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Co-Processed Excipients In Oral Solid Dosage Formulation: A Multifunctional Approach To Improved Performance

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Abstract

The formulation of oral solid dosage forms (OSDFs) has advanced significantly with the use of co-processed excipients (CPEs), which successfully get around the limitations of traditional excipient mixtures, which include poor flowability, variable compressibility, and irregular drug release. Based on recent research, CPEs—which are made using methods such as spray drying, melt granulation, and wet granulation—can combine filler, binder, disintegrant, and release-modifying agents in a synergistic way at the sub-particle level without changing their chemical identities. As compared with conventional direct-compression, a spray-dried rice starch-based CPE co-processed with cross-linked carboxymethyl rice starch (CCMS) and silicon dioxide demonstrated significantly improved flowability (angle of repose ~28–31°, Carr's index ~20–24), enhanced tensile strength, and rapid disintegration (~28 seconds). excipients. Similar to this, a multifunctional CPE made of lactose monohydrate, microcrystalline cellulose, and StarCap 1500 that was optimized using the D-optimal mixture design exhibited remarkable compressibility and flow properties, with a 40% dilution potential for the poorly compressible medication etodolac. In addition, even at 70% drug loading, lipid-based CPEs that combine lactose and glycerylpalmitostearate have allowed for the sustained release of high-dose ibuprofen for up to 10 hours while still maintaining mechanical robustness and an acceptable flow. These results demonstrate how co-processing can enhance formulation flexibility while effectively regulating flow, compressibility, and release behavior. It is expected that future advancements combining continuous manufacturing approaches, Process Analytical Technology (PAT), and Quality by Design (QbD) will establish CPEs as fundamental agents for trustworthy, scalable, and patient-oriented oral solid dosage forms.

Keywords. Co-Processed Excipients (CPEs, Oral Solid Dosage Forms (OSDFs),Direct Compression,Flow Properties,Compressibility ,Controlled Release

1. **Co-Processed Excipients (CPEs):**

Using methods like co-crystallization, melt granulation, or spray drying, two or more distinct excipients are chemically mixed at the sub-particle level to produce CPEs, which are multifunctional excipients. Without undergoing any chemical alterations, they enhance the flow, compressibility, and dilution potential of powdery substances (1), (2).

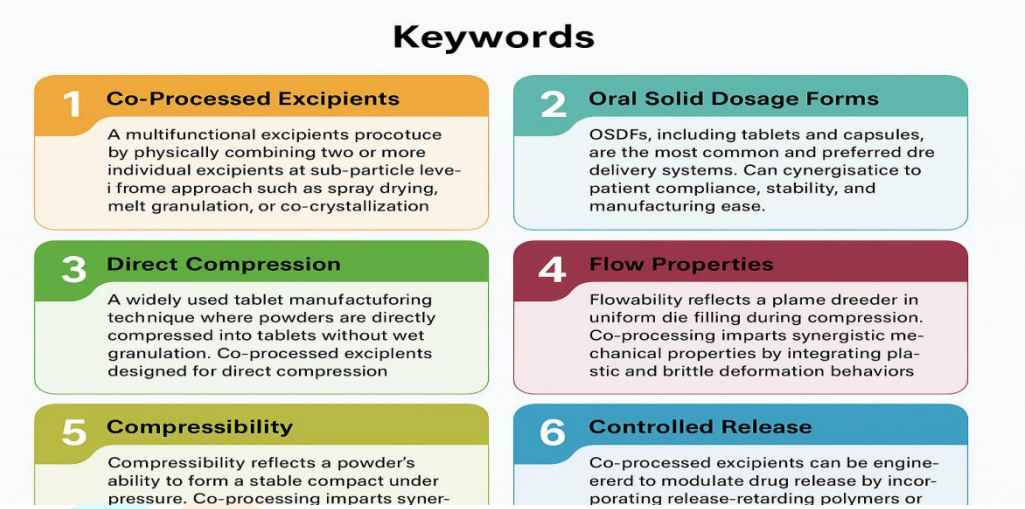

Figure no.1.Keywords

2. Oral Solid Dosage Forms (OSDFs):

due to their ease of manufacturing, stability, and patient compliance, OSDFs—including tablets and capsules—are the most commonly employed and preferred drug delivery methods. By facilitating direct compression and ensuring uniformity, CPEs enhance OSDF manufacturability (3), (4).

3. Direct Compression:
This popular method of making tablets involves compressing powders directly into tablets without the need for wet granulation. Compared to conventional excipient blends, CPEs intended for direct compression provide better flow, compactibility, and decreased lubricant sensitivity (5).

