Original Article

Study of different super-disintegrants and their use as a magic ingredient for different immediate-release tablets

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Abstract

The time taken by the tablet to break down into fragments or granules is called disintegration. The time it takes for a batch of tablets to dissolve into particles under certain circumstances is called a disintegration test. It essentially entails an aqueous liquid penetrating the tablet, disrupting internal bonds, and the tablet breaking down as a result. A gadget defined in the USP/NF is used to determine how long it requires a tablet to dissolve. The powder compact's disintegration and dissolution behavior have the greatest impact on a drug's performance. For immediate-release dose formulations, the breakdown process is very important.

Keywords: Immediate release formulations, Tablet dosage form, Disintegration time, Super disintegrants, Disintegration mechanism

INTRODUCTION

The active substance ingredient (API) and a variety of inert components known as additives make up tablet formulation. The most common method of orally delivering active substance (API) to patients is in tablet or capsule formulation. (1,2) Disintegrating tablets make up most pharmaceutical medications in this category. Tablets can be formulated to release their API immediately after orally administered or to reconfigure the drug release rate with the goal of improving therapeutic efficacy, reducing toxicity, and improving patient acceptability and comfort by selecting appropriate chemical and physical properties. When exposed to physiological fluids for a brief length of time, immediate-release tablets entirely break down and dissolve (2.5 to 10 min. Excipients must be free of microbiological contamination, commercially accessible, and capable of being made or processed in accordance with pharmaceutical standards. Because the therapeutic dosage of medicine is often modest, the API must be combined with appropriate excipients to generate the correct fill volume, which permits the powder combination to be compressed into a tablet of appropriate size. Processing restrictions such as poor flow property, mixing issues, and unwanted adherence to edges such as tablet punch tips or wall of feeder may be caused by API properties including finer particles and needle-like morphology.(3)

DISINTEGRATION

Disintegration is characterized as a condition in which no tablet or capsule residue remains on the apparatus screen, or if a residue does remain, it consists of pieces of insoluble tablet or capsule coatings or is a mushy mass with no discernible core. If the discs were utilized with capsules, the only residue left on the bottom side of the discs is shell pieces. The breakdown process is crucial for ensuring, and even maximizing, the API's bioavailability in the bulk of solid oral dosage forms.(4) Except in diffusion-controlled matrix systems, soaking and subsequent breakdown of the compact powder is the initial step in releasing the drug substance from the dosage form in tablets. Only the API at the tablet's surface would dissolve without disintegration, hence reproducible and complete break-up of the tablet when exposed to the dissolving medium is crucial for achieving dependable clinical efficacy of the dosage form. Most tablet formulations include a disintegrant, which helps the tablet break up or disintegrate when it comes into touch with fluids in the gastrointestinal system. Disintegrants may work by sucking liquid into the tablet, causing it to expand and break apart. The following dissolution of the medicine and the achievement of acceptable drug bioavailability may be hampered by tablet fragmentation. The most frequent disintegration agent is starch USP and other starch derivatives. They are also the cheapest. Starch is usually utilized at a percentage of 5% to 20% of the tablet weight.(5) Lower amounts of modified starches like Primogel and Explotab, which seem to be modified carboxyl methyl starches, are employed (1 to 8 percent, with 4 percent usually reported as optimum. As disintegrants, pre-gelatinized starches are used, generally at a concentration of 5%. At a concentration of around 10%, bentonite and Veegum HV were utilized in clay form as disintegrants. Because the clays give an off-white look, such usage of these substances is restricted unless tablets are colored. Clays are less efficient disintegrating agents than some of the latest synthetic polymeric materials and starches, which may expand in volume by 200 to 500 % in the contact with water.(6,7)

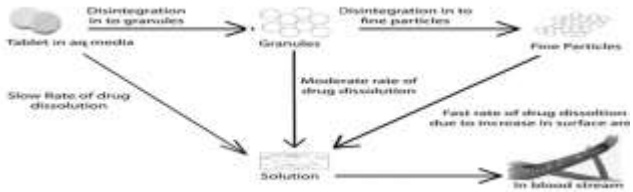


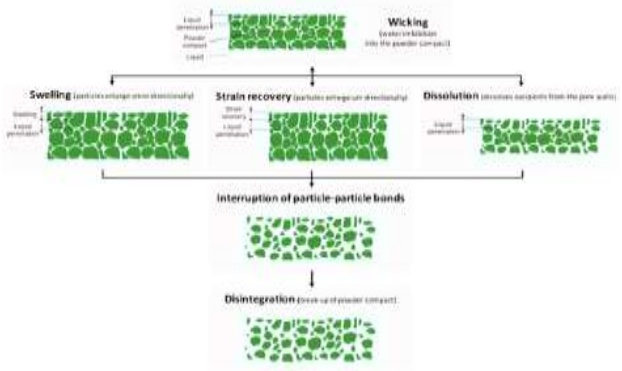
Figure-1

The disintegrating agents may be added in two **Stages I**: during granule formation, before wetting with the granulating agent (intragranular) and **Stage II**: during granule compaction into tablets (extra granular). Extra granular disintegrants break down the tablet, resulting in a finer particle, whereas intragranular disintegrants disintegrate the finer granules, resulting in a finer product. For a long time, starch was the preferred disintegrating agent. "Super disintegrants," which significantly shorten tablet disintegration time, have just been released. Some of examples of such compounds are Crospovidone, Primogel, Polacrilin potassium, and Croscarmellose sodium(7)

