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Coprocessed Excipients: A Comprehensive Review with Formulation Based Examples

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A B S T R A C T

Co-processed excipients, formed by sub-particle blending of two or more excipients without chemical change, enhance tablet manufacturing via improved flow, compressibility, disintegration, and dissolution compared to single excipients or physical mixtures. Common production methods—spray drying, fluid-bed, wet/dry granulation, melt granulation, and co-crystallization—enable tailored multifunctional performance. Commercial examples like Prosolv®, Ludipress®, and Pearlitol® demonstrate enhanced manufacturability and robustness. Being physically combined, these excipients typically retain GRAS status and avoid new toxicological testing. However, challenges remain in quality control, batch reproducibility, and production cost. This review synthesizes current technologies, commercial products, regulatory frameworks, and identifies future needs: standardized methods, advanced analytics, and expanding multifunctional libraries for optimized tablet design.

Keywords: Co-processed excipients , Solvent Evaporation Method , Ludipress, Perlitol CRH.

Introduction:

Excipients—non-active components in pharmaceutical formulations—are essential for ensuring drug stability, manufacturability, bioavailability, and patient acceptability. Rather than relying on a single excipient, co-processed excipients (CPEs) synergistically combine two or more compendial or non-compendial materials at the sub-particle level. This approach enhances functionality—such as flowability, compressibility, porosity, disintegration, and mouthfeel—that cannot be achieved by simple physical mixtures, all without altering chemical structures(ref1).

CPEs are especially valuable in direct-compression and tablet formulations. Direct compression simplifies manufacturing by bypassing wet granulation, reducing unit operations, cost, time, and degradation risks—ideal for moisture- or heat-sensitive APIs. ODTs, which disintegrate rapidly in the mouth without water, improve patient compliance, particularly for pediatric, elderly, and dysphagic populations. However, ODTs pose formulation challenges in mechanical strength, taste-masking, and dose limitations.

By offering one composite excipient with multiple optimized functional attributes, CPEs streamline formulation design, mask undesirable properties, and improve tablet performance. They support rapid dissolution, enhanced compressibility, better mouthfeel, and consistent flow, while reducing the need for additional glidants or binders. Moreover, CPEs can be tailored for specific applications, though their fixed component ratios and limited representation in pharmacopeias remain constraints.

In summary, co-processed excipients offer a modern, efficient, and cost-effective way to optimize tablet formulations—particularly for direct-compression and orally disintegrating dosage forms—by combining multiple functionalities into a single, stable excipient.

Need for Co-processing(ref 2,7):

1) Most of ingredients /excipients have drawbacks such as lack of Micromeritics properties, lack of cohesion properties & lubrication. Hence blend of few ingredients is required to achieve satisfactory condition prior to direct compression.
2) The advancements and maturation of co-processing technique explore the possibility to produce tailor made “designer excipients to cater various specific need required for formulation development.
3) Improved functionality over simple mixtures. Banana powder is rich in starch and pectin, both of which swell in water and act as superdisintegrant.
4) Co-processing with MCC can synergistically enhance the disintegration time of tablets, crucial for ODTs.
5) Reduction of individual limitations.

6) Co-processing improves physicochemical stability and compatibility with APIs due to the more uniform structure and reduced segregation.

7) Using a co-processed excipient reduces the number of ingredients and simplifies manufacturing, enhancing reproducibility and cost-effectiveness.

Advantages of Co-processed Excipients :

1) Provide a single excipient with multiple functionalities.
2) Removal of undesirable properties.
3) Overcome the limitation of existing excipients.
4) Improvement of organoleptic properties.
5) Production of synergism in functionality of individual components.
6) Reduction of company's regulatory concern because of absence of chemical change during co- processing.
7) Improvement in physico-chemical properties has expanded their use in the pharmaceutical industry.
8) Flow of Co-processed excipients was better than the flow of simple physical mixtures.
9) It can be also improving the tablet hardness and decrease disintegration time.
10) Controlled optimal particle size and particle size distribution ensure superior flow properties of Co-processed excipients without to add glidants.
11) All co-processed and adjusted excipients are playing very important role in the development of easy dosage form.
12) The co-processed excipient should be stable physically and chemically. The ingredients used should be inert and not interact with the API.

