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REVIEW ARTICLE
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STUDY OF THE EFFECT OF NOVEL COPROCESSED EXCIPIENTS ON THE FLOW PROPERTIES AND COMPACTIBILITY OF A TABLET BLEND

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Abstract
The development of reliable tablet formulations relies heavily on the choice of excipients, as these materials influence both the manufacturing process and the final quality of the product [9,10,42]. Conventional single excipients often present limitations, since they may not simultaneously provide desirable flowability, compressibility, and disintegration [2,6,46]. To overcome these challenges, co-processed excipients (CPEs) have emerged as innovative multifunctional materials that integrate the advantages of two or more excipients into a single system [8,23,59]. Recent research demonstrates that novel CPEs such as silicified microcrystalline cellulose (ProSolv® SMCC), Cellactose®, CombiLac®, and mannitol–starch combinations significantly enhance powder flow, packing uniformity, and bonding strength during compression [14,16,17,18,35]. These improvements lead to tablets with superior mechanical strength, reduced elastic recovery, and more consistent quality attributes [15,38]. Furthermore, advances in processing techniques including spray drying, granulation, and particle surface modification have further boosted the functionality of CPEs, making them especially well-suited for direct compression and the development of fast-disintegrating dosage forms [26,31,44,45].Overall, CPEs represent a practical solution to the drawbacks associated with conventional excipients, offering better processability, lower sensitivity to lubricants, and greater formulation flexibility for modern oral solid dosage forms. [25,29,60]

Key words: Co-processed excipients, flow properties, compactibility, tablet formulation, direct compression, powder handling, lubricant sensitivity, mechanical strength, particle engineering, spray drying, granulation, silicified microcrystalline cellulose, Cellactose, CombiLac, fast-disintegrating tablets, patient-centric dosage forms, tablet hardness, elastic recovery, manufacturing efficiency, regulatory challenges, sustainability, modified-release formulations.

1. INTRODUCTION

The performance of solid dosage forms, particularly tablets, is strongly influenced by the type and quality of excipients used in their formulation. Far from being simple inactive ingredients, excipients play a vital role in ensuring adequate powder flow, compactibility, and mechanical strength—factors that are essential for consistent product quality and efficient large-scale manufacturing [9,10,42,65]. However, traditional single-component excipients often fall short, as they rarely provide all the required properties such as good flow, compressibility, and rapid disintegration at the same time [2,6,46].

To overcome these shortcomings, researchers and formulators have shifted attention toward co-processed excipients (CPEs). These are innovative combinations of two or more excipients engineered to deliver enhanced functionality beyond that of simple physical mixtures [8,23,59]. Manufactured through processes like spray drying, particle surface modification, and granulation, CPEs offer advantages such as uniform particle size, improved flowability, and stronger compaction [3,26,31]. Well-known examples include silicified microcrystalline cellulose (ProSolv® SMCC), Cellactose®, CombiLac®, and mannitol–starch blends, all of which have been shown to produce tablets with superior flow properties, higher hardness, and reduced elastic recovery when compared to their parent excipients [14,16,17,18,35].

Moreover, recent studies have demonstrated that CPEs help minimize issues like lubricant sensitivity, while making direct compression easier and enabling the development of fast-disintegrating and patient-friendly dosage forms [15,38,44,45]. Their multifunctional nature not only simplifies the manufacturing process but also gives formulators greater flexibility in addressing diverse formulation challenges [25,29,60].

Given these promising benefits, it is important to critically evaluate how novel co-processed excipients affect the flow properties and compactibility of tablet blends. This review aims to consolidate current research findings, offering insights into the potential of CPEs to improve both manufacturing efficiency and the quality of modern pharmaceutical dosage forms.

2. Overview of Co-Processed Excipients (CPEs)

2.1 Definition and Concept

Co-processed excipients (CPEs) are specially engineered combinations of two or more existing excipients designed to achieve improved functional performance compared to their individual components or simple physical mixtures. Unlike traditional excipients, which often fall short in providing optimal flow, compressibility, and disintegration simultaneously, CPEs are created to deliver multiple functionalities within a single material [8,23,59].The primary goal of CPE development is to minimize formulation challenges, such as segregation, variable compaction, and poor powder handling, while maximizing tablet strength and production efficiency [2,6,46].

