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# BINDER FUNCTIONALITY IN TABLETTED SYSTEMS

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## 1) Introduction

Solid dosage formulations, due to their portability and convenience are the most widely prescribed dosage forms in the world today. A subset to this class of dosage forms, the compressed tablet is a dosage form which results from the physical process of mixing powders and by using extreme pressure, forcing these particles to rearrange and deform until a robust mass is formed. In order for this process to be successful certain pharmacologically inert compounds are included into these tablet formulations. These adjuncts, excipients, can have two main functions: a) to improve the manufacturability of the formulation; and b) to affect the release of the active medicament from the formulation. Excipients can also serve a secondary role of stabilizing, coloring, and providing bulk to dosage forms.

One major class of excipients that is used to improve tablet formulations is the pharmaceutical binders or sometimes referred to as adhesives. These binders can function to affect the development of granulations and the compaction of these granulations or powders into tablets. In directly compressible formulations a binder's sole function is during tablet compaction. Without the inclusion of pharmaceutical binders to most tablet formulations, unsuccessful deformation would take place resulting in tablets with poor mechanical strength, tablets which are prone to lamination or capping, or in extreme cases no tablet would be formed under the normal range of compaction pressures used in pharmaceutical production settings.

The purpose of this review is to evaluate the functionality of pharmaceutical binders in tablet formulations. Critical factors which can affect binder function in aiding to the successful formation of tablets will be identified, as well as, binder influence during granulation.

## 2) Binder Definition and Function

The influence of pharmaceutical excipients on the manufacture and release of drug substances has received recent attention by the new USP subcommittee devoted to excipient functionality and functional relevant compendial specifications.[1] Excipient functionality is an area of focus for this committee in their efforts for compendial international harmonization and standardization based on excipient performance.[2] The chairman of this committee recently reviewed the effect of excipient functionality on drug product development and gave clear insight into the functional role of certain excipients in the manufacture of pharmaceutical dosage forms.[3]

In the discipline of solid dosage formulation, excipients are included to impart technical functions on the manufactured system. These technical functions could be: a) to improve the compactibility of the formulation; b) to aid in the lubrication of the formulation by decreasing the adhesion of the formulation to the processing equipment; and c) to improve the flowability of the formulation reducing the variability in weight and uniformity of the dosage form.

Binders are substances which are included into solid dosage formulations as technical additives to improve the compactibility and flowability of powders or granules. This is achieved during the granulation and compaction stages of tablet manufacturing processes.

This broad definition will be expanded upon when evaluating the two specific functions of binders in solid dosage form manufacture.

In this paper the term "Binder" only refers to the materials as they are used in compressed tablet formulations. Quite often similar materials are used in pelletization or coating of particles. The materials, methods, and critical factors involved with using these same materials in this coating process may be similar to those discussed in this paper, however, the focus of this paper is on the binding functionality of these materials and the method by which they improve compressed tablet systems.

Binders are sometimes referred to as granulating agents and further explanation is warranted to this ambiguous distinction. Granulating agents are solvents used in the process of wet granulation to aid in nucleation and coalescence of particulates into granules. After exposure to a drying process the solvents are evaporated off and only a small percentage is usually left as part of the granule structure. Binders are added polymeric materials, which can be dissolved or dispersed into granulating solvents before the process begins.

These added components are intended to function in the particulate binding giving the granule its strength, and during compaction by aiding in deformation and providing sites where bonding can occur under pressure.

The polymeric systems dissolved or suspended in granulating agents may, by changes in surface tension and solution viscosity, contribute to granule formation. However, granulation can proceed without the inclustion of binders into granulating solvents. The method of binder addition may, in the case of wet granulated systems, influence the granulation process but is not necessary for granule formation.

3) Binder Function in Compaction

Pharmaceutical binders are polymeric materials which are included into tablet formulations and allow for an increase in surviving bond formation when exposed to high forces resulting in compacts (tablets) with adequate mechanical strength. Adequate tensile strength would be exhibited by a tablet which has the mechanical strength to withstand abrasion when exposed to the normal forces found in packaging and transportation of solid pharmaceutical dosage forms.[4] Table-1 lists the functional role of pharmaceutical binders in compressed tablet formulations.

