A Brief Review on Co-Processed Excipients

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Abstract: Excipients are added in formulations to facilitate the production process, provide stability, increase bioavailability, or support safety and patient acceptance. Both the efficacy and the standard of a pharmaceutical product are significantly affected by the selection of the excipients. Combining two or more excipients through physical co-processing that does not produce covalent bonds is known as co-processed excipients. Co-processed excipients are capable of functions that sample blending is unable to provide. When compared to individual excipients, these excipients work better because of flow characteristics, compressibility, with reduced lubricant sensitivity. Marketed products such as Ludi press, Ludi flash, and Prosolv, among others, have already demonstrated their value in the marketplace by lowering the cost of the product and the number of excipients while keeping the formulation's effectiveness.

Keywords: Co-processed Excipients, IPEC, Principle, Spray Drying.

INTRODUCTION

All materials other than the active medication product are known as pharmaceutical excipients that undergoes an accurate safety assessment and is added to a drug delivery system to help with product identification or improve any other aspect of the general safety and efficacy of the drug product during storage and use. It can also protect, support, or enhance stability, bioavailability, or patient acceptability. [1] According to the International Pharmaceutical Excipients Council (IPEC) as "substances other than the API that have undergone sufficient safety evaluation and are purposefully incorporated into a drug delivery system." A co-processed excipient is one that combines two or more compendial or non-compendial excipients with the intention of physically altering their qualities without changing their chemical properties. [2]

NEED OF CO-PROCESSING

• The growing popularity of the direct compression method and the need for a perfect filler-binder that can replace two or more excipients.
• The ability to change stability, permeability, or solubility.
• Effective utilization of currently available excipients: the technique for an optimum filler binder that can replace two or more excipients has increased in popularity.
• The actual number of excipients used in a composition who have certain desirable attributes.
• The compatibility of newly developed medications with already-used excipients.
• As a result, co-process excipient will be useful to solve these issues. [3]
• Excipients can be formed into granulates that have better qualities than physical mixes of components or individual components, making them particularly ideal for direct compression.
• Creating a perfect filler-binder that can take the place of two or more excipients.
• Excellent compressibility and minimal weight fluctuation, especially during short dwell times and rapid tableting rates. [4]

PRINCIPLE OF CO-PROCESSING

Particle engineering is a comprehensive term that refers to the simultaneous small modifications and alteration of particle properties like form and size distribution (5). the atomic, molecular, and bulk levels. These layers are interconnected, with changes at one level having an impact on the others. The

arrangement of each of the molecules within the crystal lattice is known as the molecular level, which also encompasses phenomena like polymorphism, pseudo-polymorphism, and the amorphous state. Individual particle characteristics including form, size, surface area, and porosity are included at the particle level. There is a collection of particles and characteristics at the bulk level. Excipient functions like flowability, compatibility, dilution potential, disintegration potential, and lubrication potential are influenced by the basic solid-state properties of the particles, which include morphology, particle size, shape, surface area, porosity, and density. Therefore, designing particles that would give the intended results is the first step in creating a new excipient. [6]

Properties of the co processed excipients

Many authors have discussed the benefits and potential drawbacks of co-processed excipients including SMCC, cellactose, and ludipress.

a) Absence of chemical change

Excipients that have undergone co-processing do not exhibit any chemical changes, according to numerous in-depth investigations of their chemical characteristics. Comprehensive investigations using solid state nuclear magnetic resonance (NMR), IR, Raman, X-ray diffraction analysis, and C13 NMR spectroscopy have shown that SMCC shares many of the physicochemical characteristics of MCC and have not revealed any chemical alterations. [24] During the development stage, a company's regulatory concerns are lessened by this lack of chemical change.

b) Physiochemical properties.

