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Review Article

Utilization of Natural Superdisintegrants in Orodispersible Tablets: A Review

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ABSTRACT
Among solid oral dosage forms, tablets have been the most popular dosage form. Nowadays orodispersible tablets are novel form of tablet, which found to be very compatible amongst all category of patients. In recent years, increasing attention has been paid to formulate not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth. The task of developing rapidly disintegrating tablets is accomplished by using a suitable superdisintegrants. The therapeutic activity of these formulations is obtained through a typical manner like disintegration followed by dissolution, in this mechanism disintegration is the key step to disperse the tablet into respected body cavity/fluid. Superdisintegrants are used to improve the disintegration, solubility and efficacy of orodispersible tablets. These agents can be obtained form natural as well as synthetic origin from which the natural form is widely used due to its easy availability, inexpensiveness and safer property. The present review comprises the various kinds of natural Superdisintegrants like Fenugreek seed mucilage and Seed mucilage of Plantago Ovata are discussed in detail along with other examples which are being used in the formulation to increase disintegration and solubility which in turn improves the bioavailability of orodispersible tablets in cheaper, non-toxic and non-irritant way.

Key Words: Natural superdisintegrants, orodispersible, disintegration, bioavailability

INTRODUCTION

Oral route of drug administration is perhaps the most appealing route for the delivery of the drugs. The various dosage forms are administered orally, among them the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquid and capsules. Orodispersible drug delivery is rapidly gaining acceptance as an important new drug delivery technology and their characteristics benefits in terms of patient compliance, rapid onset of action, increased bioavailability (sometimes bi-pass first pass effect) and good stability make these tablets popular as a dosage form of choice. This tablet disintegrates oral disperses in the saliva passes down in the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional dosage form. [1]

Superdisintegrants are the agents 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 behavior.

Desired criteria for fast disintegrating drug delivery system [3-4]:

Fast dissolving tablets should:

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Should be compatible with taste masking.
- Should be potable without fragility concern.
- Allow the manufacture of tablet using conventional processing & packaging equipment at low cost.
- Leave minimal or no residue in the mouth after oral administration.

Figure 1: Disintegration of Orodispersible tablets[2]

Mechanism of Superdisintegrants [5-9]:

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

Swelling [10]: 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) [10]: 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.

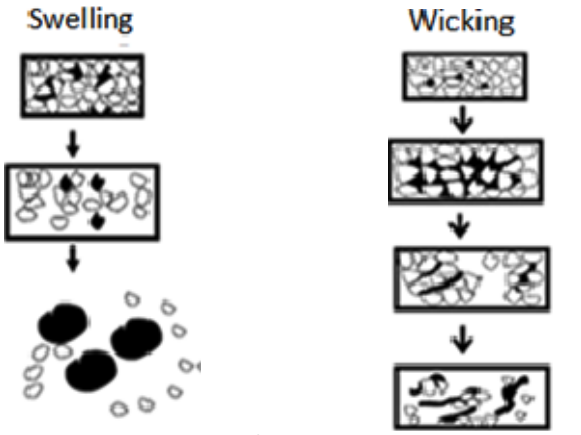

Figure 2 Disintegration of tablets by swelling and wicking mechanism

Heat of wetting [11]**:** 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 agent.

Chemical reaction (Acid-Base reaction) [11]**:** The tablet is quickly broken apart by internal liberation of CO_2 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 CO_2 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.

Particle Repulsive Forces [12]**:** This is another mechanism of disintegration that attempts to explain the swelling of tablet made with non-swellable 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.

Deformation Recovery [13]**:** 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. Such a phenomenon may be an important aspect of the mechanism of action of disintegrants such as Crospovidone and starch that exhibit little or no swelling. Fig. 3 illustrates the repulsion and deformation mechanism in tablet disintegration.

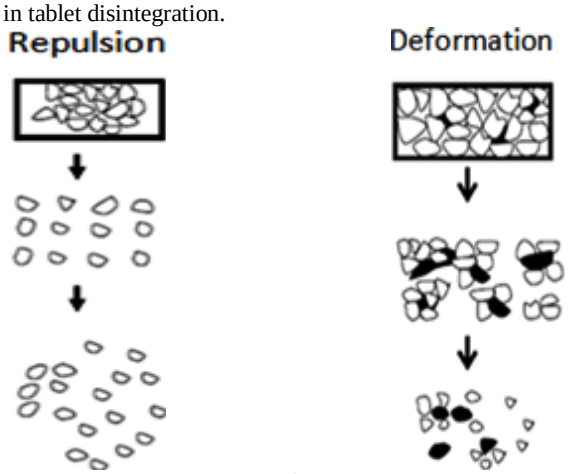

Figure 3 Disintegration of tablets by repulsion and deformation

By Enzymatic Reaction [14]**:** 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.

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. Since from last many years there is more development in the manufacturing processes of mouth dissolving solid dosage forms including changing the process of tablet preparation by wet granulation to direct compression. It requires the development of various functionality excipients, especially superdisintegrants,

which are used to achieve formulations with desired end effects. Nowadays, various kinds of superdisintegrants like synthetic, natural and co-processed blends are used in the mouth dissolving drug delivery system. This article highlights the characteristics and effectiveness of various available superdisintegrants from different sources.

Various method of preparation of ODTs [3, 8, 15, 16]:

Different methods of preparation of orally disintegrating tablets are mentioned below:

1) Lyophilisation or Freeze Drying
2) Moulding
3) Spray Drying.
4) Sublimation.
5) Direct Compression.
6) Cotton Candy Process
7) Mass Extrusion

Direct Compression is the most widely used and method and least time consuming as compared to all other methods.

