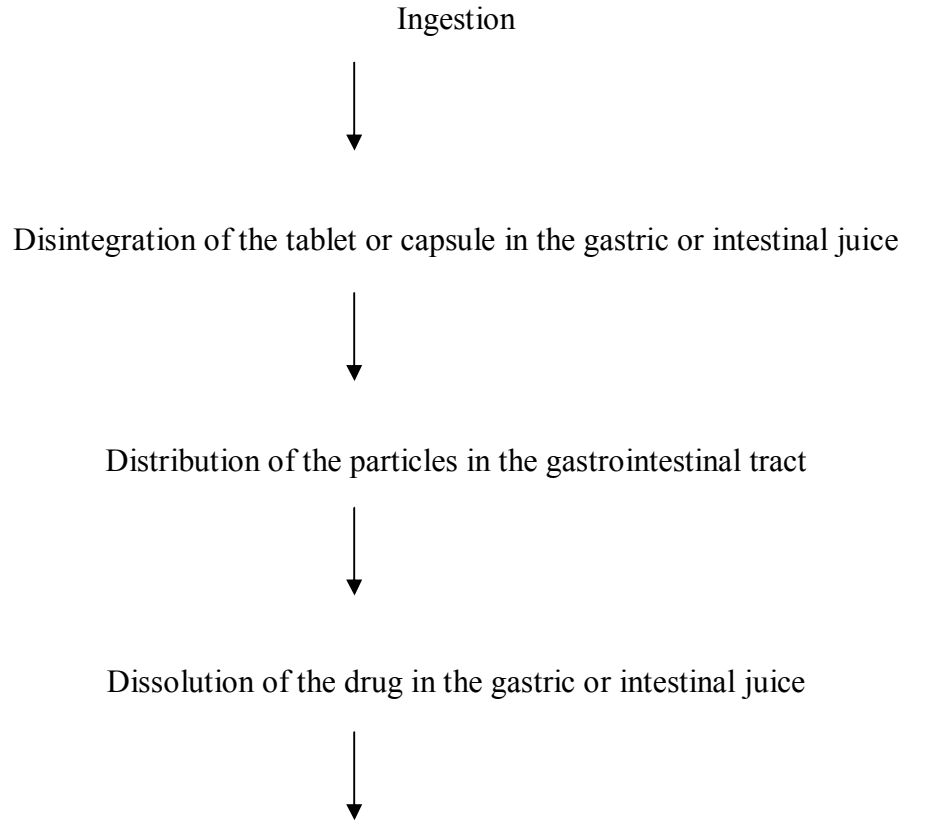
A comparison with other super disintegrants such as croscarmellose sodium [35] and carboxymethyl starch [10], it is seen that crospovidone has poorer flow properties due to its small particle size. This ability caused the flowability of physical blends of drugs and super disintegrant facing a problem in capsule filling or tableting [57]. Although crospovidone was characterized as one of the disintegrants having good swelling properties [53], Bolhuis et al. (1997) claimed that the disintegration efficiency of the crospovidone is based on capillary action rather than on swelling properties. The swelling properties of crospovidone are poor as compared with other super disintegrants such as sodium starch glycolate and croscarmellose sodium due to the absence of cationogenic groups in the crospovidone molecule. That is why the wetted surface area by crospovidone increased for which it becomes insufficient to improve the drug release to a large extent [57].

Crospovidone is also widely used as a super disintegrant in oral solid dosage pharmaceutical formulations. Trace-levels of hydrogen peroxide released from crospovidone can cause degradation of API susceptible to oxidative degradation. Thus, the hydrogen peroxide content of crospovidone may be considered as a critical quality attribute while evaluating the stability of formulations containing this super disintegrant [1]. According to Habib et al. (2001), increase in the initial moisture content (IMC) due to the presence of croscarmellose sodium is approximately six times that of crospovidone which can be attributed to the fact that croscarmellose sodium can take up more water than crospovidone without causing gross agglomeration and size enlargement of the beads during spheronization [58].

However, it is reported that super disintegrants like crospovidone and croscarmellose sodium, which were used for the remaining excipients, have only minor impact on the compactibility [59].

Tablet group

The active ingredient of a tablet must be bioavailable. To achieve or to improve this, one must be aware of the following facts (as described in the flow chart) after the tablet is taken [10].



Flow chart: Stages leading to the availability of the drug in a tablet.

The impact of optimum quantity of crospovidone in a tablet is specific to each particular formulation and cannot be predicted. It depends on the on desired disintegration time, which is different for different tablet formulations having crospovidone.

