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Review Article

Co-Processed Excipients: A Review

Prajwal K.*[1], Parthasarathi K. Kulkarni[2], Nagendra R.[3], Venkatesh K. [4], Hanumanthachar Joshi[5]

[1,2,3,4] *Department of Pharmaceutics, Sarada Vilas College of Pharmacy Mysuru, Karnataka, India*
[5]*Department of Pharmacognosy, Sarada Vilas College of Pharmacy Mysuru, Karnataka, India*

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ABSTRACT

Excipients have a clearly defined functional purpose and are no longer regarded as inert constituents in formulations. The need for high-speed manufacturing and direct compression in tableting has compelled the excipient industry to look for new excipients. Excipients are crucial for creating a dosage form. A co-processed excipient is a mixture of two or more compendial and non-compendial excipients that have been specially formulated to alter its physical characteristics in a way that cannot be accomplished by merely mixing them physically and without causing a substantial chemical shift. These excipients' have better flow ability, compressibility, tablet manufacturing. These are prepared by spray drying, solvent evaporation, spherization, melt extrusion, and granulation/agglomeration method. Products like Dipac, Ludi flash, Prosolv, and others have already shown their value in the market by lowering the price and quantity of ingredients while keeping the efficacy of the formulation. Such excipients face some limitations due to their quality assessment and reproducibility of results. This review includes a explanation on the benefits, preparation techniques, use of high-end technologies, and a compilation of research on co-processed excipients in the literature.

INTRODUCTION

A pharmaceutical excipient is defined as "a substance or a combination of substances that can form a certain volume of an agglomerating mixture, acts as a carrier, and contains active pharmaceutical ingredients (APIs)." Binders, fillers, super-disintegrants, lubricants, and glidants are a few examples of excipients. An ideal excipient is an excipient that ensures the volume, uniformity, and dose of the API in the dosage form from the manufacturing process until it is administered to the patient.[1]. According to International Pharmaceutical Excipient Council (IPEC), the co-processed excipient is "a combination of two or more compendial or non-compendial excipients designed to physically

***Corresponding Author:** Prajwal K.
Address: *Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysore*.
Email : prajwalkgowda00@gmail.com
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modify their properties in a manner not achievable by simple physical mixing and without significant chemical change". The creation of novel and inventive excipients is a burgeoning field. Excipient innovations include controlled-release formulations and excipients for tablets that dissolve orally. To speed up or raise the quantity at which medications containing novel excipients are absorbed, various technologies are being investigated. The use of nanotechnology in the development of innovative excipients for new medicinal solutions may be investigated in the future. The use of co-processing excipients (CPE) in the formulation of solid dosage forms-particularly ODTs made using the direct compression (DC) technique grown significantly. Additionally, the use of fewer excipients during formulation is made possible by these multifunctional adjuvants, which can significantly shorten the manufacturing process and processing time [2]. The development of new excipients to date has been market-driven (i.e., excipients are developed in response to market demand) rather than marketing-driven (i.e., excipients are developed first and market demand is created through marketing strategies) and has not seen much activity as shown by the fact that, for the past many years, not a single new chemical excipient has been introduced into the market. The primary reason for this lack of new chemical excipients is the relatively high cost involved in excipients discovery and development. However, with the increasing number of new drug moieties with varying physicochemical and stability properties, there is growing pressure on formulators to search for new excipients to achieve the desired set of functionalities.

Other factors driving the search for new excipients are:

- The growing popularity of the direct-compression process and a demand for an ideal filler–binder that can substitute two or more excipients.
- Tableting machinery's increasing speed capabilities, which require excipients to maintain good compressibility and low weight variation even at short dwell times.
- Shortcomings of existing excipients such as loss of compaction of microcrystalline cellulose (MCC) upon wet granulation, high moisture sensitivity, and poor die filling due to agglomeration.
- The absence of excipients designed to meet the requirements of particular patients, such as those with lactose and sorbitol sensitivity, diabetes, or hypertension.
- The capacity to alter a drug's permeability, stability, or solubility.[3]

BENEFITS OF CO-PROCESSED EXCIPIENTS

- One excipient can fulfil multiple functions.
- Surmount the limitations of the excipient.
- Better organoleptic properties.
- Exhibits positive communication.
- Enhanced physiochemical properties.
- Reduces alterations to the dissolution profile.
- Improves palatability and increases tongue feel.
- Reduce unfavourable characteristics.[4]

