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Innovative Approaches in Excipient Co-Processing: A Comprehensive Review

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Abstract

Co-processing of existing excipients is an innovative strategy in pharmaceutical formulation that offers a cost-effective, efficient alternative to the development of entirely new excipients. This process involves combining two or more well-established excipients to create new material with enhanced properties, thereby improving the functionality, performance, and manufacturability of pharmaceutical products. By leveraging the unique characteristics of each excipient, co-processing can significantly enhance attributes, such as flowability, compressibility, solubility, stability, and bioavailability, depending on the intended application. The co-processing process typically involves several key steps. Initially, the selection of compatible excipients is critical, as their chemical and physical properties must complement each other to achieve the desired outcome. This is followed by optimizing the ratio of the excipients to balance their individual strengths. The final step involves employing suitable methods to achieve uniformity and consistency in the final product. Common techniques include co-granulation, spray drying, hot melt extrusion, and solvent evaporation. These methods enable the formation of homogeneous mixtures with improved physical and chemical characteristics, leading to better performance in pharmaceutical formulations. The benefits of co-processing are numerous. It can improve drug release profiles, reduce production costs, enhance product stability, and improve patient compliance through optimized dosage forms. However, there are potential drawbacks, including the complexity of formulation development, the need for extensive characterization to ensure product quality, and potential regulatory challenges related to the approval of new co-processed materials. Overall, co-processing represents a valuable approach that offers innovative solutions to pharmaceutical formulation challenges, enabling the development of more effective, efficient, and patient-friendly drug products. This review discusses the steps involved in co-processing, different methods for combining excipients, as well as the benefits and drawbacks of the process. It also highlights examples of co-processed excipients currently available, including commercial options.

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INTRODUCTION

Oral medication is the most favored method of drug administration because of its simplicity, practicality, safety, non-invasive nature, and cost-effectiveness. Tablets are especially favored over liquids and semisolid forms because they are easier to produce, offer longer shelf lives, ensure precise dosing, and are more convenient to carry. Additionally, tablets are less susceptible to microbial contamination, enhancing their safety. However, many drugs lack inherent compressibility, making it challenging to formulate

stable, high-quality tablets. To address this, directly compressible excipients are used to improve compressibility, flowability, and stability. These excipients enhance the physical properties of the drug blend, ensuring consistent tablet quality. Direct compression is a cost-effective, time-saving manufacturing method that eliminates the need for complex processes like wet granulation. It reduces costs, shortens production time, and minimizes drug degradation risks, especially for moisture-sensitive APIs. However, not all drugs are appropriate for direct compression because of poor flowability or compressibility. Here, directly compressible excipients help improve tablet strength, uniformity, and drug release profiles. Key characteristics of suitable excipients include high flowability, good powder compatibility, excellent compressibility, low moisture sensitivity, good compatibility, and fast disintegration. These properties ensure uniform drug content, strong tablets, and efficient drug release.

Since no single excipient meets all requirements, co-processing existing excipients is an effective strategy. Co-processing combines well-established excipients to create materials with enhanced properties, like combining microcrystalline cellulose (MCC) with lactose to improve flowability and compressibility. Co-processing is cost-effective and reduces regulatory hurdles compared to developing new excipients from scratch [1].

A single excipient rarely possesses all the essential physico-mechanical characteristics needed for a reliable drug delivery system (Figure 1). Therefore, multifunctional excipients are required; those that offer improved flow properties, low sensitivity to moisture, better compressibility, and rapid disintegration. Enhancing excipient performance can be achieved either by developing new ones or by co-processing existing excipients. Among these options, co-processing is more economical and efficient, as creating entirely new excipients is often costly and time intensive [2].

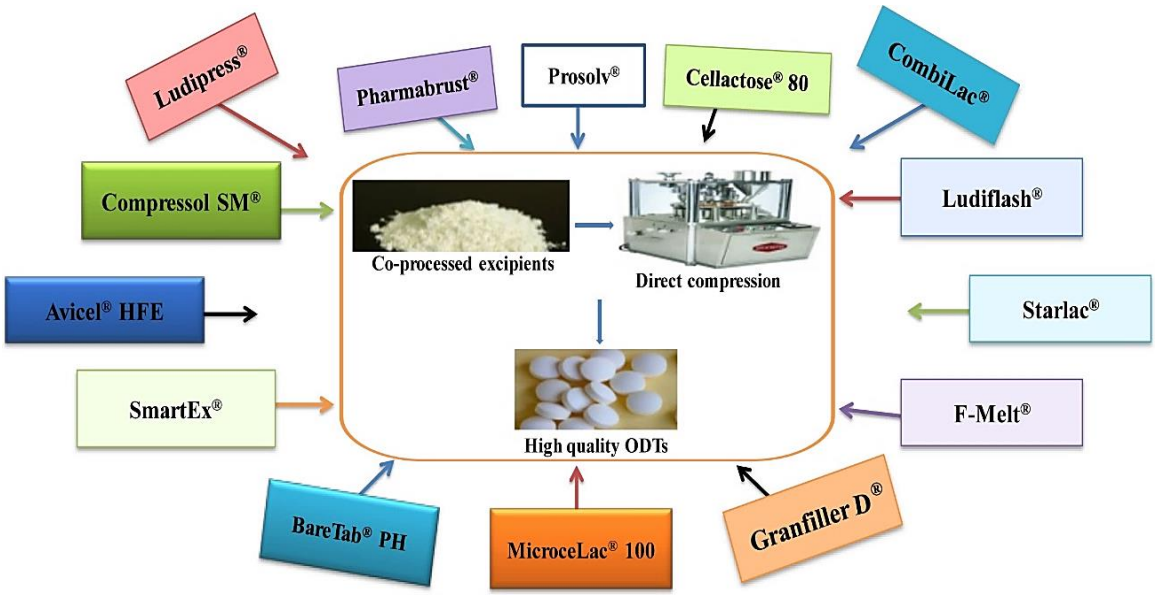


Figure 1. Patented technology platform based on co-processed excipients.

By integrating two or more established excipients through specialized techniques, like spray drying, hot melt extrusion, or co-granulation, the co-processed excipients can be produced. This approach helps overcome the limits of discrete components and offers significant benefits, including enhanced stability, optimized drug release, and better manufacturability. The aim of co-processing is to achieve improved functionality without a significant cost increase. A co-processed excipient is described as a blend of recognized pharmaceutical excipients that are combined to enhance their functional performance, which exhibits at least one unique property not found in a simple physical mixture. Importantly, co-processing does not change the chemical nature of the excipients, which ensures regulatory compliance while boosting their overall effectiveness [3–5].

Additionally, co-processing can enhance the powder's flow property, reduce segregation during manufacturing, and enhance tablet hardness without compromising disintegration. This approach also allows for the creation of excipients with tailored characteristics to meet specific formulation requirements. The resulting co-processed excipients often exhibit better compressibility, reduced dust generation, and improved uniformity, which can significantly streamline the manufacturing process and reduce production costs. This makes co-processing an attractive strategy for pharmaceutical companies seeking efficient, cost-effective, and high-quality drug formulations [2].

