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Involvement of Natural Superdisintegrants in the Development of Fast Dissolving Tablets

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ABSTRACT: Fast dissolving tablets are those solid dosage forms which disintegrate rapidly when placed on oral cavity. One of the major ingredient present in fast dissolving tablets is the superdisintegrant which is responsible for the rapid disintegration of the tablet. It is added to the tablet, which helps to break-up the intermolecular structure of the tablet. It is prepared by synthetic, semi synthetic and natural source. Natural superdisintegranting agents in fast dissolving tablets are very effective due to their eco-friendly nature as well as these are biocompatible and bio-degradable. These are abundantly and cheaply available from nature. This article describes preparation of various natural superdisintegrants from various natural sources for the development of fast dissolving tablets.

KEYWORDS: Natural superdisintegrant, Fast dissolving tablets, Rapid disintegration, Oral cavity.

I. INTRODUCTION

Tablets are the most popular solid dosage form because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention.[1]

United States Food and Drug Administration (USFDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing a medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue".[1]

Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for the pediatric and geriatric patient.[1] These tablets are solid dosage form containing medical substance which disintegrate rapidly, usually within a few seconds when placed on the tongue requiring no addition water to facilitate swallowing which provide instantaneous disintegration of tablets after placing on tongue, thereby releasing the drug in saliva.[3]

Advantages of fast dissolving tablets:[8]

- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as paediatrics, geriatric and psychiatric patients.
- Patient's compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to water.
- Good mouth feel property of Mouth dissolving drug delivery system helps to change the basic view of medication drugs.
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.

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- Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.

Criteria of fast dissolving tablets:[8]

- Require no water for oral administration, yet dissolve/disperse/disintegrate in mouth in a matter of seconds.
- It should have pleasant mouth feel.
- Should have an acceptable taste masking property.
- It should have sufficient hardness to withstand rigors during manufacturing processes and post manufacturing handling.
- It should allow high drug loading.
- Should leave minimal or no residue in mouth after disintegration.
- Should exhibit low sensitivity to environmental conditions (temperature and humidity).
- Should allow the manufacture of tablet using conventional processing and packaging equipments.
- It should be cost effective.

A "Superdisintegrants" is an excipient, which is added to tablet to aid in the breakup of the compacted mass, when put into a fluid environment. This is especially important for immediate release product where rapid release of the product is required. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. The use of superdisintegrants is the basic approach in the development of fast disintegrating tablets (FDTs). Superdisintegrants plays a major role in the dissolution and disintegration of the tablets.[4]

The fast disintegrating tablets prepared by direct compression method, in general, are based on the action established by natural and synthetic superdisintegrants.[5]

Plant products serve as an alternative to synthetic products because of local accessibility, environment friendly nature and lower prices compared to imported synthetic products. Majority of investigations on natural polymers in drug delivery systems are centered on polysaccharides and proteins. Number of natural, synthetic and semi synthetic polymer materials is used in the various drug delivery systems. Recent trend towards the use of vegetable and non-toxic products demands the replacement of synthetic additives with natural one. The natural materials like gums, mucilages have been extensively used in the field of drug delivery for their easy availability and no side effects.[5]

Advantages of natural superdisintegrants: [6]

- **Biodegradable:** Biodegradable as they are naturally available, and they are produced by all living organisms.
- **Biocompatible and non-toxic:** Basically, all of these plant materials are reiterating sugar polysaccharides.
- **Low cost:** They are cheaper to utilize as natural sources. The production cost is less compared with the synthetic material. India and many other developing countries are dependent on agriculture, and there are substantial amounts of money investment on agricultures.
- **Environmental-friendly processing:** There are many types of natural compounds obtained from different plant sources which are widely utilized in pharmaceutical industry and collected in immensely large quantities due to the simple production processes involved.
- **Local availability (especially in developing countries):** In India and homogeneous developing countries, there is promotion for the production of plants as pharmaceutical excipients being done by government, and it withal provides the facilities for bulk production, like gum and mucilage's because of their wide applications in industries.
- **Patient tolerance as well as public acceptance:** There is less chance of side and adverse effects with natural materials compared with synthetic one.

