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Multifunctional coprocessed excipients for improved tabletting performance

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With the advancement of tablet manufacturing process, the demand of excipients with improved functionalities, mainly in terms of flow and compression properties, has increased. Coprocessed excipients are a mixture of two or more existing excipients at subparticle level, offer substantial benefits of the incorporated excipients and minimize their drawbacks. These multipurpose excipients have dramatically reduced the number of incorporating excipients in the tablet. The present review discusses the potential advantages of coprocessing and coprocessed excipients, material characteristics required for coprocessing, methods of coprocessing and various coprocessed excipients for direct compression available in the market.

Keywords: coprocessed excipients, coprocessing, direct compression, tablet

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1. Introduction

Despite many advanced dosage forms, the tablet remains the most widely used dosage form owing to its stability, dose uniformity and user acceptability. However, its formulation development is challenging owing to its multifarious manufacturing procedures [1]. Many changes in tablet manufacturing process have taken place to overcome these challenges. Numerous changes have taken place in tabletting process since it was introduced in the early 1840s including regulatory, stability and technological aspects [2]. Over the time, industries have become more interested in reducing both time and cost of drug production, which led to the introduction of new processes such as direct compression, fluidized-bed granulation, automatic capsule filling and film coating [3].

Tablets are manufactured by mainly three techniques: wet granulation, dry granulation and direct compression. In wet granulation and dry granulation techniques, various processing steps and manufacturing challenges are involved, leading to higher cost and time of tablet production. In contrast to this, the direct compression technique involves simply the compression of a dry blend of powders that comprises drugs and various excipients. The simplicity and cost-effectiveness of the direct-compression process have positioned it as a preferred alternative. However, the direct-compression process is highly influenced by powder characteristics of the precompression blend such as flowability, compressibility and dilution potential. Most formulations contain higher amount of excipients compared to the active drug and, as a consequence, excipients play a major role in deciding the formulation's functionality and processability [4]. However, the numbers of excipients that can actually fulfill such performance requirements are limited.

Improved performance excipients can be obtained either as new chemical excipients, improved grades of existing materials, and processing two or more

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Table 1. Advantages of coprocessed excipients for direct compression.

Advantages	Example(s)	Ref.
Reduction in the number of incorporated excipients	All coprocessed excipients	
Multifunctional properties	Compressol S	[10]
Improved flow properties	Ludipress, Cellactose	[8,11]
Improved compressibility	Prosolv, Xylitab	[12,13]
Better dilution potential	Pharmatose DCL 40, Cellactose	[8,14]
Lesser fill weight variation during direct compression	Prosolv	[12,15]
Reduced lubricant sensitivity	Prosolv	[16]
Low degree of hygroscopicity	Ludipress, Compressol S	[8,10]
Tablet hardness independent of machine speed	Ludipress	[8]
Good disintegrating property	Cellactose	[8]
Improved organoleptic properties	Avicel CE 15	[17]

existing excipients together [5]. Any new chemical excipient has to undergo various stages of regulatory approval and patenting and copyright issues, which is a lengthy and costly process, having limited market exclusivity period. The high risk and significant investment involved in its development and low profit margin has demotivated research in this direction. Many improved grades of existing excipients such as spray dried lactose, microcrystalline cellulose (MCC), granular dicalcium phosphate, crosspovidone and pregel starch has been introduced in the market but performance improvement was achieved only up to a limited extent. On the other hand, coprocessed excipients by virtue of combining properties of two different excipients fulfill the increasing demand of multifunctional excipients for direct tabletting.

2. Coprocessing

Coprocessing was initially used by the food industry to improve stability, wettability and solubility, and to enhance the gelling properties of food ingredients such as coprocessed glucomannan and galactomanan [6]. In pharmaceutical industry, the concept of coprocessing of excipients was introduced in late 1980s with the introduction of coprocessed MCC and calcium carbonate [7]. Cellactose (Meggle Co., Wasserburg, Germany) was introduced in 1990, which is a coprocessed combination of 75% cellulose and 25% lactose. Later on, silicified microcrystalline cellulose (SMCC), the most widely used coprocessed excipient, was developed [8].

Coprocessing is a novel concept of processing two or more established excipients by some appropriate means to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients [9]. The major advantages of coprocessed excipients are the elimination of wet granulation production stages, avoidance of keeping and handling various excipients, and the synergetic effect of having homogenous free flowing directly compressible formulation of the required excipients. Coprocessing of excipients cause them to interact at the subparticle level and lead to superior properties than simple physical mixtures of their components [4]. The advantages of the coprocessed excipients are listed in **Table 1**.

