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The Functional Attributes of Co-Processed Excipients in Direct Compression

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Abstract

The pharmaceutical industry is increasingly adopting co-processed excipients as alternatives to conventional excipients in tablet manufacturing despite certain regulatory challenges. Co-processing of excipients was designed to optimize physical powder properties such as flowability, compressibility, and compactibility, which are critical attributes for efficient tablet production, especially by means of direct compression. This review summarizes the various preparation methods of co-processed excipients and comprehensively discusses the role of co-processed excipients over conventional pharmaceutical excipients in enhancing tablet formulation as well as tablet manufacturing efficiency and consistency due to their improved functionality. Furthermore, the functionality and enhancement of performance of co-processed excipients are discussed on the three levels of solid substances, namely the molecular, particle and bulk levels. It further evaluates the effectiveness of co-processed excipients in addressing common formulation challenges such as moisture, lubricant sensitivity and strain rate sensitivity.

Keywords: Co-Processed Excipients, Co-Processing, Direct Compression, Enhanced Functionality, Multifunctionality, Particle Engineering, Tablet Formulation.

1. Introduction

Tablets remain one of the most important, widely used and preferred pharmaceutical dosage forms for oral drug administration due to their numerous advantages. These benefits include relatively low production cost, high production speed, dose uniformity and precision, ease of handling and packaging, and ease of self-administration by patients, which also enhances patient compliance (Allen and Ansel 2014; Ambore et al. 2014; Osei-Yeboah et al. 2016). Among the various methods employed in tablet manufacturing, direct compression is the most cost-effective, easily scalable and preferred method of tablet manufacturing (Bolhuis and Armstrong 2006).

The increased use of the direct compression method for tablet manufacturing has heightened the requirements of pharmaceutical excipient functionality. Excipient functionality refers to the activity it provides in the tablet formulation such as flowability and compressibility, which can be described as the excipient's equivalent of the active pharmaceutical ingredient's (API) efficacy. Thus, the inherent properties of an excipient determine its functionality (Chaudhari et al. 2012). Additionally, many new APIs have poor compressibility, increasing the demand for excipient functionality to overcome the limitations of the API. This has led to the development of co-processed excipients with enhanced functionality (Garg et al. 2013; Ijaz et al. 2017).

Co-processed excipients are defined as "a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change. However, in some instances, formation of necessary components may occur, such as *in situ* salt formation" (IPEC 2023). Co-processing of two or more excipients to form a novel co-processed excipient not only enhances the functionality but also eliminates unwanted characteristics of the individual components (Nachaegari and Bansal 2004; Kolter 2011). In general, co-processed excipients possess superior flowability and compressibility, reduced moisture and lubricant sensitivity and improved machine processing ability during high-speed tablet manufacturing (Rojas et al. 2012).

The development of new grades of existing excipients resulted in only marginal enhancements of excipient functionality, whereas co-processing could produce novel excipients with substantial improvement of functionality. Substances in the solid-state are characterized on three levels, namely the molecular level (which relates to the molecular arrangement in a crystal lattice and includes polymorphism, pseudo-polymorphism and the amorphous state), the particle level (which includes the physical properties of particles such as particle shape, size, surface area and porosity) and lastly, the bulk level (which includes the properties of a bulk of powder particles such as flowability, compressibility and dilution potential). These levels are interdependently linked and change on one level may affect the other levels. Co-processing alters one or more levels of the solid-state, which in turn enhances a powder's overall functionality Chaudhari et al. 2012). Regulatory and intellectual property concerns have resulted in the commercialization of only a limited number of novel excipients (e.g., co-processed excipients). From a regulatory point of view, co-processed excipients produced from individual excipients that were already approved, retain a generally regarded as safe, i.e. "GRAS" status due to the absence of significant chemical changes resulting in there being no requirement to perform toxicological assessments. However, new guidelines from the International Pharmaceutical Excipient Council require of risk assessment studies that must be carried out on co-processed excipients (IPEC 2017).

Although excipient manufacturers have put quality control measures in place to ensure reproducible manufacturing of high quality co-processed excipients, there are a number of risk factors that make drug formulators reluctant to use co-processed excipients. As with any 'new' material to be used as an excipient, the risk to patient safety should be assessed. The user of any co-processed excipient in pharmaceutical products for human or veterinary use is responsible for assuring its fitness for purpose. One obstacle for pharmaceutical companies is the fact that many co-processed excipients

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don’t have official monographs. For this reason, the regulatory agency may request additional safety and efficacy data for co-processed excipients (IPEC 2017; Challener 2022).

The potential risk to the patient by co-processed excipients depends on the type of ‘newness’ of the co-processed excipient created. If no new covalent chemistry can be shown in the co-processed excipient through appropriate testing, then a scientific justification can be documented for linking the safety assessment of the co-processed excipient to that of the individual components. Co-processing of individual components by physical means rather than covalent chemical bonding creates a “novel regulatory entity” rather than a “novel chemical entity”. Therefore, if the co-processed excipient has not been chemically altered in comparison to the corresponding physical mixture of the individual components, the safety of the co-processed excipient can be linked to that of the individual components and assessed using analytical rather than toxicological methods (IPEC 2017).

When changes in excipient composition of pharmaceutical formulations occur post-approval of a product beyond certain specified limits (typically ± 10% for filler), then a full bioequivalence study is required. A bioequivalence study would therefore be required when switching from conventional excipients to co-processed excipients in a pharmaceutical product. However, the bioequivalence study may be waived if an acceptable *in vivo-in vitro* correlation has been verified for the specific active pharmaceutical ingredient (FDA, 1995).

2. Preparation methods of co-processed excipients

Different methods have been employed in the preparation of co-processed excipients, which are briefly described in the sub-sections below.

2.1. Spray drying

The spray drying method is currently the most widely utilized technique for the preparation of co-processed excipients owing to the advantages associated with it, which include rapid operational speed, scalability, enhanced control over the drying process and enhanced control over the final co-processed excipient’s characteristics (Kaushik et al. 2021 and Rao et al. 2021). In this method, the materials, known as the 'feed' are transformed from a fluid state (e.g., solution, suspension, dispersion, or emulsion) into a dried particulate state by spraying the feed as droplets into a heated drying gas medium. Spray drying involves five main process steps, namely concentration of the feed, atomization, droplet-air contact, droplet drying and particle separation (Patel et al. 2009). During the atomization phase, the exposed surface area of the liquid feed is increased by scattering the feed into fine droplets. This enhances subsequent heat transfer during drying and allows rapid solvent evaporation within seconds. Importantly, the droplets never reach the high inlet temperature of the drying gas, thereby rendering thermolabile materials suitable for spray drying (Cal and Sollohub 2010). The dried product obtained can be a powder, granules or agglomerates depending on the feed’s physical and chemical properties, the dryer’s design and the desired properties of the final particulate state. In general, this process renders powder particles with a more spherical shape, which are more suitable for direct compression due to the resultant enhanced flowability (Bin et al. 2019).

Table 1 contains a comprehensive list of all the commercially available co-processed excipients manufactured by means of the spray drying method, alongside their components and the enhanced functionality offered.

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Table 1: Commercially available co-processed excipients manufactured by spray drying

Name	Components	Manufacturer	Enhanced functionality	References
Advantose™ FS95	Fructose (95%) and sucrose (5%)	SPI Pharma (USA)	Produced by spray drying, this excipient co-crystallizes fructose with a minor amount of sucrose to form a porous, directly compressible sugar matrix. The modified crystalline structure facilitates rapid water penetration, which accelerates tablet disintegration and improves compressibility, while minimizing interparticle friction.	(Rojas et al. 2012; SPI Pharma 2019a)
Avicel® DG	MCC and dibasic calcium phosphate	DuPont Pharma (USA)	A synergistic blend obtained via spray drying. MCC provides plastic deformation during compression, while dibasic calcium phosphate contributes brittle fracture properties. The resulting uniform composite improves compressibility, binding, and reduces friability, leading to robust tablet formation ideal for direct compression processes.	(Vodáčková et al. 2018)
Avicel® CE 15	MCC (85%) and guar gum (15%)	DuPont Pharma (USA)	Spray-dried to produce a composite in which guar gum forms a hydrophilic coating on MCC. This modification enhances water uptake upon tablet contact, leading to rapid disintegration. The formulation also improves mouthfeel, making it particularly suitable for chewable tablets, while maintaining tablet integrity.	(Rojas et al. 2012; Vodáčková et al. 2018)
Avicel® HFE-102	MCC (90%) and mannitol (10%)	DuPont Pharma (USA)	Combines MCC's binding and plastic deformation with mannitol's non-hygroscopic and palate-friendly properties. The spray-dried particles exhibit improved uniformity and flow, resulting in tablets that are both strong on compression and rapidly disintegrate upon exposure to water.	(Rowe et al. 2009; Rojas et al. 2012; Vodáčková et al. 2018; Rao et al. 2021).
Avicel® RC-591	MCC and Na-CMC	DuPont Pharma (USA)	The co-processing of MCC with Na-CMC via spray drying yields a composite in which Na-CMC quickly swells to form a gel network upon hydration. This gel network accelerates water uptake and disintegration, while MCC provides the necessary mechanical strength and binding properties for well-formed tablets.	(Rowe et al. 2009; Rojas et al. 2012)
Cellactose® 80	Lactose monohydrate (75%) and cellulose (25%)	Meggle GmbH (Germany)	Produced by spray drying a blend of lactose and powdered cellulose, this excipient offers excellent	(Gohel and Jogani 2005; Rao et al. 2021)

