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CO-PROCESSED EXCIPIENTS AS A NEW GENERATION EXCIPIENTS WITH MULTIFUNCTIONAL ACTIVITIES: AN OVERVIEW

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ABSTRACT

This main aim of the current review article is to provide a complete overview on recent development in excipient technology and the approaches involved in development of such excipients. Formulation scientists recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately and they have focused their attention on the production of multifunctional excipients with enhanced performance to meet the needs of formulation experts in terms of costs of production, enhanced excipient functionality and quality of tablets. Manipulation in the functionality of excipient is provided by the co-processing of two or more existing excipients. Co-processing is a novel process with the interaction of two or more excipients at the sub particle level which in turn provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients. The demand for the functionality of excipients has increased mainly in terms of physico-chemical properties of the excipients for the formulation development. Co-processed excipients with combination of two or more existing excipients at sub-particle level interaction will provide an attractive tool for developing high functionality excipients.

Keywords: Excipient technology, Co-processing, Co-processed excipients.

INTRODUCTION

Pharmaceutical excipients are any substance other than the active drug product which has been appropriately evaluated for safety and is included in a drug delivery system to either aid processing of the system during manufacture or protect, support or enhance stability, bioavailability, or patient acceptability or assist in product identification or enhance any other attribute of the overall safety and effectiveness of the drug product during storage and use. According to International Pharmaceutical Excipient Council (IPEC), co-processed excipient is "a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change".

Excipients are generally originated from Mining of minerals, Vegetable source (plants and crops), Chemical synthesis, Formulated products, Biotechnology and Animal by-products. Ideal characteristics of an excipient are should be non-toxic, physically and chemically stable, commercially available, pleasant organoleptic properties and economic. A co-processed excipient is a combination of two or more compendial or noncompendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing**,** and without significant chemical change. However in some instances, formation of necessary components may occur, such as *in-situ* salt formation. Many different co-processing methods may be used, including standard unit operations such as granulation, spray drying, melt extrusion, milling etc. The choice for a specific application will depend on the materials used, their form (e.g. whether dry powders or liquid) and the specific physical properties desired. Likewise the ratios of the components may vary depending on the desired performance

Advantages of Co-Processed Excipients

The multifold advantages offered by co-processed excipients were given below.

- Provide a single excipient with multiple functionalities.

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

Types of Excipients

Generally types of excipients were classified into 4 types which were given below.

- Single entity excipients.
- Mixtures or blends of multiple excipients.
- Novel excipients or new chemical entities.
- Coprocessed excipients.

Coprocessing of Excipients

The actual process of developing a coprocessed excipient involves the following steps:

- Studying the material characteristics and functionality requirements by identifying the group of excipients to be coprocessed.
- Selecting the proportions or concentrations of various excipients.
- Assessing the particle size required for coprocessing. This is especially important when one of the components is processed in a dispersed phase. Post processing the particle size of the latter depends on its initial particle size.
- Selecting a suitable process [1-4].

Principle Involved In Coprocessing

Solid substances are characterized by three levels of solid state: the molecular, particle, and bulk level. These levels are closely linked to one another, with the changes in one level reflecting in another level. The molecular level comprises the arrangement of individual molecules in the crystal lattice and includes phenomena such as polymorphism, pseudo-polymorphism, and the amorphous state. Particle level comprises individual particle properties such as shape, size, surface area, and porosity. The bulk level is composed of an ensemble of particles and properties such as flowability, compressibility, and dilution potential, which are critical factors in the performance of excipients. Figure1 shows the various levels of solid state and how a change at one level affects the other levels. This interdependency among the levels provides the scientific framework for the development of new grades of existing excipients and new combinations of existing excipients. The fundamental solidstate properties of the particles such as morphology, particle size, shape, surface area, porosity, and density influence excipient functionalities such as flowability, compactability, dilution potential, disintegration potential, and lubricating potential. Hence, the creation of a new excipient must begin with a particle design that is suited to deliver the desired functionalities. However, particle engineering of a single excipient can provide only a limited quantum of functionality improvement. A much broader platform for the manipulation of excipient functionality is provided by coprocessing or particle engineering two or more existing excipients. Coprocessing is based on the novel concept of two or more excipients interacting at the subparticle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients. The availability of a large number of excipients for coprocessing ensures numerous possibilities to produce tailor-made "designer excipients" to address specific functionality requirements

METHODS OF COPROCESSING

Methods of coprocessing were listed below

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

1. Spray Drying

This 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 process involves the use 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 dispersed in the coating polymer solution. With agitation, the 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 may be either water -soluble or water - insoluble materials.

3. Crystallization

Crystallization is the (natural or artificial) `process of formation of solid crystals precipitating from a

solution, 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 to reduce the solubility of the solute (technique known as antisolvent or drown-out), (3) chemical reaction and (4) change in pH being the most com mon 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.

Table 1. Some Examples Commercially Available Co-Processed Excipients

S.No	Trade Name	Manufacturer	Components	Claimed benefits
1.	Ludipress®	BASF	Lactose PVP	Low hydroscopicity Good flow ability Constant tablet weight
2.	Avicel ® CE- 15	FMC	MCC Guar	Less grittiness, improved tablet palatability
3.	Pharmatose® DCL40	DMV	ß-lactose Lactitol	High Compressibility Low lubricant sensitivity
4.	Star Lac®	Meggle	Lactose Maize Starch	Good flow ability
5.	ProSolv®	JRS	MCC Silicon Dioxide	Better flow, les sensitivity to wet granulation, better tablet hardness
6.	Di-Pac®	Domino	Sucrose Maltodextrin	For direct compression
7.	StarCap1500®	Colorcon	Maize Starch Pregel Starch	Tablet disintegration and dissolution independent of pH
8.	Xylitab® 200	Danisco	Xylitol Na CMC	Directly compressible

Table 2. Methods of Preparation of Co-Processed Excipients with Their Limitations

S. No	Method of Preparation	Advantages and Limitations	Examples
1.	Physical Modification (Grinding or Seiving)	Relatively simple and economical Changes in particle properties may alter Compressibility	Dextrose or compressible sugar, Sorbitol, Dibasic calcium phosphate
2.	Chemical Modification	Time Consuming and tedious process Relatively expensive and requires technical data	Ethyl cellulose, Methyl cellulose, HPMC, Sodium CMC, Cyclodextrin from starch
3.	Crystallization	Impact flow ability of materials but not necessarily self binding properties Requires stringent control on polymorphic conversions and processing conditions	B-Lactose, Dipac
4.	Spray Drying	Spherical shape and uniform size leads to good flow ability and rework ability	Spray dried lactose, Emdex, Fast flo lactose, Avicel PH, Karion instant, Advantose 100
5.	Granulation/Agglomeration	Transformational of small, cohesive, poorly flowable materials into flowable and directly compressible	Granulated Lactitol, Tablettose
6.	Dehydration	Increased binding property by thermal and chemical dehdration	Anhydrous α- lactose

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 processes 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 [5-10].

CONCLUSION

Coprocessed excipients have yet to find their way into official monographs, which is one of the major obstacles to their success in the marketplace. The success of any pharmaceutical coprocessed excipient will depend 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 excipient. In day to day raising in development of new chemical entities, there is a huge scope for the development of coprocessed excipients. Development of new excipient requires safety evaluation which is expensive and time consuming. Instead of developing new excipient, coprocessing of existed approved excipients will reduce the safety evaluation IPEC New Excipient Safety Evaluation Procedure should be used for co-processed excipients to reduce regulatory uncertainties.

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