

Available online on 15.03.2019 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

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Review Article

Comparative study on effect of natural and synthetic superdisintegrants in the formulation of orodispersible tablets

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ABSTRACT

Now-a-days, Orodispersible drug delivery systems are extensively used to improve bioavailability and patient compliance. Over the past three decades, Orodispersible tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance, improved solubility and stability profiles. ODTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. New ODT technologies address many pharmaceutical and patient needs, ranging from enhanced life-cycle management to convenient dosing for paediatric, geriatric, and psychiatric patients with dysphagia. The therapeutic activity of these formulations is obtained through a typical manner like disintegration followed by dissolution. Hence disintegration has major role for facilitating drug activity. In recent years, several newer agents have been developed known as superdisintegrants. The objective of the present article is to highlight the various kinds of superdisintegrants (Natural & Synthetic) along with their role in tablet disintegration and drug release, which are being used in the formulation to provide the safer, effective drug delivery with patient compliance.

Keywords: ODTs, Orodispersible tablets, Disintegrants, Superdisintegrants, Natural, and Synthetic.

Article Info: Received 28 Jan 2019; Review Completed 03 March 2019; Accepted 06 March 2019; Available online 15 March 2019



Cite this article as:

Gandhi L, Akhtar MS, Comparative study on effect of natural and synthetic superdisintegrants in the formulation of orodispersible tablets, Journal of Drug Delivery and Therapeutics. 2019; 9(2):507-513
<http://dx.doi.org/10.22270/jddt.v9i2.2404>

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INTRODUCTION

Drug delivery through oral route is the most common and preferred route of drug administration both for solid and liquid dosage forms. However, solid dosage forms are popular because of the ease of administration, accurate dosage, self-medication, pain avoidance, and most importantly the patient compliance.¹ Tablets and capsules are the most popular solid dosage forms. However, many people face difficulty in swallowing tablets and hard gelatin capsules. This difficulty in swallowing is called dysphasia.² It has been found that this problem has been encountered in all groups of patient, but especially with pediatric and geriatric populations. Thus, these conventional dosage forms result in high incidence of noncompliance and ineffective therapy with respect to swallowing specially in the case of pediatric, geriatric, or any mentally retarded persons. Orodispersible tablets are also called as orally disintegrating tablets, mouth-dissolving tablets, rapid dissolving tablets, fast-disintegrating tablets, fast-dissolving tablets. Recently, European Pharmacopoeia has used the term orodispersible tablets. This may be defined as uncoated tablets intended to be placed in the mouth where they disperse readily within 3 min before swallowing.³ United States Pharmacopoeia has also approved these dosage forms as orodispersible tablets. Thus, orodispersible tablets are solid unit dosage forms like

conventional tablets, but are composed of super disintegrants, which help them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing.⁴⁻⁸

Due to the presence of super disintegrants, it gets dissolved quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action.⁸ Since the absorption is taking place directly from the mouth, so, bioavailability of the drug increases.⁹ Drugs present in orodispersible tablets are also not suffering from first pass metabolism. This type of drug delivery is becoming popular day by day due to its numerous advantages.

Advantages of ODTs^{10, 11}

1. Quick onset of action and improved bioavailability.
2. Useful for patients who cannot swallow the dosage forms and for pediatric, geriatric and mentally retard patients.
3. Improved patient compliance.
4. Frequently administered when water is not available.
5. Accurate dose can be given as compared to oral liquids.

6. Pleasant mouth feel of the tablet helps to change the perception of medication as bitter pill particularly in pediatric patients.
7. Allow high drug loading.
8. Stability of drug is improved as compared to oral dosage forms like suspensions.
9. Disintegrates rapidly which may result in rapid release of drugs.
10. High production capacity as compared to suspensions.

Properties of Orodispersible tablets ¹⁰

1. No need of water for oral administration.
2. Should have adequate taste-masking properties.
3. Pleasant mouth-feel properties, adequate hardness.
4. Leave little or no residue in mouth after oral administration.
- 5 It should be compatible with taste masking.

6. It allows high drug loading.
7. It should exhibit low sensitivity to environmental conditions such as temperature and humidity.