TYPES OF EXCIPIENTS

- *Single Entity Excipients:* They consist of only one main ingredient and are referred to as single entity substances.
- *Blends of Multiple Excipients:* These are straightforward physical mixtures of two or more excipients, whether listed in official pharmacopeia (compendial) or not, combined using low to moderate shear processes. In such mixtures, each excipient retains its original physical form, and no major chemical alterations occur [6].
- *Novel Excipients or New Chemical Entities:* These excipients are chemically altered to produce entirely new substances. They are usually not listed in the FDA's inactive ingredient database. A novel excipient is defined as any inactive substance purposefully included in a therapeutic or diagnostic formulation.
- *Co-Processed Excipients:* These are formed by combining two or more excipients, whether non-compendial or compendial, in a way that enhances their functional properties beyond what is possible through simple physical merging without producing significant chemical changes (Figure 2) [3].

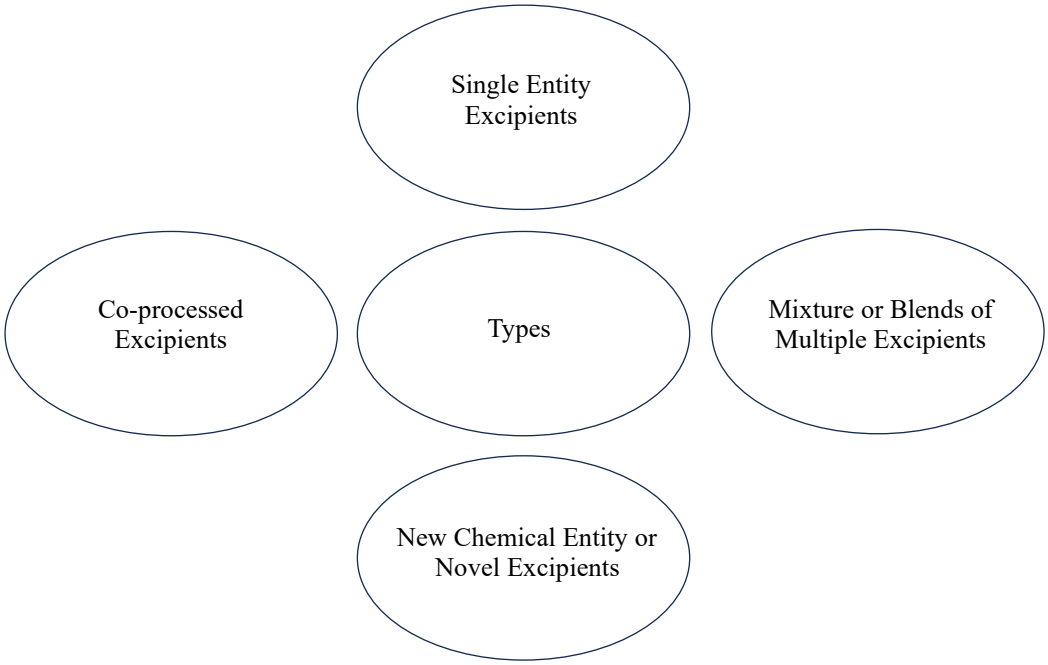


Figure 2. Types of excipients.

Need for the Co-Processed Excipients

The industry of excipients has experienced steady growth as part of the broader food sector. Since excipients are derived from food industry processes, they inherently adhere to high safety standards. In response to growing regulatory scrutiny over the safety, purity, and consistency of excipients, the International Pharmaceutical Excipients Council (IPEC) was established. This organization, comprising members from the US, EU, and Japan, has played a key role in creating standardized guidelines for assessing the quality and performance of excipients. Typically, new excipients are developed based on

market needs rather than being produced without a specific demand. Consequently, innovation in this area has been relatively limited. However, several other factors are also encouraging the pursuit of new excipient development which include [2]:

- Substitute for two or more excipients in direct compression.
- In tableting machinery, the excipients used should maintain compressibility and weight variation.
- Address limitations, such as excessive moisture content and inadequate die filling caused by particle agglomeration.
- Improve the drug's permeability, solubility, and overall stability.
- Resolve challenges related to tablet disintegration, dissolution, and bioavailability.

SELECTION OF CO-PROCESSED EXCIPIENTS

Excipients chosen for formulation must be mutually compatible. A crucial characteristic of an effective tablet excipient is strong compressibility, which depends on achieving the right balance between flowability & brittleness. As a result, co-processing typically combines plastic material with a brittle one. Nonetheless, co-processing can also involve pairing two brittle or two plastic materials to produce a co-processed excipient [7–11].

- *Brittle + Plastic Co-Processed Excipient:* This combination is for rapid disintegration (brittle) and for better compressibility and tablet hardness (plastic). This blend improves tablet properties, such as disintegration, dissolution rates and manufacturing efficiency. For example: the blend of microcrystalline cellulose and polyvinylpyrrolidone this combination improves bioavailability and better tablet processing [4].
- *Plastic + Plastic Co-Processed Excipient:* This combination enhances the tablet properties like compressibility, flowability, and strength. This also improves tablet processing, mechanical properties, and formulation consistency. For example: the blend of polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC) this combination improves better binder properties and smoother manufacturing [5].
- *Brittle + Brittle Co-Processed Excipient:* This combination improves tablet disintegration and dissolution rates. The drug bioavailability is enhanced by increasing the tablet breakdown rate. For example: microcrystalline cellulose (MCC) and dicalcium phosphate the advantage is that it causes the fast release of the formulation (Figure 3) [6].

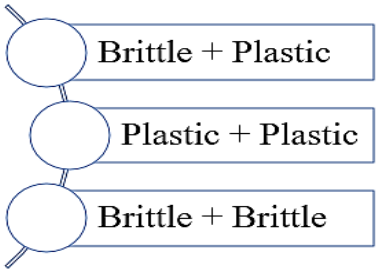


Figure 3. Selection of co-processed excipients

STEPS INVOLVED IN CO-PROCESSING

The following (Figure 4) shows the steps involved in co-processed excipient process.

Schematic Diagram 1

The steps mentioned above for developing co-processes excipients are crucial to ensure the creation of excipients with superior performance and quality. The key benefits include:

- *Improved properties:* Flowability and compressibility characteristics of the excipients are optimized.
- *Manufacturing efficiency:* Helps scale production while maintaining consistency.
- *Regulatory compliance:* Ensures the excipients meet standards for smother approval (Figures 4-6) [7, 8].

