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Review Article

REASSESSMENT OF NOVEL CO-PROCESSED MULTIFUNCTIONAL EXCIPIENTS

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Abstract: Co-processed excipients, wherever, excipients are commingled by virtue of sub-particle level interaction have provided an attractive tool for developing high functionality excipients. The multifold advantages offered by co-processed excipients such as output of synergism in functionality of mortal components, diminution of company's regulatory concern because of absence of chemical process during co-processing and improvement in physico-chemical properties have built up their use in the pharmaceutical industry. The excipient industry, which bears largely comprised an extension of the food industry, has adopted the novel usage of particle engineering and material sciences to pave the way for a Modern category of functional excipients called co processed multifunctional excipients. The co-processing comprises the most widely explored method for the formulation of directly compressible adjuvants because they are cost effective and can be prepared in-house based on the functionality required. This reassessment article is in pursuance of affording elaborated information on the sources of new excipients, potential advantages of co-processed excipients, material characteristics required for co-processing, methods of preparing various co-processed excipients for direct compression available in the market.

Key**words:** co processed excipients, co-processing, High Functionality excipients, particle engineering.

History of Co-Processed Multifunctional Excipients

Co-processing of excipients in the pharmaceutical industry can be dated back to the late 1980s with the introduction of co-processed microcrystalline cellulose and calcium carbonate, followed by cellactose in 1990[1], which is a co-processed combination of cellulose and lactose but Co-processing was initially used by the food industry to improve stability, wettability, and solubility and to enhance the gelling properties of food ingredients such as co-processed MCC and glucomannan, glucomannan and galactomanan [2,3].

What Is Co-Processing

Co-processing is another way that new excipients are coming to market without undergoing the rigorous safety testing of a completely new chemical. 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 their components[4].

Aim and Object of Co-Processing

The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price. The mechanism that occurs during the co-processing procedure is not fully understood but appears to yield a particulate product in which the components are in intimate association with each other. This intimate association cannot be achieved through simple dry blending of components, but rather requires that they can be co-processed by an appropriate process. 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[5].

Co-Processed Excipients

The IPEC- composition guide draft defines co-processed excipients are co-processing of two or more than two compendial or non-compendial excipients. They are designed for modification of physical properties which was not achievable by simple physical mixing. Excipients with improved functionality can be obtained by developing new chemical excipients, new grades of existing materials, and new combinations of existing materials[6]. Developing a new chemical excipient is uneconomical and must undergo various stages of regulatory approval aimed at addressing issues of safety and toxicity. Developing new grades of existing excipients (physicochemical) has been the most successful strategy for the development of new excipients in past three decades like pregelatinized starch, croscarmellose, and crospovidone. However, functionality can be improved only to a certain extent because of the limited range of possible modifications. New combinations of existing excipients are an interesting option for improving excipient functionality because all formulations contain multiple excipients. Combination excipients fall into two broad categories: physical mixtures and co-processed excipients. Now a day's co-processing seems to be interesting chance because the multifunctional excipients are prepared in a special way physically modified without altering the chemical structure and stability. Co-processing of 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[7,8].

Need For Developing Multifunctional Excipients

The continued popularity of solid dosage forms, a narrow pipeline of new chemical excipients, and an increasing preference for the direct-compression process creates a significant opportunity for the development of high-functionality excipients. 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.

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.

Advantages, Properties And Limitations Of Multifunctional Excipients

Co-processing excipients leads to the formation of excipient granulates with superior properties compared with physical mixtures of components or with individual components. The process is carried out to bring about a synergistic change in the individual undesirable property or improve the same. The following properties are being the criterion;

Improved flow properties:

Co-processed excipients show superior flow properties by controlled optimal particle size and particle-size distribution. Ex: cellactose shows better flow characteristics than lactose or a mixture of cellulose and lactose[9].

Improved compressibility:

There is a tremendous improvement in the pressure–hardness relation of co-processed excipients, as compared with simple physical mixtures. The co-processed excipients showing a marked improvement in the compressibility profile.

Ex: Cellactose, SMCC and Ludipress shows superior compressible properties than simple physical mixtures of their constituent excipients

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[10].

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[11]. 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.