1. Improved Flow Properties

Superior flow characteristics of co-processed excipients are ensured by controlled optimum particle size and dispersion, negating the requirement for glidants. In contrast to MCC, the volumetric flow characteristics of SMCC were investigated. Although the flow of coprocessed excipients was superior to that of simple physical mixes, the particle size range of these excipients was found to be comparable to that of the parent excipients. Additionally, a comparison of cellactose's flow characteristics was carried out. It was discovered that cellulose has superior flow properties than lactose or a combination of cellulose and lactose based on measurements of the angle of repose and the Hausner ratio.[25] The spherical shape and even surfaces of the spray-dried product also enhanced the flow characteristics.

2. Improved compressibility

Because direct compression tabletting results in a net improvement in flow characteristics and compressibility profiles and produces a filler-binder excipient, co-processed excipients have primarily been used in this setting. Plotting and comparing the pressure–hardness relation of co-processed excipients with basic physical mixes revealed a significant improvement in the compressibility profile. The ability of excipients like cellactose to compress [26], SMCC [27,28] and Ludipress [29] are better than the straightforward physical mixes of the excipients that make them up. Wet granulation is still preferred in pharmaceutical manufacturing, even though direct compression appears to be the preferred method. This is because wet granulation can improve flow properties and compressibility when an additional granular binder is added, and it can achieve better content uniformity when dealing with low dose drugs. When water is added, some excipients, including MCC, become less compressible; this is known as quasihornification.[30] But when it's co-processed into SMCC, this property gets better.

3. Better dilution potential

The excipient's capacity to maintain its compressibility when diluted with another substance is known as its dilution potential. Excipients need to have greater compressibility qualities in order to maintain adequate compaction even when diluted with a poorly compressible agent because the majority of active medicinal ingredients have low compressibility. It has been demonstrated that cellactose has a larger dilution potential than a physical amalgamation of its component excipients. [31]

4. Fill weight variation

Poor flow characteristics cause materials intended for direct compression to often exhibit large fill weight fluctuations; nevertheless, co-processed excipients have been demonstrated to exhibit lower fill weight variation issues in comparison to parent materials or simple mixtures. The impregnation of one particle into the matrix of another, which lessens the rough particle surfaces and produces a nearly ideal size distribution, leading to improved flow characteristics, is the main cause of this phenomenon. Variations in fill weight are typically more noticeable in high-speed compression machines. When fill weight fluctuation for SMCC and MCC was examined at different machine speeds, SMCC displayed less fill weight variation than MC.

5. Reduced lubricant sensitivity

The majority of co-processed goods are made up of a lesser amount of plastic material, like cellulose, that is fixed between or on the particles of the brittle material, and a comparatively high amount of brittle material, such lactose monohydrate. [32] Because the plastic material forms a continuous matrix with a sizable bonding surface, it has good bonding qualities. Due to the substantial amount of brittle material, which breaks up the lubricant network upon compression and precludes the creation of a coherent lubricant network by creating additional exposed surfaces, the lubricant sensitivity is poor.[33]

ADVANTAGES

- Enhancing flow characteristics by carefully regulating the particle size and size distribution.
- Improved lubricant sensitivity, dilution potential, fill weight variation, and compressibility.
- It may also speed up pill disintegration and increase tablet hardness.[7]
- The pharmaceutical sector has increased their use as a result of improvements in their physio-chemical characteristics.
- Compared to tablets formed from granulations, direct compression tablets are less likely to experience changes in dissolving characteristics after storage.
- Direct compression has an important cost benefit over wet granulation since it requires fewer unit operations.
- The official compendium now includes dissolving criteria for the majority of solid dosage forms; therefore, this is quite essential.
- Punches and dies have a lower risk of deterioration.
- Removing unfavourable qualities for a better tongue feel and greater palatability.

