

Coprocessed Excipients for Solid Dosage Forms

Satish K. Nachaegari and Arvind K. Bansal*



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Tablet manufacturing has been changed by the introduction of the direct-compression process and high-speed machines. These two developments have increased the demands on the functionality of excipients in terms of flow and compression properties. Particle engineering of individual excipients and excipient combinations using coprocessing, by virtue of subparticle modifications, has provided an attractive tool for developing high-functionality excipients that are suited to modern tablet manufacturing processes.

Arvind K. Bansal, PhD, is an associate professor in the Department of Pharmaceutical Technology (Formulations), National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S.A.S. Nagar, Punjab-160062, INDIA, tel. +91 172 214682, ext. 2136, fax +91 172 214692, akbansal@niper.ac.in. **Satish K Nachaegari** is a research scholar in the Department of Pharmaceutical Technology (Formulations), NIPER.

*To whom all correspondence should be addressed.

Tablets and capsules are the most preferred dosage forms of pharmaceutical scientists and clinicians because they can be accurately dosed and provide good patient compliance, they are easy for companies to manufacture, and they can be produced at a relatively low cost. This popularity of tablets coupled with an increased understanding of the physics of compression and of manufacturing process variables have matured the manufacture of tablets as a science in its own right (1). Tablets are manufactured primarily by either granulation compression or direct compression. The latter involves 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 direct compression as an attractive alternative to traditional granulation technologies. In a survey conducted in 1992 by Shangraw et al. concerning the process preferred by pharmaceutical manufacturers, nearly 41.5% indicated that direct compression was their process of choice, and 41.5% preferred both wet granulation and direct compression (2). Only 17.2% indicated that they did not prefer direct compression as a tabletting method.

Since the tableting process was introduced in the early 1840s numerous changes have taken place, apart from changes in tablet manufacturing, including the establishment of stringent regulatory requirements for the materials that should be used, the establishment of stability requirements, and the development of high-performance tableting machines that can produce 100,000–200,000 tablets/h (3). Interestingly, such developments have affected the manufacturing process negatively because the number of materials that can fulfill such regulatory and performance requirements has decreased substantially (4).

Although simple in terms of unit processes involved, the direct-compression process is highly influenced by powder characteristics such as flowability, compressibility, and dilution potential. Tablets consist of active drugs and excipients, and not one drug substance or excipient possesses all the desired physico-mechanical properties required for the development of a robust direct-compression manufacturing process, which can be scaled up from laboratory to production scale smoothly. Most formulations (~70–80%) contain excipients at a higher concentration than the active drug (5). Consequently, the excipients contribute significantly to a formulation's functionality and processability.

In simple terms, the direct-compression process is directly influenced by the properties of the excipients. The physico-mechanical properties of excipients that ensure a robust and successful process are good flowability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity, and good machineability even in high-speed tableting machinery with reduced dwell times (6). The majority of the excipients that are currently available fail to live up to these functionality requirements, thus creating the opportunity for the development of new high-functionality excipients.

A need for new excipients

The excipients industry to date has been an extension of the food industry (7). Moreover, excipients are products of the food industry, which has helped maintain a good safety profile. Increasing regulatory pressure on purity, safety, and standardization of the excipients has catalyzed the formation of an international body, the International Pharmaceutical Excipients Council (IPEC) (8). IPEC is a tripartite council with representation from the United States, Europe, and Japan and has made efforts to harmonize requirements for purity and functionality testing (9).

The development of new excipients to date has been market-driven (i.e., excipients are developed in response to market demand) rather than marketing-driven (i.e., excipients are developed first and market demand is created through marketing strategies) and has not seen much activity as shown by the fact that, for the past many years, not a single new chemical excipient has been introduced into the market. The primary reason for this lack of new chemical excipients is the relatively high cost involved in excipient discovery and development. However, with the increasing number of new drug moieties with varying physicochemical and stability properties, there is growing pressure on formulators to search for new excipients to achieve the desired set of functionalities.