Tablets are usually prepared by using the direct compression method because it is a simple procedure that depends on the characteristics of the powder [11]. Besides, tablets can also be prepared by preliminary treatment such as granulation [21**]** which may be from melt granulation process [60**],** wet granulation process [61, 62] or dry granulation process.

The mechanical properties of tablets can be quantified by friability and hardness. The friability is directly related to the hardness and indicates resistance to abrasion, which can occur inside the end packaging or during transport or manipulation. This parameter is important in choosing the adequate excipients to prevent fast disintegration of the tablet and posterior dissolution of the drug before the desired time. Hardness is an important parameter to estimate disintegration time, since resistant tablets do not disintegrate in the time required to satisfy the dissolution specifications. Tablets with lower hardness are unable to resist manipulation. Other available tablet properties include particle size and true density [9].

As expected by Solon et al. [63], the tablet with higher hardness presented a longer disintegration time. However, the generic presentation, in spite of having a greater hardness compared to the reference formulation, had a shorter disintegration time. They assumed that this fact may be due to use of crospovidone in its formulation and as it is a super disintegrant, it facilitates the disintegration process, even when used in small quantities [63].

Kanig and Rudnic (1984) have suggested that wicking and swelling were found to be the primary mechanisms of action for tablet disintegrants, while other mechanisms such as deformation recovery, particle repulsion theory, heat of wetting and evolution of a gas may play a role in particular cases of tablet disintegration [60].

For some other cases, crospovidone was used as an additive to improve the tablet hardness. As discussed by Okuda et al, when a saccharide, e.g., mannitol was spray-coated with crospovidone and other additives mixed with corn starch its usability is improved [9]. The plasticity of the tablets with crospovidone as an additive showed the lowest means of oral disintegration time in unit tablet hardness (D/H value). It was considered that (1) crospovidone can minimize the plastic deformation by compression because it forms hard particles and (2) crospovidone can keep the air spaces between the particles after tableting [9]. Since crospovidone was the original disintegranting agent, the tablet broke up very quickly. Hardness increased in the order: physical mixture < theta mixture < solid dispersion [11].

In a few cases, the inclusion of the disintegrant in to the granulation mixture can provide tablets with shorter disintegrant times. This particularly applies when the tablet disintegrates quickly enough, but the granules do not, and it is recommended to add some crospovidone before granulation and some after granulation [10]. Perissuti et al. (2003) discussed the effect of addition of intragranular and extragranular crospovidone in the different composition of tablets. The hardness was diminishing as the crospovidone content increased, while friability values were quite homogeneous. However, they reported that tablets not containing intragranular crospovidone were found to be unsatisfactory for the requisites of European Pharmacopoeia (2001) [64, 65] and they add 5% of crospovidone to overcome this problem [39]. This study showed that the addition of intragranular crospovidone is necessary to produce tablets with a satisfactory disintegration time and a

remarkable increase of the drug dissolution rate [39].

Extrusion-spheronisation aids

During last few years, crospovidone and other excipients like carrageenan [66], chitosan [67], pectin [68], Eudragit® [69] and modified starch [18] have been exploited as extrusion-spheronization aid alternate to microcrystalline cellulose (MCC). Liew et al. suggested two finer grades of crospovidone that were efficient as extrusion-spheronisation [69]. Moreover, crospovidone was also used as taste masking agent, disintegrant and alternate extrusion-spheronization aid in preparing melt-in-mouth pellets of fexofenadine hydrochloride [54]. However, crospovidone could not effectively mask the taste of fexofenadine hydrochloride although it was prepared in a bigger batch and even after triturating for 72 h in a ball mill.

Verheyen et al. (2008) working for pellets with crospovidone as pelletisation aid [70] reported that the effect of super disintegrants such as crospovidone and croscarmellose sodium on the rate of the dissolution of furosemide from extrusion-spheronization pellets was moderate and the magnitude of the effect was dependent on the solubility of the filler that accompanied the microcrystalline cellulose. But other studies [71], suggested that crospovidone was inefficient for accelerating the dissolution of propyphenazone from extrusion-spheronization pellets.

Later on, the new sustained gastroretentive release delivery system was developed with floating sodium carbonate, swellable of crospovidone and β-cyclodextrin, and bioadhesive psyllium husk and HPMC containing the active drug as ofloxacin [72].