4. Flow Properties:
During tablet compression, uniform die filling is determined by flowability. Through enhanced bulk density, decreased cohesiveness, and optimized particle morphology, CPEs enhance flow while maintaining uniform weight and content (6).

5. Compressibility:
A powder's compressibility reflects its capacity for solidifying into a compact under pressure. via the integration of the parent excipients' brittle and plastic deformation behaviors, the combined processing imparts synergistic mechanical properties (7), (8).

6. Controlled Release:
By incorporating lipids or release-retarding polymers during co-processing, CPEs can be constructed for regulating drug release. For high-dose or poorly soluble medications, this approach provides stable, predictable, and patient-tailored release kinetics (9, 10).

Introduction

due to their long-term stability, cost-effectiveness, accuracy in dosing, and ease of use, oral solid dosage forms (OSDFs) persist to be the most popular and patient-preferred approach to drug administration (11).Over 70% of all pharmaceutical formulations that are marketed are tablets and capsules (12). The production of OSDFs, however, has a number of disadvantages despite their benefits, such as insufficient powder flow, restrictions on compressibility, and problems with uniformity; particularly while working with high-dose or poorly compressible active pharmaceutical ingredients (APIs)(13). The efficiency of the excipients added to the dosage form, in addition to the drug substance, influences the performance and processability of these formulations (14).

mainly considered inert fillers, excipients are now essential functional elements that affect drug release, disintegration, mechanical strength, and manufacturability (15). For direct compression and large-scale tablet manufacturing, traditional single-component excipients frequently fall inadequate of delivering all the necessary mechanical and physical properties (16). As a result, producers turn to utilizing physical blends of excipients, including binders, disintegrants, and diluents. Inconsistent tablet weight, hardness, and dissolution profiles are often the result of these common blends' poor flowability, segregation, dusting, and variable compressibility (17).

Co-processed excipients (CPEs) are a novel class of multifunctional materials that combine the beneficial properties of two or more separate excipients while maintaining their chemical identity in order to overcome these constraints (18). To improve flow, compressibility, and dilution potential, co-processing techniques like fluid-bed coating, melt granulation, co-crystallization, and spray drying are used to engineer particles at the sub-particle level (19). Functional synergy between components can improve direct compression and overall formulation robustness, as suggested by CPEs such as Prosolv® SMCC (silicified microcrystalline cellulose), Cellecttose, Ludipress®, and F-Melt® (20).

the generation of CPEs corresponds with the Quality by Design (QbD) paradigm in the context of current pharmaceutical manufacturing, which places an emphasis on methodical formulation optimization and process understanding (21). Furthermore, real-time monitoring and control of co-processing parameters are made possible by the integration of Process Analytical Technology (PAT) tools, guaranteeing consistent product quality (22).

With a particular focus on creative preparation methods, enhancements in functional performance, and how they are improving product quality and manufacturing efficiency, this review seeks to objectively evaluate current developments in co-processed excipients for OSDFs. By analyzing emerging trends and applications, this study aims to show how CPEs are impacting the creation of patient-centric, reliable and scalable oral dosage form design.Co-processed Excipients (CPEs): a Brief Description

1. Definition and Concept : Combinations of two or more compendial or non-compendial excipients that undergo physical processing to improve their functional characteristics without undergoing considerable chemical alteration are known as co-processed excipients (CPEs) [23].2. The difference between chemical modification, physical mixing, and co-processing

Co-Processing: Multiple excipients are physically processed to produce a new entity with enhanced stability, mobility and compressibility without changing the chemical structure [2].

- **Physical Mixing:** Simple blending of excipients without altering their physical or chemical properties [24].
- **Chemical Modification:** Alteration of chemical structure of excipients to form new compounds with different properties [24].

3. Mechanism: How Co-Processing Improves Powder Characteristics

Co-processing enhances powder characteristics by:

Modifying particle size and morphology to improve flow and compressibility

- Adjusting surface area to optimize dissolution or stability
- Creating favorable inter-particulate interactions to provide multifunctionality [25]

These changes lead to better tabletability, flowability, and disintegration properties [25].