3. Material characteristics for excipient selection

When formulating direct compression tablets, the choice of excipient is extremely critical. The events that occur in the process of compression are transitional repacking, deformation at point of contact, fragmentation and/or deformation, bonding, deformation of the solid body, decompression and ejection [18]. Out of these, the tabletting of powder is predominantly affected by deformation (compressibility) and bonding (compactibility) behavior of powder under stress [19]. Compressibility refers to the property of a powder to densify under pressure whereas compactibility describes the formation of strong compacts under pressure. During the compression, when high pressure is applied to form a compact mass (tablet), stresses within the particles become great, and lead to fragmentation (in case of brittle materials, e.g., sucrose, lactose, silicon dioxide, fructose dextrins). As a result of fragmentation, the number of particles gets increased with the formation of potential new and clean surfaces for bonding. Fragmentation also leads to densification with the infiltration of the smaller fragments into the void space. In case of plastic material (*viz*, polyvinyl pyrrolidone and crospovidone, maize starch, guar gum, sorbitol), as stresses are relieved by plastic deformation, fragmentation does not occur. Plastic deformation is a change in particle shape due to the sliding of groups of particles (viscoelastic flow, e.g., MCC, hydroxyl methyl cellulose). Such deformation produces new, clean surfaces that are potential bonding areas [20]. Therefore, the ideal diluents should comprise a mixture of a component which fragments, that is, brittle and one which deforms, that is, plastic, thus, incorporating advantages of both mechanisms [11]. As shown in **Table 2**, most coprocessed products consist of a relatively less amount of plastic material fixed between or on the particles of the larger amount of brittle material. Such combinations can help improve functionalities such as compaction performance, flow properties, strain-rate sensitivity, lubricant sensitivity or sensitivity to moisture, or reduced hornification [4]. For example, Cellactose, a coprocessed excipient of large amount of brittle material (75% lactose) with 25% plastic material (cellulose) that prevents the storage of too much elastic energy during compression, results in a small amount of stress relaxation and a reduced tendency of capping and

Table 2. Proportions of brittle to plastic material in coprocessed excipients.

Trade name	Incorporated excipients			
	Brittle excipients		Plastic excipients	
Ludipress	α-Lactose monohydrate	93.4%	Polyvinyl pyrrolidone (Kollidon 30) and Crospovidone (Kollidon CL)	3.2% 3.4%
Cellactose	α-Lactose	75%	Cellulose (25%)	25%
Prosolv	Fumed colloidal silicon dioxide	2%	Microcrystalline cellulose	98%
Pharmatose DCL 40	Anhydrous lactose	95%	Lactitol	5%
Starlac	α-Lactose monohydrate	85%	Maize starch	15%
Xylitab	Xylitol	Min. 96.5%	Sodium caboxymethyl cellulose	Max. 2%
Advantose FS 95	Fructose	95%	Starch	5%
Avicel CE 15			Microcrystalline cellulose Guar gum	
Formaxx	Calcium carbonate	70%	Sorbitol	30%
Microcelac	Lactose	75%	Microcrystalline cellulose	25%
Dipac	Sucrose Dextrin	97% 3%		
Compressol S			Mannitol sorbitol	

lamination [21]. However, examples of the other extreme also exist; for example, SMCC has a large amount of MCC (98%) (plastic material) and a small amount of silicon dioxide (2%) (brittle material). Coprocessed excipients developed by coprocessing of two plastic materials (Avicel CE 15, Compressol S) or two brittle materials (Dipac) also exist (see **Table 2**).

Picker has developed a new 3D model for comprehensive and rapid determination of deforming properties (brittle, elastic and plastic compression properties) of directly compressible materials based on time plasticity (d), pressure plasticity (e) and angle of torsion (ω) [22]. With increase in d, the powder deforms faster during tabletting [23] and, therefore, with increasing densification value of d increases. With increase in e, the necessary pressure for deformation decreases. The ω is suggestive of the ratio between compression and decompression and inversely proportional to elastic deformation during the tabletting process [24]. Therefore, an ideally deforming tabletting excipient should exhibit high d, e and ω values with a constant ratio of d:ω at increasing densification [25].

Brittle materials such as dicalcium phosphate dihydrate exhibit low d, e and a strong decrease in ω values when densification increases. Whereas plastic materials such as MCC, which has much higher d, e and ω values changes only slightly when densification increases. Sugars are more brittle than the sugar alcohols. Plasticity of cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), sodium CMC and cellulose acetate are equal to that of MCC; however, their elasticity depends on substitution indicated by lower (more elastic) or higher (less elastic) ω values. The effects of compression speed and force on the compaction properties of four viscosity grades of HPMC 2208 (HPMC K100, HPMC K4M, HPMC K15M, HPMC K100M) have been studied. Increase in compression speed from 15 to 500 mm/s resulted in decrease in the tensile strength of the tablets for grades of HPMC; however, tensile strengths of HPMC Kl00 tablets were more sensitive to changes in compression speed compared to other grades. Tablets of HPMC K100 had the highest tensile strength, whereas those of HPMC K4M had the lowest tensile strength at any compression force or speed [26,27]. Native starches are very elastic in nature, whereas pregel starch and maltodextrin are less elastic and exhibited higher ω values. Deformation behavior is dependent on particle size only in case of plastic materials [25].