In order to understand the function of binders in tabletted systems the current theory on bond formation during tabletting must be reviewed. A complete understanding of how bond formation occurs on a particulate level has been alluded to by some distinguished pharmaceutical scientists, however, scientific evidence regarding the mechanism of bond formation at the particulate level is still moderately limited.[5,6,7]

3.1). Particle Attraction Without The Application of Pressure

In an attempt to explain bond formation at the particulate level, one must first evaluate the forces that attract particles without the influence of pressures seen in a conventional tabletting sequence. Attractive forces between particles can be explained by depicting two regions of a particle, region A and B. Region A would consist of an area in which an interface exists between air and the particulate surface. This area would be composed of atoms or ions which have a much greater number of unsatisfied bonding forces than can be observed inter-particulately, as considered in region B. When these particulate surfaces, having unsatisfied bonds move closer to each other, they tend to attract and the surface free energy of the particle decreases allowing for adequate but weak bonding to take place.[8]

This bonding force can be between like atoms or chemical species, which is referred to as cohesive bonding, or between unlike atoms, which is

Table-1

The Role of Binders During Compaction

| | |
|---|---|
| 1) | Contribute to the plastic deformation during the consolidation of powders or granules. |
| 2) | Generate or enhance inter-particulate surface sites where bonding can take place. |
| 3) | Contribute to the plastic deformation during decompaction. |
| 4) | Withstand shear stresses and strains which can cause crack propigation and structural failure during post compactional stages of tablet production. |



referred to as adhesive bonding. In compressed tablet formulations strict cohesive or adhesive bonding does not take place. A heterogenous tablet formulation will exhibit a combination of cohesive and adhesive bonding. The optimum conditions are achieved when this adhesion occurs to a greater extent between the particles in the formulation rather than to the formulation and the surface of the tooling. These forces can also affect other processing conditions such as powder flow from the hopper,[9] mixing & blending,[10] and sticking or picking of the formulation to punches after compaction.[8] Adhesive forces have also been identified as playing an important role in the formation and segregation in ordered mixes where coarse carrier particles are used to prevent segregation of fine particles.[11]

3.2). Particle Bonding Under Pressure

The adhesive and cohesive properties of powders previously described may influence the powder prior to compaction or at low compaction forces. Under the forces observed in a tabletting sequence tablet bonds are formed by the application of pressure to the powder mass in the die.

The tabletting sequence which is common to most compressed tablets can be observed in Table-2. The first stage involves the filling of the tablet die with the material to be compressed. The volume of material which fills the tablet die is governed by the materials bulk density. As the compression force increases the particles rearrange closer together to fill the inter-particulate void

Table-2

The Tabletting Sequence

| | | |
|---|---|---|
| **Low Pressure** | 1) | Filling of the die |
| | 2) | Rearrangement of particles |
| | 3) | Elastic deformation |
| | 4) | Plastic deformation or fracture (elastic limit reached) |
| | 5) | Repeat of step 4 (depending on nature of material) |
| **High Pressure** | 6) | Intimate contact and bond formation |



spaces. This rearrangement allows for an increase in the density of the compact. Once the particles are rearranged at increasing pressures the individual particles begin to elastically deform. This deformation continues until the materials elastic limit is reached and a point at which the material begins to deform plasticly, or fracture. The stage of compaction in which the permanent deformation takes place, whether it be by plastic deformation or brittle fracture is the stage in which inter-particulate bonds are formed.[12,13] These volume reduction mechanisms result in intimate contact between particles and the formation of inter-particulate bonds.

Inter-particulate bond formation as a result of compaction has been hypothesized by different pharmaceutical scientists. In a landmark paper, Rankell and Higuchi, applied theories of bonding in metallurgy to understand and describe the process of bond formation in pharmaceutical compacts.[7] The possible bonding mechanisms applied were of three types listed in Table-3.

Of the three identified, the mechanism which may be responsible for bond formation when a binder solution is not used is the liquid cement mechanism. This cementing mechanism is a result of heat generation at the particle surfaces due to friction, and under pressure, it forces particles to fuse or dissolve with local crystallization allowing for the formation of bridges.

