Review Article

A REVIEW : COPROCESSED EXCIPIENTS

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ABSTRACT

Excipients are all substances contained in a dosage form other than the active substance. In recent years drug formulation scientists have recognized that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. In addition to this the cost involved in 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. In order to justify the high rise in new drug development and high industrial output demand, new excipients with purpose satisfying characteristics are the need of the hour. New combinations of existing excipients are an interesting option for improving excipient functionality now-a-days. The current review article is prepared to have a look over the recent development in excipient technology and the approaches involved in development of such excipients. It signifies the synergistic outcome of the combination of excipients taking their material property into consideration. It also emphasizes on the particular material properties in terms of physic-mechanical that are useful to overcome the limitation of existing excipients. All the developed co-processed excipients are enlisted highlighting their multi-functional and beneficial characteristics. Regulatory issues concerned with the development of new excipient are also discussed.

Keywords: Coprocessing, Excipients, Engineered particles, Flowability, Compressibility.

1. INTRODUCTION

1.1. Definition of excipients

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. For example, excipients can:

- aid in the processing of the drug delivery system during its manufacture,

- protect, support or enhance stability, bioavailability or patient acceptability,

- assist in product identification, or

- enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use.[1]

Solvents used for the production of a dosage form but not contained in the final product are considered to be excipients, i.e. the granulation fluids, which might be dried off later, should comply with relevant requirements of pharmacopoeia unless adequately justified. Excipients no longer maintain the initial concept of "inactive support" because of the influence they have both over biopharmaceutical aspects and technological factors. The desired activity, the excipients equivalent of the active ingredient's efficacy, is called its Functionality. The inherent property of an excipient is its functionality. Excipients are usually produced by batch process; hence, there is a possibility of batch-to-batch variation from the same manufacturer. Excipients obtained from the different sources may not have identical properties with respect to use in a specific formulation. To assure interchangeability in such circumstances, users may wish to ascertain equivalency in final performance or determine such characteristics before use. Such tests are thus related to the functionality, that the excipient impart to a specific formulation.[2]

1.2. Types of excipients

1. Single entity excipients.

2. Mixtures or blends of multiple excipients.

3. Novel excipients or new chemical entities.

4. Coprocessed excipients.[1]

1.2.1. Single Entity excipients

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

i. Concomitant components.

ii. Residual processing aids.

iii. Additives.[1]

i. Concomitant Components

There is often a balance between excipient composition and functionality. Excipients frequently function because they contain concomitant components (substances in addition to the main components). These components should be considered as part of the composition profile, and thus not be construed as being undesirable, nor

confused with the presence of added substances (additives, processing aids or other components).

Note: Water can be classified as either a concomitant component or an undesirable inorganic component depending on its role in the pharmaceutical excipient.[1]

ii. Processing Aids

Processing aids are chemical substances which are used for a specific processing need or benefit in an excipients manufacturing process, e.g. to provide stabilization during the manufacturing process, to enhance a chemical synthesis reaction, to improve chemical or physical processability (e.g. filter aids) or to increase excipient yield. As for additives, the safety of processing aids must have been evaluated and shown to be suitable for the intended application. Processing aids may be removed during the excipient manufacturing process or, depending on the process clearance capability, may remain as low level residuals in the final excipient, in which case they should not impair the safety or efficacy of the finished drug products in which the excipient is used.[1]

iii. Additives

Additives are chemical substances which are intentionally added to excipients to improve their physico-chemical properties, e.g. antioxidants, stabilizers, pH modifiers or flow aids. Typically additives are incorporated by simple mixing procedures during manufacture of the excipient and are present only in the amounts required to provide their intended effect. While an additive need not be of compendial grade, it should be of an appropriate quality for the intended application and its safety must have been evaluated as suitable for its proposed use. Therefore, the additive must have no detrimental impact on either the excipient function or the final drug product efficacy/safety.[1]

1.2.2. Mixtures or blends of multiple excipients

Simple physical mixtures or blends of two or compendial or non-compendial excipients by means of low to medium shear processes where the individual components are mixed together without significant chemical change for solid mixtures or blends the individual excipient remain physically separate at a particulate level (unengineered particles). Mixed excipients may be either solid or liquid. Simple physical mixing is typically of short duration.[1]

1.2.3. Novel excipients or new chemical entities

It can be defined as excipients which are chemically modified to form new/novel excipients. These are generally 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 be brought up to current standards in relation to even that "similar" use". In this guidance, the phrase *new excipients* means any inactive ingredients that are intentionally added to therapeutic and diagnostic products, but that: (1) we believe are not intended to exert therapeutic effects at the intended dosage, although they may act to improve product delivery (e.g., enhance absorption or control release of the drug substance); and (2) are *not fully qualified by existing safety data* with respect to the currently proposed level of exposure, duration of exposure, or route of administration.[1]

1.2.4. Coprocessed 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. 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.[1]

2. NEED FOR DEVELOPING NEW EXCIPIENTS

The excipients industry to date has been an extension of the food industry. 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). IPEC is a tripartite council with representation from the United States, Europe and Japan and has made efforts to harmonize requirements for purity and functionality testing. The development of new excipients to date has been market driven (i.e., excipients are developed in response to market demand) rather than marketing driven (i.e., excipients are developed first and market demand is created through marketing strategies) and has not seen much 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 primary reason for this lack of new chemical excipients is the relatively high cost involved in excipients discovery and development. However, with the increasing number of new drug moieties with varying physicochemical and stability properties, there is growing pressure on formulators to search for new excipients to achieve the desired set of functionalities.[2]

Other factors driving the search for new excipients are

- The growing popularity of the direct compression process and a demand for an ideal filler–binder that can substitute two or more excipients

- Tableting machinery's increasing speed capabilities, which require excipients to maintain good compressibility and low weight variation even at short dwell times.

