



A REVIEW: NOVEL SUPERDISINTEGRANTS

Ashok Dalimbe¹, Jaydeep Pawar^{2*}, Shital Bhosale³, Nikita Shinde⁴, Rushikesh tuge⁵

Department Of Pharmaceutics, HSBPVT's GOI College of Pharmacy (Affiliated to Savitribai Phule Pune University), Kashti, Dist. Ahmednagar, 414701, Maharashtra, India.

Abstract

Fast dissolving, fast melting, chewable and orally dissolving or disintegrating tablets are solid dosage forms that disintegrate rapidly and dissolve in the mouth without water. These products have staying power in the marketplace because they appeal to consumers and support increased compliance among users as well as provide effective life-cycle management. The principle challenge with mouth dissolving tablet (MDT) is to develop tablet formulations that deliver rapid disintegration, pleasant mouth feel and high breaking force for tablet robustness. Superdisintegrants affect a range of formulation parameters; including the rate of disintegration, tablet breaking force, and mouth feel, superdisintegrant provides optimal performance in MDT formulations.

Key Words: Superdisintegrants, mouth dissolving tablet (MDT), Disintegrants, Swelling, Deformation etc.

Introduction

Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. 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.[1] 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. Superdisintegrants, are those substances, which facilitate the faster disintegration with smaller quantity in contrast to disintegrants. The disintegration of dosage forms depends upon various physical factors of disintegrants/superdisintegrants which are as follow:

1. Percentage of disintegrants present in the formulation.
2. Proportion of disintegrants used.
3. Compatibility with other excipients.
4. Presence of surfactants.
5. Hardness of the tablets.

6. Nature of Drug substances.
7. Mixing and types of addition. [2, 3]

Researchers these days are looking for a new, safe and effective disintegrating agents which can disintegrate tablets rapidly even at a tablet crushing strength of greater than 3.5 Kg. On analyzing the behavior of disintegration time in the oral cavity as well as wetting time by surface free energy we came to know, that for a faster wetting a molecule should have high polar component of surface free energy and the agents which meet these special requirements are called as superdisintegrants. [4] The ease of availability of these agents and the simplicity in the direct compression process suggest that their use would be a more profitable alternative in the preparation of ODT than the sophisticated and patented techniques. [5]

Superdisintegrants are another version of super-absorbing materials with tailor-made swelling properties. These materials are not planned to absorb significant amounts of water or aqueous fluids, but planned to swell very fast. Superdisintegrants are used as a structural weakener for the disintegrable solid dosage forms. They are physically dispersed within the matrix of the dosage form and will expand when the dosage form is exposed to the wet environment. [6]These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength.[7]Superdisintegrants are generally used at a low level in the solid dosage form, typically 1 - 10 % by weight relative to the total weight of the dosage unit. [8]Their particles are generally small and porous, which allow for rapid tablet disintegration in the mouth without an objectionable mouth-feel from either large particles or gelling. The particles are also compressible which improves tablet hardness and its friability.[6] Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs.[9]

Advantages of Superdisintegrants^{15, 16, 17}

- Remarkable tendency on wetting causing rapid disintegration.
- No lump formation on disintegration.
- Compatible with commonly used therapeutic agents and excipients.
- Does not stick to the punches and dyes.
- Effective in lower concentrations.
- Less effect on compressibility and flow ability.
- More effective intragranularly.
- Some are anionic and may cause some slight in vitro binding with cationic drugs.
- Biodegradable.

Disadvantages of Superdisintegrants

- Expensive.
- Time consuming and fragile.
- More sensitive and hygroscopic in nature.

IDEAL PROPERTIES OF SUPERDISINTEGRANTS ^{17, 19, 20, 21}

- It should produce rapid disintegration.
- It should produce good moulding and flow property.
- It should have good particle size, good hydration capacity and compressibility index.
- It should have poor water solubility.
- It should produce compactable less friable tablets.
- Effective at very low concentration and should have greater disintegrating efficiency.
- Nontoxic and should have good mouth feel.
- It should have no tendency to form complexes with the drugs.
- It should be compatible with the other excipients and should have desirable tableting properties.

