A REVIEW ARTICLE ON: SUPERDISINTEGRANTS

Shrivastava Priyanka* and Sethi Vandana

Department of Pharmaceutics, Lloyd College of Pharmacy, Greater Noida, U.P., India

ABSTRACT

Disintegration plays a major role in improving the drug activity and hence increases the patient compatibility. The therapeutic activity of the formulations is obtained by disintegration followed by dissolution. The inclusion of right disintegrants is a prerequisite to get optimal bioavailability in tablets and capsules. Disintegrants are the substances that causes the rapid disintegration of the capsules or tablets into smaller particles that dissolves more rapidly than in the absence of the disintegrants. On the other hand superdisintegrants, as it name suggests superior to disintegrants are the substances which facilitates or increases the disintegration time even at low level, typically 1-10% by weight relative to the total weight of the dosage unit. This article comprises of study of superdisintegrants which are being used in the formulation to provide safe and effective drug delivery with improved patient compliance.

Keywords: Rapid disintegrating tablets, Superdisintegrants, Disintegrants.

INTRODUCTION

Disintegrants are substances or mixture of substances added to the drug formulations, which facilitate dispersion or breakup of tablets and contents of capsules into smaller particles for quick dissolution when it comes in contact with water in the gut. They may function by drawing water into the tablet, swelling and causing the tablet to burst apart. Such tablet fragmentation may be critical to the subsequent dissolution of drug and to attainment of satisfactory of drug bioavailability. Starch USP and various starch derivatives are the most common disintegrating agents. Various pregelatinized starches are also employed as disintegrants, usually in 5% conc. The disintegrants of dosage forms are depends upon physical factors of disintegrants/superdisintegrants. They are as follows:

- Percentage of disintegrants present in formulations.
- Presence of surfactants.
- Hardening of tablets.
- Nature of drug substances
- Mixing and types of addition

Disintegration has received considerable attention as an essential step in obtaining faster drug release. The emphasis on the availability of the drug highlights the importance of disintegrating tablets. Recently chemically modified disintegrants termed as superdisintegrants have been developed to improve the disintegration processes. Super disintegrants are the agents added to the tablet and some encapsulated formulations to promote the breakup of tablet and capsules “slugs” into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of tablet matrix. The emphasis on the availability of drug highlights the importance of the relatively rapid disintegration of a tablet as a criterion for ensuring uninhibited drug dissolution behavior. Number of factors affects the disintegration behavior of tablets. A disintegrant used in
granulated formulation processes can be more effective if used both “intrgranularly” and “extragranularly” thereby acting to break the tablet up into granules and having the granules further disintegrate to release the drug substance into solution. The proper choice of a disintegrant or a superdisintegrant and it’s consist performance are of critical importance to the formulation development of such tablets. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants. Superdisintegrants with special emphasis on correlating these functional properties to disintegrant efficiency and drug release rate. Water penetration rate and rate of disintegration force development are generally positively related to disintegrant efficiency in non-soluble matrices. However, such a positive correlation is not always observed between tablet disintegration time and drug dissolution rate.

**IDEAL PROPERTIES OF SUPER-DISINTEGRANTS**

**Good Compressibility and Flow Properties**
If the powders have 12-16% compressibility, they are said to be good flow powders. Crospovidones are significantly more compressible than other superdisintegrants.

**Poor Solubility**
The solubility of the major component in a tablet formulation can affect both the rate and the mechanism of tablet disintegration. Water soluble materials tend to dissolve rather than disintegrate, while insoluble materials generally produce rapidly disintegrating tablets.

**Poor Gel Formation Capacity**
Gels can delay dissolution as the drug must first diffuse through the gel layer before being released into the body. Sodium starch glycolate is used as superdisintegrant in tablet formulation at a concentration of 4-6%.

**Good Hydration Capacity**
Drugs or other excipients, which are hydrophobic and could be adsorbed on disintegrant surfaces, inadvertently influence the extent of hydration and the effectiveness of these disintegrants. Addition of fast disintegrants of high hydration capacity is reported to minimize this problem, and therefore, enhance dissolution.\(^1,8-10\)

**Complexation**
Anionic disintegrants like croscarmelllose sodium and sodium starch glycolate may complex with cationic drug actives and slow dissolution. Crospovidone a non-ionic polymer does not interact with cationic drug actives to retard drug release.\(^11\) The effects of superdisintegrants like croscarmelllose sodium, sodium starch glycolate and polyplasdone XL on the dissolution behavior of several cationic drugs with varying water solubility reports that polyplasdone XL had a more rapid dissolution rate for the model cationic drugs, irrespective of their aqueous solubilities.\(^12\)

**METHOD OF INCORPORATION**
Superdisintegrants are incorporated by:

**Ingranular**
In wet granulation method, the disintegrant is added to other excipients before wetting the powder with the granulating fluid. Thereby, the disintegrant is incorporated within the granules. In dry granulation method, the disintegrant is added to other excipients before compressing the powder between the rollers. In this process the superdisintegrants are blend with other powders and granulation is carried out. Thus the superdisintegrants are incorporated within the granules.\(^1\) In Internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules.

