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Emerging Trends of Disintegrants used in Formulation of Solid Dosage Form

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Abstract

Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. An oral solid dosage form should ideally disperse into the primary particles from which it was prepared.Tablets and capsules which need rapid disintegration, the inclusion of the right disintegrant is a prerequisite for optimal bioavailability. Superdisintegrants are used to improve the efficacy of solid dosage forms. This is achieved by decreasing the disintegration time which in turn enhances drug dissolution rate.Disintegrants are substances or mixture of substances added the drug formulation that facilitates the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants. 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. Examples of Superdisintegrants are crosscarmelose, crosspovidone, sodium starch glycolate which represent example of a crosslinked cellulose, crosslinked polymer and a crosslinked starch respectively. With the increase demand of novel drug delivery, the fast dissolving/ disintegrating drug delivery system has become one of the mile stone of present investigations. The development of fast dissolving or disintegrating tablets provides an opportunity to take an account of tablet disintegrants. The disintegrants have the major function to appose 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. The present study comprises the various kinds of disintegrants and superdisintegrant, which are being used in the formulation to provide the safer, effective drug delivery with patient's compliance.

Key words: Disintegrants, Polymers, Na-CMC, sodium alginate.

Introduction

Disintegrants are 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 thereby 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. In recent years, several newer agents have been developed known as "Superdisintegrants". These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. 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 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 appose 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 are an essential component to tablet formulations. While rapidly disintegrating tablets do not necessarily ensure fast bioavailability, slowly disintegrating tablets almost always assure slow bioavailability. The ability to interact strongly with water is essential to disintegrant function. Combinations of swelling and/or wicking and/or deformation are the mechanisms of disintegrant action. Super disintegrants offer significant improvements over starch. But hygroscopicity may be a problem in some formulations. 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. However, the portion of disintegrant added intragranularly (in wet granulation processes) is usually not as effective as that added extragranularly due to the fact that it is exposed to wetting and drying (as part of the granulation process) which reduces the activity of the disintegrant. Since a compaction process does not involve its exposure to wetting and drying, the disintegrant used intragranularly tends to retain good disintegration activity.

Method of addition of disintegrants:

There are two methods of incorporating disintegrating agents into the tablet:
A. Internal Addition (Intragranular)
B.External Addition (Extragranular)
C.Partly Internal and External

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In Internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules. When these methods are used, part of disintegrant 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 disintegrant to the granulation surface only.

Mechanism of superdisintegrants

There are four major mechanisms for tablets disintegration as follows:

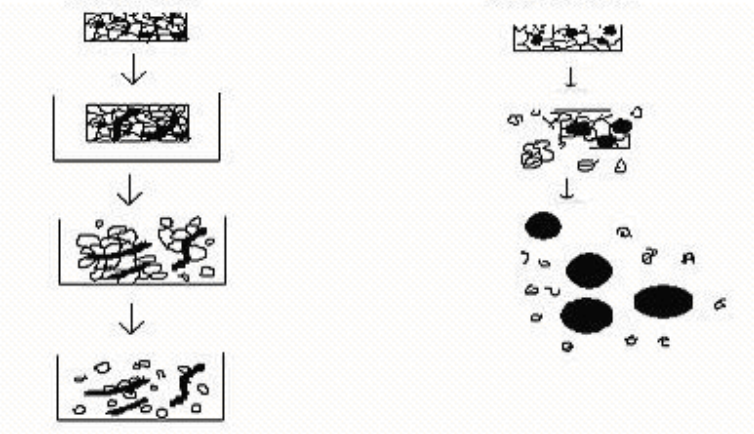
1. *Swelling:*

Perhaps 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. 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.

2. *Porosity and capillary action (Wicking):*

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.

WICKING SWELLING



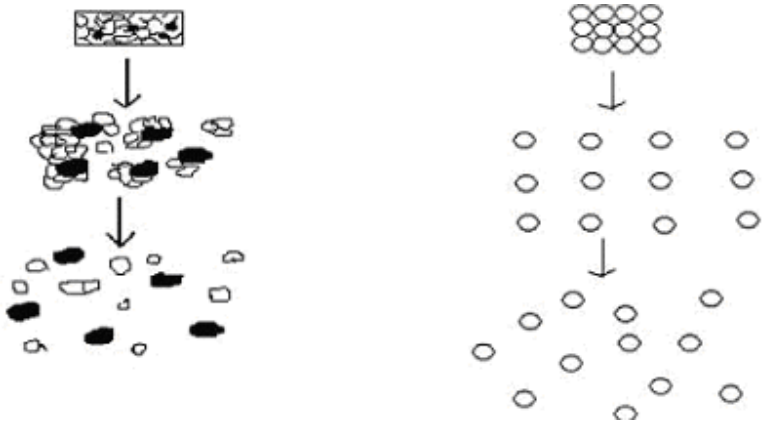
Water is pulled by disintegrant and reduced the physical bonding force between particles

Particles swell and break up the matrix form within

3. *Due to disintegrating particle/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 nonswelling 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.