Mechanism of Action of Superdisintegrants

There are five major mechanisms for tablet disintegration as follows:-

1. Swelling
2. Porosity and Capillary Action (Wicking)
3. Deformation
4. Enzymatic reaction
5. Due to disintegrating particle/particle repulsive forces

1 Swelling

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 to fall apart. [10]

E.g. Sodium starch glycolate, PlatagoOvata. [11, 12, 13] (Fig.1)

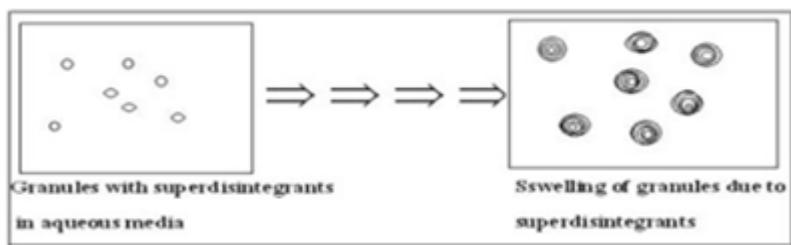
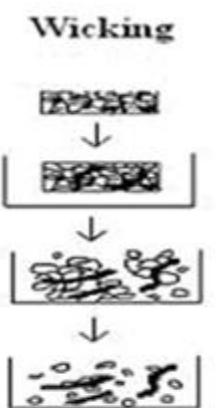


Figure 1 Disintegration by Swelling

2. Porosity and Capillary Action (Wicking)

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the penetration of fluid into tablets. The

disintegrant particles (with low cohesiveness & 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. E.g. Crospovidone, Croscarmellose Sodium. [14] (Fig.2)

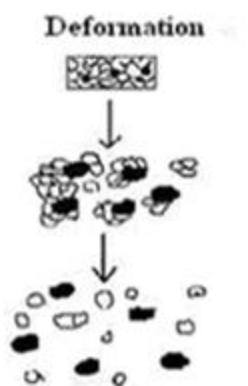


Disintegrant pulls water into the pores and reduces the physical bonding forces between particles

Figure 2 Disintegration by Wicking

3. Deformation

Starch grains are generally thought to be “elastic” in nature meaning that grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tableting, these grains are believed to be deformed more permanently and are said to be “energy rich” with this energy being released upon exposure to water. In other words, the ability for starch to swell is higher in “energy rich” starch grains than it is for starch grains that have not been deformed under pressure. [15] (Fig.3)



Particles swell to precompression size and break up the matrix

Figure 3 Disintegration by Deformation

4. By Enzymatic Reaction

Enzymes present in the body also act as disintegrants. These enzymes debar the binding action of binder and helps in disintegration. Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration. [16] (Fig. 4)

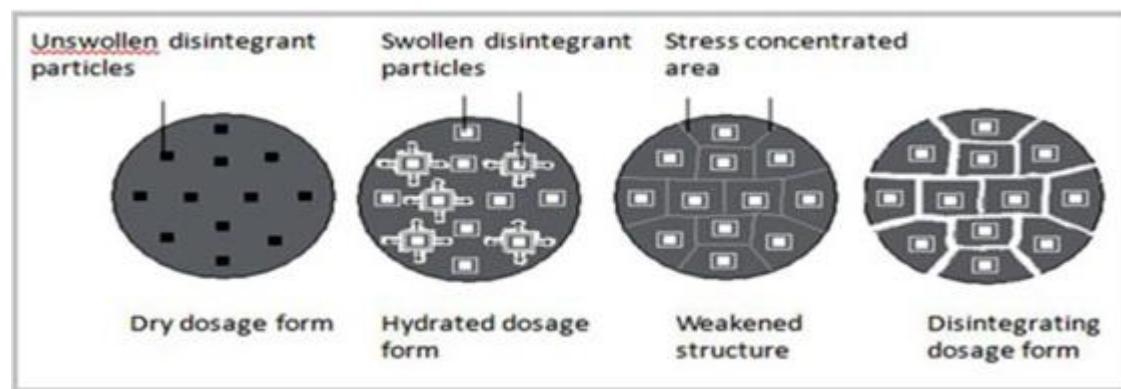


Figure 4 Disintegration by Enzymatic Reaction

5. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with “nonswellable” disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking. It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of inter-relationships between these major mechanisms. [17](Fig.5)

