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Review Article

Co-Processed Excipients in Pharmaceutical Formulation: Advances, Characterization, and Applications

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A B S T R A C T

Excipients are indispensable components of pharmaceutical dosage forms, significantly influencing product quality, safety, and performance. Conventional single excipients often fail to meet the growing demands of modern formulation technologies, particularly direct compression and fast dissolving dosage forms. Co-processed excipients have emerged as a novel class of multifunctional excipients developed by physically combining two or more excipients at the sub-particle level without altering their chemical structure. This approach results in synergistic improvement in flowability, compressibility, dilution potential, and disintegration behavior. Various techniques such as spray drying, melt granulation, solvent evaporation, and co-crystallization are employed in the preparation of co-processed excipients. Comprehensive characterization using micromeritic, physicochemical, and solid-state techniques is essential to ensure quality and performance. Co-processed excipients have found extensive applications in direct compression tablets, fast dissolving tablets, immediate-release, and modified-release dosage forms. Despite their advantages, regulatory challenges and limited pharmacopoeial recognition remain key concerns. This review highlights the principles, preparation methods, characterization techniques, applications, commercially available products, regulatory aspects, and future prospects of co-processed excipients.

Keywords: Co-processed excipients; Direct compression; Fast dissolving tablets; Multifunctional excipients; Solid oral dosage forms, QbD Framework for Co-Processed Excipients, QbD-Based Evaluation Matrix

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INTRODUCTION

Pharmaceutical excipients play a vital role in the development of safe, effective, and stable dosage forms. Traditionally, excipients are selected to perform individual functions such as filling, binding, disintegration, lubrication, or flow enhancement [1]. However, the increasing complex15, 1706, 1510, 97-10415, 1706, 1510, 97-104ity of drug molecules and preference for cost-effective manufacturing techniques such as direct compression have highlighted the limitations of conventional excipients [2].

Direct compression requires excipients with excellent flowability, compressibility, and dilution potential. Many active pharmaceutical ingredients (APIs) exhibit poor flow and compaction properties, making formulation development challenging [3]. To overcome these limitations, co-processed excipients were introduced as a novel approach to enhance excipient functionality without chemical modification [4].

Rationale for Co-Processing of Excipients

Although physical mixtures of excipients are widely used, they often suffer from segregation, non-uniform distribution, and inconsistent performance during compression [5]. In addition, the use of multiple excipients increases formulation complexity and manufacturing variability.

Co-processing offers a solution by engineering excipients at the particle level to achieve synergistic functionality. By combining excipients with complementary deformation behaviors, such as brittle fracture and plastic deformation, co-processed excipients exhibit superior compaction behavior and mechanical strength compared to physical mixtures [6-9].

Concept and Principles of Co-Processed Excipients

Co-processed excipients are defined as combinations of two or more excipients processed together to improve functional properties while retaining their original chemical identity [10]. Unlike novel excipients, co-processed excipients do not involve chemical modification, which simplifies regulatory acceptance.

The principle of co-processing lies in particle engineering, where particle size distribution, porosity, surface morphology, and bonding properties are optimized. Proper selection of parent excipients with complementary properties is essential to achieve enhanced flow, compressibility, and disintegration behavior [11-15].

