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REVIEW ARTICLE

Co-proccessed excipients with enhanced direct compression functionality for improved tableting performance

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Abstract

It is necessary to have excipients with excellent functional properties to compensate for the poor mechanical properties and low aqueous solubility of the emerging active ingredients. Therefore, around 80% of the current drugs are not suitable for direct compression and more advanced excipients are required. Further, conventional grades of excipients cannot accommodate the technologically advanced high speed rotary tablet presses which require a powder with excellent flow, good compressibility, compactibility, particle size distribution and homogeneity of the ingredients. Co-processed excipients have been created to enhance the functional properties of the excipients and reduce their drawbacks. Co-processing is defined as the combination of two or more excipients by a physical process. Co-processed excipients are adequate for direct compression since they become multifunctional and thus, their dilution potential is high eliminating the need for many excipients in a formulation. In some cases, they are able to hold up to 50% of the drug in a formulation rendering compacts of good tableting properties. This study describes and discusses the functionality enhancement of commercial and investigational excipients through co-processing.

Keywords: Co-processed excipients, co-processing, direct compression, multifunctional excipients, particle engineering

Enhancement of excipient functionality

Currently, the emerging new drugs in the market such as didanoside, lopinavir, podofilox, paclitaxel and oxaprocin exhibit physicochemical, solubility and pharmacokinetic properties, which challenge the requirements of the existing excipients during the drug product development phase. Further, the increasing speed capabilities of tablet machines are pushing excipient functionality to its limits. These problems require either the development of new excipients, or modification of commercial excipients. The pharmaceutical industry demands scientist develop excipients quickly, with limited scaling up, manufacturing and environmental costs. However, the search for new excipients requires extensive toxicology tests, which make them costly. For this reason, in the last three decades, new grades of existing excipients have been developed, but relatively few novel excipients have been introduced in the market[1]. An excipient is considered new when it contains a new chemical entity, is physically modified, is a co-processed mixture of existing excipients, is directed toward a new route of administration, or when a food additive is used for the first time in a drug product[2].

New grades of existing excipients can be achieved by modifying the powder fundamental properties leading to improved derived (functional) properties[3,4]. Fundamental characteristics, such as morphology, particle size, shape, surface area, porosity and density, determine excipient functional properties such as flowability, compressibility, compactibility, dilution potential, disintegration time and lubricant sensitivity (Figure 1).

Nevertheless, functionality can be only be improved to a certain extent because of the limited range of possible modifications[5]. Powder density and particle size could be changed to achieve better functionality. However, when one attribute is improved, another is compromised. For example, the flow of Avicel® PH-200 is improved at the expense of its compactibility and vice versa for Avicel® PH-101[6]. Further, thermal treatment of native starches

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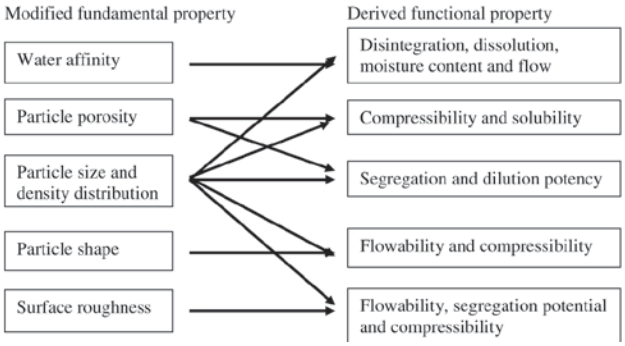

Figure 1. Effect of the material fundamental properties on the derived properties.

has led to an improved binder (pregelatinized starch). The starch granules are partially hydrolyzed and broken making them more hydrophilic[7]. This physical modification provides multiple functionality, such as excellent flow, self-lubrication property, filling application in hard gelatin capsules (5–75%), binding in wet granulation (5–20%), tablet disintegration functionality (5–10%), as well as roller compaction and direct compression applications[8].

There are three levels of the solid state that can be modified to improve excipient functionality. These comprise the bulk, molecular and particle levels. The bulk level of a material can be modified by changing particle interaction in the bulk state[5]. This approach is widely used during the drug development stage and implies only a dry blend of two or more excipients in an exact ratio. The resulting blend will exhibit intermediate properties to those of the parent materials. In select cases, the magnitude of these properties is not ratio-dependent. Particle size, particle size distribution and bulk density of materials should be similar; otherwise, segregation will take place. Segregation may occur during manipulation, handling and storage of products rendering stability and batch to batch variability issues[9]. Thus, in the design and development of a product, it is not uncommon to use two or more excipients/coadjuvants to obtain a mixture with adequate tableting properties; the properties of such blends can result in either synergistic or antagonistic effect(s) with respect to various tableting properties[6]. For example, a dry blend can be used to formulate rapidly disintegrating tablets in which a mixture of Prosolv® SMCC, mannitol and a poorly soluble drug are compressed at low pressures and then freeze dried to make solid tablets. Prosolv® SMCC can absorb sufficient quantity of fine dust of fast dissolving excipients such as mannitol. The resulting compacts are able to disintegrate within 60 sec after contact with water or saliva[10].

Similarly, mixtures of glyceryl dimenihate, a bitter drug, and microcrystalline cellulose (MCC) can be extruded-spheronized to form beads which are then coated with hydroxypropylmethylcellulose (HPMC) and compressed into tablets. These compacts disintegrate in the mouth within 20 sec[11]. In a few cases, the API can be dispersed with the excipients and then spray-dried to form a more homogeneous blend. For example, acetaminophen can be spray-dried with maltodextrin to produce oblong free-flowing particles of good compactibility. In this case, the binary mixture has good compactibility, but the compacts show a capping tendency[12]. It may be necessary to diminish the deleterious effect of adjuvants in the bulk, which can, in some cases, be done simply by changing blending time. For example, the negative effect of magnesium stearate on plastic deforming materials can be reduced by decreasing the blending time to less than 5 min[13].

