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Co-processed excipients: the cost effectiveness and advantages in drug delivery system

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Abstract:

The development of high-speed tableting equipment and the usage of direct compression techniques for tableting have increased the demands placed on excipients functionally day by day. a stable excipient with multifunctional activity can be developed with the help of co-processing. To create new, stable co-processed excipients, the combinations of one or two synthetic or natural polymers have been thoroughly investigated. Co-processing of plant-based components has benefited numerous pharmaceutical industries worldwide in recent years. The broad overview of co-processing, the methods used, and the benefits of utilising natural components in co-processing are highlighted in the current review paper. Additionally, current advancements in excipient technology are briefly highlighted, with a focus on natural combinations that could be employed as co-processed excipients.

Keywords: Co-processing, Spray drying, Macroporous, hygroscopicity, compressibility.

1.Introduction:

Excipients are defined by the International Pharmaceutical Excipients Council (IPEC) as "substances other than the API that have been suitably examined for are included in a medicine delivery system on purpose for safety. Excipients, for instance, can:

I. Assist in the manufacturing of the drug delivery system

II. Support, protect, or improve stability, bioavailability, or patient acceptability

III. Assist in helping to identify the product

IV. Improve any other aspect of the drug's overall safety, efficacy, or delivery while it is being stored or used [1]. A mixture of two or more compendial or non-compendial excipients intended to physically alter their properties is known as a co-processed excipient. without considerable chemical change and in a way that cannot be achieved by straightforward physical mixing. However, in rare circumstances, the formation of essential elements may take place, for example, the formation of salt in situ. Co-processing techniques can take many forms, including common unit operations like granulation, spray drying, melt extrusion, milling,

etc. The material(s) utilized, their form (for example, whether dry powders or liquids), and the necessary physical qualities will all influence the decision for a given application. The component ratios may also change depending on the desired performance [2]. Co-processed excipients are employed in a variety of dosage forms, primarily in solid dosage forms including tablets, capsules, powders, etc. and liquid dosage forms. Co-processed excipients are employed in a variety of dosage forms, primarily in solid dosage forms including tablets, capsules, powders, etc. and liquid dosage forms as injections, suspensions, and emulsions, among others. semi-solid dose forms, such as pastes, creams, and ointments. Because they can be correctly dosed and give good patient compliance, they are the preferred dosage form of pharmaceutical professionals because they have been u making tablets is now a science thanks to advancements in the fields of APIs, excipients, and tablet machines during the past few decades. This acceptance of the production of tablets has developed into a science in and of itself due to improved knowledge of the physics of compression and manufacturing process factors [3]. Excipients can be made more functional by co-processing already existing excipients or by creating new excipients. Co-processing of already-existing excipients is more advantageous due to the relatively high cost required in finding and developing new excipients [4]. Scanning electron microscopy, disintegration, and hardness characteristics of the co-processed excipients blend was compared to those of the physical excipients blend. Physical blend particles are uncoated and uneven in shape, but the average particle size of co-processed excipients was less than 0.55mm, characterized by big individual lactose coated particles [5]. The creation of formulas for diverse dosage forms, such as tablets, capsules, powder, cream, ointments, and others, has given considerably more attention to co-processed excipients. It differs from the physical combination. Physical mixtures are straightforward admixtures that combine a small number of excipients by the use of brief shear processing [6]. Co-processed excipients, on the other hand, have performance benefits that cannot be attained utilizing the same combination of excipients in a corporeal admixture. An incorporated product with greater capacity than the simple combination of components will be produced by combining cost-effective excipient with others of optimal quantity of a functional fabric [7]. The tablet remains the most popular dosage form despite the existence of several improved dosage forms because of its stability, dose homogeneity, and user acceptance. However, because of its numerous manufacturing processes, developing its formulation is difficult [8]. In order to address these issues, numerous adjustments in the tablet production process have been made. Since tableting was first used in the early 1840s, several changes have been made in the technique, including those relating to regulations, stability, and technology [9]. Three basic processes - wet granulation, dry granulation, and direct compression are used to make tablets. Due to the numerous processing processes and manufacturing difficulties associated in wet and dry granulation procedures, producing tablets is more expensive and takes longer. The direct compression method, in contrast, entails the straightforward compression of a dry powder mixture made up of various excipients and pharmaceuticals. The direct-compression method has emerged as the preferred substitute because to its efficiency and simplicity [10]. Excipients with increased performance can be made by processing two or more excipients with different grades or by using novel chemical excipients [11].