A similar explanation of bond formation under high pressures is described as fusion. Fusion under high pressures could be a result of a) plastic

Table-3

Possible Tablet Bonding Mechanisms

| | |
|---|---|
| 1) | Interatomic Forces |
| 2) | Liquid Surface Cements |
| 3) | Mechanical Interlocking |

(ref. 7)

flow, b) brittle fracture, and c) asperitic bonding. Plastic flow leads to bond formation by allowing particle surfaces to reposition leading to a lattice formation. Materials may also bond as a result of brittle fracture in which particles which are sintered realign to allow for greater surfaces to bond.

The third type of fusion, asperitic bonding, is characterized by melting at the particles contact points and subsequent solidification. Asperitic bonding is similar to the liquid cement mechanism described previously. This type of bond formation may occur with compounds which have low melting points but its acceptance as a universal mechanism of tablet bond formation must be taken with skepticism.[5]

Particulate bond formation has also been described in pharmaceutical tablets as a result of solid bridge formation, distance attraction forces, and mechanical interlocking. The strongest type of bond, solid bridges are a result of ionic or covalent bonds with relatively high dissociation energies of 50-200Kcal/mole. Solid bridges may be a result of melting and are synonymous to previously mentioned asperitic type bonding. The second type of bonding, distance attraction forces or intermolecular forces, are a result of hydrogen, Van der Waals, or electrostatic attractions and have weaker dissociation energies of 1-10Kcal/mole. The third possible bonding mechanism is a result of physical interlocking of nonuniform irregularly shaped particles. This type of bonding is strictly dependent on the structure of the surface of the particles and the ability of the particles to fit together similar to pieces of a puzzle. This recent description of bonding in pharmaceutical tablets is the most complete and provides evidence towards the elucidation of what factors may be responsible for a tablet bond.[6]

A model based on dispersion forces and mechanical properties, was developed to qualify and possibly quanitiate a tablet bond. In this study experimental determinations did not match with theoretical calculations

resulting in a model with limited practical utility. As an explanation the author indicated that along with dispersion forces calculated, non dispersion forces, and mechanical properties can contribute to bond formation during compaction.[14]

4) Factors which Affect Tablet Bonding Under Pressure

The formation of a table bond is influenced by many inter-particulate factors, each of which may be related to the materials and the processing conditions under which the tablet is manufactured. The following factors identified may be influenced by the inclusion of binders into compressed tablet formulations.

4.1) Plastic flow during compaction/decompaction

The process of bond formation during a tabletting sequence may be related to the influence of a materials plastic flow both during compaction and decompaction. Compounds that have the ability to form good tablets must have the ability to withstand local shear stresses seen in decompaction and tablet ejection by a mechanism of localized plastic flow. If a material cannot deform plasticly during decompression it is likely to produce tablets which laminate or fail.[15] A quality of a good tablet formulation has also been described as one with good bonding properties and the ability to absorb elastic recovery without failure.[16]

The ability to deform plasticly is not the only influence binders may have during compaction. They can influence plasticity, however, In many directly compressible formulations as well as granulations, the ability of a material to fracture under pressure has been identified to influence on bond formation and tablet strength.[17,18,19]

4.2) Bonding Surface Area

A recent review identifies the critical inter-particulate factors which may possibly influence the mechanical strength of tablets. Bonding in tablets can be a result of a very large number of intermolecular(weak attractions) or a small number of very strong attractions. Materials which have fine particle size, an increased surface roughness, are highly plasticly deforming and with little elastic deformation tend to form a large number of intermolecular bonding attractions. Certain materials that deform plasticly but also are coarse in nature tend to form a small number of strong bonds. The one common factor is the importance of a large bonding surface area.[7]

Others have identified an influence of a materials' surface area on its ability to form bonds and successful tablets.[20] A powders' ability to form a

tablet is dependent upon the type of bonding which occurs and the surface area which the bonding can take place.[21]

4.2) Particle Coatings

Particle coatings have been identified as a way to influence the intermolecular forces and effect the adhesion and cohesion of powders and tablet bonding. Model systems representing plasticly deforming, brittle fracturing, and plastic/fracturing materials were coated with Stearic acid, PVP and PEG of different molecular weights. The influence of temperature and coating material on the tensile strength of resultant tablets was identified and temperature was shown to affect the materials differently by influencing bond formation and by masking mechanical interlocking and Van der Waals forces.[22]

The effects of coated particles on the plasto-elastic characteristics of compacted materials was also investigated. Although coating materials were not considered pharmaceutical binders, the coating materials tended to decrease the plastic deformation of the particles and influenced inter-particulate bond formation.[23] This may be the explanation of why certain lubricants decrease the effectiveness of binders during compaction and why these lubricants are affected by prolonged mixing.