The molecular level can be modified by changing the arrangement of molecules in the crystal lattice, generating new allomorphs, pseudopolymorphs, making a material more amorphous or by applying a chemical treatment (crosslinking). Chemical modification of the material at a molecular level usually involves a crosslinking reaction between the excipient and a low molecular weight substance. This process is expensive and usually requires a solvent recovery technique. Furthermore, crosslinking agents are usually toxic and leave traces of by-products (impurities) that can degrade in living tissues to form toxic compounds. For example, MCC, starch, chitosan, lactose, and other sugars can be easily crosslinked with glutaraldehyde in a complex etherification reaction. However, glutaraldehyde also polymerizes, leading to the formation of undesirable by-products, which are difficult to remove[14]. There are several examples of widely used crosslinked excipients approved for pharmaceutical applications. For example, carboxymethylation of potato starch (ether synthesis), followed by neutralization with citric acid renders a superdisintegrant called sodium starch glycolate. Another type of starch crosslinking leads to a new product (hydroxyethyl starch) useful for parenteral applications. Further, cellulose derivatives such as ethyl cellulose (EC), methylcellulose (MC) and (HPMC) are other examples of chemically modified excipients[15].

Modification of the crystalline structure also renders excipients with different properties. For example, microcrystalline cellulose I (MCCI) can be transformed to microcrystalline cellulose II (MCCII) by basic treatment. MCCII has a higher porosity, less packing tendency, degree of crystallinity, degree of polymerization and density, but a faster disintegration rate than MCCI. Further, compacts made of MCCII present better mechanical properties than those of MCCI[16].

At the particle level, individual particles can be modified in shape, size, surface area and porosity by processing or co-processing with another inert material. Co-processing is based on the concept of excipient interaction at the subparticle level. It provides a synergy of functionality as well as masking the undesirable properties of the individual components[3]. Particles can be incorporated either on the surface, or within the core of the excipient particles. This process requires vigorous homogenization of the excipients, followed by a process such as spray drying, crystallization, spheronization,

bulk drying, etc. Co-processing is less expensive than crosslinking, as long as the materials involved comply with the pharmacopeia requirements because the toxicity studies required for a new material are not needed for co-processed products.

Excipient co-processing

Co-processing is defined as a combination of two or more established excipients by a pharmaceutical process. The products so formed are physically modified such that they do not lose their chemical structure and stability. This means that excipients maintain their independent chemical properties; while, synergistically increase their functional performance[17].

Usually, a co-processed material exhibits superior properties than the physical mixture of individual components. Ideally, a combination of a plastic and a brittle deforming material is desired for co-processing[5]. This combination prevents storage of too much elastic energy during compression, which is associated with the compacts tendency for capping and lamination[18].

A major limitation of a co-processed excipient is that the ratio of the excipients in the mixture is fixed and while developing a new formulation, a fixed ratio of the excipients may not be desirable for the dose and characteristics of the API[19].

Spray-drying, wet granulation, spheronization, co-milling, and co-crystallization can be used for co-processing. Spray-drying is a process in which an aqueous or organic dispersion of the materials is sprayed through a nozzle at high pressure, and the droplets formed are rapidly dried and collected as powder. Wet granulation involves the addition of an aqueous dispersion of a binder to a previously mixed powder blend followed by wet sieving and drying. In the spheronization process, first, the wet mixture of excipient(s) is extruded to produce homogeneous spaghetti-like rods. This extrudate is then converted to beads by using a spheronizer. Co-milling is used to disperse, homogenize and reduce the particle size of excipient mixtures in an aqueous media. In co-crystalization, the two materials are dissolved by heating, followed by cooling at different rates.

Co-processed excipients

The main commercial and investigational co-processed excipients are summarized in Tables 1 and 2.

Lactose–Lactitol (Pharmatose®)

It is produced by spray drying of a 95% anhydrous β-lactose and 5% anhydrous lactitol solution. It is available in different grades depending on the particle size[20]. For example, the grade 100M has a median particle size of ~122 μm and a high density (bulk density of 0.73 g/cm^3 and tap density of 90 g/cm^3), which are responsible for its good flowability (Carr's index of 16%[21]). Low particle size grades (<32 μm) are mainly used for nasal powder formulations[22]. Compacts made at 16 kN with diazepam showed disintegration times of 85 sec. It also possesses a low water uptake (5.5%) at a relative humidity (RH) of 70%[23,24].

Lactose–Cellulose (Cellactose®)

It is composed of 75% α-lactose monohydrate and 25% powder cellulose obtained by spray drying. The good compactibility (tensile strength of 3.8 MPa at a solid fraction of 0.9) of this material is attributed to the synergic effect of consolidation by fragmentation of lactose and the plastic deformation of cellulose[25]. During spray drying, lactose particles coat the cellulose fibers forming granules of good flow. This excipient combines the good flowability and solubility of lactose with the good water sorption and binding properties of cellulose (tensile strength of 3.8 MPa at a solid fraction of 0.9[26]). It has a bulk density of ~0.38 g/cm^3 and a volume-diameter particle size of ~238 μm. It exhibits higher tensile strength than lactose (3.8 MPa vs. 1.8 MPa) and the dry blend of 75% lactose and 25% cellulose (2.0 MPa, respectively). It possesses better compressibility compared to Ludipress® (co-processed lactose monohydrate, povidone and crospovidone), Fast Flo 316® (spray-dried α-lactose monohydrate), Tablettose® (spray-dried α-lactose monohydrate), Dipac® (co-processed sucrose and maltodextrin) and anhydrous lactose. It also shows superior flow than Avicel® PH-101 (Carr's index of 22% and 34%, respectively[27]).