4. Method for coprocessing

Coprocessing is a relatively simple process that involves physical mixing of two or more excipients in form of either homogenous dispersion or solution followed by co-drying, co-precipitation or co-crystallization.

Excipients are selected based on their nature, that is, material characteristics plastic, elastic or brittle material, properties, cost, and availability and proportion of selected excipients are optimized based on desired functionalities [28]. Combination of any two excipients does not result in

improved characteristics. Moreover, the defined process and appropriate experimental conditions are also very important considerations, which will ultimately lead to formation of coprocessed product with improved performance.

The first step in coprocessing involves the mixing of the starting components in form of aqueous slurry, suspension or solution. When both or one of the starting materials are water insoluble, a well dispersed aqueous slurry of the starting excipients can be prepared either by adding two excipients into a single aqueous medium, or separate slurry of each may be prepared and then combined, or other analogous procedures may be devised. When coprocessing of MCC is carried out, uniform aqueous dispersion of MCC is preferred. For example, in case of coprocessing of MCC with silicon dioxide, MCC was first added to an aqueous medium to form slurry or suspension and pH of the slurry was adjusted to neutral. The suspension or slurry is kept under constant agitation for a sufficient time to assure a uniform distribution of the MCC. The silicon dioxide is then added to the suspension or slurry and well dispersed [29]. In case of coprocessing of MCC and $CaCO_3$, MCC was first uniformly dispersed in aqueous solution followed by addition of calcium carbonate in dry form [7]. The particle size of starting material is an important parameter in deciding the particle size of the product and hence large particle sizes (< 100 μm) are generally not preferred owing to their relatively small surface area of exposure. Coprocessing of the MCC and Galactomannan gum was carried out by forming an intimate mixture of the homogeneously dispersed MCC and gum under controlled agitation to obtain flocculated MCC–Galactomannan gum particles of desired size. The mixing is usually accomplished by the use of high shear equipments such as Waring blenders, colloid mills and homogenizers [30].

When both the starting materials are water soluble, for example, coprocessing of galactomannan and glucomannan, components are dissolved either separately followed by mixing, or together in the same vessel optionally with aid of temperature and high shear mixing. Co-precipitation can be carried out with organic solvents, drum drying, spray drying, air drying, bead milling, fluid bed drying and freezing followed by pressing or drying. Co-precipitation drying methods and co-precipitation with a water-miscible solvent and possible pH adjustment are more preferred [31].

The coprocessed excipient is preferably recovered as a dry, free-flowing particulate product of substantially colloidal particle size. The recovery and drying of the excipient may be carried out by spray drying, fluidized bed drying, freeze drying, vacuum drying, flash drying, ring drying, micron drying, tray drying, radio-frequency drying or microwave drying. Some of these drying procedures require that the excipient first be separated from the aqueous slurry or other liquid suspension. This can be accomplished through conventional solid–liquid separation techniques, for example, filtration, centrifugation or the like, to recover an excipient wet-cake suitable for drying. Spray-drying is preferred because it gives precise control over particle characteristics and for ease of scale-up. Increase in droplet surface area and high temperature during spray drying results in the formation of porous spherical particles, and makes them suitable for direct compression.

5. Coprocessed excipients for direct tabletting

The particle size, flow properties and compression properties of various coprocessed excipients along with some directly compressible materials are described in **Table 3**. Few examples showing the role of coprocessed excipients in overcoming the drawbacks of tablet manufacture of poorly compressible high dose drugs prepared with their physical mixtures are depicted in **Table 4**. The detailed physical and mechanical studies of individual coprocessed excipients are described in the following sections.

5.1 Coprocessing of lactose

In solid dosage forms, lactose is probably the oldest but still one of the most important diluent in tabletting. However, the inadequate compactibility and poor flow properties of α-lactose monohydrate powder limits the use of crystalline α-lactose monohydrate as a filler-binder for direct tabletting. Many researchers and excipient manufacturers modified crystalline α-lactose monohydrate to achieve a product exhibiting good compactibility, reduced capping tendency and good flow properties to meet the need of excipients for direct compression excipients [39].