Nasal absorption-enhancing vehicle

So far our knowledge goes, crospovidone has been used for the first time as enhancer in increasing bioavailability of cyanocobalamin, and is a suitable nasal absorption-enhancing vehicle since it shares the insolubility and absorption properties of microcrystalline cellulose and dextran microspheres [73].

Clarifier

In addition, crospovidone is also used as a clarifier of alcoholic and non-alcoholic beverages. Hazing of beers and wines is caused by reaction of proteins with oxidized polyphenols and reduction of the latter is achieved by binding with polyvinylpyrrolidone. Although this may appear to be a straightforward process considerable developmental work has been undertaken industrially to ensure that beverages reaching our tables are clear and bright [5].

Adverse effect of crospovidone

In spite of various advantages of crospovidone, there are also side effects caused by it. While not frequently described in the medical literature, in addition to food and vegetable materials, there may be evidence of oral pharmaceutical tablet aspiration. It is suggested that deeply basophilic coral-like appearing matter in our open lung biopsy belongs to crospovidone aspiration. In a recent study examining [74] 59 cases of aspiration

diagnosed on biopsy or resection specimens, only four were found to have signs of pulmonary crospovidone aspiration. Some have reported crospovidone deposits along the pulmonary vasculature in intravenous drug users who inject aqueous suspensions of tablet preparations [75]. The long term consequences of crospovidone deposits within the pulmonary airways or vasculature are unknown [76].

Finally this review attempted to highlight and exhaustively cover the various applications of crospovidone.

References:

[1] Yue , H., Bu , X., Huang , M. H., Young , J., Raglione , T., Int. J. Pharm. , 2009, 375, 33-44.

[2] Machiste , E. O., Giunched , P., Setti , M., Conte , U., Int. J. Pharm. , 1995, 126, 65-72.

[3] Williams , A. C., Timmins , P., Lu , M., Forbes , R. T. , Eur. J. Pharm. Sci. , 2005, 26, 288–294.

[4] Zhu , X., Lu , P., Chen , W., Dong , J., Polymer. 2010, 51, 3054-3063.

[5] Brittain , H. G., Analytical profiles of drug substances and excipients, Book Review 1996, 24, 619.

[6] Srinarong , P., Faber , J. H., Visser , M. R., Hinrichs , W. L. J., Frijlink , H. W., Eur. J. Pharm. Biopharm. , 2009, 73, 154-161.

[7] Schulz , M., Fussnegger , B., Bodmeier , R., Eur. J. Pharm. Sci. , 2010, 41, 675-684.

[8] Bley , H., Fussnegger , B., Bodmeier , R., Int. J. Pharm. , 2010, 390, 165-173.

[9] Okuda , Y., Irisawa , Y., Okimoto , K., Osawa , T., Yamashita , S., Int. J. Pharm. , 2009, 382, 80-87.

[10] Buhler , V., Polyvinylpyyrolidone excipients for pharmaceuticals povidone, crospovidone and copovidone, Handbook Springer-Verlag Berlin Heidelberg 2005, pp. 125 - 178.

[11] Fujii , M., Okada , H., Shibata , Y., Teramachi , H., Kondoh , M., Watanabe , Y., Int. J. Pharm. , 2005, 293, 145-153.

[12] Shibata , Y., Fujii , M., Sugamura , Y., Yoshikawa , R., Fujimoto , S., Nakanishi , S., Motosugi , Y., Koizumi , N., Yamada , M., Ouchi , K., Watanabe , Y., Int. J. Pharm. , 2009, 365, 53-60.

[13] Sugamura , Y., Fujii , M., Nakanishi , S., Suzuki , A., Shibata , Y., Koizumi , N., Watanabe , Y., Chem. Pharm. Bull. , 2011, 59(2), 235-238.

[14] American Material Safety Data Sheet (MSDS) of crospovidone, http://www.aicma.com., (assessed Jun 16, 2011).

[15] Material Safety Data Sheet (MSDS) of crospovidone, 2nd edition, 2009, 1.

[16] Shin , S. C., Oh , I. J., Lee , Y. B., Choi , H. K., Choi , J. S., Int. J. Pharm. , 1998, 175, 17-24.

[17] Nakanishi , S., Fujii , M., Sugamura , Y., Suzuki , A., Shibata , Y., Koizumi , N., Watanabe , Y., Int. J. Pharm. , 2011, (Article in press).

[18] Dukic-Ott , A., Thommes , M., Remon , J. P., Kleinebudde , P., Vervaet , C., Eur. J. Pharm. Biopharm. , 2009, 71, 38-46.

