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CO-PROCESSED EXCIPIENTS: 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 excipients 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. Co-processed excipients help to overcome the deficiencies occurring with the use of general grade excipients. The co-processed excipients retain favourable attributes and are supplemented with new ones. As the chemical change is absent, they are considered to retain the "GRAS" (Generally Regarded as Safe) status. Co-processed excipients are believed to bring a drastic change in the field of pharmaceutical Research. Co-processing is interesting because the products are physically modified in a special way withoutaltering the chemical structure.

KEYWORDS: Co-Processing, Excipient Technology, pharmaceutical Research, chemical structure.

INTRODUCTION

In recent years scientists have found out that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured.[1] The excipients industry to date has been an extension of the food industry.[2] Moreover, excipients are products of the food industry, which has helped maintain a good safety profile. Increasing regulatory pressure on purity, safety and standardization of the excipients has catalyzed the formation of an international body, the International Pharmaceutical Excipients Council (IPEC).[3]

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".

There is considerable activity in the development of new and innovative excipients. Excipient Innovations include excipients for orally disintegrating tablets and controlled-release formulations. New technologies are being evaluated to increase the amount or rate of absorption of drugs with new excipients. In the future, the application of nanotechnology may be evaluated for developing novel excipients for new therapeutic solutions.

Thus this work focused on development of directly compressible co-processed excipients comprising of polyethylene oxide and Hydroxyl propyl methyl cellulose by roller compaction method and evaluation as a sustained release matrix forming polymer using water soluble Metoprolol succinate and poorly water soluble anhydrous Theophylline as model drugs.is formed into solid compacts and sheets. Roller compaction basically consists of three steps, i.e., powder feeding, predensification and ribbon formation. During the feeding step, the powder material was fed into two counter-rotating rolls by either gravity or force-feeds screws. Once the powder material was drawn into the nip angle area, it rubs against the roll surface and undergoes the pre-densification process. The predensified powder material was further subjected to pass through the rotating rolls and particles are deformed or fragmented

to form ribbons under hydraulic pressure. These ribbons were then sized through desired screens to produce granules to be compressed into tablets.

Polymers were accurately weighed as per specified ratio (1:9 to 9:1) and mixed for 10 min to form uniform blend. These blends were used for compaction using roller compactor (Clit roller compactor, India). The obtained ribbons were screened through 40# and 60# sieve. The obtained fine powder was further recycled to get granules of uniform size. About 9 cycles of roller compaction were performed to obtain the granules of desired size. Material retained on 60 # sieve was used for further study. Physical mixtures of Polyox® WSR 301 and Methocel® K4M were also prepared in same ratio in a lab scale double cone blender.

Advantages of Co-Processed Excipients

- Provide a single excipient with multiple functionalities.
- Overcome the limitation of existing excipients.
- Improvement of organoleptic properties.
- Production of synergism in functionality of individual components.
- Improvement in physico-chemical properties has expanded their use in the pharmaceutical industry.
- Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations.
- The prime advantage of direct compression over wet granulation is economic since the direct compression requires fewer unit operations
- This is extremely important because the official compendium now requires dissolution specifications in most soliddosage forms.
- The chances of wear and tear of punches and dies are less.
- Better mouth feel and improved palatiblity
- Removal of undesirable properties.
- Improvement of organoleptic properties
- Delivery of low doses of very potent compounds that require contaminent.
- Improved Flow properties.
- Improved compressibility.
- Better dilution potential.
- Fill weight variation.
- Reduced lubricant sensitivity.

DIS-ADVANTAGES

- Specalised filling equipment and high temperature processing are required.
- Some lipidic excipients are not well tolerated by pre-clinical species.
- The high materials losses.
- Process is expensive because of labour, space, time special equipment and energy requirement.
- Loss of material during various stages of processing.
- Moisture sensitive and thermolabile drugs are poor cancidates.
- The frequency of direct interaction of the formulator with the production personal in the manufacturing area will be reduced.
- Long duration.
- Large number of equipment are needed.
- High material loss.