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			compressibility and flow. Lactose provides good binding and low moisture sensitivity, while cellulose reinforces the matrix and minimizes segregation during direct compression, ensuring uniform and rapid disintegration.	
CombiLac®	Lactose monohydrate (70%), MCC (20%) and corn starch (10%)	Meggle GmbH (Germany)	The integrated system produced by spray drying combines lactose for compressibility, MCC for binding, and corn starch as a disintegrant. The result is a monoparticulate structure with excellent blend uniformity and rapid water uptake, facilitating quick tablet breakup upon administration.	(Bhavana and Reddy 2023)
F-Melt® Type M	Mannitol, MCC, xylitol, crospovidone and magnesium aluminometasilicate	Fuji Chemical Industry (Japan)	Engineered specifically for orodispersible tablets, this product uses sugar alcohols (mannitol and xylitol) to provide a non-hygroscopic, pleasant-tasting matrix. MCC ensures binding, while crospovidone acts as a superdisintegrant by rapidly swelling to create channels for water penetration, leading to ultra-fast disintegration.	(Rojas et al. 2012; Rao et al. 2021)
MicroceLac® 100	Lactose monohydrate (75%) and MCC (25%)	Meggle GmbH (Germany)	Co-processing lactose with MCC via spray drying produces a uniform porous structure that ensures excellent compressibility and consistent tablet hardness. Rapid water absorption is facilitated by the controlled porous network, leading to swift disintegration.	(Rao et al. 2021; Bhavana and Reddy 2023)
Pearlitol® SD	Mannitol (spray-dried)	Roquette (France)	The spray drying of mannitol yields spherical, low-hygroscopicity particles with smooth surfaces and excellent flow. These characteristics facilitate uniform compression and rapid water penetration upon tablet administration, resulting in fast disintegration and optimal release.	(Charoo 2019; Roquette 2020)
Pharmaburst™ 500	Mannitol, silicon dioxide, sorbitol and crospovidone	SPI Pharma (USA)	This spray-dried excipient is engineered to combine mannitol's excellent flow with silicon dioxide's high specific surface area and crospovidone's superdisintegrant properties. These structural features create numerous water channels that enable rapid tablet disintegration while preserving tablet mechanical strength.	SPI Pharma 2019c; Rao et al. 2021)
Pharmaburst™ (Sorbitol-mannitol variant)	Sorbitol-mannitol, crospovidone and silicon dioxide	SPI Pharma (USA)	Optimized for immediate release, this variant has a higher proportion of sorbitol	(Fouad et al. 2020; Rao et al. 2021)

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			to enhance water uptake. Combined with crospovidone's rapid swelling, the formulation promotes extremely rapid disintegration while ensuring strong tablet compressibility.	
Prosolv® SMCC	MCC (98%) and colloidal silicon dioxide (2%)	JRS Pharma (Germany)	A specialized silicified MCC created by co-processing with colloidal silicon dioxide to dramatically increase surface area. This modification results in enhanced binding, excellent flow and superior compressibility, yielding tablets with predictable, rapid disintegration.	(Rojas et al. 2012; Charoo 2019; Rao et al. 2021)
StarLac®	Lactose monohydrate (85%) and maize starch (15%)	Meggle GmbH (Germany)	Formulated by spray drying, this blend combines lactose for excellent compressibility with maize starch, which swells rapidly upon hydration. The integrated structure leads to enhanced tablet binding and fast disintegration due to the effective formation of water channels.	(Charoo 2019; Rojas et al. 2012, Rao et al. 2021)
StarCap® 1500	Pregelatinized starch and corn starch	Colorcon (USA)	The co-spray-dried blend utilizes pregelatinized starch for improved compressibility and corn starch for rapid water uptake. The combined process yields a product that offers strong tablet cohesion while still permitting swift disintegration and drug release.	(Rojas et al. 2012, Colorcon 2019)

MCC-Microcrystalline cellulose;

Na-CMC-Sodium carboxymethylcellulose

2.2. Granulation

The granulation method for co-processing can be divided into three sub-methods, namely wet granulation, melt granulation and dry granulation.

2.2.1. Wet granulation

Wet granulation can be performed on a large scale by either fluid bed granulators or high-shear mixers. In fluid bed granulators, an upwards stream of air is injected through the powder mixture to form a fluidized bed that hovers in mid-air inside the granulator. The binder solution is sprayed into the fluidized bed in the opposite direction of the airstream. The collision between the liquid binder droplets that hit the solid powder particles then cause granules to form due to particles sticking to each other. The granules formed are then dried by the upwards stream of hot air and finally sieved to obtain the granule mass. This method is also referred to as fluid bed spray granulation (Faure et al. 2001; Hapgood et al.2009; Daraghmeh et al. 2010).

In high shear mixers, the powder mixture is kept agitated in a closed vessel by an impeller while the binder solution is injected from above. The high shear force prevents the formation of large

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agglomerates. The granules are then dried in the same vessel using innovative single-vessel technology, also known as one-pot processing. Vacuum drying is typically employed, offering low temperatures and easy recovery of the granulation liquid through condensation. This is particularly beneficial for organic solvent-based granulations, as vacuum drying minimizes solvent emissions, aiding compliance with strict environmental regulations. However, vacuum drying is time-consuming due to limited heat transfer. To address this, microwave drying can be used, significantly speeding up the process and allowing better control, especially for water-based formulations. Generally, the granules obtained by this method have a higher density compared to those prepared by fluid bed granulators (Faure et al. 2001; Van Vaerenbergh and Stahl 2021).

2.2.2. Melt granulation

The melt granulation method begins with the mixing of powders with a suitable meltable binder. The mixture is then subjected to heat above the binder's melting point while being continuously stirred, causing agglomerates to form. The agglomerated powder is then cooled and sieved, resulting in the co-processed powder. The major drawback of this method of co-processing is the relatively high temperatures required for melting of the binder, making it unsuitable for any thermolabile materials (Gohel and Jogani 2003; Garg et al. 2015).

2.2.3. Dry granulation

Roller compaction is used for dry granulation, where powder particles are first bonded through physical compaction between rollers and then broken up to produce granules. The process commences with the powder mixture that is uniformly mixed and thereafter continuously passed in between counter-rotating compression rolls forming solid ribbons or sheets of compacted powder. These sheets are subsequently milled and sieved to obtain the desired particle size of the co-processed powder. An advantage of this method is its suitability for thermolabile and moisture-sensitive materials (Chang et al. 2008; Teng et al. 2009; Shanmugam 2015).

Table 2 contains a list of the commercially available co-processed excipients manufactured through granulation, alongside their components and enhanced functionality.

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Table 2: Commercially available co-processed excipients manufactured by granulation

Name	Components	Manufacturer	Enhanced functionality	References
Granfiller-D™ GNF-211	Mannitol, MCC, croscarmellose sodium and crospovidone	Daicel and Nichirin Chemical Industries (Japan)	Produced by wet granulation. Combines MCC's binding with mannitol's cushioning effects and crospovidone's rapid disintegration properties, making it ideal for complex formulations requiring enhanced compressibility and fast disintegration.	(Daicel 2019b)
LubriTose™ SD	Spray-dried lactose and glyceryl monostearate	Kerry (USA)	Produced by wet granulation, this excipient features glyceryl monostearate uniformly incorporated into spray-dried lactose. The internal lubrication improves granule uniformity and flow, leading to consistent compression and rapid disintegration without additional external lubricants.	(Tian et al. 2012; Kerry 2016)
Ludiflash®	Mannitol, crospovidone, polyvinyl acetate and povidone	BASF Pharma (Germany)	This all-in-one system acts simultaneously as a filler, binder, and disintegrant. Mannitol ensures a pleasant taste and flow, crospovidone rapidly swells to facilitate disintegration and additional polymers enhance mechanical strength, creating tablets with fast release and robust hardness.	(Rojas et al. 2012; Rao et al. 2021)
Ludipress® LCE	Lactose monohydrate (96.5%) and crospovidone (3.5%)	BASF Pharma (Germany)	The pre-formulated granulate offers excellent blend uniformity and flow properties. Lactose provides compressibility while crospovidone acts as a highly effective disintegrant, ensuring rapid tablet breakup and uniform tablet hardness.	(BASF, date unknown)
Ludipress®	Lactose monohydrate (93%), PVP (3.5%) and crospovidone (3.5%)	BASF Pharma (Germany)	This granulate balances the binding properties provided by lactose and PVP with the disintegration capabilities of crospovidone, yielding tablets that are hard yet rapidly disintegrate for prompt drug release.	(BASF [date unknown]; Rao et al. 2021; Medarević et al. 2021)
RetaLac®	HPMC and lactose	Meggle GmbH (Germany)	This granulated system leverages HPMC's controlled-release matrix properties with lactose's excellent compressibility, yielding tablets that maintain consistent hardness and controlled disintegration rates under varying pH conditions.	(Bhavana and Reddy 2023; Meggle 2023)
Xylitab® 100	Xylitol (96.5%) and polydextrose (3.5%)	Danisco (Denmark)	Formulated to enhance mouthfeel and compressibility, xylitol delivers sweetness and binding, while polydextrose improves powder flow.	(Rojas et al. 2012; Rao et al. 2021)

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			Together, they create tablets that disintegrate rapidly and offer an acceptable taste profile.	
Xylitab® 200	Xylitol (98%) and Na-CMC (2%)	Danisco (Denmark)	In this formulation, high-purity xylitol ensures excellent binding and palatability, while a small percentage of Na-CMC imparts rapid swelling properties, resulting in tablets with improved integrity and swift disintegration upon administration.	(Rojas et al. 2012; Rao et al. 2021)

PEG-Polyethylene glycol;

HPMC-Hydroxypropyl methylcellulose;

Na-CMC-Sodium carboxymethylcellulose;

PVP-Polyvinylpyrrolidone

2.3. Hot melt extrusion

During the hot melt extrusion method, the melted mass of excipients is pressurized through a die, forming extrudates of various sizes that solidify. The solid extrudates are then sieved to obtain the desired particle size of the co-processed excipient. This method does not require a solvent, as the melted mass moves through the extruder's orifices to form solid extrudates through thermal binding. However, the use of high temperatures in this method makes it unsuitable for thermolabile materials (Liu et al. 2001; Patil et al. 2024).