[19] Liew , C. V., Josephine , L. G., Soh , L. P., Heng , P. W., Pharm. Res. , 2005, 22, 1387–1398.

[20] Tallon , M. A., Malawer , E. G., Machnicki , N. I., Brush , P. J., Wu , C. S., Cullen , J. P., J. Appl. Polym. Sci. , 2008, 107, 2776–2785.

[21] Balamuralidhara , V., Sreenivas , S. A., Gangadharappa , H. V., Pramodkumar , T. M., Asian J. Sci. Res. , 2009, 2(4), 190-197.

[22] Lim , R. T. Y., Ng , W. K., Tan , R. B. H., J. Supercritical Fluids 2010, 53, 179-184.

[23] Tajarobi , F., Abrahmsen-Alami , S., Larsson , A., Wiley Online Library (wileyonlinelibrary.com), 2010, DOI 10.1002/jps.22248.

[24] Tajarobi , F., Abrahmsen-Alami , S., Larsson , A., Matic , H., Eur. J. Pharm. Biopharm. , 2011, 78, 125–133.

[25] Ve´laz , I., Sa´nchez , M., Martı´n , C., Martı´nez-Oha´rriz , M. C., Zornoza , A., Int. J. Pharm. , 1997, 153, 211–217.

[26] Miyazaki , T., Aso , Y., Yoshioka , S., Kawanishi , T., Int. J. Pharm. , 2011, 407, 111–118.

[27] Schulz , M., Fussnegger , B., Bodmeier , R., Int. J. Pharm. , 2010, 391, 169-176.

[28] Desai , D., Kothari , S., Huang , M., Int. J. Pharm. , 2008, 354, 77-81.

[29] Hops , C., Mueller , B., Arch. Pharm. , 1999, 332(Suppl. 2), 18.

[30] Watanabe , T., Hasegawa , S., Wakiyama , N., Kusai , A., Senna , M., Int. J. Pharm. , 2003, 250, 283–286.

[31] Grassi , M., Colombo , I., Lapasin , R., J. Cont. Rel. , 2000, 68, 97-133.

[32] Bühler , V., Kollidon-polyvinylpyrrolidone for the pharmaceutical industry, 2nd edition, 1993, BASF, Ludwigshafen.

[33] Moneghini , M., Voinovich , D., Perissutti , B., Princivalle , F., Pharm. Dev. Technol. , 2002, 7, 289–296.

[34] Jalali , M. B., Valizadeh , H., Shadbad , M. R. S., Adibkia , K., Mohammadi , G., Farahani , A., Arash , Z., Nokhodchi , A., Pow. Tech. , 2010, 197, 150-158.

[35] Solis , J. L., Robles , L. V., Int. J. Pharm. , 2001, 216, 127-135.

[36] Giunchedi , P., Conte , U., and La Manna , A., Boll. Chim. Farm., 1990, 129, 17-20.

[37] Sangalli , M. E., Giunchedi , P., Colombo , P., Conte , U., Gazzaniga , A., and La Manna , A., Boll. Chim. Farm. , 1989, 128, 242-247.

[38] Grassi , M., Colombo , I., Carli , F., Lapasin , R., Eur. J. Pharm. Sci. , 1998, 6 (1), 260.

[39] Perissutti , B., Rubessa , F., Moneghini ,M., Voinovich , D., Int. J. Pharm., 2003, 256, 53-63.

[40] Leuner , C., Dressman , J., Eur. J. Pharm. Biopharm. , 2000, 50, 47-60.

[41] Betageri , G. V., Makarla , K. R., Int. J. Pharm. , 1995, 126, 155-160.

[42] Trapani , G., Franco , M., Latrofa , A., Pantaleo , M. R., Provenzano , M. R., Sanna , E., Maciocco , E., Liso , G., Int. J. Pharm. , 1999, 184, 121-130.

[43] Karavas , E., Georgarakis , E., Bikiaris , D., Int. J. Pharm. , 2006, 313, 189-197.

[44] Schulz , M., Fussnegger , B., Bodmeier , R., Eu. J. Pharm. Biopharm. , 2011, 77, 240-248.

[45] Alsaidan , S. M., Alsughayer , A. A., Eshra , A. G., Drug Dev. Indst. Pharm. , 1998, 24(4), 389-394.

[46] Guidance for Industry Q3C Impurities: Residual Solvents, ICH, 1997.

[47] Lipp , R., J. Pharm and Pharmacology, 1998, 50, 1343–1349.