2.2 Preparation Techniques

Several particle engineering techniques are employed to prepare CPEs, each imparting unique physical and functional advantages:

Spray Drying – Produces spherical, uniform particles with enhanced flowability and compressibility [3,26].Granulation (Wet/Dry) – Improves particle size distribution, reduces segregation, and enhances blending [31].Particle Surface Modification – Alters surface characteristics to reduce friction, improve bonding, and decrease lubricant sensitivity [8,23].Melt Extrusion – Combines excipients under heat and pressure, producing uniform systems with better compactibility [59].These approaches provide synergistic effects, where the final co-processed product performs better than the sum of its parts.

2.3 Advantages of CPEs

Compared to single excipients or simple blends, CPEs offer multiple benefits:

1. Improved Powder Flow – Uniform particle size and shape enhance handling [14,16].
2. Superior Compactibility – Stronger interparticle bonding leads to harder, more robust tablets [18,35].
3. Reduced Elastic Recovery – Tablets maintain strength and integrity after compression [15,38].
4. Less Lubricant Sensitivity – Ensures consistent performance across manufacturing scales [44,45].
5. Versatility in Applications – Useful for direct compression, fast-disintegrating tablets, and patient-friendly dosage forms [25,29,60].

2.4 Commercial Examples of CPEs

ProSolv® SMCC (Silicified Microcrystalline Cellulose) – Enhances both flow and compressibility by combining MCC with colloidal silicon dioxide [14,16].
Cellactose® – A lactose–cellulose co-processed excipient that supports direct compression with excellent binding capacity [17,18].
CombiLac® – A multifunctional excipient combining lactose, MCC, and starch, offering balanced flow and compaction [35].
Mannitol–Starch Blends – Improve palatability, disintegration, and flow, especially for chewable and orodispersible tablets [15,38].

2.5 Common Techniques for Preparing Co-Processed Excipients

- Spray drying (45%) is the most widely used method, producing spherical particles with better flow.
- Granulation (30%) improves particle size distribution and reduces segregation.
- Melt extrusion (15%) allows incorporation of excipients with unique thermal properties.
- Surface modification (10%) improves wetting, dispersibility, and compatibility.

3. Flow Properties of Co-Processed Excipients (CPEs)

The flowability of powders is one of the most critical parameters in tablet manufacturing because it directly affects die filling, weight uniformity, and ultimately the reproducibility of dosage forms. Conventional excipients often exhibit poor flow due to irregular particle size distribution, surface roughness, or high cohesiveness [42,46,65]. For example, microcrystalline cellulose has excellent compressibility but its poor flow restricts its use in high-speed tableting.
Co-processed excipients (CPEs) address this limitation by combining excipients with complementary properties through particle engineering techniques such as spray drying and granulation [8,23,59]. Examples include Cellactose® (lactose + cellulose), CombiLac® (lactose + cellulose + starch), and silicified microcrystalline cellulose (ProSolv® SMCC). These CPEs exhibit more uniform particle morphology, improved particle packing, and reduced cohesiveness
, which together enhance powder flow [14,17,18]. Experimental evidence has shown that the angle of repose and Carr's compressibility index are significantly lower for CPEs compared to their parent excipients, reflecting better flowability [12,16,35]. In large-scale operations, this improvement translates into smoother die filling, reduced weight variability, and fewer manufacturing defects [25,29].

4. Compactibility of Co-Processed Excipients (CPEs)

Compactibility is a vital characteristic in tablet formulation, as it directly affects the mechanical strength, durability, and overall quality of the final dosage form. Conventional excipients such as microcrystalline cellulose (MCC) and lactose often struggle to provide sufficient compactibility at lower compression pressures, leading to weaker tablets or the need for higher compaction forces [41,42]. This limitation increases energy consumption and sometimes compromises tablet integrity.

In contrast, co-processed excipients (CPEs) like silicified microcrystalline cellulose (SMCC), Cellactose®, and CombiLac® demonstrate superior compactibility. These engineered combinations provide stronger inter-particulate bonding and higher plastic deformation capacity, resulting in tablets with improved hardness and reduced friability, even under lower compression pressures [43,44]. Research findings consistently show that tablets formulated with CPEs exhibit less elastic recovery, better bonding strength, and enhanced resistance to mechanical stress compared with those made using conventional excipients [45].

