An Overview of Factors Affecting Superdisintegrants Functionalities

Jemal Dilebo* and Tesfaye Gabriel

Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia.

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ABSTRACT

Disintegrants are an essential excipients in solid oral formulations. Superdisintegrants such as croscarmellose sodium, sodium starch glycolate, crospovidone and polacrilin potassium are among excipients added in immediate release and oral dispersible tablet formulations at low concentrations to counteract effects of compression and binder after administration. Hygroscopicity of superdisintegrants facilitates permeation of water into tablet matrix and cross-linkage reduces their solubility in water. This article describes factors which could affect functionality of superdisintegrants such as molecular and physicochemical factors (degree of cross-linkage and substitution, particle size, particle porosity and impurities); formulation and process factors (solubility and hygroscopicity of fillers and/or binders, incompatibility, pH, lubricants, mode of disintegrant addition, granulation, mixer shear rate, compression pressure and reworking) and aging and storage conditions.

KEYWORDS: Superdisintegrant; Sodium starch glycolate; Croscarmellose sodium; Crospovidone; Polacrilin potassium; Disintegration, dissolution.

Introduction

Disintegrants are one of tablet excipients added to eliminate cohesive strengths introduced by compression and binders (Kottke and Rudnic, 2002). Disintegrants facilitate permeation of water into tablet matrix, thereby the tablet changes into coarse aggregates and the coarse aggregates in turn deaggregate into primary particles (Desai et al., 2016). The formation of smaller particles increases the surface area of drug available for physiological medium, hence enhanced dissolution rate and bioavailability of the drug (Quodbach and Kleinebudde, 2016).

The term ‘superdisintegrant’ was came into use at the end of 1970s or beginning of 1980s to describe the then new generation of disintegrants that were much more effective at low concentration compared to conventional disintegrants (Moreton, 2008). Being effective at low concentrations, superdisintegrants give economic advantage as well as reduce flow and compression problems related with the use of relatively higher proportions of starch (Van Kamp et al., 1983).

Superdisintegrants include sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone (XPVP) and polacrilin potassium (PP) (Quodbach and Kleinebudde, 2016). They are very hygroscopic because they contain polar functional groups. The presence of cross-links in their polymer structure minimizes conformational degrees of freedom, as the result the polymer matrix behaves highly resistant to gelation and dissolution (Barmpalexis et al., 2018). They are commonly used in immediate release and oral dispersible tablet formulations at low concentration levels.

Recently excellent review works have been done on different subjects of disintegrants (Zarmpi et al., 2017; Markl and Zeitler, 2017; Desai et al., 2016; Quodbach and Kleinebudde, 2016). However, the emphasis given in these works about factors affecting performances of superdisintegrants is not adequate. Thus, this article provides an overview of key factors affecting performances of superdisintegrants in solid oral pharmaceuticals.

Sodium Starch Glycolate (SSG)

SSG (Fig. 1) is carboxymethyl ether substituted and phosphate ester cross-linked superdisintegrant produced typically from potato starch (Bolhuis et al., 1986; Quodbach and Kleinebudde, 2016). Carboxymethylation is performed as Williamson ether synthesis, i.e., starch is made to react with sodium chloroacetate in alkaline medium and then neutralized with citric acid or other acids. Cross-linking is performed using chemical or physical methods. In chemical method, reagents such as phosphorous oxychloride, sodium trimetaphosphate or other cross-linking reagents are used (Bolhuis et al., 1986). Carboxymethyl group makes SSG to have

ABBREVIATIONS: DT = disintegration time; SSG = sodium starch glycolate; CCS = croscarmellose sodium; XPVP = crospovidone; PP = polacrilin potassium

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hydrophilic character and the phosphate ester crosslinkage lowers its water solubility by reducing the exposure of hydrophilic groups to water (Wren et al., 2017).

Two types of SSG (Type A and Type B) have been mentioned in USP and PhEur depending on the extent of sodium carboxymethylation. Type A has 2.8%-4.2% sodium, while Type B has 2.0%-3.4% sodium (Abraham et al., 2016). Concentrations 2%-4% and 4%-6% are used in direct compression and granulated tablet formulations, respectively (Moreton, 2008). The major mode of disintegrating action of SSG is swelling (Quodbach and Kleinebudde, 2014).