• Shortcomings of existing excipients such as loss of compaction of microcrystalline cellulose (MCC) upon wet granulation, high moisture sensitivity, and poor die filling as a result of agglomeration.

• The lack of excipients that address the needs of a specific patient such as those with diabetes, hypertension, and lactose and sorbitol sensitivity.

• The ability to modulate the solubility, permeability, or stability of drug molecules.

• The growing performance expectations of excipients to address issues such as disintegration, dissolution, and bioavailability.[2]

3. COPROCESSED 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. 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.[2]

Coprocessed excipients are prepared by incorporating one excipient into the particle structure of another excipient using processes such as co-drying. Thus, they are simple physical mixtures of two or more existing excipients mixed at the particle level. Coprocessing excipients leads to the formation of excipient granulates with superior properties compared with physical mixtures of components or with individual components. They have been developed primarily to address the issues of flowability, compressibility, and disintegration potential, with filler–binder combinations being the most commonly tried. The combination of excipients chosen 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 coprocessed 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. It can be defined as combining two or more established excipients by an appropriate process. Co-processing of excipients could lead to the formation of excipients with superior properties compared to the simple physical mixtures of the components. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price. Development of co-processed directly compressible adjuvant starts with the selection of the excipients to be combined, their targeted proportion, selection of preparation method to get optimized product with desired physico-chemical parameters and it ends with minimizing avoidance with batch-to-batch variations. An excipient of reasonable price has to be combined with the optimal amount of a functional material in order to obtain integrated product, with superior functionality than the simple mixture of components.[3]

Co-processing is interesting because the products are physically modified in a special way without altering the chemical structure. A fixed and homogenous distribution for the components is achieved by embedding them within minigranules. Segregation is diminished by adhesion of the actives on the porous particles making process validation and in process control easy and reliable. The randomized embedding of the components in special minigranules minimizes their anisotropic behaviour. So, deformation can occur along any plane and multiple clean surfaces are formed during the compaction process. Thus, the use of the co-processed excipient combines the advantages of wet granulation with direct compression. The use of one-body components is justified if it results in a potentiation of the functionalities over that of the mere dry blend of the components prepared by gravity mixture. This synergistic effect should improve the quality of the tablet equally in all aspects ranging from hardness to dissolution and/or stability. Excipient mixtures in co-processing are produced to make use of the advantages of each component and to overcome specific disadvantages, if any. Most important characteristics are the binding and blending properties of the co-processed excipients, which must be better than those of a physical mixture of the starting materials. Cost is another factor to be considered in the selection of co-processed product.[4]

3.1. Consideration of material properties

Co-processing is generally conducted with one excipient that is plastic and another that is brittle. Maarschalk reports co-processing performed with a large amount of brittle material and a small amount of plastic material, as exemplified by Cellactose in which 75% lactose (brittle material) is coprocessed with 25% cellulose (plastic material). This particular combination prevents the storage of too much elastic energy during compression, which results in a small amount of stress relaxation and a reduced tendency of capping and lamination. However, examples of the other extreme also exist (e.g., SMCC has a large amount of MCC [plastic material] and a small amount of silicon dioxide [brittle material]). These two situations exemplify the fact that co-processing is generally performed with a combination of materials that have plastic deformation and brittle fragmentation characteristics. A combination of plastic and brittle materials is necessary for optimum tableting performance. Hence, co-processing these two kinds of materials produces a synergistic effect, in terms of

compressibility, by selectively overcoming the disadvantages. Such combinations can help improve functionalities such as compaction performance, flow properties, strain-rate sensitivity, lubricant sensitivity or sensitivity to moisture, or reduced hornification.[3]

3.2. Principle of coprocessing

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, 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 solid-state 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.[2]

3.3. Co-processing of excipients

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

● Identifying the group of excipients to be coprocessed by carefully studying the material characteristics and functionality requirements

● Selecting the proportions 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 of drying such as spray- or flashdrying.[2]

4. METHODS OF COPROCESSING

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

4.1. 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.[5]

Co-spray drying

Incorporation of ingredients under dry or solid form during drying, by atomizing active compounds in solution or under the form of emulsion

Advantages:

- Possibility to associate non-miscible products in continuous operation
- Possibility to blend and dry simultaneously soluble and insoluble compounds.
- Possibility to fix and protect sensitive active compounds on neutral carrier.[5]

Merits:

1. Technical advantages:

- Improves Hardness and Compressibility.
- Better Uniformity than granulated inactives.
- 60# powder with superior flow properties.
- Enhanced machine tableting speed.
- Lower D.T.
- Consistent physical parameters of excipients ensuring sturdy formulation.
- For Dispersible formulation: For compliance with the uniformity of dispersibility test.
- With the standard practice of granulation at # 40 (425 - 500 micron) results in poor flow properties thus reducing machine speed. With coprocessed excipients the particle size of 250 micron and less

gives superior flow properties and enhanced machine speed. Due to fine particle size, formulation compliance with dispersibility test of less than 710 micron is easily achieved.[5]

2. Commercial Advantage:

- No need to maintain inventory of various excipients.
- Cost saving due to elimination of wet granulation production steps.
- Productivity increase due to increased machine speed.
- Cost saving in rework expenses.[5]

Demerits:

There are some limitation that includes limited versatility in producing particles or structures with the complex morphologies, and rapid drug release rates often exhibiting a burst effect.[5]

4.2. Solvent Evaporation

This technique has been used by companies including the NCR Company, Gavaert Photo Production NV, and Fuji Photo Film Co., Ltd. to produce microcapsules. The processes are 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 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. A variety of film - forming polymers can be used as coatings 2.[3]

4.3. 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.[6]

Procedure: For crystallization (see also recrystallization) 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 common methods used in industrial practice.[6]

4.4. Melt Extrusion

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

Merits:

- Excellent repeatibility.
- Complicate and intricate shapes are possible.
- Time required is less.[7]

Demerits:

- Equipment and die cost high.
- Minimum economic length high.[7]

4.5. 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.[8]

Table 1: Methods of Coprocessing.[2]

Method	Advantages and limitations	Examples
Chemical Modification	Relatively expensive, Requires toxicological data, Time consuming	Ethyl cellulose, Methylcellulose, Hydroxypropmethylcellulose, and Sodium carboxymethyl cellulose from cellulose, Cyclodextrin from st Lactitol
Physical Modification Grinding and/ or Sieving	Relatively simple and economical Compressibility may also alter because of changes in particle properties such as surface area and surface activation	Dextrose or Compressible sugar, Sorbitol α- Lactose monohydrate, Dibasic dicalcium phosphate
Crystallization	Impart flowability to excipients but not necessarily self-binding properties. Requires stringent control on possible polymorphic conversions and processing conditions.	β- Lactose, Dipac
Spray Drying	Spherical shape and uniform size gives spray-dried materials good flowability, poor reworkability.	Spray-dried lactose, Emdex, Fast Flo Lactose,. PH, Karion Instant, TRI-CAFOS S, Advantose 1
Granulation/ Agglomeration	Transformation of small, cohesive, poorly flowable powders into a flowable and directly compressible.	Granulated Lactitol, Tablettose
Dehydration	Increased binding properties by thermal and chemical dehydration	Anhydrous α- Lactose

5. SIGNIFICANCE

5.1. Absence of chemical change

Many detailed studies of an excipient's chemical properties after coprocessing have proven that these excipients do not show any chemical change. Detailed studies of SMCC with X-ray diffraction analysis, solid-state 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. This absence of chemical change helps reduce a company's regulatory concerns during the development phase.[2]

5.2. Physicomechanical Properties

5.2.1. Improved flow properties

Controlled optimal particle size and particle-size distribution ensures superior flow properties of coprocessed 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. The spray-dried product had a spherical shape and even surfaces, which also improved the flow properties.[2]

5.2.2. Improved compressibility

Coprocessed excipients have been used mainly in direct compression tableting 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, SMCC, and Ludipress have been reported to be superior to the simple physical mixtures of their constituent excipients. SMCC was used as an ingredient in a formulation and subjected to compaction on an instrumented tableting machine. The compression force was recorded, and a graph of the tensile strength versus the compression force was used as a comparative parameter. SMCC retained its compaction properties even at high compression forces, yielding tablets of good hardness. MCC, however, lost its compaction properties. 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 extragranular binder is 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*. This property is improved, however, when it is coprocessed into SMCC.[2]

5.2.3. 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.[2]

5.2.5. Fill weight variation

In general, materials for direct compression tend to show high fill-weight variations as a result of poor flow properties, but coprocessed 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 MCC.[2]

5.2.6. Reduced lubricant sensitivity

Most coprocessed 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. 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.[2]

5.3. Non-physico-mechanical advantages

Coprocessed excipients offer the following additional advantages:

1. Pharmaceutical manufacturers have the option of using a single excipient with multiple functional properties, thereby reducing the number of excipients in inventory.
2. Improved organoleptic properties such as those in Avicel CE- 15 (FMC Corp., Philadelphia, PA), which is a coprocessed excipient of MCC, and guar gum were shown to have distinctive advantages in chewable tablets in terms of reduced grittiness, reduced tooth packing, minimal chalkiness, better mouth feel, and improved overall palatability.
3. Although coprocessing ads some cost, the overall product cost decreases because of improved functionality and fewer test requirements compared with individual excipients.
4. Because they can retain functional advantages while selectively reducing disadvantages, coprocessed excipients can be used to develop tailor-made designer excipients. This can be helpful in reducing the time required to develop formulations.
5. Coprocessed excipients can be used as proprietary combinations, and in-house formularies can be maintained by pharmaceutical companies, which could help in developing a formulation that is difficult to reproduce and provides benefits in terms of intellectual property rights.[2]