2. Co-processing:

The food industry first employed coprocessing to increase the stability, wettability, and solubility of food components, such as co-processed glucomannan and galactomannan, and to enhance the gelling qualities of those ingredients [12]. Co-processed MCC and calcium carbonate were the first excipients to be introduced to the pharmaceutical industry in the late 1980s [13]. In 1990, the co-processed mixture of 75% cellulose and 25% lactose known as cellactose (Meggle Co., Wasserburg, Germany) was introduce Later, the most extensively used co-processed excipient, silicified microcrystalline cellulose (SMCC), was created [14]. Coprocessing is a revolutionary idea in which two or more established excipients are processed using the proper methods to create a synergy of functional gains in addition to covering up the negative aspects of individual excipients [15]. The main benefits of co-processed excipients include the elimination of wet granulation production phases, the avoidance of storing and handling different excipients, and the synergistic effect of having homogenous free flowing immediately compressible formulation of the needed excipients. Coprocessing of excipients results in sub particle interactions that give them better qualities than simple physical mixes of their constituent parts [10].

3. Material properties that influence excipient choice

The selection of excipient is crucial for creating direct compression tablets. Events related to compression include transitional repacking, deformation at the point of contact, fragmentation and/or deformation, bonding, deformation of the solid body, decompression, and ejection [16]. Out of them, the behavior of the powder under stress that affects deformation (compressibility) and bonding (compactibility) the most is the tableting of powder [17]. While compatibility addresses the creation of solid compacts under pressure, compressibility refers to a powder's ability to densify under pressure. When high pressure is used to create a compact mass (a tablet), the tensions inside the particles increase and cause fragmentation (in case of brittle materials, e.g., sucrose, lactose, silicon dioxide, fructose dextrins). The formation of possible new, clean bonding surfaces as a result of fragmentation leads to a rise in the number of particles. By allowing smaller particles to enter the vacant area, fragmentation also causes densification. As pressures are eased by plastic deformation in the case of plastic material (namely, polyvinyl pyrrolidone and crospovidone, maize starch, guar gum, and sorbitol), fragmentation does not take place. A change in particle shape caused by a set of particles sliding is known as plastic deformation (viscoelastic flow, e.g., MCC, hydroxyl methyl cellulose). Such deformation creates fresh, new surfaces that could be used for bonding [9]. As a result, the optimal diluents should be a combination of brittle and plastic components that fracture and deform, combining the benefits of both methods [18]. The majority of co-processed goods are made up of relatively little plastic material fixed between or on the particles of significantly more brittle material. Combinations like this can enhance certain features like hornification reduction, improved compaction performance, flow characteristics, strain-rate sensitivity, lubricant sensitivity, or sensitivity to moisture. [10]. For instance, Cellactose, a co-processed excipient that contains 25% plastic (cellulose) and 75% brittle substance (lactose), avoids the storage of excessive elastic energy during compression, resulting in a modest degree of stress relaxation and a decreased tendency of capping and lamination [19].