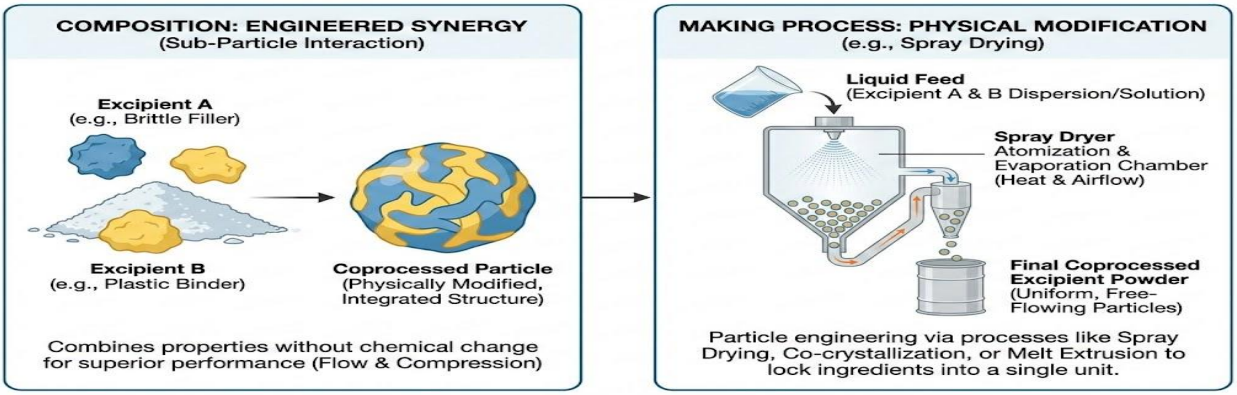

Figure: 1 Steps in Co-Processing of Excipients

Table: 1 Physical Mixture vs. Coprocessed Excipient [16]

Feature	Simple Physical Mixture	Coprocessed Excipient
Manufacturing	Simple dry blending of powders.	Spray drying, crystallization, or granulation of combined dispersions.
Particle Structure	Distinct individual particles of each ingredient.	A single particle containing all ingredients embedded together.
Segregation	High risk (particles separate during vibration).	Low risk (ingredients are locked into one particle).
Flow/Compression	Limited by the worst ingredient.	Significantly improved (engineered properties).

Methods of Preparation of Co-Processed Excipients

1. Spray Drying

Spray drying is the most widely used technique for preparing co-processed excipients due to its scalability and reproducibility. It produces spherical and porous particles with improved flowability and compressibility [17].

2. Solvent Evaporation

In this method, excipients are dissolved or dispersed in a common solvent followed by solvent removal. Although it ensures intimate mixing, residual solvent concerns limit its industrial applicability [18].

3. Melt Granulation

Melt granulation involves agglomeration of excipients using a meltable binder. This solvent-free technique improves compactibility and tablet strength and is suitable for thermally stable excipients [19].

4. Co-Crystallization

Co-crystallization produces crystalline systems with modified physical properties such as improved compactibility and stability. However, process complexity limits its widespread industrial use [20].

Table 2: Methods Used for Preparation of Co-Processed Excipients

Method	Principle	Key Advantages	Limitations	References
Spray drying	Atomization of excipient solution/suspension followed by rapid solvent evaporation	Uniform particle size, improved flow & compressibility, scalable	High equipment cost, thermal stress	[6,20]
Solvent evaporation	Dissolution or dispersion of excipients in solvent followed by evaporation	Intimate mixing, uniform distribution	Residual solvent, environmental concerns	[11]
Melt granulation	Agglomeration using meltable binder without solvent	Improved compactibility, eco-friendly	Limited to thermally stable excipients	[12]
Co-crystallization	Formation of crystalline system with modified physical properties	Improved stability & compactibility	Complex process, limited industrial use	[13]
Wet granulation	Granulation using binder solution followed by drying	Improved flow and uniformity	Multiple steps, time-consuming	[5,14]
Hot-melt extrusion	Melting and mixing excipients under heat and shear	Continuous process, solvent-free	High temperature limitations	[20]

Table 3: Applications of Co-Processed Excipients in Pharmaceutical Dosage Forms

Dosage Form	Purpose of Co-Processed Excipients	Benefits Achieved	References
Direct compression tablets	Improve flow and compressibility	Reduced processing steps, uniform tablets	[1,3,11]
Orodispersible tablets	Enhance disintegration and mouthfeel	Rapid disintegration, patient compliance	[18]
Immediate-release tablets	Improve dissolution and mechanical strength	Faster drug release, robust tablets	[4,10]
Modified-release tablets	Control matrix integrity	Improved release profile	[18]
High-dose formulations	Increase dilution potential	Acceptable tablet hardness	[4]
Poorly compressible drugs	Enhance compaction behavior	Reduced capping & lamination	[7,14]

5. Evaluation of Co-Processed Excipients

Evaluation of co-processed excipients is a critical step to ensure enhanced functionality, reproducibility, and suitability for solid oral dosage forms, particularly for direct compression and fast dissolving tablets. A systematic evaluation includes pre-compression, physicochemical, solid-state, functional, and advanced compaction analyses in accordance with Quality by Design (QbD) principles [21-25].

1. Pre-Compression Evaluation Parameters

Pre-compression studies assess powder flow, packing behavior, and compressibility, which directly influence tablet uniformity and manufacturability [26-30].

