Review Article

Traditional and Emerging Disintegrants – A Review

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ABSTRACT

The desire of improved palatability in orally administered products has prompted the development of numerous formulations with improved performance and acceptability. Orally disintegrating tablets are an emerging trend in novel drug delivery system and have received ever-increasing demand during the last few decades. The field has become a rapidly growing area in the pharmaceutical industry and gaining popularity due to ease of administration and better patient compliance especially for geriatric and paediatric patients. This type of property in dosage form can be attained by addition of different excipients, from which disintegrant is the key adjuvant. In recent years, several newer agents have been developed for fast disintegrating action known as super disintegrants. Diverse categories of super disintegrants such as synthetic, natural and co-processed blends etc. have been employed. The objective of the present article is to highlight the various kinds of traditional and emerging disintegrants along with their role in tablet disintegration. This review focuses on various synthetic disintegrants and super disintegrants, natural disintegrants from different plant sources, co-processed disintegrants and their efficiency.

Keywords: Co-processed excipients, Disintegration, Natural and synthetic disintegrants.

INTRODUCTION

Disintegrants are the agents that are added to tablet and some encapsulated formulations to promote the breakup of the tablet and capsule "slugs' into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix. 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 behaviour.[1,2] Most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). The proper choice of disintegrant and its consistency of performance are of critical importance to the formulation development of tablets.[3,4]

Ideal Properties of Disintegrants[5,6]

- Poor solubility
- Poor gel formation
- Good hydration capacity
- Good flow properties
- No tendency to form complexes with the drugs

Method of Addition of Disintegrants[7]

I. Internal Addition (Intra-granular)

II. External Addition (Extra-granular)

III. Partly Internal and External

I. Internal Addition (Intra-granular)

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.

II. External Addition (Extra-granular)

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression.

III. Partly Internal and External

In this method, part of disintegrant can be added internally and part externally. This results in immediate disruption of the tablet into previously compressed granules while the disintegrating agent within the granules produces additional erosion of the granules to the original powder particles.

MECHANISM OF ACTION OF DISINTEGRANTS[8,9]

1. Capillary action (Wicking).

2. Swelling.

3. Heat of wetting.

4. Release of gases.

5. Enzymatic action.

6. Particle repulsive forces.

7. Deformation recovery.

1. Capillary action

Effective disintegrants that do not swell, impart their disintegrating action through porosity and capillary action. Porosity provides pathway for the penetration of

fluid which weakens the intermolecular bond and breaks the compact into fine particles. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles. Fig. 1(a) shows the disintegration of tablet by wicking mechanism.

2. Swelling

Swelling is probably the most widely accepted mechanism of action for disintegrants. Particles of disintegrants swell on coming in contact with suitable medium and a swelling force develops which leads to break-up of the matrix. Porosity and swelling behaviours are inversely proportional to each other i.e., tablets with high porosity show poor disintegration due to lack of adequate swelling force. Fig. 1(b) shows the disintegration of tablet by swelling mechanism.

3. Heat of wetting (air expansion)

When disintegrants with exothermic properties get wetted, localized stress is created due to capillary air expansion, which aids in disintegration. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

4. Release of gases

Internal liberation of CO2 in water occurs due to interaction between tartaric acid and citric acid (acids) with alkali metal carbonates or bicarbonates (bases) which generates the pressure within the compact and facilitate disintegration. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during preparation of the tablets.

5. Enzymatic reaction

Enzymes present in the GIT act as disintegrants by demolishing the binding action of binder and helps in disintegration. Enzymes and its action on binding agents are presented in Table 1.

Table 1: Examples of enzymes as disintegrants

Enzyme	Binder
Amylase	Starch
protease	Gelatin
Cellulase	Cellulose
Invertase	Sucrose

6. Particle repulsive forces

This mechanism is seen in compacts made with non-swellable disintegrants. Water penetrates into compact through hydrophilic pores and breaks the hydrogen bonds and other forces holding the compact together. Fig. 2 (a) illustrates the repulsion mechanism in tablet disintegration.

7. Deformation Recovery

The shape of disintegrant particles is distorted during compression and the particles return to their pre-compression shape upon wetting. This increase in size of the deformed particles causes the tablet to break apart. Figure 2 (b) illustrates the deformation mechanism in tablet disintegration.