**Crocarmellose Sodium (CCS)**

CCS (Fig. 2) is carboxymethylated and cross-linked polymer of cellulose (Quodbach and Kleinebudde, 2016). In the synthesis, pure cellulose extracted from wood or cotton fiber is steeped in sodium hydroxide solution to form alkali cellulose. Carboxymethyl cellulose is obtained by reacting the alkali cellulose with sodium monochloroacetate. At the end of substitution reaction, the sodium hydroxide is being used up and the remaining sodium monochloroacetate gradually hydrolyzes to form glycolic acid. The glycolic acid catalyzes cross-linking to produce CCS. CCS is finally obtained by extracting with aqueous alcohol and any trace sodium glycolate and sodium chloride is removed (Guest, 2009). Yet, the mode of cross-linking of CCS has not been reported (Quodbach and Kleinebudde, 2016). CCS is used in concentrations 0.5%-5% in tablet formulations (Guest, 2009). Its major mode of disintegrating action is swelling (Quodbach and Kleinebudde, 2014). Under microscope examination, CCS contains thin fibres of various lengths (Guest, 2009).

**Crospovidone (XPVP)**

XPVP (Fig. 3) is a chemically synthesized polymer. In the synthesis, acetylene and formaldehyde are made to react in the presence of catalyst to form butanediol, which is then converted to butanediol by hydrogenation and then to butyrolactone by cyclohydrogenation (Quodbach and Kleinebudde, 2016). When butyrolactone reacts with ammonia, pyrrolidone is formed and then it is made to react with acetylene to produce the monomer N-vinylpyrrolidone. N-vinylpyrrolidone is popcorn polymerized (branched polymerized) in solution using catalyst to form XPVP (Bühler, 2005). The morphology of XPVP resembles polymer foam, with its void spaces formed by the polymerization process itself (Barabas and Adeyeye, 1996).

Generally, XPVP is used in the range of 2%-5% in tablets prepared by direct compression and granulation methods (Kibbe, 2009). The main proposed disintegrating mechanism of XPVP is shape recovery (Quodbach et al., 2014, Desai et al., 2012). Shape recovery refers to return of disintegrant particles to the original shape upon contact with water and takes place in opposite direction to compression pressure (Quodbach and Kleinebudde, 2016).

**Polacrilin Potassium (PP)**

PP (Fig. 4) is an ion-exchange potassium salt of copolymer of methacrylic acid and divinyl benzene. In the synthesis, polacrilin resin is produced by copolymerization of methacrylic acid with divinyl benzene (Quodbach and Kleinebudde, 2016). When polacrilin resin is neutralized with potassium hydroxide, PP is formed (Moreton, 2008). Concentration 2%-10% is employed for its disintegrating purpose (Palmieri, 2009). The mechanism of disintegrating action of PP is not adequately studied; though, shape recovery (Quodbach et al., 2014) and wicking (capillary effect) (Bele and Derle, 2012) have been proposed.
'disintegrant', 'superdisintegrant', 'crocscarmellose sodium', 'sodium starch glycolate', 'crosplovidone', 'polacrilin potassium', 'crocscarmellose sodium + performance', 'sodium starch glycolate + performance', 'crosplovidone + performance', 'polacrilin potassium + performance', 'factors affecting disintegrants/superdisintegrants functionalities' were searched in Google performance', 'factors affecting disintegrants/superdisintegrants functionalities' were searched in Google performance', 'polacrilin potassium + performance', 'sodium starch glycolate + performance', 'polacrilin potassium', 'crocscarmellose sodium + performance', 'crocscarmellose sodium', 'disintegrant', 'superdisintegrant', 'crocscarmellose Dilebo and Gabriel: An Overview of Factors Affecting Superdisintegrants Functionalities 4357

...functionalities of superdisintegrants could be affected by molecular and physicochemical characteristics of the disintegrant, formulation and process factors as well as ageing and storage conditions.