This material is virtually not affected by lubricants. During compaction, at low compression pressures, the fragmenting behavior predominates as many new surfaces of lactose are generated under compression and therefore, the lubricant sensitivity is low. However, at pressures higher than 180 MPa, plastic deformation given by the MCC component is prevalent since the outer lactose coating has already undergone fragmentation for both, the lubricated and non unlubricated materials. It has higher tensile strength than the physical mixture because of favorable interactions between lactose and MCC particles. It is also less sensitive to magnesium stearate than the physical mixture of 75% lactose and 25% MCC. Both, Cellactose® and the physical mixture exhibit an increase in tablet relaxation at high compression speeds[25]. Disintegration is slow and pressure-dependant, since it requires the lactose outer shell to dissolve and the resulting viscous layer recedes allowing access to the cellulose core. For example, compacts made at a compression pressure of 160 MPa, have a disintegration time of ~14 min, whereas compacts made at 100 MPa have a disintegration time of 80 sec[28]. Further, compacts of made of Cellactose® at 150 MPa have comparable hardness (130–140 N), disintegration time (50–80 sec) and lower ejection forces (0.11 kN vs. 0.30 kN) than StarLac®[23].

Lactose–MCC (Microcelac 100®)

It is a spray-dried material intended for direct compression composed of 25% MCC and 75% α-lactose monohydrate. It has a median particle size of ~150 μm, superior

Table 1. Starch-based and cellulose-based co-processed excipients.

Type	Brand name	Manufacturer	Ingredients	%	Processing
Starch-based	Advantose® FS	SPI Pharma	Fructose	95	Spray-drying
			Starch	5	
	StarCap® 1500	Colorcon	Corn starch	90	Spray-drying
			Pregelatinized starch	10	
	a	[10]	Silica	50	cocrystallization
			Starch	50	
Cellulose based	Avicel® HFE	FMC	MCC	90	Spray-drying
			Mannitol	10	
	Avicel® RC-591	FMC	MCC	89	Milling, Spray-drying
			Na CMC	11	
	Avicel® RC-581	FMC	MCC	89	Milling, Bulk drying
			Na CMC	11	
	Avicel® CL-611	FMC	MCC	85	Milling, Spray-drying
			Na CMC	15	
	Avicel® HFE	FMC	MCC	90	Spray-drying
			Mannitol	10	
	Avicel® RC-591	FMC	MCC	89	Milling, Spray-drying
			Na CMC	11	
	Avicel® RC-581	FMC	MCC	89	Milling, Bulk drying
			Na CMC	11	
	Avicel® CL-611	FMC	MCC	85	Milling, Spray-drying
			Na CMC	15	
	Avicel® CE15	FMC	MCC	85	Spray-drying
			Guar gum	15	
	Barcroft® CS90	SPI Pharma	Calcium carbonate	90	Spray-drying
			Starch	10	
	ForMaxx®	Merck/EMD	Calcium carbonate	70	Spray-drying
			Sorbitol	30	
	ProSolv® SMCC50	JRS Pharma	MCC	98	Spray-drying
			Colloidal silicon dioxide	2	
	ProSolv SMCC90®	JRS Pharma	MCC	98	Spray-drying
			Colloidal silicon dioxide	2	
	Xylitab®200	Danisco	Xylitol	98	Granulation
			Na CMC	2	
	a	[44,45]	MCC	80	Spray-drying
			Calcium carbonate	20	
	a	[97,98]	MCCII	95	Spray-drying
			Colloidal silicon dioxide	5	
	a	[64]	Rice starch	70	Spray-drying
			MCC	30	

[a] Under research

flowability and binding properties compared to the physical mixture of MCC with different lactose grades, such as α-lactose monohydrate, anhydrous β-lactose and spray-dried lactose[23,29]. At compression forces between 6 and 8 kN the strength of its compacts is higher than that of Cellactose® with and without the addition of magnesium stearate. Compacts made at 6 kN disintegrate much faster than those made with Cellactose®80. Further, compacts made with ascorbic acid and Microcellac® possess higher strength than the ones made with Cellactose®80[30].

Lactose–PVP (Ludipress®)

It consists of 93.4% α-lactose monohydrate (filler), 3.2% Kollidon®30 (binder) polyvinyl pyrrolidone, (M_v 44–54 kD) and 3.4% Kollidon®CL (disintegrant). It is produced by coating lactose with Kollidon®30 and Kollidon®CL[27]. It has good flow (Hausner ratio of 1.2) due to the predominant spherically-shaped particles, which contain a large number of small lactose crystals with smooth surfaces held together by Kollidon®30 and Kollidon®CL[27]. It has a bulk density from 0.50 to 0.57 g/cm^3. It requires magnesium stearate for lubrication since it develops friction during compression. However, magnesium stearate increases tablet friability and disintegration times. Compacts made at >100 MPa show friability values lower than 1%[13]. Its volume-diameter particle size is ~210 μm. Although it contains disintegrant, disintegration of the tablets takes longer than those containing

Table 2. Lactose-based, sugar-based and other co-processed excipients.