2. Bulk Density

Procedure:
A known mass (M) of the co-processed excipient is accurately weighed and gently poured into a graduated cylinder. The apparent bulk volume (Vb) is recorded.

Formula:

$$\rho_b = \frac{M}{V_b}$$

Significance:
Indicates packing ability and die-filling behavior.

3. Tapped Density

Procedure:
The cylinder is mechanically tapped until a constant volume (Vt) is obtained.

Formula:

$$\rho_t = \frac{M}{V_t}$$

Significance:
Reflects powder consolidation behavior.

4. Carr's Compressibility Index

Formula:

$$CI(\%) = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

Interpretation:
Values < 15% indicate excellent flow; > 25% indicate poor flow.

5. Hausner Ratio

Formula:

$$HR = \frac{\rho_t}{\rho_b}$$

Interpretation:
HR ≤ 1.25 indicates good flowability.

6. Angle of Repose

Procedure:
Powder is allowed to flow through a funnel to form a conical heap. Height (h) and radius (r) are measured.

Formula:

$$\tan\theta = \frac{h}{r}$$

Significance:
Lower values indicate better flow.

Table 4: Angle of Repose and Flow Property Classification

Angle of Repose (θ°)	Flow Property	Interpretation / Significance
< 25°	Excellent	Free-flowing powder; ideal for direct compression
25–30°	Good	Good flow; suitable for direct compression
30–35°	Fair	Acceptable flow; may require glidant
35–40°	Passable	Flow problems likely; needs flow enhancers
40–45°	Poor	Poor flow; not suitable for direct compression
> 45°	Very poor	Highly cohesive; unsuitable for tableting

5.2 Physicochemical and Solid-State Characterization

These studies confirm that co-processing improves physical properties without altering chemical identity [7,15].

1. Fourier Transform Infrared Spectroscopy (FTIR)

Procedure:
Sample is mixed with KBr, compressed into pellets, and scanned between 4000–400 cm^{-1}.

Interpretation:
Absence of peak shifts confirms compatibility.

2. Differential Scanning Calorimetry (DSC)

Procedure:
3–5 mg of sample is heated at a controlled rate in sealed aluminum pans.

Significance:
Detects thermal events and physical interactions.

3. X-Ray Diffraction (XRD)

Procedure:
Samples are scanned over a suitable 2θ range.

Significance:
Evaluates changes in crystallinity due to co-processing.

4. Scanning Electron Microscopy (SEM)

Procedure:
Samples are mounted, gold-coated, and examined under SEM.

Significance:
Provides insight into particle morphology and surface characteristics.

5. Functional Evaluation Parameters

Functional studies determine excipient performance during tablet manufacture [6,16].

6. Compressibility and Compactibility

Procedure:
Tablets are compressed at increasing pressures, and hardness or tensile strength is measured.

Interpretation:
Higher strength at lower pressure indicates good compactibility.

7. Dilution Potential Study

Procedure:
Tablets are prepared with increasing API concentration while keeping excipient level constant. Hardness, friability, disintegration time, and dissolution are evaluated.

Significance:
Represents maximum drug load that maintains acceptable tablet quality [16,19].

8. Advanced Compaction and Compression Analysis

Advanced compression models provide insight into deformation mechanisms of co-processed excipients [5,6].

9. Kawakita Analysis

Purpose:
Evaluates powder compressibility and packing behavior under low compression pressures.

Procedure:
A fixed powder mass is compressed at increasing pressures. Initial volume (V_0) and volume at pressure (V) are recorded.

Formula:

$$C = \frac{V_0 - V}{V_0}$$

Kawakita equation:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab}$$

Where a = compressibility, b = plastic deformation constant.

Interpretation:
Higher a and lower $1/b$ values indicate better compressibility and plastic deformation.

5.3 Heckel Analysis

Purpose:
Assesses densification behavior and plastic deformation during compression.

Procedure:
Relative density (D) is calculated at different pressures, and ln[1/(1−D)] is plotted against pressure (P).

Equation:

$$\ln\left(\frac{1}{1-D}\right) = KP + A$$

Mean yield pressure:

$$P_y = \frac{1}{K}$$

Interpretation:
Lower Py values indicate greater plastic deformation [6,14].

5.4 Lubricant Sensitivity Study

Procedure:
Tablets are prepared with increasing lubricant concentrations, and hardness and friability are measured.