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 MCC.

Co-processed excipients offer the following additional advantages:

- Pharmaceutical manufacturers have the option of using a single excipient with multiple functional properties, thereby reducing the number of excipients in inventory.
- Some cost, the overall product cost decreases because of improved functionality and fewer test requirements compared with individual excipients.
- Co-processing excipients help in designing tailor-made excipients. They can retain functional advantages and selectively reduce disadvantages.

- Reduction in development timelines and process validation efforts
- Co-processed excipients by virtue of non-obvious advantages hold the possibility of patenting the dosage form.

Limitations:

- Major limitation of co-processed excipients mixture is 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 dose per tablet under development.
- Co-processed adjuvant lacks the official acceptance in pharmacopoeia.

Steps Involved In Coprocessing

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

a) Identifying the group of excipients to be co-processed by carefully studying the material characteristics and functionality requirements.
b) Selecting the proportions of various excipients.
c) 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.
d) Selecting a suitable process of drying such as spray- or flash drying.
e) Development of controlled production parameters to avoid batch to batch variation

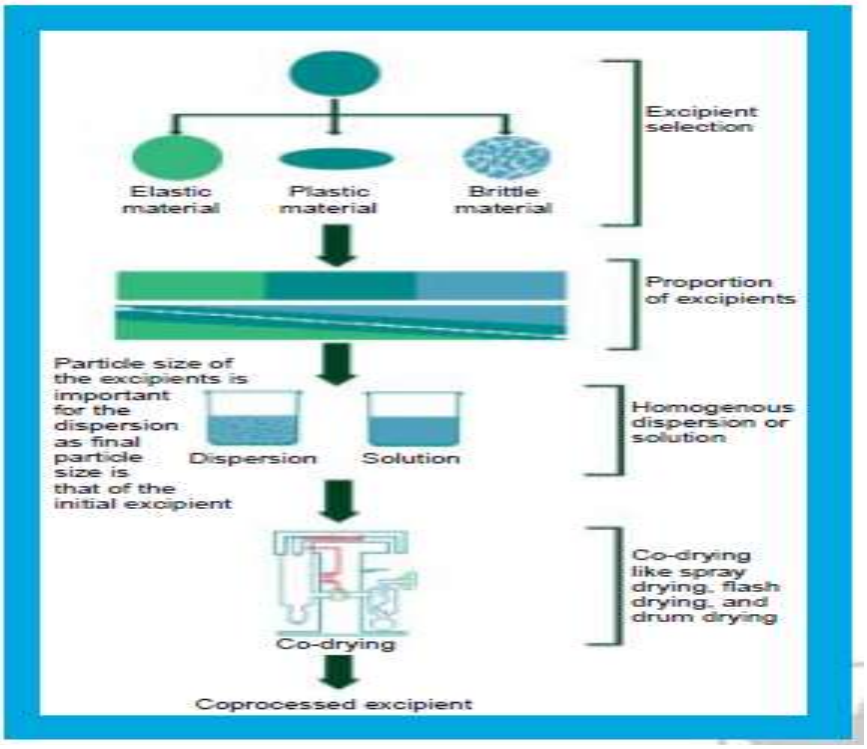

Figure 1:Schematic representation of steps involved in co-processing

Selection of the excipients to be coprocessed

Excipients selection is most important task to go for co-processing technique. Materials, by virtue of their response to applied forces, can be classified as elastic, plastic, or brittle material. But, pharmaceutical materials exhibit all three types of behavior, with one type being the predominant response. This makes it difficult to demarcate which property is good for compressibility. Maarschalk reports co-processing performed with a large amount of brittle material and a small amount of plastic material, as exemplified by Cellactose (Meggle Corp.) 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. 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. A few examples of co-processed excipients that are developed by co-processing brittle and plastic materials are enlisted in **Table 1.** However, co-processed excipients are also developed by co-processing of two plastic materials or two brittle materials (for example Dipac). **Table 2** provides a list of co-processed excipients that are developed by co-processing of two or three plastic materials.

