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CO-PROCESSED EXCIPIENTS: A REVIEW

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ABSTRACT

Excipients play an important role in formulating a dosage form. These are the inactive ingredients which along with Active Pharmaceutical Ingredients make up the dosage forms. In recent years drug formulation scientists have recognized that single-component excipients do not always provide the required performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. In addition to this, the cost involved in the development of new chemical excipients with improved properties is quite high. In response to these deficiencies, drug formulation scientists have relied on increasing numbers of combination excipients introduced by excipient manufacturers into the commercial market. The combinations of excipients are an alternative for better excipient functionality. Co-processing of excipients could lead to the formation of excipients with superior properties compared to simple physical mixtures of their components. The main aim of co-processing is to obtain a product with an added value related to the ratio of its functionality /price.

KEYWORDS: Excipients, combination of excipients, Co-processing, functionality, synergistic outcome.

INTRODUCTION[1,2]

Definition of excipients

According to the International Pharmaceutical Excipients Council (IPEC) excipient defines as “substances other than the API which have been appropriately evaluated for safety and are

intentionally included in a drug delivery system. For example, excipients can:

1. Support, protect or enhance stability, bioavailability or patient acceptability,
2. Aid in the processing of the drug delivery system during its manufacture,
3. Assist in product identification,
4. Enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use.

Development of co-processed excipients starts with the selection of the excipients to be combined with their targeted proportion, physico-chemical parameters, selection of preparation methods. An excipient of reasonable price has to be compared with the optimal amount of a functional material in order to obtain integrated product, with superior functionality than the simple mixture of components. Co-processing may be intresting because the products are physically modified in a unique way without altering their chemical structure. A fixed and homogenous distribution for the components is achieved by converting them within mini granules. Segregation is compact by adhesion of the actives on the porous particles making process validation and in process control easy and reliable.

Advantages of Co-Processed Excipients[3]

- Overcome the limitation of existing excipients.
- Provide a single excipient with multiple functionalities.
- Removal of undesirable properties.
- Improvement of organoleptic properties.
- Production of synergism in functionality of individual components.
- Improvement in physico-chemical properties has expanded their use in the pharmaceutical industr.
- Reduction of company's regulatory concern because of absence of chemical change during co-processing.

TYPES OF EXCIPIENTS[1,4]

1. Single entity excipients.
2. Novel excipients or new chemical entities.
3. Mixtures or blends of multiple excipients.
4. Coprocessed excipients.

1. Single Entity excipients

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

i. Concomitant components.
ii. Residual processing aids.
iii. Additives.

2. Novel excipients or New Chemical Entities

It can be defined as excipients which are chemically changed to form new excipients. These are usually not listed in FDA Inactive Ingredient Database (IID).IID is not an approval but the 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 can be brought up to current standards in relation to even that "similar" use.

3. Mixtures or Blends of multiple excipients

Mixtures or blends of two or more than two excipients by the mean of low to medium shear processes within which the individual components of excipients are mixed together without any significant chemical change for solid mixtures or blends. The individual excipient stay separate at a particulate level. Mixed excipients may be solid or liquid. Simple physical mixing is typically of short duration.

4. Co-processed excipients

Co-processes excipients are developed by adding one excipient into the particle structure of another excipient using processes like co-drying. Co-processing excipients leads to formation of excipients granulates with superior properties compared with physical mixtures of components or with individual components.

NEED FOR DEVELOPING NEW EXCIPIENTS[5,6,7]

The excipients industry up to now has been a very important part of the food industry. Moreover, excipients are unit products of the food industry, which has helped maintain a good safety profile. Increasing regulative pressure on purity, safety, and standardization of the excipients has catalyzed the formation of an international body, the International Pharmaceutical Excipients Council (IPEC). IPEC is a multilateral council with representation from the U.S, Europe and Japan has made efforts to harmonize requirements for purity and functionality testing. The development of new excipients up to know has been market driven

rather than marketing driven (i.e., excipients are developed first and market demand is created through marketing strategies) and has not seen lots of 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 first reason for this lack of latest chemical excipients is the relatively high cost involved in excipients discovery and development. However, with the developing number of new drug moieties with varying stability and physicochemical properties, there 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 method and a requirement for an ideal filler–binder that can substitute two or more than two excipients
- Tableting machinery's increasing speed capabilities, that need excipients to maintain good compressibility and low weight variation even at short dwell times.
- Shortcomings of excipients like loss of compaction of microcrystalline cellulose upon wet granulation, high moisture sensitivity and poor die filling as a results of agglomeration.
- The ability to modulate the solubility, permeability or stability of drug molecules.
- The lack of excipients that are the needs of a selected patient like those with diabetes, hypertension and lactose and sorbitol sensitivity.

PRINCIPLE OF COPROCESSING[2,8]

Particle Engineering

Solid substances are characterized by three levels of solid-state that is the bulk, particle and molecular level. These levels are closely related to one another, with the changes in one level reflecting in another level.

- The bulk level is formed from associate degree particles and its properties like flowability, compressibility, and dilution potential, this particles and properties are important factors within the performance of excipients.
- The particle level content with the individual particle properties like, shape, surface area, size, and porosity.
- The molecular level includes the arrangement of individual molecules inside the crystal lattice and phenomena like amorphous, polymorphism, pseudo-polymorphism state.