Significance:
Lower reduction in hardness indicates low lubricant sensitivity.

5.5 Evaluation of Tablets Prepared Using Co-Processed Excipients

Tablet Hardness

Measured using Monsanto or digital hardness tester.

Friability

Procedure:
Pre-weighed tablets (W_0) are rotated at 25 rpm for 4 min and reweighed (W).

Formula:

$$\text{Friability (\%)} = \frac{W_0 - W}{W_0} \times 100$$

Disintegration Time

Measured using USP disintegration apparatus at 37 ± 0.5 °C.

Dissolution Study

Performed using USP Apparatus I or II under specified conditions [18].

5.6 Evaluation Parameters for Fast Dissolving Tablets

FDTs require additional performance testing to ensure rapid dispersion and patient acceptability [18,20].

Wetting Time

Tablet is placed on water-soaked tissue paper, and time required for wetting is recorded.

Water Absorption Ratio

Formula:

$$R = \frac{W_a - W_b}{W_b} \times 100$$

In-Vitro Dispersion Time

Tablet is placed in a small volume of buffer, and time required for complete dispersion is recorded [31].

Table 5: Evaluation Parameters for Tablets and Fast Dissolving Tablets (FDTs)

Sr. No.	Evaluation Parameter	Test Condition / Procedure	Measurement Unit / Expression
1	Tablet hardness	Measured using Monsanto or digital hardness tester	kg/cm² or Newton (N)
2	Friability	Tablets rotated at 25 rpm for 4 min in Roche friabilator	% weight loss
3	Disintegration time	USP disintegration apparatus at 37 ± 0.5 °C	Seconds (s) or minutes (min)
4	Dissolution study	USP Apparatus I (basket) or II (paddle) under specified conditions	% drug released
5	Wetting time	Tablet placed on water-soaked tissue paper	Seconds (s)
6	Water absorption ratio	Calculated using weight before (Wb) and after wetting (Wa)	Percentage (%)
7	In-vitro dispersion time	Tablet placed in a small volume of buffer	Seconds (s)

5.7 Stability Studies

Procedure:
Samples are stored at accelerated conditions (40 °C/75% RH) and periodically evaluated for physical appearance, hardness, disintegration, and dissolution.

"Stability studies were carried out under accelerated (40 ± 2 °C/75 ± 5 % RH) and long-term (25 ± 2 °C/60 ± 5 % RH) conditions as per ICH guidelines. Tablets were periodically evaluated for physical appearance, hardness, friability, disintegration time, and dissolution behavior to assess formulation stability.[32]

Table 6: Marketed Formulations of Co-Processed Excipients [33]

No.	Commercial name (manufacturer)	Typical composition (major components)	Primary function(s)	Typical applications
1	**PROSOLV® SMCC** (JRS Pharma)	Microcrystalline cellulose (MCC) + colloidal silicon dioxide (silicified MCC; ~98% MCC / ~2% silica)	High-function filler/binder for direct compression; improved flow and compactibility	Direct compression tablets, nutraceuticals, high speed tabletting
2	**PROSOLV® 730** (JRS Pharma)	MCC + colloidal silicon dioxide + copovidone	Oil-adsorbing, directly compressible carrier; improved binding & handling of lipophilic APIs	Direct compression with oily/lipophilic actives, nutraceuticals, capsule filling
3	**PROSOLV® ODT G2** (JRS Pharma)	MCC + colloidal SiO_2 + mannitol + fructose + crospovidone	Orally-disintegrating tablet matrix (ODT): fast disintegration, good mouthfeel	ODTs, chewables, immediate-release pediatric/geriatrics
4	**Ludipress® / Ludipress LCE** (BASF)	Predominantly lactose monohydrate with povidone and small % crospovidone / povidone binder variants	Direct compression filler–binder with built-in disintegrant/binder	Immediate release tablets, low-dose uniformity, capsules/granules
5	**Ludiflash® / Ludiflash (ODT)** (BASF)	D-mannitol + crospovidone + polyvinyl acetate dispersion (plus small PVP)	Ready-to-use ODT excipient: filler, binder, disintegrant; pleasant mouthfeel	Orally disintegrating tablets, paediatric ODTs
6	**MicroceLac® 100** (Meggle)	75% α-lactose monohydrate + 25% microcrystalline cellulose (spray-dried co-processed)	Direct compression diluent with improved tabletability & flow	Direct compression tablets, dispersible tablets, ODTs