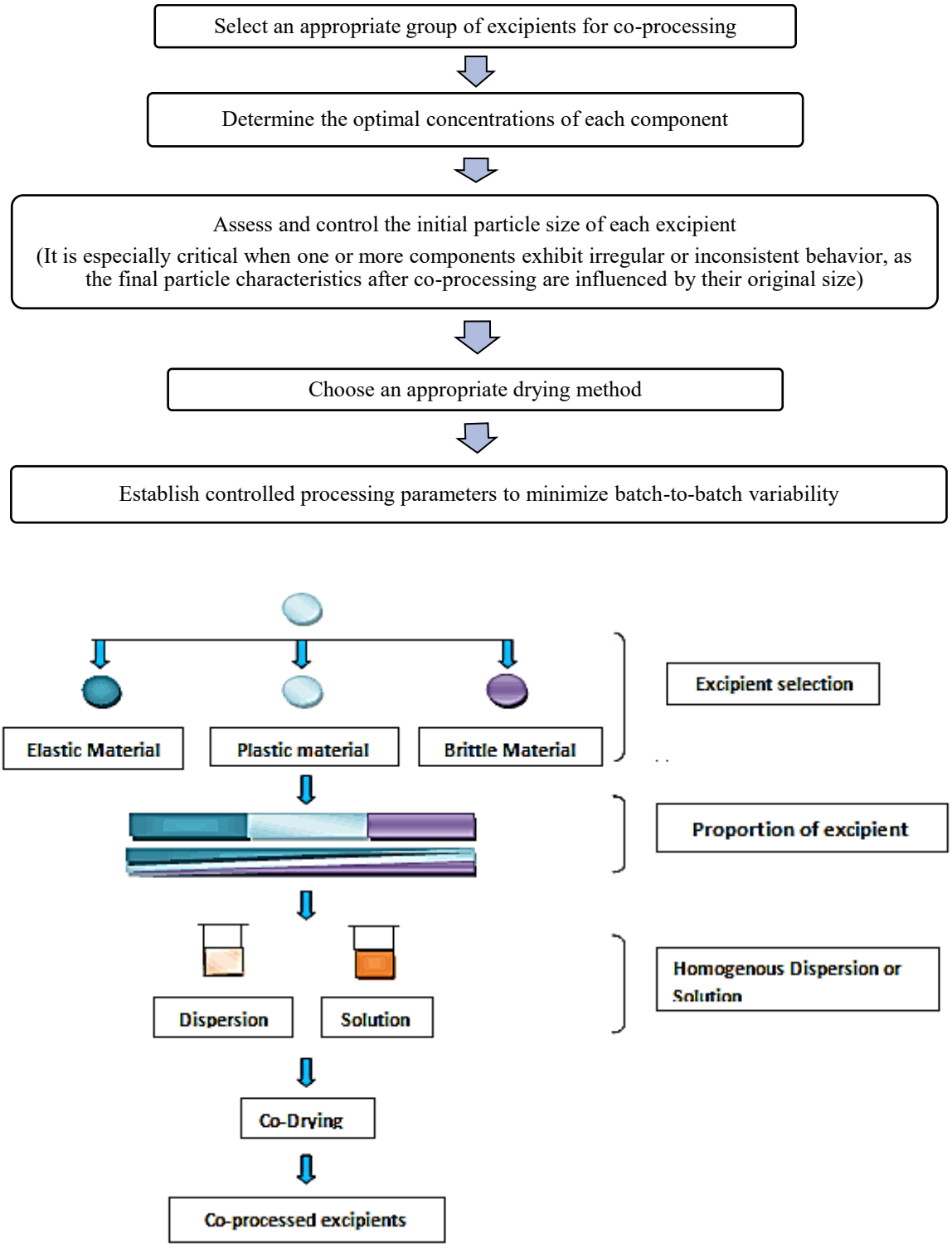


Figure 4. Steps involved in co-processing.

METHODS

Melt Granulation

A solventless method that blends excipients under controlled conditions using a suitable meltable binder is known as melt granulation [12–16]. This process creates granules with reduced pore size and a more intricate, maze-like internal structure, resulting from the formation of solid bonds between excipients or between the excipients and drug (Figure 7).

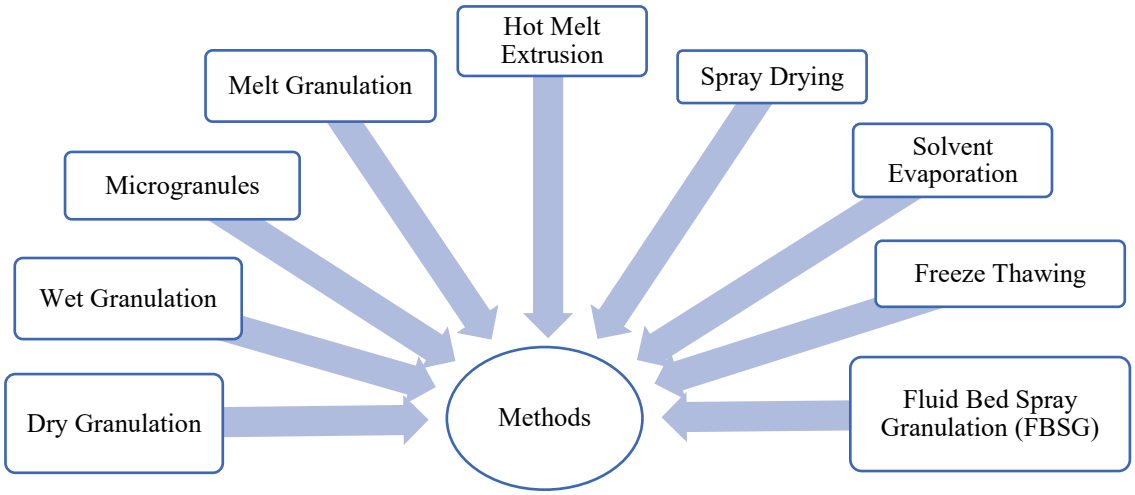


Figure 5. Methods of granulation techniques.