Table 3 contains a list of the commercially available co-processed excipients manufactured through hot melt extrusion, alongside their components and the enhanced functionality offered.

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Table 3: Commercially available co-processed excipients manufactured by hot melt extrusion

Name	Components	Manufacturer	Enhanced functionality	References
Compressol® SM	Mannitol (70%) and sorbitol (30%)	SPI Pharma (USA)	Manufactured via hot melt extrusion, where the high - temperature process fuses mannitol and sorbitol into a homogeneous polyol matrix. Mannitol contributes crystalline strength while sorbitol imparts plasticity. This results in an excipient with excellent compressibility and low moisture content, ideal for high-dose formulations.	(Rojas et al. 2012; SPI Pharma 2019b)
Parteck® ODT	Mannitol and croscarmellose sodium	Merck KGaA (Germany)	Designed for orally disintegrating tablets, this product is produced by hot melt extrusion. The process yields a matrix in which mannitol's non-hygroscopic nature provides hardness and croscarmellose sodium rapidly swells upon hydration, ensuring swift tablet disintegration at low compression forces.	(Rao et al. 2021, Merck 2019)

2.4. Miscellaneous

Less commonly used preparation methods such as solvent evaporation, milling, co-crystallization, co-precipitation, gelatinization and freeze-thawing for the manufacturing of co-processed excipients are discussed in this section for reasons of completeness.

2.4.1 Solvent evaporation

The solvent evaporation method is conducted in a liquid medium, where the selected excipients, combined in specified ratios, are dispersed in an appropriate volume of an organic solvent, such as isopropyl alcohol. The resulting mixture is subjected to continuous stirring using a magnetic stirrer, with the temperature maintained between 65°C and 70°C to promote solvent evaporation. Once the formation of a cohesive wet mass is reached, the material is granulated through a sieve and subsequently dried in a hot air oven. The dried granules are then re-sieved using a suitably sized mesh to obtain a co-processed excipient with the desired particle size (Gohel et al. 2007; Ladola and Gangurde 2014).

2.4.2 Milling

Milling is a co-processing method in which a mixture of excipients is exposed to mechanical forces using high-speed milling equipment. This causes inter-particle collisions that promote bond formation between particles, leading to the formation of co-processed granules/particles (Bin et al. 2019). This technique was applied to co-process cross-linked polyvinylpyrrolidone (crospovidone) with calcium silicate, resulting in a co-processed excipient that demonstrated a significantly improved dissolution profile compared to a simple physical mixture of the individual excipients (Rao et al. 2012).

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2.4.3 Co-crystallization

During the co-crystallization method, a supersaturated solution of the excipients is prepared in a suitable solvent. Crystals can then be obtained from the solution by various methods such as cooling the solution while agitating it, adding a second solvent that reduces the solute's solubility (i.e. antisolvent), a chemical reaction or changing the solution's pH. The crystals are separated from the solution by means of filtration whereafter they are dried to render co-processed excipient particles (Chaudhari et al. 2012; Mishra et al. 2022).

The only commercially available co-processed excipient manufactured through co-crystallization is Di-Pac® (Domino, USA) consisting of 97% sucrose and 3% dextrin. The co-crystallization process forms a uniform, porous crystalline lattice by integrating a small amount of dextrin into sucrose. This unique structure enhances compressibility and facilitates rapid water penetration leading to accelerated tablet disintegration and improved moisture resistance (Gohel and Johani 2005).

2.4.4 Co-precipitation

The co-precipitation method entails the rapid precipitation of an excipient mixture from a solvent or solvent mixture. The excipient mixture is dissolved in the solvent system, and an anti-solvent is then added to induce solid particle formation. The precipitated particles are subsequently isolated, dried and milled (if necessary) resulting in the formation of a co-processed excipient with enhanced functional attributes. This enhancement is attributed to the method's ability to provide precise control over particle morphology (Amornrojvaravut and Peerapattana 2023; Dhondale et al. 2023; Sachdeva et al. 2024).

2.4.5 Gelatinization

The gelatinization method can only be utilized to produce co-processed excipients when at least one of the components to be co-processed is starch. This is attributed to starch's unique thermal properties that renders it ideal to undergo gelatinization (Bhatia et al. 2022). One method entails adding an admixture of starch and povidone to a fluid bed granulator and thereafter spraying an aqueous povidone solution onto the admixture. The mixture is then dried with hot air (Menon et al. 1996). An alternative method entails mixing starch and polymer(s) with water to create a slurry and thereafter adding the slurry to boiling water while continually stirring. The slurry is then dried, grinded and sieved to the desired particle size (Ramja and Chowdary 2013). Both methods render a free-flowing co-processed excipient with enhanced compressibility.

2.4.6 Freeze thawing

During the freeze thawing method - also referred to as spherical crystallization - both crystallization and agglomeration occur simultaneously. The excipient mixture is dissolved in an aqueous vehicle and subjected to a series of freezing and thawing cycles. The agglomerates formed are then dried and sieved to achieve the desired co-processed particle size. Although not commonly employed, this method has been shown to enhance the flowability and compactibility of excipients (Patel and Patel 2009).

Table 4 contains additional commercially available co-processed excipients produced by miscellaneous methods or methods not specified by the manufacturer. Their components and the enhanced functionality offered by co-processing are also provided.

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Table 4: Commercially available co-processed excipients manufactured by miscellaneous methods

Name	Components	Manufacturer	Enhanced functionality	References
HiSORAD™ HSR-D03	Mannitol, MCC and croscarmellose sodium	Daicel (Japan)	Formulated to leverage the swelling capacity of croscarmellose sodium alongside the plasticity of MCC, this excipient improves tablet binding and accelerates disintegration, resulting in superior mechanical strength and dissolution.	(Daicel 2019a)
SmartEx® QD 100	Mannitol, polyvinyl alcohol and HPC	Shin-Etsu Pharma (Japan)	Combines the roles of binder, filler and disintegrant within a single matrix. This integration yields sustained drug release and excellent compression properties, making it especially suitable for orally disintegrating formulations.	(Dziemidowicz et al. 2018; Rao et al. 2021)
Pharmatose® DLC14	Anhydrous lactose (95%) and lactitol (5%)	DFE Pharma (Germany)	Reduces moisture uptake while enhancing taste and flow, this excipient improves both compressibility and rapid disintegration, ensuring lower hygroscopicity and better shelf-life for tablet formulations.	(Gohel and Jogani 2005)

HPC-Hydroxypropyl cellulose;

MCC-Microcrystalline cellulose

3 Functionality enhancement of co-processed excipients

It has been shown that co-processed excipients display enhanced functionality when compared to their conventional single excipient components and/or simple physical mixture and/or binary mixtures of the single components (Chaudhari et al. 2012; Bhavana and Reddy 2023). As mentioned before, the functionality and performance enhancement of co-processed excipients can be described on three levels of solid substances, namely the molecular, particle and bulk levels, which are discussed in detail below.

3.1 Molecular level

The molecular level of solid-state substances involves aspects such as the molecular weight and molecular arrangement in a crystal lattice (Bhavana and Reddy 2023). Substance modification on the molecular level can be achieved by altering the organization of molecules within the crystal lattice, which leads to the formation of new allomorphs, pseudo-polymorphs or an amorphous character. Additionally, chemical reactions (e.g., crosslinking) can be applied to achieve changes on the molecular level. However, this process tends to be costly and often involves the need for solvent recovery. Furthermore, the crosslinking agents used may be toxic and may leave behind by-products, which can break down in biological systems and potentially produce harmful compounds. Regardless, several crosslinked excipients are commonly used in pharmaceutical formulations as discussed below (Rojas et al. 2012).

Co-processing has demonstrated the ability to enhance excipient performance on a molecular level by stabilizing superior polymorphic forms and mitigating the undesirable effects of less stable forms

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through tailored polymorphic compositions (Charoo 2019). Furthermore, molecular characteristics such as polymorphic form may significantly affect excipient performance in terms of stability, solubility and compressibility (Chaudhari et al. 2012).

3.1.1 Polymorphism and pseudo-polymorphism

Polymorphism refers to the existence of multiple crystalline forms of the same chemical substance, each with distinct physical and chemical properties such as solubility, compressibility, flowability and stability. On the other hand, pseudo-polymorphism refers to hydrates and solvates where solvent molecules are incorporated into the crystal lattice of the chemical substance (Alsirawan and Paradkar 2020). Polymorphic transitions, which can be induced by processing methods like milling, granulation or drying may influence critical mechanical properties of powders (including plastic deformation, elastic recovery and brittle fracture). Since variations in polymorphs can significantly impact excipient performance, especially in excipients used for direct compression of tablets, it is important to ensure the correct polymorphic form is obtained in the co-processed excipient (Charoo 2019; Dzoagbe et al. 2024).

Co-processing aims to transform excipients into stable and functional polymorphic forms, addressing issues associated with polymorphic transitions. As mentioned earlier, the co-processed excipient should exist in the correct polymorphic form to possess the desired mechanical properties and compaction behavior, through enhanced plasticity, reduced brittleness, and controlled moisture interactions (Charoo 2019; Dzoagbe et al. 2024).

When microcrystalline cellulose (MCC) and crospovidone are combined into a co-processed excipient, it creates a composite material with a modified crystalline structure that enhances compaction and tableting properties. Compared to MCC alone, the composite material (or co-processed excipient) exhibited lower plasticity, which contributed to the production of tablets with faster disintegration times. Tablets produced from this co-processed excipient typically disintegrated within the required 15 minutes for immediate release tablets. This improvement was attributed to the synergistic enhancement of the functionality of the individual excipients achieved through co-processing (Haruna et al. 2020).