MECHANISM OF DISINTEGRATION

1. **Wicking:** Wicking is the process of liquid entering via capillary action into the micro-structured crevices of a solid to displace air. Capillary action allows liquid to enter the DF compact via the pores. As a result, the interparticle linkages formed during tablet compressions, like molecular interactions, solid bridging, and mechanical interlocking, are disturbed, causing the DF's structural integrity to be compromised. As a result, one of the most important processes in the dissolution of a DF is wicking (liquid penetration).(8)
2. **Swelling:** Disintegrant swelling is the most widely acknowledged process for tablet disintegration. Swelling is the all-directional expansion of particles, which builds pressure, pushes adjacent particles apart, causes overall system stresses, and eventually breaks apart the tablet. Swelling is linked to dimensional amplification, in which particles increase in all directions to push away adjacent components, causing the tablet matrix to break apart. Most common disintegrants expand to some degree, and swelling has been thoroughly documented. Disintegrants' swelling capacity is greatly influenced by two basic elements the structure of the chemical compound and the nature of cross-linking. The porosity of the compact also has a significant influence on the effectiveness of swelling disintegrants. The swelling effect of disintegrants might be suppressed by a permeable tablet matrix with vast void spaces, reducing their effectiveness in tablet disintegration. Low porosity compacts made with very high compression pressures, on the other hand, may obstruct a liquid entrance, lengthen disintegration time, or fail to dissolve altogether.(9)
3. **Strain recovery**: The strain inside a tablet is caused by pushing macromolecules to metastable shape, either by the interlocking of polymer chains or spontaneous crystallization during tablet compaction. The disintegrant particles are distorted during tableting. When exposed to water, the disintegrant returns to its original structure, regaining its former shape.(10) The disintegration medium may also encourage the disintegrant's polymer chains to choose the most energetically advantageous configuration.(9,10)

Figure- 2



DIFFERENT DISINTEGRANTS USED IN TABLET FORMULATION AND THEIR MECHANISM

Table-1: List of different Disintegrating agents and their concentrations

Sl No	Disintegrant	Proprietary name	Concentration used (%)
1	Alginic acid	Norgine	2-10
2	Carboxymethylcellulose sodium		1-5
3	Cellulose, microcrystalline	Avicel, Emcocel, Vivacel	Upto 10
4	Starch, pregelatinized	Lycatab, Pharma-Gel, Pre-Jel, Sepistab	5-10
5	Starch		2-10
6	Sodium starch glycolate	Explotab, Primojel	2-8
7	Croscarmellose sodium	Ac-di-Sol, Solutab	0.5-5
8	Dioctyl sodium sulfosuccinate	Colace	0.5-1
9	Crosprovidone	Kollidon CL, Polyplasdone XL	2-5
10	Guar gum		2-8
11	Sodium alginate	Manucol	2.5-10
12	Polacrilin potassium	Amberlite	2-10

1. Alginic acid: Alginic acid has a good wicking ability in aqueous and HCl solutions as well as a good swelling ability in buffers. It fell apart because of a blending action between swelling and shape-recovery systems. The effectiveness of alginic acid in dissolving is unaffected by the characteristics of the media. When used sparingly in tablet formulations, alginic acid, sodium starch glycolate, and crospovidone, may enable very quick disintegration. Even in the more hydrophobic formulations, Alginic acid's disintegration activity was only modestly worse than other super-disintegrants. In the supplement and nutraceutical industries, where the use of all-natural additives is regularly becoming a requirement, alginic acid is thus advised as the tablet's super disintegrating agent, particularly in simple aqueous preparations of natural goods.(11)

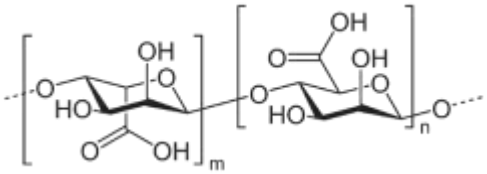


Figure-3: Structure Of Alginic Acid

2. Carboxymethyl cellulose sodium: The FDA has approved carboxymethylcellulose sodium as a common disintegrant used in the production of pharmaceuticals. It has the appearance of a white, fibrous, free-flowing powder. After oral delivery, disintegrants make it easier for a pill to break up in the intestinal tract. Tablets without a disintegrant may not dissolve properly, which could impact how much of the active ingredient is absorbed and reduce effectiveness. Tablets containing sodium carboxymethyl cellulose, a rather insoluble material, initially show a quick increase in dissolution efficiency, which peaks at 1000 kg cm-2 pressure and remains unchanged above that point. With increased pressure, the sodium carboxymethyl cellulose tablets' dissolving efficiency initially slightly rises, then gradually declines. Due to their increased porosity, insoluble tablet systems compressed at low pressure reduced the effectiveness of a swollen type disintegrant.(12)