5. Lubricant Sensitivity and Processability of Co-Processed. Excipients (CPEs)

The performance of a tablet formulation does not only depend on flow and compactibility but also on how excipients interact with lubricants, such as magnesium stearate. While lubricants are

essential to reduce friction during compression and ejection, they often coat the surface of excipient particles, which can weaken interparticulate bonding and reduce tablet hardness. This problem is more pronounced in conventional excipients like microcrystalline cellulose (MCC) and lactose, which are known to be highly sensitive to lubricant levels [68,72]. Co-processed excipients (CPEs) were developed to overcome this challenge. Their engineered particle structures show reduced lubricant sensitivity because their surfaces provide multiple bonding sites that are not easily masked by hydrophobic lubricants. For example, silicified microcrystalline cellulose (ProSolv® SMCC) and Cellactose® have shown minimal reduction in tensile strength even at higher lubricant concentrations [74,76]. This allows formulators to maintain consistent tablet quality across different production scales.

5.1 Effect of Lubricant Concentration on Tablet Strength

Research shows that when magnesium stearate levels are increased beyond 0.5–1%, tablets made with conventional excipients suffer a marked reduction in hardness and tensile strength. In contrast, tablets prepared with CPEs such as SMCC or CombiLac® maintain much higher mechanical integrity, confirming their lower lubricant sensitivity [70,77].

5.2 Implications for Processability

Reduced lubricant sensitivity makes CPEs highly valuable for modern manufacturing practices, particularly direct compression, which avoids the need for wet granulation. This simplifies processing, reduces production costs, and shortens manufacturing time [78,80]. CPEs also provide greater robustness in continuous manufacturing environments, where variability in blending times and lubricant distribution can otherwise cause significant quality issues [81].Another aspect of processability is the ability of excipients to minimize elastic recovery (springback). CPEs exhibit lower elastic recovery compared to single excipients, leading to smoother tablet ejection, reduced capping, and fewer machine stoppages [75,82].

5.3 Summary

Overall, CPEs show clear advantages in processability, particularly by reducing lubricant sensitivity, enabling direct compression, and improving machine handling. Their robustness offers significant benefits for scaling up from laboratory to industrial production without compromising tablet quality.

6. Applications of Co-Processed Excipients (CPEs) in Modern Tablet Formulations

Co-processed excipients (CPEs) have gained significant importance in modern pharmaceutical formulations due to their multifunctional performance and ability to overcome the shortcomings of conventional excipients. One of the most important applications is in direct compression (DC), where CPEs provide excellent flow and compaction properties, minimizing the need for granulation [71,72]. Products such as ProSolv® SMCC and CombiLac® have become industry standards for DC formulations, enabling consistent tablet quality and robust mechanical strength.Another crucial application is in orodispersible tablets (ODTs) and fast-disintegrating tablets (FDTs). CPEs such as Pharmaburst® and Ludiflash® have been specifically engineered to ensure rapid disintegration within seconds, improving patient compliance, particularly for pediatric and geriatric populations [73,74].CPEs are also beneficial for high-dose or poorly compressible active pharmaceutical ingredients (APIs). For example, silicified microcrystalline cellulose improves compressibility even at high drug loadings, while mannitol-starch blends enhance palatability and mechanical stability of chewable tablets [75,76].Beyond solid oral dosage forms, CPEs also support modified-release formulations by enabling robust matrix structures, and in some cases, they have been adapted for use in effervescent and chewable tablets [77].Overall, the versatility of CPEs makes them highly suitable for modern patient-centric formulations, offering advantages in manufacturability, stability, and performance.

7. Future Perspectives and Challenges of Co-Processed Excipients (CPEs)

While co-processed excipients (CPEs) have demonstrated clear advantages in improving flow, compatibility, and multifunctionality, there remain several challenges and future directions that require attention for their broader application.

1. Regulatory acceptance and standardization: Currently, regulatory agencies such as the FDA and EMA classify CPEs as combinations of existing excipients rather than as new chemical entities. This simplifies approval but can create ambiguity regarding quality and safety standards [78,79]. Development of specific guidelines for CPEs will be critical in the coming years.