Co-Processed Excipients Enhanced Performance[4]

- Combination ("intimate" mixtures) of established excipients that possess performance advantages and improvements: increased surface area, improved flow, compaction, etc.
- Covalent bonds usually not formed
- High-functionality excipients (perform multiple functions)
- Produced using specialized manufacturing process: high shear dispersion, granulation, spray drying, melt extrusion
- One or more components may be formed in situ
- Appropriate for monograph consideration in the United States Pharmacopeia/National Formulary
- Several listed in FDA Inactive Ingredient Database
- May create new intellectual property

Sources of New Excipients

Excipients with improved functionality can be obtained by developing new chemical excipients, new grades of existing materials and new combinations of existing materials4. Any new chemical excipient being developed as an excipient must undergo various stages of regulatory approval aimed at addressing issues of safety and toxicity, which is a lengthy and costly process. In addition, the excipient must undergo a phase of generic development, which shortens the market exclusivity period.[5] The high risk and significant investment

involved are not justified in view of the meagre returns from the new excipients. A plausible solution is for excipient and pharmaceutical manufacturers to develop drug products jointly, during which a new excipient becomes part and parcel of the eventual new drug application. This type ofarrangement already has been successfully applied in theintravenous delivery field, in which CyDex and Pfizer workedcollaboratively to obtain the approval of a solubilizer.[6,7]

The combined expertise of pharmaceutical and excipient companies can lead to the development of tailor made innovative excipients. Developing new grades of existing excipients (physicochemical) has been the most successful strategy for the development of new excipients in past three decades[8], a process that has been supported by the introduction of better performance grades of excipients such as pre gelatinized starch, croscarmellose and crospovidone9. However, functionality can be improved only to a certain extent because of the limited range of possible modifications. A new combination of existing excipients is an interesting option for improving excipient functionality because all formulations contain multiple excipients. Many possible combinations of existing excipients can be used to achieve the desired set of performance characteristics. However, the development of such combinations is a complex process because one excipient may interfere with the existing functionality of another excipient. Over the years, the development of single bodied excipient combinations at a subparticle level, called co processed excipients, has gained importance. New physical grades of existing excipients and co processed excipients are discussed further in the following section of this article that explains particle engineering. Particle engineering is a broad based concept that involves the manipulation of particle parameters such as shape, size, size distribution, and simultaneous minor changes that occur at the molecular level such as polytypic and polymorphic changes. All these parameters are translated into bulk level changes such as flow properties, compressibility, moisture sensitivity, and machinability.

Particle engineering as source of new excipients 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. The fundamental

solid-state properties of the particles such as morphology, particle size, shape, surface area, porosity and density influence excipient functionalities such as flowability, compactibility, dilutionpotential |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 functionalities10.Varying the crystal lattice arrangement by playing with parameters such as the conditions of crystallization and drying can create particles with different parameters.

Lactose is examples in which such an approach has been successfully applied. However, particle engineering of a single excipient can provide only a limited quantum of functionality improvement. Co processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients.[9] The availability of a large number of excipients for co processing ensures numerous possibilities to produce tailor-made "designer excipients" to address specific functionality requirements or improve the desired properties of excipients. For example, if a substance used as a filler–binder has a low disintegration property, it can be co- processed with another excipient that has good wetting properties and high porosity because these attributes will increase the water intake, which will aid and increase the disintegration of the tablets.

Table 1: Various particle properties influencing excipient functionality.[10]

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

Properties and advantages of the co processed excipients

Several authors have reported the advantages and possible limitations of the properties of co processed excipients such as SMCC, Cellactose and Ludipress.

a) Absence of chemical change

Many detailed studies of excipients chemical properties after co processing have proven that theseexcipients do not show any chemical change. Detailed studies of SMCC with X-ray diffraction analysis, solidstate nuclear magnetic resonance (NMR), IR spectroscopy, Raman spectroscopy and C13 NMR spectroscopy have detected no chemical changes and indicate a

similarity to the physicochemical properties of MCC.[11] This absence of chemical change helps reduce a company's regulatory concerns during the development phase.

b) Physico mechanical properties.