4. *Due to deformation.*
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 break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

DEFORMATION REPULSION



Particles swell to precompression size and break up matrix

Water is drawn into pores and particles repel each other because of Resulting electrical force

Types of disintegrants

Starch
Starch was the first disintegrating agent widely used in tablet manufacturing. Before 1906 potato starch and corn starch were used as disintegrants in tablet formulation. However, native starches have certain limitations and have been replaced by certain modified starches with specialized characteristics. The mechanism of action of starch is wicking and restoration of deformed starch particles on contact with aqueous fluid and in doing so release of certain amount of stress which is responsible for disruption of hydrogen bonding formed during compression. Lowenthal & Wood proved that the rupture of the surface of a tablet employing starch as disintegrant occurs where starch agglomerates were found. The conditions best suited for rapid tablet disintegration are sufficient number of starch agglomerates, low compressive pressure and the presence of water. The concentration of starch used is also very crucial part. If it is below the optimum

concentration then there are insufficient channels for capillary action and if it is above optimum concentration then it will be difficult to compress the tablet.

Pregelatinized starch

Pregelatinized starch is produced by the hydrolyzing and rupturing of the starch grain. It is a directly compressible disintegrants and its optimum concentration is 5-10%. The main mechanism of action of Pregelatinized starch is through swelling.

Modified starch

To have a high swelling properties and faster disintegration, starch is modified by carboxy methylation followed by cross linking, which is available in market as cross linked starch. Mechanism of action of this modified starches are rapid and extensive swelling with minimum gelling. And its optimum concentration is 4-6 %. If it goes beyond its limit, then it produces viscous and gelatinous mass which increases the disintegration time by resisting the breakup of tablet. They are highly efficient at low concentration because of their greater swelling capacity.

Table.1. List of disintegrants

DISINTEGRANTS	CONCENTRATION IN GRANULES (%W/W)	SPECIAL COMMENTS
Starch USP	5-20	Higher amount is required, poorly compressible
Starch 1500	5-15	-
Avicel®(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	Sodium starch glycolate, superdisintegrant.
Polyplasdone®(XL)	0.5-5	Crosslinked PVP
Amberlite® (IPR 88)	0.5-5	Ion exchange resin
Methyl cellulose, Na CMC, HPMC	5-10	-
AC-Di-Sol®	1-3	Direct compression
2-4	Wet granulation	
Carbon dioxide	_	Created insitu in effervescent tablet

Cellulose and its derivatives

Sodium carboxy methylcellulose (NaCMC and CARMELLOSE sodium) has highly hydrophilic structure and is soluble in water. But when it is modified by internally crosslinking we get modified crosslinked cellulose i.e. Crosscarmellose sodium which is nearly water insoluble due to cross linking. It rapidly swells to 4-8 times its original volume when it comes in contact with water.

Microcrystalline cellulose (MCC)
MCC exhibit very good disintegrating properties because MCC is insoluble and act by wicking action. The moisture breaks the hydrogen bonding between adjacent bundles of MCC. It also serves as an excellent binder and has a tendency to develop static charges in the presence of excessive moisture content. Therefore, sometimes it causes separation in granulation. This can be partially overcome by drying the cellulose to remove the moisture.

Alginates
Alginates are hydrophilic colloidal substances which has high sorption capacity. Chemically, they are alginic acid and salts of alginic acid. Alginic acid is insoluble in water, slightly acidic in reaction. Hence, it should be used in only acidic or neutral granulation. Unlike starch and MCC, alginates do not retard flow and can be successfully used with ascorbic acid, multivitamin formulations and acid salts of organic bases.

Ion-exchange resin
Ion exchange resin (Ambrelite®IPR-88) has highest water uptake capacity than other disintegrating agents like starch and Sodium CMC. It has tendency to adsorb certain drugs.

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 disintegrant include agar, locust bean, karaya, Pectin and tragacanth.

Gum Karaya
Karaya has the natural gum exudates from the traces of Sterculia urens belonging to family sterculiacea. Chemically the gum has an anionic polysaccharide, containing 43%. D-galacturonic acid, 13% D-galactose and 15 percent L-rhamnose. The high viscosity nature of gum limits its uses as binder and disintegrant in the development of conventional dosage form.

