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REVIEW ARTICLE

Natural & Synthetic Superdisintegrants in FDT: A Review

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Abstract

Disintegrants are substances or mixtures of substances added to the drug formulation that facilitate the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants. Recently new materials termed as superdisintegrant have been developed to improve the disintegration processes. Selecting appropriate formulation excipients and manufacturing technology can obtain the design feature of fast disintegrating tablet. The disintegrants have the major function to affect the efficiency of the tablet binder and the physical forces that act under compression to form the tablet. 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. Various natural disintegrants like gum karaya, mucilage of plantago ovata, agar, modified starch and synthetic disintegrants like microcrystalline cellulose, crospovidone, crosscarmellose sodium, sodium starch glycolate etc. have been used in the formulation of fast dissolving tablets. The present review comprises the various kinds of Superdisintegrants like natural and synthetic which are being used in the formulation to provide the safer, effective drug delivery with patient's compliance.

Introduction

The oral route of administration still continues to be the most preferred route due to its diverse advantages including ease of administration, precise dosage, self-medication, versatility and most importantly patient compliance. Therefore, oral solid dosage forms are more popular[1]. Fast dissolving tablets (FDT) are a solid single-unit dosage form that are placed in mouth, allowed to disperse/dissolve in the saliva without the need of water and provides a quick onset of action[2- 4]. Some drugs are absorbed from mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[5]. United States Food and Drug Administration (FDA) defined FDT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tounge". The disintegration time for FDTs generally ranges from several seconds to about a minute6.The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pre gastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets[7].

A disintegrant used in granulated formulation processes can be more effective if used both "intragranularly" and "extragranularly" thereby acting to break the tablet up into granules and having the granules further disintegrate to release the drug substance into solution. 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 such tablets[8]

The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the pediatric and geriatric population, as well as other patients who prefer the convenience of easily swallowable dosage forms. This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva[9]. Most commonly used methods to prepare FDT are freezedrying/lyophilization, tablet molding and direct compression. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva in to the cost-intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentrations of active drug. Molded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern. The main advantages of direct compression are low manufacturing cost and high mechanical integrity of tablets. Therefore, direct compression appears to be a better option for manufacturing the fast disintegrating tablets[10].

SELECTION CRITERIA FOR SUPERDISINTEGRANT

Although superdisintegrants primarily affect the rate of disintegration, but when used at high levels it can also affect mouth feel, tablet hardness and friability. Hence, various ideal factors to be considered while selecting an appropriate superdisintegrants for a particular formulation should:

1. Proceed for rapid disintegration, when tablet comes in contact with saliva in the mouth/oral cavity.
2. Be compactable enough to produce less friable tablets.
3. Produce good mouth feel to the patients. Thus, small particle size is preferred to achieve patient compliance.
4. Have good flow, since it improves the flow characteristics of total blend.[11-12]

Mechanism action of disintegrants:

· By capillary action
· By swelling
· Because of heat of wetting
· Due to release of gases
· By enzymatic action
· Due to disintegrating particle/particle repulsive forces
· Due to deformation

Despite all the theories proposed the Mechanism action of disintegrant is still not completely understood. The rate of water uptake is of critical importance for a number of tablet disintegrants[14].

The three major mechanism affecting tablet disintegrants include water uptake.The combination of swelling; wicking & deformation were found to be the primary action mechanism for tablet disintegrants[15].

Swelling: The swelling of disintegrant is the most widely accepted mechanism for tablet disintegration. One of the mosyt significant factors in the disintegration processes of many formulations in water uptake by capillary forces. The contact with water causes swelling which in consequence reduces the adhesiveness of other excipients in a tablet resulting in a break apart of the tablets constituents.

Two types of swelling are of a particular intrest i.e intrinsic swelling & bulk swelling

Porosity & Capillary Action (Wicking)

Disintegrants do not swell,act through porosity & capillary action .The tablet porosity provides pathways for the penetration of fluids into the tablets. The disintegrants particles (with low cohesiveness & compressibility) themselves enhance the porosity & provide pathways into the tablet. The ability to draw water by pathways created in the particles or by "wicking" through capillary action results in the breakup of the tablet.