6. LIMITATIONS

- 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.
- Coprocessed adjuvant lacks the official acceptance in pharmacopoeia [with few exceptions like Ammonio Methacrylate Copolymer Dispersions alkalinizing & antimicrobial preservative, Microcrystalline Cellulose & Carboxymethylcellulose Sodium co-attrited, Ethyl Acrylate & Methyl Methacrylate CoPolymer Dispersion suitable emulsifier, Ethylcellulose Aqueous Dispersion (Ethylcellulose, Cetanol, Sodium Lauryl Sulfate), Methacrylic Acid Copolymer Dispersion suitable surfactant,Compressible Sugar (starch, maltodextrin, or invert sugar, and suitable lubricant), confectioners Sugar (Co-ground starch sucrose (>95%)), Sugar Spheres (62.5-91.5% sucrose, chiefly starch, colour permitted)] For this reason, a combination filler binder will not be accepted by the pharmaceutical industry until it exhibits significant advantages in the tablet compaction when compared to the physical mixtures of the excipients. Although the spray-crystallized dextrose-maltose (Emdex) and compressible sugar are co-processed products, they are commonly considered as single components and are official in USP/NF.[3]

7. EXAMPLES OF COPROCESSED EXCIPIENTS

7.1. Ludipress

Ludipress, a co-processed product, consists of 93.4% lactose monohydrate, 3.2% polyvinyl Pyrrolidone (Kollidon 30) and 3.4% crospovidone (Kollidon CL). It consists of lactose powder coated with polyvinyl pyrrolidone and crospovidone. Although, Ludipress contains disintegrant, the disintegration of tablets takes longer than tablets containing β-lactose monohydrate, Tablettose and anhydrous β-lactose. At low compression force Ludipress gives harder tablets but the addition of glidant and disintegrant is needed. It is reported that binding capacity of Ludipress was higher than that of microcrystalline cellulose. The dilution potential was high (up to 70%) when aspirin was used a model drug. Baykara *et al.,* reported that the dilution potential of Ludipress R with paracetamol is lower than that of Avicel PH 101, Elcema G250 and Elcema P050. The binding properties of Ludipress, both unlubricated and lubricated with 1% magnesium stearate was found to be much better than corresponding physical mixture. Plaizier-Vercammen *et al.,* reported that the addition of a lubricant was necessary and its mixing time had little effect on crushing strength of Ludipress tablets. Authors also reported that Ludipress exhibits better tableting characteristics for low dose APIs, and good batch-to-batch uniformity than Cellactose. The compressibility of Ludipress is similar to that of Avicel PH 200. The disintegration time of Ludipress containing tablets remained unchanged at about 100 MPa compaction pressure while significant prolongation was observed with Cellactose. Schmidt and Rubensdorfer reported that the tablets manufactured with Ludipress exhibited optimum disintegration time and compaction pressure independent dissolution of glibenclamide. While, increasing compaction pressure had a negative effect on drug dissolution from compacts containing Cellactose. It has been reported that among various lactose based directly compressible excipients, Ludipress exhibited a better flow rate compared to Avicel PH 101. Ludipress exhibited highest flowability followed by Cellactose, Tablettose, Fast Flo lactose and anhydrous lactose as demonstrated by lower static and dynamic angles of repose than the other excipients. The values of compressibility could be ranked from maximum to minimum in the following order: Tablettose, Cellactose, Ludipress and Fast Flo lactose. Fragmentation propensity was from maximum to minimum in Tablettose, Cellactose, Ludipress and Fast-Flo lactose.[2]

7.2. Cellactose

Cellactose is a co-processed product consisting β-lactose monohydrate (75%) and cellulose (25%). Apart from good flowability, it has good compactibility. The compactibility is attributed to a synergetic effect of consolidation by fragmentation of lactose and plastic deformation of cellulose. Because the lactose covers the cellulose fibers, moisture sorption is much lower than that of microcrystalline cellulose alone. Aufmuth *et al.,* reported that the Cellactose exhibited increased crushing strength of the compacts along with reduced friability and lower disintegration time than the dry blend of lactose and cellulose. Armstrong et al. pointed that Cellactose exhibit the dual consolidation behaviour since it contains a fragmenting component (lactose) and a substance that consolidates primarily by plastic deformation (Cellulose). Ruiz *et al.,* and Reimerdes found that the Cellactose exhibited better compressibility compared to Ludipress, Fast Flo lactose, Tablettose, Di-pac and anhydrous lactose. Belda and Mielck found that due to co-processing Cellactose exhibited enhanced crushing strength compared to the powder mixtures each containing 25% w/w Avicel PH-101 or Elcema P-100 and 75% w/w Tablettose or lactose (100#). Casalderrey *et al.,* reported that the Cellactose tablets prepared at a compression pressure that largely eliminated macro pores had better mechanical properties but much poorer disintegration than tablets of the other blends having similar composition, particle size, and true density at the same punch pressure. Authors further reported that the tensile strength and disintegration time of Cellactose tablets decreased rapidly as the compression pressure is reduced. Gohel and Jogani prepared and evaluated co-processed directly compressible adjuvant containing lactose and microcrystalline cellulose using starch as a binder. The percentage fines, Carr's index of the agglomerates as well as friability and tensile strength of the tablets were affected by the ratio of lactose to microcrystalline cellulose and percentage of starch in

