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A review on co-processed excipients used in direct compression of tablet dosage form

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Abstract

Co-processed excipients may enhance functionality and reduce drawbacks of traditional excipients for the manufacture of tablets on a commercial scale. The following study aimed to characterize a range of co-processed excipients that may prove suitable for dispersible tablet formulations prepared by direct compression. The dosage form that is used the most is tablets. Their accessibility, simplicity of administration, consistency, and affordability are advantages. Direct compression is the most straightforward method for making tablets, despite the fact that it comes with several challenges, including those connected to the homogeneity and mass variation of the content, disintegration, dissolution, and the radial hardness of the tablets. In today's world, "co-processed excipients," which include frequently processed mixtures of fillers, binders, disintegrants, lubricants, and other excipients, are becoming more popular. Spray drying, fluid bed granulation, wet granulation, melt granulation, dry granulation, and co-crystallization are used to create these mixes. This review article lists technologies, co-processed excipients that are commercially available, and excipients that are typically utilized to make them.

Keywords: Co-processed excipients; Direct compression; Blends; Tablets; Physical characteristics

1. Introduction

The pharmaceutical industry first started to use co-processed excipients from the late 1980s, with early examples including co-processed microcrystalline cellulose and calcium carbonate, introduced in 1988, MEGGLE's co-processed cellulose and lactose (1990), and co-processed glucomannan and galactomannan (1996). The International Pharmaceutical Excipients Council (IPEC) defines excipient as "substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system". An excipient that has undergone co-processing is a combination of two or more compendial or non-compendial excipients with the goal of physically changing their properties without altering chemical properties.[1]

1.1. Advantages of co-processed excipients

- One excipient can serve many purposes.
- Overcome the excipients limitations.
- Improved organoleptic qualities.
- Displays constructive interaction.
- Improved physiochemical characteristics.
- Minimises modifications to the profile of dissolution.
- Enhanced palatability and increased tongue feel.
- Reduce unfavourable characteristics.
- Enhance the flow qualities.

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- Increasing compressibility.
- Increased potential for dilution.
- Lessen sensitivity of the lubricant.

1.2. Disadvantages of co-processed excipients

- Elevated temperature enprocessing and specialised filling equipment are needed.
- Pre-clinical species do not always tolerate some lipidic excipients well.
- Cost of process is high due to labour costs, space costs, time, energy, and specialised equipment needs.
- Material loss throughout different processing phases.
- Drugs that are thermolabile or moisture sensitive are not good candidates.
- Long duration.

2. Principle of co-processing

2.1. Particle Engineering

Solid substances are characterized by three levels of solid-state: the molecular, particle, and bulk level. These levels are closely linked to one another, in which changes in one level reflect another. The molecular level includes arrangement of molecules in the crystal lattice and includes polymorphism, pseudo-polymorphism, and amorphous state. The particle level includes particle properties such as shape, size, surface area, and porosity. The bulk level includes ensemble of particles and properties such as flowability, compressibility, and dilution potential. The scientific framework for the development of new grades of current excipients and novel combinations of existing excipients is provided by the interdependence among the levels.[1]

2.2. Steps involved in co-processing of excipients

- Selection of the excipients group to be co processed by carefully studying the material (elastic, plastic or brittle) characteristics and functionality requirements.
- Choose required proportions of excipients.
- Examine the particle size required for co processing.
- Choose a suitable drying method, such as spray drying or flash drying.