II. SELECTION OF NATURAL SUPERDISINTEGRANTS:

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 disintegrant should be clearly defined. The ideal disintegrant should have:[2]

1. Poor solubility:[7]

The solubility is an important physical property accompanying by the particles which affect the effectiveness of the disintegrant. In a tablet formulation, solubility of the major component may affect both the rate and mechanism of tablet disintegration. Water soluble materials are more susceptible to dissolve than disintegration, while insoluble materials generally produce rapidly disintegrating tablets. And because of the presence

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of porous structure liquid may drawn up into these pathways via capillary action and results in the breakage of interparticulate bonds cause the tablet to break.

2. Poor gel formation:[7]

When fully hydrated, disintegrants forms gel. For certain formulations they are required in a high level in order to achieve desired tablet disintegration or drug dissolution. As the drug must first diffuse through the gel layer before being released into the body and gel delay dissolution. Disintegration time may increase due to gelling and its subsequent viscosity producing effect, when the concentration become above 8%.

3. Good hydration capacity: [7]

The drugs or other excipients which have a hydrophobic nature, and could be adsorbed on the disintegrant surfaces, may influence the extent of hydration and also the effects of disintegrants. When fast disintegrants, which are having high hydration capacity were added, this problem can be reduced and thus enhance the dissolution.

4. Good compressibility and flow properties:[7]

The powders in the formula for tablet preperation, must attain a consistent particle size distribution and density to achieve proper flow. If the powders have a compressibility of 12-16%, then they are said to be good flow powders.

5. No tendency to form complexes with the drugs:[2]

6. Good mouth feel.[2]

7. It should also be compatible with the other excipients and have desirable tableting properties.[2]

Although some are better than others, the currently marketed superdisintegrants exhibit an optimum combination of properties.[2]

III. MECHANISM OF ACTION OF SUPERDISINTEGRANTS:

1. Swelling:[8]

The most widely accepted general mechanism of action for tablet disintegration is swelling. 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.

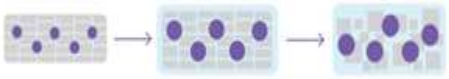

Fig: 1. Swelling

2. Porosity and Capillary Action (Wicking):[8]

Disintegration by capillary action is always the first step. 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.

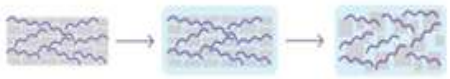

Fig: 2. Wicking

3. Deformation:[8]

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet.

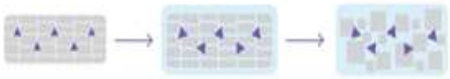

Fig: 3. Deformation

4. Due to disintegrating particle/particle repulsive forces:[8]

Another mechanism of disintegrant attempts to explain the swelling of tablet made with nonswellable disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that no swelling particle also causes disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

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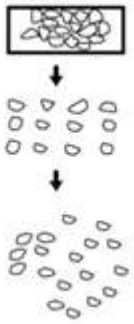

Fig: 4. Repulsion

5. Heat of wetting:[9]

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.

6. Due to release of gases:[9]

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

7. Enzymatic reaction:[9]

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.

8. Combination action:[9]

In this mechanism, the combination of both wicking and swelling action facilitate disintegration.