**Extragranular**
This is generally done prior to compression. In both wet and dry granulation method, the superdisintegrant is added to the granules during dry mixing prior to compression.\(^2,13\)

**Intra and Extragranular**
It is also called as internal and external mixing of disintegrants. In this part of superdisintegrants are added to intragranules and a part to extragranules. Superdisintegrant is divided into two portions. One portion is added before granule formation (intra) and remaining portion is added to granules.
(extra) with mixing prior to compression. This method can be more effective. If both intragranular and extragranular methods are used, extragranular portion break the tablet into granules and the granules further disintegrate by intragranular portion to release the drug substance into solution.\textsuperscript{1,16}

**TABLET COMPRESSION METHOD**

**Wet granulation Method**

Wet granulation forms the granules by binding the powders together with an adhesive, instead of by compaction. This technique employs a solution, suspension, or slurry containing a binder, which is usually added to the powder mixture. The method of introducing the binder depends on its solubility and on the components of its mixture the liquid plays an important role in granulation process. Once the process is completed, the wet mass is milled and dried to produce the granules. The wet mass usually is passed through a low-shear mill and then dried for 8-24 h. The resulting granules are then blended with additional excipients prior to being compressed into a tablet.\textsuperscript{1,3}

**Dry Granulation**

The dry granulation process is used to form granules without using a liquid solution because the product may be sensitive to moisture, heat or both. There are two techniques to produce dry granules.\textsuperscript{1}

- **Direct Compression**
  In direct compression process, drug is blended with a variety of excipients, subsequently lubricated and directly compressed into a tablet.\textsuperscript{3} A disintegrant used in this type of formulation, simply has to break the tablet apart to expose the drug substance for dissolution. Example: Lamotrigine orally disintegrating tablets prepared by direct compression technique using three different superdisintegrants like Sodium starch glycolate, Croscarmellose sodium and Crosspovidone XL-10.\textsuperscript{14}

- **Compression Granulation**
  This technique has been used for many years and is a valuable technique in situations where the effective dose of a drug is too high for direct compaction and the drug is sensitive to heat, moisture or both, which precludes wet granulation. It involves 2 steps:

  **Slugging**
  When the initial blend of powders is forced into the dies of a large capacity tablet press and is compacted by means of flat faced punches, the compacted masses are called slugs and the process is referred to as "slugging". The slugs are then screened or milled to produce granules.

  **Roller Compaction**
  Powder material is fed between the rollers by a screw conveyor system. After passing through the rollers, the compacted mass resembles a thin wide ribbon that has fallen apart into large segments. Then segments are screened or milled for the production of granules. The resulting granules are then blended with additional excipients prior to being compressed.\textsuperscript{4,14}

**MECHANISM OF ACTION**

**By Swelling Action**

Swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet fall apart\textsuperscript{7,15} as in figure 1.\textsuperscript{32} eg : Sodium starch glycolate.

**By Capillary Action / Wicking**

In this mechanism, the disintegrants that do not swell facilitate disintegration by their physical nature of low cohesiveness and compressibility.\textsuperscript{4} The disintegrant particles (with low cohesiveness and compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the interparticulate bonds causing the tablet to break apart as shown in figure 2.\textsuperscript{17,33}

**Deformation**

Starch such as potato or corn starch is believed to be elastic in nature, but due to high compaction force in case of tableting the elasticity deformed to plasticity with energy rich potential. When these tablets are exposed to aqueous environment, the energy potential of deformed starch grain will
be triggered to cause disintegration as shown in figure 3.33

**By Electrostatic Repulsion**
Guyot-Hermannet *et al.*, has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it[4] as shown in figure 4.33