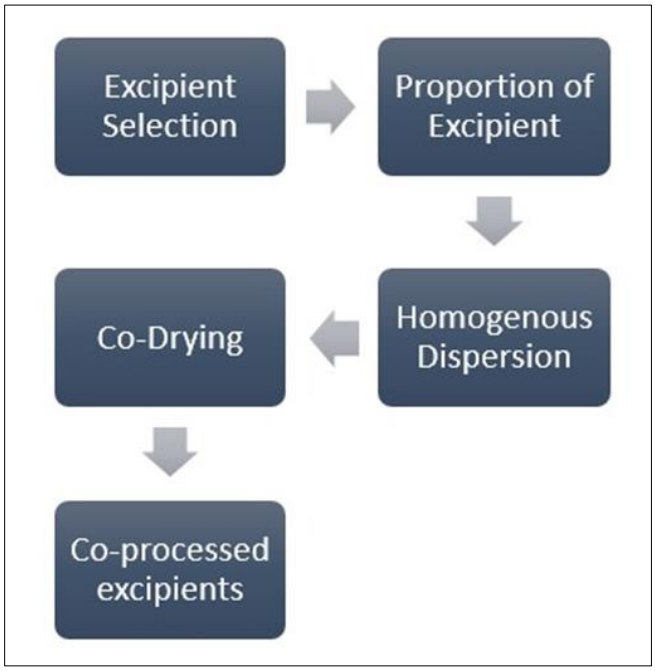

Figure 1 Steps involved in co-processing of excipients

3. Methods of co-processing

- Spray drying
- Wet granulation
- Melt extrusion
- Granulation
- Solvent evaporation
- crystallisation
- Roller drying
- Hot melt extrusion
- Co-transformation
- Milling

3.1. Spray drying

This spray drying technique allows the conversion of feed from a fluid state into dried particle. The feed can be a solution, suspension, dispersion, or emulsion. The dried product can be formed in the powders, granules, or agglomerates and these are depending upon the physical and chemical properties of feed and the dryer design final powder properties needed. It is a continuous particle processing drying operation. The spray drying process parameters like inlet air temperature, atomization air pressure, feed rate, liquid viscosity, solid content in feed, disc speed can be helped in design particle with desire characteristics. hence spray drying process can be desire as consisting of four steps:

- Atomization of the liquid into droplets.
- Contact of the droplet with the warm drying gas.
- Fast evaporation of the droplets to form dry particles.
- Recovery of the dry particles from the drying gas, using a cyclone.[3]

3.1.1. Advantages of spray drying

- It is possibile to associate non-miscible products in continuous operation.
- It allows blending and drying simultaneously for soluble and insoluble compound.
- Fix and protect sensitive active compound on natural carrier.
- Improves hardness and compressibility.
- Decreases disintegration time and enhances machine tableting speed. [3]

3.2. Wet granulation

Wet granulation is a conventional and simple method for co-processed adjuvant production. Fluid bed granulators and high shear mixers are two commonly used equipment used for the same. In fluid bed granulation, the powder mix is subjected to fluidization by a flow of air injected upwards through the bottom screen of the granulator. The binding solution is sprayed in the opposite direction to the air flow on the powder bed. The solid particles are mixed with the liquid droplets and hit the bed which results in adhesion and eventually the formation of granules. Partial drying by the fluidizing air occurs continuously during granulation. In high-shear granulation, an impeller keeps the powder in agitation in a closed vessel. The binder solution is sprayed from the top. Development of large agglomerates is prevented by high shear force. With the new single-pot technology, drying occurs in the same system. The granules formed are understandably denser than those obtained in fluid bed granulation.[2,6]

3.3. Melt extrusion

Melt extrusion is a process of formation of small beads, pellets from the molten mass which extruded through extruder. Extruders consist of four distinct parts:

- An opening though which material enters the barrel that may have a hopper that is filled with the materials to be extruded.
- A conveying section (process section), which forms the barrel and the screws that transport, and where applicable, mix the material.
- An orifice (die) for shaping the material as it leaves the extruder.
- Downstream auxiliary equipment for cooling, cutting and/or collecting the finished product. [1,3]

3.4. Granulation

Granulation is the act or process of forming or crystallizing into grains. Granules typically have a size range between 0.2 to 4.0 mm depending on their use. In pharmaceutical industry, two types of granulation technologies are employed, namely, Wet Granulation and Dry Granulation. Wet granulation is the most preferred method for coprocessing.[1]

3.5. Solvent evaporation

This process is carried out in a liquid manufacturing vehicle. The coating excipient is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core excipient material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the proper size microcapsule. The mixture is then heated (if necessary) to evaporate the solvent. Once all the solvent is evaporated, the liquid vehicle temperature is reduced to ambient temperature (if needed) with continued agitation. At this stage, the microcapsules can be used in suspension form, coated on to substrates or isolated as powders. The core materials may be either water -soluble or water - insoluble materials.[1]