Deformation: Starch grains are "elastic" and once deformed under pressure they return to their original shape when the pressure is removed. With compression forces involved in tableting, these grains deform more permanently and a higher ability to swell than starch grains which have not been deformed under pressure.

Three major groups of compounds have been developed which swell to many times their original size when placed in water while producing minimal viscosity effects:

1. Modified Starches- Sodium Carboxymethyl Starch (Chemically treated Potato Starch) i.e. Sodium Starch Glycolate (Explotab, Primogel)

Mechanism of Action: Rapid and extensive swelling with minimal gelling.

Effective Concentration: 4-6%. Above 8%, disintegration times may actually increase due to gelling and its subsequent viscosity producing effects.

2. Cross-linked polyvinylpyrrolidone- water insoluble and strongly hydrophilic. i.e. crospovidone (Polyplasdone XL, Kollidon CL)

Mechanism of Action: Water wicking, swelling and possibly some deformation recovery.

Effective Concentration: 2-4%

3. Modified Cellulose- Internally cross-linked form of Sodium carboxymethyl cellulose. i.e. Ac-Di-Sol (Accelerates Dissolution), Nymcel

Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling.

Effective Concentrations: 1-3% (Direct Compression), 2-4% (Wet Granulation)

ADVANTAGES:[13]

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

Natural superdisintegrants:

Lepidium sativum (family: Cruciferae) is known as asaliyo and 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 etc.[16] Hence a method is developed to isolate the mucilage from seeds and its use to develop the fast dissolving tablet in a study.[17]

***Hibiscus rosa-sinens*:** *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,methylsterculate,methyl_2_hydroxy sterculate, 2_hydroxysterculate malvate and rosasterol. The leaves contain carotene (7.34 mg/100g of fresh material) moisture, protein, fat, carbohydrate, fibers, calcium, and phosphorus. Mucilage of *Hibiscus rosa-sinensis* contains Lrhamnose, Dgalactose, Dgalactouronic acid, and Dglucuronic acid. The percentage yield of mucilage is estimated as 17%. Other physicochemical parameters of mucilage are also evaluated. The results of swelling ratio, angle of repose, bulk density and compressibility index are observed as 9,26.5oC,0.65g/cc, 16% respectively.[18,19]

Trigonella Foenum-graceum : It is commonly known as Fenugreek. Fenugreek is an herbaceous plant of the Leguminous family. 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. Hence, the study revealed that this natural disintegrant (fenugreek mucilage) showed better disintegrating property than the most widely used synthetic superdisintegrants like Ac-di-sol in the formulations of FDT's. Studies indicated that the extracted mucilage is a good pharmaceutical adjuvant, specifically a disintegrating agent.[20]

***Plantago ovata*:** It is also known as 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±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[21,22].

Soy polysaccharide: It is a natural superdisintegrant that does not contain any starch or sugar so can be used in nutritional products. Khalidindi[23] et al 1982 evaluated 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. Soy polysacchardie performs well as a disintegrating agent in direct compression formulations with results paralleling those of cross-linked CMC.[24]

Agar: Agar is the dried gelatinous substance obtained from *Gelidium amansii* (Gelidanceae) and several other species of red algae like, Gracilaria (Gracilariaceae) 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 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 .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[25].

Gellan gum: Gellan gum is a water-soluble polysaccharide produced by *Pseudomonas elodea*, a bacterium. Gellan gum is an anionic, high molecular weight, deacetylated exocellular polysaccharide gum produced as a fermentation product by a pure culture of Pseudomonas elodea2, with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucose residues. Antony et al 1997 studied the Gellan gum as a disintegrant and the efficiency of gum was compared with other conventional disintegrants such as dried corn starch, explotab, avicel (pH 10.2), Ac-di-sol. and Kollidon CL. The disintegration of tablet might be due to the instantaneous swelling characteristics of gellan gum when it comes into contact with water and owing to its high hydrophilic nature. The complete disintegration of tablet was has proved itself as superior disintegrant.[26]