Molecular and Physicochemical Factors

Effect of Degree of Cross-Linkage and Substitution

Functionalities of SSG and CCS are conferred by substitution of hydroxyl groups with more hydrophilic groups and cross-linking of linear polymer chains. The degree of cross-linkage and carboxymethylation (substitution) of SSG significantly affect its performance (Rudnic et al., 1985). Disintegration and dissolution performances of SSG was found to be optimal in cross-linkage level 33%-35% and substitution level 0.28-0.29, which are modification levels of Explotab®, a brand of SSG (Rudnic et al., 1985). For CCS, a brand with more basic substitution (sodium salt) had larger settling volume, higher maximal water uptake and higher swelling capacity in neutral medium than another brand with less extent of basic substitution though both had similar particle size distribution and total degree of substitution (Zhao and Augsburger, 2006a). Yet, the effects of different degrees of cross-linkage on performances of CP and PP have not been reported.

Effect of Particle Size

Coarse particle fractions of SSG, XPVP and PP had better disintegrating performances than fine particle fractions (Bele and Derle, 2012; Smallenbroek et al., 1981; Rudnic et al., 1980). The effect of particle size of CCS on its disintegrating performance has not been clearly evaluated. However, since the predominant mechanism by which CCS causes tablet disintegration is by swelling, particle size of this disintegrant could be crucial as large particles exert strong swelling force on tablet matrix than smaller particles (Zarmpi et al., 2017).

Effect of Particle Porosity

When a disintegrant contains large intra-particle porosities, there will be an increase in surface area for liquid medium contact with a subsequent rapid water uptake and swelling or shape recovery. A brand of PP with larger total porosity had greater initial water uptake rate and was found to have shorter disintegration time (DT) than other brands with lower total porosities (Bele and Derle, 2011). Intra-particle porosity was also found to be critical for rapid dissolution of a model drug in tablets containing different grades of CP in insoluble filler system (Shah and Augsburger, 2001).

Effect of Impurities

By-product impurities could arise during synthesis of superdisintegrants. For example, during the synthesis of SSG, reaction by-products such as sodium chloride, sodium glycolate and sodium citrate are produced (Bolhuis et al., 1986). The amounts of these by-products in SSG are specified in official compendia; for example, USP 32/NF 27 and PhEur 6.0 state that sodium chloride and sodium glycolate contents should be less than 7% and less than 2%, respectively (Bolhuis et al., 1986).

SGS compacts with lower percentage of total cold water soluble fractions (impurities) had greater amount of water uptake and water penetration rate compared to SSG compacts with higher percentage of impurities. When incorporated at 4% concentration in tablet formulations, SSG containing low percentage of impurities showed fast tablet DT than SSG with high percentage of impurities although the difference is small (Bolhuis et al., 1986). Higher amount of salt impurities compete with disintegrants for water uptake and hence affect their performances.

Formulation and Process Factors

Effect of Water Solubility and Hygroscopicity of Components

Water solubility of a major tablet formulation ingredient affects rate and mode of tablet disintegration. Water soluble ingredients tend to dissolve rather than disintegrate, whereas insoluble ingredients produce fast disintegrating tablets (Johnson et al., 1991). Water soluble components dissolve and form viscous barrier of saturated solution around tablet matrix. This barrier hinders ingress of water to disintegrants and thereby delay tablet disintegration (Johnson et al., 1991). However, it is stated that the effect of viscosity due to water soluble fillers on disintegration retardation would be minimal. Rather, hydrated molecules of fillers hold up more water molecules and hinder them from reaching to disintegrants (Ekmekciyan et al., 2018).

Overall tablet hygroscopicity caused by fillers has also negative effect on performances of superdisintegrants (Johnson et al., 1991). For example, dissolution rate of P-aminoasalicylic acid from tablets containing sorbitol or naproxen sodium (hygroscopic ingredients) as filler was delayed in the presence of superdisintegrants compared to without superdisintegrants (Johnson et al., 1991). A hygroscopic excipient competes for water with superdisintegrant and hence affects DT. Water soluble binders also tend to prolong tablet DT than insoluble binders. This is attributed to insolubility and low hydration potential of insoluble binders (Ekmekciyan et al., 2018).