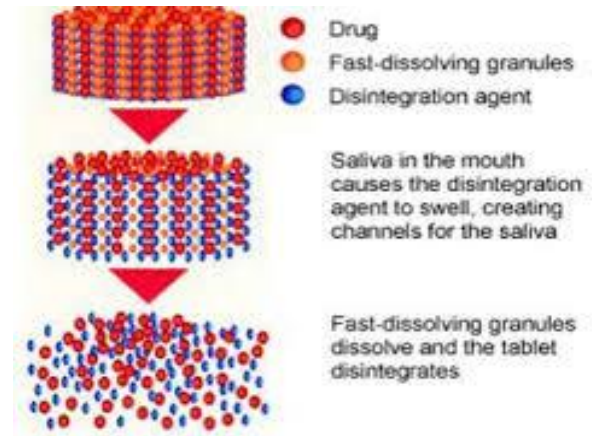


Figure 1: Showing process of fast drug release involving superdisintegrants.

Table 1: Common reasons and conditions for using ODT ¹²

Medication type	Indication
Fast – acting	Pain , fever, heartburn, diarrhoea, migraine, anxiety, insomnia
Compliance critical	Parkinson’s disease, Alzheimer’s disease, psychosis, Schizophrenia, Hypertension, Cholesterol, Transplantation
Paediatric	Cough/cold/allergy, Pain, fever, ADHD

Mechanisms of fast dissolving tablets

To achieve the tablets fast dissolving properties:

1. Water must quickly enter into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet.
2. Incorporation of an appropriate disintegrating agent or highly water soluble excipients in the tablet formulation.

3. There are some under mentioned mechanisms by which the tablet is broken down into the smaller particles and then subsequently result a solution or suspension of the drug.

The mechanisms are

- High swellability of disintegrants
- Chemical reaction
- Capillary action

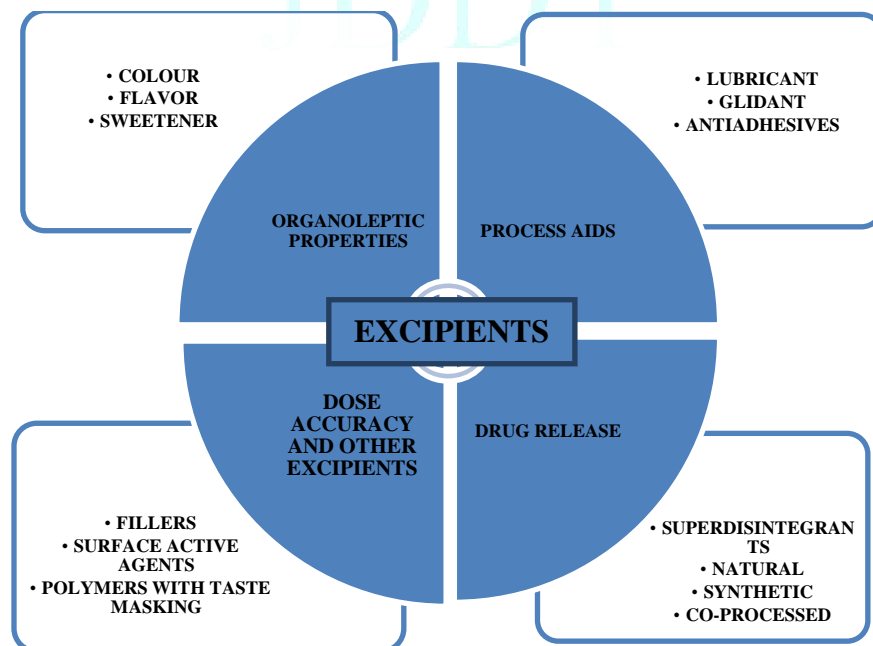


Figure 2: Classification of excipients used in orodispersible tablets¹³

Superdisintegrants

Disintegrating agents are substances routinely included in the tablet formulations to aid in the break-up of the compacted mass into the primary particles to facilitate the dissolution or release of the active ingredients when it is put into a fluid environment. They endorse moisture penetration and dispersion of the tablet matrix. The major function of disintegrants is to oppose the efficiency of the tablet binder and physical forces that act under compression to structure the tablet.