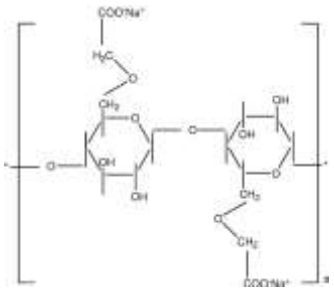


Figure- 4: Structure Of Carboxy Methyl Cellulose Sodium

3. Microcrystalline cellulose: MCC is frequently used as a disintegrating agent in wet granulation and dry compression processes. By accelerating tablet disintegration, it improves drug dissolution. It also offers the highest amount of disintegration power at low use levels and uses two disintegration mechanisms like wicking and swelling for faster disintegration. Water quickly absorbs into Avicel, and its elastic deformation is minimal. These two characteristics help its disintegration effects. However, as moisture content rises, Avicel has a propensity to accumulate static charges, which can occasionally cause granulation to striate or separate. When Avicel's moisture content rises above 3 percent, static charges are created during mixing as well as compression. By dehydrating the Avicel to reduce the moisture content, this problem can be solved. When crushed and dried, wet granular Avicel reduces some of its ability to disintegrate. It is quite impossible to be wet granulated, like starch can, without losing part of its disintegrating qualities. Typically, starch and Avicel are combined to promote efficient and quick tablet disintegration. In addition to working as a dissolving enhancer, avicel has been employed as a disintegrating agent in orally disintegrating tablets. According to US6350470, Avicel can be used to promote effervescent penetration or act as a disintegrant in effervescent medication delivery systems intended for oral administration. Avicel performs as a disintegrant in a level of 5 - 20 % when compacted dry.(13)

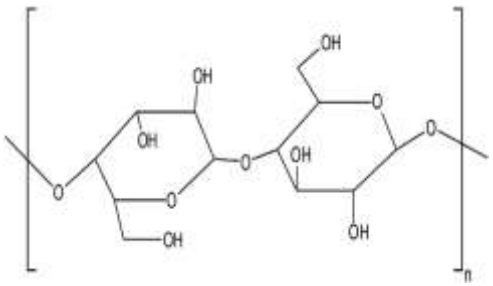


Figure-5: Structure Of Microcrystalline Cellulose

4. Pre-gelatinized starch: Compared to tablets made with povidone, those made with Starch 1500 worked excellently as a binder, creating a granule that can be compressed and yield tablets with better hardness and friability. In addition to this, it performs quite well in terms of disintegration and dissolution. The level of liquid penetration and tablet breakdown is largely determined by the capillary morphology (porosity) of the tablets. The major mechanism of action of such disintegrating agents as starch and cellulose fibers is generally acknowledged to be swelling and capillary action caused by the tablet's pore structure. Additionally, natural starches' swellability and water absorption are frequently increased by pre-gelatinization. Thus, the effectiveness of these materials as disintegrants depends on criteria including swelling ability water holding capacity, moisture content, and solubility. The pregelatinized starches had a much greater capacity for swelling, percent solubility, and water absorption. The starches' ability to swell in cold water was improved by pre-gelatinization.(14)

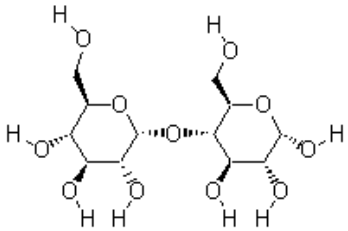


Figure- 6: Structure Of Pre-Gelatinized Starch

5. Starch: In pills, starch is frequently employed as a disintegrating agent. It is widely acknowledged that when exposed to water, it swells and serves as a disintegrant. When exposed to a 95 % relative humidity environment at 27°C, starch will absorb roughly 20 % of its weight in water in 24 hours. They give no indication of volume changes involved with the process. In its native state, starch is water-insoluble, but it seems to soak 25 to 30 % but does not swell noticeably. It is observed that capillary action, not swelling, is what causes the disintegrating effect. (6,15,16)

