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A BRIEF REVIEW ON DISINTEGRANTS

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ABSTRACT

Disintegrating agents is a substance or mixture of substances added to tablets to facilitate its break up or disintegration. The active constituents must be released from the tablet as efficiently as possible to allow its rapid action. Hence the therapeutic action is based on the amount of drug released from the tablet, these disintegrants which allows rapid de-aggregation of solid in to solution and followed by which absorption of the drug takes place. Most of the conventional and in novel preparation the impact of disintegrating agents had given a new dosage form such as rapid disintegrating tablets and mouth dissolving tablets. By fair choice of the disintegrating agents which has a greater impact in the final formulation to enhance the drug bio-availability.

KEY WORDS: Disintegration, Bio-availability, Hydration, Swelling.

1. INTRODUCTION

Despite increasing interest in controlled-release drug delivery systems, the 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 disintegrants or super disintegrants and its consistency of performance are of critical importance to the formulation development of such tablets. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants (Alekha,2002). In more recent years, increasing attention has been paid to formulating 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 (Bi al yen,1995). Disintegrants are substances or mixture of substances added 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 (Antonyi,1997). Super-disintegrants 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. Examples of super disintegrants are Croscarmellose, Crosprovidone, Sodium starch glycolate which represent example of Cross-linked cellulose, Cross-linked polymer and a Cross-linked starch respectively (Hector,2000). 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. Number of factors affects the disintegration behavior of tablets. The development of fast dissolving or disintegrating tablets provides an opportunity to take an account of tablet disintegrants. Recently new materials termed as super disintegrants 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 oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet. The stronger the binder, the more effective must be the disintegrating agents in order for the tablet to release its medication (Onali,1998). Ideally, it should cause the tablet to disrupt, not only into the granules from which it was compressed, but also into powder particles from which the granulation was prepared.

1.1 Ideal characteristics of disintegrants: 1.Poor solubility, 2.Poor gel formation, 3.Good hydration capacity, 4.Good molding and flow properties, 5.No tendency to form complexes with the drugs

1.2 Method of addition of disintegrants: Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment.

There are two methods of incorporating disintegrating agents into the tablet:

1.Internal Addition (Intra-granular), 2.External Addition (Extra-granular), 3.Partly Internal and External

In external addition method, the disintegrants is added to the sized granulation with mixing prior to compression. In Internal addition method, the disintegrants is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrants is incorporated within the granules. When these methods are used, part of disintegrants can be added internally and part externally. This provides

immediate disruption of the tablet into previously compressed granules while the disintegrating agent within the granules produces further erosion of the granules to the original powder particles. The two step method usually produces better and more complete disintegration than the usual method of adding the disintegrants to the granulation surface only (Botzalakis and Dngsburger,1988)

1.3 Mechanism of disintegration: The mechanism by which the tablets are broken into small pieces and then produces a homogeneous suspension is based on:

a.By Porosity and Capillary Action, b.By swelling, c.Because of heat of wetting, d.Due to disintegrating particle/particle repulsive forces, e.Due to deformation, f.Due to release of gases, g.By enzymatic action.

1.3.1. 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. The disintegrants particles (with low cohesiveness & compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the inter-particulate bonds causing the tablet to break apart.

1.3.2. Swelling: Although not all effective disintegrants swell in contact with water, swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart (Korunubhum,1973).

1.3.3. Because of heat of wetting (air expansion): When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps 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 (Liberman,1989).

1.3.4. Due to disintegrating particle or particle repulsive forces: Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause 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 (Liberman,1989).

1.3.5. Due to deformation: It had proved that 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. This may be a mechanism of starch and has only recently begun to be studied. Starch grains are generally thought to be "elastic" in nature meaning that grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tabulating, these grains are believed to be deformed more permanently and are said to be "energy rich" with this energy being released upon exposure to water. In other words, the ability for starch to swell is higher in "energy rich" starch grains than it is for starch grains that have not been deformed under pressure.