4. Ideal Characteristics of a CPE

An ideal co-processed excipient should have:

- **Compatibility:** With API and other excipients
- **Flowability:** Good powder flow for uniform tablet compression
- **Compressibility:** Adequate mechanical strength
- **Stability:** Maintain physical and chemical stability during storage [23,25]

5. Overview of Preparation Techniques

a. Spray Drying: Atomization of a liquid feed into a hot gas stream to rapidly form solid particles with improved flow and uniform size [26].

b. Melt Granulation: Using a molten binder to agglomerate powders without solvents, suitable for heat-sensitive drugs [27].

c. Fluid-Bed Coating: Coating excipient particles in a fluidized bed to enhance flowability and stability [28].

d. Co-Crystallization: Crystallizing excipients with APIs together to form a single crystalline phase, enhancing solubility and stability [29].

e. Freeze Drying: Freezing the mixture and sublimating the solvent under reduced pressure to produce porous structures [30].

Classification and Examples of Co-Processed Excipients (CPEs)

1. Binders and Fillers

- **Cellactose® 80**: A co-processed excipient composed of 75% α-lactose monohydrate and 25% microcrystalline cellulose, designed for direct compression. It offers excellent flowability, compressibility, and blending properties. MEGGLE Excipients
- **Ludiflash®**: A co-processed excipient containing 90% D-mannitol, 5% crospovidone, and 5% polyvinyl acetate dispersion, used for direct compression of orally disintegrating tablets. BASF Pharma

2. Diluents for Direct Compression

- **Prosolv® SMCC**: A combination of microcrystalline cellulose and colloidal silicon dioxide, providing enhanced flow and compressibility for high-speed tableting. jrspharma.com
- **Avicel® CE-15**: A blend of 85% microcrystalline cellulose and 15% guar gum, optimized for chewable tablets with low friability and rapid disintegration. Pharma Excipients

3. Disintegrant-Based CPEs

- **F-Melt®**: A proprietary co-spray dried formulation containing carbohydrates, disintegrants, and inorganic ingredients, developed for fast-dissolving tablets. f-melt.jp
- **Ludipress®**: A co-processed excipient comprising 93% lactose monohydrate, 3.5% medium-molecular weight povidone, and 3.5% crospovidone, facilitating rapid tablet disintegration. BASF Pharma

4. Lubricant or Multifunctional Excipients

- **StarLac®**: A co-processed excipient made of 85% alpha-lactose monohydrate and 15% native maize starch, offering excellent flow and rapid disintegration for direct compression. Roquette
- **Pearlitol® Flash**: A co-processed excipient composed of mannitol and starch, providing filler/binder and disintegrant properties for orally dispersible tablets. Roquette

summary table: co-processed excipients

Brand Name	Composition	Functionality	Key Features	Reference
Cellactose® 80	75% α-Lactose Monohydrate, 25% MCC	Binder, Filler	Excellent flowability, compressibility, and blending properties	[31]
Ludiflash®	90% D-Mannitol, 5% Crospovidone, 5% Polyvinyl Acetate	Binder, Filler, Disintegrant	Rapid disintegration for ODTs	[32]
Prosolv® SMCC	MCC + Colloidal Silicon Dioxide	Filler, Binder	Enhanced flow and compressibility for high-speed tableting	[33]
Avicel® CE-15	85% MCC, 15% Guar Gum	Binder, Filler	Optimized for chewable tablets with low friability	[34]
F-Melt®	Proprietary Blend	Disintegrant	Fast-dissolving tablet formulation	[35]
Ludipress®	93% Lactose Monohydrate, 3.5% Povidone, 3.5% Crospovidone	Binder, Filler, Disintegrant	Facilitates rapid tablet disintegration	[36]
StarLac®	85% α-Lactose Monohydrate, 15% Maize Starch	Binder, Disintegrant	Excellent flow and rapid disintegration for direct compression	[37]
Pearlitol® Flash	Mannitol + Starch	Filler/Binder, Disintegrant	Suitable for orally dispersible tablets	[38]

Table no.1 co-processed excipients

Technological Advances in Co-Processing Pharmaceutical Excipients

1. Recent Processing Innovations

Recent innovations in co-processing have focused on enhancing the functional properties of excipients:

- **Nano-Level Blending:** Nanotechnology has been applied to produce co-processed excipients with improved solubility, bioavailability, and uniformity. For example, incorporation of nanostructured carriers in excipients can enhance dissolution of poorly soluble drugs [39].
- **Continuous Co-Processing:** Continuous manufacturing techniques allow real-time blending and processing of excipients, improving scalability and reducing batch-to-batch variability [40].