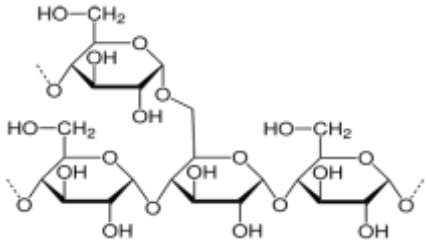


Figure-7: Structure of Starch

6. Sodium starch glycolate: SSG, a cross-linked synthetic potato starch, is used in a pharmaceutical solid dosage form as a disintegrant. SSG is referred to chemically as a carboxymethyl ether derivative of starch with sodium as the salt. To create SSG from starch, two chemical modifications were made: cross-linking and substitution, which decreased gel formation and increased solubility when in contact with water. A few producers sell the substance under brand names such Primogel, Explotab, and Vivastar. For Sodium starch glycolate and Explotab, the ingredients are made by reacting potato starch with sodium chloroacetate. However, it is unclear whether cross-linking of the potato starch occurs before or after replacement. The substance is cross-linked because Vivastar P uses the Na carboxylate moieties and the starch alcohol group following replacement. The sodium salt form of carboxymethyl ether is called Primogel. The origin of starch glycolates is either from corn, wheat, rice, or potatoes. Sodium starch is a powder that is white to off-white, tasteless, Dodorless, and only moderately free flowing. For tablets or capsules, Primogel is used as an excipient to aid in dissolving. Because Primogel absorbs water quickly, it causes swelling that causes tablets and granules to break down swiftly. It is used as a gelling agent, a disintegrant, and a suspending agent. Tablets without a disintegrant may not dissolve properly, which may affect how much of the active substance is absorbed. The substance is offered by a number of producers under numerous brand names, including Explotab, Primogel, and Vivastar.(17)

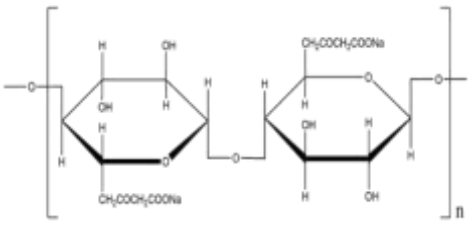


Figure- 8: Structure Of Sodium Starch Glycolate

7. Croscarmellose sodium: Croscarmellose sodium, as well as crospovidone, are two popular superdintegrants used in FDTs. They are really good at breaking down. When croscarmellose sodium gets in touch with water, it expands noticeably and breaks down the tablets. Additionally, it possesses a polymeric fabric structure that promotes water wicks even at low concentrations of extra- and intra-particulate matter. When exposed to water, croscarmellose sodium is believed to quickly inflate and wick, aiding in disintegration. Wicking is a "whipping" movement that helps to maintain capillary flow by replacing the material-air as well as material-material contact with the material-water interface in an instant. Longer disintegration durations have been seen when CCS is employed at high concentrations. The most likely cause of such is partial gelling, which may act as a viscous wall and delay the entry of water into the tablet.(18)

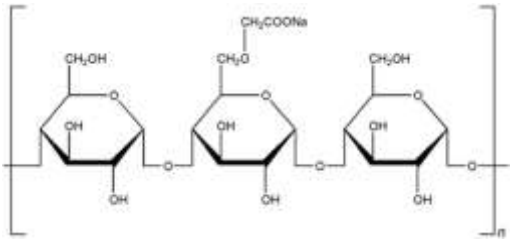


Figure 9: Structure Of Croscarmellose Sodium

8. Dioctyl sodium sulfosuccinate: An anionic surfactant chemical called DSS that is Dioctyl sodium sulfosuccinate has long been advised as a laxative as well as a stool softener for a range of vertebrates, including humans and rodents. Dioctyl sodium sulfosuccinate is an anionic surface-active agent that works by lowering surface tension so that gastrointestinal fluids and compounds can pass through the pill and have an impact.(19)

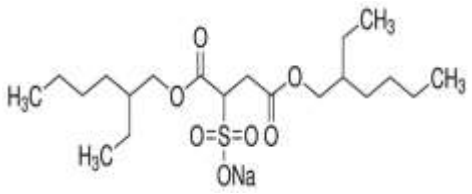


Figure-10: Structure Of Dioctyl Sodium Sulfosuccinate

9. Crospovidone: A synthesized cross-linked PVP that is hydrophobic in nature, crospovidone is largely used in pharmaceutical products. Swelling, wicking, and strain recovery are only a few of the hypothesized operational mechanisms. Tablets that dissolve when taken orally offer the benefit of expanding without gelling, which helps speed up the dissolving process. The polymer deforms when compression pressure is applied. When it meets water, it absorbs it via capillary action and changes back to its original shape, energy is released and causes the tablet to crumble. The faster disintegration and significant impact of crospovidone's larger particle size on the breakdown process. More water was absorbed, and the material broke down more quickly when the intra-particular porosity increased in proportion to size. The different classes of crospovidone differ in terms of particle sizes (standard particle size, ultrafine particles, superfine particles, and micronized particles), dehydration capability, peroxide concentrations, and bulk density. Typical weight-for-weight concentrations of crospovidone vary from 2 to 5 percent. Tablets that contain more crospovidone than 8% of their weight degrade more quickly. Crospovidone is a possible disintegrant for cationic medications due to its non-ionic nature, which has a disintegration rate independent of media pH.(20,21)

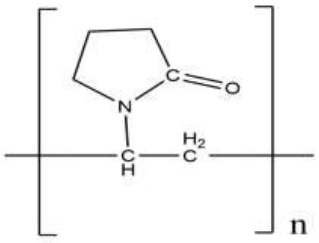


Figure-11: Structure Of Crospovidone

10. Guar Gum: Guar gum, a polymer isolated from Cyamopsis tetragonolobus seeds, is extensively used in food products, cosmetics, and pharmaceutical formulations. In oral solid dosage forms, it acts as a binding agent and/or disintegrant. Some topical preparations have used it as a suspending, stiffening, and stabilizing component. Guar gum also has been investigated to be used in colonic drug delivery and is frequently mentioned as a controlled-release medication carrier. Guar gum which has been treated exhibits improved deformation behaviors, a reduction in gel rheological properties, and an increase in water uptake. It is believed that treated guar gum will provide more efficient tablet breakdown than native guar gum because the effectiveness of disintegrating agent is impacted by how fast as well as how much it expands.(22)