1.3.6. Due to release of gases: 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.

1.3.7. By enzymatic reaction: Here, enzymes presents in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in 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. The classical example of the earliest known disintegrants is Starch. Corn Starch or Potato Starch was recognized as being the ingredient in tablet formulations responsible for disintegration as early as 1906 (even though tablet disintegration was itself not given much importance in tablet formulations until much later). Until fairly recently, starch was the only excipient used as a disintegrants. To be effective, corn starch has to be used in concentrations of between 5-10%. Below 5%, there

is insufficient "channels" available for wicking (and subsequent swelling) to take place. Above 10%, the incompressibility of starch makes it difficult to compress tablets of sufficient hardness.

Although the connection between bioavailability of drug and tablet disintegration took some time to become appreciated, it is now accepted that the role of the disintegrants is extremely important.

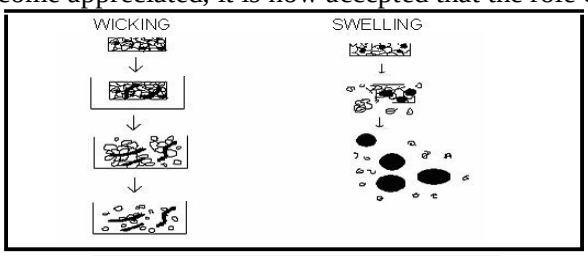

Fig: 1 Mechanism of Disintegration through Capillary and Swelling

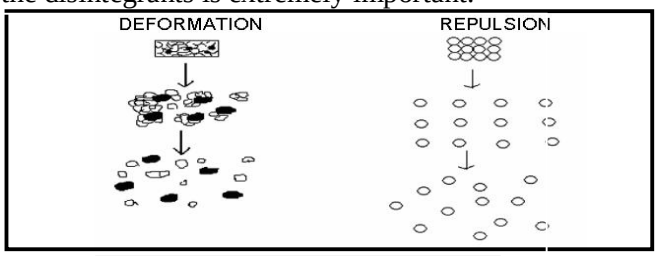

Fig: 2 Mechanism of Disintegration through Deformation and Repulsion

Other factors which affect the dissolution of Drugs from tablets are: *Type and Concentration of Active Ingredient, *Type and Concentration of Binder Used, *Type and Concentration of Fillers Used (soluble vs. insoluble), *Type and Concentration of Lubricant Used, *Type of Dissolution testing Used (Apparatus, Speed, Media), *Manufacturing Process (wet granulation vs. compaction vs. direct compression)

In a direct compression process, drug is blended with a variety of excipients, subsequently lubricated and directly compressed into a tablet. A disintegrants used in this type of formulation, simply has to break the tablet apart to expose the drug substance for dissolution.

In a wet granulation process, the drug substance is combined with other excipients and processed with the use of a solvent (aqueous or organic) with subsequent drying and milling to produce granules. The resulting granules are then blended with additional excipients prior to being compressed into a tablet. A disintegrants used in granulated formulation processes can be more effective if used both "intra-granularly" and "extra granularly" thereby acting to break the tablet up into granules and having the granules further disintegrate to release the drug substance into solution. However, the portion of disintegrants added intra-granularly (in wet granulation processes) is usually not as effective as that added extra granularly due to the fact that it is exposed to wetting and drying (as part of the granulation process) which reduces the activity of the disintegrants. Since a compaction process does not involve its exposure to wetting and drying, the disintegrants used intra-granularly tends to retain good disintegration activity.

1.4.Factors affecting action of disintegrants: *Percentage of disintegrants present in the tablets, *Types of substances present in the tablets, *Combination of disintegrants, *Presence of surfactants, *Hardness of the tablets, *Nature of Drug substances, *Mixing and Screening.

1.4.1. Effect of fillers: The solubility and compression characteristics of fillers affect both rate and mechanism of disintegration of tablet. If soluble fillers are used then it may cause increase in viscosity of the penetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agents and as they are water soluble, they are likely to dissolve rather than disintegrate. Insoluble diluents produce rapid disintegration with adequate amount of disintegrants. Tablets made with spray dried lactose (water soluble filler) disintegrate more slowly due to its amorphous character and has no solid planes on which the disintegrating forces can be exerted than the tablet made with crystalline lactose monohydrate.

1.4.2. Effect of binder: As binding capacity of the binder increases, disintegrating time of tablet increases and this counteract the rapid disintegration. Even the concentration of the binder can also affect the disintegration time of tablet.