Limitation of Co-Processed Excipients(ref1,3,7):

1) Major limitations of co-processed excipients are the ratio of the excipients in a mixture is fixed and in developing a new formulation, a fixed ratio of the excipients may not be an optimum choice for the API and the dose per tablet under development.
2) Co-processed adjuvant lacks the official acceptance in pharmacopoeia.
3) A regulatory perspective of the excipient mixtures with the absence of a chemical change during processing, co-processed excipients can be considered generally regarded as safe (GRAS) if the parent excipients are also GRAS-certified by the regulatory industry until it exhibits significant advantages in the tablet compaction when compared to the physical agencies. Hence, these excipients do not require additional toxicological studies.
4) Excipient mixtures or co-processed excipients have yet to find their way into official monographs, which is one of the major obstacles to their success in the market place.

TYPES OF CO-PROCESSING TECHNIQUES (ref 3,6,10):

Methods of Co-processing are as:

1. Solvent evaporation
2. Spray drying
3. Wet granulation
4. Dry granulation
5. Co- transformation
6. Roller Compaction
7. Roller dryer
8. Hot melt extrusion
9. Milling
10. Crystallization

- **Solvent Evaporation:**

In this method, the process happens in a liquid base used during manufacturing. The main excipient (core ingredient) is either dissolved or mixed in the coating solution. This coating solution contains a volatile solvent that doesn't mix with the liquid base. To form the coating, stirring is done to help form the coating layer, and heat is applied to remove the solvent by evaporation.

- **Spray drying:**

Spray drying is a method used to turn liquid feed—like a solution, suspension, or emulsion—into dry powder by spraying it into hot air. The liquid quickly evaporates, leaving behind fine particles. The final product's form (powder, granules, or agglomerates) depends on the feed properties and equipment design. Key factors like inlet air temperature and atomization control the quality and characteristics of the dried particles.

- **Wet granulation:**

Wet granulation is a common technique to prepare co-processed excipients. It uses equipment like high-shear mixers or fluid-bed granulators. In this method, powder is lifted by air (fluidization), and then a liquid binder is sprayed onto it, forming granules. The granules are then dried to complete the process.

- **Dry granulation:**

Dry granulation, particularly using roller compaction (RC), is a widely used method for processing powders or powder mixtures without the use of liquids. This process involves passing the material between rotating rollers, which compress it into solid sheets or compacts. These are then milled into granules.The resulting granules usually have a higher density and a more uniform shape compared to those produced by other methods, although they tend to have poorer flow and compression properties. Interestingly, the irregular shapes formed in this process can sometimes enhance tablet hardness.One advantage of this method is that it doesn't require any liquid, making it ideal for moisture-sensitive materials. It's also capable of handling large quantities of powder at once. However, it requires specialized equipment and can be expensive.

- **Co- transformation:**

This method uses heat or solvents to temporarily expand the excipient particles, allowing other excipients to enter and combine with them. These excipients become "opened-up" and can better perform their intended function. This process helps improve the physical and functional properties of the resulting mixture.

- **Roller Compaction:**

Roller compaction is a dry granulation method where powder particles are compressed between counter-rotating rollers to form solid sheets, which are then milled into granules. This method is well-suited for moisture- and heat-sensitive materials. It enhances flowability, ensures better uniform distribution of the drug, and helps prevent segregation.

- **Roller dryer:**

Here, a uniform solution or dispersion containing excipients is dried using a roller dryer. This method was applied to co-process lactose with sorbitol and lactitol. The temperature used was high enough to produce a product mainly made of crystalline β-lactose.

- **Hot melt extrusion:**

This process involves creating small pellets or beads by melting ingredients and pushing them through an extruder. It works well for materials that can handle heat (above 80°C), as the mixture is melted, shaped, and then cooled into solid form. It's slightly complex but has benefits like being solvent-free, fast, and giving consistent results.