Other factors driving the search for new excipients are

- the growing popularity of the direct-compression process and a demand for an ideal filler–binder that can substitute two or more excipients
- tableting machinery's increasing speed capabilities, which require excipients to maintain good compressibility and low weight variation even at short dwell times
- shortcomings of existing excipients such as loss of compaction of microcrystalline cellulose (MCC) upon wet granulation, high moisture sensitivity, and poor die filling as a result of agglomeration (10)
- the lack of excipients that address the needs of a specific patients such as those with diabetes, hypertension, and lactose and sorbitol sensitivity
- the ability to modulate the solubility, permeability, or stability of drug molecules

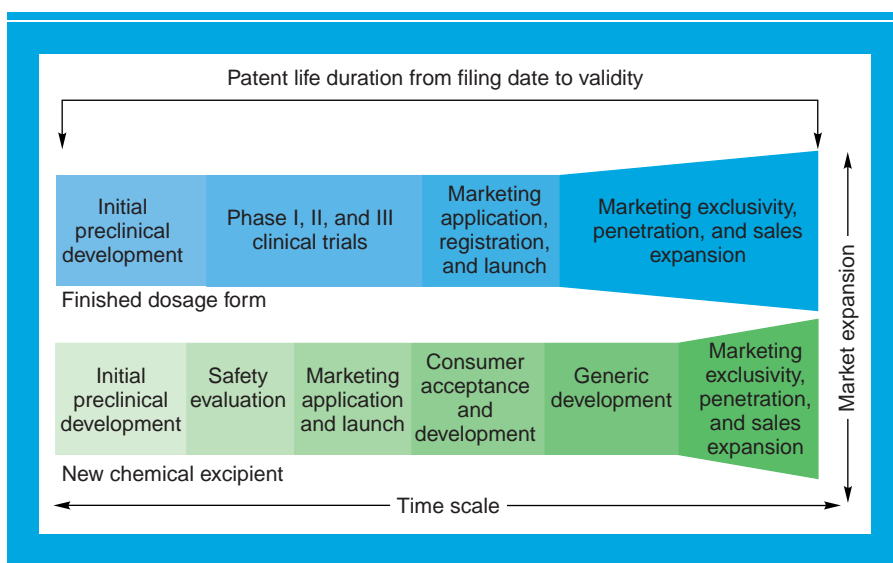


Figure 1: Comparative developmental timelines for finished pharmaceutical dosage form and a new chemical excipient.

- the growing performance expectations of excipients to address issues such as disintegration, dissolution, and bioavailability.
- The continued popularity of solid dosage forms, a narrow pipeline of new chemical excipients, and an increasing preference for the direct-compression process creates a significant opportunity for the development of high-functionality excipients.

Routes or sources of new excipients

Excipients with improved functionality can be obtained by developing new chemical excipients, new grades of existing materials, and new combinations of existing materials (11). Any new chemical excipient being developed as an excipient must undergo various stages of regulatory approval aimed at addressing issues of safety and toxicity, which is a lengthy and costly process. In addition, the excipient must undergo a phase of generic development, which shortens the market exclusivity period as shown in Figure 1 (12). The high risk and significant investment involved are not justified in view of the meager returns from the new excipients. A plausible solution is for excipient and pharmaceutical manufacturers to develop drug products jointly, during which a new excipient becomes part and parcel of the eventual new drug application (3). This type of arrangement already has been successfully applied in the intravenous delivery field, in which CyDex and Pfizer worked collaboratively to obtain the approval of a solubilizer (13,14). The combined expertise of pharmaceutical and excipient companies can lead to the development of tailor-made innovative excipients.

Developing new grades of existing excipients (physicochemical) has been the most successful strategy for the development of new excipients in past three decades (15), a process that has been supported by the introduction of better performance grades of excipients such as pregelatinized starch, croscarmellose, and crospovidone (16). However, functionality can be improved only to a certain extent because of the limited range of possible modifications.