Type	Brand name	Manufacturer	Ingredients	%	Processing
Lactose-based	Cellactose®	Meggle	α-Lactose monohydrate	75	Spray-drying
			Powder cellulose	25	
	Ludipress®	[27]	α-Lactose monohydrate	93.4	Roller drying
				3.4	
			Crosspovidone		
			PVP	3.2	
	Microcellac®	Meggle	α-Lactose monohydrate	75	Spray drying
			MCC	25	
	Pharmatose®DCL40	DMV Vengel	β Lactose	95	Spray drying
			anhydrous Lactitol	5	
	StarLac®100	Meggle/Roquette	α-Lactose monohydrate	85	Spray drying
			Corn starch	15	
Sugar-based	Di-Pac®	Domino Specialty Ingredient	Sucrose	97	co-crystallization
			Maltodextrins	3	
	Compressol®S	SPI Pharma	Mannitol	70	Melt extrusion
			Sorbitol	30	
	F-Melt®	Fuji health Science	Xylitol, calcium hydrogen	40–90	Spray drying
			phosphate	1–30	
			Crospovidone	5–40	
	LudiFlash®	BASF	Mannitol	90	Granulation
			PVA latex solids	5	
			Crospovidone	5	
	Sugar Tab®	JRS Pharma	Sucrose	93	Crystallization
			Invert sugar	7	
	Xylitab®100	Danisco	Xylitol	96.5	Granulation
			Polydextrose	3.5	
	a	[78]	Sucrose	95	co-crystallization
			Sorbitol	5	
Others	Effer Soda®	SPI Pharma	Na carbonate	10	Spray coating
			Na bicarbonate	90	
	Timerx®	Penwest	Xanthan gum	NR	NR
			Locust bean gum		
	a	[43]	Chitosan	50	Codrying
			Silica	50	
	a	[59]	PVP	75	co-crystallization
			Sodium starch glycolate	25	
	a	[86]	Wax	5	Hot melting
			Calcium phosphate	95	

NR, Not reported; a, Under research.

α-lactose, β-lactose and spray-dried lactose alone, because of the presence of Kollidon® 30 in the excipient. For example, if compacts are made at 250 MPa, they disintegrate in ~4 min, whereas compacts made of Tablettose® and the physical blend take about 13 min and 1 min, respectively. It has a lower compactibility (160 N) than Cellactose® (180 N), but larger than that of Avicel® PH-200, Tablettose® and its physical blend (140 N, 90 N and 60 N, respectively[27]). It also shows a lower yield pressure than that of Avicel® PH-102 (86 vs 49 MPa, respectively) and it also has good tableting characteristics for low dose APIs such as glibenclimide (2 mg) and its hardness is not affected by tableting speed[32]. It also exhibits better flowability than Cellactose® Tablettose® and Avicel® PH-200 (angle of repose of 31°, 36°, 36° and 36°, respectively[27,33]).

Lactose–starch (StarLac®)

It is produced by spray-drying of 85% lactose monohydrate and 15% native maize starch. It is an adaptable excipient since the two materials alone present poor flow and segregation problems, which restrict them to use in the wet granulation process. Crystalline lactose monohydrate provides a good diluent capacity; whereas, native starch functions as a tablet disintegrant. It has a median particle size of ~55 μm, bulk density of ~0.6 g/cm^3 and its particles exhibit a spherical shape. In this excipient, starch is dispersed within a matrix of predominantly crystalline α-lactose monohydrate. It also exhibits excellent direct compression capability similar to that of spray-dried lactose. Tablets made between 40 and 120 kN show disintegration times within 23 sec[34]. Moreover, different levels of lubricants do not affect tablet disintegration time. This

means that tablets maintain their porosity and the presence of starch allows for rapid tablet disintegration, irrespective of the tablet hardness, eliminating the need of a super disintegrant[35]. It also has excellent flow due to the uniform particle size and hence, presents little risk of segregation. It does not have a gritty taste, provides a creamy texture in the mouth, and therefore, is appropriate for use in soft chewable tablets applications. It does not cross-link with gelatin capsule shells and hence, does not delay disintegration. StarLac® is better for roller compaction than MCC since it generates less dust during milling of the resulting ribbons. It also has higher compressibility and less elastic recovery than MCC[8]. At high relative densities, compact elastic recovery and disintegration time are lower, compactibility is higher and, compared to the physical mixture of the individual components. StarLac® produces tablets with lower crushing strength than tablets made using the physical mixture containing 0.5% magnesium stearate. However, for the physical mixtures, disintegration time increases with increasing levels of magnesium stearate[36]. Compared with other co-processed excipients, the lubricant sensitivity to magnesium stearate varies as: StarLac®>Ludipress®>Cellac tose®80>Microcellac®100. The elasticity of StarLac® is influenced at low compression forces by lactose and at high compression forces by starch[34].

Starch–fructose (Advantose FS®95)

This material is produced by spray drying of 95% fructose and 5% starch. This excipient overcomes the poor dissolution and compactable properties of fructose alone. It is ideal to formulate chewable vitamins. It is a white crystalline powder of a porous granular shape and rough surface[37,38]. It has a moisture content of ~2%, a bulk density between 0.55 and 0.75 g/cm^3 and a mean particle size of ~ 300 μm. It also has good flow and compressibility. It is less hygroscopic, and easier to handle than fructose, and it is more compactable than Dipac®[39].

Starch–pregelatinized starch (StarCap®1500)

This is a co-processed mixture of corn starch and pregelatinized starch for use in capsule applications. It is an inert, free-flowing, low dust excipient with disintegration and dissolution properties independent of the medium pH. It has better flow properties than MCC. It allows for minimal dusting or adherence to contact surfaces, leading to a cleaner filling operation and lower tablet weight variation. StarCap® at >75% level makes the release profile of propranolol pH-independent and at a 24.75% level allows for the release of 90% of gabapentin within 6 min[40]. Other studies suggest StarCap® 1500 to have better compressibility, shorter disintegration time, higher lubricant sensitivity and lower elastic component of energy comparison to Starch® 1500[41].