- **Milling:**

Milling involves using machines like roller mills, ball mills, or hammers to grind premixed excipients into fine particles. High-speed machines create granules by repeated particle contact. A common example is using ball mills to co-process cross-linked PVP and calcium silicate.

- **Crystallization:**

Crystallization is the process of forming a solid crystal phase from a homogeneous fluid phase, which can be a solution, melt, or gas. It is extensively used for purification, particle size control, and solid-state modification of materials. The process occurs when a system becomes supersaturated, meaning it contains more solute than can be dissolved under equilibrium conditions. Supersaturation can be induced through several methods such as cooling the solution, adding an anti-solvent, altering pH, or initiating a chemical reaction. The nucleation and growth of crystals are influenced by various parameters including temperature, solvent type, concentration, and agitation. Crystallization is a fundamental unit operation in both research and industrial-scale production for isolating and purifying compounds.

GENERAL STEPS IN DEVELOPING CO-PROCESSED EXCIPIENTS (1,3,7):

- **Choose appropriate excipient components**

First, identify which excipients to combine. The goal is to balance their mechanical properties—like flexibility and brittleness—so that when compressed, the blend minimizes elastic rebound, reduces stress-relaxation, and improves tableting performance with less capping or lamination.

- **Ensure consistent particle size**

Particle size directly influences flow and compressibility. If the individual excipients vary in size, you should process them (e.g., milling, sieving) to achieve a uniform particle size distribution in the final co-processed material.

- **Select an appropriate co-processing method**

There are several techniques to fuse the excipients together—such as wet granulation, melt granulation, spray drying, freeze drying, or hot-melt extrusion. Choose the method that best suits the properties you want in the finished excipient.

- **Refine formulation and process parameters**

Finally, optimize both the ratio of each excipient and the processing conditions. Use experimental design and statistical analysis to fine-tune the formulation, ensuring the co-processed excipient consistently delivers the desired performance characteristics.

CO-PROCESSED EXCIPIENTS AVAILABLE IN MARKET (ref1,12):

Following are the examples of Coprocessed excipients which are available in market:

Sr. No.	Trade Name	Composition	Advantages	Mfg. By.
1.	Ludiflash	Mannitol , Crosspovidone, Polyvinyl acetate	Low Friability,Good Flowability ,Suitable for high speed tabletting	BASF
2.	Ludipress	Lactose Monohyadrate(93.4%),Polyvinyl Pyrollidone (Kollidon 30-3.2%),Crosspovidone (kollidon 20-3.4%)	Excellent Flowability, Low Friability,Excellent Binding Power	BASF
3.	Dipac	Sucrose & Dextrin	Directly Compressible Grade	Penwest Pharmaceutical Co.USA
4.	Prosolv	MCC & Colloidal Silica	Better Flowability,Hardness,Reduced Friability	Penwest Pharmaceutical Co.USA
5.	Microcell	MCC & Lactose	High Doses can be formulated	Meggle, GmbH Germany
6.	StarLac	Lactose & Maize Starch	Good flow	Roquette, France
7.	Formaxx	Calcium Carbonate & Sorbitol	Controlled Particle Size Distribution	Merck
8.	Avicel CE 15	MCC & Guar Gum	Less Grittiness, Reduced Tooth Packing ,Minimal chalkiness creamier mouthfeel improved overall palatability	FMC USA
9.	Copovidone	Kollidon VA 64 & Plasdone S630	Excellent flow properties & Dry binder	Ashland
10.	Cellactose	Lactose & Cellulose	Highly Compressible , Good Mouthfeel, Better Tabletting at Low Cost	Meggle, GmbH Germany