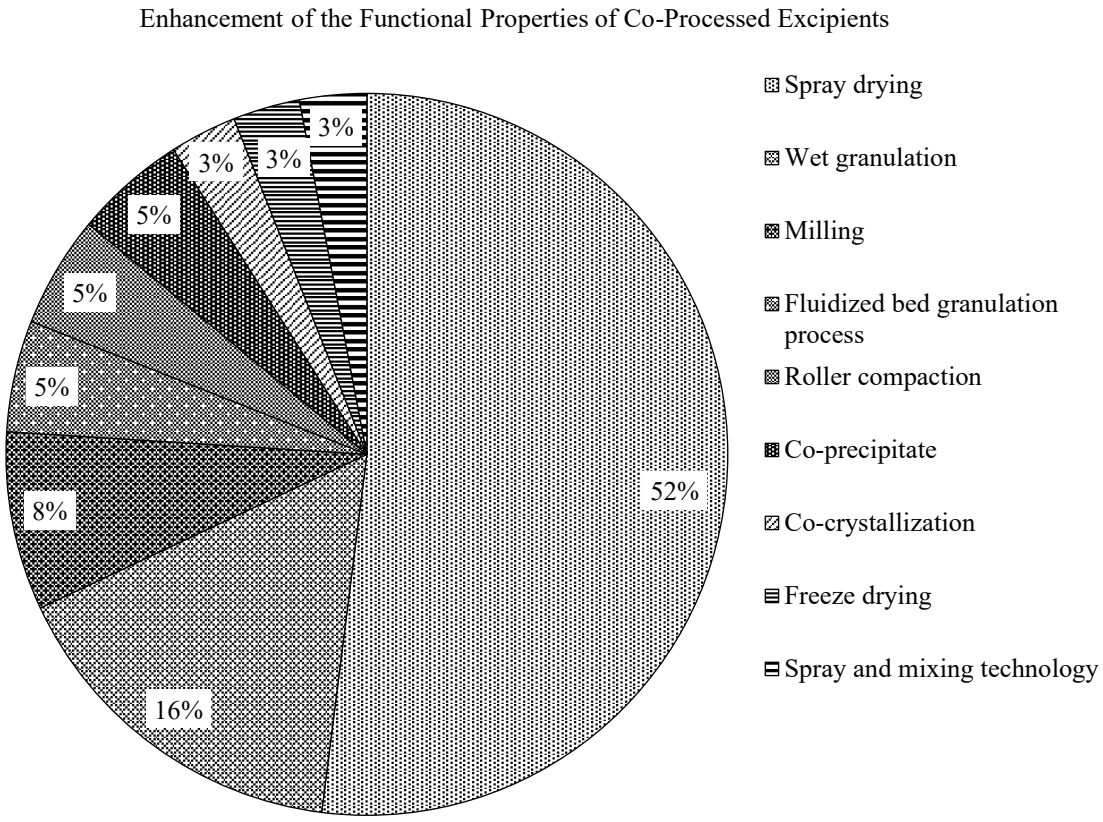
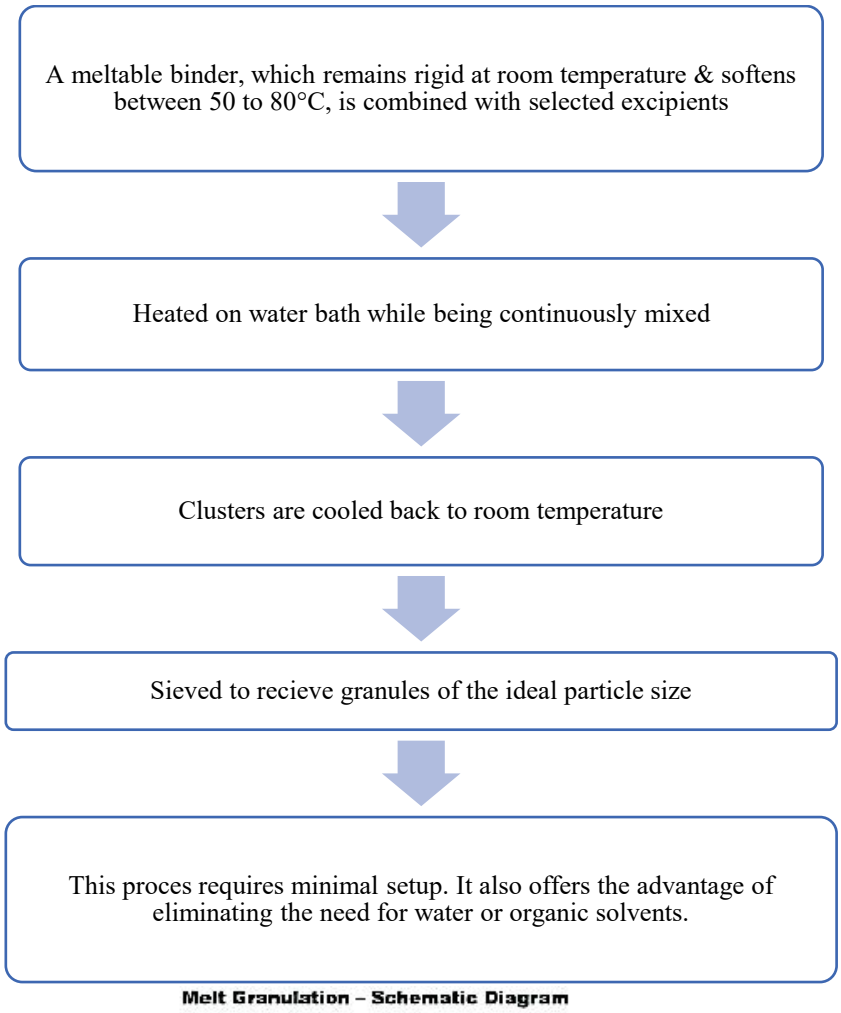


Figure 6. Enhancement of the functional properties of co-processed excipients.

Schematic Diagram 2

Vaingankar et al. investigated the use of continuous melt granulation technology to create a sustained release formulation by co-processing HPC Nisso-H as a binder and stearic acid as a thermal lubricant with metformin HCl [17–20]. Scanning electron microscopy (SEM) images demonstrated that melt granulation produced granules with smooth low porosity and surfaces, featuring small voids. In contrast, conventional granulation led to rough, cracked surfaces with high porosity and large voids. The resulting tablet formulation delivered an optimal drug release profile, closely matching that of a

marketed product, with release percentages falling within USP standards and surpassing those of standard granulation methods (Tables 1 and 2) [9].



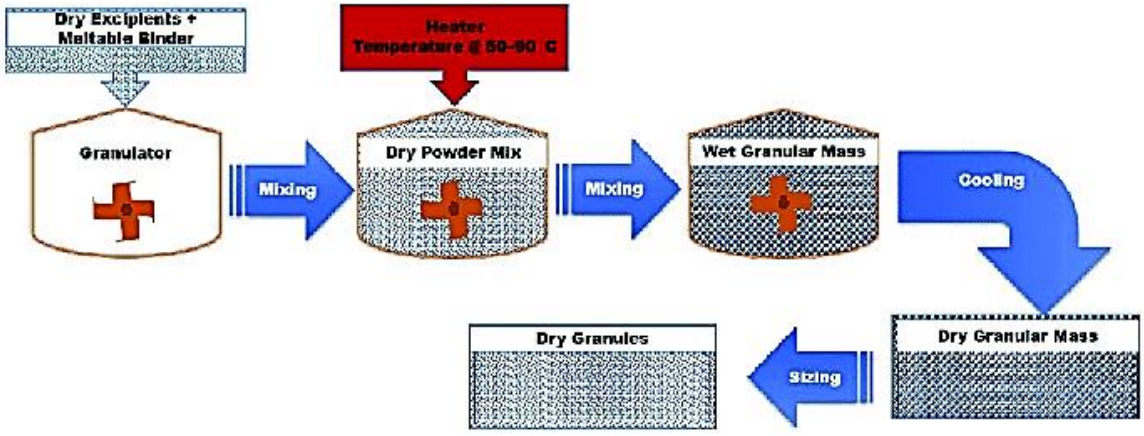


Figure 7. Melt granulation.

Critical Variables

1. Concentration of binder.
2. Diluent to binder ratio.

Table 1. Meltable hydrophilic binders (melt granulation).

S.N.	Hydrophilic Meltable Binder	Melting Range (°C)
1	Gelucire 50/13	44–50
2	Poloxamer 188	50.9
3	Polyethylene glycol	??
4	2000	42–53
5	3000	48–63
6	6000	49–63
7	8000	54–63
8	10000	57–64
9	20000	53–66
10	Stearate 6000 WL1644	46–58

Table 2. Meltable hydrophobic binders (melt granulation).

