

## Co-processed excipients demystified.

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### ABSTRACT

Despite decades of use and escalating availability, co-processed excipients (CPEs) continue to be surrounded by misconceptions. CPEs are physically and functionally different than admixtures of the individual components used in their manufacture, yet appear equivalent when analyzed through various spectroscopic methods. Unlike admixtures, which are discrete particles mixed and remaining structurally independent, CPEs combine the individual components at the particle level yielding an integrated structure with synergistic properties. CPE monograph development and adoption, while desirable, presents some challenges, which has limited the number of monographs specific to CPEs. However, even though there is an absence of monographs for many CPEs, there is regulatory acceptance, demonstrated by the many drug product approvals where CPEs are used in dosage form production. The above points will be explored with the goal of providing a better understanding of CPEs.

**KEY WORDS:** Co-processed, excipient, monograph, regulatory

### INTRODUCTION

Co-processing has a long-established history in the food industry, where co-processed ingredients have been utilized for nearly a century. Similarly, excipient manufacturers have produced, and pharmaceutical formulators have used, co-processed excipients (CPEs) in pharmaceutical formulations for several decades.

Despite their long history of use, there remains uncertainty about what a co-processed excipient is, how they are manufactured, what benefits they offer, and their industry and regulatory acceptance. This was highlighted at the recent ExcipientWorld Conference where several questions about CPEs were raised. CPEs differ from excipient admixtures prepared by direct blending or granulation. Additional confusion surrounds their novelty and how CPEs are differentiated from new chemical entities and chemical modifications made to existing excipients.

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CPEs are not simply premixed blends of one or more components where discrete, preformed particles are combined through blending or granulation processes. Instead, CPEs are often produced from individual components in their primary particle configuration, which are integrated at the particle level during manufacture. Moreover, once co-processed, the individual components typically cannot be separated easily. Since the CPE components are integrated at the particle level, each component's functional characteristics are also brought together at the particle level. This particle-level integration often provides functional performance synergies that are impossible to achieve through simple blending. Another important goal during the CPE manufacture is that no new chemistries are created. That is, no covalent bonds are formed among the constituents that comprise the CPE. To confirm this, various spectroscopic, spectrometric, or other analytical techniques have been employed, demonstrating that the individual components maintain their individual chemistries (1, 2).

## CPE COMPOSITIONS AND MANUFACTURING METHODS

Among the first CPEs used in the pharmaceutical industry was the co-processed combination of microcrystalline cellulose (MCC) and sodium carboxymethyl cellulose (NaCMC). This CPE was initially developed for the food industry and later determined to have unique properties beneficial to liquid pharmaceutical formulations. While the use of MCC and NaCMC as separate excipients in a dosage form could be used, they will not function as well in the final product compared to the CPE. Other common co-processed systems used for tableting, encapsulation, and powder filling include MCC with colloidal silicon dioxide (CSD), lactose with povidone (PVP) and copovidone, and MCC with lactose.

A review of the patent landscape suggests that more than 125 CPEs have been developed for pharmaceutical use, and many have also been adopted for nutraceutical applications. Among CPEs, cellulose, lactose, mannitol, calcium carbonate ( $\text{CaCO}_3$ ) and dibasic calcium phosphate (DCP) in both the dihydrate and anhydrous forms are among the most used in

various combinations with other ingredients (Table 1); however, ingredients such as starches, metal oxides, povidones, and others also have been used in co-processed excipient combinations.

**Table 1** Frequently used excipient components in CPE development

| COMPONENT                             | NUMBER OF CPEs DEVELOPED |
|---------------------------------------|--------------------------|
| Microcrystalline & Powdered Cellulose | ~39                      |
| Lactose                               | ~31                      |
| Mannitol                              | ~10                      |
| $\text{CaCO}_3$                       | ~8                       |
| DCP(A)                                | ~4                       |

Note: Data generated through inspection of USPTO database. Not all excipients used in co-processing are presented, only those most common.