New combinations of existing excipients is an interesting option for improving excipient functionality because all formu-

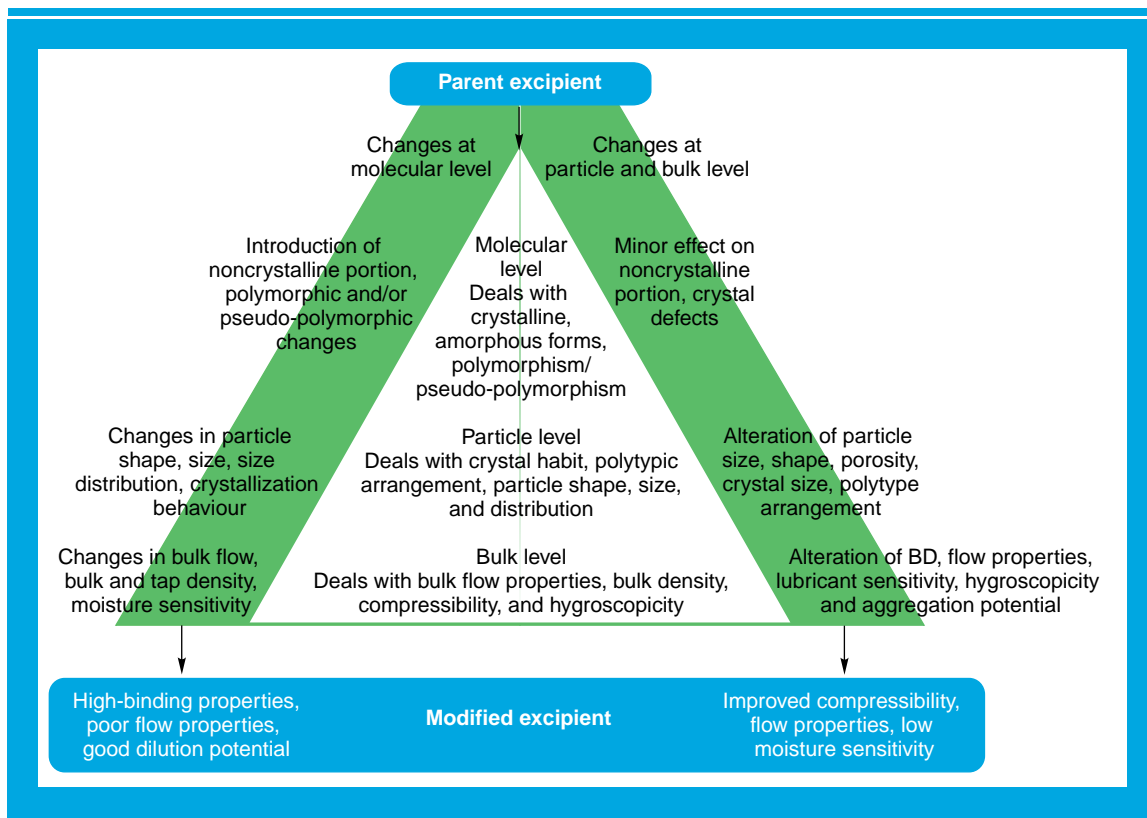


Figure 2: The solid-state pyramid.

lations contain multiple excipients. Many possible combinations of existing excipients can be used to achieve the desired set of performance characteristics. However, the development of such combinations is a complex process because one excipient may interfere with the existing functionality of another excipient. Over the years, the development of single-bodied excipient combinations at a subparticle level, called *coprocessed excipients*, has gained importance (11). New physical grades of existing excipients and coprocessed excipients are discussed further in the following section of this article that explains particle engineering. Particle engineering is a broad-based concept that involves the manipulation of particle parameters such as shape, size, size distribution, and simultaneous minor changes that occur at the molecular level such as polytypic and polymorphic changes. All these parameters are translated into bulk-level changes such as flow properties, compressibility, moisture sensitivity, and machineability.