S.N.	Hydrophobic Meltable Binder	Melting Range (°C)
1	Beeswax	56–60
2	Carnauba wax	75–83
3	Cetyl palmitate	47–50
4	Glyceryl behenate	67–75
5	Glyceryl monostearate	47–63
6	Glyceryl palmitostearate	48–57
7	Glyceryl stearate	54–63
8	Hydrogenated castor oil	62–86
9	Microcrystalline wax	58–72
10	Paraffin wax	47–65
11	Stearic acid	46–69
12	Stearic alcohol	56–60

Dry Granulation

Dry granulation is a technique employed in the production of co-processed excipients, where powder mixtures are compacted without the addition of moisture. This approach is especially advantageous for active pharmaceutical ingredients (APIs) and excipients that are sensitive to moisture [21–23]. The process typically includes blending the powders and compacting them using equipment, such as roller compactors, followed by milling the compacted mass into granules. Dry granulation enhances powder flow properties, reduces dust, improves compressibility, and ensures uniform distribution of the API within the granules. This technique is advantageous in producing co-processed excipients with improved stability, better handling properties, and optimized flow characteristics for tablet manufacturing (Figure 8) [24–30].

The following are the steps (Figure 8) involved in dry granulation [11]:

Schematic Diagram 4

Wet Granulation

This is a traditional and straightforward method to create co-processed adjuvants. It involves combining two/more excipients using a granulating liquid. The typical steps include mixing the excipients, adding the granulation fluid to form a damp mass, followed by granulation, drying, and sieving to achieve granules of the anticipated size. This process improves the flowability, compressibility, and uniformity of the excipients, making them well-suited for direct compression tablet production. Its main advantages lie in its simplicity and the relatively few process variables that need to be validated. Commonly used equipment includes fluid bed granulators & high-shear mixers [12].

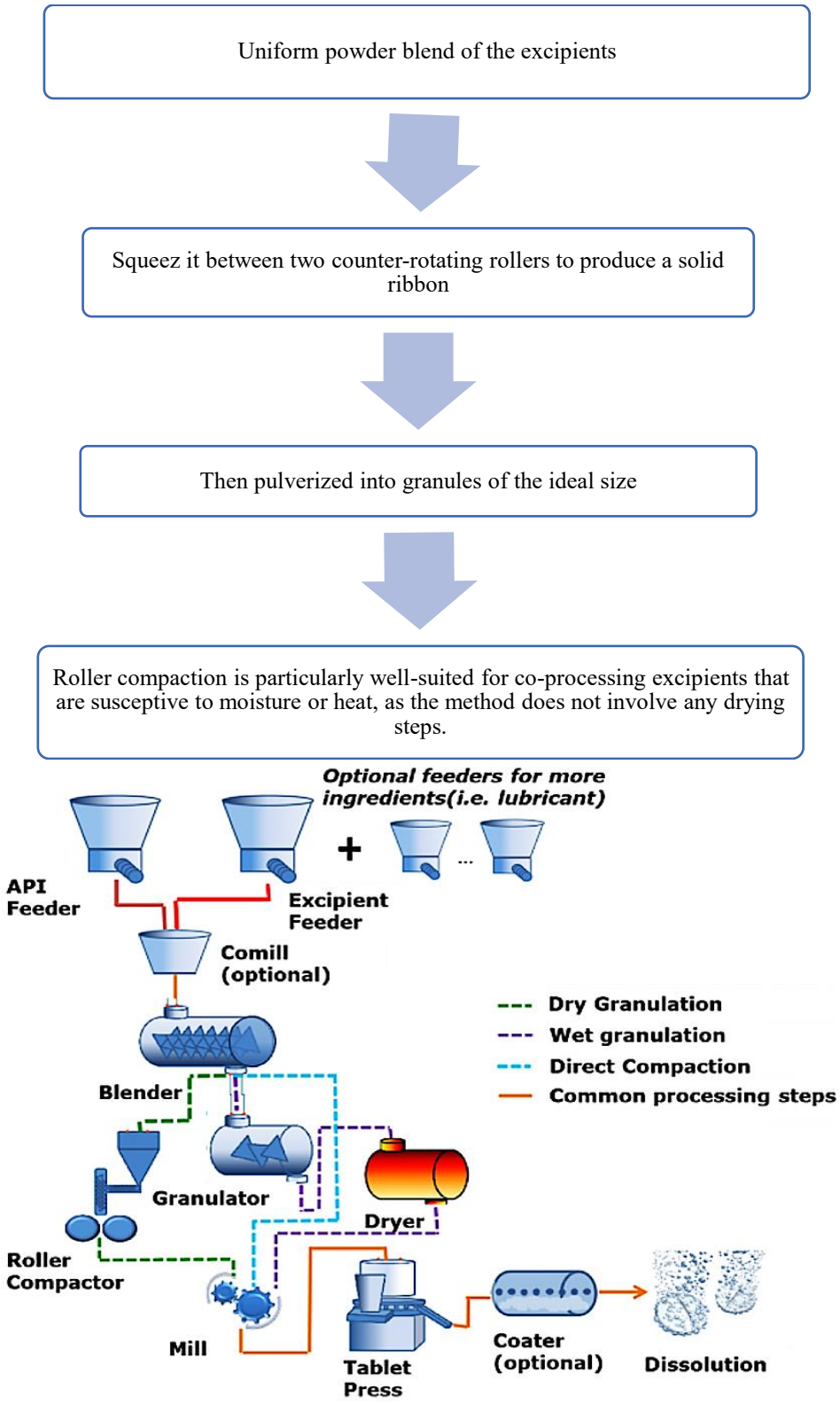


Figure 8. Dry granulation.

Schematic Diagram 5

Microgranules

Microgranules are small, spherical agglomerates of excipients or active pharmaceutical ingredients (APIs) produced through processes like wet granulation or spray drying. In the context of co-processed

excipients, microgranules enhance functionality by improving flowability, compressibility, and uniformity, which are crucial for direct compression tablet formulations. By integrating multiple excipients at the particle level, co-processing aims to synergistically enhance desired properties, such as tabletability and disintegration, while minimizing segregation issues. This approach leads to more efficient manufacturing processes and potentially superior tablet quality (Figure 9).