7	**Cellactose® 80** (Meggle)	75% α-lactose monohydrate + 25% powdered cellulose (co-processed)	Improved flow, tabletability and reduced lubricant sensitivity vs physical mix	Direct compression, particularly low-dose formulations and ODTs
8	**CombiLac® / CombiLac (MEGGLE)**	e.g., 70% lactose + 20% MCC + 10% corn starch (co-spray dried, grade dependent)	Multifunctional lactose-based diluent with improved compressibility & disintegration	Direct compression, chewables, dispersible tablets
9	**StarLac®** (MEGGLE / Roquette listing)	~85% α-lactose monohydrate + 15% native maize starch (co-spray-dried)	Combines lactose flowability with starch hydration/disintegration	ODTs, fast--dispersing tablets, direct compression
10	**Pharmaburst® 500** (SPI Pharma)	Engineered blend of polyols (mannitol, sorbitol), precipitated silica, crospovidone (proprietary granule matrix)	ODT platform — smooth mouthfeel, rapid disintegration, high API load possible	Orally disintegrating tablets (many marketed products use it)
11	**F-MELT®** (Fuji Chemical — Type C / M / F1)	Co-spray dried mix: mannitol/xylitol + microcrystalline cellulose + crospovidone + inorganic (e.g., Neusilin® or calcium phosphate) (varies by type)	ODT platform: optimized disintegration, mouthfeel and compressibility	ODTs, chewables, nutraceutical ODTs
12	**Avicel® HFE-102** (IFF/Avicel)	Spray-dried MCC (≈90%) co-processed with mannitol (≈10%)	High-function MCC/mannitol for improved flow, compaction and mouthfeel (chewables)	Dispersible/chewable tablets, direct compression
13	**Avicel® DG** (IFF / FMC history)	~75% MCC + 25% anhydrous dibasic calcium phosphate (spray-dried co-processed)	High functionality for dry granulation and direct compression; improved re-compactability	Dry granulation (roller compaction), direct compression, robust tablets
14	**PEARLITOL® Flash** (Roquette)	Mannitol + maize starch (co-processed)	ODT filler/binder with disintegrant behavior; pleasant taste/texture	Orally dispersible / fast melt tablets, chewables
15	**PROSOLV® EASYtab (SP / Nutra)** (JRS Pharma)	MCC + colloidal SiO_2 + sodium starch glycolate (or croscarmellose in some grades) + sodium stearyl fumarate (pre-lubricated variants)	All-in-one directly compressible excipient (binder/filler/glidant/superdisintegrant/ lubricant)	Direct compression for nutraceutical and pharmaceutical tablets; improves content uniformity & reduces feeders
16	**Prosolv® 730** (JRS) — included above; if extra entry needed, include **Prosolv® NX / RX** family	Microcrystalline cellulose (binder), silicon dioxide (glidant), and copovidone (binder/stabilizer)	High-function composites for specific API needs (e.g., lipophilic APIs)	Specialized carriers for difficult actives
17	**Avicel® CE-15** (IFF)	~85% MCC + 15% guar gum (co-processed)	Designed to improve organoleptic (mouthfeel) properties and produce chewables/chewable texture	Chewable tablets, low-friability chewables and molds
18	**Prosolv® 730 / Prosolv family (other grades)** — (JRS Family)	MCC + silica + functional polymers (copovidone etc.)	Specialty carriers (oil binding / improved compactibility)	Direct compression with poorly compressible/lipophilic actives, nutraceuticals

6. Characterization of Co-Processed Excipients

6.1 Micromeritic Properties

Micromeritic evaluation includes bulk density, tapped density, angle of repose, Carr's index, and Hausner ratio to assess flow and packing behavior [34].

6.2 Physicochemical Properties

Moisture content, porosity, and compatibility with APIs are evaluated to ensure stability and consistent performance during formulation development [35].

6.3 Solid-State Characterization

Solid-state techniques such as differential scanning calorimetry (DSC), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM) are used to confirm absence of chemical interaction and to evaluate morphological changes induced by co-processing [36].