Most CPEs are binary combinations; however, there are also tertiary and quaternary combinations, with a few containing as many as five components (Figure 1). While formulation applications vary, most CPEs have been developed for oral solid dosage forms, specifically tablets. Some CPEs are more specialized, having applications in orally disintegrating tablets (ODT) and controlled-release dosage forms.

CPE manufacturing processes vary, with the most common including co-agglomeration, co-crystallization, and co-spray drying. Of these, co-spray drying has been the preferred method (Table 2).

**Table 2** Frequency of manufacturing methods used to produce co-processed excipients

| MANUFACTURING METHOD | FREQUENCY |
|----------------------|-----------|
| Co-spray-dried       | ~33       |
| Co-agglomerated      | ~9        |
| Co-crystallized      | ~8        |

Note: Data generated through inspection of USPTO database. Most commonly used processes are shown.

## FUNCTIONAL PERFORMANCE BENEFITS

Performance enhancement is a key feature of CPE development and their applications. Co-processed

CPEs by the Numbers

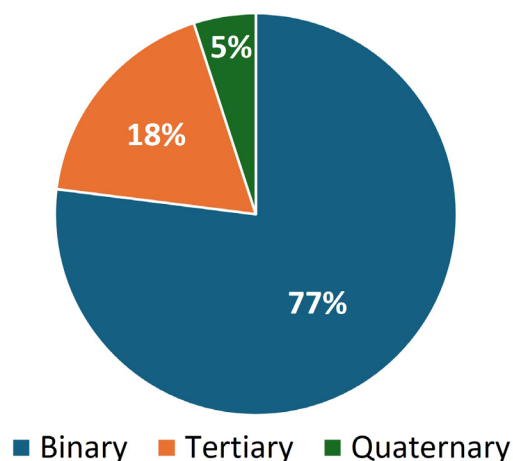


**Figure 1** CPE by number of components.

excipient developments aim to create materials with performance characteristics greater than the sum of its individual parts. Without the performance enhancement, the CPE might be considered as one of convenience. Numerous CPEs have the potential to illustrate enhanced performance in liquid and solid dosage forms. Compaction enhancement in tableting is one of many examples where enhanced performance can be observed. In this example, CPE tensile strength improved to a greater degree as compared to an excipient physical blend (Figure 2). This objective is as true for liquid and semi-solid applications as it is for solid dosage forms. It could be questioned, “If only for convenience purposes and not performance enhancement, does CPE use offer any benefit?” One exception for the convenience position could be continuous manufacturing, where the number of process addition ports is limited, and CPEs offer a potential solution (3).

## MONOGRAPH DEVELOPMENT CHALLENGES

Most pharmacopeial organizations, including United States Pharmacopeia, actively seek new excipient monographs; however, drafting CPE monographs can be challenging. The first challenge, which is no different than for any excipient, is that the ingredient must have a precedence of use and be listed in FDA’s Inactive Ingredients Database (IID).