3.6. Crystallization

Crystallization is the natural or artificial process of formation of solid crystals precipitating from a solution, melted or more rarely deposited directly from a gas. Crystallization is also a chemical solid– liquid separation technique, in which mass transfer of a solute from the liquid solution to a pure solid crystalline phase occurs. Procedure: For crystallization to occur from a solution it must be supersaturated. This means that the solution must hold more solute entities dissolved than it would have under the equilibrium. This can be achieved by various methods, with

- Solution cooling,
- Addition of a second solvent to reduce the solubility of the solute (technique known as antisolvent or drown-out),
- Chemical reaction
- Change in pH being the most common methods used in industrial practice [1]

3.7. Roller drying

A roller dryer is used to dry the homogeneous solution or dispersion containing the pre-blended excipients. Meggelaars et al. (1996) applied this technique to co-process lactose with sorbitol and lactitol. The temperature used was sufficiently high to obtain a product that consists principally of β-lactose in crystalline form.[2]

3.8. Hot melt extrusion

Hot melt extrusion uses heat with a temperature greater than 80 °C. This method is not suitable for thermos labile materials. The excipients are melted and then pressurized through the die and solidify into a variety of shapes. The solvent is not needed in the process as the molten polymer can function as a thermal binder.[2,6]

3.9. Co-transformation

Co-transformation technique involves the application of heat or solvent effect to “open-up” that is for swelling the particle of one excipient. The other excipients are incorporated into the “opened-up” structure of the forementioned excipient. The augmented excipient strengthens the functionality of the end product.[2,6]

3.10. Milling

A roller mill, ball bill, bead mill, millstone mill, jet mill or a hammer mill can be used to perform milling or dry grinding. The excipients are premixed and passed through a high-speed milling machine. During the process of milling, the particles meet each other and form bonds when they are subjected to force to mill or pass through the screen. Rao et al. (2012) applied this technique to co-process cross-linked polyvinylpyrrolidone and calcium silicate.[2,6]

4. Co-processed excipients used in direct compression of tablet dosage forms

Direct compression (DC) is a commonly used method for the preparation of oral solid dosage forms such as tablets. Benefits include avoiding process steps such as wet or dry granulation, providing less variable dissolution profiles compared to granulation methods, reduced wear and tear of punches, improved stability of API and reduced microbial contamination. The challenge associated with the development of tablets using Direct Compression is often the sub-optimal compression and flow properties of the active pharmaceutical ingredient, especially if the drug loading in the formulation is very high. As such, the feasibility of the DC route is highly dependent on the physicochemical properties of the API which determine its flow and compression behavior the formulation, especially when these constitute a large proportion of the tablet. When the loading and properties of the API allow for DC, selection of excipients becomes a key consideration in the development of tablets by DC. To ensure formulation success, it is necessary to fully characterize and understand the flow and compression properties of the excipients.

At present, conventional grades of excipients do not always exhibit the necessary flowability, compressibility, high dilution potential and homogeneity to accommodate different APIs DC. The extensive development process for a new product typically involves multiple investigations using a range of excipient material grades and suppliers. One way to ease the development process could be to use co-processed excipients that are suitable for commercial scale manufacture. Co-processed excipients are the combination of two or more excipients, prepared by processes such as spray drying, wet granulation and co-crystallization.

Co-processing of excipients physically modifies the individual materials without altering their chemical structure. Co-processed excipients may be advantageous in a number of ways providing improved functionality in comparison to physical mixtures of individual excipient components combining a range of different materials such as plastic and brittle deforming materials, which prevents storage of excess elastic energy during compression, hence reducing the risk of capping and lamination during compression and accelerating the speed that new products can enter the market without the need for extensive and expensive testing. One drawback of co-processed excipients is that they are not always recognized by the different pharmacopoeias. An area where co-processed excipients may have a particular advantage is in the development and manufacture of dispersible tablets. Dispersible tablets are intended to be dispersed in a liquid (typically water) before administration giving a homogeneous dispersion.