TYPES OF EXCIPIENTS

There are classified into 4 types

1. Single entity excipient.
2. Mixtures or blends of multiple excipients.
3. Novel excipient or new chemical entities.
4. Co-processed excipient.[5]

1. Single entity excipient

Single entity excipients can be defined as excipients containing one component which is the primary component called as excipient. It may contain other components like

i. Concomitant components.
ii. Residual processing aids.

iii. Additives.[5]

2. Mixtures or blends of multiple excipients

Simple physical mixtures or blends made with two compendial or non-compendial excipients using low- to medium-shear processes, in which the constituent parts are combined without undergoing a substantial chemical change. The individual excipients in solid mixtures or blends continue to exist as distinct particles at the particulate level (referred to as "unengineered particles"). Excipients in a mixture can be liquid or solid. Usually, simple physical mixing is done quickly.[5]

3. Novel excipient or new chemical entities.

It can be defined as excipients that undergo chemical modification to create new or novel excipients. These are typically not included in the FDA Inactive Ingredient Database (IID). An excipient is "likely deemed to be safe for use in other products that involve use under similar circumstances, but the agency may ask that the database be brought up to current standards about even that "similar" use" according to the IID, which is not an approval.[9]

4. Co-processed excipient

Combining two or more compendial or non-compendial excipients to physically alter their properties without significantly changing their chemical makeup is known as co-processing. On the other hand, in certain cases, like in-situ salt formation, the necessary components may form. A wide range of co-processing techniques are available, including common unit operations like granulation, spray drying, melt extrusion, milling, and so forth.[1]

NEED OF CO-PROCESS EXCIPIENTS

- The growing acceptance of the direct compression method, which is necessary to create the perfect filler-binder that can replace two or more excipients.
- The ability to adjust permeability, stability, or solubility.
- To solve the disintegration potential, compressibility, and flowability issues.
- Effective use of currently available excipients: the search for the perfect filler binder that can replace two or more excipients is becoming more and more popular.
- Compared to a completely new development, the process of appreciating new applications for economical excipients is less expensive and time-consuming.
- The quantity of real excipients with certain desirable qualities that fit a particular formulation.
- The compatibility of newly developed drugs with currently used excipients.
- Therefore, co-process excipients will be suitable to solve these issues. The advancement and refinement of pharmaceutical formulation techniques and equipment, in particular, improves production rates at a reasonable cost. [6]

CO-PROCESSING OF EXCIPIENTS

The actual process of developing a co-processed excipient involves the following steps:

1. Selecting the excipient group to be co-processed by closely examining the functionality requirements and material characteristics
2. Selecting different excipient proportions
3. Determining the size of particles needed for coprocessing. This is particularly crucial if one of the constituents is being processed during a dispersed phase. The latter's post-processing particle size is contingent upon its initial particle size.
4. Choosing an appropriate drying method, such as spray or flash drying, and optimizing the procedure (because even this can lead to variations in functionality).
5. The coprocessing method is schematically represented in Figure 1.[7]