1. Improved Flow Properties

Controlled optimal particle size and particle size, distribution ensures superior flow properties of co-processed excipients without the need to add glidants. The volumetric flow properties of SMCC were studied in comparison with MCC. The particle size range of these excipients was found to be similar to those of the parent excipients, but the flow of coprocessed excipients was better than the flow of simple physical mixtures. A comparison of the flow properties of Cellactose was also performed. The angle of repose and the Hausner ratio were measured and Cellactose was found to have better flow characteristics than lactose or a mixture of cellulose and lactose.[12] The spray dried product had a spherical shape and even surfaces, which also improved the flow properties.

2. Improved compressibility

Coprocessed excipients have been used mainly in direct compression tabletting because in this process there is a net increase in the flow properties and compressibility profiles and the excipient formed is a filler–binder. The pressure– hardness relation of coprocessed excipients, when plotted and compared with simple physical mixtures, showed a marked improvement in the compressibility profile. The compressibility performance of excipients such Cellactose[13], SMCC[14,15] and Ludipress[16] are superior to the simple physical mixtures of their constituent excipients. Although direct compression seems to be the method of choice for pharmaceutical manufacturing, wet granulation is still preferred because it has the potential advantages of increasing flow properties and compressibility when an extra granular binder introduced, and it achieves a better content uniformity in case of low dose drugs. Excipients such as MCC lose compressibility upon the addition of water, a phenomenon called quasihornification.[17] This property is improved, however, when it is co-processed into SMCC.

3. Better dilution potential

Dilution potential is the ability of the excipient to retain its compressibility even when diluted with another material. Most active drug substances are poorly compressible and as a result, excipients must have better compressibility properties to retain good compaction even when

diluted with a poorly compressible agent. Cellactose is shown to have a higher dilution potential than a physical mixture of its constituent excipients.[18]

4. Fill weight variation

In general, materials for direct compression tend to show high fill weight variations as a result of poor flow properties, but co-processed excipients, when compared with simple mixtures or parent materials, have been shown to have fewer fill weight variation problems. The primary reason for this phenomenon is the impregnation of one particle into the matrix of another, which reduces the rough particle surfaces and creates a near optimal size distribution, causing better flow properties. Fill weight variation tends to be more prominent with high speed compression machines. Fill weight variation was studied with various machine speeds for SMCC and MCC and SMCC showed less fill weight variation than MC.

5. Reduced lubricant sensitivity

Most co-processed products consist of a relatively large amount of brittle material such as lactose monohydrate and a smaller amount of plastic material such as cellulose that is fixed between or on the particles of the brittle material.[19] The plastic material provides good bonding properties because it creates a continuous matrix with a large surface for bonding. The large amount of brittle material provides low lubricant sensitivity because it prevents the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network.[20]

Table: 2 Co-processed directly compressible excipients.

Coprocessed excipients	Trade name	Manufacturer	advantage
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	Megglegmbh & co. Kg, germany	Highly compressible, good mouthfeel, better tabletting at low cost
Sucrose 3%, dextrin Microcrystalline cellulose, silicon dioxide	Dipac Prosolv	Penwest pharmaceuticals company	Directly compressible, Better flow, reduced sensitivity to wetgranulation, better hardness of tablet, reduced friability
Microcrystalline cellulose, guar gum	Avicelce 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 flowableactive ingredients
95% β lactose + 5% lactitol	Lactitol Pharmatose dcl 40	Dmvveghel	High compressibility

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.
- Co-processed excipients.

Co-processing of Excipients

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

- Studying the material characteristics and functionality requirements by identifying the group of excipients to be co-processed.
- Selecting the proportions or concentrations of various excipients.
- Assessing the particle size required for co-processing. 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.[21]

Principle Involved In Co-processing

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. 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.