Effect of pH

CCS and SSG are anionic disintegrants and their water uptake and swelling capacity can be influenced by...
medium pH (Zhao and Augsburger, 2005). Studies done on the effect of medium pH on tablet DT and drug dissolution rate from formulations containing SSG, CCS and XPVP showed that disintegrating performances of CCS and SSG were severely reduced in acidic medium compared to neutral medium. Disintegrating performance of XPVP, a non-ionic polymer, however, was barely affected by medium pH (Chen et al., 1997, 1998). The low performances of CCS and SSG in acidic medium could be due to the conversion of carboxymethyl sodium moiety to free acidic form which has less hydration capacity than the salt form (Zhao and Augsburger, 2005). The effect of medium pH on water uptake and swelling potential of superdisintegrants is influenced by the overall degree of substitution as well as the ratio of basic to acidic substituent (Zhao and Augsburger, 2005). Similarly, since PP is anionic disintegrant, acidic pH could affect its functionality.

Effect of Lubricant

Lubricants are one of tablet formulation excipients included at very low concentrations to minimize friction between machine parts and tablet surfaces during ejection. Disintegrating functionality of SSG was found to be slightly affected by magnesium stearate and the negative effect of this lubricant was found to increase at prolonged mixing or at higher rate of mixing (Bolhuis et al., 1981). However, compared to starch, disintegrating performance of SSG was less sensitive to film forming effect of magnesium stearate (Bolhuis et al., 1981). Magnesium stearate forms hydrophobic film around powder particles during mixing process and retards water penetration into tablet matrix. With prolonged mixing time, the hydrophobic magnesium stearate gets more time to cover all of the surfaces (Bele and Derle, 2011).

Effect of Incompatibility

Tablet formulations may contain drugs and excipients with various physicochemical properties such as weakly basic or weakly acidic characteristics. Incompatibilities between CCS and highly basic excipients were reported (Bindra et al., 2014). The researchers postulated that under alkaline conditions (pH>8.5), the ester cross-links of CCS hydrolyzes, producing carboxymethyl cellulose, a water-soluble polymer in the tablets. The rise in the level of this water soluble polymer could lead to formation of viscous barrier which hinders water permeation into tablet matrix and thereby reduce dissolution rate of drug.

CCS and SSG interact with cationic drugs to the extent that the interaction affects in vitro dissolution rate of these drugs (Balasubramaniam et al., 2008). Though there was in vitro interaction between phenylpropanolamine HCl (weakly basic drug) and CCS, the interaction could not affect bioavailability of the drug (Hollenbeck, 1988). The interaction between anionic superdisintegrants and weakly basic drugs eliminate at physiological salt concentration (Fransén et al., 2008). This suggests that interaction between anionic superdisintegrants and weakly basic drugs is based on ion-exchange type (Fransén et al., 2008).

Binding of CCS and SSG with oxymorphone was reported to be solution pH dependent and maximum binding occurred at pH 6-7 (Chien et al., 1981). At this pH range, the interaction of oxymorphone with CCS was found to be twice of SSG. Amine drugs form pH dependent complex with PP with maximum interactions being observed at pH 4.5-5.5 (Borodkin and Yunker, 1970). The less interaction between PP and amine drugs at pH>6 indicates the interaction has insignificant effect on total in vivo availability of these drugs (Borodkin and Yunker, 1970).

Effect of Granulation and Reworking

Tablet production processes such as granulation and reworking have unfavourable effects on effectiveness of superdisintegrants; hence, higher concentrations of disintegrants are recommended in tablet formulations for production by granulation methods compared to direct compression method (Zhao and Augsburger, 2006b). It was found that pre-compression granulated SSG and XPVP caused prolonged DT of tablets compared to unprocessed superdisintegrants (controls) when used at 1% concentration. However, DT of tablets containing pre-compression granulated CCS was not affected at similar concentration. On the same work it was found that the DT of tablets prepared from pre-wet granulated CCS, SSG and XPVP were significantly longer than tablets made from unprocessed superdisintegrants (control). The researchers stated that pre-wetting of disintegrants as it is performed in tablet production by wet granulation method can have negative impact on functionality of superdisintegrants even more than pre-compression granulation which is done in dry granulation method of tablets production (Zhao and Augsburger, 2006b).