The fundamental solid-state properties of the particles like morphology, surface area, particle

size, shape, porosity, and density influence excipient functionalities like compactability, flowability, dilution potential, lubricating potential, and disintegration potential. Hence, the creation of a new excipient should begin with a particle design that is suited to deliver the need functionalities. However, the particle engineering of a single excipient can provide only a limited quantum of functionality improvement.

Table 1: Various particle properties influencing excipient functionality[9]

Particle property	Excipient functionality
Enlargement of particle size	Flowability,compressibility
estricting particle size distribution	Segregation potency
Enlargement of particle porosity	Compressibility, solubility
Surface roughness	Flowability, Segregation potency

Co processing of Excipients[9]

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

1. Studying the material characteristics and functionality requirements by identifying the group of excipients to be coprocessed.
2. Selecting the proportions of various excipients
3. Assessing the particle size required for co-processing. Particle size is very important when one components is processed in a dispersed phase. The post processing the particle size of the latter depends on its initial particle size.
4. Selecting a suitable drying process like spray or flash drying optimizing the process.

Table 2: Examples of marketed coprocessed excipients.[10]

Coprocessed excipients	Trade name	Manufacturer	Added advantage
Lactose, 3.2% Kollidon 30, Kollidon CL	Ludipress	BLASF AG, Ludwigshafen, Germany	Low degree of hygroscopicity, good flowability, tablet hardness independent of machine speed
Lactose, 25% cellulose	Cellactose	Megglegmbh & co. Kg, Germany	Highly compressible, good mouthfeel, better tabletting at low cost
Sucrose 3%, dextrin Microcrystalline cellulose, silicon dioxide	DipacProsolv	Penwest pharmaceuticals company	Directly compressible, Better flow, reduced sensitivity to wetgranulation, better hardness of tablet, reduced friability
Microcrystalline cellulose, guar gum	Avicel ce-15	Fmc corporation	Less grittiness, minimal chalkiness
Calcium carbonate, sorbitol	Formaxx	Merck	Controlled particle size distribution
Microcrystalline cellulose, lactose	Microlela	Meggle	Capable of formulating high dose, small tablets with poorly flowable active ingredients
95% β-lactose + 5% Lactitol	Pharmatose dcl 40	Dmvveghel	High compressibility

Role of Material Science In Coprocessing[11]

Material science plays a big role in altering the physico-mechanical characteristics of a material, especially with regard to its compression and flow behavior. Coprocessing excipients offers an interesting tool to alter these physico-mechanical properties. Materials, by virtue of their response to applied forces, can be classified as elastic, plastic, or brittle materials. Pharmaceuticals materials exhibit three types of behavior, with one type being the predominant response. This makes it difficult to demarcate which property is good for compressibility. Coprocessing is generally conducted with two excipient that is plastic and another one is brittle. A combination of brittle and plastic materials is necessary for optimum tableting performance. Hence, coprocessing this two kinds of materials i.e. plastic and elastic produces a same effect, in terms of compressibility. This types of combination can also help in improving functionalities such as compaction performance, floe properties, strainrate selectivity, lubricant sensitivity or sensitivity to moisture, or reduced hornification.

METHODS OF COPROCESSING.[6,12,13,14]

Methods of coprocessing were listed below

1. Spray Drying
2. Solvent Evaporation
3. Crystallization
4. Melt Extrusion
5. Granulation/Agglomeration

1. Spray Drying

Spray drying technique enables the transformation of feed from a fluid state into dried particulate form by spraying the feed into a hot drying medium. It is a continuous particle processing drying operation. The feed can be a solution, suspension, dispersion or emulsion. The dried product can be in the form of powders, granules or agglomerates depending upon the physical and chemical properties of the feed, the dryer design and final powder properties desired.

2. Solvent Evaporation

Solvent evaporation method involves the utilization of 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 distributed within the coating polymer solution. With the agitation, core coating material

mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate 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 required) 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 is also either water - soluble or water - insoluble materials.

3. Crystallization

Crystallization is the (natural or artificial) `process of formation of solid crystals precipitating from asolution, melt 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 has to contain more solute entities (molecules or ions) dissolved than it would contain under the equilibrium (saturated solution).

This can be achieved by various methods, with

1. Solution cooling,
2. Addition of a second solvent toreduce the solubility of the solute (technique known as antisolvent or drown-out),
3. Chemical reaction and,
4. Change in pH being the most common methods used in industrial practice.

4. Melt extrusion

Melt extrusion is a process of formation of small beads, pellets from the molten mass which is extruded through extruder.

5. Granulation/agglomeration

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 subsequent use. Synonym “agglomeration”. Agglomeration process or in a more general term particle size enlargement technologies are great tools to modify product properties. Agglomeration of powders is widely used to improve physical properties like: wettability, flowability, bulk density and product appearance. In pharmaceutical industry, two types of granulation technologies are employed, namely, Wet Granulation and Dry Granulation. Wet granulation is the more

preferred method for coprocessing.

CONCLUSION

Co-processed excipients or excipients of mixture have yet to find their way into official monographs, which is one of the major problem to their success in the market. The success of any pharmaceutical excipient depends on quality, safety, and functionality. There is an increase in use of coprocessed excipients due to the improvement of functionality by overcoming the limitations with the single excipients. Development of new excipients requires safety evaluation which is expensive and time consuming. Instead of developing new excipients, coprocessing of existed approved excipients will reduce the safety evaluation.

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