11.	Vitacel VE-650	MCC & Calcium Carbonate	Suitable for direct compression & encapsulation	FMC Biopolymer
12.	Perlitol SD	Granulated Mannitol	Suitable for Chewable Tablet Application with good mouth feel& palatability	Roquette Pharma
13.	Finlac DC	Directly Compressible Lactito	Good mouthfeel& Rapid DT Properties , Used for neutraceuticals & chewable vitamin application	Cultor Food Science
14.	Neusilin	Amorphous Magnesium alumino metasilicate	Superior flow property, anticacking ,Good Compressibility & can be used for solid dispersion	Fuji chemicals
15.	Pharmatose DCL 40	95% α Lactose & 5% anhydrous lactitol	Good flowability& Better Binding property	-
16.	Avicel CL 611	MCC & Sodium Carboxymethyl cellulose	Increase formulation Stability	FMC USA
17.	GRANFILLER –D	D- mannitol, Crosspovidone , Carmellose & MCC	Shows good disintegratibility, good Hardnness property	Diacel
18.	HISORAD	D-Mannitol, MCC ,Crosscarmellose Sodium	Excellent compatibility, Rapid disintegration	Diacel
19.	Kollidon	80% Polyvinyl acetate,19% Povidone , 0.8%SLS & 0.2% Silica	-	BASF
20.	Microlela	MCC & Lactose	Capable of formulate high dose, small tablet with flowable API	Meggle Pharma
21.	Vivasol	Croscarmellose Sodium	Superdisintegrant	JRS Pharma
22.	Vivapur^{R} MCG	MCC & Carboxymethyl cellulose	Free flowing , unique suspending &emulsifying agent Superior suspension stability(used in liquid dosage forms)	JRS Pharma
23.	Prosolv^{R} 730	MCC , Silicon Dioxide & Copovidone	Adsorption & Direct compression of oils	JRS Pharma
24.	Prosolv^{R} EASY tab Nutra	MCC, Colloidal Silicon dioxide Croscarmellose /Sodium Strach glycolate, Mg. Stearate	Good Flowability, low friability, less sticking, good hardness,high intrinsic flow,etc	JRS Pharma
25.	Prosolv^{R} EASY tab SP	MCC, Colloidal Silicon dioxide Croscarmellose /Sodium Strach glycolate, Sodium Stearyl Fumarate	Good Flowability, low friability, less sticking, good hardness	JRS Pharma
26.	Prosolv^{R} ODT G2	MCC, Colloidal Silicon dioxide, Mannitol, Fructose, crosspovidone	Fast disintegration , pleasant mouthfeel	JRS Pharma

27.	Partek ODT	D-Mannitol,Croscarmellose Sodium	Rapid disintegration ,plesant mouthfeel	Merck
28.	Retalac	Hypromellose & lactose	Improve flow & binding property, enhance compatibility in direct compression	Meggle Pharma
29.	Disintequik MCC	MCC & Monohydrate lactose	Fast disintegration	Kerry
30.	Dicom DC S -604	Calcium carbonate & Polyvinyl Pyrollidone	Excellent flowability, better compressibility & uniform particle size distribution	Penwest Pharmaceuticals
31.	Dipa Prosolv	Sucrose 3%, Dextrin MCC , Silicon dioxide	Excellent flowability , better hardness	Penwest Pharmaceuticals
32.	Dicom Sanaq SP 206	MCC, Colloidal Silicon Dioxide	Excellent flow properties, used in direct compression of hygroscopic & moisture sensitive APIs	Pharmatrans sanaq
33.	Dicom Sanaq ML 011	Lactose monohydrate,MCC	Enhance stability& effectiveness during manufacturing product ,fast disintegration	Pharmatrans sanaq
34	Disintequik ODT	Crosspovidone Dextrose, monohyadrate mannitol, monohydrate lactose	Suitable lubricant , additional sweetner if desired	Kerry
35.	Compressol^{R} S	Polyols	Direct compression, Superior compatibility, high active loading	SPI, USA
36.	PanExcea^{TM} MHC300G	MCC, Hydroxypropyl methyl cellulose, crospovidone	Direct compression,Particle engineered with Filler, binder and disintegrants functionality, high Flowability	Mallinckrodt Baker, Inc.
37.	StarCap^{R} 1500	Corn starch , Pregelatinized starch	Wet & Dry granulation binder, enhances functionality of other binders	BPSI H ol dings, Inc.
38.	RanExplo^{TM} S	MCC, Silica, Sodium Starch glycolate	Improved Flowabiliy, Superdisintegrant	RarQ Pharmaceutical India
39.	RanExplo^{TM} C	MCC, Silica, Crospovidone	Colloidal grade, suspension stabilization and granulation aid, improved Flowability, superdisintegrants	RarQ Pharmaceutical India
40.	Ceolus^{TM} RC	MCC, NaCMC	Colloidal grade, suspension stabilization and granulation aid, improved Flowability, superdisintegrants	Asahi kasel America, Inc.
41.	Avicel HFE 102	MCC, Mannitol	Direct Compression ,Maximizes compatibility at high lubricant level	FMC, USA