Recently new materials termed as “superdisintegrants” have been developed to improve the disintegration processes.¹⁴ 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.¹⁵ These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. 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. 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. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. Generally, one gram of superdisintegrant absorbs 10-40 g of water or aqueous medium. After absorption, swelling pressure and isotropic swelling of the superdisintegrants particles create stress concentrated areas where a gradient of mechanical properties will exist due to which whole structure will break apart.¹⁵

Selection of Superdisintegrants^{16, 17}

Since superdisintegrant is used as an excipient in the tablet formulation, it has to meet certain criteria other than its swelling properties. The requirement placed on the tablet disintegrants should be clearly defined. The ideal disintegrants should have:

1. Poor solubility.
2. Poor gel formation.
3. Good hydration capacity.
4. Good moulding and flow properties.
5. No tendency to form complexes with the drugs.
6. Good mouth feel.
7. It should also be compatible with the other excipients and have desirable tableting properties.

Mechanism of Superdisintegrants:^{18, 19, 20, 21, 22}

Superdisintegrants are used to improve the efficacy of solid dosage forms. This is achieved by various mechanisms. The mechanism by which the tablets are broken into small pieces and then produces a homogeneous suspension is based on:

- 1) Swelling
- 2) Porosity and capillary action (Wicking)
- 3) Heat of wetting
- 4) Chemical reaction (Acid-Base reaction)

- 5) Particle repulsive forces
- 6) Deformation recovery
- 7) Enzymatic reaction

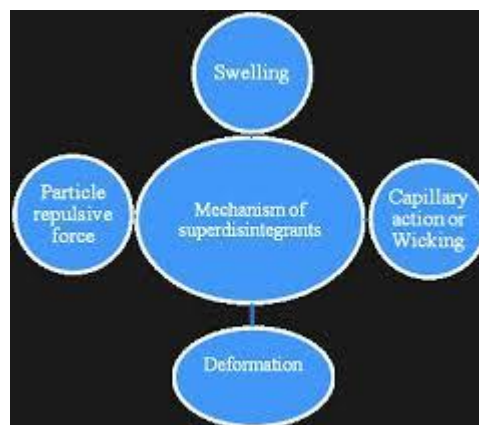


Figure 3: Disintegration mechanism of superdisintegrant materials

Swelling:

Although water penetration is a necessary first step for disintegration, swelling is probably the most widely accepted mechanism of action for tablet 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. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

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. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. 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. 4 shows the disintegration of tablet by swelling and wicking mechanism.

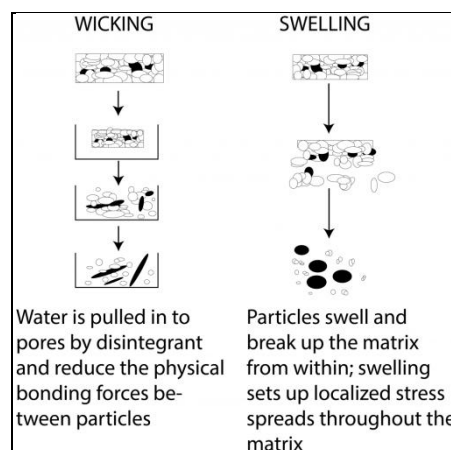


Figure 4: disintegration of tablets by swelling and wicking mechanism

Heat of wetting

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

Chemical reaction (acid base reaction)

The tablet is quickly broken apart by internal liberation of CO₂ in water due to interaction between tartaric acid and citric acid (acids) with alkali metal carbonates or bicarbonates (bases) in presence of water. The tablet disintegrates due to generation of pressure within the tablet. Due to liberation in CO₂ gas, the dissolution of active pharmaceutical ingredients in water as well as taste masking effect is enhanced. 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. The effervescent blend is either added immediately prior to compression or can be added in two separate fraction of formulation. The effervescent blend is added immediately prior to compression or can be added into two separate fraction of formulation.

Particle repulsive forces/ due to disintegrating particle

This is another mechanism of disintegration that attempts to explain the swelling of tablet made with non-swelling disintegrants. According to Guyot-Hermann's particle-particle repulsion theory, water penetrates into tablet through hydrophilic pores and a continuous starch network is created that can convey water from one particle to the next, imparting a significant hydrostatic pressure. The water then penetrates between starch grains because of its affinity for starch surfaces, thereby breaking hydrogen bonds and other forces holding the tablet together. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researcher found that particle repulsion force is secondary to wicking.