4.3) Particle Size and Shape

The effect of particle size on the ability of a material to bond was shown to be dependent on the substances' mechanism of deformation. This was illustrated by evaluating the mechanisms of two drugs: a) sulfadimethoxine which deforms by particle fragmentation; and b) sulfaphenazole which deforms plasticly,[24] with a series of drugs and excipients,[25] and excipients alone.[26] In the case where substances deform by fragmentation larger particles tend to form bonds more effectively than smaller particles. In the case of plasticly deforming compounds, tablet structure and the ability to form bonds was not affected by particle size.

These evaluations were made in model homogenous systems. In a practical formulation setting particles in a tablet formulation may deform by both mechanisms and possibly have an elastic component also. In this respect, particle size may be an important factor in bond formation during compaction.

As with particle size, particle shape factors may have an influence on binding depending upon the materials ability to fracture or deform.[27]

4.4) Type of Binder

To elucidate the influence of type of binding agents on bond formation during tabletting, the effect of different agents on the energy utilized to form

tablet bonds as measured by the net work of compaction, after multiple compactions of a dicalcium phosphate dihydrate based formulation was identified.[28] By dividing the total work of compaction into components of work derived to form the tablet and work lost through elastic recovery, the influence of six commonly used binding agents on the plasto/elastic properties of a granulated system was studied. The six compounds were rank ordered on their ability to influence the plasticity of the system.

The use of multiple tablet compaction as a model to determine bond formation may be limited by the heat formation within a tablet which occurs during compaction. If allowable time is not permitted between compaction cycles heat not dissipated may have an influence on inter-particulate bond formation.[29]

4.5 Granule Strength

Although binder type and concentration have been shown to affect granule strength, granule strength does not correlate well with tablet strength. A greater influence of compaction force and binder concentration was seen on tablet strength.[4] A correlation was identified between the degree of fragmentation of a granule and tablet tensile strength. Granules that tend to fragment well during compaction tend to produce good tablets due to a great number of formed areas for inter-particulate binding.[30] Fragmentation has also been identified as a critical parameter in the formation of tablets by direct compression.[31] In evaluating the effect of binding agents on the ability to influence the plasticity of a non-plastic deforming model material, binding agents were shown to contribute to the plasticity of the studied granulation.[29]

4.6) Binder Distribution

In all the systems mentioned the main factor which effects binder effectiveness is binder distribution within the granule or directly compressible system. Binder distribution was evaluated in model formulations and unique patterns were identified which depend upon method of manufacture. Using a solvent extraction method these authors were able to identify the regions of binder distribution in granules prepared by wet massing, slugging (precompression) and spray drying. The wet massing granules tended to have a matrix-like binder distribution while the granules prepared by spray drying had a localized binder shell on the surface of the granule. The precompression process tended to produce a binder distribution of discrete particles.[32]

In a follow up study, the compactibility of these formulations was studied to identify how binder distribution may have an effect on tabletting properties. The tabletting properties evaluated indicated that binder distribution in spray dried granules led to a greater amount of binder to binder

bond formation and resulted in the most favorable tensile performance of the three processes studied. Matrix binder distribution in a wet massed system was described as leading to bond formation between particles of the drug, in this case paracetamol, the drug and the binder (paracetamol and hydrolyzed gelatin), and between particles of the binder. It was identified that the poor performance of the precompressed granulation, as far as tablet qualities, was a result of only bond formation between particles of the drug.[33]

These systems studied were mainly of an elastically deforming material. Recent work focusses on binder distribution in a lactose based formulation which is known to be a fracturing/plastic material. This recent evaluation indicated that binder distribution as a homogenous matrix was optimal as far as tablet strength was concerned.[19]