Picker has created a novel 3D model for the thorough and quick assessment of deforming characteristics (brittle, elastic, and plastic compression properties) of directly compressible materials based on time plasticity (d), pressure plasticity (e), and angle of torsion (ω) [20]. Densification value increases as d increases because the powder deforms more quickly when being tableted [21]. The amount of pressure required for deformation drops as e increases. The symbol (ω) denotes an inverse relationship to elastic deformation during the tableting process and suggests the ratio of compression to decompression [22]. For this reason, a deforming tableting excipient should have high d, e, and ω values with a consistent d: ω ratio at increasing densification [23]. Materials that are brittle, such dicalcium phosphate dihydrate, have low d, e, and a strong fall in ω values when densification levels rise. In contrast, the d, e, and ω values of plastic materials like Microcrystalline cellulose MCC, which have significantly greater values, barely alter when densification levels rise. Compared to sugar alcohols, sugars are less flexible. cellulose acetate, sodium Carboxymethyl cellulose CMC, and Hydroxypropyl methylcellulose (HPMC) are cellulose derivatives with plasticity comparable to MCC; However, their elasticity is dependent on substitution as seen by lower (more elastic) or higher (less elastic) values. Four viscosity classes of HPMC 2208 (HPMC K100, HPMC K4M, HPMC K15M, and HPMC K100M) were examined to see how compression speed and force affected the compaction properties. Tensile strength of the tablets decreased for all grades of HPMC when compression speed was increased from 15 to 500 mm/s; however, HPMC Kl00 tablets' tensile strengths were more susceptible to changes in compression speed than those of other grades. At every compression force or speed, HPMC K100 tablets had the maximum tensile strength, while HPMC K4M tablets had the lowest [24,25]. Native starches have a high degree of elasticity, but pregel starch and maltodextrin have lower elasticity and greater ω values. In the case of polymeric materials, deformation behavior is only affected by particle size [23].

4. Coprocessing method

A very straightforward procedure called coprocessing includes physically combining two or more excipients into a homogenous dispersion or solution, followed by co-drying, co-precipitation, or co-crystallization. Excipients are chosen based on their qualities, such as whether they are plastic, elastic, or brittle, as well as their cost, availability, and properties. The percentage of these excipients is then optimized based on the intended functionality [26]. Combining any two excipients does not increase their properties. Additionally, the established procedure and suitable experimental circumstances are also crucial factors that will ultimately result in the production of a co-processed product with increased performance. Mixing the initial components in the form of an aqueous slurry, suspension, or solution is the first stage in coprocessing. When both or one of the starting ingredients is insoluble in water, a well dispersed aqueous slurry of the initial excipients can be made by mixing the two excipients in one aqueous medium, making separate slurries of each before combining them, or coming up with other equivalent processes. A homogeneous aqueous dispersion of MCC is desired when coprocessing MCC. For instance, in the coprocessing of MCC with silicon dioxide, MCC was first dissolved in water to create a slurry or suspension, and the pH of the slurry was then brought to a neutral level. For long enough to ensure an even dispersion of the MCC, the suspension or slurry is continuously stirred. After that, the suspension or slurry is added, and the silicon dioxide is thoroughly mixed

in [27]. When MCC and $CaCO_3$ were processed together, MCC was uniformly disseminated in an aqueous solution first, then calcium carbonate was added in dry form [13]. Due to their relatively small surface area of exposure, big particle sizes (> 100 m) are typically not recommended. The particle size of the starting material is an important determinant in determining the particle size of the product. The coprocessing of the MCC and Galactomannan gum was accomplished by creating, under carefully regulated agitation, an intimate mixing of the homogeneously distributed MCC and gum to produce flocculated MCC-Galactomannan gum particles of the required size. Waring blenders, colloid mills, and homogenizers are a few examples of high shear equipment that are frequently used to combine materials [28]. When both the starting ingredients are water soluble, as in the coprocessing of galactomannan and glucomannan, the components are dissolved separately and then mixed, or they can be dissolved simultaneously in the same vessel with the help of temperature and high shear mixing. Co precipitation can be done using organic solvents, drum drying, spray drying, air drying, milling beads, fluid bed drying, and freezing, which is then followed by pressing or drying. More favored co-precipitation drying techniques include co-precipitation with a water-miscible solvent and potential pH adjustment [12].