Deformation Recovery:

Deformation recovery theory implies that the shape of disintegrant particles is distorted during compression and the particles return to their pre-compression shape upon wetting, thereby this increase in size of the deformed particles causing the tablet to break apart.

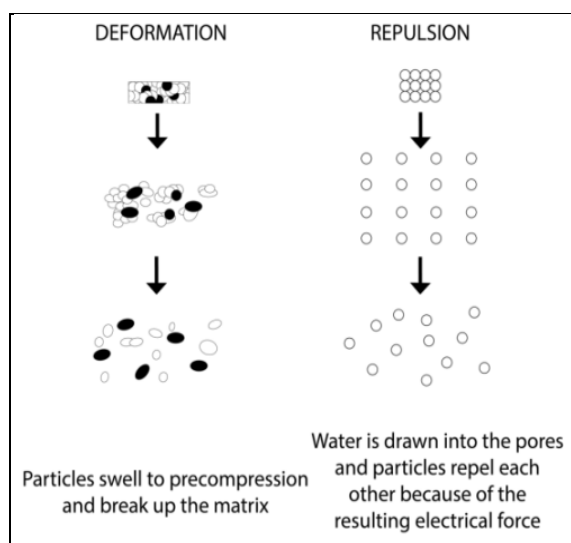


Figure 5: Disintegration of tablets by repulsion and deformation

Such a phenomenon may be an important aspect of the mechanism of action of disintegrants such as Croscopovidone and starch that exhibit little or no swelling. Fig. 5 illustrates the repulsion and deformation mechanism in tablet disintegration.

Enzyme reaction

Enzymes present in the body also act as disintegrants. These enzymes dearth 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.

Type of Superdisintegrant and their example

Two types of Superdisintegrant:

A) Synthetic superdisintegrant

B) Natural superdisintegrant

A) Natural superdisintegrant

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 mucilage's 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 mucilage's are available which have super-disintegrating activity.

Mucilages as Superdisintegrants

Plantago ovata Seed Mucilage (Isapgula)

Isapgula consists of dried seeds of the plant *Plantago ovata* and it contains mucilage which is present in the epidermis of the seeds. The seeds of *Plantago ovata* were soaked in distilled water for 48 hrs and then boiled for few minutes for complete release of mucilage into water. The material was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filtrate so as to precipitate the mucilage. The separated mucilage was dried in oven at temperature less than 60°C. The mucilage of *Plantago ovata* is a recent innovation for its superdisintegration property when compared with Croscopovidone. It shows faster disintegration time than the superdisintegrant, Croscopovidone.

Lepidium sativum Mucilage

Lepidium sativum (family: Cruciferae) is known as asaliyo and is widely used as herbal medicine in India. It is widely available in market and has very low cost. Parts used are leaves, root, oil, seeds etc. Seeds contain higher amount of mucilage, dimeric imidazole alkaloids lepidine B, C, D, E and F and two new monomeric imidazole alkaloids semilepidinoside A and B. Mucilage of *Lepidium sativum* has various characteristic like binding, disintegrating, gelling.

Gum Karaya

Gum Karaya is a negative colloid and a complex polysaccharide of high molecular weight. On hydrolysis it yields galactose, rhamnose and galacturonic acid. Gum Karaya occurs as a partially acetylated derivative. It is a dried exudation of *Sterculia Uren* tree (Family: Sterculiaceae). Its synonyms are Karaya, sterculia, Indian tragacanth, Bassora tragacanth, kadaya, Kadira, katila. Gum

Karaya is compatible with other plant hydrocolloids as well as proteins and carbohydrates.