To overcome the brittle fracture nature of alpha-lactose monohydrate in its natural polymorphic form, it is spray-dried to convert it into a mixture of crystalline and amorphous forms. This results in a powder with enhanced flowability and compressibility, making it more suitable for direct compression. The spherical morphology and increased particle size accounts for the enhanced flowability, while the amorphous fraction contributes to better compressibility through greater plasticity and binding capacity. This example highlights the value of co-processing to manipulate polymorphic and pseudo-polymorphic forms to improve the functional properties of pharmaceutical excipients, as demonstrated in formulations like FlowLac® 90 and Pharmatose® DCL 14 (Rassu et al. 2006; Al-Zoubi et al. 2021).

To overcome the limitations of alpha-lactose monohydrate, it can also be co-processed with various other excipients (Charoo 2019). Cellactose® is the product of co-spray dried alpha-lactose monohydrate with cellulose, which provides a product that combines lactose's solubility and cellulose's plastic deformation properties, which yielded superior powder flowability, compressibility and crushing strength, along with reduced tablet friability and rapid disintegration when compared with its single components or physical mixtures thereof (Gohel and Jogani 2005; Arida and Al-Tabakha 2008). StarLac® is the product of co-spray dried alpha-lactose monohydrate with starch, which has similarly enhanced the hardness and disintegration of tablets without changing its sensitivity to compression pressure (Hauschild and Picker 2004).

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One study investigated the effect of proteins on the polymorphic forms of mannitol during co-spraying. The findings suggested that co-processing mannitol with proteins offers a strategy for stabilizing preferred polymorphs to enhance the performance of mannitol in pharmaceutical formulations. For example, it has reduced the moisture sensitivity of mannitol and thereby prevented undesired moisture-induced polymorphic transitions that can affect functionality (Hulse et al 2009). Furthermore, a co-processed sorbitol-mannitol excipient was produced, using a novel spray-drying-based technique, namely NanoCrySP technology. During the solvent evaporation phase, the small-molecule excipient (sorbitol) initially converts to its amorphous form due to rapid solvent evaporation. As evaporation continues, sorbitol partially crystallizes in nano-sized domains on the surface of the crystallization-inducing carrier excipient (mannitol). The surface crystallization reflects polymorphic transitions and molecular-level interactions between the components. By tailoring these microstructural features, NanoCrySP results in synergistic enhancement of excipient functionality, rendering a co-processed product with improved compactibility and tabletability (Roa et al. 2021).

3.1.2 Amorphous state

The amorphous state of chemical substances is characterized by a lack of long-range molecular order, resulting in higher solubility and faster dissolution rates compared to crystalline forms. Co-processing of excipients can cause the resultant excipient to exist in the amorphous state, leading to enhanced excipient functionality.

Different combinations of spray-dried MCC and mannitol were investigated. It was found that a ratio of 1.25:1 exhibited improved compressibility and rapid disintegration (< 15 s) of tablets. Photomicrographs showed fine, uniformly distributed mannitol particles within an MCC matrix, which was different from physical mixtures of these two substances. The enhanced performance of the resultant excipient was linked to partial amorphization and submicron mannitol particles formed during co-processing (Jacob et al. 2007).

Despite the advantages offered in terms of solubility enhancement associated with the amorphous form of solid substances, the conversion of excipients into the amorphous state has often rendered thermodynamically unstable substances that were consequently prone to recrystallization into the less soluble crystalline form (Valenti et al. 2021). Co-processed excipients with amorphous character may therefore not always be the preferred choice due to this type of physical instability.

3.2 Particle level

Powder particle characteristics (e.g. particle size, particle size distribution, particle porosity, particle shape and particle density) influence the performance of directly compressed formulations. Therefore, modifying the physical attributes of excipient particles through co-processing can substantially increase excipient functionality (Bhavana and Reddy 2023).

3.2.1 Particle shape

Particle shape or morphology exerts a profound influence on a powder's physical and mechanical properties, particularly in terms of flowability, packing density, blending efficiency, segregation and compressibility, all of which are critical factors in the development of solid dosage forms (Pabst and Gregoravá 2007). Generally, spherical particles demonstrate superior flow properties due to their low contact area and minimal mechanical interlocking. In contrast, irregular, angular, or elongated particles (such as needle-, rod-, or flake-shaped particles) exhibit increased interparticle friction and interlocking, thereby impeding flow and reducing packing efficiency. While particle size remains the dominant factor governing segregation, particle shape can also contribute to this, especially when fine spherical particles are mixed with coarse angular ones. During blending of such mixtures,

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spherical particles tend to mix efficiently but may segregate more readily post-mixing. Conversely, irregular particles, with higher surface areas and stronger cohesive forces, resist segregation and promote content uniformity, albeit requiring extended mixing times. Furthermore, particle shape significantly impacts compressibility and tablet mechanical strength. Irregular particles typically form stronger compacts due to increased surface roughness and a greater number of bonding sites, which enhance interparticle bonding; although they may exhibit less uniform packing than spherical particles, their ability to interlock and fill voids can result in higher overall compact density and mechanical strength. To optimize these properties, co-processing is employed as a particle engineering tool to yield morphologies that enhance flowability and compressibility, while also reducing lubricant sensitivity and disintegration times. Since irregular particle shapes hinder flowability and complicate manufacturing steps such as mixing and die filling, co-processing techniques are generally employed to yield spherical, uniformly shaped particles that enhance flow properties while preserving sufficient compressibility (Charoo 2019).

In a study where spray drying an aqueous slurry of MCC and mannitol was used to produce a co-processed excipient with altered particle shape, the resulting excipient exhibited reduced lubricant sensitivity, higher compactibility, and a lower tablet ejection force profile compared to its individual components or physical mixtures. It was concluded that the particle morphological changes resulting from co-processing contributed to these improved powder properties, making it particularly useful as an excipient for tablet formulations manufactured by direct compression (Daraghmeh et al. 2010).

In another study, researchers developed a co-processed excipient composed of MCC, sorbitol, chitosan and Eudragit® E through wet massing. Pellets prepared with this co-processed excipient demonstrated a higher drug dissolution rate compared to those prepared with MCC alone. The co-processing resulted in spherical pellets with improved porosity and morphology, enhancing their flowability and disintegration properties (Goyanes and Martínez-Pacheco 2013).

A co-processed excipient composed of MCC and mannitol was produced by using fluid bed agglomeration. Tablets prepared with this co-processed excipient demonstrated reduced lubricant sensitivity, higher compactibility and improved tablet performance compared to tablets made from physical blends of the individual excipients. It was observed that co-processing eliminated the irregular particle shape and this contributed to the enhanced properties of the co-processed excipient Jain et al. 2023).

An optimized co-processed excipient, consisting of MCC in combination with the polymeric binder, hydroxypropyl methylcellulose (HPMC) and the cross-linked hygroscopic disintegrant, crospovidone was patented. The co-processed excipient was produced via a modified spray-drying granulation technique wherein all three components were dispersed in water to form a homogenized slurry. This ensured close contact between the two insoluble components (i.e. MCC and crospovidone), while the viscous binder (i.e. HPMC) promoted cohesion within the mixture. Subsequent spray drying of the slurry at high temperatures (≥ 120 °C) rapidly removed the solvent, enabling the binder to form robust intraparticle bonds. The resulting granules exhibited improved structural integrity and a unique porous morphology. These features enhanced flowability, compactibility and blendability, while also enabling higher API loading compared to individual components or their physical mixtures (Deorkar et al. 2008).

3.2.2 Particle size and particle size distribution

The powder particle size of pharmaceutical excipients plays a crucial role in determining certain physical and chemical properties, which directly impact their flowability and packing. A smaller particle size is associated with an increased drug dissolution rate, but it can also exacerbate cohesiveness, thereby impeding flow. This cohesiveness can also lead to challenges such as percolation segregation, especially when smaller particles settle through voids in larger ones. Size-

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induced segregation can occur due to turbulent air currents during mixing, which may significantly affect tablet uniformity. To mitigate these effects, maintaining a narrow particle size distribution is critical for improving powder flow, blending efficiency and dosage form consistency (Charoo 2019). Supporting this, another study reported that even the smallest particle size fraction of ibuprofen demonstrated better flow than the bulk powder, highlighting that particle size distribution plays a more pivotal role in flowability than particle size alone. Their findings also showed that for powders with a uniform size distribution, flowability increased with particle size, thereby reinforcing the significance of both size and distribution in excipient performance (Liu et al. 2008).

Co-processing calcium carbonate and sorbitol rendered an excipient with controlled particle size distribution, which resulted in enhanced flowability and consequent manufacturability in comparison with its single constituents (Pawar et al. 2019). In a separate study it was found that Ludipress® prepared by spray-drying lactose together with Kollidon® 30 (soluble povidone) and Kollidon® CL (crosslinked, water-insoluble povidone) resulted in spherical particles with a uniform particle size, which resulted in enhanced flowability, reduced segregation and improved blend uniformity in comparison to its single components and physical mixtures (Schmidt and Rubensdörfer 1994). Three co-processed excipient formulations containing varying ratios of MCC and alginic acid (F1: 95:5%, F2: 90:10% and F3: 85:15% w/w) were also investigated. The wet granulation process used in this instance led to particle agglomeration, which resulted in increased particle size compared to the individual components and their simple physical mixtures. The co-processed excipients exhibited a relatively narrow and uniform particle size distribution, which contributed to improved flowability, better compaction behavior and more consistent die filling during tablet compression (Benabbas et al. 2021).