Processing of lactose into small α-lactose monohydrate agglomerates (e.g., Tablettose, Pharmatose DCL 15) or spray-dried lactose was performed to improve its direct tabletting characteristics. This processed lactose has better fluidity and compactibility than regular lactose. However, the compressibility of spray-dried lactose is borderline, and furthermore, it has relatively poor dilution potential. As spray-dried lactose loses compressibility on initial compaction, it does not lend itself to rework [2]. Later on, binary mixtures of crystalline α-lactose monohydrate with MCC, povidone or starch have been tried but it only results in increase of the compressibility of the mixtures but no improvement in flowability as compared with pure α-lactose monohydrate [39]. Hence, efforts were made towards the development of coprocessed lactose.

Coprocessing of α-lactose monohydrate with povidone and crospovidone resulted in Ludipress (BASF AG, Ludwigshafen, Germany), which is a suitable filler for direct tabletting on high speed presses. It is odorless, tasteless, white free-flowing granules especially developed for direct compression, but is also suitable as filler for hard gelatin capsules. Formation of polyvinyl pyrrolidone and crospovidone coat over lactose powder imparted excellent flowability and low degree of hygroscopicity to the lactose. Moreover, hardness of the tablets produced is also independent of machine speed. The binding properties of Ludipress, both unlubricated and lubricated

Table 3. Properties of various directly compressible excipients.

Trade name	Particle size distribution	Hausner ratio	Bulk Density (g/cm³)	Tapped density (g/cm³)	Angle of repose	Compressibility index	Ref.
Pharmatose DCL 11	< 45 µm max.15% < 100 µm 30 – 60% < 250 µm min. 98%	1.20	0.61	0.73	31	16.44	[32]
Pharmatose DCL 21	< 45 µm max. 20% < 150 µm 40 – 65%	1.27	0.67	0.85	39	21.18	[33]
Avicel PH 102	Mean = 100 µm	1.19	0.307	0.37	36	17.02	[34]
Avicel PH 200	Mean = 180 µm	1.22	0.357	0.435	34	17.93	[34]
Ludipress	< 63 µm max. 20% < 20 µm 40 – 65% > 400 µm max. 20%	1.20	0.517	0.618	30.3	16.14	[35]
Cellactose 80	< 32 µm NMT 20% < 160 µm 35 – 65% < 250 µm NLT 80%	1.21	0.380	0.462	36.2	17.75	[36]
Prosolv	20 – 200 µm	1.26	0.31	0.39	NMT 30	20.51	[37]
Starlac	< 32 µm NMT 15% < 160 µm 35 – 65% < 250 µm NLT 80%	1.19	0.57	0.68	NMT 30	16.18	[38]

Table 4. Improved tabletting performance of poorly compressible high dose drugs with coprocessed excipients.

Active agent (poorly compressible)	Coprocessed excipient	Physical blend	Improved parameters compared to physical blend	Ref.
Acetaminophen (paracetamol)	Ludipress	α-Lactose monohydrate, Kollidon 30 and Kollidon CL	Stable flow properties	[46]
	Prosolv 90	Avicel PH 102 and Aerosil	Improved powder and tablet properties except flowability	[62]
	Cellactose	Cellulose and lactose	Improved mechanical properties	[81]
Glibenclamide	Ludipress	α-Lactose monohydrate, Kollidon 30 and Kollidon CL	Disintegration time and compression pressure independent dissolution of glibenclamide	[45]
Folic acid	MicroceLac 100	Microcrystalline cellulose and lactose	Flow and binding properties	[53]
Cefixime trihydrate and ibuprofen	Coprocessed superdisintegrant consisting of crospovidone and sodium starch glycolate	Crospovodone and sodium starch glycolate	Quick disintegration and improved drug dissolution	[79]

with 1% magnesium stearate, are good and were found to be much better than those of the physical mixture [8]. Although Ludipress contains a disintegrant, the disintegration of tablets takes longer than tablets containing α-lactose monohydrate, anhydrous β-lactose, spray-dried lactose or Tablettose. The length of disintegrating time is attributed to the presence of polyvinylpyrrolidone [40]. Ashrafi *et al.* reported that Ludipress, when used in high amount, can extend the sustaining effect of the formulation to some extent [41].