The distribution of a binding agent is affected by processing conditions and formulation factors which inhibit the wetting of the substrate particles. This was illustrated by evaluating granule qualities of a system granulated with a surfactant compared to using modified starch and starch paste. The surfactant may increase the spreading of the binding liquid but leads to granules with decreased strength.[34]

4.7) Binder concentration

The concentration of the binding agent has been shown to affect the degree of plastic deformation imparted on a model non plastic deforming system.[35] In another study, the concentration of starch in a dicalcium phosphate system was found to reach an optimum of ten percent. A quantity greater than ten percent led to cohesion between starch molecules an increase number of fine particles which led to poor granule properties for tabletting.[36]

4.8) Polymer Properties

Polymer molecular weight,[37] mechanical properties,[38] wetability and swellability, [39] have all been shown to have an influence on binder functionality during granulation and compaction. The ability of binder substances to form films, and the properties of these films have been shown to influence tablet strength. Films prepared with binder polymers tended to perform well when they exhibited a high tensile strength, low brinell hardness (soft), and have a high compliance when dry. These characteristics describe a strong readily deforming material.[40]

5) Binder Function In Particle Agglomeration

Quite often, raw materials intended for manufacture into tablets or capsules, do not exhibit the bulk particle characteristics necessary to ensure

production into an adequate and reproducible dosage form. In these instances where flow, compressibility, or homogeneity are concerns wet granulation is used to improve the original poor powder characteristics.

In the process of wet granulation (wet massing, fluid bed, or high shear), as well as certain pelletting and powder layering processes, pharmaceutical binders are included to promote adhesion between individual particles in the formulation. The resultant granulation/pellets can maintain their new shape and size and will improve the flow, and compaction into tablets or filled into capsule shells. The mechanism of particle agglomeration and the resultant function of pharmaceutical binders in this process are important in the overall functional evaluation of binders in tabletted systems.

5.1) Agglomeration Mechanism

To identify the role of binders in maintaining the integrity of granulations one must first evaluate the granulation process itself. Granulation, a size enlargement process, begins with the addition of a liquid to a powder mass under agitated conditions. This added liquid wets the surface of the solid particles and provides binding forces. The further size enlargement and granule growth follows the stages of nucleation, coalescence, and layering.[41]

A theoretical approach using surface free energy and polarity was recently used to evaluate binder-substrate influences on granulation formation.[42] In granule formation cohesion and adhesion exist between the powder being granulated (substrate) and the binder. If the spreading coefficient of the binder over the substrate is positive, a strong adhering binder film is formed at all points of contact between substrate particles. This adhering film leads to granules which tend to be strong and dense. Likewise, if the spreading coefficient between the substrate and the binder is high, the binder's film forming abilities lower and granules tend to be more porous with lower strength. This may identify two possible mechanisms of granule formation.

Other models, with little experimental evidence, have been developed which use the solubility parameter of the binder and the substrate to characterize particle agglomeration in two component systems.[43] More experimental evidence is needed to identify the practical usefullness of these theoretical models.

The ultimate strength of a granule has been shown to be dependent upon the surface tension of the binding solution and the interacting forces between the solution and the solid particles. These factors are dependent on processing conditions listed in Table-4.[37]

Table-4

Processing conditions that may effect binder function on granule properties.

| |
|---|
| 1) Type and concentration of binder |
| 2) Drying time / temp |
| 3) Drying equipment |
| 4) Granulation equipment |
| 5) Time in which granulation solution applied |

(ref. 37)

Binder substances are intended to maintain the physical integrity of the granules prior to compaction.[44] These substances can be added as dry powders prior to granulation and activated by the granulating agent, as solutions where the binding agent is dissolved in the granulating agent, as a dispersed system where the binding agent is dispersed in the granulating agent, and as a semisolid where the binding agent is in the form of a paste. Each method of addition depends on the manufacturing process as well as the binding substance used.