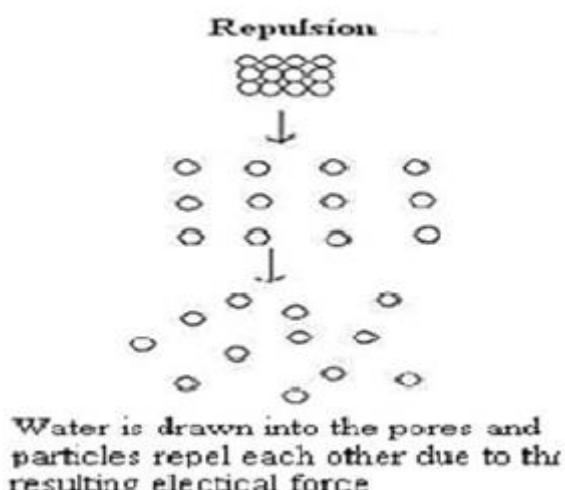


Figure 5 Disintegration by Repulsion

Types of Superdisintegrants

The Superdisintegrants can be classified into two categories on the basis of their availability:

- 1. Natural Superdisintegrants**
- 2. Synthetic Superdisintegrants.**

1. Natural Superdisintegrants

These superdisintegrating agents are natural in origin and are preferred over synthetic substances because they are comparatively cheaper, abundantly available, non-irritating and nontoxic in nature. The natural materials like gums and mucilages have been extensively used in the field of drug delivery for their easy availability, cost effectiveness, Eco friendliness, emollient and non-irritant nature, non-toxicity, capable of multitude of chemical modifications, potentially degradable and compatible due to natural origin. There are several gums and mucilages are available which have superdisintegrating activity. [18]

2. Soy polysaccharide

It is a natural super disintegrant that does not contain any starch or sugar so can be used in nutritional products. Soy polysaccharide (a group of high molecular weight polysaccharides obtained from soy beans) as a disintegrant in tablets made by direct compression using lactose and dicalcium phosphate dihydrate as fillers. A cross-linked sodium carboxy-methyl cellulose and corn starch were used as control disintegrants. Parameters studied were compressibility, friability and disintegration times. Dissolution studies were conducted on tablets containing hydrochlorothiazide as a model drug of low water solubility. Soy polysaccharide performs well as a disintegrating agent in direct compression formulations with results paralleling those of cross-linked CMC at the 2% level and superior to corn starch at the 8% level. Dissolution rates of the drug from tablets were rapid, particularly at the 5% level and were not adversely affected by aging at room temperatures.

2. Isapghula Husk Mucilage (*Plantago ovata*)

Isapghula Husk consists of dried seeds of the plant known as *plantago ovata*. The plant contains mucilage in the epidermis of the seeds. Mucilage of *plantago ovata* has various characteristics like binding, disintegrating and sustaining properties. Mucilage can be used as superdisintegrant to formulate fast dissolving tablets because it has very high percentage of swelling index (around $89 \pm 2.2\%$ v/v) as compared to the other superdisintegrating agents. The rapid disintegration of the FDTs is due to the swelling of superdisintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablet. The rate at which swelling develops and significant force of swelling also determine its disintegrating efficiency. [19, 20]

3. Chitosan

Chitosan is a natural polymer obtained by deacetylation of chitin which is the second most abundant polysaccharides in nature after cellulose. Superdisintegrant property of chitosan has been utilized to develop a fast mouth dissolving tablet by utilizing a novel method of treatment. Similar to the other

superdisintegrants chitosan too generously engulf water when in contact with aqueous media and burst due to the pressure exerted by their capillary action thereby impart instantaneous disintegration of the dosage form and resulting in formation of a uniform dispersion in the surrounding media which behave like a true suspension formed inside the body leading to rapid and complete absorption of drug. [21]

4. Guar Gums

Guar gum is naturally occurring guar seed extract, containing about 80% of galactomannan (guaran), 10% moisture, 5-7% protein and trace amounts of heavy metals and ash. It is free flowing, completely soluble, neutral polymer and is approved for use in food. It is not sensitive to pH, moisture contents or solubility of the tablet matrix. It is not always pure white and sometimes varies in color from off-white to tan tends to discolour with time in alkaline tablets. As a disintegrant, guar gum has been found to be superior to some common disintegrants such as corn starch, celluloses, alginates and magnesium aluminium silicate. Particle size can affect disintegration, with finer particle sizes having greater disintegrating capabilities. It is available in the market under the trade name jaguar. [22, 23]