Ludipress exhibited better flow rate compared to Avicel PH 101 and has the highest flowability among various lactose based directly compressible excipients (Cellactose, Tablettose, Fla flo lactose) as inferred from its lower static and dynamic angle of repose than other excipients [42,43]. Determination of tablet disintegration time revealed a disintegration time minimum at about 100 MPa for Ludipress compacts. Tablet disintegration time of Ludipress based compacts were not influenced at above 100 MPa compaction pressure whereas Cellactose showed a significant increase in disintegration time (> 20 min) at compaction pressures above 100 MPa [44,45]. The ability to form coherent compacts of Ludipress was similar to Cellactose and Avicel PH 200, whereas tablets

made from the physical mixture resulted as significantly softer. At a compaction pressure of 100 MPa, friability of Ludipress compacts was ~ 0.2%. To obtain similar values for tablets prepared with Tablettose, compaction load of 200 MPa was necessary. Authors have also concluded that in terms of a multipurpose-excipient, Ludipress should be given preference in the formulation of low dosed drugs as Ludipress based tablets exhibited optimum disintegration time and compression pressure independent dissolution of glibenclamide [45]. However, in one study, Baykara *et al.* reported that Ludipress has stable flow properties but its dilution potential with Acetaminophen is lower than Avicel PH 101, Elcema G250 or Elcema P050 [46].

Schmidt and Rubensdorfer evaluated the powder and tabletting properties of Ludipress and found that Ludipress samples exhibited a good batch-to-batch uniformity and flow characteristics compared with the physical blends and other excipients investigated. Moreover, Ludipress has the ability to form coherent compacts similar to Cellactose and Avicel PH 200, whereas tablets made from the physical blend resulted as significantly softer [44]. Heinz *et al.* found that the tensile strength of tablets made of Ludipress increased linearly with compaction pressures up to 300 MPa and independent of the geometry of the tablets (diameter, thickness, shape). It was found that the tensile strength of tablets made of Ludipress increased linearly with compaction pressures up to 300 MPa, which was independent of the geometry of the tablets. The equation can be derived to correlate compaction pressure and hardness of the tablet and with slight modification for scale-up from a single-punch press to a rotary tabletting machine. Tablets produced in the rotary machine at the same pressure have a slightly higher tensile strength. The rate of increase in pressure and, therefore, the throughput, has no effect on the tensile strength of Ludipress tablets. It is thought that a certain minimum dwell time is responsible for this difference. They concluded that the production of tablets based on Ludipress can be scaled up from one rotary press to another without problem if the powder mixtures are prepared with the same mixing energy [47].

Coarse and regular grade sieved crystalline fractions of lactose monohydrate have good flow properties but lack compressibility [2]. Coprocessing of crystalline α-lactose monohydrate with powdered cellulose (Cellactose, Meggle) [11] or MCC (MicroceLac, Meggle) [48] has resulted in improved bonding ability and excellent flow properties [39].

Cellactose was designed especially for direct tabletting combined filling and binding properties of the lactose and cellulose provides better tabletting performance at lower cost. It has excellent flowability attributed to its regular particle shape and favorable particle size distribution [11]. Improved compactibility of Cellactose is owing to the principle consolidation mechanism of plastic deformation of cellulose and fragmentation of lactose [49]. Moreover, Cellactose is shown to have a higher dilution potential than a physical mixture of its constituent excipients [14]. The presence of cellulose fibers in the macroporous particles provides good disintegration properties to Cellactose. The moisture sorption of Cellactose is much lower than that of cellulose alone as it is covered with lactose [8]. Belda and Meilck found that Cellactose exhibited improved compactibility but impeded compressibility as compared to powder mixtures, each containing 25% (w/w) of Avicel PH101 or Elcema® P100 and 75% Tablettose® or lactose (100 mesh) [50]. Arida and Al-Tabakha have found that tablet strength of Cellactose was higher than their physical mixture with same ratio. Improved tablet strength with Cellactose was attributed to the enhanced interparticle bonding in this coprocessed excipient. Reduction of interparticle bonding by the presence of a lubricant film on the particles and the relaxation of lubricated tablets is higher than that of unlubricated tablets in which interparticle attractions are large. However, the negative effect of magnesium stearate (lubricant) on interparticle bonding of Cellactose particles is smaller than the physical mixture particles [51]. Jogani and Gohel prepared lactose and MCC (3:1) base, and coprocessed directly compressible adjuvant using melt granulation technique using 12.5% of the polymer blend containing 1:9 ratio of PVP:PEG as meltable binder. The prepared agglomerates were evaluated for percentage fines and Carr's index and compressed tablets were evaluated for tensile strength, friability and disintegration time. The authors concluded that melt granulation technique can successfully replace the classical wet granulation and spray-drying for the development of multifunctional directly compressible adjuvant for use in pharmaceuticals [52].

MicroceLac 100 is another marketed spray-dried product, containing α-lactose monohydrate (75%) and MCC (25%) [53]. Microcelac with both filling properties of lactose and binding capacity of MCC provides better tabletting performance at lower cost [48]. Muzíková and Zvolánková found that the tablet strength from pure Cellactose 80 was lower than that of those from MicroceLac 100 both without and with the lubricant in the compression forces of 6 and 8 kN. Disintegration time of the tablets from Cellactose 80 was longer than those from MicroceLac 100, except the tabletting materials containing 0.4% sodium stearylfumarate (Pruv) with a compression force of 6 kN [54]. Michoel *et al.* showed that Microcelac 100 has superior flow and binding properties and do not get influenced even on addition of folic acid. These improved characteristics are attributed to spray-drying [53].