Another study compared three different co-processed starches that were each prepared by a different method namely the co-dispersion, co-fusion and co-granulation method. The excipient produced by the co-granulation method exhibited superior flow properties, compressibility, and tabletability as compared to the other two excipients. This powder performance enhancement was attributed to the specific particle size and size distribution achieved through co-granulation, which led to improved interparticle bonding during compression and reduced lubricant sensitivity. This demonstrated the modification in co-processed excipient functionality that can be obtained by the type of co-processing technique to produce the ideal particle size (Apeji et al. 2017).

3.2.3 Particle surface area and porosity

It has been shown that increased surface area and porosity of powder particles can enhance compressibility by facilitating particle deformation and bonding under pressure. Moreover, increased particle porosity has been correlated with reduced disintegration times of tablet compacts, primarily due to accelerated liquid penetration and consequent wetting within the porous matrix. Co-processing is widely used as a tool to render excipients displaying advantageous properties such as increased particle surface area and porosity (Charoo 2019; Pabari and Ramtoola 2012).

A co-processed excipient was developed by spray-drying an aqueous slurry consisting of α-chitin and mannitol. The resulting excipient exhibited reduced lubricant sensitivity, higher compactibility, a lower tablet ejection force profile, as well as enhanced mechanical strength compared to its individual components or their physical mixture. The enhanced functionality was attributed to the increased particle surface area as well as particle porosity achieved through the co-processing method, which strengthened inter-particle bonding (Daraghmeh et al. 2010). Co-processing MCC with colloidal silicon dioxide to create silicified MCC (Prosolv®) significantly improved flowability and compactibility by altering particle surface structure and increasing surface area up to fivefold. An improvement in binding performance of 20% was reported compared to MCC alone, which was attributed to the increased particle surface area (Mužíková and Nováková 2007). Moreover, the distinct microstructure of Prosolv®, obtained by the uniform distribution of silicon dioxide on and

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within MCC particles, reduced cohesiveness, thereby promoting superior flow and blend uniformity, which is especially beneficial for low-dose or micronized APIs (JRS Pharma 2018). Another study demonstrated that the increased porosity, obtained by co-processing MCC with colloidal silicon dioxide, enhanced compressibility and mechanical strength in direct compression applications, outperforming both its physical mixture and individual components (Rojas et al. 2012). In another study, researchers evaluated a co-processed excipient composed of MCC, sorbitol, chitosan and Eudragit® E, prepared by wet massing. Pellets formulated with this co-processed excipient showed higher drug dissolution rates and complete disintegration in less than three minutes, outperforming those made with MCC alone. The improvements were attributed to the increased micropore volume and subsequent porosity of the pellets, resulting from the inclusion of sorbitol in the co-processed excipient (Goyanes and Martínez-Pacheco 2013).

However, it is noteworthy to mention that excessive porosity can compromise the mechanical strength of tablets, leading to decreased hardness and increased friability. Therefore, achieving an optimal balance in the porosity of co-processed excipients is essential to ensure their effectiveness and reliability in tablet formulations (Johansson and Alderborn 2001).

Figure 1 depicts micrographs of the powder particles of selected co-processed excipients to illustrate differences in particle size and particle shape with physical mixtures of their individual components.

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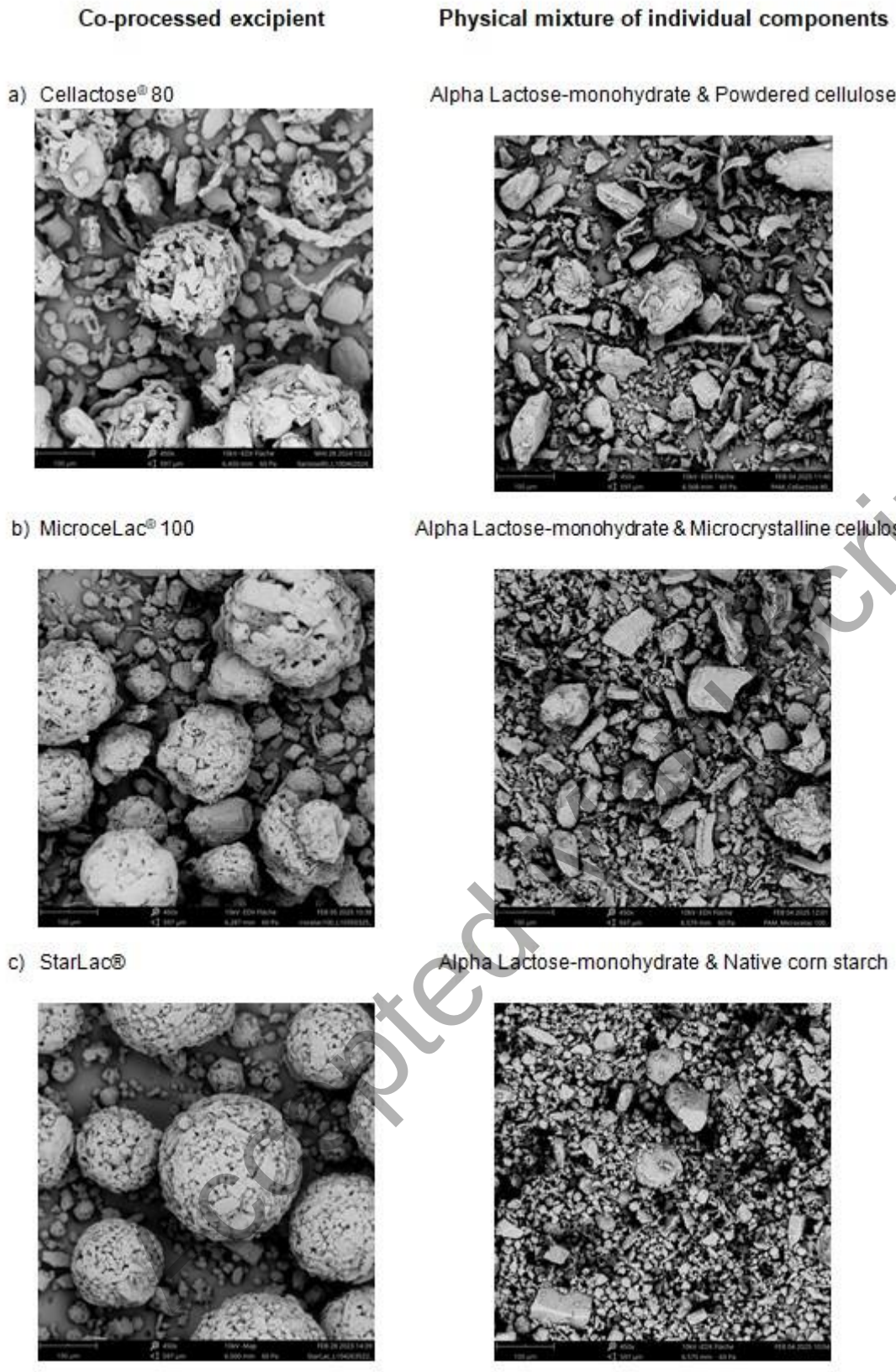

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Figure 1: Micrographs of powder particles and compactibility profiles of selected co-processed excipients, namely a) Cellactose® 80, b) MicroceLac®100, c) StarLac® as well as physical mixtures of their individual components to demonstrate differences with regards to particle shape and particle size (Meggle 2023).

3.3 Bulk level

The bulk-level powder properties of solid-state substances include properties such as flowability, compression characteristics (i.e., compressibility, compactibility and tabletability), mechanical properties and dilution potential. These bulk-level powder properties are critical for ensuring manufacturability and tablet quality. Furthermore, they ultimately determine the final mechanical characteristics of tablets produced by direct compression (Bhavana and Reddy 2023).

3.3.1 Flowability

Powder flowability is a key characteristic that is determined by how easily particles move relative to each other, which is essential for consistent die filling during tablet compression. Co-processed excipients often demonstrate improved flowability compared to their single components or physical blends thereof, because of control over their particle shape, size, and size distribution. One aim with the development of co-processed excipients is to produce a powder that has spherical particles with a uniform and narrow size distribution. This characteristic removes the need for adding glidants to the powder mixture to obtain acceptable powder flow. High powder flowability is especially important for the efficient operation of high-speed rotary tablet presses. One study highlighted that the co-processed excipient Cellactose® consisting of powdered cellulose and alpha-lactose monohydrate offered superior flowability over its individual components, owing to the spray drying process that produces spherical particles with smooth surfaces (Bin et al. 2019). A co-processed excipient was also created that consists of a combination of polacrilin potassium (12 to 22% w/w), MCC (40 to 58% w/w) and partially pregelatinized starch (25 to 35% w/w). The resulting co-processed excipient exhibited outstanding flow properties and compactibility compared to its single components (Nathwani et al. 2015).

Moreover, co-processed excipients with improved flowability helped to reduce fill-weight variation, a common issue associated with poor flow properties in directly compressed materials. For example, a research study that compared silicified MCC with MCC showed that silicified MCC resulted in less fill-weight variation, even when high-speed compression machines were used, making it more suitable for consistent tablet production (Paul 2002).

Since co-processed excipients exhibit superior flowability compared to their individual components or physical mixtures or other conventional excipients, they are well-suited for direct compression processes. Better flowability of co-processed excipients is one of the main reasons for increased manufacturing efficiency and greater product consistency (Chaudhari et al. 2012).

3.3.2 Compression characteristics

3.3.2.1 Compressibility

Compressibility refers to the ability of a powder to decrease in volume under applied pressure and it is a fundamental feature in tablets, especially for direct compression processes. Good compressibility of powders ensures efficient compaction of powders into tablets with good mechanical strength, uniformity and minimal defects. A powder that displays good compressibility enhances manufacturing efficiency and product quality. Optimizing the compressibility of powders is crucial for developing robust pharmaceutical formulations, ensuring batch-to-batch consistency, and achieving efficient large-scale production. Studies have shown that compressibility can be significantly improved through the co-processing of excipients (Mohan 2012).