Particle engineering as source of new excipients

Solid substances are characterized by three levels of solid-state: the molecular, particle, and bulk level. These levels are closely linked to one another, with the changes in one level reflecting in another level. The molecular level comprises the arrangement of individual molecules in the crystal lattice and includes phenomena such as polymorphism, pseudo-polymorphism, and the amorphous state. Particle level comprises individual particle properties such as shape, size, surface area, and porosity. The bulk level is composed of an ensemble of particles and properties such as flowability, compressibility, and dilution potential, which are critical factors in the performance of excipients. Fig-

ure 2 shows the various levels of solid state and how a change at one level affects the other levels. This interdependency among the levels provides the scientific framework for the development of new grades of existing excipients and new combinations of existing excipients (12).

The fundamental solid-state properties of the particles such as morphology, particle size, shape, surface area, porosity, and density influence excipient functionalities such as flowability, compactability, dilution potential, disintegration potential, and lubricating potential. Hence, the creation of a new excipient must begin with a particle design that is suited to deliver the desired functionalities (17). Varying the crystal lattice arrangement by playing with parameters such as the conditions of crystallization and drying can create particles with different parameters. It is also possible to engineer particles without affecting the preceding molecular level. Table I shows how particle engineering can help achieve the desired excipient functionalities (5). Avicel 101 and 102 (microcrystalline cellulose) and spray-dried lactose are examples in which such an approach has been successfully applied. However, particle engineering of a single excipient can provide only a limited quantum of functionality improvement.

A much broader platform for the manipulation of excipient functionality is provided by coprocessing or particle engineering two or more existing excipients. Coprocessing is based on the novel concept of two or more excipients interacting at the subparticle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients (18). The availability of a large number of excipients for coprocessing ensures numer-

Table I: Various particle properties influencing excipient functionality.

Particle property	Excipient functionality
Enlargement of particle-size	Flowability, compressibility
Restricting particle-size distribution	Segregation potency
Enlargement of particle porosity	Compressibility, solubility
Surface roughness	Flowability, segregation potential

granulates with superior properties compared with physical mixtures of components or with individual components. They have been developed primarily to address the issues of flowability, compressibility, and disintegration potential, with filler–binder combinations being the most commonly tried. The combination of excipients chosen should complement each other to mask the undesirable properties of individual excipients and, at the same time, retain or improve the desired properties of excipients. For example, if a substance used as a filler–binder has a low disintegration property, it can be coprocessed with another excipient that has good wetting properties and high porosity because these attributes will increase the water intake, which will aid and increase the disintegration of the tablets.

Coprocessing of excipients

The actual process of developing a coprocessed excipient involves the following steps:

- identifying the group of excipients to be coprocessed by carefully studying the material characteristics and functionality requirements
- selecting the proportions of various excipients
- assessing the particle size required for coprocessing. This is especially important when one of the components is processed in a dispersed phase. Postprocessing the particle size of the latter depends on its initial particle size.
- selecting a suitable process of drying such as spray- or flash-drying
- optimizing the process (because even this can contribute to functionality variations).

Figure 3 shows a schematic representation of the coprocessing method.

Considering material characteristics in coprocessing

Material science plays a significant role in altering the physico-mechanical characteristics of a material, especially with regard to its compression and flow behavior. Coprocessing excipients offers an interesting tool to alter these physico-mechanical properties. Materials, by virtue of their response to applied forces, can be classified as elastic, plastic, or brittle materials. In the truest sense, materials cannot be classified in one category absolutely. Pharmaceutical materials exhibit all three types of behavior, with one type being the predominant response. This makes it difficult to demarcate which property is good for compressibility. Coprocessing is generally