5. Agar

Agar is the dried gelatinous substance obtained from *Gelidium amansii* (Gelidaceae) and several other species of red algae like, *Gracilaria* (Gracilariaeae) and *Pterocadia* (Gelidaceae). Agar is yellowish gray or white to nearly colorless, odorless with mucilaginous taste and is accessible in the form of strips, sheet flakes or coarse powder. Agar consists of two polysaccharides as agarose and agarpectin. Agarose is responsible for gel strength and Agarpectin is responsible for the viscosity of agar solutions. It is a potential candidate to act as a disintegrant due to its high gel strength. Gums are used in concentration from 1 to 10%. However, these are not as good disintegrating agents as others because capacity development is relatively low. [24]

2 Synthetic Superdisintegrants

A group of superdisintegrants including Croscarmellose sodium (Ac-Di-Sol), sodium starch glycolate (Primogel, Explotab) and crospovidone (Polyplasdone XL) alleviate most of these problems. Use of the superdisintegrants in fast dispersible tablet is possible as tablet shows optimum physical properties. [25]

Advantages of Synthetic Superdisintegrants

- 1 Effective in lower concentrations than starch.
- 2 Less effect on compressibility and flow ability.
- 3 More effective intragrularly. [26]

Limitations of Synthetic Superdisintegrants

- 1 More hygroscopic (may be a problem with moisture sensitive drugs)
- 2 Some are anionic and may cause some slight in-vitro binding with cationic drugs (not a problem in-vivo). [27]
- 3 An acidic medium significantly reduces the liquid uptake rate and capacity of sodium starch glycolate and croscarmellose sodium, but not crospovidone. [28, 29]
3. The degree of swelling of Primogel (sodium starch glycolate) and Polyplasdone XL101 (crospovidone) is minimized following wet granulation formulation. Finally, the medium ionic strength was found to have an adverse effect on the swelling capacity of croscarmellose. [30, 31]

1. INDION 414

The INDION 414 has been used as a superdisintegrant for ODT. It is chemically cross-linked polyacrylic, with a functional group of – COO – and the standard ionic form is K⁺ and is a weak acid cationic exchange resin. It has a high water uptake capacity. It is a high purity pharmaceutical grade weak acid cation exchange resin supplied as a dry powder. It is an extremely effective superdisintegrant which provides the necessary hardness and chemical stability to the tablet. The product swells up to a very great extend when in contact with water or gastrointestinal fluids causing rapid disintegration without the formation of lumps. It is a high molecular weight polymer, therefore it is not absorbed by the human tissues and totally safe for human consumption.

The advantages of Indion 414 as a tablet disintegrant include remarkable swelling tendency on wetting, thus causing rapid disintegration; there is no lump formation on disintegration; and it is compatible with commonly used therapeutic agents and excipients. Indion 414 does not stick to punches and dies.

2. KYRON T-314

KYRON T-314 is “Polacrilin Potassium” which confirms to USP/NF specifications. It is derived from crosslinked polycarboxylic acids and has K⁺ ionic form. It is a very high purity polymer used in pharmaceutical formulations as a tablet super-disintegrant in the oral dosage formulations.

KYRON T-314 is used as:

As Disintegrating agent: Kyron T-314 has a very high swelling tendency of hydration either in contact with water or G.I. fluids causing fast disintegration without the formation of lumps and thus acts as an effective tablet super disintegrant. Required quantity is from 0.5% to 4.0% to get fast disintegration.

As Dissolution Improver: Kyron T-314 breaks the tablets into very smaller particles, thus it increases the effective surface area for the absorption of the active substances and thus it increases the dissolution and bioavailability of the active substances. Required quantity is from 2.0% to 6.0% for dissolution improvement.

Advantages of Kyron T-314 are:

Super rapid Disintegration. Direct compressible grade. Elimination of lump formation. Compatibility with other therapeutic agents- Imparts excellent strength to the tablet and also eliminates the sticking to the dyes and punch. Only 0.4 to 2.0% quantity required. Swelling Index 12. (Cross PVP and Cross carmellose are of Swelling Index 7 and 9 respectively.)