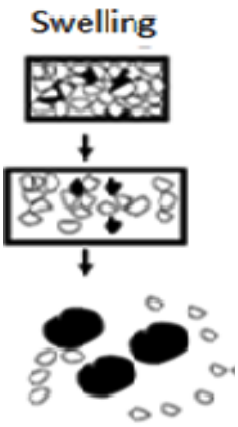

Figure 1(a)

Liquid is drawn up into the pores and rupture the inter particulate bonds causing the tablet to break apart

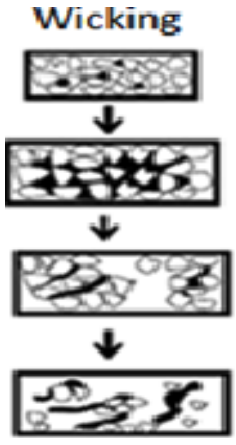

Figure 1(b)

Particles swell, volume increases to break apart the tablet; swelling sets up; localized stress spreads throughout the matrix

Figure 1: Disintegration of Tablets by Swelling and Wicking Mechanism

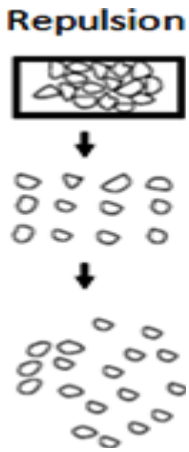

Figure 2 (a)
Water is drawn into the pores and size particles repel each other

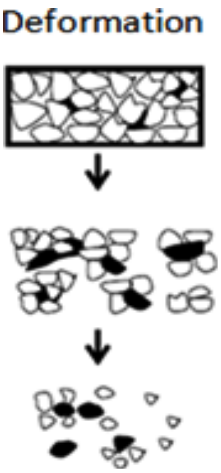

Figure 2(b)
Particles swell to pre-compression and break-up the matrix of the tablet

Figure 2: Disintegration of Tablets by Repulsion and Deformation Mechanism

Table 2: Characteristics of synthetic super disintegrants

Synthetic disintegrants	Mechanism of disintegration	Effective concentration for disintegration	Commercially available grades
Crospovidone	Swelling	1-3% w/w.	Polyplasdone XL, Polyplasdone XL 10, Kollidon CL
Croscarmellose sodium	Swelling	1 - 5% w/w	AC-Di-Sol, Nymce ZSX, Primellose, Vivasol, Solutab
Sodium starch glycolate	Swelling up to 6%. High concentration causes gelling and loss of disintegration.	4-6% w/w	Primo gel, Explotab, Tablo, Vivastar
Pregelatinised starch	Swelling	5 – 10% w/w	PPG Starch,Starch 1500, Colorcon
Ion exchange resins	Wicking	0.5 – 2% w/w	Indion 414, Tulsion 339, Amberlite IRP 88
Chitosan	Wicking	3 – 6% w/w	Chitosan LA, Chitosan AA

Types of Super disintegrants

- ✓ Natural
- ✓ Synthetic
- ✓ Co-processed

Synthetic Disintegrants

Sodium Carboxy methyl Starch (Sodium Starch Glycolate)

These are modified starches with dramatic disintegrating properties and are available as explotab and primogel which are low substituted carboxy methyl starches. 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. After selection of the appropriate starch source the second step is the cross linking of the potato starch.[10,11]

Pregelatinised Starch (Starch 1500)

Pregelatinised starch is a modified starch prepared from potato starch. It is a directly compressible form of starch consisting of intact and partially hydrolyzed ruptured starch grains. It has multiple uses in formulations as a binder and filler.[11,12]

Cross-linked polyvinylpyrrolidone *(crospovidone)*

Crospovidone quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth. Due to its high crosslink density, crospovidone swells rapidly in water without gelling. These are highly compressible materials as a result of their unique particle morphology.[20] In contrast to sodium starch glycolate and croscarmellose sodium, Crospovidone super disintegrants exhibit virtually no tendency towards gel formation, even at high use levels.[1]

Croscarmellose sodium

Croscarmellose sodium is described as a cross-linked polymer of carboxy methylcellulose. A key difference from the chemistry of SSG is that some of the carboxy methyl groups themselves are used to cross-link the cellulose chains.[14,15]

Ion exchange resins

It is highly porous, light weight super disintegrant and is chemically cross-linked polyacrylic acid with standard ionic form is K+. It has several advantages.[16,17]

- Remarkable tendency on wetting causing rapid disintegration.
- No lump formation on disintegration
- Compatible with commonly used therapeutic agents and excipients.
- Work equally effective in hydrophilic and hydrophobic formulations.
- Provides good mechanical strength to the tablet facilitating easy packing and transportation

Chitosan

Chitosan, β (1, 4)2-amino-2-d-glucose, is a cationic biopolymer produced by alkaline N-deacetylation of chitin, which is the main component of the shells of crab, shrimp, and krill. Chitosan engulf water when it is in contact with aqueous media and burst due to the pressure exerted by their capillary action thereby impart instantaneous disintegration of the dosage form.[16]

Advantages of Synthetic Super disintegrants[17]

- Effective in lower concentrations than starch.
- Less effect on compressibility and flow ability.
- More effective intra-granularly.