IV. VARIOUS TYPES OF NATURAL SUPERDISINTEGRANTS PREPARED FROM NATURAL SOURCES:

1. Hibiscus rosa-sinensis mucilage powder:

It is withal called shoe flower plant, China rose, and Chinese hibiscus and belongs to the family Malvaceae. Mucilages are utilized as thickeners, suspending agent, water retention agent, and disintegrants. The plant is facilely available and its leaves contain mucilage and is present in mucilage L-rhamnose, D-galactose, D-galacturonic acid and D-glucuronic acid.[6]

Extraction of mucilage from Hibiscus rosa - sinensis:

The fresh leaves of Hibiscus rosa - sinensis Linn. were collected, washed with water to remove dirt and debris, and dried. The powdered leaves were soaked in water for 5-6 h, boiled for 30 min, and kept aside for 1 h for complete release of the mucilage into water. The material was squeezed from an eight fold muslin cloth bag to remove the marc from the solution. Acetone was added to the filtrate to precipitate the mucilage in a quantity of three times the volume of the total filtrate. The mucilage was separated, dried in an oven at a temperature < 50°C, collected, dried powdered, passed through a sieve (number 80), and stored for further use in desiccators.[5]

Fig: 5. Hibiscus rosa-sinensis

2. Modified gum karaya:

Gum karaya is a vegetable gum produced as an exudate by trees of the genus Sterculia. Chemically, gum karaya is an acid polysaccharide composed of the sugars galactose, rhamnose, and galacturonic acid. The high viscosity nature of gum limits its uses as binder and disintegrant in the development of conventional dosage form. Gum karaya has been investigated for its potential as a tablet disintegrant. Different results showed that modified gum karaya produces rapid disintegration of tablets. Gum karaya can be utilized as an alternative superdisintegrant to commonly available synthetic and semisynthetic superdisintegrants due to its low cost, biocompatibility as well as facile availability.[6]

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Preperation of modifies gum karaya:

Powdered gum was taken in a porcelain bowl and subjected of heating using sand bath for different time periods at different temperatures. The results of swelling capacity and viscosity studies revealed that the modified forms possessed swelling property similar to GK, but viscosity was decreased as a function of temperature and time period of heating. However, it was observed that GK samples were charred, when heated at 140°C. In the preparation of modified form of GK, no further change in viscosity of GK was observed by heating it at 120°C for more than 2h. Hence, these conditions of heating at 120°C for 2h were selected to prepare modified form of GK. The prepared modified form of GK was finally resieved (100 mesh) and stored in airtight container at 25°C.[5]

Fig: 6. Gum karaya

3. Plantago ovata seed mucilage powder:

Psyllium or ispaghula is the prevalent name utilized for several members of the plant genus Plantago whose seeds are utilized commercially for the production of mucilage. Mucilage of Plantago ovata has different characteristics like binding, disintegrating, and sustaining properties. In an investigation fast disintegrating tablets of amlodipine besylate was yare by direct compression method utilizing different concentrations of Plantago ovata mucilage as natural superdisintegrants. All formulations were evaluated for weight variation, hardness, friability, disintegration time, drug content, and dissolution. The optimized formulation shows less in vitro disintegration time of 11.69 seconds with rapid in vitro dissolution within 16 minutes. Invitro disintegration time decreases with increase in concentration of natural superdisintegrant.[6]

Preparation of Isapghula Mucilage powder:

Plantago ovata seeds, were steeped in distilled water for 48 hours before being cooked for a few minutes. To separate the materials, they were squeezed through muslin fabric. The filtrate was then treated with an equivalent volume of acetone to precipitate the mucilage. In a tray drier, the separated mucilage was dried at 40°C. Sieve no. 80 was used to sieve the powdered mucilage. The resulting powder was kept in a desiccator.[10]

Fig: 7. Plantago ovata

4. Dehydrated banana powder:

Banana is additionally called plantain. DBP is yare from the variety of banana called Ethan and nenthran (nenthra vazha) and belongs to the family Musaceae. It contains vitamin A, so it is utilized in the treatment of gastric ulcer and diarrhoea. It withal contains vitamin B6, which avails in reducing the stress and solicitousness. It is a very good source of energy due to high carbohydrate content, and it contains potassium, which is responsible for more preponderant brain functioning.[6]

Preparation of Banana Powder:

Fresh whole bananas, were gathered and weighed after being cleaned of any debris. In 5 minutes, the skinned bananas were soaked in ethanol. The banana was then weighed and squished into a paste, which was then mixed with citric acid (2-3%) to remove the sticky properties. After that, centrifugation and processing are used to separate the water. The compacted bulk is next dried in a tray dryer. To obtain fine powder, the dry ingredients were ground and filtered in a sieve #80.[10]

Fig: 8. Banana

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5. Treated agar:

It is the dried gelatinous substance obtained from Gelidium amansii (Gelidanceae) and several other species of red algae like Gracilaria (Gracilariaceae) and Pterocladia (Gelidaceae). Agar is yellowish-gray or white to proximately colorless, inodorate with mucilaginous taste and is available in the form of divests, sheet flakes, or coarse powder. Agar consists of two polysaccharides, agarose and agar pectin. Agarose is responsible for gel vigor and agar pectin is responsible for the viscosity of agar solutions. High gel vigor of agar makes it a potential candidate as a disintegrants.[6]

Preparation of Treated agar:

Suitable quantity of agar powder (5-10 g) weighed and added in distilled water (100 ml). Agitation was done continuously for 1 day by stirrer to swell the contents. The swollen contents were dried for 3 days at room temperature. The dried powder was ground and passed through sieve no. 100.[12]

Fig: 9. Agar powder

6. Locust Bean Gum:

It is known as carob bean gum. It is a galactomannan vegetable gum extracted from the seeds of carob tree (Ceretonia siliqual) found in Mediterranean region. Locust bean gum is utilized as gelling and thickening agent in food industry and utilized as bio adhesive, and it enhances the solubility. The gum is a white to yellowish-white, odourless powder. It is insoluble in most organic solvents including ethanol. It is partially soluble in water at ambient temperature and soluble in hot water and needs heating to above 850 for 10 min for complete solubility.[6]

Fig: 10. Locus bean

7. Fenugreek Seed Mucilage powder:

Trigonella foenum-graceum commonly kenned as 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). Albeit 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 more preponderant disintegrating property than the most widely used synthetic superdisintegrants like Ac-di-sol in the formulations of FDTs. Studies betokened that the extracted mucilage is a good pharmaceutical adjuvant and concretely a disintegrating agent.[6]

Extraction of Mucilage powder:

The seeds were powdered using pestle and mortar and 100 g of the powder was extracted with hexane to remove lipophilic compounds using a soxhelet apparatus. To remove pigments and to deactivate enzyme, the defatted powder was boiled in ethanol for 20 min. This treated powder was then soaked in 10 litres water and the pH was adjusted to 3.5 using 0.5 M Hydrochloric acid. The mixture was stirred by a mechanical stirrer for 12 h and then filtered through filtration paper. The filtrate was centrifuged (5000 g) and the supernatant was concentrated in vacuum to 50% of its initial volume. The resulting solution was mixed with the same volume of 96% ethanol and stored in a refrigerator for 4 h. The precipitated mucilage was separated by centrifugation (5000 g). The collected mucilage was re-suspended in distilled water, agitated for 20 min and re-precipitated one more time to eliminate chloride ions and other impurities. Finally the residue was washed with diethyl ether and acetone and dried overnight at 45°C, resulting in an off-white powder.[11]

Fig: 11. Fenugreek seed

8. Mango Peel Pectin:

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Mango peel which constitutes 20–25% of the mango processing waste was found to be a good source for the extraction of pectin of good quality, felicitous for the preparation of film, and acceptable jelly. Pectin is an in volute heteropolysaccharide which is a hydrophilic colloid and found that mango peel pectin stands as a good candidate as superdisintegrant, though not as more strong than synthetic superdisintegrants, but due to its good solubility and higher swelling index, it may be utilized in the formulation of fast dispersible tablets.[6]

Isolation of pectin:

Dried mango peel powder was used for extracting pectin using Soxhlet apparatus. Round bottom flask containing acidified water [water acidified (pH 2) using 0.5 N citric acid] was heated continuously at 75°C for 7-8 h after start of first siphon cycle. Powder to solvent ratio was 1:8. After heating period was over, mixture was passed through two fold muslin cloth and cooled to room temperature. Double amount of ethyl alcohol was added to solution with continuous stirring for 15 min. Mixture was kept for 2 h without stirring. Pectin was precipitated and filtered through 4-layered muslin cloth. Precipitate was washed 2-3 times by ethyl alcohol, to further remove any remaining impurity. Finally, precipitate was kept for drying at 35-40°C in hot air oven, sieved (#80) and stored in desicator until use.[12]

Fig: 12. Mango peel

9. Lepidium sativum Mucilage:

Lepidium sativum (family: Cruciferae) is kenned as Asaliyo and is widely utilized as herbal medicine in India. It is widely available in market and has very low cost. Components used are leaves, root, oil, seeds, and so forth. Seeds contain higher amount of mucilage, dimeric imidazole alkaloids lepidine B, C, D, E, and F, and two incipient monomeric imidazole alkaloids, semilepidinoside A and B. Mucilage of Lepidium sativum has different characteristics like binding, disintegrating, gelling, and so forth.[6]

Isolation of Mucilage from Lepidium Sativum:

The seeds of Lepidium sativum contain the mucilage around the outer layer. The seeds were boiled with distilled water for 15 min and the mass was filtered through Buckner funnel without filter paper and the retained residue was boiled with distilled water for 15 min and the combined liquid was passed through eight folds of muslin cloth. Then the mucilage was precipitated from the filtrate by adding ethanol. The precipitated mucilage was dried in oven at 45° C till it was completely dried. The dry powder was passed through 80 mesh sieve and stored in dissector.[14]

Fig:13. Lepidium sativum

10. Ficus Indica Fruit Mucilage:

The mucilage of ficus indica fruit is utilized as superdisintegrant which is obtained from the pulp of fruit ficus indica. Ficus indica is an astronomically immense tree up to 3 meters and very fast-growing with spread branches and arial roots. The fruits of ficus indica are of the size of cherry. It has nutritional as well as medicinal value. The dried and uncooked ficus indica fruit gives 230 kcal (963 KJ) of energy per 100 gm or 3.5 oz. (ounce). It is utilized in assuaging fever, pain, inflammation, wound rejuvenating, blood quandaries, and urinary quandaries.[6]

Extraction of fruit mucilage:

The fruits were crushed and soaked in water for 5-6 hours, boiled for 30 minutes and left to stand for 1 hour to allow complete release of the mucilage in to the water. The mucilage was extracted using multi-layer muslin cloth bag to remove the marc from the solution. Acetone (in the volumes of three times to the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40˚c, collected, grounded and passed through a #80 sieve and stored in desiccator at 30˚C.[15]

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Fig: 14. Ficus indica fruit

V. CONCLUSION:

The increase demand of novel drug delivery, FDTs has become one of the milestone of the present investigation. Development of FDTs are aimed to increase performance of dosage form by decreasing it's disintegration time. Superdisintegrant plays an vital role to achieve better and fast disintegration of FDTs. In which natural superdisintegrant have more preponderant effects on FDTs than synthetic superdisintegrant. This article attempts to unveil the strategies to prepare various natural superdisintegrants from different natural sources for the development of FDTs. That are used to improve efficacy of tablet by decreasing it's disintegration time which in turn enhance drug's dissolution rate. Natural superdisintegrants are preferred over synthetic superdisintegrants as they are non toxic, available at low cost, patient tolerance as well as public acceptance and they are naturally extracted, also provide nutritional supplement. The disintegrating properties of hibiscus rosa-sinensis mucilage powder, treated agar, Plantago ovata and so on are studied in comparison to artificial superdisintegrants. Thus natural superdisintegrant exhibit increased bioavailability and improved patient compliance. Thus the natural superdisintegrants can be efficaciously utilizes as disintegrants in tablet formulations.

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