1. Standard Excipients

Are defined as compendial or non-compendial substances that are neither mixed excipients nor co-processed excipients. They may contain other components including concomitant components, residual processing aids and/or additives.

2. Mixed Excipients

A mixed excipient is defined as a simple physical mixture of two or more compendial or non-compendial excipients produced by means of a low- to mediumshear process where the individual components are mixed but remain as discrete chemical entities, i.e. the nature of the components is not chemically changed,. Mixed excipients may be either solid or liquid.

3. Co-processed Excipients

A 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. 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 mayvary depending on the desired performance.

Need For Co-Processed Excipients

It has been found that less than 20 per cent of pharmaceutical materials can be compressed directly into tablets due to lack of flow, cohesion properties and lubrication. Therefore, they must be blended with other directly compressible ingredients to manufacture satisfactory tablets. In the development of directly compressible granules by the modification of a single substance, Co-processing involves interaction of two or more excipients at the sub-particle level, aimed at providing a synergy of functionality improvements, as well as masking the

undesirable properties of the individual excipients. The composite particles or co-processed multi-component-based excipients are introduced to achieve better powder characteristics and tableting properties than a single substance or the physical mixture. The availability of a large number of excipients for co-processing provides a plethora a opportunities to produce tailor made designer excipients catering to specific functionality requirements.[22] The combination of excipients chosen for co-processing should complement each other to mask the undesirable properties of individual excipients and at the same time, retain or improve the desired properties of excipients. For example, if a substance used as a filler–binder has a low disintegration property, it can be co-processed with another excipient that has good wetting properties and high porosity because these attributes will increase the water intake, which will aid and increase the disintegration of the tablets.

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Difference between physical mixtures and co-processed excipients

Physical mixtures, as the name suggests, are simple admixtures of two or more excipients typically produced by short duration low-shear processing. They may be either liquids or solids and are generally used for convenience rather than for facilitating the manufacturing process or improving the resultant pharmaceutical product.[24] Co-processed excipients are combinations of two or more excipients that possess performance advantages that cannot be achieved using a physical admixture of the same combination of excipients. Typically they are produced using some form of specialized manufacturing process. The performance benefits relate to the manufacture or performance of the finished pharmaceutical product.[25] Co-processed excipients are appropriate for consideration as new monographs because one or more of the components may be formed in situ, or the component may not be isolated prior to co-processing.

Limitation of co-processed Excipient

Major limitation of co-processed excipient mixture is that the ratio of the excipients in a mixture is fixed and in developing a new formulation, a fixed ratio of the excipients may not be an optimum choice for the API and the dose per tablet under development. Co processed adjuvant lacks the official acceptance in pharmacopoeia. For this reason, a combination filler binder will not be accepted by the pharmaceutical mixtures of the excipients. Although the spray crystallized dextrose-maltose.[26] (Emdex) and compressible sugar are co-processed products as single components and are official in USP/NF.

A regulatory perspective of the excipient mixtures

With the absence of a chemical change during processing, co processed excipients can be considered generally regarded as safe (GRAS) if the parent excipients are also GRAS-certified by the regulatory industry until it exhibits significant advantages in the tablet compaction when compared to the physical agencies.[27] Hence, these excipients do not require additional toxicological studies. Excipient mixtures or co processed excipients have yet to find their way into official monographs, which is one of the major obstacles to their success in the market place. The mixture of excipients was presented as a topic to the National Formulary and was assigned a priority on the basis of the use of the mixture in marketed dosage forms in which processing has provided added functional value to the excipients mixture.

CONCLUSION

This main aim of the current review article is to provide a complete overview on recent development in excipients 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. Co-processed excipients help to overcome the deficiencies occurring with the use of general grade excipients. The co-processed excipients retain favourable attributes, and are supplemented with new ones. As the chemical change is absent, they are considered to retain the “GRAS” (Generally Regarded as Safe) status. Co-processed excipients are believed to bring a drastic change in the field of pharmaceutical Research. Co-processing is

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