Aloe vera: The genus, Aloe, belongs to the family, Liliaceae, and includes the species *Aloe barbadensis* Miller, commercially known as Aloe vera. Fast dissolving tablets offer the combined advantages of performance, convenience, rapid onset of action and patient compliance and allow administration of an oral solid dose form in the absence of water or fluid intake[27] . When placed on the tongue, it disintegrates instantaneously, releasing the drug which dissolves or disperses in the saliva[28]. They are prepared by techniques such as tablet molding, spray drying, lyophilization, sublimation, or addition of disintegrants[10]. Pharmaceutical formulators often face the challenge of finding the right combination of formulation variables that will produce a product with optimum properties.[29]

Locust bean gum: Locust bean gum also called as carob bean gum is a galactomannan
vegetable gum extracted from the seeds of the Carob tree (Ceretonia siliqua), mostly found in the mediterranean regions. 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 ioadhesive and solubility enhancement properties.[30] Malik K et al carried out formulation and evaluation nimesulide
orodispersible using locust bean gum as superdisintegrant.The gum was evaluated for powder flow properties, swelling index and loss on drying. Excellent powder flow properties were observed, swelling index was found to be 20 sec. which indicated appreciable capability of locust bean gum to be used as superdisintegrant. The prepared tablets were evaluated against standard superdisintegrant i.e. crosscarmellose sodium. Disintegration time of tablets containing 10 % locust bean gum was found to be 13 second.[31]

Cucurbita maxima pulp powder: Cucurbita maxima fruit was cleaned with water to remove dust from surface and further peel was removed. The seed was removed and pulp was put into juicer mixer to form highly viscous liquid. This was further lyophilized to get solid porous mass. Size reduction was done and powder was collected. The collected powder was passed through 80 # sieve and stored for further study. Study revealed that Cucurbita maxima pulp powder have comparable dissolution behaviour to that of sodium starch glycolate. It also has comparable hardness and friability thus the naturally obtained Cucurbita maxima pulp powder stands as a good candidate to act as disintegrant and it is possible to design promising Fast disintegrating tablet using this polymer.[32]
Polysaccharide hydrocolloids including mucilages, gums and glucans are abundant in nature and generally found in many higher plants. Mucilages are merely secondary plant metabolites, but due to the high concentration of hydroxyl groups in the polysaccharide, mucilages generally have a high waterbinding capacity and this has led to studies of their role in plant water relations. It has been suggested that the ability of mucilage to hydrate may offer a mechanism for plants to resist drought [33].Plant products serve as an alternative to synthetic products because of local accessibility, eco-friendly nature, bio-acceptable, renewable source and lower prices compared to important synthetic products. Majority of investigations on natural polymers for disintegrant activity are centered on polysaccharides and proteins, due to their ability to produce a wide range of materials and properties based on their molecular structures. [34]

Mangifera indica gum: Common name of mangifera indica is mango belongig to Anacardiaceae family.It is non toxic and used as disintegrant, binder, suspending agent, emulsifying agent in different formulations. The gum is white to off white in colour to cream colour powder, the powder was soluble in water and practically insoluble in acetone chloroform, ether, methanol and ethanol It is easily available and gum is deviod of toxicity and each and every part of the tree has pharmacological activity

like diuretic, astringent, diabetes, asthma, diahorrea, urethritis, and scabies.[35]

Synthetic Superdisintegrants: Synthetic superdisintegrants 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 polyvinylpyrrolidone (crospovidone, polyplasdone XL, polyplasdone XL 10, kollidon CL)

M.O.A- Swells very little and returns to original size after compression but act by capillary action. Recommended concentration 1 to 3%. Available in micronized grades if needed to improve uniform dispersion in the powder blend. Crospovidone quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth. Unlike other superdisintegrants, which rely principally on swelling for disintegration, crospovidone superdisintegrant use a combination of swelling and wicking. When examined under a scanning electron microscope, crospovidone particles appear granular and highly porous. This unique, porous particle morphology facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. Due to its high crosslink density, crospovidone swells rapidly in water without gelling. Other superdisintegrants have a lower crosslink density and, as a result, form gels when fully hydrated, particularly at the higher use levels in orally disintegrating tablet formulations. Unlike other superdisintegrants which are either poorly compressible or non-compressible, crospovidone disintegrants are highly compressible materials as a result of their unique particle morphology. In contrast to sodium starch glycolate and croscarmellose sodium, crospovidone superdisintegrant exhibit virtually no tendency toward gel formation, even at high use levels. Disintegrants that gel can result in orally disintegrating tablet and chewable products with an unpleasant, gummy texture. Crospovidone superdisintegrant provide the best overall sensory experience as well as rapid disintegration and robust tablets.[36]