Limitations

- More hygroscopic
- Some are anionic and may cause slight *in-vitro* binding with cationic drugs (not a problem *in-vivo*).[17]
- Acidic medium significantly reduces the liquid uptake rate and capacity of sodium starch glycolate and croscarmellose sodium
- The degree of swelling of Primojel and Polyplasdone XL101 is minimized in wet granulation formulation. The medium ionic strength was found to have an adverse effect on the swelling capacity of croscarmellose.

Therefore, natural superdisintegrants serve as a better alternative to overcome the shortcomings of these superdisintegrants.[12]

Natural Disintegrants

Various researchers have explored the utility of certain plant-based materials as disintegrants which serve as an alternative to synthetic products due of following reasons[20-22]

- ✓ Local accessibility
- ✓ Eco-friendly
- ✓ Bio-acceptable
- ✓ Renewable source and low price as compared to synthetic products

Plant products which are used as disintegrants fall into two categories[23,24]

1. Water soluble substances - Gums
2. Water insoluble substances - Mucilages

Mucilages as Disintegrants

Ispaghula Husk (Botanical Name: Plantago ovata Family: Plantaginace Common Name: Ispaghula, Psyllium, Isabgul, Isabgol)

It is widely used as herbal medicine in India and is available in market at low cost. Seeds are non toxic, ight brown and oval shaped. It contains a core portion covered by outer husk layer. Separated husk is fibrous in nature which consists of 34% insoluble fiber and 66% soluble fiber. Psyllium husk contains about 30% mucilage, mainly xylose, arabinose and galacturonic acid. Mucilage of P.ovata husk has various characteristics like binding, gelling and suspending.[25-27]

Musa paradisiaca Starch (Botanical Name: Musa paradisiaca Family: Musaceae Common Name: Plantain)

The powders are edible and contain 20-60% starch.[28] Starch extracted from Musa paradisiaca had a light brownish tinge. The whole plant as well as specific parts (Flowers, banana bracts, ripe, unripe fruits, leaves and stems) of plant extract and its active constituents have been used for the treatment of large number of human ailments. Flower consists of tannins, saponins, reducing and non reducing sugars, sterols and triterpenes. Musa paradisiaca starch can be used as a promising pharmaceutical excipient in tablet technology as, it showed adequate binding and disintegrating properties.

Ocimum americanum mucilage (Botanical Name: Ocimum americanum Family: Lamiaceae Common Name: Hoary Basil)

The seeds of Ocimum americanum Linn contain the mucilage around the outer layer. The major problem in isolation of mucilage is that it swells but does not separate from the seeds. The material showed good gelling property and can be used as matrixing agent in sustained release tablets.[29]

Hibiscus rosa-sinensis Linn. Mucilage (Botanical Name: Hibiscus rosa-sinensis Family: Malvaceae Common Name: Shoe Flower)

The plant is available in India in large quantities and its mucilage has been found to act as a superdisintegrant. Mucilage contains L-rhamnose, D-galactose, D-galactouronic acid, and D-glucuronic acid.[30]

Cucurbita maxima pulp powder (Botanical Name: Cucurbita maxima Family: Curcubitaceae Common Name: Pumpkin)

Fruits are variable in size, color, shape, and weight. They have a moderately hard rind, with a thick, edible flesh below, and a central seed cavity. There are numerous seeds in the fruit. Pumpkin seeds are excellent sources in both oil (37.8-45.4%) and protein (25.2-37%) Study revealed that Cucurbita maxima pulp powder have comparable dissolution behaviour to that of sodium starch glycolate.[31]

Lepidium sativum Seed Mucilage (Botanical Name: Lepidium sativum Family: Brassicaceae Common Name: Garden Cress)

It has wide application in pharmaceutical field as disintegrating agent and as herbal medicine. Mucilage has various characteristic like binding, gelling. The extracted mucilage is used to develop fast dissolving tablets. Mucilage is found to be a brownish white powder.[30]

Fenugreek Seed Mucilage (Botanical Name: Trigonella foenum-graecum Family: Fabaceae Common Name: Methi).