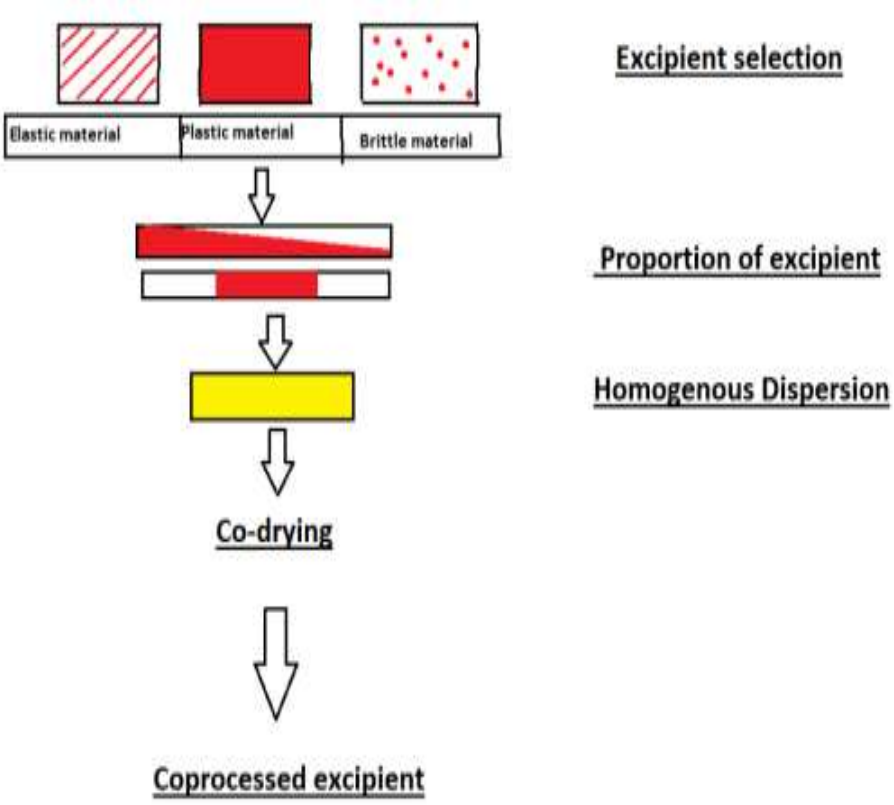

Figure1: Co-processing of excipients

METHODS TO PREPARE CO-PROCESSED EXCIPIENTS

a. Roller compaction
b. Spray drying
c. Solvent evaporation
d. Hot melt extrusion
e. Roller dryer
f. Wet granulation
g. Crystallization

A. Roller compaction:

This technique is applied to excipients that are sensitive to heat and moisture. The dry granulation principle is applied in this technique to facilitate the bonding of the particles. The homogeneous powder blend is taken and subsequently compressed between revolving rollers to produce a solid ribbon of compacted material, which is then milled into the proper granule particle sizes [8]. Using mannitol and chitin as raw materials, Daraghmeh N. Patel et al. (2015) investigated the development of a co-processed excipient called Cop-CM using the roller compaction method. ODTs, orally dispersive tablets, contain this Cop-CM. [9]

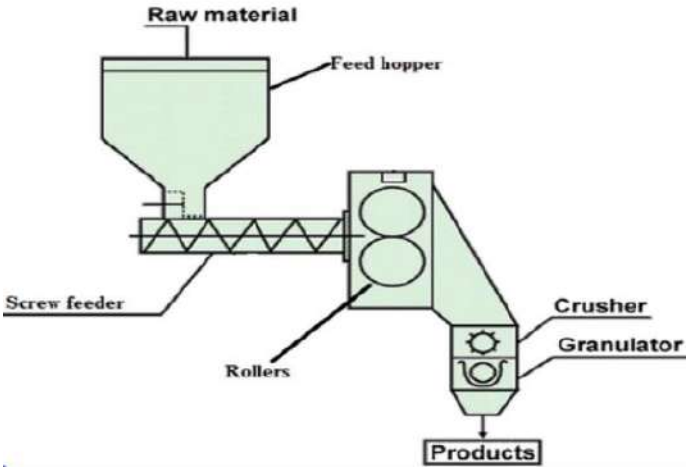

Figure 2: Roller compaction method

B. Spray drying

The process of spray drying enables the transformation of feed from a liquid into a dried particle. An emulsion, suspension, dispersion, or solution can be the feed. The final powder properties required by the dryer design and the physical and chemical properties of the feed determine whether the dried product forms granules, agglomerates, or powders. It is a drying process for particle processing that is ongoing. Particles with desired characteristics can be designed with the aid of spray drying process parameters such as inlet air temperature, atomization air pressure, feed rate, liquid viscosity, solid content in the feed, and disc speed. Thus, the four-step spray drying process may be desired.[6]

- Liquid atomization into droplets.
- Make contact between the droplet and the heated drying gas.
- The droplets evaporate quickly to produce dry particles.
- The cyclone is utilized to retrieve the dry particles from the drying gas.