Starch–silica (50:50)

This excipient is prepared by adding SiO_2 to a 4% dispersion of corn starch at 100°C. After the dispersion is cooled down, the addition of ethanol causes precipitation and thus, the particles are collected by filtration. Co-processing resulted in a crystalline form of starch within the amorphous SiO_2 matrix. The co-precipitate has a surface area between ~15 m^2/g vs 200 m^2/g of SiO_2 and 0.28 m^2/g for starch, respectively[42]. It has a good flow (Carr's index ~12%), tensile strength (3.0 MPa) and compressibility. Tablets of this excipient show better disintegration time (5 sec) than the one produced from starch (5 min), sodium starch glycolate (10 min), and croscarmellose (10 min). This excipient was designed as superdisintegrant and it alone renders a disintegration time of less than 10 sec for tablets compressed at 50 kN. It produces granules with good strength when hydroxypropyl cellulose is used as a binder[43].

MCC–Calcium carbonate (80:20)

This co-processed excipient is composed of 80% MCC and 20% $CaCO_3$, prepared by spray drying. The $CaCO_3$ component provides a more uniform surface, giving a smooth appearance to the tablets. The particle size ranges from 20 to 150 μm. Ground limestone and MCC have bulk densities of 0.67 g/cm^3 and 0.29 g/cm^3, respectively; whereas, the co-processed product has a bulk density of 0.41 g/cm^3,. The increased bulk density of the co-processed product allows for making smaller tablets and improved powder flow into the dies. Its aqueous slurry has a pH between 9.5 and 10. It also contains low moisture content (<8%). This co-processed excipient is useful to load drugs with bulk density lower than 0.30 g/cc[44,45]. The co-processed product exhibits low lubricant sensitivity and its compressibility is high even at high levels of API.

MCC–guar gum (Avicel® CE15)

This material is produced by spray drying of a dispersion made of 85% MCC and 15% guar gum. It has a nominal particle size of 75 μm. The presence of guar gum decreases the chalkiness, grittiness, and taste caused by MCC. The presence of guar gum makes it suitable to formulate chewable compacts[45–47]. Compared to MCC:NaCMC, Avicel®CE15 granules made by roller compaction renders granules of poor compactibility[48].

MCC–mannitol (Avicel®HFE)

This co-processed excipient is produced by spray drying a mixture of 90% MCC and 10% mannitol. The bulk density of the co-processed product is ~0.4 g/cm^3. The MCC component imparts greater compressibility and compactibility to the composite particles, but it compromises flow. The mannitol component provides good mouth-feel (due to its negative heat of solution), low grittiness, low chalkiness, low sensitivity to humidity, low plasticity and high dissolution rate (due to its high aqueous solubility and wetting properties). As a result, the co-processed product has excellent compressibility, good water wicking, and good water absorption capacity. The co-processed material provides good powder and compressibility properties with disintegration times within 15 sec. Mannitol crystals

are uniformly distributed within the MCC matrix, as opposed to the physical mixture. It has been reported that the fast compact disintegration is due to the partial amorphization and formation of submicron particles of the soluble mannitol on the surface and within the MCC matrix by spray drying. This co-processed product has higher porosity than the physical mixture and this effect is reflected in the faster disintegration time of compacts made with glyzipide (1.3 min vs. 4.1 min). This excipient is ideal for making fast dissolving tablets[18]. Compacts containing Avicel®HFE and acetaminophen are less friable and significantly more compactable than those containing MCC and mannitol alone[49]. However, they suffer from loss of compactibility after reprocessing. For example, the initial compact strength of 10 MPa is reduced to 6.2 MPa after further milling and recompression.[50]

MCC–NaCMC (Avicel®RC591/RC581/Avicel®CL611)

Avicels® RC591/581 are composed by 89% MCC and 11% sodium carboxymethylcellulose (NaCMC). Avicel® RC-591 is produced by spray drying of their aqueous slurry, while Avicel® RC-581 is produced by bulk drying of the slurry of both components. Avicel® CL-611 is produced by spray drying of an aqueous dispersion of 85% MCC and 15% sodium carboxymethylcellulose. Compacts made of Avicel® RC-581 and Avicel® PH-101 release ~77.1% and 38.9% of glizipide within 360 min, respectively[51]. Avicel® RC-591/RC-581/Avicel® CL-611 are dispersible celluloses used as suspending aids to improve the stability and texture of dispersed systems, like suspensions, emulsions, creams, lotions, etc. They produce a firm gel structure via steric stabilization due to particle interactions[52,53]. NaCMC is added to aid the dispersion and to serve as a protective colloid. As the proportion of CMC is increased to about 10% w/w in mixtures of MCC and CMC, gels are formed having a maximum yield stress, while a proportion of CMC exceeding 10% results in decreased values of yield stress. Avicel®RC-591 and Avicel® RC-581 are used from 1 to 2% for nasal sprays, topical sprays, lotions and oral suspensions. Avicel® CL-611 is mainly used for reconstitutable suspensions and oral suspensions[54].

MCC–SiO_2 (Prosolv®)