[48] Karmwar , P., Graeser , K., Gordon , K. C., Strachan , C. J., Rades , T., Int. J. Pharm. , 2011, (Article in press).

[49] Bikiaris , D., Papageogiou , G. Z., Stergiou , A., Pavlidou , E., Karavas , E., Kanaze , F., Georgarakis , M., Thermochimica Acta, 2005, 439, 58-67.

[50] Bhugra , C., Pikal , M. J., J. Pharm. Sci. , 2008, 97, 1329–1349.

[51] Doherty , C., York , P., J. Pharm. Sci. , 1987, 76, 731–737.

[52] Taylor , L. S., Zografi , G., Pharm. Res. , 1997, 14, 1691–1698.

[53] Moneghini , M., Carcano , A., Zingone , G., Perissutti , B., Int. J. Pharm. , 1998, 175, 177-183.

[54] Jain , S. P., Mehta , D. C., Shah , S. P., Singh , P. P., Amin , P. D., AAPS PharmSciTech, 2010, 11(2), DOI: 10.1208/s12249-010-9443-7.

[55] Shah , U., Augsburger , L., Pharm. Dev. Technol. , 2001, 6 (1), 39–51.

[56] Bussemer , T., Peppas , N. A., Bodmeier , R., Eur. J. Pharm. Biopharm. , 2003 , 56, 261–270.

[57] Bolhuis , G. K., Zuurman , K., Wieric , G. H. P., Eur. J. Pharm. Sci. , 1997, 5, 63-69.

[58] Habib , Y. S., Augsburger , L. L., Shangraw , R. F., Int. J. Pharm. , 2002, 233, 67-83.

[59] Stoltenberg , I., Breitkreutz , J., Eur. J. Pharm. Biopharm. , 2011, In Press.

[60] Kowalski , J., Kalb , O., Joshi , Y. M., Serajuddin , A. T. M., Int. J. Pharm. , 2009, 381, 56-61.

[61] Fini , A., Bergamante , V., Ceschel , G. C., Ronchi , C., Moraes , C. A. Fd., Eur. J. Pharm. Biopharm. , 2008, 69, 335-341.

[62] Thoma , K., Bechtold , K., Eur. J. Pharm. Biopharm. , 1999, 47, 39–50.

[63] Solon , L. G. dS., Oliveira , A. I. Md., Guerra , G. C. B., Soares , L. A. L., de Araujo , A. A., Braz. J. Pharm. Sci. , 2010, 46.

[64] European Pharmacopoeia 2001, 4th ed., Strasbourg, France.

[65] United States Pharmacopoeia-National Formulary (USP-NF), United States Pharmacopeia Convention, 2011.

[66] Bornhoft , M., Thommes , M., Kleinebudde , P., Eur. J. Pharm. Biopharm. , 2005, 59, 127-131.

[67] Steckel , H., Nogly , F. M., Eur. J. Pharm. Biopharm. , 2004, 57, 107-114.

[68] Tho , I., Sande , S. A., Kleinebudde , P., Eur. J. Pharm. Biopharm. , 2003, 56, 371-380.

[69] Mehta , K. A., Kislalioglu , M. S., Phuapradit , W., Malick , A. W., Shah , N. H., Int. J. Pharm. , 2001, 213, 7-12.

[70] Verheyen , P., Steffens , K. J., Kleinebudde , P., Biopharm. Pharm. Tech. , Barcelona, 6th World Meeting on Pharmaceutics, 2008, 1-2.

[71] Wlosnewski , J. C., Vollrath , M. K., Sriamornsak , P., Chem. Eng. Res. Des. , 2010, 88, 100-108.

[72] Chen , R. N., Ho , H. O., Yu , C. Y., Sheu , M. T., Eur. J. Pharm. Sci. , 2010, 39, 82–89.

[73] Alfredo , G. A., Santiago , S. T., Goya , L., Torrado , J. J., Biol. Pharm. Bull. , 2001, 24(12), 1411—1416.

[74] Mukhopadhyay , S., Katzenstein , A. L. A., Am. J. Surg. Pathol, 2007, 31(5).

[75] Ganesan , S., Felo , J., Saldana , M., Kalasinsky , V. F., Smith , M. R. L., Tomashefski , J. F., Mod Pathol. , 2003, 16(4), 286-292.

[76] Timpone , V., Didomenico , P., Huynh , B., Bravo , L., Eur. J. Radio. Extra, 2008, 67, 99-101.