The wet agglomerates, when dried, allow for the binder substance to form bridges between the powder particles. The location of the binder, as described previously, depends on the method of granule manufacture and can have an effect on tablet properties.(Section 4.6)

5.2) Processing Conditions

The wet granulation process is a multivariate process in which many technologies can be utilized to agglomerate particles, which in the case of this paper, are intended for compaction. The processing variables associated with these technologies, as well as the type and amount of binder and method of binder addition have a major influence on binder performance, and subsequent tablet performance. In order to identify the effect of some critical processing factors on binder performance, the technologies will be categorized as wet massing granulation, high shear granulation, fluid bed granulation, and melt granulation. Each category of granulation has both common and unique influences of binding compounds on granule and tablet properties.

5.2a) Wet Massing

In wet granulation by wet massing, the binder used can be added as 1) a solution in which the binder is dissolved in the granulating agent, 2) a solid in which the binder is dispersed during the mixing process and the powder mixture is granulated with an appropriate granulating solution, 3) a semisolid paste which is prepared by mixing the binder (starch) with water under heated conditions and allowing for gelatinization to take place forming a paste, and 4) as a dispersed system in which the binder is suspended in the granulating agent and sprayed into the powder mass during mixing. Of the four methods of addition the preference for method of binder addition must be chosen on an individual formulation basis. Some argue that adding the binder as a dry powder and then granulating is advantageous because it eliminates one step to an already lengthy process. Others contend that by adding the binder as a solution or suspension in some formulations, better distribution, and more uniform granules are achieved. These arguments justify the selection of type of binder should be made on the individual basis depending on the formulation, the processing equipment used, past experience with particular binder systems, and regional or national availability of binding agents Granules prepared by wet-massing tend to exhibit a sponge-like matrix structure

5.2b) High Shear Granulation

In high shear granulation binder addition methods are similar to those observed in wet massing granulation. The extreme shear forces used in this granulation process make the method of addition of the binder less influenced by differences in processing conditions. Quite often in conventional wet granulation the binder solution is added by spraying fine droplets of solution into the powder mass while agitation of the particle bed takes place. The high speeds of the mixing and chopping blades used in high shear granulation contribute to a complete distribution of binder without using atomized binder solution.

All types of binder forms, solution, solid, suspension, and paste may be used with a high shear system. Concerns of possible binder breakdown under high shear conditions have recently surfaced indicating high shear systems may in the cases of pregelatinized starches, have a negative effect on their binding ability. The extreme shear forces may contribute to the breakdown of polymer branches which can be responsible for binder function both during granulation and compaction. This phenomenon has been identified the proper selection of starch in food processing.[45,46]

The method of binder addition and concentration of binder were evaluated with respect to their influence on granule growth in a high intensity mixer. When the binders were dry mixed a good correlation was established

between concentration of binder, and granule size. However, when the binder was added as a aqueous solution a negative effect on granule growth was observed and attributed to a greater degree of mechanical resistance in the system.[47]

5.2c) Fluid Bed Granulation

The fluid bed method of granulation is unique in that the formed granulation is being dried simultaneously during the agglomeration phase. In the fluid bed process the binder solution is atomized into a powder bed suspended in a stream of heated air. The solution adheres to the surface of the particles and when the particles collide they form granules. The continuous drying while the granule is being formed tends to force the binder to distribute to the surface of the granulation. This surface distribution of binder was initially believed to be beneficial to overall particulate bonding during compaction.[32,33] Recent work has refuted the initial claims of benefits to the outermost binder distribution on the granule in terms of superior tablets.[19]

Claims have been made as to the superiority of granule characteristics when dried in a fluid bed system as compared to conventional tray drying.[48] Binders may be added as dry powders then granulated with an appropriate solvent or they may be added as atomized solutions(binder dissolved in the granulating agent). The addition of the binder as a dry powder has been shown to lead to granules with the lowest percentage of fine particles as compared to adding the binder as a solution.[49]

The interdependence between formulating and processing conditions in fluid bed granulation and granule and tablet properties has been illustrated by evaluating processing effects on granule properties and the effect of granule properties on tablets.[50] Changes in fluid bed processing conditions affecting granule properties were concluded as a method to match target tablet properties. This conclusion may be of restricted practical value in that process validation requirements may limit the posibility of altering a granulation process in settings beyond initial formulation scale-up.