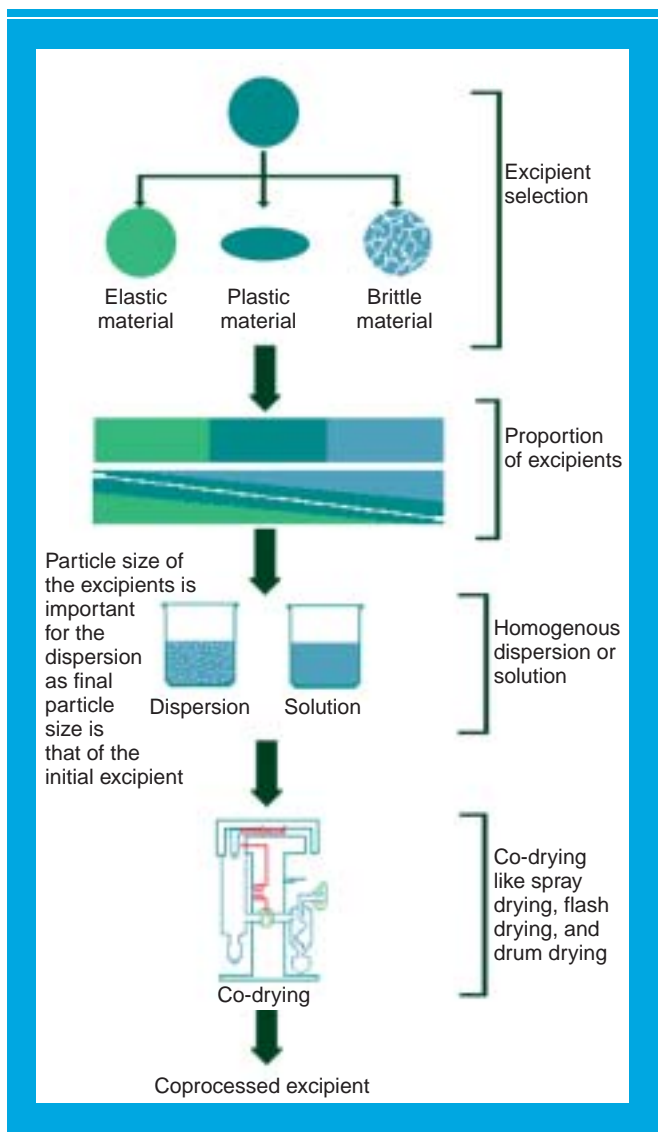


Figure 3: Schematic representation of coprocessing method.

ous possibilities to produce tailor-made “designer excipients” to address specific functionality requirements.

Coprocessed excipients are prepared by incorporating one excipient into the particle structure of another excipient using processes such as co-drying. Thus, they are simple physical mixtures of two or more existing excipients mixed at the particle level. 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 (19). Coprocessing of excipients in the pharmaceutical industry can be dated back to the late 1980s with the introduction of coprocessed microcrystalline cellulose and calcium carbonate (20), followed by Cellactose (Meggler Corp., Wasserburg, Germany) in 1990, which is a coprocessed combination of cellulose and lactose. A similar principle was applied in developing silicified microcrystalline cellulose (SMCC), which is the most widely used coprocessed excipient (21).

Coprocessing excipients leads to the formation of excipient

Table II: Examples of marketed coprocessed excipients.

Coprocessed excipients	Trade name	Manufacturer	Added advantage
Lactose, 3.2% Kollidon 30, Kollidon CL	Ludipress	BASF AG, Ludwigshafen, Germany	Low degree of hygroscopicity, good flowability, tablet hardness independent of machine speed
Lactose, 25 % cellulose	Cellactose	Meggle GmbH & Co. KG, Germany	Highly compressible, good mouthfeel, better tableting at low cost
Sucrose, 3% Dextrin	DiPac		Directly compressible
MCC, silicon dioxide	Prosolv	Penwest Pharmaceuticals Company	Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability.
MCC, guar gum	Avicel CE-15	FMC Corporation	Less grittiness, reduced tooth packing, minimal chalkiness, creamier mouth-feel, improved overall palatability
Calcium carbonate Sorbitol	ForMaxx	Merck	Controlled particle-size distribution
Microcrystalline cellulose, lactose	Microcelac	Meggle	Capable of formulating high dose, small tablets with poorly flowable active
95% β -lactose + 5% Lactitol	Pharmatose DCL40	DMV Veghel	High compressibility, low lubricant sensitivity
85% α lactose MH + 15% native corn starch	StarLac	Roquette	Good flow