Compaction Profile CPE versus Blend

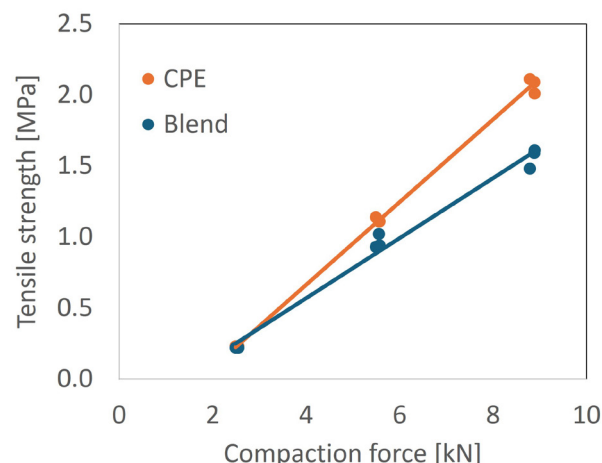


**Figure 2** CPE functional performance benefit.

Another challenge affecting monograph creation is the development of robust testing methods that can identify and distinguish the CPE from an admixture of the individual components. Discerning CPEs from admixtures using spectroscopic methods is confounded since both yield equivalent spectra. The creation of such testing can become further complicated as CPE compositions may vary by design or due to normal variations in manufacture. While this has not been the case for every current CPE monograph, it has limited the number of new monographs. Even those that may already be listed on the IID, for example the USP-NF monograph for Silicified Microcrystalline Cellulose (SMCC). Here, individual sieve fractions are assessed using residue on ignition (ROI), General Chapter <281> and compared (Figure 3). While this approach can be applied to SMCC, it is not universal across all CPEs, necessitating other methods to determine whether the excipient is co-processed or a blend.

## REGULATORY LANDSCAPE

CPEs have been accepted globally for decades, supported by the many products commercially manufactured using a CPEs as part of the dosage form composition. The European Union (EU) has recently taken a revised view of CPEs, starting to view CPEs as drug product intermediates. Yet, there are

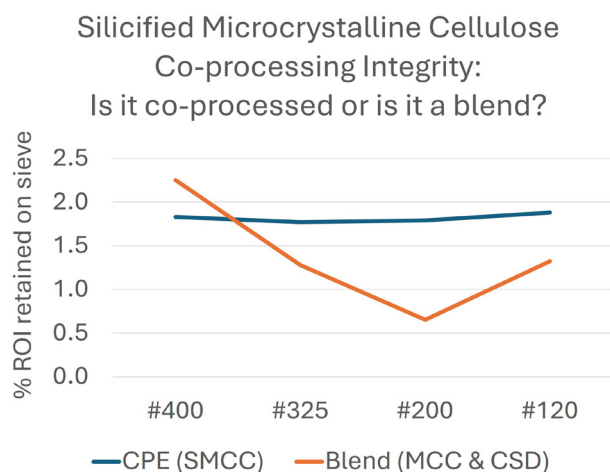


**Figure 3** USP SMCC CPE confirmation assessment by ROI - USP General Chapter <281>.

drug products with CPEs that have been approved and manufactured for decades as an integral part of the drug product composition. This revised view creates a misalignment between the EU and other regions, particularly North America. Given the growth of continuous manufacturing and the importance of CPEs in this process, this may present additional challenges for companies wanting a single formulation and process with global acceptance. Discussions continue in the EU and elsewhere with the hope of a future harmonized position.

### CPE SOURCING CHALLENGES

While it is true that some CPEs are single-sourced due to intellectual property protections, this should not preclude their use. MCC, DCP, sodium stearyl fumarate, poloxamers, carbomers, hypromellose (and its many sub-derivatives: phthalate, acetate succinate, etc.), which were once single-sourced novel excipients, are now common ingredients in many drug products globally. CPEs are similarly positioned. Some CPEs are still “new” while others have been available for many years. Likewise, some are still patent protected, while others’ patents have expired allowing additional sourcing options.

It should be noted that many CPE manufacturers with single-sourced patented materials have contingency

plans and risk mitigation strategies to ensure stable CPE supply. This should help mitigate availability concerns for those that have avoided their use. These procurement concerns should not overshadow the CPE performance enhancements that can lead to better medicines and patient outcomes.

### CONCLUSIONS

As previously mentioned, CPEs are not new, and many have been used globally for decades in drug product development and manufacture. Several also appear in FDA’s Inactive Ingredients Database, yet few possess monographs owing to the challenge of distinguishing CPEs from simple blends. CPEs offer numerous advantages, especially due to their enhanced functional performance, which is beneficial not only in batch processing but also in continuous manufacturing. While single sourcing for some CPEs has raised some concerns, it has not prevented CPE use by many pharmaceutical companies with numerous products approved and marketed globally. Therefore, understanding the true nature, benefits, and regulatory landscape of CPEs will be crucial to furthering their use in pharmaceutical and nutraceutical applications.

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