The latest material on the market is Starlac, a coprocessed filler-binder consisting of 85% α-lactose monohydrate and 15% native corn starch [38]. Starch is a bifunctional excipient, used as binder and disintegrant; however, it exhibits the lowest elastic recovery at high binding capacity. When starch is coprocessed with α-lactose monohydrate, it resulted in a product with excellent compactibility [39]. The volume–pressure deformation properties of StarLac were found to be dependent

on the lactose properties. Flowability of StarLac is dependent on the spray-drying process. Moreover, starch imparts its rapid disintegration property. Starlac was proven to have improved compactibility and flowability to starch and its physical mixtures [55]. Gohel and Jogani demonstrated use of several linear regressions in development of coprocessed lactose and starch. The authors concluded that as the lactose:starch ratio increased, Carr's index of the adjuvant and crushing strength of the tablets increased although friability decreased. The percentage of starch paste has inverse effect on the friability [56].

Anhydrous lactose is a free flowing and directly compressible crystalline material with no water of hydration. However, its fluidity is less than optimal as it contains high amount of fines. Furthermore, it picks up moisture to form the hydrated compound at relatively high humidity. This is often accompanied by an increase in the size of the tablets if the excipient makes up a large portion of total tablet weight [2]. Coprocessing of anhydrous lactose (95%) with lactitol (5%) into Pharmatose DCL 40 has helped to overcome these problems. Its flow properties improve because of its spherical form and favorable particle size distribution. The water uptake of Pharmatose DCL 40 at increasing humidity is very low. Moreover, its binding properties and dilution potential are much better than those of all known lactose based products [8].

5.2 Coprocessing of cellulose

MCC is a commonly employed direct compression excipient with good lubricity and low hygroscopicity. It has the highest dilution potential. When compressed, the MCC particles are deformed plastically due to presence of slip planes and dislocations on a microscale, and the deformation of the spray-dried agglomerates on a macroscale [2]. However, MCC loses its compressibility on addition of water during wet granulation. This phenomenon is known as quasihornification [4]. The loss of compressibility of MCC is particularly problematic when it is used in a major proportion in tablet. The fluidity of MCC is poor compared to that of most of other direct-compression fillers because of its relatively small particle size. Coprocessing of MCC (98%) with fumed colliodal silicon dioxide (2%) into SMCC (Prosolv) results in improved strength of tablet compacts and reduced sensitivity to wet granulation [4,12]. SMCC has also better flowability than MCC [57]. Fraser *et al.* reported that there is no discernible chemical or polymorphic difference among the SMCC, MCC and dry mixes of MCC and silicon dioxide, indicating that the material produced by 'silicification' process is chemically and physically very similar to standard MCC [58]. In spite of being very similar structures, analytical techniques such as near IR cannot provide an explanation for the improvements in compressibility of SMCC over MCC. Internal bonding in SMCC accounts for change in compressibility from MCC after wet granulation [59].

Luukkonen *et al.* studied the rheological behavior of the wet powder masses of SMCC (Prosolv), and standard grades of MCC (Emcocel 50 and Avicel PH 101) as a function of mixing time using a mixer torque rheometer. They found that SMCC has improved flow characteristics and specific surface area, whereas it reduced swelling compared to standard MCC grades [57]. Bolhuis *et al.* reported a small negative effect of colloidal silicon dioxide on the interparticle bonding strength of unlubricated MCC. However, SMCC showed no significant effect on the tablet strength of lubricated tablets compared to physical mixtures [16]. The strength of SMCC compacts was markedly increased with increasing compression force [60]. Staniforth *et al.* reported that compacts of SMCC exhibited greater strength and stiffness than those of MCC [61]. Lahdenpää *et al.* have demonstrated that SMCC is useful when cohesive, poorly compressible ingredients are formulated into direct compressed tablets [62].

Kachrimanis *et al.* found a slight increase in the tensile strength but a marked increase in the disintegration time of Prosolv compared with Avicel in the packing fraction range 0.7 – 0.9, the range for pharmaceutical tablets. The MCC grade or silicification affects the moisture sorption and the packing during tapping as well as the particle deformation during tabletting. The incorporated silicon dioxide acts as a barrier or sinks for the moisture sorbed only for relative humidity up to 52%. At higher relative humidity (72%), the incorporated silicon dioxide does not increase the particle deformation, and results in more extended disintegration time owing to its probable saturation [63].