conducted with one excipient that is plastic and another that is brittle. Maarschalk reports coprocessing performed with a large amount of brittle material and a small amount of plastic material, as exemplified by Cellactose (Meggle Corp.) in which 75% lactose (brittle material) is coprocessed with 25% cellulose (plastic material) (22). This particular combination prevents the storage of too much elastic energy during compression, which results in a small amount of stress relaxation and a reduced tendency of capping and lamination (23). However, examples of the other extreme also exist (e.g., SMCC has a large amount of MCC [plastic material] and a small amount of silicon dioxide [brittle material]). These two situations exemplify the fact that coprocessing is generally performed with a combination of materials that have plastic deformation and brittle fragmentation characteristics.

A combination of plastic and brittle materials is necessary for optimum tableting performance. Hence, coprocessing these two kinds of materials produces a synergistic effect, in terms of compressibility, by selectively overcoming the disadvantages. Such combinations can help improve functionalities such as compaction performance, flow properties, strain-rate sensitivity, lubricant sensitivity or sensitivity to moisture, or reduced hornification.

Properties, advantages, and disadvantages of the coprocessed excipients

Several authors have reported the advantages and possible limitations of the properties of coprocessed excipients such as SMCC, Cellactose, and Ludipres (BASF, Ludwigshafen, Germany); however, few authors have evaluated the possible location of coprocessed ingredients in the excipient matrix and the mechanisms involved therein. The primary attribute associated with these excipients is that no chemical change exists during coprocessing, and all the reflected changes show up in the physical properties of the excipient particles.

Absence of chemical change. Many detailed studies of an excipient's chemical properties after coprocessing have proven that these excipients do not show any chemical change. Detailed studies of SMCC with X-ray diffraction analysis, solid-state nuclear magnetic resonance (NMR), IR spectroscopy, Raman spectroscopy, and C13 NMR spectroscopy have detected no chemical changes and indicate a similarity to the physicochemical properties of MCC (10). This absence of chemical change helps reduce a company's regulatory concerns during the development phase.

Physicomchanical properties. Improved flow properties. Controlled optimal particle size and particle-size distribution ensures superior flow properties of coprocessed excipients without the need to add glidants. The volumetric flow properties of SMCC were studied in comparison with MCC. The particle-size range of these excipients was found to be similar to those of the parent excipients, but the flow of coprocessed excipients was better than the flow of simple physical mixtures. A comparison of the flow properties of Cellactose was also performed. The angle of repose and the Hausner ratio were measured, and Cellactose was found to have better flow characteristics than lactose or a mixture of cellulose and lactose (5). The spray-dried product had a spherical shape and even surfaces, which also improved the flow properties.

Improved compressibility. Coprocessed excipients have been used mainly in direct-compression tableting because in this process there is a net increase in the flow properties and compressibility profiles and the excipient formed is a filler-binder. The pressure-hardness relation of coprocessed excipients, when plotted and compared with simple physical mixtures, showed a marked improvement in the compressibility profile. The compressibility performance of excipients such Cellactose (24), SMCC (25,26), and Ludipres (27) have been reported to be superior to the simple physical mixtures of their constituent excipients. SMCC was used as an ingredient in a formulation and

subjected to compaction on an instrumented tableting machine. The compression force was recorded, and a graph of the tensile strength versus the compression force was used as a comparative parameter. SMCC retained its compaction properties even at high compression forces, yielding tablets of good hardness. MCC, however, lost its compaction properties.

Although direct compression seems to be the method of choice for pharmaceutical manufacturing, wet granulation is still preferred because it has the potential advantages of increasing flow properties and compressibility when an extragranular binder is introduced, and it achieves a better content uniformity in case of low-dose drugs. Excipients such as MCC lose compressibility upon the addition of water, a phenomenon called *quasihornification* (28). This property is improved, however, when it is coprocessed into SMCC.

Better dilution potential. Dilution potential is the ability of the excipient to retain its compressibility even when diluted with another material. Most active drug substances are poorly compressible, and as a result, excipients must have better compressibility properties to retain good compaction even when diluted with a poorly compressible agent. Cellulose is shown to have a higher dilution potential than a physical mixture of its constituent excipients (29).