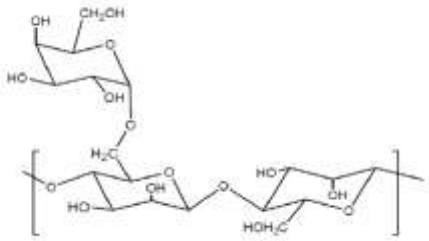


Figure-12: Structure Of Guar Gum

11. Sodium Alginate: Alginates are natural polymers that were researched for their potential in the domains of food and medicine. Regarding their prospective use as tablet super-disintegrants, little information is currently available. In phosphate buffer, swelling-driven liquid uptake of calcium alginate as well as alginic acid is much more pronounced; in corrosive acid and water, wicking-driven liquid uptake is more pronounced. Alginic acid and calcium alginate both work through swelling as well as shape-recovery mechanisms. Due to gelling, sodium alginate is not utilized as a disintegrant.(23)

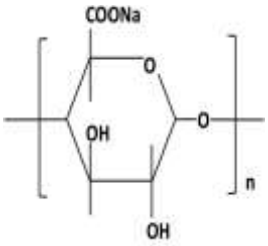


Figure-13: Structure Of Sodium Alginate

12. Polacrilin potassium: PP is a potassium salt of the divinylbenzene and methacrylic acid copolymer. Methacrylic acid and divinylbenzene are copolymerized to create polacrilin resin during the process of synthesis. PP is created when the polacrilin polymer is neutralized with potassium hydroxide. A concentration between 2 and 10 percent is used for the disintegration process (Palmieri, 2009). Though wicking (capillary effect) and shape recovery have been hypothesized, the mechanism of PP's disintegrating action has not been sufficiently researched.

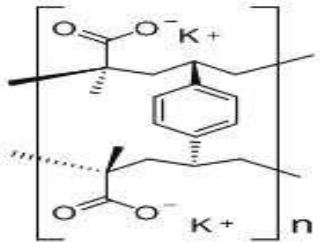


Fig 14: Structure Of Polacrilin Potassium

The result of the literature search showed that functionalities of super disintegrants could be affected by molecular and physicochemical characteristics of the disintegrant, formulation, and process factors as well as aging and storage conditions.(24)

13. Chitosan: The swelling capacity of disintegrant powders was in the following order: chitosan > Avicel PH102 > Avicel PH101> starch> PVP (dissolved) in both deionized water and 0.1(N) HCl. The swelling capacity of chitosan in diluted hydrochloric acid was significantly different ($p < 0.05$) than that in water. It was observed that chitosan dissolved in diluted hydrochloric acid solution and formed a viscous translucent gelatinous solution.(25,26)

FACTORS AFFECTING THE ROLE OF DISINTEGRANTS INCLUDE

1. Molecular and physicochemical factors

1.1 The impact of cross-linkage and substitute levels

By substituting hydroxyl groups with any more hydrophilic ones and cross-linking linear polymer chains, SSG and CCS gain their functionalities. Cross-linking and carboxymethylation (substitution) levels of SSG have a big impact on how well it works. Cross-linkage levels of 33 to 35 percent and substitution levels of 0.28 to 0.29, which are alteration values of Explotab®, a brand of SSG, were shown to have the best disintegrating and dissolution performances. Although both brands of CCS had a comparable distribution of particle size and overall degree of modification, the brand with some

more basic replacement (sodium salt) had a bigger settling volume, higher greatest possible water uptake, and higher swelling ability in the neutral medium than the brand with less basic replacement. However, there hasn't been any information given on how different cross-linkage levels affect CP and PP performance.(27)

1.2 The impact of particle size

SSG, XPVP, and PP coarse particle fractions performed better when it came to dissolving than fine particulate matter fractions. The impact of CCS's particle size on how well it disintegrates has not been assessed. The size of the particles of this disintegrant, however, may be essential since large particles impose a stronger swelling effect on solid matrix than smaller ones do because the swelling is the primary mechanism through which CCS promotes tablet disintegration. A disintegrant's effectiveness as a tablet excipient can be impacted by changes in its particle size. When the composition was squeezed without a lubricant, the starch disintegration time reduced as the starch particle size increased. With a lubricant, however, disintegration time is reduced with a smaller disintegrant particle size because lubricant coverage is reduced with an increase in the surface area, leading to a faster disintegration rate with smaller disintegrant particles. This results from larger size particles efficiently forming hydrophilic networks. The overall acidic (acid forms) and basic (sodium salts) constituents of super disintegrants determine the degree of substitution. After the fracture by disintegration, the hardness controlled the dissolution at all stages, from tablet to tiny particles.(28)