Sodium Starch Glycolate: Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is recommended to use in tablets prepared by either direct-compression or wet-granulation processes. The recommended concentration in a formulation is 2-8%, with the optimum concentration about 4% although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.Thedisintegrant efficiency of sodium starch glycolate is unimpaired in the presence of hydrophobic excipients, such as lubricants unlike many other disintegrants. Increasing the tablet compression pressure also appears to have no effect on disintegration time. These are modified starches with dramatic disintegrating properties and are available as explotab and primogel which are low substituted carboxy methyl starches. Explotabconsisting of granules that absorb water rapidly and swell. The mechanism by which this action takes place involves rapid absorption of water leading to an enormous increase in volume of granules result in rapid and uniform disintegration. The natural predried starches swell in water to the extent of 10-20 percent and the modified starches increase in volume by 200-300 percent in water.[37,38]

Low-substituted hydroxypropyl cellulose:

It is preferable in wet granulation and directly compressed tablets. Larger particle size and higher hydroxypropyl content show higher degree of swelling. It is useful to prevent capping. Now a day it is widely used as a super-disintegrate in fast dissolving tablets. Bi *et al* and Watanabe *et al* used microcrystalline cellulose and Low substituted hydroxy propyl cellulose (L-HPC) as disintegrant to prepare rapidly disintegrating tablets. Ratio of the MCC and L- HPC was in the range of 8: 2 – 9: 1 resulted in tablets with shortest disintegration time.[39, 40]

Resins Resins although insoluble, have great affinity for water and hence, act as disintegrant. Moreover, because of their smaller particle size the rate of swelling is high making them superdisintegrant. Like conventional disintegrant, they don‟t lump but additionally impart strength to the tablets. The use of ion exchange resins into drug delivery systems have been encouraged because of their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment. Ion exchange resins are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them.[41]

Croscarmellose sodium : Swells 4-8 folds in < 10 seconds. Swelling and wicking both. High swelling capacity, effective at low concentration (0.5-2.0 can be used up to 5.0%) Croscarmellose sodium is described as a cross-linked polymer of

carboxymethylcellulose. Apart from the differences between the starch and cellulose polymer backbones, there are Differences between the synthetic processes used to modify the polymer. Most importantly, the DS of croscarmellose sodium is higher than that of sodium starch glycolate, and the mechanism of cross-linking is different. The substitution is performed using Williamson's ether synthesis to give the sodium salt of carboxy-methylcellulose. A key difference from the chemistry of sodium starch glycolate is that some of the carboxy-methyl groups themselves are used to cross-link the cellulose chains, the process being accomplished by dehydration. Thus the cross-links are carboxyl ester links rather than phosphate ester links as in Primojel.[42]

Conclusion

It was concluded from the above study that Natural and synthetic superdisintegrants both have better effects on fast dissolving tablets. Fast Dissolving tablets prepared by direct compression method s using natural superdisintegrants in different combination in . From the observed parameters it was concluded that the formulations satisfied all the official requirements. Natural Polymers increased the drug release rate from the tablet, decrease the dissolution and disintegration time, used as binder superdisintegrant, diluent. Natural superdisintegrants are preferred over synthetic superdisintegrants as they are nontoxic, easily available at low cost used in low concentration and as they are naturally extracted provide nutritional supplement. The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet. Disintegrants expand and dissolve when wet causing the tablet to break apart in the digestive, releasing the active ingredients for absorption. They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, thereby facilitating dissolution until fairly recently, starch was the only excipient used as a disintegrant. Rapidly disintegrating dosage forms have been successfully commercialized by using various kinds of superdisintegrants.

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