5.2d) Melt Granulation

Melt granulation is employed less often than the other granulation methods in the production of tablets however, the role of binder substances in this process deserves further comment. In melt granulation the binder substances, usually polyethylene glycol, is added as a dry powder and the system is heated while simultaneously being mixed. The temperature is raised over the melting point of the PEG. Ideally, the melting point of the binder chosen should be between 45°C and 100°C. This range was identified as optimal because melting points below that range will lead to problems in

melting during storage, and above that range manufacturing speed would be a concern.[51] The melted PEG behaves like a granulating agent allowing for granule formation while agitation takes place. The system is then cooled and the granulation contains PEG which has solidified and which may form bonds during compression of these granules Comparison of this method to directly compressible systems as to effect on drug release has been identified in the literature and systems granulated with PEG were shown to be influenced by the pH of the dissolution media.[52]

6) Binder Function in Direct Compression Formulations

The only function of binders in directly compressible(DC) formulations is to increase the compactability of those powdered systems. The inclusion of excipients into direct compression formulations can be identified by the percentage w/w they are included into the formulation and by their function in the formulation. Binders can be added to the formulations in small percentages up to 20%w/w as adjunct binders to moderately compressible direct compression matrices in order to improve the compactibility of such formulations. The goal or purpose of adding an adjunct binder to a DC matrix is to produce a tablet without exposing the formulation to extreme compaction forces which may affect the dissolution of that product in both a positive and possibly a negative manner. This was demonstrated by the superior tablet properties achieved when combining two directly compressible tablet matrices.[53]

In certain instances the DC matrix is commonly referred to as a binder/diluent. In these cases, the matrix, which makes up often greater than 75% w/w of the formulation has the ability to deform and form inter-particulate bonds during compaction. If no adjunct material is included these materials, due to their compactibility, and ease of deformation, are often termed as binder/diluents or dry binders[54] but may properly be referred to as "binding" diluents. The influence of binding diluents on the dissolution and subsequent bioavailibity of model drugs was evaluated and the need for complete evaluation of binder performance and of a possible binder influence on dissolution was identified.[55] Intrinsic dissolution rates of binder / diluents were characterized and identified as essential when formulating tablets where the binder may make up almost 95% of the formulation.

A critical factor in directly compressible systems may be the binders ability to fragment. A binders ability to fragment may have more of an influence on materials used in DC formulation than their ability to deform plasticly. Particle fragmentation may provide for a better packing arrangement in the tablet die, as well as providing for more contact points to relieve pressure during decompaction.[31]

7) Binder Classes and Categories

The pharmaceutical excipients used as binders are intended only to impart particulate bonding and ideally not to influence the disintegration or dissolution of the active medicament form the dosage form. A complete list of the compounds which are classified as binders in the "Handbook of Pharmaceutical Excipients" can be seen in tables 5-8.[56] In this review each excipient will not be discussed individually as current reviews illustrate their appropriate use and function.[57,58,59,60]

The materials employed as binders in tablet formulations can be classified in two ways. The first classification can be made by the source of the polymeric material and the second, by the method in which the binder is included into the tablet formulation and how the tablet formulation is manufactured.

7.1) Chemical Origin (Source)

One most common way to classify binders is by their chemical origin. These compounds may be of 1) Natural, 2) Semisynthetic, or 3) Synthetic origin. Examples from each category can be identified in Tables 5-8.

Some confusion may be attributed to the "natural" distinction as none of these binders are pure unprocessed natural binders. All of the natural products go through a purification process but do not undergo harsh modification of their chemical or physical structure. Excipients of natural origin may have the potential for the greatest lot-to-lot variability but are still used frequently world-wide.[59,60]

The semisynthetic class consists of products of natural origin which have been modified by chemical, physical, or thermal processes to impart the desired polymeric characteristics. In the case of the natural starches, their initial form may be of a natural product, but during the processing, perhaps by producing a paste by using heat and water, this natural product is transformed to a semisynthetic physically modified starch. Binders that exist as synthetic polymers are synthesized by step or condensation reactions from synthetic starting materials to produce compounds with the desired physical and toxicological properties.