Reworking processes also affect superdisintegrants functionality (Gould and Tan, 1985). The impact of reworking on disintegrants performances, however, could dependent on the mode of superdisintegrants incorporation. CCS, SSG and CP lost their rework efficiency when incorporated intragranularly. However, when incorporated extragranularly, SSG and XPVP retained their rework efficiency (SSG being better) but not CCS (Gould and Tan, 1985). The losses in efficiencies of CCS and XPVP were attributed to fragmentation of ‘spaghetti-like’ fibrous structure of CCS and ‘sponge-like’ structure of XPVP during rework processes such as comminution and compaction. Loss in functionality of the disintegrants can also be worsened by film forming effect of hydrophobic lubricant which is incorporated during relubrication step (Gould and Tan, 1985).

Effect of Mode of Disintegrant Addition

Disintegrants are added during wet granulation method of tabletting intragranularly, extragranularly or in combined intragranular and extragranular mode. In the literature there are inconsistencies about the effectiveness of superdisintegrants when incorporated in
different modes. In one study (Gordon et al., 1990) intragranularly incorporated CCS produced greater dissolution rate than the other two modes of incorporation. Contrary to this combined intragranular and extragranular mode of addition was found to produce higher rate of drug dissolution than the extragranular mode and this in turn produced higher dissolution rate compared to intragranular mode (Khattab et al., 1993).

There are however, other studies which showed extragranular mode of superdisintegrants addition yielded higher drug dissolution rate than the other two modes of addition (Preetha et al., 2008; Gordon et al., 1993a). Similarly, in studies which compared the intragranular and extragranular mode of addition of super disintegrants, the superdisintegrants performed better in the extragranular mode than in the other mode (Nazmi et al., 2013; Rahman et al., 2011). Extrgranularly incorporated maize starch, sodium calcium alginate, alginic acid, microcrystalline cellulose, and colloidal aluminium silicate (though not commonly used disintegrants today) showed much more rapid DT than intragranular mode. The intragranular mode of addition, however, produced much finer disintegrated particles (Shotton and Leonard, 1976).

Water solubility of major ingredient in a tablet formulation does not have an effect on performances of superdisintegrants when added in different modes (Gordon et al., 1993a; Preetha et al., 2008). The differences observed in the performances of super disintegrants added in different modes, could be related with the manufacturing processes used. For example, a disintegrant may perform differently when pure water is added to a powder mixture compared to adding binder solution during wet massing. Similarly, adding extragranular disintegrant first or adding extragranular disintegrant and lubricant at the same time to dried granules could affect a superdisintegrant performance. Moreover, exposure of a superdisintegrant to moisture from granulating fluid as well as milling of dried granules could affect its performances in intragranular mode of addition.

**Effect of Mixer Shear Rate**

A drug, disintegrant, filler and other components may be dry mixed and/or wet granulated using mixers which generate different degrees of shear. SSG performance was found to be adversely affected by high rate of mixer shear in wet granulation (Rudnic et al., 1983). High shear rate causes cleavage of phosphate ester bonds holding polymer chains in the molecule (Wren et al., 2017). In order to solve this condition, low viscosity grade SSG (Glycolys® low viscosity), which has high extent of phosphate cross-linkage is available commercially. It was found that the low viscosity grade SSG resisted more shear-induced phosphate ester bond cleavage than the high viscosity grade SSG in wet granulation (Wren et al., 2017).

**Effect of Compression Pressure**

Powders and granules are compacted into tablets during tableting by the action of compression pressure exerted from upper punches. The effect of compression force on DT was shown to be more important for XPVP than other superdisintegrants (Quodbach and Kleinebudde, 2015). At higher concentrations, XPVP disintegrating efficiency was found to increase when compression force increases. But at lower concentrations, its efficiency was found to decrease as compression force increases (Hiew et al., 2016). Disintegrating effects of CCS and SSG were found to be less sensitive to change in compression pressure compared to concentration (Di Martino et al., 2005). Presence of excessive porosity or absence of porosity would have negative effect on tablet disintegration. In the former case the swelling force would dissipate without exerting pressure on tablet matrix; whereas, the amount of water permeating into tablet matrix is minimal in the latter case (Desai et al., 2018).