binder solution. A product containing lactose: microcrystalline cellulose (9:1) and 1% starch paste exhibited satisfactory flow, compressibility and friability. Tablets of diltiazem hydrochloride and acetaminophen prepared using the co-processed excipients exhibited satisfactory tableting properties. Gohel *et al.*, prepared and evaluated coprocessed diluents containing lactose and microcrystalline cellulose using a 23 factorial design. Ratio of lactose to MCC (75: 25 and 85:15), type of binder (hydroxypropyl methylcellulose or dextrin) and binder concentration (1 or 1.5%) were studied as independent variables. The results revealed that the lactose: microcrystalline cellulose ratio 75:25 and dextrin as a binder are better than the ratio of 85:15 and hydroxypropyl methylcellulose as a binder. The tableting properties of the developed adjuvant were ascertained using diltiazem HCl as a model drug. Gohel and Jogani prepared co-processed directly compressible adjuvant containing lactose and microcrystalline cellulose using melt granulation technique. Gohel *et al.,* demonstrated use of factorial design in development of directly compressible adjuvant of desired characteristics consisting of lactose, dicalcium phosphate and microcrystalline cellulose.[2]

7.3. Pharmatose DCL 40

It is a co-processed product consisting of 95% α-lactose and 5% anhydrous lactitol. Due to spherical shape and favourable particle size, it exhibits good flowability. It has high dilution potential than other lactose based products due to better binding property. It has very low water uptake at high humidity.[2]

7.4. Microcrystallinecellulose-Silicondioxide

Trade name- Prosolv / Silicified Microcrystalline cellulose.
Composition - Simultaneous trituration of 2% Silicon dioxide with MCC to form a dispersion of silicified MCC followed by drying.

Characteristics - When microcrystalline cellulose is silicified in the preparation of SMCC, no bulk chemical change in the MCC is observed at the resolutions tests and no observable polymorphic changes are induced. The process of silicification leads to the deposition of silicon, presumably in the form of silicon dioxide, both on the outer envelope surface of the particle and on exposed surfaces within the particle. In addition, SMCC has been shown to possess a number of pharmaceutical advantages in terms of powder flow, tablet strength, lubricant sensitivity and wet granulation. Preliminary data also suggests that the material performs well in direct compression formulations and roller compaction. Available in three grades: Prosolv SMCC 50, SMCC 90, and SMCC HD 90, which differ in average particle size and bulk density[13]. The manufacturer claim better flowability and compressibility compared to Emcocel and Avicel PH 101 or physical mixture of MCC with colloidal silicone dioxide. Author further reported that Prosolv is about 20% more compactable than regular cellulose. Fraser et al reported that silicified microcrystalline cellulose has some improvement in flow but considerably enhanced mechanical properties. Lahdenpaa *et al.*, demonstrated that Silicified microcrystalline cellulose is useful to prepare tablet containing poorly compressible ingredients by direct compression. The silicification affects the moisture sorption and the packing during tapping as well as the particle deformation during tableting. Prosolv showed slight increase in the tensile strength but marked increase in the disintegration time of the tablets compared to Avicel. Bolhuis *et al.,* demonstrated that the co-processing of microcrystalline cellulose with colloidal silicone dioxide has no significant contribution on the tablet strength of lubricated tablets containing the physical mixture of microcrystalline cellulose and colloidal silicone dioxide.[2]

7.5. Microcrystalline Cellulose–Starch

Trade name - Not recognised.

Composition - Formation of dispersion of maize-starch and solution of MCC separately. Addition of starch dispersion into MCC solution adjusting pH of the mixture followed by spray drying to produce micro-particles.

Characteristics - A new polymer type was generated from the pH and temperature controlled hybridization effected by mixing colloidal dispersions of MCC and Maize-starch. A more efficient multifunctional excipient in terms of disintegration efficiency and loading capacity for the formulation of oral tablets for rapid release of APIs by direct compression process along with other enhanced physic-mechanical properties is obtained.[3]

7.6. Microcrystalline Cellulose-Mannitol

Trade name- Avicel HFE 102

Composition - Co-processing of 90% Avicel PH102 and 10% mannitol.

Characteristics - Flow properties of Avicel HFE102 are significantly better than those of Avicel PH 102. The Avicel HFE 102 exhibits a better tabletability at a slower tableting speed, especially when lubricated. Avicel HFE 102 is also less sensitive to lubrication.[3]

7.7. MCC-Guar Gum

Trade name - Avicel CE-15

Composition - Co processed MCC and Guar gum in a common solution and spray dried.