DISADVANTAGES

- High temperature processes and specialized filling equipment are required.
- Pre-clinical species may not always handle some lipidic excipients well.
- The substantial material losses.
- The need for labour, space, time, specialized equipment, and energy results in a costly process.
- material loss throughout different processing phases.
- Drugs that are thermolabile and moisture sensitive are poor candidates.
- There will be less direct communication between the formulator and the production staff in the manufacturing area.
- long time frame.
- A lot of equipment is required.
- extreme material loss. [8]

METHOD OF DEVLOPMENT

The co-processed excipients involve the following steps

1. Excipient Selection

By carefully studying the excipient group, identify them for co-processing. requirements for functioning and material properties.

2. Proportion of Excipients
   Decide the quantity of each excipient to use in what amounts.
3. Homogeneous Dispersion
   Determine the minimum particle size necessary for coprocessing. This is crucial because the particle size of one of the components that is processed in a dispersion phase post processing depends on the size of its original particle.
4. Co Drying
   Choosing an appropriate drying method, such as flash or spray drying the co-processing method is represented schematically in figure.1 [9][10]
5. Co-Processed Excipients

METHODS OF COPROCESSING

- Spray drying
- Solvent evaporation
- Crystallization
- Melt extrusion
- Granulation/Agglomeration
- Roller drying
- Co-transformation
- Milling

1.Spray drying

With the help of this spray drying technology, feed can be transformed from a fluid condition to a dried particle. A solution, suspension, dispersion, or emulsion can be the feed. Depending on the

physicochemical characteristics of the feed and the desired final powder attributes, the dried product may take the shape of powders, granules, or agglomerates. It is a continuous operation for drying and particle processing. Inlet air temperature, atomization air pressure, feed rate, liquid viscosity, solid content in feed, and disc speed are spray drying process variables that might help in designing particles with desired properties. so, it is possible to envision the spray drying process as having four steps.[11]

• Droplets of the liquid being atomized.
• The droplet coming into contact with the warm drying gas.
• The droplets quickly evaporate to become dry particles.
• Using a cyclone to recover the dry particles from the drying gas.

Advantages of spray drying:

• The ability to mix and dry both soluble and insoluble compounds concurrently;
• The ability to continuously operate with non-miscible goods.
• Offers a chance to secure and safeguard a delicate active ingredient on a natural carrier.
• Increases compressibility and toughness.
• Quicker tablet production with less time for disintegration. [12]

2. Solvent evaporation:

The procedure is completed in a liquid production machine. The liquid production vehicle phase and the volatile solvent in which the coating excipient is dissolved are incompatible. An agitated coating polymer solution is used to dissolve or scatter a core excipient substance that will be microencapsulated. To create the correct size microcapsule, the core coating material mixture is disseminated in a liquid production vehicle phase. After the combination is heated to evaporate, the temperature of the liquid is lowered to room temperature while it is still being stirred. At this point, microcapsules can be employed as powders, coatings, or suspensions on substrates. Either water-soluble or water-insoluble materials can make up the core components.[13]

3. Crystallization:

Crystallization, which can occur naturally or artificially, is the process by which solid crystals form from melts, solutions, or, less frequently, gases when they are precipitated from these sources. Crystallization from a solution requires supersaturation. This implies that the solution must include more dissolved solute entities (molecules or ions) than it would in a saturated solution at equilibrium. The most often employed techniques in industrial practice are (1) solution cooling, (2) addition of a second solvent to decrease the solubility of the solute (technique known as antisolvent or drown-out), (3) chemical reaction, and (4) change in pH. Sugar Tab is an example [Sucrose, Invert sugar]. [11,14]

4. Melt extrusion:

Melt extrusion is a method that turns molten substance that is extruded through an extruder into tiny beads and pellets. Extruders are made up of four separate components: [15]

1. A hole via which materials are introduced into the barrel, which may have a hopper containing the materials to be extruded.
2. A conveying portion (process section), made up of a barrel and screws that move and, in some cases, mix the material, is included.
3. A die opening that allows the material to be shaped as it exits the extruder.
4. Auxiliary equipment for cutting, chilling, and/or gathering the completed product downstream. An illustration is Compressor S [Mannitol, Sorbitol]. [11,14]

Advantages

- Very high repeatability.
- Shapes can be complex and complicated.
- Less time is needed.