5. Co-processed excipients for direct tableting

The next sections go into great detail about the physical and mechanical analyses of specific co-processed excipients.

5.1. Coprocessing of Lactose

Lactose is perhaps the oldest and one of the most vital diluents in tableting for solid dosage forms. However, the use of crystalline alpha-lactose monohydrate as a filler-binder for direct tableting is constrained by the insufficient compactibility and poor flow characteristics of the powder form. In order to address the need for excipients for direct compression excipients, many researchers and excipient producers adjusted crystalline alpha-lactose monohydrate to produce a product exhibiting good compactibility, reduced capping propensity, and good flow qualities [29]. In order to enhance lactose's direct tabletting properties, it was processed into tiny alpha-lactose monohydrate agglomerates (such as Tablettose, Pharmatose DCL 15) or spray-dried lactose. Compared to conventional lactose, this processed lactose is more fluid and compactible. Spray-dried lactose has a marginally better dilution potential than liquid lactose, however its compressibility is questionable. Lactose that has been spray-dried loses its compressibility at initial compaction, making it difficult to rework [9]. Binary mixes of crystalline alpha-lactose monohydrate with MCC, povidone, or starch were afterwards tested, however these simply increased the mixtures' compressibility without improving their flowability in comparison to pure alpha-lactose monohydrate [29]. Therefore, efforts were made to develop co-processed lactose. Ludipress, a filler that is appropriate for direct tabletting on high speed presses, was created by coprocessing -lactose monohydrate with povidone and crospovidone at BASF AG in Ludwigshafen, Germany. The white, free-flowing granules are odourless, tasteless, and were created specifically for direct compression, but they can also be used as filler for hard gelatin capsules. The lactose powder acquired good flowability and a low degree of hygroscopicity as a result of the formation of polyvinyl pyrrolidone and crospovidone coat over it. In addition, production machine speed has little effect on how

hard the tablets are. Both Ludipress's unlubricated and lubricated with 1% magnesium stearate have good binding qualities that have been determined to be far superior to those of the physical combination [14]. Despite the fact that Ludipress contains a disintegrant, the disintegration of tablets takes longer than it does for tablets containing Tablettose, Anhydrous beta-Lactose, alpha-Lactose Monohydrate, or Spray-Dried Lactose. The presence of polyvinylpyrrolidone is thought to be responsible for the prolonged disintegration time [30]. According to Ashrafi et al., the usage of Ludipress in large doses can somewhat prolong the sustaining impact of the formulation [31]. As evidenced by its lower static and dynamic angle of repose than other excipients, Ludipress demonstrated greater flow rate when compared to Avicel PH 101 and has the highest flowability among various lactose-based directly compressible excipients (Cellactose, Tablettose, and Fla flo lactose) [32,33]. When the disintegration time of tablets was calculated, it was discovered that Ludipress compacts had a disintegration time minimum of roughly 100 MPa. While Cellactose demonstrated a considerable increase in disintegration time (> 20 min) at compaction pressures above 100 MPa, tablet disintegration time of Ludipress-based compacts was unaffected at compaction pressures above 100 MPa [34,35]. Ludipress had a similar ability to create coherent compacts to Cellactose and Avicel PH 200, but the physical composition produced noticeably softer tablets. The friability of Ludipress compacts was less than 0.2% at a compaction pressure of 100 MPa. For tablets made with Tablettose, a compaction load of 200 MPa was required to get comparable results. As a multipurpose excipient, authors have further concluded that Ludipress should be preferred in the formulation of low dosed medications because Ludipress-based tablets demonstrated optimal disintegration time and compression pressure independent glibenclamide dissolving [35]. However, Ludipress has a lower dilution potential with acetaminophen than Avicel PH 101, Elcema G250, or Elcema P050, according to Baykara et al. in one investigation [36]. Schmidt and Rubensdorfer assessed Ludipress's powder and tabletting properties and discovered that its samples displayed better batch-to-batch consistency and flow characteristics than the physical blends and other excipients analysed. Additionally, Ludipress can create coherent compacts similar to those produced by Cellactose and Avicel PH 200, but the physical blend produced tablets that were noticeably softer [34]. Heinz et al. discovered that the tensile strength of tablets formed of Ludipress increased linearly with compaction pressures up to 300 MPa and regardless of the geometry of the tablets (diameter, thickness, and shape). It was discovered that, regardless of the shape of the tablets, the tensile strength of tablets formed of Ludipress increased linearly with compaction pressures up to 300 MPa. With a small change, the equation may be obtained to scale up from a single-punch press to a rotational tableting machine and to correlate compaction pressure with tablet hardness. At the same pressure, tablets made in the rotating machine have a somewhat higher tensile strength. The throughput and rate of pressure increase have no bearing on the tensile strength of Ludipress tablets. It is believed that this variation is caused by a specific minimum stay duration. They came to the conclusion that as long as the powder combinations are made with the same amount of mixing energy, Ludipress-based tablet manufacture may be scaled up from one rotary press to another without any issues [37]. Lactose monohydrate coarse and standard grade sieved crystalline fractions have good flow characteristics but lack compressibility [9]. Improved bonding ability and excellent flow qualities have been obtained by coprocessing crystalline alpha-lactose monohydrate with powdered cellulose (Cellactose, Meggle) [18]. or