Toxicity: KYRON range is high molecular weight polymer so doesn't get absorbed by body tissues and safe for human consumption. It has no Physiological action at recommended dosage. It is non-toxic.

3. Starch Glutamate: Modified Potato Starch

Superdisintegrants have been developed to improve the disintegration process of the fast dissolving tablets. Superdisintegrants acts as structural weaker in fast dissolving tablets and helps in the quick breakup of the tablet into small particles. A new novel superdisintegrant starch glutamate has been synthesized by esterification process. It was free flowing, amorphous in nature, having good swelling index, excellent flow property.

4. Starch Oxalate

Starch oxalate as a novel superdisintegrant in fast dissolving tablet. Oxalic acid, a strong dicarboxylic acid mainly come from starch, was used to esterify gelatinized corn starch under nonaqueous conditions to give a material with degrees of substitution (DS) ranging from 0.08 to 0.87 depending on the oxalic acid/starch molar ratios used.

5. Starch tartrate

Starch tartrate as novel superdisintegrant by chemical modification of starch upon treating with tartaric acid. More particularly application of this polymer in the design and development of fast disintegrating tablets. The starch tartrate a novel polymer by modification of starch treating with tartaric acid at elevated temperatures.

6. Starch-urea

Cross-linked starch-urea polymer was synthesized by gelatinization of starch in the presence of urea and crosslinking by treatment with calcium chloride. starch-urea-citrate could be used as an excellent super disintegrant.

Cross linked starch - urea, a new starch based polymer has been synthesized and its application in controlled release Cross-linked starch-urea polymer was synthesized by gelatinization of starch in the presence of urea and crosslinking by treatment with calcium chloride. Starch (9 parts) was dispersed in purified water (10 parts) to form starch slurry. Urea (1 part) and calcium chloride (1 part) were dissolved in purified water (40 parts) and the solution was heated to boiling. While boiling, the starch

slurry was added and mixed. Mixing while heating was continued for 20 minutes to form cross-linked starchurea polymer. The mass formed was spread on to a stainless steel plate and dried at 850C for 6-8h. The dried polymer was powdered and passed through mesh No.100.

7. Starch Xanthates

Water-insoluble starch xanthates were prepared by xanthation of highly crosslinked starches under various conditions. After isolation of the products by solvent. Starch xanthate use as a superdisintegrant in the formulation of fast dissolving tablets of poorly soluble drugs.

It is possible to synthesize sodium starch Xanthates from a wide range of native starches, but in practice potato starch is used as it gives the product with the best disintegrating properties. After selection of the appropriate starch source the second step is the crosslinking of the potato starch. This is typically carried out using an FDA approved starch esterifying agent such as sodium trimetaphosphate or phosphorus oxychloride in alkaline suspension. 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 crosslinking is to reduce both the water soluble fraction of the polymer and the viscosity of dispersion in water. The optimum balance between the degree of substitution and the extent of cross-linking allows for rapid water uptake by the polymer without the formation of a viscous gel that might impede dissolution.

8. Crospovidone

Unlike other superdisintegrants, which rely principally on swelling for disintegration, crospovidone use a combination of swelling and wicking. Due to its high crosslink density, crospovidone swells rapidly in water without gelling. Crospovidone particles are found to be granular and highly porous which facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. [32]Larger particles provide a faster disintegration than smaller particles. [33] Crospovidone disintegrants are highly compressible materials as a result of their unique particle morphology. [32]Crospovidone can also be used as solubility enhancer. It is available in two particle sizes in the form of Polyplasdone XL and Polyplasdone XL-10.