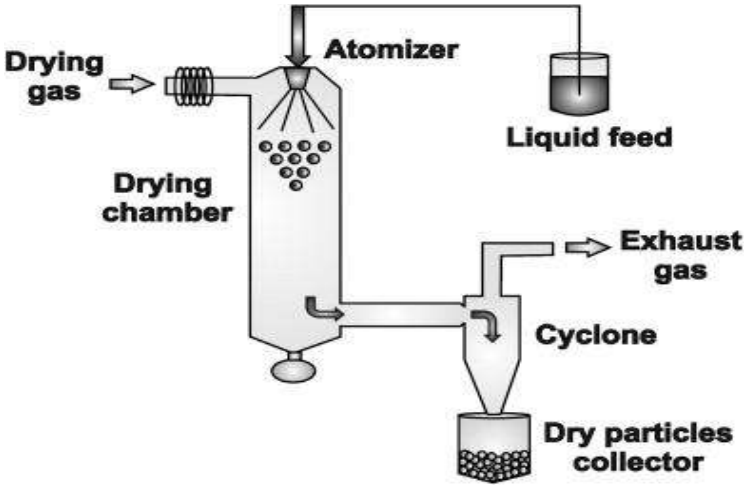

Figure3: Spray drying

Advantages of spray drying

- Non-miscible products can be operated with one another continuously.
- It permits drying and blending of both soluble and insoluble compounds at the same time.

- Secure and shield delicate active ingredients on organic carrier.
- Increases compressibility and hardness.

C. Solvent evaporation:

Solvent evaporation took place in a liquid manufacturing vehicle. The core excipient is dissolved or dispersed in the coating solution after the coating excipient has been dissolved in a volatile solvent that is immiscible with the liquid production carrier. Agitation force is used to obtain the proper encapsulation size. Heat is used to evaporate the solvent.[10]

D. Hot melt extrusion:

Small beads or pellets are created during the hot melt extrusion process when the molten mass is forced through an extruder. Melt extrusion is limited for thermolabile materials because it requires temperatures higher than 80 °C. After melting, the excipients are forced through a die and solidified. Although a little more complicated, this method has the advantages of being less time-consuming, reproducible, solvent-free, and able to form thermal binders with molten polymers.[11]

E. Roller dryer

The homogenous solution or dispersion containing the pre-blended excipients is dried using a roller dryer. This method was used by Meggelaars et al. (1996) to co-process lactose with sorbitol and lactitol. The temperature that was utilized was high enough to produce a product that mostly consists of crystalline β-lactose.[12]

F. Wet granulation method

The wet granulation method is a conventional and simple type of method used for co-processed excipient manufacturing. This process is based on high-shear mixers or fluid-bed granulators. In a fluid-bed granulator, the powder material is introduced to fluidization by providing an upward flow of air from the granulator's bottom screen and then binding solution sprayed in the opposite direction to the powder bed. The liquid droplets and solid particles are mixed, results in adhesion, and further granule formation takes place.[8]

G. Crystallization

The process of solid crystals forming (naturally or artificially) through precipitation from a solution, melting, or, less frequently, direct deposition from a gas is known as crystallization. Another chemical method for separating solids from liquids is crystallization, which involves the mass transfer of a solute from a liquid solution to a pure solid crystalline phase. Method: Any solution that wants to crystallize needs to be supersaturated. This implies that the solution must have a higher concentration of dissolved solute entities (molecules or ions) than it would have at equilibrium (a saturated solution). This can be accomplished in several ways, including (1) cooling the solution, (2) adding a second solvent to lessen the solute's solubility (a process called antisolvent or drown-out), (3) chemical reaction, and (4) The most popular techniques utilized in industrial practice are those that alter pH.[5]

PROPERTIES OF CO-PROCESSED EXCIPIENT

1. No significant chemical change:

Many studies have been conducted to study the chemical change. No discernible chemical change in the co-processed excipients was found in these investigations. Using nuclear magnetic resonance (C13), infrared spectroscopy, XRD, and Raman spectroscopy, a study of silicified microcrystalline cellulose found no appreciable chemical changes.[13]

2. Physio-mechanical properties

- **Improved Flowability:**

When comparing co-processed excipients to simple excipients, a volumetric study of silicified microcrystalline cellulose with similar particle sizes as the parent excipient showed that the flow of SMCC was better than that of MCC.