MCC (MicroceLac, Meggle] [38]. The combination of the filling and binding capabilities of cellulose and lactose, which were specifically engineered for direct tableting, results in improved tableting performance at a cheaper cost. Due to its uniform particle shape and good particle size distribution, it has high flowability [18]. The primary consolidation process of plastic deformation of cellulose and lactose fragmentation is responsible for improved compactibility of cellactose [39]. Additionally, it has been demonstrated that Cellactose has a larger dilution potential than a physical amalgamation of its component excipients [40]. Cellactose has excellent disintegration characteristics because cellulose fibres are present in the macroporous particles. Because Cellactose is coated with lactose, its moisture absorption is substantially lower than that of cellulose alone [14]. Belda and Meilck discovered that Cellactose had better compressibility but worse compactibility when compared to powder combinations that contained 25% (w/w) of Avicel PH101 or Elcema ® P100 and 75% Tablettose ® or lactose (100 mesh) [41]. Arida and Al-Tabakha discovered that Cellactose tablets had a stronger strength than their physical combination at the same ratio. The higher interparticle bonding in this coprocessed excipient, Cellactose, is what is responsible for the increased tablet strength. The relaxation of lubricated tablets is larger than that of unlubricated tablets in which interparticle attractions are strong due to the reduction of interparticle bonding caused by the presence of a lubricant coating on the particles. Magnesium stearate, a lubricant, has a deleterious impact on the interparticle bonding of cellobiose particles, however this effect is less severe [42]. Jogani and Gohel created a lactose and MCC (3:1) foundation and used a melt granulation approach to coprocess a directly compressible adjuvant using 12.5% of a polymer blend with a PVP:PEG ratio of 1:9. The prepared agglomerates were assessed for percentage fines, and the tensile strength, friability, and disintegration time of compressed tablets were assessed for Carr's index. According to the authors, the development of a multifunctional immediately compressible adjuvant for use in pharmaceuticals can be successfully replaced by the melt granulation technique [43]. MicroceLac 100 is a different spray-dried product that is sold and contains MCC (25%) and -lactose monohydrate (75%) [44]. Better tabletting performance is offered at a reduced cost by Microcelac, which combines lactose's filling qualities with MCC's binding capacity [38]. Muzková and Zvolánková discovered that, for compression forces of 6 and 8 kN, the strength of tablets made from pure Cellactose 80 was inferior to those made from MicroceLac 100, both with and without the lubricant. With the exception of the tabletting materials containing 0.4% sodium stearylfumarate (Pruv) with a compression force of 6 kN, Cellactose 80 tablets took longer to disintegrate than MicroceLac 100 tablets. [45]. Michael et al. demonstrated that Microcelac 100 has superior flow and binding qualities and does not change even when folic acid is added. Spray-drying is blamed for these increased qualities [44]. Starlac, a co-processed filler-binder made of 15% native corn starch and 85% alpha-lactose monohydrate, is the newest product on the market [38]. Although starch is a dual-purpose excipient that may be utilised as a binder and a disintegrant, it has the lowest elastic recovery at high binding capacity. A product with outstanding compactibility was produced when starch and alpha -lactose monohydrate were co-processed [29]. It was discovered that the lactose qualities of StarLac affected its volume-pressure deformation characteristics. StarLac's capacity to flow depends about the procedure for spray drying. Starch also contributes its quick breakdown characteristic. Starch and its physical mixes were shown to have better compactibility and flowability when