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 make it a potential candidate as a disintegrant.

Ambrelite IPR 88 (Ion Exchange Resins)
Ion exchange resin has ability to swell in the presence of water. When used as a disintegrant 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

Miscellaneous

This miscellaneous category includes disintegrants like surfactants, gas producing disintegrants and hydrous aluminium silicate. Polyplasdone®XL and Polyplasdone®XL10 act by wicking, swelling and possibly some deformation recovery. Polyplasdone®XL do not reduce tablet hardness, provide rapid disintegration and improved dissolution. Polyplasdone® as disintegrating agent has small particle size distribution that impart a smooth mouth feel to dissolve quickly. Chewable tablet does not require addition of disintegrant.

Superdisintegrants

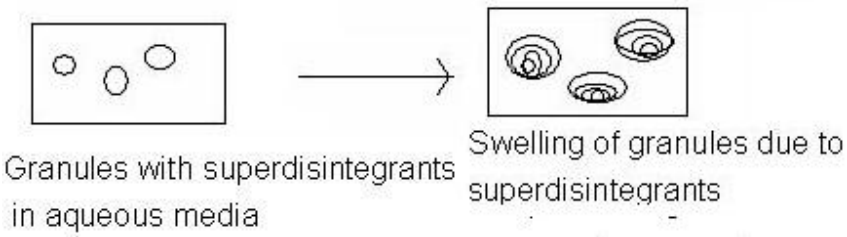
As day's passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs. And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.Because of the increased demands for faster dissolution requirements, there are now available, a new generation of "Super Disintegrants" in addition to the disintegrants discussed earlier.

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)



Mechanism of superdisintegrants by swelling

Table. 2 List of superdisintegrants

SUPERDISINTEGRANTS	EXAMPLE	MECHANISM OF ACTION	SPECIAL COMMENT
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol® L-HPC	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action	Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	Swells 7-12 folds in < 30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural super disintegrant		Does not contain any starch or sugar. Used in nutritional products.
Calcium silicate		Wicking action	-Highly porous, -Light weight -Optimum concentration is between 20-40%

Microcrystalline Cellulose (Avicel 102)

Microcrystalline cellulose is partially depolymerised cellulose prepared from alpha cellulose. Microcrystalline cellulose for direct compression tabletting comes in a number of grades like PH 101 (original product) & PH 102 (more agglomerated, large particle size with better fluidity). When compressed, the MCC particles are deformed plastically due to the presence of slip planes & dislocation. A strong compact is formed due to the extremely large number of clean surfaces brought in contact during plastic deformation & the strength of hydrogen bonds formed. Here Avicel 102 used as diluent cum disintegrant. The mechanism of Avicel 102 is interlocking .The particle size of Avicel 102 is small. The decrease in particle size increases binding strength and decreases disintegration time so here we used Avicel 102. MCC is found in the concentration of 10-25% as a filler binder disintegrant MCC can be used as a disintegrant at a level of 5-15%. The MCC is effective as a binder in direct compression. Its binding advantages in granulation decrease with an increase in water addition. MCC is useful as a disintigrant when used in proportion of at least 5-15%. The disintegration time of tablets of cation exchange resin was reduced significantly in the presence of MCC.

L-HPC (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-disintegrant in fast dissolving tablets.

Crospovidone (Kollidone)
It is white, free flowing and compressible powder. It is synthetic homopolymer of cross-linked N-vinyl-2-pyrrolidone. It is completely insoluble in water, acids, alkalis, and all organic solvents and swells rapidly in water. Rapidly disperses in water, but does not gel even after prolonged exposure. It is chemically inert and has a high adsorptive capacity, forms reversible physical complexes with many molecules without the formation of covalent chemical bonds. It is used as super-disintegrant and dissolution agent in granules, hard gelatine capsules and tablets prepared by direct compression method. Greatest rate of swelling compared to other disintegrants.

Croscarmellose Sodium (Ac-di-sol)
Croscarmellose sodium is a cross linked polymer of carboxymethyl cellulose sodium. Cross linking makes it an insoluble, hydrophilic, highly absorbent material, resulting in excellent swelling properties and its unique fibrous nature gives it excellent water wicking capabilities. Croscarmellose sodium provides superior drug dissolution and disintegration characteristics, thus improving bioavailability of formulations. Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for Capsules, Tablets and Granules. In tablet formulations, Croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations the Croscarmellose sodium is best added in both the wet and dry stages of the process (intra- and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Concentrations of up to 5% w/w of Croscarmellose sodium may be used as a tablet disintegrant although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Conclusion

Disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants.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. 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 disintegrant is extremely important.

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