Types of Superdisintegrants:

The Super-disintegrants can be classified into two categories:

1. Synthetic Super-disintegrants
2. Natural Super-disintegrants

Synthetic super-disintegrants: Synthetic super-disintegrants are frequently used in tablet formulations to increase the rate and extent of tablet disintegration thereby increasing the rate of drug dissolution.

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 invitro binding with cationic drugs (not a problem in-vivo).
- 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 synthetic superdisintegrants.

Natural super-disintegrants: They are natural in origin and are preferred more over synthetic substances because they are comparatively cheaper, abundantly available, non irritating and non toxic 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 super-disintegrating activity.

Table 1 Representing characteristics of synthetic superdisintegrants employed in formulations of ODT [10, 16]

Synthetic Superdisintegrants	Properties	Effective Concentration for disintegration
Crospovidone	It is completely insoluble in water. Rapidly disperse and swells in water. Greatest rate of swelling compared to other disintegrants. Greater surface area to volume ratio than the 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.

PLANTAGO OVATA (ISABGOL) [19,20]**:**

Plantago Ovata Mucilage is used as natural super-disintegrants in the tablet dosage form.

Chemical Constituents

The husk of the seed contains a colloidal mucilage (polysaccharide), mainly consisting of xylose arabinose, galacturonic acid with rhamnose and galactose. Two polysaccharide fractions have been isolated from the mucilage. The first fraction is soluble in cold water containing 20% uronic acid and on hydrolysis yields 46% aldobiouronic acid, 7% L-arabinose and 2% insoluble residue.

The second fraction dissolves in hot water and yields on hydrolysis 3% uronic acid, 80% D-xylose, 14% arabinose, 3% aldobiouronic acid and a trace of D-

galactose. The mucilage is approximately 30% by weight of whole seed. In addition the seed also contains some oil and a small amount of glycoside aucubin and tannin. The seed contain a significant amount of protein (17% to 19%). Chromatographic screening of proteins of the seeds indicated presence of seven amino acids in free and 8 amino acids in bound form.

Medicinal Properties:

Psyllium is used in the treatment of a variety of health conditions. It is an effective ingredient to lower cholesterol & reduce the risk of heart disease. Psyllium is used in treating:

Bleeding hemorrhoids, Boils, Bronchitis, colon cancer, Crohn's Disease, Dysentry, Gallstones, High BP, Irritable Bowel Syndrome (IBS), Stings and insect bites and ulcers.

Uses:

- It is diuretic, Emollient and cooling.
- Used in inflammatory conditions of mucous membrane of gastro intestinal and genitourinary tracts. Very well known as a laxative.
- It restores proper bowel movements and used in treatment of chronic constipation, amoebic and bucillary dysentary.
- As a thickener, it has been used in ice-cream and frozen desserts. Technical grade psyllium has been used as a hydro colloidal agent to improve water retention for newly seeded grass areas & to improve transplanting success with woody plants.

This Plantago Ovata Mucilage is used as superdisintegrant between 2-10 % concentration.

Mechanism: 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.

FENUGREEK SEED MUCILAGE (Trigonella Foenum-graceum) [15, 21, 22, 23]**:**

Fenugreek Seed Mucilage is used as natural superdisintegrants in the tablet dosage form.

Chemical Constituents [21]**:**

Fenugreek seeds contains 45-60% carbohydrates,mainly mucilaneous fiber,(galactomannas), 20-30% proteins high in lysine and tryptophan, 5-10% lipids,pyridine type alkaloids,mainly choline (0.5%).The seeds also contain saponin, fenugrin Bcoumarin compounds,alkaloids and 8% fixed oils.

Uses:

- Fenugreek has been used in treating colic flatulence, dysentery, diarrhoea, dyspepsia with loss of appetite, chronic cough, dropsy, enlargement of liver and spleen, rickets, gout, and diabetes.
- It is also used as gastroprotective, 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 seed is widely used as a galactagogue (milk producing agent) by nursing mothers to increase inadequate breast milk supply. Studies have shown that fenugreek is a potent stimulator of breast milk production and its use was associated with increases in milk production.
- It can be found in capsule form in many health food stores. Several human intervention trials demonstrated that the antidiabetic effects of fenugreek seeds ameliorate most metabolic symptoms associated with type-1 and type-2 diabetes in both humans and relevant animal models by reducing serum glucose and improving glucose tolerance

Fenugreek seed mucilage is used as natural superdisintegrant from 1-7 % concentration.

Mechanism: Fenugreek seed Mucilage is an off white-cream yellow coloured amorphous powder that quickly dissolves in warm water to form viscous colloidal solution.

Table 2 Representing applications of various Mucilages [17,18]

Mucilage (used as superdisintegrants)	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, found better than other synthetic disintegrants like Ac-di-sol and SSG
Plantago Ovata mucilage	Prochlorperazine maleate	Direct compression	Dispersion time of 8 sec. at concentration of 8% w/w
Hibiscus rosa-sinesis Linn. Mucilage powder	Acelofenac	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 gratissimum mucilage powder and seed powder	Metformin hydrochloride	Direct compression	Mucilage powder and seed powder both at concentrations of 5% w/w showed disintegration time of 43 sec. and 45 sec. respectively
Chitosan	Cinnarizine	Wet granulation	Good mouth feel and disintegration time of 60 sec. at the level of 3 % w/w

CONCLUSION

In the present scenario, there is an increase demand of novel drug delivery, and in that 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 natural products like Fenugreek seed mucilage, Plantago Ovata mucilage, Chitosan, Cucurbita pulp powder, Ocimum gratissimum mucilage, Lepidium Sativum etc. Superdisintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier.

Therefore, in coming era, there is going to be continued interest for the development of natural polymers based orally disintegrating tablets. The future trends in innovations of drug delivery systems will continue to bring together different technological disciplines and formulation aspects to create novel technologies.

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