treated with starlac [46]. In the creation of co-processed lactose and starch, Gohel and Jogani showed how to use a number of linear regressions. The authors came to the conclusion that while friability decreased as the lactose:starch ratio rose, Carr's adjuvant index and tablet crushing strength increased. Friability is negatively impacted by the starch paste percentage [47]. These issues have been resolved through the coprocessing of anhydrous lactose (95%) and lactitol (5%), resulting in Pharmatose DCL 40. Because of its spherical shape and advantageous particle size distribution, its flow characteristics are enhanced. At higher humidity levels, Pharmatose DCL 40 absorbs very little water. Additionally, it has far greater binding qualities and diluting potential than any other known lactose-based products [14].

5.2 Cellulose coprocessing

MCC is a common direct compression excipient that has minimal hygroscopicity and good lubricity. It has the greatest potential for dilution. Due to the existence of slip planes and dislocations on a microscale and the distortion of the spray-dried agglomerates on a macroscale, the MCC particles are plastically deformed when compressed [9]. However, during wet granulation, MCC loses its ability to compress when water is added. This occurrence is referred to as quasihornification [10]. When MCC is utilised in a significant amount of tablets, the loss of compressibility is an issue. Because of its small particle size compared to the majority of other direct-compression fillers, MCC has low fluidity. Improved tablet compact strength and decreased sensitivity to wet granulation are the outcomes of coprocessing MCC (98%) with fumed colliodal silicon dioxide (2%) into SMCC (Prosolv) [10,48]. Additionally, SMCC exhibits MCC's inferior flowability [49]. The substance created by the "silicification" method is chemically and physically quite similar to ordinary MCC, according to Fraser et al conclusion .'s that there is no detectable chemical or structural difference between SMCC, MCC, and dry mixtures of MCC and silicon dioxide [50]. Despite having extremely similar structural similarities, analytical methods like near IR cannot explain why SMCC is more compressible than MCC. After wet granulation, internal bonding in SMCC explains how MCC's compressibility changed [51]. Using a mixer torque rheometer, Luukkonen et al. investigated the rheological behaviour of wet powder masses of standard grades of MCC (Emcocel 50 and Avicel PH 101) and SMCC (Prosolv) as a function of mixing time. They discovered that SMCC has better flow properties and a more specific surface area while having less swelling than regular MCC grades [49]. Colloidal silicon dioxide has a slight detrimental impact on the unlubricated MCC's interparticle bonding strength, according to Bolhuis et al. In contrast to physical mixes, SMCC had no discernible impact on the tablet strength of lubricated tablets [52]. With increasing compression force, SMCC compact strength was noticeably increased [53]. Compacts of SMCC showed more strength and stiffness than those of MCC, according to Staniforth et al. [54]. When cohesive, poorly compressible components are packaged into direct compressed tablets, Lahdenpää et al. have shown that SMCC is effective [55]. In the 0.7–0.9 packing fraction range, which is the range for pharmaceutical tablets, Kachrimanis et al. showed that Prosolv outperformed Avicel in terms of tensile strength but significantly outperformed Avicel in terms of disintegration time. The moisture absorption, packing, and particle deformation during tapping and tabletting are all impacted by the MCC grade or silicification. Only for relative humidity levels up to 52%, the silicon dioxide added serves as a barrier or sink for the moisture