**TYPES OF SUPERDISINTEGRANTS**

**Crosscarmellose Sodium**
It is modified cellulose and is a cross linked polymer of carboxymethylcellulose as shown in figure 5.4 The disintegration rate of crosscarmellose sodium is higher than that of sodium starch glycolate and the mechanism is also different. The carboxymethyl groups themselves are used to cross link the cellulose chains, process is accomplished by dehydration. The substitution is performed by using Williamson’s ether synthesis to give the sodium salt of carboxymethyl cellulose. Thus the crosslinks are carboxyl ester links rather than phosphate ester links as in Primojel. Cross linking makes it insoluble, hydrophilic, highly absorbent material, resulting in excellent swelling properties and its unique fibrous nature gives it excellent water wicking capabilities. It is used in oral pharmaceutical formulations as a superdisintegrant for capsules, tablets and granules. Concentrations of crosccarmellose sodium range between 1-5% w/w, although normally 1-3% w/w is used in tablets prepared by direct compression and 2-4% w/w in tablets prepared by a wet granulation process. Botzolakis *et al.* have studied the wicking and swelling properties of pure superdisintegrants from the plugs which are prepared under condition similar to those used in encapsulation of powder mixture into hard gelatin capsules.

**Advantages**
It uses a combination of swelling and wicking mechanism for disintegration, disintegrates within 2 minutes, easily available and cheap.

**Disadvantages**
It has lower cross linking density and form gels when fully hydrated, is poorly compressible and since it is anionic in nature, may form complexes with the cationic drugs.4

**Sodium Starch Glycolate**
It is a cross linked polymer of carboxymethyl starch as shown in figure 6.4 It is possible to synthesize sodium starch glycolate from a wide range of native starches but in practice potato starch is used as it gives the product with the best disintegrating properties. The effect of introduction of the large hydrophilic carboxymethyl groups is to disrupt the hydrogen bonding within the polymer structure. This allows water to penetrate the molecule and the polymer becomes cold water soluble. The effect of the cross-linking is to reduce both the water soluble fraction of the polymer and the viscosity of dispersion in water.2 The mechanism by which disintegration action takes place is rapid absorption of water and swell leading to an enormous increase in volume of granules which result in rapid and uniform disintegration. The natural predried starches swell in water to the extent of 10-20 percent and the modified starches increase in volume by 200-300 percent in water. The tablets formulated by using these superdisintegrants are disintegrated in less than two minutes.

**Advantages**
It absorbs water rapidly and swells in water to the extent of 200-300%, disintegrates within 2 minutes and is easily available and cheaper.

**Disadvantages**
At high usage level (>8%), disintegration increases due to gelling and its subsequent viscosity producing effects, has lower cross linking density and form gels when fully hydrated, is poorly compressible and since it is anionic in nature, may form complexes with the cationic drugs the gas evolving disintegrant, CaCO₃. Sallem *et al.* (1998),20 studied the effect of four superdisintegrants on the dissolution of terfenamide tablet containing. The four superdisintegrants improved disintegration and dissolution of the original formulation and their
relative efficiency of improvement is in order of crospovidone > Ac-di-sol > SSG > low substituted HPC.

Cross-Linked Polypyrrolidinone (Crosnovidone, PolyplasdoneXL, XL10)

Crosnovidones are synthetic, insoluble, crosslinked homopolymers of N-vinyl-2-pyrrolidinone as shown in figure 7. When examined under scanning electron microscope, crospovidone particles appear as granular and are highly porous. Due to its high crosslink density, crospovidone swells rapidly in water without gelling.4 Crosnovidones are highly compressible materials as a result of their unique particle morphology. Crospovidone is used as superdisintegrant at low concentration levels (2-5%) in direct compression, wet and dry granulation processes. Rahman et al. (2011),21 reported that acetaminophen release is faster from tablet formulations containing crospovidone than sodium starch glycolate(SSG), sodium carboxymethyl cellulose (Na CMC) and is unaffected by the mode of crospovidone addition. Formulations containing SSG, Na CMC extragranular mode of addition seems to be the best mode of incorporation. Yeli Zhang et al.22 carried out a study on the functionality and performance of three types of commonly used commercial superdisintegrants i.e crospovidone croscarmellose sodium, crospovidone, and sodium starch glycolate (SSG), in the application of ODTs. For each superdisintegrant, a wide range of disintegrant use levels (0.5–20%) is investigated in commonly used ODT model matrices at different compaction forces (4–12kN). An optimal use level is identified for each superdisintegrant, which is 2% for Ac-Di-Sol, 5% for PVP XL-10, 5% for Kollidon CL-SF, and 5% for Glycolys.