The co-processed excipient Compressol®, produced via melt extrusion of mannitol and sorbitol, has been shown to exhibit superior flow properties, enhanced compressibility, and reduced hygroscopicity compared to a simple physical mixture of the two (Franc et al. 2018). Similarly, the

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co-processed excipient Ludipress®, which consists of lactose monohydrate, Kollidon® 30, and Kollidon® CL, demonstrated better compressibility than the physical mixture of its individual components (Bin et al. 2019).

3.3.2.2 Compactibility

Compactibility refers to the ability of a powder to form a coherent, mechanically strong compact (e.g., tablet) when subjected to compression. It reflects the material's capacity to undergo deformation and interparticle bonding during compaction, directly influencing the tablet's hardness, tensile strength and structural integrity. High compactibility indicates that the powder can produce strong tablets at relatively low compression forces, which is desirable in tablet formulation. Both compressibility and compactibility are essential for efficient tablet manufacturing, particularly in direct compression processes, but each focus on different aspects of the tablet formation (Leuenberger and Rohera 1986).

In a study involving the co-processed excipient Cellactose®, tablets produced from it showed higher crushing strength than those produced from simple physical mixtures of its components. The enhanced compactibility was attributed to a synergistic effect where the fragmentation of lactose and plastic deformation of cellulose worked together to aid in consolidation (Arida and Al-Tabakha 2008). A co-processed excipient that was created by drying aqueous slurries of MCC and calcium phosphate demonstrated enhanced compactibility when compared to simple dry physical mixtures of the same components (Thoorens 2010).

Figure 2 shows the compactibility profiles of selected co-processed excipients to illustrate differences in tablet hardness versus compaction force of the co-processed excipients and the physical mixtures of their individual components.

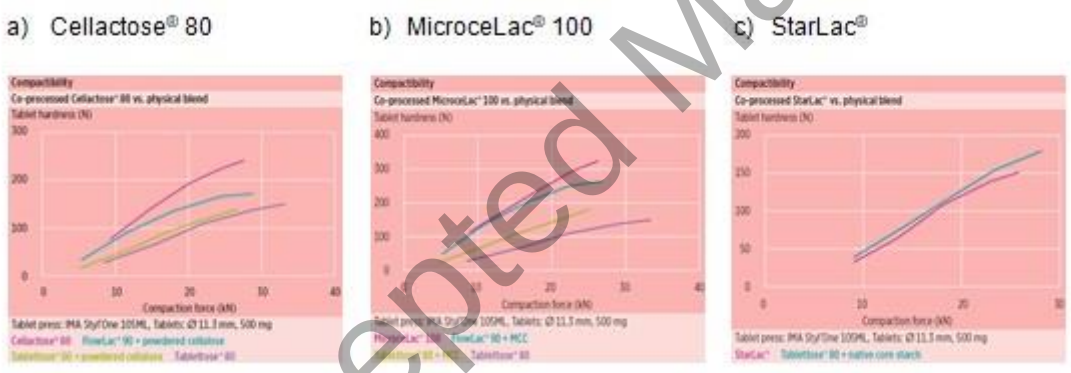

Figure 2: Compactibility profiles of selected co-processed excipients, namely a) Cellactose® 80, b) MicroceLac®100, c) StarLac® as well as physical mixtures of their individual components to demonstrate differences with regards to compactibility (Meggle 2023).

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3.3.2.3 Tabletability

Tabletability is a term that is similar in meaning to compactibility and refers to the ability of a powder or powder mixture to form a tablet with adequate mechanical strength and functionality during the tableting process. A powder with good tabletability ensures that the compressed tablets are robust enough to withstand handling, packaging and transportation, while providing appropriate disintegration properties (Tho and Bauer-Brandl 2011).

The co-processed excipient Avicel® HFE-102, formed by co-processing Avicel® PH-102 (MCC) with mannitol, demonstrated enhanced flow properties and tabletability in comparison with its single components, especially when lubricated (Panda et al. 2011). In a separate study, researchers explored the blending of acetaminophen with nanocellulose, a submicron cellulose powder, using a twin-screw process. The resulting co-processed formulation notably enhanced tabletability, enabling acetaminophen to be directly tableted without the need for additional excipients (Capece 2025).

3.3.3 Mechanical properties

The mechanical properties of excipients incorporate their deformation behavior (including plastic or elastic deformation) as well as brittle fracture, which directly impact the strength and integrity of tablets. Pharmaceutical materials often display a combination of elastic, plastic and brittle behaviors, but one will usually be dominant. The diversity in mechanical properties of excipients makes it difficult to obtain the ideal powder with optimum compressibility. Co-processing offers an effective solution by combining plastic materials, which deform under compression, with brittle materials, which fragment under pressure. This type of co-processing thereby establishes a synergistic effect in mechanical properties to improve tableting performance. This also mitigates the weaknesses of each mechanical property such as the tendency of plastic materials to store excessive elastic energy or the poor bonding of brittle materials and additionally reduces the occurrence of challenges such as lamination and capping, thereby enhancing overall excipient functionality and tablet formation (Pusapati 2014; Dzoagbe 2024).

Cellactose®, a co-processed excipient composed of 25% powdered cellulose (plastic material) and 75% brittle α-lactose monohydrate, offers significant advantages in solid oral dosage formulation. In comparison to its individual components, Cellactose® exhibits improved binding properties, enhanced flowability and consequent die filling, as well as increased compressibility, making it highly suitable for direct compression applications (Dzoagbe 2024). In another study, CombiLac®, a spray-dried ternary blend of alpha-lactose monohydrate (70%), MCC (20%) and white native corn starch (10%), was analysed for its flowability, compactibility and tablet properties. Compared to a physical mixture of its components, CombiLac® demonstrated superior flowability (lower Hausner's ratio) and enhanced tabletability. However, it exhibited greater sensitivity to lubricants during compaction, likely due to the reduced fragmentation tendency of lactose when co-spray dried with starch and MCC (Mužíková et al. 2016). A co-processed excipient combining mannitol (brittle) and chitin (plastic) was also developed its compression properties evaluated. The Kawakita equation, which assesses the extent of volume reduction during powder compression, was used to evaluate the compressibility of co-processed chitin. The constant 1/b, an inverse indicator of the degree of plastic deformation occurring during compression, revealed that co-processing with mannitol significantly enhanced chitin's ability to deform plastically. This improvement was attributed to the formation of intermolecular hydrogen bonds and the presence of moisture within chitin's porous structure, which not only promoted bonding but also acted as an internal lubricant, thereby increasing the compact's crushing strength. Moreover, mannitol improved chitin's packing efficiency by minimizing surface irregularities and facilitating better particle rearrangement under pressure. Collectively, these effects contributed to a marked enhancement in the compressibility of chitin through co-processing with mannitol (Daraghmeh 2010).

3.3.4 Dilution potential

Dilution potential refers to an excipient's ability to retain its compressibility and binding properties when combined with APIs and other excipients that may exhibit poor compressibility. Dilution potential of an excipient is crucial in the manufacture of tablets via the direct compression method. A high dilution potential ensures that the final tablet maintains adequate mechanical strength and uniformity, even when large amounts of poorly compressible APIs are incorporated. The development of co-processed excipients has become an effective strategy to enhance the dilution

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potential of excipients. The result is excipients delivering improved flowability, compressibility and reduced sensitivity to lubricants, which in turn optimizes the direct compression process' efficacy and ensures consistent tablet quality (Bin et al. 2019).

It was determined that co-processed isomalt exhibited enhanced packing ability in comparison to standard isomalt, with a notable rearrangement occurring during the initial stages of compression, as indicated by the modified Kawakita equation. It demonstrated a 40% dilution potential for paracetamol, significantly higher than the 20% dilution potential observed with isomalt alone. Moreover, the co-processed form of isomalt effectively mitigated the lamination and sticking problems commonly associated with isomalt. Co-processing therefore enhanced its tabletability and improved its performance in tablet formulation and production (Sandhan and Wagh 2023). Another study focused on developing a co-processed excipient for fast-dissolving tablets of irbesartan, a poorly compressible API, using the melt agglomeration technique. The co-processed excipient, consisting of lactose monohydrate, mannitol, PEG 4000 and crospovidone, demonstrated increased dilution potential. Up to 40% of the drug could be incorporated into the tablet while maintaining acceptable compressibility, whereas the simple physical mixtures were not able to yield acceptable tablets at this percentage (Madhvi et al. 2014). Researchers utilized spray drying to formulate co-processed excipients composed of lactose monohydrate, MCC and StarCap 1500® to improve the compressibility of etodolac. The study demonstrated that the optimized co-processed excipient, with a composition of 25% lactose, 30% MCC and 45% StarCap 1500®, significantly enhanced the flow properties, dilution potential and immediate compressibility of etodolac, thereby improving its suitability for direct compression (Alsirawan and Paradkar 2020).

Figure 3 illustrates how co-processing alters properties at the molecular, particle, and bulk levels of solid-state substances, highlighting the interdependence between these levels.