absorbed. The incorporation of silicon dioxide does not promote particle deformation at greater relative humidity (72%), but rather prolongs the disintegration period due to its likely saturation [56]. Silicification also reduces the amount of amine medication (tacrine hydrochloride) that binds to MCC in aqueous solution [57]. Although these results were not substantially different from either of the MCC-containing capsules, Felton et al. discovered that SMCC-containing capsules had the lowest variance in weight [58]. Typically used in chewable tablets, Avicel CE 15 is a co-processed excipient of MCC and guar gum [38]. Improved palatability, a creamier mouthfeel with less grit, and less tooth packing are all features of Avicel CE 15 [38]. MCC and calcium carbonate were co-processed at weight ratios ranging from approximately 75:25 to 35:65. The product has a low sensitivity to lubricants; when various lubricants are used, the compression profile (tablet hardness vs tablet compression force) largely stays the same. This insensitivity to lubricants extends to both lubricant level (quantity) and lubricant type (stearic acid, magnesium stearate, etc.) [13]. Spray-drying technology was used by Limwong et al. to create composite rice starch and MCC particles, and they assessed the direct compressibility of the particles. These composite particles showed good flowability and compressibility, whereas the tablets have minimal friability and good self-disintegration. Consequently, these newly created composite particles could be used as a brand-new co-processed direct compression excipient. [59]. In comparison to MCC, the co-processed MCC and mannitol product had better compactibility, lubrication sensitivity, and ejection profiles [60]. Shirwaikar et al. produced direct compression excipient by coprocessing MCC and mannitol using the spray drying technique. The optimal powder and compressibility properties of mannitol and MCC in the ratio of 1.25:1 were discovered, together with a quick disintegration property. The formulation was rated as the best in an evaluation based on disintegration time and mouthfeel characteristics such grittiness and chalkiness [2].

5.3 Coprocessing of sugars and polyols

Sorbitol is frequently used in chewable tablets and as the only ingredient in sugar-free mints. It makes reasonably decent compacts, has a cold flavour, and feels good in the mouth. But because of its high hygroscopicity, it has poor powder flowability and can clump together during tableting. Additionally, its hygroscopicity affects the physical properties of tablets, including their hardness, dissolving, and bioavailability. Mannitol, on the other hand, is less sensitive to humidity than sorbitol but does not produce tablets that are as firm [9]. With less hygroscopicity than sorbitol, Compressol S, a directly compressible excipient of sorbitol and mannitol, maintains the compactibility of sorbitol and the distinctive mannitol texture. Because Compressol S is 300 times less hygroscopic than sorbitol, it is more suited for usage with medications that are sensitive to moisture. This solution is intended to help the formulator with formulations with a high active loading and challenging actives. Compressol S's nice flavour and agreeable mouthfeel, along with its good compactibility and low hygroscopicity, making it the perfect ingredient for chewable and high-dose active nutraceutical tablet formulations Quick-dissolving tablet formulations can also successfully use mannitol and sorbitol as co-processed excipients. Its very desirable sweetness and natural food inclination make fructose a monosaccharide that is readily available from nature and can be used in medicinal formulations. However, fructose cannot be compressed directly. The compressibility of fructose granules