Fenugreek Seed Mucilage

Trigonella Foenum-graceum, commonly known as Fenugreek, is an herbaceous plant of the leguminous family. It has found wide applications as a food, a food additive, and as a traditional medicine. The leaves and both the ripe and unripe seeds of *Trigonella Foenum-graceum* are used as vegetables. Fenugreek has been used in treating colic flatulence, dysentery, diarrhea, dyspepsia with loss of appetite, chronic cough, dropsy, enlargement of liver and spleen, rickets, gout, and diabetes. It is also used as gastro protective, antiurolithiatic, diuretic, antidandruff agent, Anti-inflammatory agent and as antioxidant. The seed is stated to be a tonic. It also is used in post-natal care and to increase lactation in nursing mothers. Fenugreek seeds contain a high percentage of mucilage (a natural gummy substance present in the coatings of many seeds). Although it does not dissolve in water, mucilage forms a viscous tacky mass when exposed to fluids. Like other mucilage-containing substances, fenugreek seeds swell up and become slick when they are exposed to fluids. The resulting soft mass is not absorbed by the body, but instead passes through the intestines and triggers intestinal muscle contractions.

Guar gum

Guar gum is a galactomannan, commonly used in cosmetics, food products and in pharmaceutical formulations. Guar gum is mainly consisting of the high molecular weight (approximately 50,000-8,000,000) polysaccharides composed of galactomannans and is obtained from the endosperm of the seed of the guar plant, *Cyamopsis tetragonoloba* (L) Taub (Synonym-Cyamopsis sorsaloides). It is used as thickener, stabilizer and emulsifier, and approved in most areas of the world (e.g. EU, USA, Japan, and Australia). Its synonyms are Galactosol; guar flour; jaguar gum; meprogat; meyprodor. It has also been investigated in the preparation of sustained release matrix tablets in the place of cellulose derivatives such as methylcellulose. In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant, and in oral and topical products as a suspending, thickening, and stabilizing agent, and also as a controlled-release carrier. Guar gum has also been examined for use in colonic drug delivery.

Cassia fistula gum

Seeds of Cassia fistula gum obtained from *Cassia fistula* tree. Gum obtained from the seeds of Cassia fistula comprises β -(1 \rightarrow 4) linked d-mannopyranose units with random distribution of α (1 \rightarrow 6) linked d-galactopyranose units as

side chain. Carboxymethylation as well as carbamoylethylation of Cassia gum is reported to improve cold water solubility, improve viscosity and increase microbial resistance as compared to native gum. Therefore, an attempt was made to incorporate calcium or sodium salts of carboxymethylated or carbamoylethylated *C. fistula* gum as superdisintegrant in the formulation development of FDT.

Locust Bean gum

Locust bean gum is extracted from the endosperm of the seeds of the carob tree *Ceretonion siliqua*, which grows in Mediterranean countries. It is also called Carob bean gum. Some other familiar polysaccharides are starch and cellulose, which are made of long chains of the sugar glucose. In locust bean gum, the ratio of mannose to galactose is higher than in guar gum, giving it slightly different properties, and allowing the two gums to interact synergistically so that together they make a thicker gel than either one alone. It shows as a binder and as a disintegrants property at different concentration. Pharmaceutical application of locust bean gum in various novel drug delivery systems. Locust bean gum has been widely used in food industry as a thickening and gelling agent. Locust bean gum has also been reported to have bioadhesive and solubility enhancement properties. There are various reports that Locust bean gum can be used in pharmaceutical and biotechnological purpose.

Hibiscus rosa-sinensis Linn. Mucilage

Hibiscus rosa-sinensis Linn of the Malvaceae family is also known as the shoe-flower plant, China rose, and Chinese hibiscus. The plant is available in India in large quantities and its mucilage has been found to act as a superdisintegrant. The plant contains cyclopropanoids, methyl sterulate, methyl-2-hydroxysterulate, 2-hydroxysterulate malvate and β -rosasterol. The leaves contain carotene (7.34 mg/100 g of fresh material) moisture, protein, fat, carbohydrate, fibers, calcium, and phosphorus. Mucilage of *Hibiscus rosa-sinensis* contains L-rhamnose, D-galactose, D--galactouronic acid, and D-glucuronic acid.

Mango Peel Pectin

Dried mango peel powder is used for extracting pectin. Rather mango peel pectin cannot be used for promising the behavior of superdisintegrants, but due to its good swelling index and good

solubility in biological fluids it can be used to prepare fast dispersible tablets (Shihora H & Panda S, 2011; Mangal M et al., 2012). Various Natural Superdisintegrant along with different drugs and method adopted for their preparation as described in table 2.