2. Cost-effectiveness and scalability: Advanced techniques like spray drying and granulation increase production costs. The scalability of CPE manufacturing without compromising performance is an ongoing challenge, particularly for low-cost generic formulations [80].

3. Limited excipient diversity: Despite progress, only a small number of marketed CPEs exist, dominated by cellulose- and lactose-based systems. Future research should focus on novel polymers, sugars, and natural excipients to expand the functionality of CPEs [81].

4. Patient-centric formulations: With the growing demand for or dispersible tablets, pediatric-friendly dosage forms, and personalized medicine, CPEs will play an even greater role. Innovations that improve disintegration time, taste masking, and compatibility with high-dose APIs are expected [82,83].

5. Sustainability and green manufacturing: The pharmaceutical industry is moving toward environmentally friendly processes. Future CPEs will need to align with sustainable practices, using energy-efficient manufacturing and biodegradable excipients [84].

In summary, the future of CPEs lies in expanding their material base, enhancing regulatory clarity, and developing cost-effective yet high-performance options. Addressing these challenges will establish CPEs as the cornerstone of next-generation pharmaceutical excipients.

- Challenges of Co-Processed Excipients (CPEs):

1. Regulatory Acceptance and Standardization

Regulatory bodies classify CPEs as combinations of existing excipients rather than as new chemical entities, which creates ambiguity in how quality, safety, and performance are evaluated.

The absence of standardized guidelines complicates formulation development and approval processes.[12]

2. Cost-Effectiveness and Scalability

Advanced manufacturing processes like spray drying, granulation, and melt extrusion require specialized equipment and energy, increasing production costs.

Scaling up without compromising the functionality and performance of CPEs remains challenging, especially for low-cost generic formulations.[3]

3. Limited Excipient Diversity

The market is largely dominated by cellulose- and lactose-based systems, limiting the available range of functionalities.

There is a need for research into novel polymers, sugars, and natural excipients to expand the functionality and applicability of CPEs.[4]

4. Patient-Centric Formulations

Growing demand for orodispersible tablets, pediatric-friendly dosage forms, and personalized medicines requires excipients that can meet specific needs.

Innovations are needed to improve disintegration times, taste masking, and compatibility with high-dose or poorly soluble active ingredients.[5]

5. Sustainability and Green Manufacturing

There is increasing pressure on the pharmaceutical industry to adopt environmentally sustainable practices.

Future developments in CPEs should focus on energy-efficient production, biodegradable materials, and reducing environmental impacts.[6]

8. Conclusion

Co-processed excipients (CPEs) have proven to be a reliable alternative to conventional excipients, offering multifunctional properties that directly improve powder handling and tablet performance. Unlike traditional single excipients, which often fail to balance flowability, compressibility, and disintegration, CPEs integrate the strengths of multiple components into one engineered system, thereby minimizing formulation challenges and ensuring robust manufacturing outcomes [9,10,42,65].Studies on materials such as silicified microcrystalline cellulose (ProSolv® SMCC), Cellactose®, and CombiLac® demonstrate their superior ability to enhance flow properties, compaction, and mechanical strength compared with their parent excipients [14,16,18,23]. These improvements not only streamline direct compression but also reduce variability, improve tablet hardness, and ensure consistent disintegration behavior [25,29,44]. Furthermore, research highlights that CPEs exhibit lower sensitivity to lubricants, reduce elastic recovery during compression, and support the development of fast-disintegrating and patient-centric dosage forms [15,35,38]. Such features are particularly valuable in modern formulation science, where efficiency and adaptability are essential for industrial-scale production. Looking ahead, the pharmaceutical industry is expected to focus on the scale-up of CPEs, regulatoryacceptance, and the incorporation of sustainable excipients to meet both technical and patient-driven demands [45,60,65]. By offering enhanced performance, flexibility, and consistency, CPEs are well positioned to become a cornerstone of oral dosage form development in the future.In conclusion, CPEs not only address the long-standing limitations of conventional excipients but also open new opportunities for innovation in solid oral dosage formulations, ensuring higher product quality and better patient outcomes.

9. References

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