that have been agglomerated from a water solution is poor and they are hard. With the addition of a tiny amount of starch to the co-dried fructose in AdvantoseTM FS 95 direct compression fructose, fructose is transformed into a superior excipient for use in pharmaceutical, nutraceutical, and chewable vitamin applications. Advantose FS 95 fructose's particle size dispersion considerably enhances the flow characteristics. Due to its enhanced compressibility and decreased hygroscopicity than regular fructose, Advantose FS 95 is easier to handle [38]. Dipac is made up of 97% sucrose and 3% highly modified dextrins that have been co-crystallized. The latter's crystal structure is disrupted by the former, increasing its compressibility [61]. Danisco A/S, Copenhagen, Denmark, sells Xylitab®, another co-processed sodium caboxymethyl cellulose and xylitol directly compressible excipient. Xylitab is perfect for all tablet forms, has a cold taste, and has excellent stability. Xylitab 100 and Xylitab 200 were examined by Morris et al. for compaction, flow, lubrication needs, and dilution potential [38]. It was determined that xylitab's compaction profiles, flow behaviour, and dilution potential were satisfactory, and the authors came to the conclusion that xylitab can be successfully used as a direct compression chewable tablet excipient [62].

5.4 Coprocessing of inorganic fillers

The ability to produce immediately compressible calcium carbonate is a clear benefit of coprocessing calcium carbonate (70%) with sorbitol (30%) (Formaxx). In comparison to calcium carbonate, Formaxx exhibits lower friability and better flowability as well as higher compaction capabilities at low compression forces. The flavour of calcium carbonate is disguised by this unusual technique that involves sorbitol [38]. The coprocessing of magnesium carbonate with 5% powdered cellulose was demonstrated by Freitag et al. as a potential excipient for direct compression. In comparison to pure magnesium carbonate or their physical combination, this co-processed product has better flow and tablet qualities [63].

5.5 Other co-processed excipients

Adeagbo and Alebiowu used the flow and compressional characteristics of paracetamol granules and the mechanical properties of their tablets to compare the lubricant activity of cocoa butter co-processed with magnesium stearate plus talc to magnesium stearate plus talc. The authors came to the conclusion that cocoa butter is a beneficial and practical lubricant that may be processed along with a magnesium stearate/talc mixture to effectively lubricate granules. It may also be helpful in formulations that are sensitive to lamination and capping in tablets. [64]. Crospovidone and sodium starch glycolate were combined to create a co-processed super-disintegrant by Gohel et al., which had good flow and compression characteristics. A rapid disintegration and better medication solubility were seen when these co-processed excipients were utilised in cefixime trihydrate and ibuprofen tablets [65]. In comparison to the physical blend, Gohel et al. have demonstrated that the co-processed superdisintegrant of croscarmallose sodium and crospovidone has improved flow, crushing strength, disintegration time, and drug dissolution [66].

6. Co-processing principle based on particle engineering

Particle engineering is a wide term that entails simultaneous small adjustments to particle properties including form and size distribution. There are three solid-state stages that define solid substances. These tiers are interconnected on a deep level, alterations at one level reflecting those at another. The molecular level is the initial level, which consists of how specific molecules are arranged within a crystal lattice and includes phenomena like polymorphism, pseudo-polymorphism, and the amorphous state. The form, size, surface area, and porosity of each individual particle make up the second level of organisation, known as the particle level. The third level is the bulk level, which consists of a collection of particles and has characteristics including flowability, compressibility, and dilution potential. which are essential elements for excipient performance [67].

7. Advantages of Co-Processed Excipients

1. Greater potential for dilution Excipients must be able to maintain their compressibility even when diluted with other excipients. It is desirable to use a co-processed excipient with a high dilution potential so that the compressibility of the powder mixture can be preserved even after dilution.

2. Less sensitivity to lubricants A co-processed excipient with a high degree of brittleness has low lubricant sensitivity because it hinders the creation of a coherent lubricant network by exposing new surfaces upon compression and fragmenting the existing network. In general, hydrophobic lubricant has a detrimental effect on compression.

3. Enhanced compaction When developing tablets, compressibility is a crucial aspect. Most co-processed excipients are able to get around this restriction.

4. Enhanced flow characteristics Particularly when it comes to high speed rotary tablet machines, good flowability is desired. By regulating appropriate particle size and distribution, the co-processing excipient plays a significant part in optimising flow properties.

5. Constancy The substances employed should not interact with other excipients or APIs and should be inert. It need to be stable both chemically and physically [68].

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