1.3 The impact of particle porosity

Large intra-particle porosities in a disintegrant will increase the surface area of liquid medium contact, leading to immediate water uptake and expanding or shape restitution. A brand of PP with a higher total porosity had a quicker disintegration time compared to brands having lower total porosities, and it also had a higher initial water uptake rate. Additionally, it was discovered that intra-particle porosity was essential for a model drug's quick breakdown. The more permeable a product is, also more water or digestive juice ought to be able to permeate the pill and dissolve it, releasing the API.(29)

1.4 The impact of impurities

Excipient impurities instead of the excipient itself are to blame for problems with chemical stability. Small molecules are typically the most reactive contaminants. This is certainly relevant for solid dose forms, where there is very little mobility for big molecules. Impurities in pharmacological formulations can also affect safety or dosage form effectiveness in terms of chemical stability. Quantitative analysis of the presence of significant contaminants in pharmaceutical goods and source tracing are frequently useful. Variation from lot to lot may render a marginal product unreliable if the source is an excipient. Consider technologies and procedures that produce less of the unwanted contaminant if the source is connected to the process of preparing the dosage form.(30)

FORMULATION AND PROCESS FACTORS

Super disintegrants synthesis could produce by-product contaminants. Examples of reaction byproducts created during the manufacture of SSG include sodium chloride, sodium glycolate, and sodium citrate. Sodium chloride as well as sodium glycolate levels should be less than 7% as well as less than 2%, respectively, according to USP and PhEur, two official compendia, which also specify the proportions of that by in SSG. In comparison to SSG compacts with larger percentages of impurities, those with lower percentages of cumulative cold water-soluble components (impurities) exhibited higher water absorption and penetration rates. SSG with low percentages of impurities demonstrated faster tablet DT than SSG with large percentages of impurities when included at a concentration of 4 percent in tablet formulations, albeit the difference is negligible. Higher levels of salt impurities make disintegrants less effective at absorbing water, which affects their efficacy.(31)

1.5 Effect of water solubility and hygroscopicity of components

The rate and mechanism of tablet disintegration are influenced by an important tablet formulation ingredient's water solubility. While insoluble components result in quickly disintegrating tablets, water-soluble compounds typically dissolve rather than disintegrate. Components that are water soluble dissolve, creating a viscous membrane of saturated solution all around the tablet matrix. This barrier prevents water from entering the disintegrants, delaying the breakdown of the tablet. The influence of viscosity caused by water-based fillers on the delay of disintegration, it is said, would be modest. Instead, extra water molecules are held up by the hydrated filler molecules, preventing them from contacting the disintegrants. Overall tablet hygroscopicity brought on by fillers is detrimental to the effectiveness of super disintegrants. For instance, the efficiency of P-amino salicylic acid dissolution from tablets with sorbitol as well as naproxen sodium (water-absorbing substances) as filler was slowed down when super disintegrants were present as opposed to when they were absent (Johnson et al., 1991). A hygroscopic excipient challenges super disintegrants for water, which impacts DT. Additionally, compared to insoluble binders, water-soluble binders prefer to prolong tablet DT. This is explained by the insoluble nature of the binders and their low hydration potential.(32)

1.6 Effect of pH

Since CCS, as well as SSG, are anionic disintegrants, medium pH may have an impact on their capacity to absorb water and swell. Studies on the impact of intermediate pH on tablet disintegration time (DT) and medication dissolve rate from formulations comprising SSG, CCS, and XPVP revealed that CCS and SSG's disintegrating abilities in an acidic medium

were significantly decreased relative to a neutral medium. However, the non-ionic polymer XPVP's disintegration ability was hardly impacted by the medium pH. It is possible that the conversion of the carboxymethyl sodium molecule to the free acidic form, which has a lower capacity for hydration than the salt form, is what causes CCS and SSG to perform poorly in acidic media. The overall level of modification and the proportion of basic to acidic components have an impact on the function of intermediate pH on moisture absorption and swelling properties of super disintegrants. Similar to this, PP's functionality may be impacted by an acidic pH due to its anionic disintegrant nature. When the pH was changed, the disintegration time was cut in half (pH 0.05).(33)

1.7 Effect of Lubricant

To reduce friction between machine portions and tablet edges during ejection, lubricants are one of the excipients used in tablet formulation that is included in very small doses. Magnesium stearate was shown to have a negligible effect on the SSG's ability to disintegrate, and this effect grew as the lubricant was mixed for longer or at a faster rate. Furthermore, compared to starch, SSG's performance in disintegrating was less susceptible to the magnesium stearate's ability to create films. During the mixing process, magnesium stearate creates a hydrophobic layer surrounding the powder particles, delaying the passage of water into the tablet matrix. Longer mixing times provide magnesium stearate more opportunity to coat all edges.(34)