Silicification also results in reduction of the adsorption of amine drug (tacrine hydrochloride) from aqueous solution onto MCC [64]. Felton *et al.* found that SMCC containing capsules exhibited the lowest variation in weight, although these findings were not significantly different from either of the MCC-containing capsules [15].

Avicel CE 15 is a coprocessed excipient of MCC and guar gum, mainly used in chewable tablets [65]. Avicel CE 15 offers improved palatability, creamier mouthfeel with less grittiness and reduced tooth packing [17].

Coprocessing of MCC with calcium carbonate was carried out in a weight ratio from about 75:25 to 35:65. The product exhibits low lubricant sensitivity; its compression profile (tablet hardness versus tablet compression force) remains relatively unchanged when various lubricants are employed. This lubricant insensitivity extends both to lubricant level (amount) and lubricant type (magnesium stearate, stearic acid, etc.) [66]. Limwong *et al.* fabricated composite particles of rice starch and MCC by spray-drying technique and evaluated its direct compressibility. These composite particles exhibited good compressibility and flowability whereas its tablets show low friability and good self-disintegrating property. Thus, these developed composite particles could be introduced as a new coprocessed direct compression excipient [67].

Coprocessed product of MCC and mannitol has an improved compactibility profile, lubricant sensitivity and ejection profile compared to MCC [68]. Shirwaikar *et al.* used spray drying technique for coprocessing of MCC and mannitol to obtain direct compression excipient. Mannitol and MCC in the ratio 1.25:1 was found to have optimized powder and compressibility characteristics with fast disintegrating property. Evaluatory study on disintegration time and mouthfeel attributes such as grittiness and chalkiness ranked the formulation as the best [69].

5.3 Coprocessing of sugars and polyols

Sorbitol is widely used as the sole ingredient in sugar-free mints and as a vehicle in chewable tablets. It has a cool taste and good mouthfeel and forms relatively good compacts. But its highly hygroscopic nature leads to its poor powder flowabiltiy and caking, sticking during tabletting. Moreover, its hygroscopicity has its impact on the physical characteristics of tablets such as hardness, dissolution and bioavailability. On the other hand, mannitol does not make as hard a tablet as sorbitol but is less sensitive to humidity [2]. Compressol S, a directly compressible excipient of sorbitol and mannitol retains the compactibility of sorbitol and characteristic mannitol texture with lower hygroscopicity than sorbitol. Compressol S is 300 times less hygroscopic than sorbitol, which makes it more suitable to use with moisture-sensitive drugs. This product is designed to assist the formulator with high active loading formulations and difficult to compress actives [10]. Good compactibility and low hygroscopicity combined with pleasant taste and favorable mouthfeel of Compressol S makes it ideal for use in chewable and high dose active nutraceutical tablet formulations [70]. The coprocessed excipient of mannitol and sorbitol can also successfully be included in quick dissolving tablet formulations [71].

Fructose is a monosaccharide widely available from nature having very desirable sweetness and a natural food orientation that makes it suitable to use in pharmaceutical formulations. Fructose is, however, not directly compressible. Fructose granules agglomerated from a water solution are hard and the compressibility is unsatisfactory [72]. Advantose™ FS 95 direct compression fructose is a co-dried system of fructose and a small amount of starch, which turns fructose into an excellent excipient for pharmaceutical, nutraceuticals and chewable vitamin applications. The particle size distribution of Advantose FS 95 fructose significantly improves the flow properties. The Advantose FS 95 product has lower hygroscopicity than standard fructose, making it easier to handle with improved compressibility [73].

Dipac consists of a co-crystallized 3% highly modified dextrins and 97% sucrose. The former acts to interrupt the crystal structure of the latter, thereby improving its compressibility [74].

Another coprocessed directly compressible excipient of xylitol and sodium caboxymethyl cellulose is marketed as Xylitab® (Danisco A/S, Copenhagen, Denmark). Xylitab has a cool taste, great stability and is ideal for all tablet forms. Morris *et al.* evaluated Xylitab 100 and Xylitab 200 for compaction, flow, lubrication requirements and dilution potential [75]. Compaction profiles, flow behavior, and dilution potential of xylitab was found to be acceptable and the authors concluded that xylitab can be successfully utilized as direct compression chewable tablet excipient [13].

5.4 Coprocessing of inorganic fillers

Coprocessing of calcium carbonate (70%) with sorbitol (30%) (Formaxx) offers a distinct advantage of producing directly compressible calcium carbonate. Formaxx offers improved flowability, superior compaction properties at low compression forces and has low friability compared to calcium carbonate. This unique processing of calcium carbonate with sorbitol masks the chalky and gritty taste of calcium carbonate [76]. Freitag *et al.* showed that coprocessing of magnesium carbonate with 5% powdered cellulose seems to be a promising excipient for direct compression. This coprocessed product combines good flow and tablet properties, and is superior to pure magnesium carbonate or their physical mixture [77].