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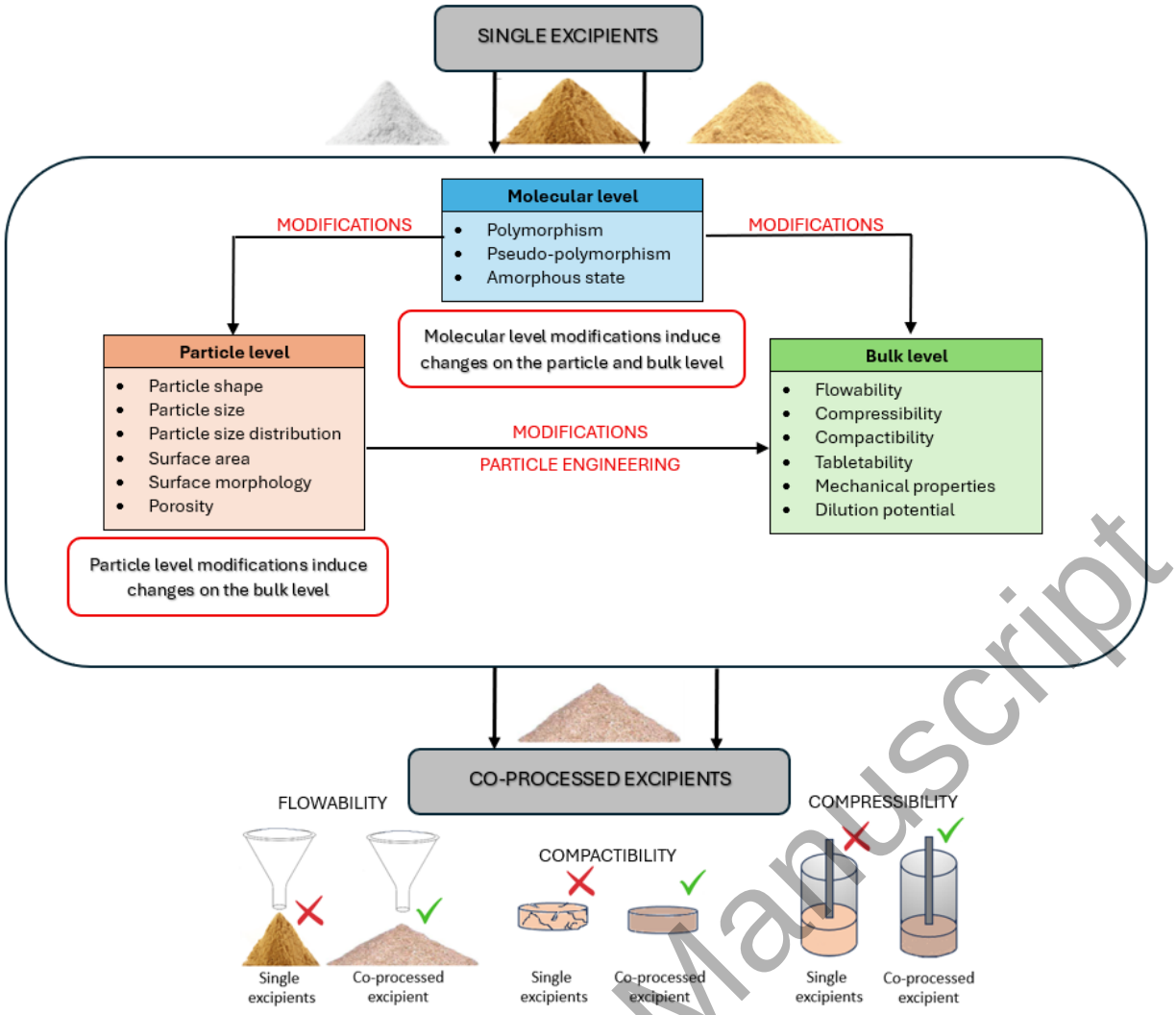

Figure 3: Illustration of changes induced in excipients by co-processing on the molecular, particle and bulk level

3.4 Sensitivity parameters

Excipients exhibit sensitivity to various factors, which include lubricant, moisture and strain rate sensitivity. These parameters play a critical role in both the compression process of pharmaceutical powders and the post-compression stability of tablets. The stability of powders should be ensured both during and after tablet manufacturing to maintain powder performance and product quality. Co-processing offers an effective approach to modify these sensitivity parameters in excipients, thereby enhancing the manufacturability, mechanical strength and overall stability of tablets (Thoorens et al. 2014).

3.4.1 Lubricant sensitivity

Lubricant sensitivity refers to the detrimental effects that lubricants can have on tablet performance, such as reduced hardness, poor compressibility, slower dissolution and impaired disintegration. These issues arise because lubricants, while necessary to reduce friction during compression and ejection, can form surface films that inhibit interparticle bonding. Co-processing has emerged as an effective strategy to mitigate lubricant sensitivity by producing excipients that fragment during compression, exposing fresh surfaces and thereby disrupting the formation of continuous lubricant layers (Thoorens et al. 2014). Mannitol (water-soluble filler) and calcium carbonate (water-insoluble filler) were selected as model excipients to which hydroxypropyl methylcellulose was applied as a

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surface modifier using two co-processing techniques, i.e., fluid bed coating and spray drying. These co-processed excipients demonstrated both deformation and fragmentation under compression. These mechanisms help maintain tablet strength by exposing fresh surfaces and preventing the formation of a continuous lubricant film (Dong et al. 2018). Similarly, it was demonstrated that co-processing mannitol and chitin via spray and wet granulation significantly reduced sensitivity to magnesium stearate, compared to simple physical mixtures of the components. This improvement was attributed to increased surface area from surface folding during granulation, which helped maintain mechanical integrity and dissolution properties, ultimately rendering a co-processed excipient with enhanced manufacturability (Daraghmeh et al. 2010).

A novel patented co-processed excipient was formulated through the spray drying of an aqueous slurry containing MCC and mannitol. This process resulted in an excipient system that exhibited lower sensitivity to lubricants, enhanced compactibility and a reduced tablet ejection force when compared to its separate components or their physical blend (Li et al. 2008). To address the functional drawbacks of MCC, which limits its effectiveness during direct compression, it has been co-processed with silicon dioxide, i.e., Prosolv®. Upon investigation, silicified MCC possesses enhanced functionality in comparison with MCC including, inter alia, reduced sensitivity to lubricants. Similarly, co-processing MCC with calcium carbonate renders a co-processed excipient with enhanced compactibility and reduced lubricant sensitivity. Moreover, MicroceLac® 100, prepared by spray-drying alpha-lactose monohydrate and MCC, demonstrated the lowest sensitivity to lubricants. In addition, it showed enhanced flowability and binding properties compared to physical mixtures of MCC with various lactose grades, such as alpha-lactose monohydrate (Pharmatose® 100 M), anhydrous beta-lactose (Pharmatose® DCL21) and spray-dried lactose (Pharmatose® DCL11) (Panda et al. 2011).

3.4.2 Moisture sensitivity

Moisture sensitivity refers to the propensity of excipients and/or APIs to absorb or interact with moisture from the environment, which can adversely affect the stability, efficacy and manufacturability of powder formulations into tablets. Furthermore, excipients that readily absorb moisture can facilitate degradation pathways for APIs (e.g. hydrolysis), which may lead to reduced potency and compromised product quality. The presence of moisture can also influence the physical properties of excipients, which affect critical parameters in tablet manufacturing such as powder flowability and compressibility. Increased moisture content of powder particles can lead to stronger interparticle liquid bridges, which results in decreased flowability accompanied by associated challenges during tablet processing Rajabi-Siahboomi et al. 2015). To mitigate these issues, it is essential to select excipients with appropriate moisture sorption characteristics and consider strategies such as co-processing to enhance moisture resistance. Understanding the interactions between moisture and excipients is crucial for designing stable and effective pharmaceutical products. Only a few commercially available excipients are explicitly marketed for use with moisture sensitive APIs, which include pregelatinized maize starch, i.e., Starch1500® and a co-processed mixture of native starch and pregelatinized maize starch, i.e., Sepistab™ ST 200. Pregelatinized maize starch is effective due to its ability to absorb moisture, reduce water activity and thereby prevent moisture from affecting the drug. Studies have shown that co-processing starch-based excipients, like pregelatinized maize starch, help stabilize moisture-sensitive drugs better than other excipients with lower moisture-binding capacities, such as dicalcium phosphate dihydrate (Crouter and Briens 2013; Veronica et al. 2022).

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3.4.3 Strain rate sensitivity

Strain rate sensitivity refers to the ability of an excipient to adapt to pressure changes with varying compression speeds. Excipients with a high strain rate sensitivity exhibit significant changes in yield pressure between slow and fast compression, indicating greater elasticity and can therefore potentially lead to challenges during tablet manufacturing (Merlin 2025). In tablet production, especially during high-speed direct compression, a high strain rate sensitivity can lead to issues such as inconsistent tablet hardness and difficulties during scale-up, as the excipient's behavior varies with different compression rates (Thomas 2025). By co-processing excipients with different deformation behaviors, excipients with improved strain rate sensitivity profiles can be produced. This is exemplified by the co-processing of lactose (brittle) and cellulose (plastic), i.e., Cellactose®, which effectively minimizes the elastic energy storage during compression, reducing stress relaxation and the propensity for capping and lamination. This is attributed to the mitigation of the impact of compression speed on tablet compactibility achieved through co-processing, ultimately aiding in achieving acceptable and consistent tablet quality and performance (Panda et al. 2011).

3.5 Stability

Critical stability factors of excipients to consider during tablet formulation include hygroscopicity, sensitivity to temperature and light exposure and susceptibility to polymorphic transformation. These factors play a pivotal role in determining the shelf-life and overall performance of excipients. Co-processing can be employed as a valuable tool to enhance the stability of excipients and APIs prone to degradation due to inherent instability (Dzoagbe et al. 2024).