Seeds contain a high percentage of mucilage which can be used as disintegrant in mouth dissolving tablets. Mucilage is an off white-cream yellow coloured amorphous powder that quickly dissolves in warm water to form viscous colloidal solution.[23]

Gums as Disintegrants

Gums have been used as disintegrants because of their tendency to swell in water. They can perform good disintegration characteristics (2-10% w/w of tablet weight) and the amount of gum must be carefully titrated to determine the optimum level for the tablet.

Guar Gum (Botanical Name: Cyamopsis tetragonolobus Family: Fabaceae Common Name: Guar)

It is naturally occurring gum (marketed under the trade name jaguar). It is free flowing, completely soluble, neutral polymer composed of sugar units and is approved for use in food. It is not sensitive to pH, moisture contents or solubility of the tablet matrix. It varies in colour from off-white to tan and tend to discolour with time in alkaline tablets.[31]

Gum Karaya (Botanical Name: Sterculia urens Family: Sterciliaceae Common Name: Indian tragacanth)

The gum has an anionic polysaccharide, containing 43%. D-galacturonic acid, 13% D- galactose and 15% L-rhamnose. It absorbs water and swells to 60-100 times their original volume. The high viscosity nature of gum limits its uses as binder and disintegrant in the development of conventional dosage form.[31]

Gellan gum (Organism: Pseudomonas elodea Family: Pseudomonadaceae)

Gellan gum is a linear anionic polysaccharide, biodegradable polymer produced by the microbe Pseudomonos elodea consisting of a linear tetrasaccharide repeat structure. It consists of monosaccharide α-L-rhamnose, β-D-glucuronic acid and β-D-glucose in molar ratio of 1:1:2 linked together to form a linear primary structure. The disintegration of tablet might be due to the instantaneous swelling when it comes into contact with water owing to its high hydrophilic nature.[32]

Xanthan gum (Organism: Xanthomonas campestris Family: Xanthomonadaceae)

Xanthan Gum derived from Xanthomonas campestris is official in USP with high hydrophilicity and low gelling tendency. It has low water solubility and extensive swelling properties for faster disintegration.[33]

Agar (Organism: Gelidium amansii Family: Gelidiaceae)

Agar is the dried gelatinous substance. It is yellowish gray or white to nearly colorless, with mucilaginous taste and is accessible in the form of strips, sheet flakes or coarse powder. It consists of two polysaccharides as agarose and agaropectin. Agarose is responsible for gel strength and Agaropectin is responsible for the viscosity of agar solutions. It is a potential candidate to act as a disintegrant due to its high gel strength.[34]

Co-Processed Disintegrants

New and improved super disintegrants continue to be developed to meet the needs of advanced tablet manufacturing. Until now only super disintegrants are available to prepare the dosage forms, but now days different blend of excipients are available which can give disintegration property.

Co-processed blend is the mixture blend of more than two excipients which satisfy the required quality using different technique like spray drying and freeze drying etc.

Ludiflash

Ludiflash is an innovative, unique co-processed blend of mannitol (90%), crospovidone (5%) and polyvinyl acetate (5%) manufactured in a validated patented process [38]. It disintegrates rapidly within seconds with soft, creamy consistency. It is specially designed for direct compression on standard high speed tablet machine for hard tablet with very low friability.[35,36]

F-melt

F-MELT® is a spray-dried excipient used in orally disintegrating tablets that contain saccharides, disintegrating agent, and inorganic excipient.[37] F-MELT exhibits excellent tabletting properties and facilitates rapid water-penetration for a fast disintegration time.

Pharmaburst

Pharmaburst is a co-processed excipient system, which allows rapid disintegration and low adhesion to punches.[35,38]

Modified chitosan with silicon dioxide

It is based on co-precipitation of chitosan and silica. The physical interaction between chitosan and silica create an insoluble, hydrophilic highly absorbent material, resulting in superior water uptake. Studies have shown that chitosan–silica delivers superior performance in wet granulation formulations and is the only disintegrant that is effective at all concentrations in tablet formulation.[39]

Table 3: Data on applications of mucilages [25-31]