Advantages

Crosnovidone uses a combination of swelling, wicking and deformation mechanism for rapid disintegration of tablets, swells rapidly in water without forming gel, is highly compressible, unaffected by pH media.4 It is a natural super disintegrant that does not contain any starch or sugar as shown in figure 8 and so can be used in nutritional products. Mihirkumar Modh (2009),5 formulated and evaluated rapidly disintegrating tablets, formulated by direct compression method using aspirin as a model drug containing increasing concentration of superdisintegrants such as Emcosoy STS IP, Ac-Di-Sol, and Explotab. The aspirin tablets containing Emcosoy STS IP has a bursting effect resulting in a dispersion of drug particles facilitating their contact with the medium yielding a faster drug dissolution rate.4

Gellan Gum

Gellan gum is a linear anionic polysaccharide biodegradable polymer obtained from Pseudomonas elodea consisting of a linear tetrasaccharide repeat structure as shown in figure 9.4 Antony et al.6 studied that the Gellan gum as a superdisintegrant and the efficiency of gum is compared with other conventional disintegrants such as dried corn starch, explotab, avicel (pH 102), Ac-di-sol and Kollidon CL. The disintegration of tablet might be due to the instantaneous swelling characteristics of gellan gum when it comes into contact with water and owing to its high hydrophilic nature. The complete disintegration of tablet is observed within 4 minutes with gellan gum concentration of 4 percent w/w and 90 percent of drug dissolved within 23 minutes. Ac-di-sol and Kollidon CL shows very similar pattern of disintegration and in vitro dissolution rates. With the same concentration tablet with explotab show 36 minutes for 90% of drug release and with starch show 220 minutes. From this result gellan gum has been proved itself as a superdisintegrants.

Alginates

These are hydrophilic colloidal substances extracted naturally from certain species of Kelp or chemically modified from natural sources like alginic acid or salt of alginic acid. They are having higher affinity for water absorption and capable for an excellent disintegrants. They can be successfully used with ascorbic acid, multivitamins formulation.4 It is a hydrophilic
colloidal substance, which has high sorption capacity. It is also available as salts of sodium and potassium as shown in figure 10.4

**Chitin/Chitosan-Silica Coprecipitate**

Naturally Chitin is extracted from the shell wastes of shrimp, crab, lobster, krill, and squid and used for the production of chitosan by a deacetylation reaction in alkaline medium. The comparative study of other superdisintegrants with Chitin–silica coprecipitate has proved better function.1

**Advantages**
The good compressibility and the good compactability properties of chitin–silica allow its use in direct compressions.

**Disadvantages**
Both chitin and chitosan powders show poor bulk density, thus results in poor flowability and compressibility, to overcome this they may be coprecipitated with colloidal silicon dioxide to improve their physical properties.

**Indion 414**
It is ion exchange resin and if used as superdisintegrants, swell on getting hydrated without dissolution and devoid of adhesive tendency cause uniform tablet disintegration.23,24 Model drugs belonging to various classes were taste masked and formulated into palatable tablets. Experiments were carried out to evaluate the disintegrating property of Indion 414 in fast disintegrating dosage form like mouth dissolving tablets they offer better hardness to the tablets on compression. Indion 414 is more effective in hydrophobic formulations, as compared to the conventional disintegrants.25,26

**Advantages**
They do not form lumps, do not stick to tablet press components and are compatible with commonly used active pharmaceutical ingredients as well as other pharmaceutical necessities.1

**Mucilage of Plantago Ovate Seed Husk (Isapghula)**
The mucilage of plantago ovata is a recent innovation for its superdisintegration property. It shows faster disintegration time than the superdisintegrant, Crosspovidone.1

**Modified Polysaccharides**
They are biodegradable, directly compressible, having desirable swelling dynamics. The above modified polysaccharides were further used as superdisintegrants in Roxithromycin fast dispersible tablets and compared with conventional tablets containing MCC. The C-TAG and C-TGG have shown better disintegration for their porous nature, better water intake ability and free flowing property than others.27 Agar (AG) and guar gum (GG), natural polysaccharides are treated with water and co grinded further with mannitol which exhibit superdisintegration property. These modified polysaccharides may call C-TAG (co grinded treated agar) and C-TGG (co grinded treated guar gum) respectively.28,29

**Microcrystalline Cellulose (Avicel)**
Avicel concentration of less than 10%, exhibits better disintegration. This mechanism is depending on entry of water to the tablet matrix through capillary pores, which breaks the hydrogen bonding between adjacent bundles of cellulose microcrystals. With more concentration, particularly in oral disintegrating tablet, it shows a tendency to stick to the tongue due to rapid capillary absorption and faster dehydration of the tablet surface. As Avicel has a fast wicking rate for water, hence this in combination with starch makes an excellent and rapid disintegration in OTD formulations.30-31

**Others**
Although there are many superdisintegrants, which show superior disintegration, the search for newer disintegrants is ongoing and researchers are experimenting with modified natural products, like formalincasein, chitin, chitosan, polymerized agar acrylamide, xylan, smecta, key-jo-clay, crosslinked carboxymethylguar and modified tapioca starch. Studies have suggested that the water insoluble superdisintegrants show better disintegration property than the slightly water soluble agents, since they do not have a tendency to swell. Superdisintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier.
There is no particular upper limit regarding the amount of superdisintegrant as long as the mechanical properties of the tablet are compatible with its intended use. The superdisintegrant may be used alone or in combination with other superdisintegrant.