1.4.3. Effect of lubricants: Mostly lubricants are hydrophobic and they are usually used in smaller size than any other ingredient in the tablet formulation. When the mixture is mixed, lubricant particles may adhere to the surface of the other particles. This hydrophobic coating inhibits the wetting and consequently tablet disintegration. Lubricant has a strong negative effect on the water uptake if tablet contains no disintegrants or even high concentration of slightly swelling disintegrants. On the contrary, the disintegration time is hardly affected if there is some strongly swelling disintegrants are present in the tablet. But there is one exception like sodium starch glycolate whose effect remains unaffected in the presence of hydrophobic lubricant unlike other disintegrants.

1.4.4. Effect of surfactants: Sodiumlaurylsulphate increased absorption of water by starch or had a variable effect on water penetration in tablets. Surfactants are only effective within certain concentration ranges. Surfactants are recommended to decrease the hydrophobicity of the drugs because the more hydrophobic the tablet the greater the disintegration time. Disintegration time of granules of water-soluble drugs did not seem to be greatly improved by the addition of nonionic surfactant during granulation, but the desired effect of a surfactant appeared when granule were made of slightly soluble drugs. The speed of water penetration was increased by the addition of a surfactant (Jia Ai Allen Zhang and Mark Christensen,1996).

1.5 Disintegrants used in tablets

1.5.1.Starch: Starch is the oldest and probably the most widely used disintegrants in the pharmaceutical industry. Regular cornstarch USP, has certain limitation and has been replaced to some extent by modified starches with specialized characteristics to serve specific functions. The mode of action of starch is that the disintegrants forms pathways throughout the tablet matrix that enable water to draw into the structure by capillary action, thus leading to disruption of tablet. Other concept relates to swelling of starch grains on exposure to water, a phenomenon that physically ruptures the particle – particle bonding in tablet matrix (Caramella,1987).

1.5.2. Sodium starch glycolate: These are modified starches with dramatic disintegrating properties and are available as explotab and primogel which are low substituted carboxy methyl starches. Explotab consists 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 pre-dried starches swell in water to the extent of 10-20 percent and the modified starches increase in volume by 200-300 percent in water. This modified starch is that the disintegration time may be independent of compression force; the tablets formulated by using these disintegrants were disintegrated within two minutes. The higher dissolution rates observed with super-disintegrants may be due to rapid disintegration and fine dispersion of particles formed after disintegration (Noor Fitrah,1996).

1.5.3.Cross-linked polyvinyl pyrrolidone (crosprovidone): The Cross linked polyvinyl pyrrolidone and evaluated as tablet disintegrants and compared to Starch USP and Alginic acid. The capillary activity of Cross povidone for water is responsible for its tablet disintegration property. Cross linked PVP has maximum moisture absorption and hydration capacity and can be considered for the selection of new disintegrants. They possess apparent binding property resulting in low percent of tablet friability, where it is employed as disintegrants even in low concentration 0.5 to 5 percent. Alesandro (2001) formulated fast dissolving composition of Ibuprofen tablet by using 0.5 to 10 % linear Polyvinyl pyrrolidone with respect to Ibuprofen. The tablet was dissolved completely into solution in 10 minutes

1.5.4.Alginates: Alginates are hydrophilic colloidal substances extracted from certain species of Kelp. Chemically they are available as alginic acid or salt of alginic acid. Alginic acid is a polymer derived from seaweeds comprising D-mannuronic and L-glucoronic units. Its affinity for water absorption and high sorption capacity make it an excellent disintegrants. It can be successfully used with ascorbic acid, multivitamins formulation (Noor Fitrah,1996).

1.5.5.Cellulose: Cellulose such as purified cellulose, Methylcellulose, Cross-linked sodium carboxy methyl cellulose (Ac-Di-Sol) and Carboxymethylcellulose are disintegrants to some extent depending on their ability to swell on contact with water. A cross-linked form of Ac-Di-Sol has been accepted as tablet disintegrants and it is essentially water insoluble. It has high affinity for water, which results in rapid tablet disintegration (Blank,1990).