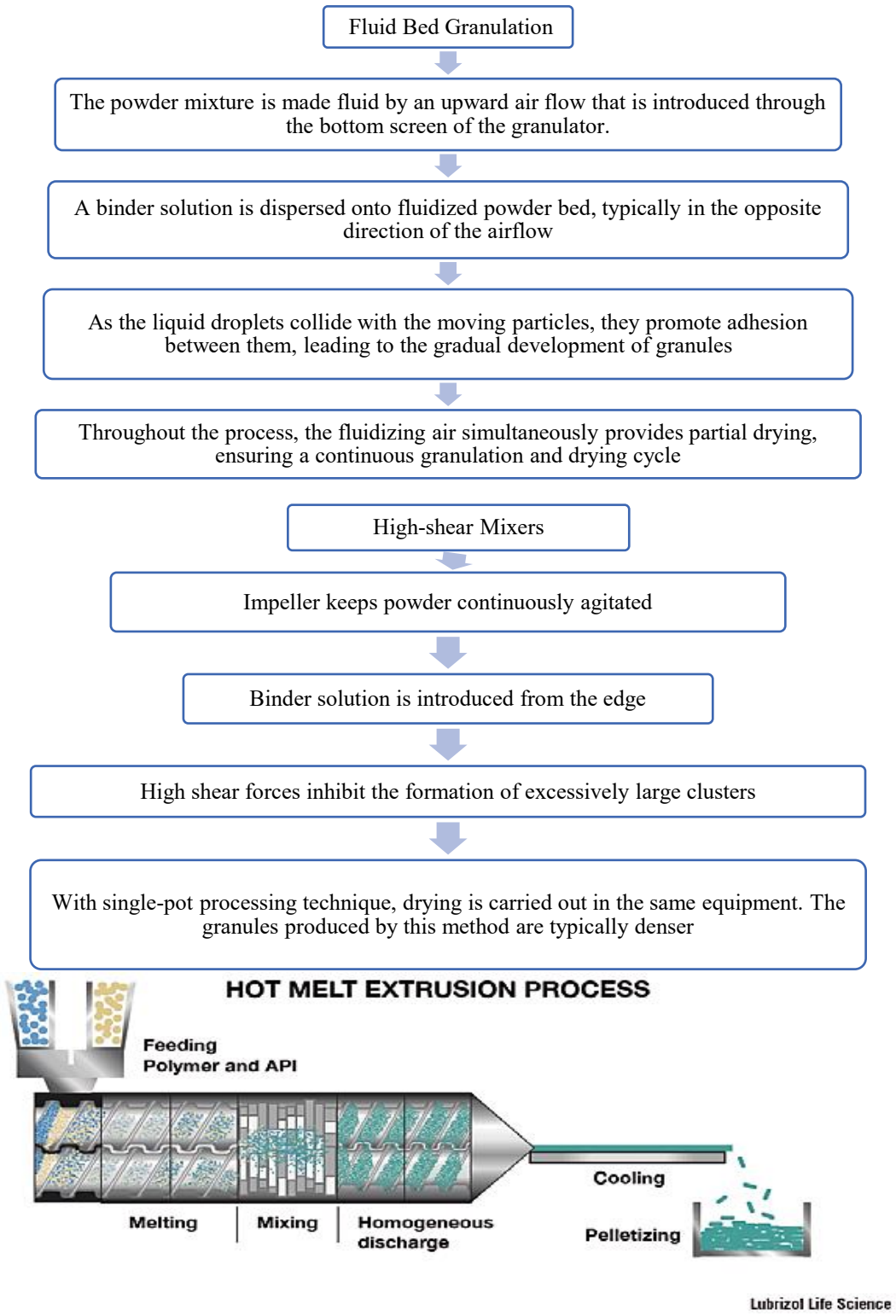


Figure 9. Hot melt extrusion.

To produce microgranules the wet mass was processed using an oscillating granulator to produce microgranules. The optimized tablet batch demonstrated superior flow characteristics, enhanced compressibility, improved binding capacity, and a short disintegration time [1].

HOT MELT EXTRUSION

It is a co-processing method used to enhance the properties of pharmaceutical excipients. In this process, a mixture of excipients and active pharmaceutical ingredients (APIs) is heated above their melting points and then pressed into a die to form uninterrupted strands. The strands are cooled and sliced in pellets or granules. HME improves the flowability, compressibility, and uniformity of the resulting co-processed excipients, making them ideal for direct compression tablet formulations.

In this process, excipients are heated until they melt, then forced through a dye under pressure, where they cool and solidify into various shapes. It does not require any solvent, as the molten polymer itself acts as a thermal binder during shaping (Figure 9) [12].

Spray Drying

It is a technique employed in the development of co-processed excipients, involving the atomization of a liquid feed into a heated gas stream to produce dry particles. In context of co-processing, spray drying facilitates the formation of solid dispersions by combining two or more excipients, resulting in particles with enhanced properties suitable for direct compression tablet formulations. This method offers advantages, such as the ability to process heat-sensitive materials and the production of excipients with improved flowability, compressibility, and uniformity compared to simple physical blends. In this process, the larger surface area of the droplets combined with elevated temperatures leads to the formation of spherical particles, resulting in enhanced flow properties and making them well-suited for direct compression applications.

As per the process, sprays a feed, which may be a solution, suspension, or dispersion, into a hot drying medium to convert it into dry particulates. Throughout the process, excipients form particle-particle bonds (Figure 10) [12].

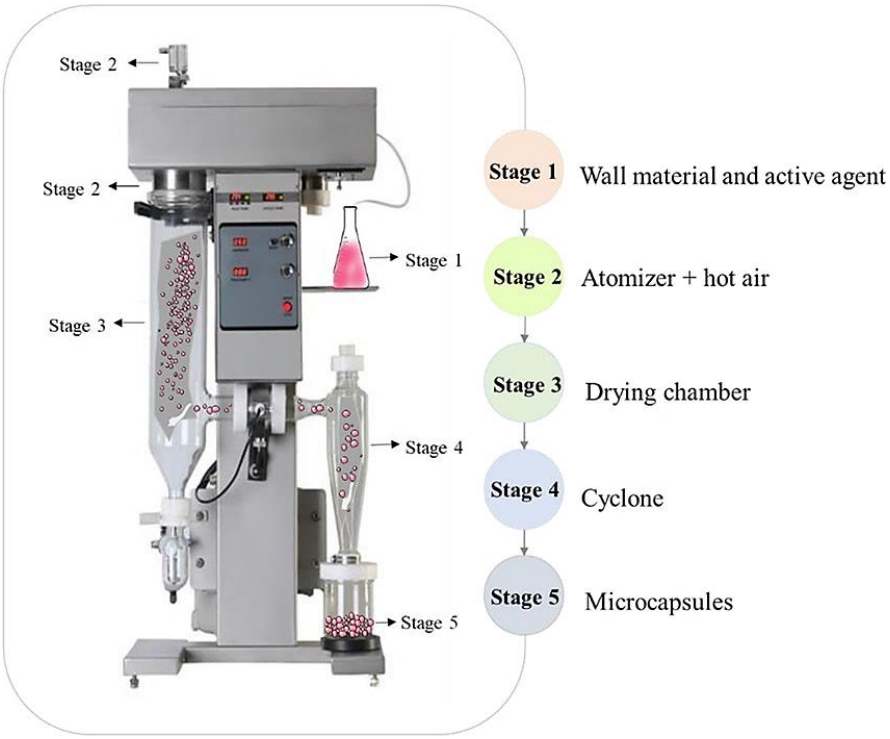


Figure 10. Spray drying.

Solvent Evaporation

Solvent evaporation is a technique used in the production of co-processed excipients, where a solvent is removed to create solid particles. In this process, a solution containing one or more excipients is prepared, and the solvent is subsequently evaporated, resulting in the formation of solid particles with desired properties. This method enhances the flowability, compressibility, and uniformity of excipients, which are crucial for direct compression tablet formulations. This process occurs in a liquid manufacturing medium [12].

In this method, coating excipient is solubilized in a volatile solvent which is immiscible with the liquid vehicle used in manufacturing. The core excipient is then dissolved or dispersed in the coating solution, and agitation is applied to achieve the desired encapsulation size. Heat is applied to evaporate the solvent, completing the process (Figure 11).