7. Applications of Co-Processed Excipients

Co-processed excipients are extensively used in direct compression tablets, orodispersible tablets, immediate-release, and modified-release dosage forms. They are particularly advantageous for high-dose drugs and poorly compressible APIs, where conventional excipients fail to produce tablets with acceptable hardness and disintegration characteristics [37].

8. Co-Processed Excipients for Fast Dissolving Tablets

Fast dissolving tablets (FDTs) require excipients that provide rapid disintegration, pleasant mouthfeel, and adequate mechanical strength. Co-processed excipients combining diluents such as mannitol or lactose with superdisintegrants like crospovidone or croscarmellose

sodium have shown excellent performance in FDT formulations [38].

8.1 Future Perspectives

Future research should emphasize harmonized regulatory guidelines, pharmacopeial inclusion, and development of novel excipient combinations to meet evolving pharmaceutical challenges. Collaboration between academia, industry, and regulatory bodies is essential for the successful integration of co-processed excipients into mainstream pharmaceutical manufacturing [39].

9. Commercially Available Co-Processed Excipients

Several commercially available co-processed excipients, particularly lactose-based and microcrystalline cellulose-based systems, provide multifunctional performance and simplify formulation development. These excipients reduce the number of formulation components and improve batch-to-batch consistency [40].

10. Regulatory and Pharmacopoeial Aspects

Despite their advantages, co-processed excipients face regulatory challenges due to limited pharmacopoeial recognition. Regulatory authorities generally evaluate them as physical mixtures, requiring extensive characterization and quality documentation [41].

11. Advantages and Limitations

Advantages

- Enhanced flowability and compressibility
- Reduced excipient load
- Improved manufacturing efficiency
- Suitability for direct compression

Limitations

- Regulatory uncertainty
- Higher development and validation costs
- Limited pharmacopoeial monographs

12. Recent Advances and Emerging Trends

Recent research focuses on Quality-by-Design-based development, natural and sustainable excipient combinations, and application of co-processed excipients in continuous manufacturing systems [42].

13. Quality by Design (QbD)–Based Evaluation of Co-Processed Excipients

Quality by Design (QbD) provides a systematic approach to pharmaceutical development by emphasizing product and process understanding and process control. Application of QbD in the development of co-processed excipients ensures consistent performance, improved functionality, and reduced batch-to-batch variability[43-45].

QbD Framework for Co-Processed Excipients

Table 7: Quality Target Product Profile (QTPP)[46]

QTPP Element	Target Requirement
Dosage form	Tablet / Fast Dissolving Tablet
Manufacturing method	Direct compression
Performance	Rapid disintegration, adequate strength
Stability	Physically and chemically stable
Patient acceptability	Good mouthfeel (for FDTs)

Table 8: Identification of Critical Quality Attributes (CQAs)[47]

CQA	Impact on Product Quality
Flowability	Uniform die filling
Compressibility	Tablet formation
Compactibility	Mechanical strength
Disintegration time	Drug release
Dissolution rate	Bioavailability
Moisture content	Stability

Table 9: Identification of Critical Material Attributes (CMAs)[48]

CMA	Effect on CQAs
Particle size	Flow and compaction
Particle shape	Packing behavior
Porosity	Disintegration
Excipient ratio	Functional performance
Moisture level	Stability

Table 10: Identification of Critical Process Parameters (CPPs)[49]

CPP	Impact
Spray-drying temperature	Particle morphology
Feed rate	Particle size
Binder concentration	Compactibility
Mixing time	Content uniformity
Compression force	Tablet hardness

14. QbD-Based Evaluation Matrix

Table 11: Risk Assessment Matrix (CQAs vs CMAs & CPPs)[50]

Parameter	Flowability	Compressibility	Disintegration	Dissolution
Particle size	High	Medium	Medium	Low
Porosity	Medium	Medium	High	High
Excipient ratio	High	High	High	High
Moisture content	Medium	Low	Medium	Medium
Compression force	Low	High	Medium	Medium

Risk level: High = Critical, Medium = Moderate, Low = Minor

CONCLUSION

Co-processed excipients represent a significant advancement in pharmaceutical excipient technology by offering multifunctional performance and improved manufacturability. Their growing application in solid oral dosage forms, particularly direct compression and fast dissolving tablets, highlights their importance in modern formulation development. Addressing regulatory challenges and expanding pharmacopoeial recognition will further enhance their industrial adoption.

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