Characteristics - Provide smoother, creamier mouth feel, less tooth-packing, and all this without sacrificing flow or compaction.[4]

7.8. MCC-Sodium Carboxymethyl Cellulose

Trade name - Avicel CL-611

Composition - Co processed MCC and sodium carboxymethyl cellulose via co-drying process.

Characteristics - Impart a thixotrophic viscosity profile, and increase formulation stability across a wide range of pH. Used as a stabilizer.[4]

7.9. MCC–Calcium Carbonate

Trade name - Not recognised.

Composition-Co-processed from MCC and Calcium carbonate by spray drying.

Characteristics - a mixture with very good compactibility as compared MCC alone. Also has a little lubricant sensitivity. Along with PVP and Mg-St produces direct compressible powder.[4]

7.10. Lactose–Cellulose

Trade name - Cellactose.

Composition - co processed α-lactose and cellulose.

Characteristics - improved flow property and high dilution potential along with excellent binding properties.[4]

7.11. Lactose-Microcrystalline Cellulose

Trade name - Microcelac 100.

Composition - A co processed spray dried filler/binder for direct compression and composed of 75% w/w a-lactose monohydrate and 25% w/w microcrystalline cellulose.

Characteristics - Superior flow ability and binding properties compared to physical mixtures of microcrystalline cellulose with different lactose grades e.g. α-lactose monohydrate (lactose 100 M), anhydric β-lactose (Pharmatose DCL21), and spray dried lactose (Pharmatose DCL11). It also shows the least lubricant sensitivity.[4]

7.12. Lactose-Maize Starch

Trade name – StarLac

Composition - A co processed spray dried filler/binder for direct compression and composed of α-lactose monohydrate and Maize-starch.

Characteristics - The new product should combine the good flowability and plastic deformation of spray-dried lactose with the elastic deformation and rapid disintegration of native maize starch. StarLac demonstrated good compactibility and release behaviour. It exhibited deformation behaviour with higher parts of plastic and elastic deformation than FlowLac, therefore StarLac is of interest for the manufacture of pressure-sensitive drugs. The advantage of Starlac are its good flowability depending on the spray-drying process, an acceptable crushing force due to its lactose content, its rapid disintegration depending on starch. Gohel and Jogani demonstrated use of multiple linear regression in development of co-processed lactose and starch. Authors concluded that as the lactose/starch ratio increased Carr's index of the adjuvant and crushing strength of the tablets increased while friability decreased. Percentage of starch paste has inverse effect on the friability.[4]

7.13. α-Lactose Monohydrate & β-Cyclodextrin

Trade name - Not recognised.

Composition - Co processed by taking 75:25 and 60:40 ratio of α-lactose monohydrate & β-cyclodextrin via spray drying.

Characteristics - Excipient with good flowability, compressibility and compactibility. The limitations of β-CyD for its flowability and lubricant sensitivity is overcome.[4]

7.14. Pregelatinised Starch

Trade name - Insta starch / Lycatab / Sepistab.

Composition - By heating aqueous slurry containing up to 42% w/w of starch at 62-720C, having additives such as gelatinisation aid (salt or bases) and surfactants. Then they are spray-dried, roll-dried or drum-dried.

Characteristics - As binder-diluent in oral capsule and tablet. Having enhanced flow and compression characteristics. Tablet-binder in dry compression.[4]

7.15. Copovidone

Trade name - Kollidon VA 64/Plasdone S 630.

Composition - Copovidone is a linear random co-polymer based on N-vinyl-2 pyrrolidone and vinyl acetate in the ratio of 6:4 by mass.

Characteristics - Copovidone is a white/yellow-white with fine particle size and excellent flow properties. Dry Binder in Tablets (Direct compression), Binder in Tablets, Pellets & Granules (Wet Granulation), Dry Binder in Granules (Roller Compaction), and Film Former for tablet Film Coating & Sugar Coating, Film Former for Subcoating Tablets and Matrix Former for Melt-Extrusion for tablets.[4]

7.16. Mannitol-Povidone

Trade name - Ludiflash.

Composition - Coprocesed blend of 90% Mannitol, 5% Kollidon CL-SF (Crospovidone) 5% Kollicoat SR 30 D (polyvinyl Acetate).

Characteristics - Specially designed for directly compressible, high speed tableting and hard tablet with very low friability. Ludiflash have good flowability, less water absorption, and no segregation of the active ingredients.[5]

7.17. Orocell

Trade name - Orocell 200 & Orocell 400.

Composition - Spheronised mannitol with different particle size.

Orocell 200 with 90% mannitol (<315µm)

Orocell 400 with 90% mannitol (<500µm).

Characteristics - A developed filler-binder with high dilution potential and good disintegrating property useful for orally disintegrating tablets.[5]

7.18. Cellulose-Calcium Sulphate

Trade name - Cel–O–Cal.

Composition - Coprocessed from Cellulose and Calcium sulphate by spray drying.

Characteristics - Used widely as a filler.[5]

7.19. Fructose

Trade name - Not recognised.

Composition - Fructose coprocessed with polysaccharide.