Disadvantages

- High cost of dies and equipment.
- High cost of the minimum economic length.[16]

5. Granulation/agglomeration:

The process of forming or crystallizing into grains is called granulation. Depending on their intended purpose, granules might be anywhere from 0.2 and 4.0 mm in size. Agglomeration is a word used to describe granulation. Particle size enlargement methods, often known as agglomeration techniques, are excellent tools for changing a product's qualities. Powder

agglomeration is frequently utilized to enhance the physical characteristics of a product, including wettability, flowability, bulk density, and appearance [17].

Advantages

- It does not require the use of any solvent, including water.
- Quick processing time.
- It might work with standard machinery.[18]

6. Roller Drying

The homogenous solution or dispersion comprising 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 utilized was high enough to produce a substance that is primarily crystalline -lactose.[19]

7. Co-transformation

In the co-transformation process, the excipient particle is "opened-up," or made to swell, by applying heat or a solvent action. The "opened-up" structure of the aforementioned excipient is combined with the additional excipients. The added excipient improves the final product's functionality. [2,19]

8. Milling

To achieve milling or dry grinding, a roller mill, ball mill, bead mill, millstone mill, jet mill, or hammer mill can be utilized. After being combined, the excipients are run through a high-speed milling machine. When the particles are forced to mill or pass through the screen during the milling process, they come into contact with one another and create bonds. This method was used by Rao et al. (2012) to co-process calcium silicate and cross-linked polyvinylpyrrolidone. [2,19]

OVERVIEW OF MARKETED CO-PROCESSED EXCIPIENTS

Co-Processed Excipients	Manufacturer	Components %	Claimed benefits	Ref.
Ludipress®	BASF	Lactose monohydrate- 93.4 Kollidon30- 3.2 Kollidon CL-3.4	Low hygroscopicity, good flowability, constant tablet weight	(21)
Ludiflash®	BASF	Mannitol-90 Kollidon® CL-SF-5 Kollicoat® SR30D- 5	Rapidly disintegrating, mechanically stable tablets	(22)
Avicel ® CE- 15	FMC	MCC- 85 Guar- 15	Less grittiness, improved tablet palatability	(20)
Pharmatose® DCL40	DMV	ß-Lactose- 95 Lactitol- 5	High compressibility, Low lubricant sensitivity	(20)
Microcelac® 100	Meggle	α-Lactose monohydrate- 75 MCC- 25	Better tablet performance at lower cost	(21)
StarLac®	Meggle	Lactose- 85 Maize Starch- 15	Good flowability	(20)
ProSolv®	JRS	MCC- 98 Silicon Dioxide- 2	Better flow, less sensitivity to wet granulation, better tablet hardness	(23)
Di-Pac®	Domino	Sucrose- 97 Maltodextrin- 3	For direct compression	(20)
StarCap1500®	Colorcon	Maize Starch, Pregelatinized Starch	Tablet disintegration and dissolution properties that are independent of media pH	(20)
Xylitab® 200	Danisco	Xylitol- 98 Sodium carboxymethyl cellulose- 2	Directly compressible	(20)

CONCLUSION

Co-processed excipients, or designer excipients, are increasingly used in drug formulations to address specific functionality requirements. These excipients can enhance design space and improve critical quality attributes and process parameters compared to traditional non-co-processed excipients. They can reduce drug dosages, minimize side effects, and make medicines safer. The International Pharmaceutical Excipients Council (IPEC) is drafting a guideline to facilitate the development and adoption of co-processed excipients. These excipients are also being developed for targeted drug delivery, such as Peptide Dalargin, using Polyisobutylcyano acrylate modified with Tween 80. However, they have yet to find official monographs, a major obstacle to their success.

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