Table 1 Commercially available Co-processed Excipients Used in Direct Compression

Co-processed excipients	Trade name	Manufacturer	Advantages
Mannitol, hydroxypropyl methylcellulose	Pearlitol	Roquette	Used in direct compression of controlled oral tablets, binder
Microcrystalline cellulose, colloidal silicon dioxide	Dicom sanaq® sp206	Pharma trans sanaq	Used in direct compression of hygroscopic and moisture sensitive apis and has excellent flow properties
Lactose monohydrate, cellulose micro crystalline	Dicom sanaq ml 011	Pharma trans sanaq	Enhance the stability and effectiveness during manufacturing product process and high compressibility, superior dilution properties and rapid disintegrating
Spray granulated d-mannitol and croscarmellose sodium	Parteck® odt	Merck kgaa	Directly compressible excipient designed for orally disintegrating tablets and provided rapid disintegration and exceptional strength as well as a pleasant taste and mouthfeel
Hypromellose and lactose	Retalac®	Meggle	Improved flow and bendability, enhancing compatibility in direct compression

70 % alpha-lactose monohydrate, 20 % microcrystalline cellulose (mcc) and 10 % white, native corn starch	Combilac®	Meggle	Improved compaction properties compared to an equivalent admixture of individual ingredients, providing robust tablets with minimal friability, and assuring rapid, hardness independent tablet disintegration for effective api release
Microcrystalline cellulose, colloidal silicon dioxide, mannitol, fructose, crospovidone	Prosolv® odt g2	Rs pharma	Smooth and creamy mouthfeel, Excellent flowability, excellent blending characteristics for improved content uniformity, High patient compliance
Crospovidone, dextrose monohydrate, mannitol, monohydrate lactose	Disintequik™ odt	Kerry	Direct tableting operations for use in orally disintegrating tablets. It can be blended with a flavor, active, suitable lubricant, additional sweetener if desired
Microcrystalline cellulose, monohydrate lactose	Disintequik mcc	Kerry	Direct tableting operations where hard tablets and fast disintegration are required.
Carmellose,crospovidone,mannitol, microcrystalline cellulose	Granfiller-d	Daicel group and nichirin-chem	Direct compression odts, high tablet hardness and rapid disintegration
Calcium carbonate & polyvinyl pyrrolidone	Dicom-dc® s-604	Gangwal healthcare private limited	Excellent flowability, better compressibility & uniform particle size distribution.
Sucrose 3%, dextrin microcrystalline Cellulose, silicon dioxide	Dipa prosolv	Penwest pharmaceuticals company	Directly compressible, better flow, reduced sensitivity to Wet granulation, better hardness of tablet, reduced friability
Lactose and cellulose	Cellactose	Meggle	High compressibility, good mouth feels, better tableting at low cost
Sucrose and dextrin	Dipac	Penwest pharm	Directly compressible grade
Microcrystalline cellulose and silicon dioxide	Prosolv	Penwest pharmaceuticals	Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability
Microcrystalline cellulose and guar gum	Avicel ce-15	Fmc corp.	Less grittiness and minimal chalkiness
Calcium carbonate and sorbitol	Formaxx	Merck	High compressibility, excellent taste masking, free flow, superior content uniformity, controlled particle size distribution
Microcrystalline cellulose and lactose	Microcelac	Meggle	Capable of formulating high dose, small tablets with Poorly flowable active ingredients
Lactose and maize starch	Starlac	Meggle	Good flowability due to spray drying, the acceptable crushing force due to lactose content and rapid disintegration

Lactose,3.2%kallidone kallidone cl	Ludipress	Basfag,ludwigshafen ,Germany	Low degree of hygroscopicity, good flowability, tablet hardness independent of machine speed
Lactose,25% cellulose	Cellactose	Meggleg mbh&co.Kg, Germany	Highly compressible, good Mouthfeel, better tableting at low cost

5. Conclusion

Co-processed excipients play important roles in direct compression of tablet dosage forms providing improved physical, chemical and mechanical properties. The Co-processed excipient helps to overcome the problem related to the use of a single excipient and gives rise to the preparation of various novel formulations. These excipients show rapid disintegration, good flow properties, high compressibility, and improve hardness of tablets. Considerable research must be done in areas of coprocessing of excipients used in direct compression of tablets.

Compliance with ethical standards

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Disclosure of conflict of interest

All the authors declare no conflict of interest.

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