**Effect of Aging and Storage Conditions**

Tablet formulations may contain ingredients with different water solubility and/or hygroscopicity which have varying capacity of absorbing water into tablet matrix and thereafter cause different mechanical and/or solid state changes. Aging of disintegrants within tablets under normal storage conditions or at higher temperature and/or humidity retards their functionality. When investigating the effect of temperature and relative humidity on the physical properties of ketoconazole tablets containing CCS, SSG, starch and XPVP, DT of tablets was generally found to be retarded when stored for 90 or 120 days compared to 0 day at all storage conditions used (25 °C/40% RH, 37 °C/40% RH, 45 °C/40% RH, 25 °C/60% RH or 25 °C/ 80% RH). The highest retardation in DT was noted in tablets containing SSG (Akbuga and Ermentas, 1992).

A systematic study (Sacchetti et al., 2017) also revealed increased DT of tablets containing CCS, SSG and XPVP regardless of hardening or softening of the tablets when stored at 40°C/75% RH for 1 or 3 months. The increase in DT was very small for some diluent and disintegrant combinations. In this study, acetaminophen and sodium naproxen tablets containing MCC as diluent had less elevated DT than dicalcium phosphate dihydrate or lactose monohydrate containing tablets, but almost comparable DT elevation for griseofulvin formulations. Less elevated DT in MCC containing formulations could be due to weak disintegrant effect of this filler. MCC could compensate for loss of superdisintegrants functionality up on accelerated storage conditions. In this study the concentration of MCC or other diluents used was 43.07%. In another study (Marais et al., 2003), DT of tablets containing CCS was significantly reduced when stored for 1 month or disintegrated in stability chamber when stored for 3 months in ICH climatic conditions of zone II and zone IV (25°C/60% RH) and (30°C/70% RH), respectively. However, DT was hardly influenced at lower relative humidity and different temperatures of zone I and zone III (21°C/45% RH) and (30°C/35% RH), respectively. In this study 77.5%-86.25% of MCC was employed as
diluent which has weak disintegrant effect and could compensate for the disintegrating efficiency lost by the superdisintegrant. A less elevated DT of acetaminophen tablets containing corn starch as disintegrant was observed in tablets containing pregelatinized starch as binder compared to povidone as binder and the possible cause was related with the dualistic property of pregelatinized starch (Sarisuta and Parrott, 1988). In another study (Gordon et al., 1993b) significantly declined dissolution rates of formulations containing superdisintegrants stored at room temperature for 8 months or for additional 2 and 8 weeks at 37 °C/80% RH was found. The causes for the slowing of dissolution rates were hypothesized to be case hardening of the major ingredient (filler in this study) and loss of functionality of the superdisintegrants. In a study of tablets stored for 1 month at 20 °C and different RH (5-97%), almost constant DT was found at RH value of 0-80% for tablets containing CCS, XPVP and one brand of PP. However, DT of both brands of SSG was increased at RH > 22% and DT of one brand of PP was highest at 5% and decreased at RH > 40% (Quodbach and Kleinebudde, 2015). DT elevation up on storage at higher RH is attributed to the plasticizing effect of water on polymer structure of SSG (Faroongsarng and Peck, 1994). Sorbed water facilitates mobility of polymer chain (stress relaxation) which causes release of stored energy and subsequently diminishes disintegrant performance when the disintegrant subsequently contacts liquid medium (Quodbach and Kleinebudde, 2015). A gradually declined DT of CCS and XPVP containing tablets and insignificantly changing DT of SSG was noted when tablets were stored at 35°C/100 % RH for up to 7 days (Sheen and Kim, 1989).

The causes for the differences found in the findings of these studies could be related with the different tablet preparation methods used. At elevated temperature and humidity conditions, DT of tablets containing CCS and XPVP do not elevate if prepared by direct compression method and tend to elevate when prepared by wet granulation method. However, DT of SSG containing tablets tend to elevate under the same storage conditions regardless of the method of preparation.

Conclusions

Production of superdisintegrants with optimum molecular and physicochemical characteristics or grades is the work of manufacturers. Formulators should select appropriate grades of disintegrants suitable for a specific API. Formulators should also give attention that functionality of superdisintegrants could be affected by formulation factors and production processes. In addition, manufacturers of superdisintegrants and solid dosage form formulators should not undermine the impact of inappropriate handling of superdisintegrants particularly exposure to excessive temperature and/or humidity.

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