42.	KLEPROSE DC	Cyclodextrin	Direct compression , Insitu encapsulation of APIs	Rouquette pharma , France
43.	Isomalt galen IQ-721	I-O-Dglucopyranosyl,6-0-D glucopyranosyl D-sorbitol (1:3) particle size 90%,50%.	Highly soluble agglomerated spherical isomer for fast dissolving and fast disintegration time	-
44.	Manogem™ EZ	Mannitol particle size 60%	Assist in formulating difficult to use non hygroscopic orodispersible tablet containing find drug	-
45.	Vitacel VE-650	Microcrystalline cellulose and calcium carbonate	Suitable for direct compression and encapsulation	FMC Biopolymer

PRINCIPLE INVOLVED IN CO-PROCESSING:

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. This interdependency among the levels provides the scientific framework for the development of new grades of existing excipients and new combinations of existing excipients. The fundamental solidstate 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. 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 co-processing or particle engineering two or more existing excipients. Co-processing 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. The availability of a large number of excipients for co-processing ensures numerous possibilities to produce tailor-made “designer excipients” to address specific functionality requirements (ref 3).

REGULATORY ASPECTS:

Since excipients are a part of the final drug product, they must comply with regulatory standards. When applying for marketing authorization (MA), it's essential to verify the acceptability of these excipients with the relevant regulatory body. In many countries, including those in the European Union, excipients must meet specific safety and quality criteria (e.g., ICH guideline Q8 and EMEA documents like EMEA/CHMP/QWP/396951/2006).Co-processed excipients may raise additional regulatory questions. This is because they often involve combining substances chemically or physically, which may not yet be officially recognized as a single excipient. Regulatory bodies may require detailed information about the components used, how they are processed, and the rationale for their combination.While many co-processed excipients consist of previously approved components, they may still need to be reviewed as new substances, especially if their properties or functions differ significantly from individual ingredients.In the United States, for example, co-processed excipients that meet the safety standards set by the FDA can be considered GRAS (Generally Recognized as Safe), especially if their parent components are already GRAS-approved(ref 2,3).

CONCLUSION:

Co-processed excipients (CPEs) have emerged as a significant innovation in pharmaceutical formulation development, offering synergistic improvements in functionality without altering the chemical structure of individual components. By combining the desirable characteristics of multiple excipients at the sub-particle level, CPEs provide enhanced flowability, compressibility, and disintegration—critical attributes for direct compression of tablets . The incorporation of co-processing techniques such as spray drying, solvent evaporation, and granulation has enabled the production of tailor-made excipients that address the limitations of conventional agents and reduce the need for additional formulation aids.

Despite the promising benefits, CPEs still face certain limitations, such as fixed component ratios and limited recognition in pharmacopeias. However, their regulatory acceptability continues to evolve, especially when parent excipients are classified as GRAS. As the demand for robust, patient-friendly, and cost-effective dosage forms grows, the role of co-processed excipients will become increasingly central in pharmaceutical innovation. Continued research, coupled with regulatory support, will further enhance their applicability and acceptance in mainstream drug development.

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