Mucilages used as disintegrants	Drug	Approach used	Results
Lepidium Sativum	Nimesulide	Direct compression	Disintegration time of 17 sec. and mean dissolution time 5.27 sec. at 10% w/w concentration.
Plantago ovata mucilage	Prochlorperazine maleate	Direct compression	Dispersion time of 8 sec. at concentration of 8 % w/w
Hibiscus rosa-sinensis Linn. mucilage powder	Aceclofenac	Direct compression	At concentration of 6 % w/w showed disintegration time of 20 sec.
Fenugreek seed mucilage	Metformin hydrochloride	Direct compression	It shows 15.6 sec. disintegration time and 100% drug release within 18 min. at concentration of 4 % w/w.
Cucurbita maxima pulp powder	Diclofenac sodium	Wet granulation	Disintegration time of 7.23 min. at the concentration of 2.5 % w/w
Ocimum americanum mucilage powder and seed powder	Propranolol hydrochloride	Wet granulation	At concentration of 10 % w/w showed disintegration time of 154 sec.
Muca paradisiacal Starch	Paracetamol	Wet granulation	Tablets showed faster disintegration in 2.5%, 5% and 10% concentrations and found to be better than corn starch

Table 4: Description and applications of Co-processed Excipients

Grade	Description	Applications
Ludiflash	Have mild sweet taste and cooling effect in the mouth. Have superior flowability and low hygroscopicity.	Excellent excipient for direct compression of fast-disintegrating solid oral dosage
F-melt	Highly flowable with spherically dense particles, disintegration time within 30 seconds, less sticking or capping.	Suitable for direct compression manufacturing of fast-dissolving oral tablets
Modified chitosan with silicon dioxide	Water wicking and swelling properties with improved flow and compaction properties.	Acts as superdisintegrant and filler.
Pearlitol SD	Spheronised granulated mannitol. Sweetening power about 40% that of sucrose.	Excellent excipient for direct compression especially for chewable and effervescent tablets.
Mannogem EZ	Excellent compressibility due to its open crystal-line structure. Sweetening power about 50% that of sucrose	Quick dissolve application and an excellent carrier for active moieties which are sensitive to hydrolysis.
Polacrilin Potassium	No lump formation after disintegration. High compatibility with excipients and common therapeutic agent.	Used as a tablet disintegrant and as a taste-masking agent for various drugs.
Glucidex IT	Free-flowing due to fewer fine particles, quick dispersion, and quick dissolution.	Used as diluent for tablet, capsule, used for directly compressible formulation of vitamins and supplement tablets.

Modified Mannitols

Pearlitol 200 SD

It is white, odourless, slightly sweet tasting, crystalline powder. It has a unique blend of exceptional physical and chemical stability, with great organoleptic, non-carcinogenic, sugar-free properties. It can be used in different processes like wet or dry granulation, direct compression, compaction or freeze-drying. It has properties like flowable, excellent compressibility, non-hygroscopic, excellent chemical stability. Pearlitol SD dissolves very rapidly because of its porous crystalline particles.[35]

Mannogem EZ

It is spray dried Mannitol, specially designed for direct compression. It has advantages of highly compatible, non hygroscopic, chemically inert, narrow particle size

distribution and mainly rapid disintegration property. It is highly stable and inert to many of the chemical reactions which are problematic with lactose, microcrystalline cellulose, or starch.[40,41]

Modified sugars

Glucidex IT

It is obtained by moderate hydrolysis of starch and is micro granulated form which enables instantaneous dispersal and dissolution in water.[43]

Modified Resins

Polacrillin Potassium (Tulsion 339)

It is a crosslinked polymer of methacrylic acid and divinylbenzene supplied as potassium salt [60]. Polacrilin potassium is weakly acidic cation exchange resin. On wetting, the resin swells by approximately 150%, thereby causing the compact to disintegrate. Water can exert force between particles within tablet pores, but this force is low. This is used effectively at 1-2% in solid dosage forms because of its feature like.[42]

- ✓ Faster rate of swelling.
- ✓ No lump formation after disintegration / dispersion.
- ✓ High compatibility. With excipients and common therapeutic agent.
- ✓ Does not stick to punches and dies.

All co-processed and modified excipients are playing a vital role in the development of novel dosage forms which are resistant to environmental conditions with improved physical, chemical and mechanical properties as compared to existing excipients, and in solving formulation problems such as flowability, compressibility, hygroscopicity, palatability, dissolution, disintegration, sticking, and dust generation.

CONCLUSION

Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. With the increase demand of novel drug delivery, the fast disintegrating drug delivery system has become one of the mile stone of present investigations. Although, there are many disintegrants and super disintegrants, the search for newer disintegrating agents is ongoing and researchers are experimenting with modified natural products. Studies have suggested that the water insoluble super disintegrants show better disintegration property than the slightly water soluble agents, since they do not have a tendency to swell. Super disintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier. Therefore, there is a huge potential for the evaluation of new disintegrants or modification of an existing disintegrants into super disintegrants, so as to formulate fast dissolving dosage form.

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