1.8 Effect of Incompatibility

Drugs and inert ingredients with different physicochemical qualities, including weakly basic or acidic characteristics, may be present in tablet formulations. There have been reports of incompatibilities with CCS and extremely basic excipients. According to the researchers' hypotheses, carboxymethyl cellulose, a hydrophilic polymer found in tablets, is produced when the ester bridge of CCS hydrolyzes in alkaline conditions (pH > 8.5). As the concentration of this hydrophilic polymer increases, a viscous barrier that prevents water from penetrating the tablet matrix may form, slowing the pace at which drugs dissolve. The drug in vitro dissolution rates for cationic medicines is impacted by interactions between CCS and SSG. Although there was an in vitro relationship between CCS and the weakly basic medication phenylpropanolamine HCl, the interaction had no effect on the drug's bioavailability. At physiological salt concentrations, the interaction between weakly basic medicines and anionic super disintegrants disappears. This shows that the type of ion exchange determines how anionic super disintegrants as well as weakly basic medicines interact. According to reports, CCS and SSG binding to oxymorphone is solution pH dependent, with maximum binding occurring at pH 6-7. The association of oxymorphone and CCS at these pH levels was discovered to be twice that of SSG. Amine medicines and PP combine in a pH-dependent complex, with the strongest interactions occurring between pH 4.5 and 5.5. Because PP and amine medicines interact less frequently at pH levels over 6, this suggests that the interaction has little bearing on the overall in vivo bioavailability of these treatments.(35)

1.9 Effect of Granulation and Reworking

Super disintegrant effectiveness is adversely affected by tablet production procedures including granulation and reworking; as a result, larger disintegrant concentrations are advised in tablet dosage form for granulation methods as opposed to the direct compression technique of manufacture. When employed at a 1 % concentration, it was discovered that pre-compression granules SSG and Crospovidone prolonged DT of tablets relative to untreated super disintegrants (controls). However, at the same dosage, the DT of tablet formulations in granular CCS from pre-compression was unaffected. The DT of tablets formed from pre-wet granulated CCS, SSG, and XPVP were found to be much longer than tablets created from unprocessed super disintegrants in the same study (control). According to the researchers, pre-wetting of disintegrants, which is done in the production of tablets using the wet granulation method, can negatively affect the function of super-disintegrants even more than pre-compression granulation, which is carried out in the production of tablets using the dry granulation method. Additionally, reworking procedures impact how well super disintegrants perform. However, the mechanism of super disintegrants integration may have an impact on how well disintegrants perform after reworking. When implemented intragranular, CCS, SSG, and CP decreased their rework efficiency. SSG and XPVP, however—SSG being better—maintained their rework efficiency when added extra granular, and not CCS. The decreases in the effectiveness of CCS and XPVP were related to the rework operations including comminution and compaction, which caused the "spaghetti-like" porous material of CCS and the "sponge-like" structure of XPVP to fragment. The hydrophobic lubricant that is introduced during the relubrication stage has a film-forming effect that may make the disintegrants less effective (Gould and Tan, 1985).(36)

1.10Effect of Mode of Disintegrant

Addition Disintegrants are added when making tablets using the wet granulation method, whether they are intragranular, extra granular, or both. The efficiency of super disintegrants, when used in various modalities, is inconsistently discussed in the literature. The dissolution rate of CCS that was intragranular integrated into one investigation was higher than that of the other two ways of incorporation. Contrarily, it was discovered that the combination of intragranular and extra-granular addition caused a larger rate of drug dissolution than extra-granular addition, which in turn created a higher dissolution rate than intragranular addition. The extra granular way of super disintegrants addition, however, produced a higher drug dissolving rate than the other two modes of addition, according to previous research. Similar to this, research comparing the intragranular as well as extra granular modes of adding super disintegrants found that the extra granular technique was more effective for the super disintegrants. Even though they are not currently widely used disintegrants, extra granular integrated, calcium alginate, alginic acid, microcrystalline cellulose, maize starch, and colloidal aluminium

silicate demonstrated significantly faster DT than intragranular mode. However, the intragranular mechanism of addition resulted in significantly smaller disintegrating particles. The performance of super disintegrants when introduced in various ways is not affected by the solubility of the main constituent in tablet formulation in water. The variations in how super disintegrants operate when introduced in various modes may be connected to the manufacturing procedures employed. In contrast to applying binder solutions during wet massing, a disintegrant may react differently as pure water is mixed with a powder mixture. The performance of super disintegrants may also be impacted by introducing an extra granular disintegrating agent first or by introducing extra granular disintegrant as well as lubricant simultaneously to dried granules. A super disintegrant performance in the intragranular method of addition may also be impacted by exposure to moisture from the granulating fluid and by grinding dried granules.(37)

1.11Effect of Mixer Shear Rate

Using mixers that produce various levels of shear, a medication, disintegrant, filler, and other ingredients could be dry mixed and/or wetly granulated. High mixer shear rates during wet granulation were discovered to have a negative impact on SSG performance. Phosphate ester linkages anchoring polymer chains in the molecule are broken by high shear rates. Low-viscosity grade SSG, which has a high amount of phosphate cross-linkage, is commercially available to address this issue. In wet granulation, it was discovered that the low-viscosity grade SSG outperformed the high-viscosity grade SSG in resisting shear-induced phosphate ester bond cleavage.(33)