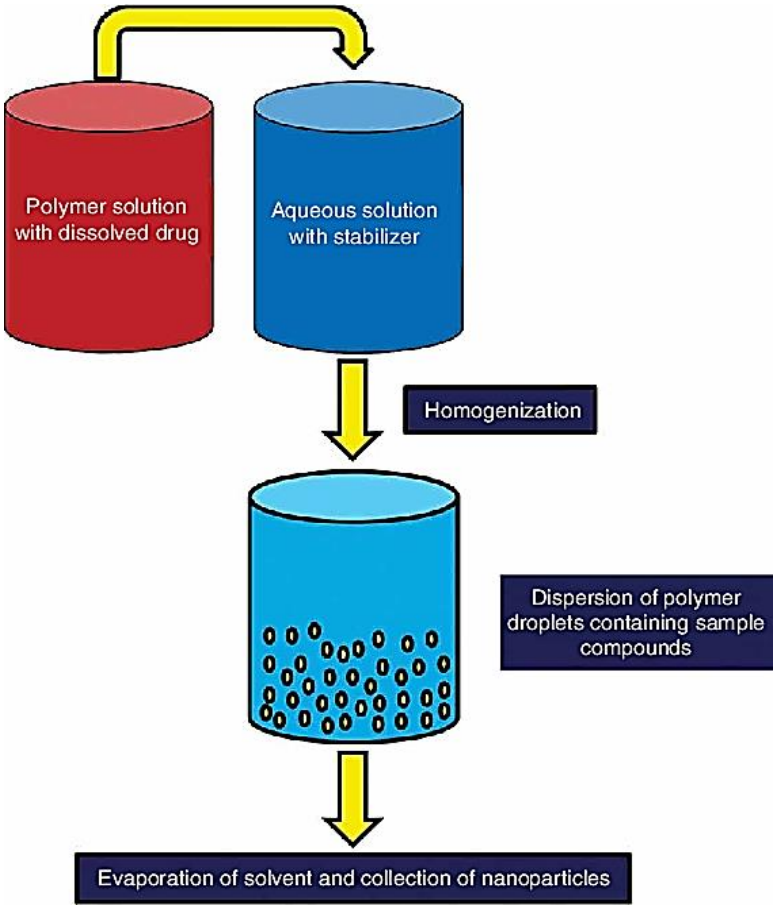


Figure 11. Solvent evaporation.

Freeze Thawing

This particle design process combines crystallization and agglomeration in a single phase, allowing for more efficient excipient modification. By doing so, it enhances properties like flowability and compatibility with active pharmaceutical ingredients (APIs). The process provides better control over particle size and surface characteristics, improving tablet uniformity, dissolution rates, and compressibility. This approach simplifies production while optimizing excipient performance in the final formulation (Figure 12) [1].

Fluid Bed Spray Granulation (FBSG)

This process includes spraying on fluidized bed of excipient with the solution of another excipient, followed by drying to form solid particles for co-processing. The granules can be screened if needed to

achieve the desired particle size. This technique creates co-processed excipients with enhanced properties, making it an effective approach to improve the functionality of excipients in pharmaceutical formulations [13].

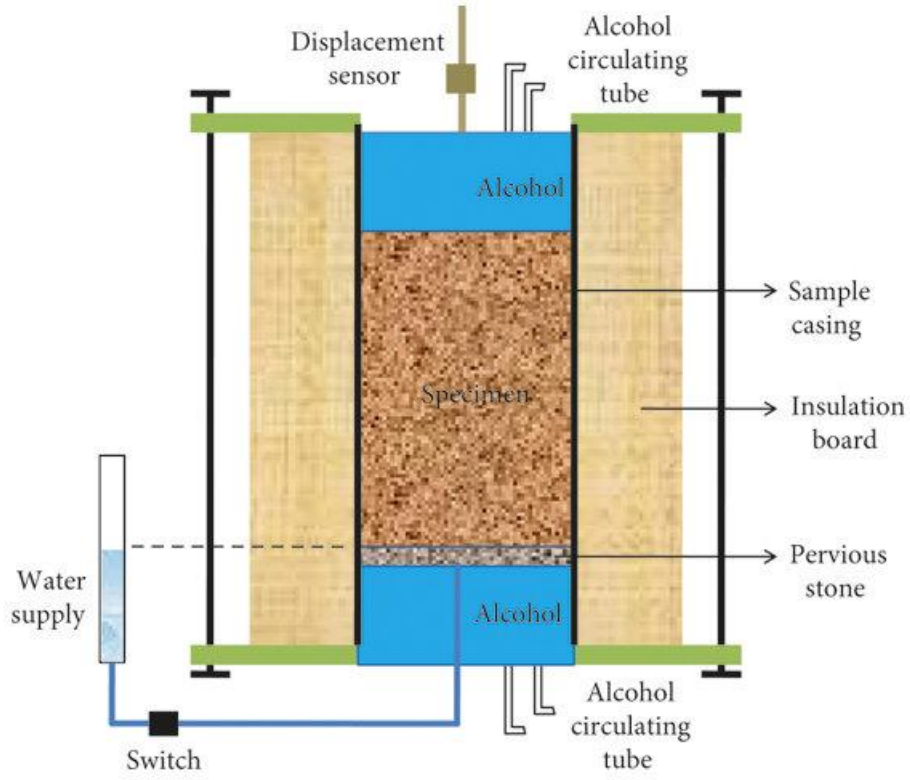


Figure 12. Freeze thawing.

Advantages, Limitations and Evaluation Parameters

Co-processed excipients offer significant advantages, such as enhanced flowability, compressibility, and improved physicochemical properties, making them ideal for direct compression and simplifying dosage form development (Table 3).

Commercial Examples

Pearlitol

- *Components:* Mannitol and Hydroxypropyl Methylcellulose (HPMC).
- *Manufacturer:* Roquette.
- *Benefits:* This blend is particularly suited for direct compression applications in controlled-release oral tablet formulations. Mannitol contributes to tablet integrity and palatability, while HPMC functions as a binder and release-controlling agent.

Dicom Sanaq SP206

- *Components:* Microcrystalline Cellulose and Colloidal Silicon Dioxide.
- *Manufacturer:* Pharma Trans Sanaq.
- *Benefits:* Microcrystalline cellulose offers strong binding and compressibility, while colloidal silicon dioxide enhances powder flowability and prevents clumping. The result is a formulation base that ensures consistent tablet formation, even under challenging humidity conditions.

Dicom Sanaq ML 011

- *Components:* Lactose Monohydrate and Microcrystalline Cellulose.

- *Manufacturer:* Pharma Trans Sanaq.
- *Benefits:* This combination excipient enhances both the physical stability and manufacturing performance of solid dosage forms. Lactose monohydrate contributes to fast disintegration and solubility, while microcrystalline cellulose offers excellent compressibility and dilution capacity, allowing for flexible API loading. The synergy between the two ensures reliable tablet formation with rapid breakdown in the digestive tract.

Table 3. Advantages, limitations and evaluation parameters of CPE.