2. Use of Quality by Design (QbD) and Design of Experiments (DoE)

- **QbD:** A systematic approach focusing on predefined objectives, identifying critical quality attributes (CQAs) and critical process parameters (CPPs) to ensure consistent product quality [41].
- **DoE:** Employed to optimize formulation and process conditions of co-processed excipients. Systematic variation of parameters helps identify optimal processing conditions and improve tablet performance [42].

3. Role of Process Analytical Technology (PAT)

- **Real-Time Monitoring:** PAT tools such as near-infrared (NIR) spectroscopy and Raman spectroscopy enable monitoring of CQAs during manufacturing, allowing immediate adjustments [43].
- **Integration with Co-Processing:** Co-processed excipients facilitate more reliable PAT measurements due to uniformity in powder properties, enhancing overall quality control [44].

4. Integration in Continuous Manufacturing Systems

- **Seamless Integration:** Co-processed excipients are increasingly used in continuous manufacturing, enabling uninterrupted production and consistent product quality [40].
- **Enhanced Efficiency:** Their use improves flowability, compressibility, and disintegration, reducing manufacturing time and cost [45].

summary table: technological advances in co-processing

Innovation Area	Description	Reference
Nano-Level Blending	Incorporation of nanoscale carriers into excipients to enhance solubility and bioavailability	[39]
Continuous Co-Processing	Real-time blending and processing of excipients to improve efficiency and consistency	[40]
Quality by Design (QbD)	Systematic development approach ensuring consistent product quality by defining CQAs and CPPs	[41]
Design of Experiments (DoE)	Optimization of formulation and process by systematic variation of factors	[42]
Process Analytical Technology (PAT)	Real-time monitoring of critical quality attributes during manufacturing	[43]
Integration in Continuous Manufacturing	Incorporation of co-processed excipients into continuous manufacturing for uninterrupted production	[40], [45]

Table no.2 technological advances in co-processing

Functional Advantages of Co-Processed Excipients (CPEs)

7.1 Flow Properties

Co-processed excipients are engineered to improve particle size uniformity and powder flow characteristics. By combining excipients with complementary properties, co-processing reduces interparticle friction and agglomeration, resulting in improved **bulk density**, **tap density**, and **flowability**.

- **Carr's Index and Hausner Ratio:** Co-processed excipients demonstrate lower Carr's index and Hausner ratio compared to physical mixtures, indicating enhanced flow properties. For example, Prosolv® SMCC showed a Carr's index of 12–14% and Hausner ratio of 1.14, significantly better than individual excipients [46].
- **Practical Impact:** Improved flowability facilitates uniform die filling in tablet presses, reducing weight variability and ensuring consistent drug content [47].

7.2 Compressibility

CPEs are designed to enhance tablet **compactibility** by balancing plasticity and brittleness:

- **Plasticity vs. Brittleness:** Co-processing enables excipients to undergo plastic deformation during compression, improving interparticle bonding and producing stronger compacts.
- **Tablet Hardness and Friability:** Tablets prepared with co-processed excipients such as Ludipress® and Cellactose® show higher hardness and lower friability compared to blends of individual excipients [48].

7.3 Dissolution / Release Profile

- **Dissolution Enhancement:** Co-processed excipients improve drug dissolution by increasing wettability, dispersibility, and surface area.
- **Controlled and Fast-Dissolving Formulations:** CPEs like F-Melt® facilitate rapid disintegration and dissolution in orally disintegrating tablets, while others can be tailored for controlled release, providing flexibility in formulation design [49,50].

7.4 Compatibility and Stability

- **API Interaction:** CPEs are generally chemically inert but co-processing can reduce interactions with APIs. Thermal and chemical stability are maintained during compression and storage [51].
- **Moisture and Hygroscopicity Control:** Co-processed excipients can incorporate moisture-protective components (e.g., silica) to reduce hygroscopicity, enhancing stability of moisture-sensitive drugs [52].

summary table: functional advantages of cpes

Function	Description	Example / Metrics	Reference
Flow Properties	Improved particle uniformity, bulk/tap density, reduced interparticle friction	Carr's index 12–14%, Hausner ratio 1.14 (Prosolv® SMCC)	[46]
Compressibility	Enhanced plasticity, tablet hardness, low friability	Hardness ↑, Friability ↓ (Ludipress®, Cellactose®)	[48]
Dissolution / Release	Faster disintegration, improved dissolution, controlled release capability	Fast-dissolving ODTs (F-Melt®)	[49,50]
Compatibility & Stability	Reduced API interactions, controlled hygroscopicity, thermal and chemical stability	Stability during storage and compression	[51,52]

Table no.3 functional advantages of CPEs

Applications in Dosage Form Development

1. Direct Compression Tablets

Co-processed excipients are primarily used in **direct compression (DC) tablets**, a widely employed manufacturing method due to its simplicity and cost-effectiveness.