Fill weight variation. In general, materials for direct compression tend to show high fill-weight variations as a result of poor flow properties, but coprocessed excipients, when compared with simple mixtures or parent materials, have been shown to have fewer fill-weight variation problems. The primary reason for this phenomenon is the impregnation of one particle into the matrix of another, which reduces the rough particle surfaces and creates a near-optimal size distribution, causing better flow properties.

Fill-weight variation tends to be more prominent with high-speed compression machines. Fill-weight variation was studied with various machine speeds for SMCC and MCC, and SMCC showed less fill-weight variation than MCC (25).

Reduced lubricant sensitivity. Most coprocessed products consist of a relatively large amount of brittle material such as α -lactose monohydrate and a smaller amount of plastic material such as cellulose that is fixed between or on the particles of the brittle material (22). The plastic material provides good bonding properties because it creates a continuous matrix with a large surface for bonding. The large amount of brittle material provides low lubricant sensitivity because it prevents the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network.

Other properties. Coprocessed excipients offer the following additional advantages:

- Pharmaceutical manufacturers have the option of using a single excipient with multiple functional properties, thereby reducing the number of excipients in inventory.
- Improved organoleptic properties such as those in Avicel CE-15 (FMC Corp., Philadelphia, PA), which is a coprocessed excipient of MCC, and guar gum were shown to have distinctive advantages in chewable tablets in terms of reduced grittiness, reduced tooth packing, minimal chalkiness, better mouthfeel, and improved overall palatability.

- Although coprocessing adds some cost, the overall product cost decreases because of improved functionality (30) and fewer test requirements compared with individual excipients (18).
- Because they can retain functional advantages while selectively reducing disadvantages, coprocessed excipients can be used to develop tailor-made designer excipients. This can be helpful in reducing the time required to develop formulations.
- Coprocessed excipients can be used as proprietary combinations, and in-house formularies can be maintained by pharmaceutical companies, which could help in developing a formulation that is difficult to reproduce and provides benefits in terms of intellectual property rights.

Regulatory perspective of the excipient mixtures

With the absence of a chemical change during processing, coprocessed excipients can be considered generally regarded as safe (GRAS) if the parent excipients are also GRAS-certified by the regulatory agencies (11). Hence, these excipients do not require additional toxicological studies. Excipient mixtures or coprocessed excipients have yet to find their way into official monographs, which is one of the major obstacles to their success in the marketplace. The mixture of excipients was presented as a topic to the National Formulary and was assigned a priority on the basis of the use of the mixture in marketed dosage forms in which processing has provided added functional value to the excipient mixture (21).

Although spray crystallized dextrose-maltose (EMDEX) and compressible sugars are coprocessed, they are commonly considered as single components and are listed as such in the *USP-NF*. The third edition of the *Handbook of Pharmaceutical Excipients* has listed SMCC as a separate excipient (31).

Commercial status

Many coprocessed excipients have been launched in the market in the past few years, and a few formulations are commercially available. Table II lists some of the marketed coprocessed excipients along with their manufacturers and benefits.

Conclusion

The shift in tableting toward direct-compression and high-speed manufacturing has forced the excipient industry to search for new excipients. The excipient industry, which has largely been an extension of the food industry, has taken up the novel use of particle engineering and material sciences to pave the way for a new category of functional excipients called coprocessed excipients. The success of any pharmaceutical excipient depends on quality, safety, and functionality. Although the first two parameters have remained constant, significant improvements in functionality open the door for the increased use of coprocessed excipients. The advantages of these excipients are numerous, but further scientific exploration is required to understand the mechanisms underlying their performance. The main obstacle to the growth of this area of excipients is the non-inclusion of their monographs in pharmacopoeias, which discourages pharmaceutical manufacturers to use them. With recommendations from IPEC, these products could find their way into official monographs either as mixtures or as single-bodied excipients.

Once the obstacles are overcome, the use of coprocessed excipients can be expected to increase dramatically.

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