Prosolv® is the spray-dried product of MCC and SiO_2 made at the 98:2 ratio. It is available in three grades: Prosolv® SMCC90, Prosolv® SMCC50 and Prosolv® SMCC HD90 which corresponds to a mean particle size of 110 μm, 60 μm, and 110 μm, and a bulk density of ~0.30 g/cm^3, 0.30 g/cm^3 and 0.44 g/cm^3, respectively. Prosolv® SMCC50 is recommended for direct compression of poorly compactable API and for roller compaction[55]. Prosolv® SMCC90 is desirable to improve flow of the powder mixture and reduce the need for glidants. Prosolv® SMCC HD90 which is produced from hardwood sources is suggested for formulations which require good flow, good consolidation and when denser compacts are needed. It has particles with a more spherical shape and it is less tableting rate sensitive than Prosolv®SMCC50 and Prosolv®SMCC90. Prosolv®SMCC90 has better flow and produces stronger compacts than Avicel®PH-200 (28 and 32°, and 170 N and 95 N, respectively). This represents a considerable increase in the binding capability of Prosolv® and is responsible for the good "dilution potential" of this material[56,57]. Prosolv® SMCC90 and Prosolv® SMCC HD90 have low sensitivity to magnesium stearate (0.12 and 0.19, respectively). Silicon dioxide markedly suppresses the negative effect of stearate on the binding properties of MCC. This is explained by the interaction of silicon dioxide and magnesium stearate in the sense of competitive inhibition of stearate in the sites of adhesion, which are blocked by SiO_2. The physical blend has no significant contribution on the tablet strength of lubricated and non-lubricated tablets. Dissolution rate and friability are similar to conventional MCC[30,58]. However, Prosolv® compacts have poor disintegration properties (from 20 to 30 min for compacts compressed at 4 kN)[59]. Further, the compactibility of Prosolv® is slightly affected by wet granulation[60]. The above mentioned properties are due to the uniform adhesion of SiO_2 to the surface of MCC. The increased compact strength is most likely a consequence of surface interaction between SiO_2 and MCC[61]. SiO_2 interacts with cellulose possibly through hydrogen bonding and dipole-dipole interactions and thus, SiO_2 leads to a five-fold surface increase compared to MCC[62,58]. Further, SMCC has also been reported to decrease the lower punches stickiness compared to the physical mixture of MCC and SiO_2[62].

For developing orally disintegrating compacts, Prosolv® cannot comprise > 30% level in the compact because it leaves an unpleasant gritty sensation in the mouth and it does not dissolve in saliva. Prosolvs® possess a high degree of surface roughness, which increases powder shear in the dry blending process and ease low dose API loading. Prosolvs®, also might prevent oxidation of some APIs (i.e., iron and levothyroxyne). It is also good for tacky or cohesive APIs and retains high compactibility after reworking[63].

MCC–Rice starch

This is produced by spray drying of 70% rice starch and 30% MCC. The use of starch as the major component in the composite is preferred because of the abundance of inexpensive rice starch. The cellulose component imparts greater compressibility to the composite particles, but makes particles less spherical, with rougher surfaces, resulting in a decrease in flowability. Among several native starches, rice starch is the most compressible, but the flowability of rice starch is very poor because of the small size range of starch grains. During spray drying, the heat could induce partial gelatinization of the surface of the starch grains. Gelatinization of starch grains might be responsible for binding rice grains and cellulose fibers together through solid bridge forming granular particles. Spray drying affects particle shape, but not the compactibility of rice starch. Compacts made of this material show good compactibility (~189 N), low friability

(0.6 %), good flow (Carr's index of 19.2%) and disintegration properties (2.6 min), compared to rice starch (131 N, 0.6%, 44.6% and 1.9 min, respectively) and MCC (490 N, 0.0%, 38%, and >30 min, respectively[64]).

Dextrose–Maltose-Maltodextrin (Emdex®)

This commercial material is produced by spray drying a solution composed of 92% dextrose, 4% maltose and 4% maltodextrin. Emdex® is 74% as sweet as sucrose and it is composed of porous spheres[65]. It has good flow, compressibility, lubricity, non-hygroscopicity, controlled particle size, cool mouth-feel, negative heat of solution, and stability to heat and moisture, making it useful for direct compression of lozenges and chewable soluble compacts. The spherical porous granules consist of flat microcrystals bound together by higher saccharides[66]. It is reported that compacts produced from Emdex® using the direct compression method showed low elastic work (6 J) and ejection forces (0.8 kN), requiring less lubrication than compacts produced by wet granulation (elastic work of 1.6 kN and ejection force of 12 kN, respectively). Similarly, if used for wet granulation, it decreased the crushing force of the tablets and enhanced lubrication, compared to direct compression formulations. The Heckel analysis shows that this material exhibits a plastic deformation mechanism[67].

Mannitol–Kollidon (LudiFlash®)

It is a co-processed product intended for use as an excipient for orally disintegrating tablets. It is composed of 90% mannitol, 5% Kollidon® and 5% polyvinyl acetate. It possesses rapid dissolution, smooth mouth feeling and excellent compressibility[31]. It has a bulk and tap densities of 0.45 and 0.55 g/cm^3, respectively, and a mean particle size and moisture content (MC) of ~190 μm and ~4%, respectively. It imparts no chalky or sandy sensation, but a creamy consistency. It exhibits high swelling in contact with water and saliva. Tablets made at 10 kN pressure exhibit good hardness (120 kN), low friability (0.12%), and low ejection forces (50 kN). It can be used for direct compression, wet granulation or roller compaction. It serves as a filler, a binder and a disintegrant all-in-one. It requires low lubricant levels for tableting and has no segregation tendency. Compacts made of LudiFlash® and loperamide at 3.7 kN have a hardness of 30 N, disintegration time of 11 sec and drug release of 95% within 30 min[68,69].

Mannitol–Sorbitol (Compresol ®S)

It is a co-processed excipient made up of 70% mannitol (a low hygroscopic material with a pleasant sweet taste) and 30% sorbitol (a highly compactable and very hygroscopic material). It is produced by melt extrusion. It has a volume-diameter of ~360 μm. It is 300% less hygroscopic than sorbitol and a moisture content <1%. This material does not have the sticking problem of sorbitol during tableting. It is suitable for development of orally disintegrating compacts of moisture sensitive drugs, as well as for lozenges and chewable compacts. For example, tablets made of ascorbic acid and Compresol® disintegrate within 70 sec; whereas, those made with glucosamine (high dose drug) disintegrate within 130 sec. At 30 kN compression force compacts of mannitol have a crushing force of ~15 kP and those of Compressol® of ~35 kP[70].