Characteristics - Good flowability and ccompressability.[5]

7.20. Other Carbohydrates

Trade name - F-melt type C & M.

Composition - Coprocessed by forming dispersion at a fixed ratio followed by spray drying and is produced from Mannitol, Xylitol, Calcium sulphate, and Crospovidone.

Characteristics - F-MELT exhibits excellent tabletting properties and facilitates rapid water-penetration for a fast disintegration time. It has advantages of highly flowable with spherically dense particles, less sticking or capping, excellent tablet hardness and low friability, high API Loads.[5]

7.21. Chitin-Sillica

Trade name - Not recognised.

Composition - Coprocessed by coprecipitation from a mixed dispersion of Mg-sillicate and Chitin followed by oven drying and passing through 200µm sieve.

Characteristics - Minimises the deleterious effect of Mg-silicate. The physical interaction between chitosan and silica create an insoluble, hydrophilic highly absorbent material, resulting in superiority in water uptake, water saturation for gelling formation. It has water wicking and swelling properties. It is super-disintegrant with improved flow and compaction proper-ties. It acts as super-disintegrant and filler both. Super disintegrant property as compared to that of Avicel-silicate.[5]

7.22. HPMC-Lactose

Trade name - Not recognised.

Composition - Agglomerates (60-80#) are prepared using different proportions of hydroxypropyl ethylcellulose, lactose and starch. 5% polyvinyl pyrrolidone in isopropyl alcohol is used as agglomerating agent. Characteristics- A proper combination of HPMC (bio-adhesive and hardness), lactose (flow and compressibility), and starch (synergist in bio-adhesion) yield a co-processed, directly compressible multipurpose excipient that can serve as a diluents and a bio-adhesive material.[4]

Table 3: Examples of Coprocessed excipients

Trade Name	Excipients	Supplier	Manufacture
Dipac	Sucrose (97%) Dextrin (3%)	Domino	
Emdex	Dextrose (92%) Maltose (4%) Maltodextrin (4%)	JRS	Spray Crystallised
SugarTab	Sucrose (93%) Invert sugar (7%)	JRS	Cocrystallised
Compressol S (Pharmaburst)	Mannitol (70-97%) Sorbitol (3-30%)	SPI	Melt Extrusion
TimerX	Xanthan Locust Bean Gum Calcium Sulphate Filler	Endo	Granulate
Xylitab 200	Xylitol (98%) SCMC (2%)	Danisco	Granulate
Xylitab 100	Xylitol (96.5%) Polydextrose (3.5%)	Danisco	Granulate
StarCap 1500	Corn Starch (85-95%) Pregelatinised Starch (5-15%)	Colorcon	Co-spray dried
Advantose FS	Fructose (95%) Starch (5%)	SPI	Codried
PanExcea MHC 333G	MCC HPMC Crospovidone	Covidien	Granulated
Formaxx	Calcium Carbonate (70%) Sorbitol (30%)	EMD	Coprocessed (unique process)

8. REGULATORY CONCERN

As excipients are incorporated in the final formulations that also remain in the final product they should have safety concern. To support marketing authorisation (MA) applications, increased information is required on active ingredients. Genuinely new excipients, those not previously registered with the regulatory authority, are to undergo a full safety evaluation, because of the requirement in Directive 75:318: EEC. Compatibility of excipients with other ingredients may have to be demonstrated in the development pharmaceutics (Euro Direct 155:96) and analytical validation (European Commission, 1998b) sections of the MA application dossier. An excipient can be the subject of a 'PhEur Certificate of Suitability' (Council of Europe Resolution, 1998) which can partly and sometimes fully satisfy the data requirements, within a MA application dossier, for that ingredient (European Commission, 1998). 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 agencies.[3]

Independent Evaluation: The IPEC New Excipient Safety Evaluation Procedure

• Excipient manufacturers submit dossiers in DMF format to independent expert committee who evaluates:-

Ø Newness

Ø Bridging arguments

Ø Safety data and rationale for co-processed excipient safety

• FDA/global health authority would consider results during drug registration

Ø Retain authority to approve final drug product

• Positive appraisal from independent expert committee limits risk of FDA rejection of drug based on excipient

Ø Could encourage innovation & minimize risk for pharmaceutical company.[1]

Current Status of Co-Processed Excipient Monographs in Nf

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 coprocessing. That is, the manufacturing process for one component may not have been taken to completion before the addition of the other components, and/or the co-processed excipient combination cannot be adequately controlled using the monograph tests for the individual component excipients. Because many co-processed excipients contain a macromolecular excipient as one of the constituents, responsibility for reviewing these monographs and recommending them for inclusion in NF falls within the purview of the EM2 Expert Committee, one of three Expert Committees that set excipient standards for NF in USP's Council of Experts.

The co-processed excipient monographs meet current NF submission requirements as defined by the following: Each of them is either included in an approved drug application (in the FDA inactive ingredient database) or has a Generally Recognized as Safe (GRAS) designation. The excipients typically are manufactured using some type of specialized manufacturing process such as high-shear dispersion, granulation, spray drying, or melt extrusion. Such combination excipients produced using these specialized manufacturing processes are commonly called co-processed excipients.[2]

Recommendations from EM2 Expert Committee

The Expert Committee has formulated the following guidelines that may help determine whether or not such combination excipients are co-processed and whether they will be eligible to be considered for a NF monograph.