- **Improved Compressibility:**

Co-processed excipient compressibility is seen to be improved primarily in tablet manufacturing via direct compression. If we examine the pressure-hardness relationship plot of co-processed excipients and a simple physical mixture of excipients, the compressibility profile of co-processed excipients appears to be improved, for example, the compressibility profile performance of Cellactose16, SMCC17, and Ludipress19 showed a better result than of simple physical mixtures of excipients.

- **Improved dilution performance:**

The ability of an excipient to maintain compressibility after being diluted with another material is known as its dilution capacity. Most active ingredients found in pharmaceuticals have low compressibility. When it came to dilution performance, cellactose outperformed simple physically mixed excipients.[8]

Table 1. Overview Of Marketed Co-Processed Excipients

Trade name	Excipients	Manufacturers	Advantages	Reference
Ludiflash	Mannitol, crospovidone and polyvinyl acetate	BASF	Suitable for high-speed tableting, low friability, and good flowability	8
Prosolv	MCC, colloidal Silica	Penwest, USA	better flow, hardness, reduced friability	3
Dipac	Sucrose and dextrin	Penwest Pharmaceuticals Co. USA	Directly compressible grade	14
Microcell	Microcrystalline cellulose and lactose	Meggle, GmbH Germany	High doses can be formulated.	15
Starlac	Lactose, maize starch	Roquette, France	Good flow	7
Formaxx	Calcium carbonate, sorbitol	Merck	Controlled particle size distribution	2
Avicel CE 15	Microcrystalline cellulose, guar gum	FMC USA	Less gritiness, reduced tooth packing, minimal chalkiness, creamier mouth feed, improved overall palatability.	6
Copovidone	Kollidon VA 64 and plasdone S630	Ashland	Excellent flow properties and dry binder	16
Cellactose	Lactose,25% cellulose	Megglegmbh & co. Kg, Germany	Highly compressible, good mouthfeel, better tableting at low cost	2
Vitacel VE-650	Microcrystalline cellulose and calcium carbonate	FMC Biopolymer	Suitable for direct compression and encapsulation	17
Pearlitol SD	Granulated mannitol	Roguette	Suitable for chewable tablet application with good mouth feel and palatability	18
Finlac DC	Directly compressible lactito	Cultor Food Science	Good mouth feels2 and rapid disintegration properties. Used for nutraceuticals and chewable vitamin applications	19
Neusilin	Amorphous magnesium aluminometasilicate	Fuji Chemicals	Superior flow property, anti-caking, good Compressibility, and can be used for solid dispersion	20

LIMITATIONS CO-PROCESSED EXCIPIENTS

1. **Fixed proportion**

One of the main drawbacks of co-processed excipient mixtures is that their excipient ratios are fixed. This means that when creating a new formulation, a fixed excipient ratio might not be the best option for the API and the dosage per tablet.[21]

2. **Expensive**

Specialized products such as spray drying, fluid bed drying, roller drying, and other patented processes are produced to create directly compressible co-processed excipients. As a result, these goods are more expensive than the corresponding raw materials used to make them.[22]

3. **Rework ability issues with co-processed spray-dried excipients**

Reworking the excipient results in the loss of its intrinsic property—the spherical nature of the particles—as well as an increase in the disintegration and dissolution profiles.[23]

4. **Potential dilution of up to 40%**

Up to 40% of the poorly compressible active ingredients, such as acetaminophen, can be accommodated by the majority of directly compressible co-processed excipients. This means that the final tablet containing 500 mg of medication would weigh more than 1.3 grams, making it large and potentially difficult to swallow.[24]

5. **Pharmacopeial acceptance is lacking**

Pharmacopoeia does not officially accept co-processed adjuvants. Because of this, the pharmaceutical industry won't accept a combination filler binder until it shows appreciable improvements in tablet compaction over the physical mixtures of the excipients.,[25]

CONCLUSION

The current review article's primary goal is to give a thorough overview of recent advancements in excipient technology and the methods used in their development. Formulation scientists have turned their attention to the creation of multifunctional excipients with enhanced performance to meet the demands of formulation experts in terms of production costs, enhanced excipient functionality, and tablet quality. They have realized that single component excipients sometimes do not always provide the necessary performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. The drawbacks of using general-grade excipients are mitigated by co-processed excipients. The co-processed excipients are enhanced with new qualities while retaining their positive qualities.

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