7.2) Method of Manufacture

A second method of classification is by the method of tablet manufacture. Tablets can be produced from formulations which are processed by 1) direct compression, 2) wet granulation, and 3) Slugging (dry granulation). In each of these processes the materials used and the concentrations employed

Table-5

Compounds Used as Binders in Tablet Manufacture

(ref. 56)

*Natural Origin*

| Binder | Regulatory Acceptance | Usual Concentration (%w/w) |
|---|---|---|
| Acacia | NF XVI<br>BP 1980 | 1 - 5 |
| Alginic Acid | NF XVI<br>BPC 1973 | 1 - 5 |
| Gelatin | NF XVI<br>BP 1980 | 1 - 3 |
| Guar gum | NF XVI | 1 - 10 |
| Magnesium Aluminum Silicate | NF XVI<br>BP 1980 | 2 - 10 |
| Sodium Alginate | NF XVI<br>BPC 1973 | 1 - 3 |
| Zein | GRAS listed | 1 - 30 |

Table-6

Compounds Used as Binders in Tablet Manufacture

(ref. 56)

*Semisynthetic Origin*

Starch Byproducts

| Binder | Regulatory Acceptance | Usual Concentration (%w/w) |
|---|---|---|
| Liguid Glucose | NF XVI | 5 - 10 |
| Dextrin | NF XXI<br>BP 1980 | 1 - 10 |
| Pregelatinized starch | NF XVI<br>BP 1980 | 5 - 10 |



are dramatically different. Quite often, compounds which are intended as being used as a diluent in one process, say wet granulation, are also used as binders when used in DC systems. It is well understood that many excipients have multifunctionality and that a compound that functions as a diluent in one formulation at one concentration may function as a binder when included into another formulation at another concentration.

8) Concluding Remarks

With the recent focus of excipient functionality, and compendial specifications for excipients, binder functionality may include compactibility, and disintegration studies as applied functional evaluations of this class of excipients in tablet production. Simple functionality, as well as applied functionality, and the critical physical properties of particle size, shape, density, and flowability, are important to identify and standardize. Excipient functionality has been proposed as part of new compendial requirements to influence international excipient harmonization, however, standard methods to assess function must be developed and validated.

Table-7

Compounds Used as Binders in Tablet Manufacture

(ref. 56)

*Semisytnthetic Origin*

Cellulose Byproducts

| Binder | Regulatory Acceptance | Usual Concentration (%w/w) |
|---|---|---|
| Carboxymethylcellulose Sodium | NF XXI BP 1980 | 1 - 6 |
| Ethylcellulose | NF XVI | 1 - 5 |
| Hydroxypropylcellulose | NF XVI | 2 - 4 |
| Hydroxypropylmethyl-cellulose | NF XXI BPC 1973 | 2 - 5 |
| Methylcellulose | NF XXI BP 1980 | 1 - 20 |

A functional evaluation of binders in directly compressible tablet systems would include an evaluation of simple functionality (eg. critical particle size and shape, moisture content, crystal habit) as well as an applied evaluation into the compactibility, lubricity, and effect on dissolution. An applied functional evaluation of directly compressible systems should include an evaluation into the mechanism of material deformation under normal pressures observed in a tabletting sequence.

A complete functional evaluation of binders in wet granulated systems would require the evaluation of binder performance both during the granulation and the compaction steps of a tablet manufacturing process. Effects during the granulation

Table-8

Compounds Used as Binders in Tablet Manufacture

(ref. 56)

*Synthetic Origin*

| Binder | Regulatory Acceptance | Usual Concentration (%w/w) |
|---|---|---|
| Polymethacrylates | NF XVI | 5 - 20 |
| Polyethylene glycol | NF XVI<br>BP 1980 | 5 - 15 |
| Povidone | USP XXI<br>BP 1980 | 0.5 - 5 |

process, granule properties, compaction, ejection, and tablet properties would give insight into the performance of binders in more complex wet granulated systems.

This review outlines the need for further evaluation into the applied functionality of pharmaceutical binders in wet granulated systems. Simple functionality, due to complex processing conditions, may not correlate well with granule or tablet properties in a granulated system. A complete applied functional evaluation can provide for identification of binder effects on the manufacturability, end-product, and release characteristics of tabletted systems. Since binders function during the compaction stages of a tabletting process insight into possible compaction variables and possible effects on binder functionality must also be determined.

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