Table 2: A list of natural Superdisintegrants used in formulation

Name of drug	Superdisintegrants	Method of compression
Glimepride	Ocimum tenuiflorum	Direct compression
Lisinopril	<i>Plantago Ovata</i> mucilage, Alovera mucilage, Mucilage of hibiscus rosasinesis	Direct compression
Nimesulide	<i>Lipidium sativum</i> (Cruceferae)	Direct compression
Ondansetron HCl	<i>Plantago ovate</i> husk	Direct compression
Fexofenadine HCl	<i>Plantago ovate</i> mucilage, Seed	Direct compression

Synthetic Superdisintegrants:

Synthetic super- disintegrants are frequently used in tablet formulations to improve the rate and extent of tablet disintegration thereby increasing the rate of drug dissolution. The most widely used synthetic superdisintegrants are illustrated below.

Cross-linked polyvinyl Pyrrolidone (Crosopovidone):

Unlike other superdisintegrants, which rely principally on swelling for disintegration, crosopovidone use a combination of swelling and wicking. Due to its high crosslink density, crosopovidone swells rapidly in water without gelling. Crosopovidone particles are found to be granular and highly porous which facilitates wicking of liquid into the tablet and

particles to generate rapid disintegration. Larger particles provide a faster disintegration than smaller particles. Crospovidone disintegrants are highly compressible materials as a result of their unique particle morphology. 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.

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. Due to fibrous structure, croscarmellose particles also show wicking action. 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.

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 31. The degree of cross-linking and substitution are important factors in determining the effectiveness of these materials as superdisintegrants 30. 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 24. 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 30. Table 3 shows a brief description on properties of synthetic superdisintegrants.

Table 3: Characteristics of synthetic superdisintegrants employed in formulation of ODTs ^{23, 24, 25}

Synthetic Superdisintegrants	Properties	Effective Concentration for disintegration
Crospovidone	It is completely insoluble in water. Rapidly disperses and swells in water. Greatest rate of swelling compared to other disintegrants. Greater surface area to volume ratio than other disintegrants. Available in micronized grades if needed for improving state of dispersion in the powder blend. Swelling index- 58±1.5% v/v.	It is used in the range of 1-3% w/w.
Croscarmellose sodium	It is insoluble in water, although it rapidly swells to 4-8 times its original volume on contact with water. Specific surface area- 0.81-0.83 m ² /g. Swelling index- 65±1.7% v/v.	It may be used as a tablet disintegrant at concentration upto 5% w/w, although normally 2 % w/w is used in tablets prepared by direct compression and 3 % w/w in tablets prepared by wet-granulation process.
Sodium starch glycolate	Absorbs water rapidly, resulting in swelling up to 6%. High concentration causes gelling and loss of disintegration. Swelling index- 52±1.2% v/v.	It is used in the range of 4-6%. Above 8%, disintegration times may actually increase due to gelling and its subsequent viscosity producing effects.

Advantages of Synthetic Superdisintegrants:

- Effective in lower concentrations than starch.
- Less effect on compressibility and flow ability.
- More effective intragranularly. However, there are a number of limitations that superdisintegrants practically impose in pharmaceutical applications. For example More hygroscopic (may be a problem with moisture sensitive drugs)

Some are anionic and may cause some slight *in-vitro* binding with cationic drugs (not a problem *in-vivo*) [26]. An acidic medium significantly reduces the liquid uptake rate and capacity of sodium starch glycolate and croscarmellose sodium, but not crospovidone. The degree of swelling of Primojel1 (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. Therefore, natural superdisintegrants serve

as a better alternative to overcome the shortcomings of these superdisintegrants.

CONCLUSION

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 superdisintegrants, the search for newer disintegrating agents is ongoing and researchers are experimenting with modified natural products like formalin casein, chitin, chitosan, polymerized agar acrylamide, xylan, smecta, key-jo-clay, crosslinked carboxymethyl guar, mango peel pectin, cassia tora, cassia nodosa and modified tapioca starch etc. 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. The comparative studies concluded that the use of Natural Superdisintegrant is more advantageous over the synthetic superdisintegrants in the formulation of Orodispersible Tablets.

The use of Natural superdisintegrants serves as a best alternative in the formulation of Fast dissolving tablets.

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