1.5.6. Microcrystalline cellulose: Microcrystalline cellulose exhibits good disintegrants property at low as 10 percent concentration. It functions by allowing water to enter the tablet matrix by means of capillary pores, which break the hydrogen bonding between adjacent bundles of cellulose microcrystal's. Tablets with excess microcrystalline cellulose have a tendency to stick to the tongue due to rapid capillary absorption and dehydrating the most surface. Microcrystalline cellulose has a fast wicking rate for water, hence this and starch makes an excellent combination for effective and rapid disintegration in tablet formulation. To develop a rapidly disintegrating tablet, a mixture of MCC and L-HPC was in the range of 8:2 – 9:1 shown shortest disintegration time. MCC was used as disintegrating agent in the formulation of fast releasing compressed propranol hydrochloride suppositories as reported by Malladi (1993). The concentration of MCC Shows faster drug release from suppository and evaluated their pharmacokinetics and pharmacodynamics performance and

compared the result obtained with oral administration (Chilamkurti,1983).

1.5.7.Ambrelite Ipr88 (ion exchange resins): Ion exchange resin has ability to swell in the presence of water. When used as a disintegrants care must be taken that many resins have the ability to absorb drug particles. Anionic and Cationic resins have been used to absorb substances and release them when the charge changes (Medwick and Bailey,1998).

1.5.8.Gums: Gums have been used as disintegrants because of their tendency to swell in water. They can display good binding characteristics (1 to 10 percent of tablet weight). This property can oppose the desired property of assisting disintegration and the amount of gum must be carefully titrated to determine the optimum level for the tablet. Common gums used as disintegrants include Agar, Locust bean, Karaya, Pectin and Tragacanth (Bhargava,1991).

1.5.9.Guar gums: It is naturally occurring gum (marketed under the trade name jaguar). It is free flowing, completely soluble, neutral polymer composed of sugar units and is approved for use in food. It is not sensitive to pH, moisture contents or solubility of the tablet matrix. It is not always pure white and sometimes varies in color from off-white to tan tends to discolor with time in alkaline tablets. It is used as disintegrants in the range of 0.5-5% showed rapid rate disintegration due to swelling of the gum.

1.5.10.Gum Karaya: Karaya has the natural gum exudates from the traces of *Sterculia urens* belonging to family sterculiacea. The high viscosity nature of gum limits its uses as binder and disintegrants in the development of conventional dosage form (Sallam,1998).

1.5.11.Chitin and chitosan: Chitin and chitosan obtained from marine sources. Chitin a structural constituent in the sheels of crutacean and insect has an acylated polyamine, which is biodegradable and non-toxic. It is the most abundant natural polymer after cellulose. Chitin and Chitosan as disintegrants in paracetamol tablets were evaluated and compared with four commonly used disintegrants such as corn starch, sodium starch glycolate, methyl cellulose and croscarmellose sodium, reported by Ritthidej(1994). Tablets containing Chitosan shows faster disintegration, greater dissolution and are slightly softer than those containing Chitin. An increment in concentration of these polymers causes markedly faster disintegration and better dissolution. Tablet containing seven percent Chitosan disintegrate within one minute which was much faster than those containing sodium starch glycolate and croscarmellose sodium. Moisture sorption and water uptake was found the major mechanism of disintegration while dissolution related to swelling capacity (Bhargava,1991).

1.5.12.Smecta: Smecta is clay mostly composed of smectile, a non-fibrous Attapulgite (magnesium aluminium phyllosilicate), belonging to the family montomorillonite. Its layered leaf like structure consists of aluminium and octahydral layers sandwiched between two tetrahydral silica layers. Smecta has a large specific area and high affinity for water. Smecta was found more adsorptive than other anti-diarrheal clays, as fibrous attapulgite and kaolin. Smecta is evaluated as disintegrants in tablet made by compression and by wet granulation using lactose, dicalciumphosphate as water soluble and water insoluble fillers. An inorganic clay, magnesium aluminum silicate (Veegum), modified starch, Ac-di-sol and cross linked PVP as a disintegrants evaluated by Bhargava(1991). Smecta performed well as a disintegrants in tablet superior to Veegum and starch, but inferior to Ac-di-sol and cross linked PVP.