9. Croscarmellose Sodium

It is an internally cross linked polymer of carboxymethyl cellulose sodium. It has high swelling capacity with minimal gelling resulting in rapid disintegration. [32] Due to fibrous structure, croscarmellose particles also show wicking action. [35] In tablet formulations, croscarmellose sodium may be used in both direct compression and wet-granulation processes. When used in wet-granulation, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extra-granularly) so that the wicking and swelling ability of the disintegrant is best utilized. [34, 35]

10. Sodium Starch Glycolate

Sodium Starch Glycolate is the sodium salt of a carboxymethyl ether of starch. These are modified starches made by crosslinking of potato starch as it gives the product with the best disintegrating properties. [37] The degree of cross-linking and substitution are important factors in determining the effectiveness of these materials as superdisintegrants.[36]The effect of the crosslinking is to reduce both the water soluble fraction of the polymer and the viscosity of dispersion in water. 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 mechanism by which this action takes place involves rapid absorption of water leading to an enormous increase in volume of granules that result in rapid and uniform disintegration. These are available as explotab and primogel which are low substituted carboxy methyl starches. [22]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. [36]

Method of Incorporation of superdisintegrants

The incorporation of superdisintegrants in the dosage forms are mainly of three types:

1 Intragranular or during granulation

In this process the superdisintegrants are blend with other powders and granulation is carried out. Thus the superdisintegrants are incorporated within the granules.

2 Extragranular or prior to compression

In this process, the superdisintegrants are mixed with prepared granules before compression.

3 Incorporation of superdisintegrants at intra and extra granulation steps

In this process part of superdisintegrants are added to intragranular and a part to extragranules. This method usually produces better results and more complete disintegration than type 1 and type 2. [38]

Applications of Superdisintegrants:

Superdisintigrant used in:

1. Pharmaceutical superdisintigrant: Superdisintegrants which provide improved compressibility compared to prior art superdisintegrants. The superdisintegrants include a particulate agglomerate of coprocessed starch or cellulose and a sufficient amount of an augmenting agent to increase the compactibility of the superdisintigrant.

2. Rapidly disintegrating enzyme-containing solid oral dosage compositions: Invention relates to rapidly disintegrating solid oral dosage forms having an effective amount of an enzyme and a superdisintigrant. The enzyme lactase is claimed in this patent for solid oral formulations.

3. Fast disintegrating tablets: A fast disintegrating tablet comprising Nimesulide and one or more disintegrants. In this research superdisintegrants used are croscarmellose cellulose, crospovidone and sodium starch glycolate.

4. Method of producing fast dissolving tablets: A method of producing a fast-melt tablet. The process does not involve any granulation step, thereby making the process more energy efficient and cost effective. The fast dissolving sugar alcohol is selected from the group comprising: mannitol; sorbitol; erythritol; xylitol; lactose; dextrose; and sucrose. The active component is suitably provided in the form of microparticles or microcapsules having an average diameter of less than 125 microns.

5. Disintegrating Loadable Tablets: A disintegrating loadable tablet product in compressed form. A disintegrant or a mixture of disintegrants has a) porosity of 45% v/v or more, b) a hardness of at least 20 Newton, and c) a loading capacity of at least 30% of a liquid.

6. Rapidly disintegrating tablet: The study relates to rapidly disintegrating tablets intended to be used as orodispersible tablets or dispersible tablets. The tablets include silicified microcrystalline cellulose. They are especially suitable for antibiotics. Rapidly disintegrating tablets which contain amoxicillin and clavulanic acid are also described.

7. Superdisintegrants provide rapid disintegration in oral solid dosage formulations. With its unique particle morphology, Polyplasdone crospovidone is the disintegrant of choice in the following applications:

- In wet granulation tablet processes, polymer, with its small average particle size, is highly effective at rapid disintegration when used intragranularly.
- Polyplasdone disintegrants are highly compressible, thus they are ideally suited for use with poorly compressible drug actives and in direct compression tablet processes.
- As Polyplasdone polymers are non-ionic, they will not form complexes with ionic drug actives that would slow drug release. Recent data show Polyplasdone disintegrants provide fastest dissolution with cationic drug actives in a model tablet formulation.³⁵
- Polyplasdone XL-10 disintegrant is well suited for orally disintegrating and chewable tablet formulations. It provides rapid disintegration, smooth mouth feel and high tablet breaking force with low friability.³⁶
- With poorly soluble drugs, Polyplasdone XL-10 crospovidone increases the rate and extent of dissolution.³⁷

Conclusion

Nowadays Fast Dissolving Tablets have a broader market in Pharmaceutical Industry. FDT'S are mostly used for its fast dissolution and thus by fast absorption and at last immediate action which can be only achieved by using superdisintegrants. The present article revealed about superdisintegrants and their importance in pharmaceutical Industry.

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