**SOME APPLICATIONS OF SUPER-DISINTEGRANTS**

**Formulation of Oral Disintegrating Tablet**

One of the major streams of application of superdisintegrants is in the formulation of oral disintegrating tablets/mouth dissolving tablets. An oral disintegrating tablet is a solid dosage form that disintegrates and dissolves in the mouth, either on or beneath the tongue or in the buccal cavity without water, within 60 s or lower. The tablets include silicified microcrystalline cellulose. They are especially suitable for antibiotics.

**Pharmaceutical Superdisintegrants**

Superdisintegrants which provide improved compressibility compared to prior art superdisintegrants. The superdisintegrants include a particulate agglomerate of co-processed starch or cellulose and a sufficient amount of an augmenting agent to increase the compatibility of tablets.

**Mouth Dissolving Tablets**

Mouth dissolve tablets are dosage forms, which when placed in the mouth, disintegrate or dissolve in the saliva within a minute without the aid of water or chewing. Indion 414 is a high-purity pharmaceutical grade weak acid cation exchange resin available as a dry powder in potassium form. It is manufactured in an FDA-approved manufacturing facility. The advantages of ion exchange resins as superdisintegrants as compared to conventional ones are that they swell on getting hydrated but do not dissolve or have an adhesive tendency. Thus the tablet disintegrates evenly. Ion exchange resins are efficient at considerable lower levels than recommended for conventional disintegrants.

**CONCLUSION**

With the improvement in the formulation of Rapid disintegrating tablets, it has now become possible to formulate these tablets with lesser amount of superdisintegrants. Rapidly disintegrating dosage forms have been successfully commercialized by using various kinds of superdisintegrants. With the help of various and different kinds of superdisintegrants patient compliance, commercial and therapeutic benefits has improved. At a time when formulators are faced with increasing numbers of poorly soluble drugs, it is very important to select superdisintegrants that maximize drug dissolution. Due to rapid acceptance of RDTs by patients and pharmaceutical companies, the market for this dosage form is increasing and the product pipeline rapidly, but without the field of superdisintegrants it would not have been possible.
Figure 2: Wicking Action

Figure 3: Deformation

Figure 4: Electrostatic Repulsion
Figure 5: Structure of crosscarmellose sodium

Figure 6: Structure of Sodium starch glycolate

Figure 7: Structure of Crosspyrrolidone
Figure 8: Structure of Polysaccharide

Figure 9: Structure of Gellan Gum

Figure 10: Structure of Alginic Acid

Figure 11: Structure of Chitosan
Table 1: List of Common Disintegrants and Superdisintegrants

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Name of excipients</th>
<th>Category</th>
<th>Conc.</th>
<th>Stability criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alginic acid</td>
<td>Disintegrants</td>
<td>1-5%</td>
<td>Hydrolyzes slowly at room temperature</td>
</tr>
<tr>
<td>2</td>
<td>Colloidal Silicon Dioxide</td>
<td>Disintegrants</td>
<td>5-10%</td>
<td>Hydroscopic, but do not liquefy upon absorption of water</td>
</tr>
<tr>
<td>3</td>
<td>Cross-povidone</td>
<td>Superdisintegrants</td>
<td>2-5 %</td>
<td>As hygroscopic in nature, stored in an air-tight container, in a cool and dry place.</td>
</tr>
<tr>
<td>4</td>
<td>Methyl cellulose</td>
<td>Disintegrants</td>
<td>2-10%</td>
<td>Slightly hygroscopic, but stable</td>
</tr>
<tr>
<td>5</td>
<td>Micro-crystalline cellulose</td>
<td>Superdisintegrants</td>
<td>5-15%</td>
<td>Stable at dry and air tight condition</td>
</tr>
<tr>
<td>6</td>
<td>Starch</td>
<td>Superdisintegrants</td>
<td>5-10%</td>
<td>Stable at dry and air tight condition</td>
</tr>
</tbody>
</table>

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