Sucrose–Invert Sugar (Sugartab®)

It is a white, crystalline, odorless and free flowing, powder used for direct compression of tablets. It is produced by co-crystalization of 93% sucrose and 7% invert sugar. It is a white granular powder having an average particle size of 300 μm. It has a tap density of 0.7 g/cm^3 and a moisture content of 1%[71]. It has the same sweetness value as sucrose. It is sweeter than Emdex®, and it is able to produce zinc acetate lozenges with good taste. When blended with the active ingredient and a suitable lubricant, direct compression produces non-friable tablets with moderate hardness. This excipient has a poor flow (angle of repose of 36°), moderate compactibility (hardness/friability ratio of 3.4), and taste-masking characteristics. Further, it has a low hygroscopicity, good chemical stability, and gradual disintegration (~12 min). Avicel®PH-101 has an angle of repose of 48°, a hardness/friability ratio of 8.8 and a disintegration time of 75 min[72]. It has been used in the development of vitamin formulations, which might have compression problems. However, scientists reported that it is not the best excipient for formulating vitamin B1[73].

Sucrose–Maltodextrin (Di-Pac®)

It is a co-crystallized product made by combining 97% sucrose and 3% maltodextrin. It is a white, crystalline, soluble powder of high flowability (angle of repose of 49°), high bulk density (0.66 g/cm^3), hygroscopicity, low MC (0.5%) and good sweetness. It consolidates into a tablet by both, brittle and plastic deforming mechanisms, attributed by the sucrose and maltodextrin components, respectively. This excipient overcomes the poor compression properties of sucrose. It has a mean particle size of ~280 μm[74–76]. Granules are composed of hundreds of sucrose crystals entrapped within a maltodextrin matrix exhibiting a porous structure and a large surface area. It has excellent color stability on aging and its dilution potential ranges from 20 to 35%[77]. It flows better when the moisture content is from 0.4 to 0.8%. However, it requires a glidant if stored at (RH) >50%. High relative humidities have a negative effect on compactibility. For instance, its compacts harden hours after manufactured, or if stored at high RH followed by storage at low RH. This behavior is typical for sucrose[49].

Sucrose–Sorbitol

It is a free flowing compressible sucrose with a pleasant taste, consisting of 95% sucrose and 5% sorbitol obtained by co-crystallization. The new directly compressible sucrose absorbs three times more oil than sucrose and 2.5 times more oil than the dry blend of sucrose and

sorbitol. This material renders stronger tablets than the individual components. Its compressibility can be attributed to the small sorbitol component, since sorbitol itself compresses into a very strong tablet. Sucrose-sorbitol tablets disintegrate quickly regardless of the tablet hardness. This compressible sucrose disintegrates and dissolves quickly, in ~30 sec, due to the porous and open crystalline structure of the excipient. Since sucrose has a high heat of fusion (126.6 J/g) and strong sweet taste, this excipient is useful to mask the bitter taste of active ingredients, leaving a cool sensation in the mouth[78,79].

Xylitol–Dextrose (Xylitab®100)/Xylitol–NaCMC (Xylitab®200)

They are produced by granulation of 96.5% xylitol and 3.5% polydextrose, and 98% xylitol and 2% sodium carboxymethyl cellulose for Xylitab®100 and Xylitab®200, respectively. Xylitabs® have a cool taste and good physical and chemical stabilities. Morris and collaborators[80] found compaction profiles, flow behavior and dilution potential of Xylitabs® as acceptable. They have been successfully utilized as a chewable tablet excipient for direct compression[81]. Compacts made of Xylitab®100 possess higher tensile strength, but more sensitivity to magnesium stearate than compacts of Xylitab®200. Disintegration time is longer for compacts made of Xylitab®200 than those containing Xylitab®100. Disintegration time is also delayed in presence of lubricants[82].

Xylitol–Crospovidone–Calcium hydrogen phosphate (F-Melt®)

It is a spray-dried product composed of xylitol (40–90%), crospovidone (5–40%) and calcium hydrogen phosphate (1–30%). The actual composition of the excipient can be changed, rendering two grades designated as C and M, where C is used for fast disintegrating excipients and type M for excipients that show better flow and compactibility. It is comprised of porous spherical particles of bulk density from 0.53 to 0.6 g/cm^3 and a mean particle size from 100 to 130 μm. It is non-hygroscopic since it only adsorbs 5% water at 75% RH. This excipient provides a good mouth-feel, stability, flow, tablet hardness, low friability and high API loading. It does not cause sticking or capping problems. It is designed for manufacturing oral disintegrating tablets (ODTs). Usually these ODTs have *in vitro* disintegration time of ~30 seconds. It is usually employed at a level ranging from 10 to 65% in a drug formulation. For instance, compacts made using 30% acetaminophen, 64.6% F-Melt, 5% crospovidone and 0.4% magnesium stearate have a disintegration time of ~12 sec and a hardness of ~53 N[83].

Calcium Carbonate–Sorbitol (ForMaxx®)

This co-processed excipient is composed of 70% calcium carbonate and 30% sorbitol prepared by spray drying. It has a bulk density of 0.7 g/cm^3 and moisture content of <1%. This material is highly compressible, possesses excellent taste-masking effect and free flowing properties, rendering superior drug content uniformity than the individual components and the physical blend. For example, compacts made at 20 kN have a hardness of 300 kN and ~40 kN for ForMaxx® and the physical mixture, respectively. It is used for formulating antacids, calcium supplements, and its compacts show low friability. Sorbitol also masks the chalkiness and gritty taste of calcium carbonate[5,84].