Advantages	**Limitations**	**Evaluation Parameters**
Help in achieving single excipient with multi functionality.	Advanced equipment is required	Bulk density
Superior flow characteristics are ensured by controlled optimum particle size and particle size dispersion	Expensive process	Tapped density
Enhance the flow properties	Labor and energy are required	True density
Enhance compressibility	Material loss during process	Hausner ratio
Minimize weight variation.	Thermolabile and moisture sensitive materials cannot be used	Carr's index
Enhanced dilution potential.	Time consuming	Angle of repose
Reduced sensitivity to lubricants	The co-processed mixture has a fixed ratio of excipients.	Porosity
It may also shorten the period for tablet disintegration and increase tablet toughness	-	Particle size analysis
Undesirable properties removed while desirable properties can be incorporated	-	Percentage fines
Improved physicochemical properties	-	Morphology study
All co-processed and modified excipients have a noteworthy effect on the creation of simple dosage forms	-	Equilibrium moisture sorption (EMS)
Direct compression is the major application for co-processed excipients because this process results in an improvement in flow characteristics and compressibility	-	Loss on drying (LOD)
	-	Compatibility of co-processed excipients
	-	Heckle's plot

Parteck ODT

- *Components:* D-Mannitol and Croscarmellose Sodium.
- *Manufacturer:* Merck KGaA.
- *Benefits:* Specifically developed for orally disintegrating tablets (ODTs), Parteck ODT leverages the sweet-tasting, D-Mannitol for palatability and the superdisintegrant croscarmellose sodium for rapid tablet breakdown in the mouth. This combination ensures fast disintegration without water, along with pleasant taste and durable tablet strength, making it ideal for pediatric, geriatric, or convenience-focused drug delivery.

Retalac

- *Components:* Hypromellose (HPMC) and Lactose.
- *Manufacturer:* Meggle.
- *Benefits:* Retalac is engineered to improve powder flow properties and compressibility, essential for efficient direct compression processes. Hypromellose enhances binder strength and tablet consistency, while lactose contributes to a smoother compression process and acceptable disintegration behavior. The blend is particularly useful when formulating consistent, high-quality tablets across different production scales.

Ludipress

- *Components:* Lactose, Kollidon 30 (Povidone), and Kollidon CL (Crospovidone).
- *Manufacturer:* BASF AG, Ludwigshafen.
- *Benefits:* Ludipress is a multifunctional excipient system designed to provide excellent flowability, low moisture absorption (low hygroscopicity), and uniform tablet hardness, even when machine speed varies. Lactose provides compressibility and solubility; Kollidon 30 acts as a binder, and Kollidon CL serves as a superdisintegrant, supporting quick tablet breakup upon administration. This makes Ludipress an efficient, all-in-one solution for high-speed tablet production.

Cellactose

- *Components:* Lactose and Cellulose.
- *Manufacturer:* Meggle.
- *Benefits:* This combination results in a material that is highly compressible, making it ideal for direct compression processes. It also improves the organoleptic properties of tablets by providing a pleasant mouthfeel and supports cost-effective manufacturing due to its versatility and reliability in tableting performance.

DiPac

- *Components:* Sucrose and Dextrin.
- *Benefits:* DiPac is a co-crystallized mixture of sucrose and dextrin, engineered for direct compression tablet manufacturing. The sucrose provides excellent sweetness and binding properties, while the dextrin improves flow and compressibility. This formulation is often used in chewable and lozenge tablets, offering good taste and mechanical strength without requiring granulation steps.

Prosolv

- *Components:* Microcrystalline Cellulose (MCC) and Silicon Dioxide.
- *Manufacturer:* Penwest Pharmaceutical Company.
- *Benefits:* It demonstrates lower sensitivity to moisture during wet granulation, while still achieving excellent tablet hardness and reduced friability. This makes it a robust choice for formulations requiring high mechanical strength and stable processing.

Avicel EC-15

- *Components:* MCC and Guar Gum.
- *Manufacturer:* FMC Corporation.
- *Benefits:* The combination of MCC for structure and compressibility, with guar gum for its smooth texture, results in tablets that exhibit minimal chalkiness, less grit, and reduced tooth-packing. This makes it particularly suitable for chewable or orally disintegrating tablets (ODTs) that prioritize mouthfeel.

ForMaxx

- *Components:* Calcium Carbonate and Sorbitol.
- *Manufacturer:* Merck.
- *Benefits:* This blend features a controlled particle size distribution, contributing to uniform blending, enhanced compressibility, and better flow properties, making it well-suited for nutraceutical and chewable formulations.

Microcelac

- *Components:* Microcrystalline Cellulose and Lactose.
- *Manufacturer:* Meggle.
- *Benefits:* Microcelac is optimized for the direct compression of formulations with poor flowability. The microcrystalline cellulose provides binding and structural integrity, while the lactose supports rapid disintegration and good tablet hardness. It is especially valuable in high-dose formulations where space is limited, helping to form small, high-potency tablets efficiently.

Pharmatose DCL 50

- *Components:* β-Lactose and Lactitol.
- *Manufacturer:* DMV Veghel.
- *Benefits:* It offers superior compressibility, ensuring solid tablets even with low compression forces. Notably, it exhibits minimal sensitivity to lubrication, allowing for consistent tablet hardness and reducing processing variability in tablet manufacturing.

StarLac

- *Components:* Lactose and Corn Starch.
- *Manufacturer:* Roquette.
- *Benefits:* This co-processed excipient supports excellent flow behavior, making it easier to handle automated tablet production and ensuring uniform filling and consistent tablet weight. It's especially useful in direct compression formulations that require efficient processing and fast tablet disintegration.

CONCLUSIONS

Source for New Era

Excipient co-processing as an origin of novel excipients. Excipient co-processing as a means of developing new excipients involves merging two or more established excipients via a specialized method to create excipients with improved properties, surpassing those of basic physical mixtures. This approach allows for the introduction of new recruits to the market, excluding the obligation of extensive safety testing required for entirely novel chemicals. The primary objective of co-processing is to develop a product that offers better value by improving the functionality-to-cost ratio. The process of creating a co-processed, directly compressible adjuvant starts with selecting the appropriate excipients to combine and determining their desired proportions. The next step is choosing the right preparation method to achieve a product with optimized physicochemical properties. Finally, the process ensures that the co-processed excipient minimizes any negative interactions or incompatibility with other excipients in the formulation.

Regulatory Perspective

Co-processed excipients can be classified as Generally Recognized as Safe (GRAS) when the original excipients are GRAS-approved via regulatory authorities and demonstrate notable improvements in tablet compaction contrast to physical mixtures. Consequently, these excipients do not need further toxicological testing. One of the main obstacles to the commercial viability of excipient blends or co-processed excipients is their lack of inclusion in official monographs. The National Formulary has recognized the topic of excipient combinations and prioritized it based on their use in commercial dosage forms where the added processing benefits are evident [2].

The 2013 IPEC-Americas Co-processed Excipients Workshop highlighted the importance of developing an IPEC-Americas Co-processed Excipient Guide. This guide provides recommendations on addressing technical, safety, and legal concerns related to the development and commercialization of co-processed excipients. Manufacturers of new co-processed excipients are strongly encouraged to submit a Type 4 DMF for the US market, which will facilitate regulatory submissions until a USP-NF monograph is available. If required and available, a safety data package should be submitted as a Type 5 DMF. The DMF submissions will require letters of access [14].

Conflict of Interest

The authors declare that there are no conflicts of interest.

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