1.5.13. Gellan gum: It is a linear anionic polysaccharide, biodegradable polymer obtained from *Pseudomonos elodea* consisting of a linear tetra-saccharide repeat structure and use as a food additive. Antony (1997) studied the Gellan gum as a disintegrants and the efficiency of gum was compared with other conventional disintegrants such as dried corn starch, explotab, Microcrystalline cellulose (pH 102), 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 observed within 4 minutes with gellan gum concentration of 4%w/w and 90%of drug dissolved within 23 min. (Andries F Marais,2003).

1.5.14. *Isapghula husk*: It is a natural substance as disintegrants. It consists of dried seeds of the plant known as plantago ovata. It contains mucilage which is present in the epidermis of the seeds. The mucilage is used as binding agent in the granulation of material for compressed tablets. *Plantago ovata* seeds husk has high swellability and gives uniform and slightly viscous solution hence it is used as thickening and suspending agent. Gupta and Gaud (2000) has investigated the disintegrating property of the *isapghula husk*, *cassia tora* and *cassia nodosa* and the formulations were evaluated for the standard of dispersible tablets and were

compared with marketed products. The study shown that the natural gums used as disintegrants were effective in low (5%) concentrations.

1.5.15. Polacrillin potassium (tulsion): Tulsion (339) is a resin consisting of highly purified cross-linked polacrillin copolymer in potassium form. It is used as a tablet disintegrants and as a taste-masking agent for various drugs. when tulsion-339 is used as disintegrants, it swells up at very fast rate upon contact with water or gastro intestinal fluid and act as an effective tablet disintegrants. It is to be added in a dry form in the proportion of 0.5 to 5% of the total weight of tablet, amount may vary depending upon nature of tablet. polacrillin potassium is high molecular weight polymer so can't be absorbed by body tissues & is safe for human consumption. It has no any physiological action at recommended dosage & it is non-toxic. Specific features of tulsion-339 as a disintegrants: a.Faster rate of swelling, b.No lump formation after disintegration/ dispersion, c.High compatibility With excipitients and common therapeutic agent, d.Does not stick to punches and clays.

1.5.16. 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 available 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. High gel strength of agar makes it a potential candidate as a disintegrants. Ito et.al investigated the use of agar powder as a disintegrating agent for the development of rapidly disintegrating oral tablets. Agar was chosen because it absorbs water and swells significantly but do not become gelatinous in water at physiological temperature (Medwick and Bailey,1998).

1.5.17. Gas–evolving disintegrants: Another approach for the disintegration of tablet is inclusion of citric acid and tartaric acid along with the sodium bicarbonate, sodium carbonate, potassium bicarbonate or calcium carbonate. These react in contact with water to liberate carbon dioxide that disrupts the tablet. Onali (1998) described the process of making rapidly disintegrating tablets. The tablets consisting of malic acid or effervescence base, calcium carbonate as an active ingredient (antacid) and cornstarch as a bulking agent and disintegrating agent. The tablets prepared from these ingredients disintegrated within 20 second. (Chilamkurti,1983).

Table.1 List of disintegrating agents

Disintegrantsss	Concentration In Granules (%W/W)	Special Comments
Starch USP	5-20	Higher amount is required, poorly compressible
Starch 1500	5-15	-
Microcrystalline cellulose® (PH 101, PH 102)	10-20	Lubricant properties and directly compressible
Solka floc®	5-15	Purified wood cellulose
Alginic acid	1-5	Acts by swelling
Na alginate	2.5-10	Acts by swelling
Explotab®	2-8	superdisintegrants.
Polyplasdone®(XL)	0.5-5	Crosslinked PVP
Amberlite® (IPR 88)	0.5-5	Ion exchange resin
Methyl cellulose, NaCMC, HPMC	5-10	-
AC-Di-Sol®	1-3	Direct compression

2. CONCLUSION

Selecting appropriate formulation excipients and manufacturing technology can obtain the design feature of fast disintegrating tablet. The disintegrants have the major function to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet. The stronger the binder, the more effective must be the disintegrating agents in order for the tablet to release its medication. Ideally, it should cause the tablet to disrupt, not only into the granules from which it was compressed, but also into

powder particles from which the granulation was prepared. Disintegrants prepared by intra and extra granulation method was found to be the most effective as they disintegrate rapidly when compared to other disintegrants, and the percentage drug release also shows a higher dissolution profile.

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