As mentioned before, moisture content significantly influences the stability, flowability, compressibility and mechanical strength of pharmaceutical excipients. Hygroscopic excipients, which absorb moisture from the environment, can experience various issues affecting pharmaceutical formulations. Moisture adsorption in these materials can lead to increased chemical instability among other unwanted mechanical properties such as decreased flowability and compressibility. Conversely, non-hygroscopic excipients typically maintain stability under relative humidity levels below 90%, remaining unaffected by moisture-induced changes. Utilizing co-processing to optimize moisture-related behavior of excipients can contribute to ensuring the stability of pharmaceutical formulations (Crouter and Briens 2013). The co-processed excipient Prosolv® (MCC and colloidal silicon dioxide) exhibited improved moisture resistance compared to unprocessed MCC. This was attributed to the moisture protective effects of colloidal silica that helped to maintain compressibility and tensile strength, even at high humidity levels. Similarly, co-processing MCC with mannitol (e.g., Avicel® HFE-102) reduced hygroscopicity, enhanced moisture resistance and maintained high compressibility and compactibility. Additionally, moisture-related issues of tablets during storage were also mitigated (Charoo 2019). In another study it was demonstrated that co-processing starch with either NaCl or $Mg(NO_3)_2.6H_2O$ altered the number of water molecule binding sites on the starch, thus altering hygroscopicity and water content, and also influenced the distribution of the sorbed moisture. The co-processed excipients led to reduced drug degradation and minimal changes in tablet tensile strength during post-compaction storage. In contrast, tablet formulations containing simple physical mixtures of starch and salts rendered unfavorable results. This research highlighted the benefits of co-processing common excipients to synergistically reduce the negative effects of moisture and enhance product stability, specifically when developing formulations for moisture-sensitive drugs (Vernoica et al. 2024). Furthermore, co-processing ginsenoside, obtained from red ginseng extract, with silicon dioxide, reduced the water sorption rate to less than 12% across relative humidity levels ranging between 30% and 70% compared to a water sorption rate of just less than 20% for the unprocessed pure extract. The reduced hygroscopic nature obtained by co-processing ensured acceptable water content of the formulation and maintained stability under varying humidity conditions (Jin et al. 2021). It was also found that co-processing *Physalis peruviana* fruit extract with a combination of corn starch and MCC improved the hygroscopicity of the powder, transitioning it

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from class III (moderately hygroscopic) to class II (slightly hygroscopic). This approach also prevented deliquescence and enhanced the stability of the extract (Bernal et al. 2016).

3.6 Disintegration and dissolution

Disintegration is the process by which a tablet breaks into smaller particles upon contact with liquid, facilitating drug release. On the other hand, dissolution is when the drug dissolves into solution upon release from the dosage form, which enables absorption of the drug molecules into the bloodstream. Both processes are crucial for ensuring acceptable bioavailability of drugs from solid oral dosage forms such as tablets (Markl and Zeitler 2017). Co-processing enhances both disintegration and dissolution of tablets by improving excipient properties. It can increase tablet porosity, improve wetting, and cause faster disintegration and dissolution rates (Dzoagbe et al. 2024).

Research showed that co-processing mannitol and MCC rendered tablets with reduced disintegration times compared to tablets produced from simple physical mixtures of the components. Additionally, compared to directly compressed tablets containing physical mixtures of mannitol and MCC, tablets produced from the spray-dried co-processed excipient exhibited faster drug release, likely due to the increased porosity of the spray-dried formulation (Jacob et al. 2007). A co-processed excipient of chitin and mannitol was also developed by using roller compaction for orodispersible tablets of metronidazole. Different ratios of chitin to mannitol (10:90, 20:80, and 30:70 w/w) were tested. This co-processed excipient material exhibited superior disintegration and wetting properties compared to commercially available bases for the orodispersible tablets (Daraghmeh et al. 2010). A patented co-processed excipient consisting of crospovidone and calcium silicate was prepared and demonstrated that this co-processed combination effectively enhanced the dissolution rate and extent of hydrophobic drugs (Rao et al. 2012).

4 Functionality enhancements by co-processing of excipients with APIs

The utility of co-processing extends beyond enhancing excipient functionality and offers significant advantages when applied directly to active pharmaceutical ingredients (APIs). Co-processing APIs with excipients, such as appropriate carriers or polymers, provides a strategic approach to overcoming challenges associated with poor physicochemical properties of the APIs. This technique can improve key material attributes such as flowability, compressibility and particle morphology, while also offering opportunities to modify and control drug release profiles. These enhancements are particularly valuable in the formulation of high-dose or poorly compressible APIs, where traditional processing methods may fall short in achieving robust tablet properties (Chaturvedi et al. 2023).

It was demonstrated that co-spraying beta-mannitol with paracetamol transformed the drug to its delta-polymorph, a crystalline form known for improved compressibility and tabletability. This transformation rendered the paracetamol more suitable for direct compression, illustrating the impact of co-processing on polymorphic form and subsequent manufacturability (De Pauw et al 2022). Similarly, employing co-precipitation to co-process metformin hydrochloride, a commonly used API with poor compressibility, with hydroxypropyl methylcellulose resulted in agglomerates that exhibited a more spherical morphology, significantly enhancing bulk density and flow properties. This modification facilitated the direct compression of metformin hydrochloride, which is typically a challenging API due to its irregular particle shape and poor mechanical strength (Chaturvedi et al. 2023). Another researcher also sought to improve the direct compressibility of metformin hydrochloride by co-spray drying it with aqueous solutions of povidone in concentrations ranging from 0 to 3% w/v. They found that co-spray drying with 2% povidone markedly enhanced both flowability and compressibility, allowing the API to be directly compressed into tablets without compromising performance (Barot et al. 2010).

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It was also reported that co-processing gabapentin with fine Methocel® guest particles significantly improved tablet tensile strength and interparticle contact area. The co-processed formulation displayed negligible strain rate sensitivity and maintained a consistent compactibility profile, even at varying compression speeds. These improvements were attributed to enhanced bonding, which surpassed the effects of particle fragmentation alone, and were not observed in either unprocessed gabapentin or physical mixtures of the components (Roopwani and Buckner 2019).

Beyond improving mechanical properties, co-processing also enables the development of modified-release formulations. Crystallo-co-agglomeration was used to co-process an API with hydroxypropyl methylcellulose at a 3:1 ratio. The resulting co-processed product exhibited not only enhanced flow characteristics, but also sustained-release behavior compared to the pure drug. This highlights the potential of co-processing to control drug release kinetics while simultaneously improving manufacturability (Rosenbaum et al. 2018).

Case studies with respect to functionality enhancements for selected drugs formulated with the co-processed excipient, Prosolv®, are shown in table 5 below.

Table 5: Examples of APIs formulated with the co-processed excipient, Prosolv®, as examples of functionality enhancements of tablets

API	Co-processed excipient	Functionality enhancement description	References
Atenolol	PROSOLV® EASYtab SP	Tablets with PROSOLV® EASYtab SP achieved 20% better compactibility, 10 – 15% lower ejection forces, shorter disintegration times, superior content uniformity results alongside improved hardness and mass uniformity when compared to physical mixture formulations.	(JRS Pharma, [date unknown-b])
Diclofenac sodium	PROSOLV® EASYtab SP	PROSOLV® EASYtab SP formulations had 30 – 35% improved compressibility, 20% lower ejection forces (even at high compression forces) and quicker disintegration compared to physical mixtures. An increase in content, mass and hardness uniformity whilst resisting demixing was also observed.	(JRS Pharma, [date unknown-b])
Hydrochlorothiazide	PROSOLV® EASYtab SP	Compared to physical mixtures, PROSOLV® EASYtab SP improved compactibility by 20 – 30%, reduced ejection forces by 25 – 50%, shortened disintegration times and increased uniformity. Dissolution consistency was also improved due to the composite structure preventing lubricant accumulation on the API surface.	(JRS Pharma, [date unknown-b])
Paracetamol	PROSOLV® EASYtab SP	In a 40% paracetamol formulation, PROSOLV® EASYtab SP produced noticeably stronger tablets, reduced sensitivity to lubricant level and prevented segregation during blending, resulting in more consistent dissolution and improved content uniformity compared to physical mixtures.	(JRS Pharma, [date unknown-a])
Piroxicam	PROSOLV® EASYtab SP	The content uniformity of low dose piroxicam preparations was significantly increased by PROSOLV® EASYtab SP in comparison with physical mixtures.	(JRS Pharma, [date unknown-a])
Propranolol HCl	PROSOLV® EASYtab SP	Tablets formulated with PROSOLV® EASYtab SP achieved a 20 – 30% compactibility increase, a 30 – 40% ejection force reduction, faster disintegration as well as an increase in content uniformity, mass uniformity and tablet hardness compared to physical mixtures.	(JRS Pharma, [date unknown-b])

It is clear that co-processing APIs with excipients offers a powerful strategy to overcome formulation challenges. This approach addresses key limitations of many APIs and holds broad applicability in

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pharmaceutical development. As the demand for efficient and patient-friendly dosage forms grows, API co-processing is set to play a critical role in advancing robust and innovative formulations.

5 Conclusion

Co-processed excipients are combined materials that offer a powerful approach to optimize tablet formulations. By enhancing essential excipient powder properties such as flowability, compressibility and compactibility, co-processed excipients support more efficient tablet manufacturing, especially by means of direct compression. Direct compression is a tablet manufacturing method increasingly favored for its simplicity and cost-effectiveness. Excipient performance is critical to ensure the successful manufacture of acceptable tablets by means of direct compression. Furthermore, the superior functional attributes of co-processed excipients help address common challenges like moisture sensitivity and lubricant sensitivity, improving the stability and quality of tablets.

Studies have shown the improved performance of co-processed excipients over their individual components as well as simple physical mixtures. Co-processed excipients formed from compendial excipients listed in the inactive ingredient database of the FDA by means of physical changes rather than chemical changes require limited additional safety data. While the potential benefits of co-processed excipients are clear, there are some challenges to overcome such as scaling up of the manufacturing processes, ensuring excipient-API compatibility and navigating regulatory approval. Nonetheless, as research and technological advances continue, co-processed excipients are poised to play an increasingly important role in the development of high-quality pharmaceutical products.

With technological advances, co-processed excipients with better properties and more advanced functionalities can be produced, which holds great promise for the pharmaceutical industry. Co-processed excipients should therefore not only be considered as functional additives, but they should be recognized as strategic enablers of innovation, quality and sustainability in modern pharmaceutical manufacturing.

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Conflict of interest

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