5.5 Other coprocessed excipients

Adeagbo and Alebiowu assessed the lubricant activity of cocoa butter coprocessed with magnesium stearate plus talc in comparison with magnesium stearate plus talc using flow and compressional characteristics of paracetamol granules and mechanical properties of their tablets. The authors concluded that cocoa butter is an effective and viable lubricant that can be coprocessed with magnesium stearate/talc mixture for an efficient lubrication of granules and may be useful in reducing lamination and capping in formulations that are susceptible to these defects of tablets [78].

Gohel *et al.* prepared coprocessed super-disintegrant consisting of crospovidone and sodium starch glycolate, which exhibited good flow and compression characteristics. When these coprocessed excipients were used in cefixime trihydrate and ibuprofen tablets, a quick disintegration and improved drug dissolution were observed [79]. Gohel *et al.* have shown that coprocessed superdisintegrant of crosccarmallose sodium and crospovidone has better flow, crushing strength, disintegration time and drug dissolution than the physical blend [80].

6. Regulatory considerations

Before introducing into the pharmaceutical market, each new excipient has to undergo various regulatory approvals and toxicological studies to prove safety and efficacy. The FDA requires that NDA (new drug applications) and ANDA (abbreviated new drug applications) applicants submit information about all components of the drugs, including all excipients. Additionally, the applicant must provide sufficient information to establish that the use of each excipient

is safe for its intended use, at its intended quantity. This information includes safety data, a statement of the composition, specifications and any analytical methods used for the excipient. This information can be placed in the application directly or in a drug master file. Information on the safety of excipients used in drug product has been required by federal laws since the enactment of the first modern national food and drug legislation, the food, drug and cosmetic act, in 1938. The required safety information includes manufacturing information and full toxicology studies to demonstrate that the excipient is safe for the intended use. New excipients should be appropriately evaluated for pharmacological activity using a battery of standard tests as per ICH guidance. These evaluations can be performed during the course of toxicology studies or as independent safety pharmacology studies [82,83].

However, every excipient is unique and scientifically valid reasons may exist for modifying and deleting certain preclinical studies listed in the guidance for a given combination of excipient and proposed use. For example, excipients that are large polymers that differ from previously characterized excipients only in molecular mass (chain length) can be adequately characterized in an abbreviated manner using less safety data, provided that the new excipient and the previously studied excipient are sufficiently similar with regard to physical state, pharmacokinetics, and levels of unreacted monomers and other impurities [73]. As many detailed studies of coprocessed excipients have proved that the incorporated excipients do not undergo any chemical change after coprocessing, these coprocessed excipients are considered as safe if the parent excipients are also GRAS-certified by regulatory agencies [5] and, hence, these excipients do not require any further approval and toxicological studies.

Guidance states that when USP/NF (the US Pharmacopeia/ the National Formulary) monograph exists for an excipient, the applicant may state that the excipient in the drug will comply with the standards in the monograph of providing composition, specifications and any analytical information and, hence, inclusion of coprocessed excipients in pharmacopeia can affect the popularity and acceptance of coprocessed excipients by the industry. However, these coprocessed excipients are still not included in the pharmacopeia, which is the biggest hurdle of its success in the market. Although the spray-crystallized dextrose-maltose (Emdex) and compressible sugar are coprocessed products and considered as single components, they are able to find their place in USP/NF. Recently, SMCC and Avicel CE15 have found their place in the handbook of pharmaceutical excipients.

7. Conclusion

The increased demand of excipients with improved functionalities without compromising with quality, safety, regulatory and economic aspects has forced industries to search for new excipients. The concepts of material science and advanced technologies have shown an alternate path to obtain a new class of excipients known as coprocessed excipients. Their manufacture is very simple with marginal cost of production. They serve as multipurpose excipients, providing a better option of excipient selection to the growing industries. However, owing to their non-official status, coprocessed excipients are still not widely accepted by the industry.

8. Expert opinion

Coprocessed excipients provide very much useful yet simpler alternatives, which not only reduces the complexity of the tablet manufacturing by replacing large number of required excipients with few, but also reduces the time and cost of the production and hence is beneficial to the industry and lowers cost to patients. However, their non-inclusion in pharmacopeia affects their growth. With recent recommendations from the International Pharmaceutical Excipients Council, these products will find their way into official monographs and we will able to see a large number of coprocessed excipients in the market in near future.

Declaration of interest

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