1. A co-processed excipient is a combination of existing pharmacopoeial excipients, and it must be distinguishable in at least one non–performance-related property from the admixture obtained by physically mixing the corresponding constituent excipients. A co-processed excipient typically is produced by some specialized manufacturing process such as high-shear dispersion, granulation, spray drying, or melt extrusion. When it is submitted as a potential NF monograph, information relating to its quality must meet current NF submission requirements:

The claimed co-processed excipient is either included in an FDA-approved drug application or has a GRAS designation or is under special consideration by the Council of Experts.

2. A physical mixture of the various excipient components which have not been individually modified in order to change their inherent thermodynamic state prior to being physically mixed will not quantitatively exhibit one or more characteristics of the co-processed excipient. Co-processed excipients demonstrate one or more different properties regardless of whether a comparative analysis is performed using the physical mixture as is or using a sample of the physical mixture whose particle size distribution is very similar to that of the co-processed excipient. This or other characteristics of the co-processed excipient can be determined by a suitable test method.

3. The physical or chemical characteristic(s) of the coprocessed excipient that differ from those of the physical mixture may cause or may be correlated with improvements in the performance of the finished product. However, these unique characteristic(s) must be inherent, demonstrably analyzable, and quantitatively different in the co-processed excipient itself before incorporation into the finished product. Thus, if the proposed co-processed excipient does not exhibit any analytical differences from the physical mixture, then it may not be considered a coprocessed excipient even if it alters the performance of the finished product.

4. At least one of the components of the co-processed excipient is capable of being analyzed qualitatively and quantitatively in the co-processed state, i.e., without the use of any specific physical or chemical methods to separate the components of the coprocessed excipient before analysis of the individual component(s).

5. No unintended covalently bonded chemical entity is formed when the individual ingredients are mixed to form the co-processed excipient. The absence of any chemical reaction(s) between individual ingredients in the co-processed excipient must be analytically demonstrated initially and over the proposed storage period of the co-processed excipient. However, intentional in situ salt formation, or formation of a known excipient by in situ polymerization or covalent cross-linking would be allowed.

6. The individual ingredients used in a co-processed admixture must have USP–NF monographs, or at least monograph proposals published in Pharmacopeial Forum as part of in-process revision. This does not necessarily imply that those individual ingredients must demonstrably meet monograph specifications in USP–NF before being incorporated or processed into the co-processed excipient. Indeed, this may not be possible because one or more individual component of the co-processed excipient may not be capable of being isolated before co-processing.

7. However, the proposed co-processed excipient cannot be considered for inclusion as a monograph in NF if its

production or manufacture involves incorporation of a noncompendial ingredient. In such cases, the co-processed excipient is excluded from NF regardless of whether or not the noncompendial ingredient is isolated before co-processing. Thus, if a sponsor wishes to propose a monograph for a coprocessed excipient that contains a noncompendial excipient, the sponsor would first be required to secure an approved NF monograph for the noncompendial excipient.[9]

9. FUTURE PROSPECTIVE

The particular phenomenon of co-processed excipient is a field having vast scope for development of excipient with desirable property for direct compression as well as for specific method and formulation. The limitation of the existing excipients for new rapidly developing API's can be overcome. The process also opens opportunity for development and use of single multifunctional excipient rather than multiple excipients in formulation. Now a day's many excipients are also being co-processed directly with API's to develop a composition ready for direct compression, e.g. co-spray drying of acetaminophen, mannitol, erythritol, maltodextrin and a super disintegrant in spray dryer yields powders with improved tablet disintegration in combination with acceptable physicochemical powder properties, tablet hardness and friability, while Kollidon CL minimised tablet disintegration time. Also some of the excipients can be co-processed to have a better physio-chemical property, e.g. granules of Carbopol and MCC prepared from dried sodium hydroxide solution is pressed into tablet and is used for treatment of gastro-esophageal reflux. Newer excipients are being developed to aid in targeted drug delivery e.g peptide Dalargin to brain using Polyisobutyl cyano acrylate whose surface is being modified with Tween 8021. 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.[3]

10. CONCLUSION

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 marketplace. The success of any pharmaceutical excipient depends on quality, safety, and functionality. Although the first two parameters have remained constant, significant improvements in functionality open the door for the increased use of co-processed excipients. The advantages of these excipients are numerous, but further scientific exploration is required to understand the mechanisms underlying their performance. With development a number of new chemical entity rising day by day, there is a huge scope for further development of and use of these excipients in future. Exploring material property of natural polymers and co-processing them with the existing ones will create a large inventory of new developed excipients. Rather than developing an entirely new excipient which would have to undergo a full safety evaluation, and would be enormously expensive, it is better to develop physico-mechanical property of an established product. IPEC New Excipient Safety Evaluation Procedure should be used for co-processed excipients to reduce regulatory uncertainties. IPEC will be developing a guideline on Co-processed excipients to further clarify an appropriate approach.

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