Chitosan–silica

This excipient is produced by co-precipitation of 50% chitosan and 50% silica. SiO_2 is incorporated via partial coating, without any evidence of chemical interaction between the two ingredients. SiO_2 is responsible for increasing the bulk and tap densities giving better flowability and a more fragmenting behavior to the composite material. It has a high bulk density (0.5 g/cm^3) and good flow (Carr's index of 10%). This excipient is water insoluble and non-hygroscopic at RH lower than 76%, but is able to accelerate compact disintegration upon contact with water. It has superior water uptake, disintegration characteristics with improved powder flow and compaction properties than the physical mixture of chitosan and silica. It also exhibits superior performance in wet granulation formulations than the physical blend. This excipient could act as disintegrant and pharmaceutical filler at the same time. Compacts made at 30 kN show a hardness of 55 N and a disintegration time of less than 5 sec[43,85].

C–Crospovidone:sodium starch glycolate

The co-crystallized disintegrant is composed of 75% crospovidone (Polyplasdone-XL10) and 25% sodium starch glycolate. The two materials are dissolved in isopropyl alcohol at 65°C and then stirred until most of the isopropyl alcohol is evaporated. The wet mass is then passed through a 60 mesh sieve and tray-dried at 60°C for 20 min. Polyplasdone® XL10 exhibits good compressibility and a high rate and extent of water uptake irrespective of the medium pH. On the other hand, sodium starch glycolate (SSG) has good hydration and swelling capacity and its disintegration ability is not affected by hydrophobic lubricants. In general, the composite disintegrant is used from 4 to 66%. Since, the bulk density of both materials is very different (0.40 vs. 0.76 g/cm^3, respectively), the physical mixture is not suggested to use because of the inherent risk of segregation. Interestingly, compacts made of the physical blend showed higher crushing strength than tablets made of the co-processed disintegrant. However, compacts of both physical blend and co-processed products disintegrate within 4 min. If SiO_2 is added to the co-processed disintegrant, the tensile strength is virtually unchanged. Compacts made of Cefixime trihydrate presented a disintegration time of ~170 sec and release of 72% of the drug after 5 min. However, ibuprofen formulations with the disintegrant had a hardness of 6 N and disintegration time of 0.45 min, whereas, if croscarmellose sodium is used, compact hardness is 50 N, and disintegration time of 8 min. Further, if crospovidone is used compact hardness is 100 N, and disintegration time of 10 min[33,86].

Wax–calcium diphosphate

It is composed of 5% fatty acid wax and 95% calcium diphosphate. It can be produced by hot melting using a high shear granulator, or by extrusion of the hot mass under vacuum or nitrogen. The resulting particle size ranges between 75 and 200 μm. Calcium phosphate alone is abrasive and triggers lamination and capping in the compacts, especially at high compression pressures. This effect is exacerbated by the use of concave tooling. It is incompatible with pH sensitive active ingredients since the surface of milled anhydrous calcium phosphate is alkaline. Wax delays the disintegration time and decreases compressibility of calcium phosphate. Wax alone has poor flow properties due to its large particle size and interparticle adhesion. The acidic nature of wax also reduces the pH of calcium phosphate[87]. This co-processed excipient has a higher bulk density (0.76–0.86 g/cm^3), porosity (70%) and abrasion tendency than calcium phosphate (bulk density and porosity of 0.66–0.71 g/cm^3 and 64%, respectively) and at the same time overcomes the poor flow characteristic of the wax, leading to a good content uniformity and minimization of segregation. Tablets made from this composite erode slowly since the hydrophobicity of the excipient reduces the accessibility to water, including gastric and intestinal fluids. Compacts made of this excipient and venlafaxime releases about 75% of this API after 2 h[87].

Xanthan–locust bean gum–dextrose (Timerx®)

It is a co-processed product made from the bacterial polysaccharide named xanthan gum, a plant polysaccharide (locus bean gum), and dextrose at different ratios, which determine the release profile. By changing these ratios the release profiles of the API could be zero, first or second order[88,89]. Thus, it can be used to develop formulations from insoluble to highly-soluble drugs, at different doses[90]. Tobyn and collaborators found that high shear mixer granulation was superior to fluid bed granulation to produce granules of high density, mean particle size and flow (0.53 g/cm^3, 380.5 μm and 9.86 g/sec) on mixtures containing 25% xanthan gum, 25% locust bean gum and 50% dextrose[91,92]. Compacts made from the mix shear granules were stronger than the ones produced by fluid bed granules (crushing strength of 0.89 MPa and 1.51 MPa, respectively)[93].

Microcrystalline cellulose II: Silicon dioxide (95:5)

A Cellulose II-based microcrystalline cellulose was introduced as a new direct compression excipient[94-96]. It is produced by mercerization of MCCI in an aqueous sodium hydroxide solution (>5N)[97]. MCCII is less ductile than MCCI, and its compacts, irrespective of the compression force used to prepare them, show rapid disintegration (within 30 sec). A new co-processed product was formed by spray drying of MCCII and SiO_2 at the 95:5 ratio. This material produced compacts of superior mechanical properties than MCCII alone, but comparable to those of Avicel® PH-102 and preserved the fast disintegrating properties of MCCII[98]. It also showed a high specific surface area, a very low sensitivity to magnesium stearate, good flow, dilution ability and a more brittle deforming ability than MCCII. These properties result from the physical interaction of fumed silica when coating MCCII particles[99].

Conclusions

The pharmaceutical industry has been forced in recent years to search for excipients with improved functionality due to the high demands for productivity. The most economical, simple and efficient approach to improve particle engineering has been through co-processing of two or three conventional excipients. These multifunctional excipients are usually employed for direct compression due to the improved functionality respect to the parent materials and their mere physical blending. In most cases, properties such as flowability, compactibility, dilution ability, and compressibility are enhanced with co-processing.

Declaration of interest

The authors report no conflicts of interest.

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