- **Advantages:** CPEs provide enhanced flow, compressibility, and uniformity compared to physical mixtures, reducing the need for multiple excipients and improving tablet weight and content uniformity [53].
- **Examples:**Prosolv® SMCC, Ludipress®, and Cellactose® are extensively used in DC formulations for both low- and high-dose drugs [54].

2. Orally Disintegrating Tablets (ODTs)

- **Rapid Disintegration:** CPEs like F-Melt® and Ludiflash® are engineered to facilitate rapid disintegration in the oral cavity, improving patient compliance, particularly in pediatrics and geriatrics [55].
- **Performance:** These excipients enhance tablet hardness while maintaining rapid dissolution, which is crucial for ODTs [56].

3. Controlled-Release and Multiparticulate Systems

- **Controlled-Release Formulations:** Co-processed excipients can be tailored to modulate drug release by adjusting composition and particle size, aiding in sustained or delayed-release tablets [57].
- **Multiparticulate Systems:** In pellet or granule-based formulations, CPEs improve flowability and compressibility, ensuring uniform filling and consistent drug release [57,58].

4. High-Dose and Poorly Compressible Drugs

- **High-Dose Drugs:** CPEs with high compressibility allow incorporation of large drug loads without compromising tablet hardness or increasing friability [54].
- **Poorly Compressible Drugs:** Drugs like paracetamol, which exhibit poor compression properties, benefit from CPEs that act as binders and fillers while maintaining flow and compressibility [57].

5. Industrial Case Examples and Marketed Products

- **Prosolv® SMCC:** Used in direct compression tablets of ibuprofen and paracetamol [1].
- **F-Melt®:** Applied in marketed orally disintegrating formulations such as Risperidone ODTs [55].
- **StarLac® and Ludipress®:** Employed in chewable and fast-dissolving tablets for pediatric formulations [58].

summary table: applications of cpes in dosage form development

Dosage Form Application	CPE Example	Functional Benefit	Reference
Direct Compression Tablets	Prosolv® SMCC, Ludipress®, Cellactose®	Enhanced flow, compressibility, weight uniformity	[53,54]
Orally Disintegrating Tablets (ODTs)	F-Melt®, Ludiflash®	Rapid disintegration, high hardness	[55]
Controlled-Release &Multiparticulate	Custom co-processed excipients	Modulated drug release, uniform filling	[56,57]
High-Dose & Poorly Compressible Drugs	Prosolv® SMCC, Cellactose®	High compressibility, low friability	[53,57]
Marketed Products	StarLac®, F-Melt®, Ludipress®	Pediatric, ODT, and chewable formulations	[55,58]

Table no.4 applications of CPEs in dosage form development

Challenges and Limitations of Co-Processed Excipients

1. Lack of Regulatory Monographs

- **Regulatory Gap:** Most co-processed excipients are combinations of existing excipients and do not have independent monographs in pharmacopeias such as USP, EP, or BP.
- **Implication:** This can complicate regulatory submissions and quality control requirements for new drug products, as each manufacturer may provide different specifications for the same CPE [59,60].

2. Variability Between Manufacturers

- **Source Variability:** Differences in raw material sources, processing techniques, and particle engineering can lead to batch-to-batch variability in flow, compressibility, and disintegration properties.
- **Impact:** Such variability can affect tablet quality, dissolution, and bioavailability, necessitating thorough in-house evaluation before formulation [60,61].

3. Limited Information on Long-Term Stability and Drug-Excipient Interactions

- **Stability Concerns:** Long-term stability data for co-processed excipients are often limited, particularly under varying storage conditions.
- **Drug-Excipient Interactions:** Co-processing may mask subtle incompatibilities between excipients and APIs. Thermal, moisture, or chemical interactions may occur during storage or compression, potentially affecting drug efficacy or safety [61,62].

4. Scale-Up and Cost Considerations

- **Scale-Up Challenges:** Transitioning from lab-scale to industrial-scale manufacturing can be complex due to changes in powder flow, mixing, and compressibility.
- **Economic Factors:** CPEs are generally more expensive than traditional excipients due to specialized processing, which may limit their use in cost-sensitive formulations [63].