1.12Effect of Compression Pressure

During tableting, the compression pressure applied by the top punches causes powders and granules to be compressed into tablets. For XPVP compared to other super disintegrants, the impact of compression on DT was demonstrated to be more significant. It was discovered that as compression force is increased at greater concentrations, XPVP disintegration efficiency increases. However, it was shown that at a lower concentration level, its effectiveness fell as compression force rose. CCS and SSG's disintegrating effects were discovered to become less responsive to changes in compression pressure than concentration. Tablet disintegration would be negatively impacted by excess porosity or a lack of porosity. In the former scenario, the expanding force would diminish without applying pressure to the tablet matrix, whereas in the latter scenario, there is barely any water leaking into the matrix.(12,37)

1.13Effect of Aging and Storage Conditions

Tablet formulations may include chemicals that are diverse in terms of their ability to absorb water into the tablet matrix and, as a result, induce various mechanical and/or solid alterations. Tablets' functionality is slowed down by the aging of their disintegrants under standard storage circumstances or at higher temperatures and/or humidity.(38) The DT of tablets was typically found to be delayed when preserved for 90 or 120 comparisons to 0 days throughout all storage periods utilized (25 o C/40 percent RH, 37 o C/40 percent RH, 45 o C/40 percent RH, 25 o C/60 percent RH, or 25 o C/80 percent RH) when exploring the impact of temperature and humidity on the material characteristics of ketoconazole tablet formulations CCS, SSG, starch, and the tablets containing SSG showed the greatest retardation in DT. The enhanced DT of tablet formulations CCS, SSG, and XPVP, while stored at 40° C/75 % RH for 1 to 3 months, was also found by a systematic investigation, regardless of the tablets' hardness or softening. For some mixtures of the diluent and the disintegrant, the elevation in DT was hardly noticeable. In this investigation, DT increase in paracetamol and sodium naproxen tablet utilizing MCC as diluent was less than that in tablets containing lactose monohydrate or dicalcium phosphate dihydrate but was nearly same in formulations containing griseofulvin. The mild disintegrant action of this filler may be the cause of the lower increased DT in formulations containing MCC. In accelerated storage circumstances, MCC could make up for the functional loss of super disintegrants. The amount of MCC or even other fillers utilized in this study was 43.07 percent. In a different study, DT of tablets formulations containing CCS considerably decreased after one month of storage or disintegrated in a stability chamber after three months of storage in ICH climate zones II and IV (25°C/60% RH and (30°C/70% RH), respectively). However, at lesser humidity and differing temperatures in zones I and III (21°C/45% RH and 30°C/35% RH, respectively), DT was little affected. In this investigation, MCC, which has a modest disintegrant action and can make up for the disintegration performance lost by the super disintegrants, was used as a diluent in the proportion of 77.5 percent to 86.25 percent. Pregelatinized starch, as opposed to povidone, had a lower increased DT of paracetamol tablets containing maize starch as the disintegrant, and the dualistic characteristic of pregelatinized starch was thought to be the likely cause. In a different investigation, it was discovered that formulations containing super disintegrants had considerably decreased dissolving rates when kept at room temperature for 8 months or for an additional 2 and 8 weeks at 37 o C/80 percent RH. The principal element (in this study, the filler) was case-hardened, and the super disintegrants' ability to work was thought to be the reason for the slower dissolution rates. A nearly constant DT was discovered at an RH value of 0-80 percent for tablet formulations containing CCS, XPVP, and one brand containing PP in a trial of tablets maintained for a month at 20°C and various RH values (5-97 percent). However, DT from one brand containing PP was maximum at 5% and dropped at RH > 40%, whereas DT among both brands containing SSG was enhanced at RH > 22%. The plasticizing impact of water on the polymeric matrix of SSG is what is responsible for the DT rise on storing at higher RH. When a disintegrant comes into contact with a liquid medium, absorbed water reduces the performance of the disintegrant by facilitating the mobility of the polymer chain (stress relaxation), which releases stored energy (Quodbach and Kleinebudde, 2015). When tablets were kept at 35o C/100% RH for 7 days, the DT of those containing CCS and XPVP steadily decreased, whereas the DT of SSG barely changed. The reasons for the variations in these research findings may be connected to the various tablet production techniques that were employed. The disintegration time of tablet formulations containing CCS and XPVP tends to raise when

manufactured using the wet granulation process as opposed to the direct compression method at high temperatures and humidity levels. However, regardless of the production process, the DT of SSG-containing tablets tends to increase under the same storage conditions.(39)

CONCLUSIONS

Manufacturers are responsible for creating super disintegrants with the best molecular and physicochemical qualities or grades. Disintegrant grades should be chosen by formulators to suit a particular API. The functionality of super disintegrants may be impacted by formulation parameters and production methods, therefore formulators should be aware of this possibility. Additionally, producers of super disintegrants and those responsible for formulating solid dosage forms should not minimize the effects of improper handling of super disintegrants, particularly exposure to high temperatures and/or humidity.

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