Summary table: challenges and limitations of cpes

Challenge / Limitation	Description	Reference
Lack of Regulatory Monographs	No independent monographs; complicates regulatory submissions	[59,60]
Variability Between Manufacturers	Differences in raw materials and processing affect performance	[60,61]
Limited Stability and Drug-Excipient Interaction Data	Insufficient long-term stability and potential API interactions	[61,62]
Scale-Up and Cost Considerations	Difficult industrial scale-up and higher cost compared to standard excipients	[63]

Table no.5 challenges and limitations of CPEs

Future Perspectives of Co-Processed Excipients (CPEs)

1. Nanotechnology-Enabled Co-Processing

- **Nano-Enhanced Properties:** Incorporating nanomaterials into co-processed excipients can improve solubility, dissolution rates, and bioavailability of poorly water-soluble drugs. Nanostructured excipients also offer more uniform particle size distribution and improved flow [64].
- **Example:** Nano-MCC or nanostructured lipid carriers integrated into co-processed excipients for enhanced oral bioavailability [65].

2. 3D-Printed and Personalized Oral Dosage Forms

- **Personalized Medicine:** CPEs with defined flow and compressibility characteristics are compatible with 3D printing technologies, enabling patient-specific dosing and shape customization.
- **Impact:** Allows precise control of drug loading, release profiles, and tablet geometry for individualized therapy [66].

3. Green Processing Technologies

- **Sustainable Manufacturing:** Emphasis on solvent-free and energy-efficient processes (e.g., melt granulation, spray drying without organic solvents) reduces environmental impact and improves safety.
- **Benefits:** Minimizes residual solvents, reduces cost, and aligns with green chemistry principles in pharmaceutical production [67].

4. Need for Standardization and Regulatory Recognition

- **Monographs and Guidelines:** Currently, most CPEs lack independent USP/NF or EP monographs, complicating regulatory approval.
- **Future Direction:** Development of standardized testing, characterization protocols, and regulatory guidance is essential for broader adoption [68].

5. Application in Biologic Oral Delivery Systems

- **Oral Biologics:** CPEs can be engineered to protect sensitive biomolecules (peptides, proteins) from degradation in the gastrointestinal tract, enabling oral delivery of biologics.
- **Potential:** Combining CPEs with protective carriers or mucoadhesive polymers could improve stability, permeability, and absorption of biologics [69].

6.Scale-up and industrialization

- Methods that are scalable, robust, cost-efficient.
- Better production processes that ensure batch-to-batch consistency.

Summary table: future perspectives of cpes

Future Trend	Description	Reference
Nanotechnology-Enabled Co-Processing	Integration of nanoscale materials to improve solubility, dissolution, and flow	[64,65]
3D-Printed / Personalized Dosage Forms	Patient-specific tablets with controlled drug loading and geometry	[66]
Green Processing Technologies	Solvent-free, energy-efficient manufacturing for sustainable production	[67]
Standardization and Regulatory Recognition	Development of monographs and guidelines (USP/NF, EP)	[68]
Application in Biologic Oral Delivery	Protection and enhanced absorption of peptides and proteins	[69]

Table no.6 future perspectives of CPEs

Conclusion

Co-processed excipients (CPEs) have emerged as a pivotal innovation in modern pharmaceutical formulation, providing multifunctional properties that significantly enhance tablet manufacturability and performance. By combining excipients with complementary functionalities, CPEs improve powder flow, compressibility, and particle uniformity, which are critical parameters for direct compression processes. Enhanced flowability, reflected in improved Carr's index and Hausner ratio, ensures consistent die filling and uniform tablet weight, while optimized compactibility enables tablets with higher hardness and lower friability. These properties make CPEs particularly suitable for high-dose formulations, orally disintegrating tablets (ODTs), controlled-release systems, and multiparticulate dosage forms.

The application of CPEs in contemporary tablet technology offers several advantages, including improved dissolution rates, better stability of active pharmaceutical ingredients (APIs), and reduced sensitivity to

moisture and thermal stress. Industrial case studies demonstrate that CPEs streamline manufacturing processes, reduce the need for multiple excipients, and enhance batch-to-batch consistency, contributing to efficient and cost-effective production.

Looking ahead, future research should focus on integrating nanotechnology, 3D printing, and green, solvent-free processing to further expand the functional versatility of CPEs. Establishing standardized characterization methods, pharmacopeial monographs, and regulatory guidelines is essential for broader adoption and quality assurance. Overall, co-processed excipients offer a robust platform for innovation in tablet formulation, combining enhanced performance with simplified manufacturing, and are poised to play a critical role in the development of next-generation oral dosage forms.

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