Table 1: Co-processed excipients developed by co-processing brittle and plastic materials

Excipients Co-processed		Improved properties compare to physical blend	Reference
Brittle Component	**Plastic Component**		
Colloidal silicon dioxide	MCC	Novel MCC based excipient is free flowing ,posses excellent disintegration properities has improved compressibility relative to normal off the shelf commercially available MCC.	[25]
Dibasic calcium phosphate	HPMC crospovidone	Has increased flowability ,an increased API loading and blendin and higher compactability	[26]
Calcium phosphate	MCC	Novel MCC based excipient has improved compactability and recompactability	[27]
β lactose	Sorbital	Produce tablet with improved recompactability	[28]
Calcium carboante	MCC	Novel MCC based excipients has improved recompactability	[29]
Lactose	Polyviny Pyrrolidine (PVP) Crospovidone	Novel excipient posses good flowability and good compressibility under low pressure Produce tablets that exhibit excellent disintegration properties coupled with great hardness and low abrasion	[30]

Table 2: Co-processed excipients developed by co-processing two/three plastic materials

Excipients Co-processed	Improved properties over physical blend	Reference
MCC Guar gum	Improved smell, taste, texture and mouth feel.	[31,32]
Mannitol, Sorbitol	Good compactability and less hygroscopicity	[33]
MCC HPMC	Better flowabilty and higher compactability. Retains compressibility on wet granulation	[34]
MCC HPMC Crospovidone	Exhibit enchanced flowability, excellent compactability, increased API loading and blendability	[35]

Methods of Coprocessing

Co-processing methods are generally simple, versatile and well known. Co-processing method, along with its experimental conditions plays a very critical role in the development of co-processed excipients. The methods employed for co-processing of excipients are

1) Spray Drying:

Co-processing of excipients using spray drying technique involves atomizing the solution or homogenous dispersion of the excipients to be co-processed into fine droplets. Fine droplets are then thrown radially into moving stream of hot gas. The increased droplet surface area and high temperature causes the formation of spherical particles, which makes them suited for the direct compression process. Precise control of various spray drying process parameters like inlet air temperature, atomization air pressure, feed rate, liquid viscosity, solid content in the feed, disc speed can help in designing particles with desired characteristics. Spray drying by virtue of precise control over particle characteristics and easy scale up has been extensively used for the production of co-processed excipients[12].

2) Fluid Bed Spray Granulation (FBSG):

FBSG method of co-processing involves spraying a solution of one excipient onto a fluid bed of other excipient, drying and optionally screening to obtain the granules of co-processed excipients. Menon *et al.* described FBSG for co-processing of corn starch and polyvinyl pyrrolidone. The developed co-processed excipient is free flowing and exhibit good compressibility[13]. Davar *et al.* described co-processing of sodium carbonate with poly ethylene glycol using FBSG technique. Co-processing of sodium carbonate with poly ethylene glycol protect it from moisture, thus, prevent caking of sodium carbonate. The developed co-processed excipient was used as pH modifying agent in non-effervescent pharmaceutical composition of zolpidem or scopolamine[14]. Al Omari *et al*developed co-processed excipient containing α-chitin and mannitol. Co-processed α-chitin and mannitol was used in the preparation of orally disintegrating tablets. Tablets made with this improved composite exhibit low friability, low ejection force and hardness sufficient to be processed in high speed tableting machines, while retaining rapid disintegration or dissolution properties[15].

3) Wet Granulation:

Co-processing of excipients using wet granulation technique simply involves wet massing of the blend of the excipients to be co-processed with a granulating liquid, wet sizing, drying and finally screening of dry granules. Wet granulation is a cost-effective method of co-processing as it can be adopted for conventional equipments like a planetary mixer/high shear mixer and requires validation of fewer process variables[16].

4) Dry Granulation/Roller Compaction:

In this technique a uniform powder blend of the excipients to be co-processed is compressed between counter rotating rollers to form a ribbon of compacted material that is then milled into granules. Roller compaction is suitable for co-processing of moisture or heat sensitive excipients because there is no drying. Bauer *et al.* described co-processed excipient derived from a polysaccharide product and an insoluble disintegrating agent. The polysaccharide is powdered and/or MCC and insoluble disintegrating agent comprise acrylamide homopolmer, acrylic acid homopolymer and/or acrylic acid-acrylamide copolymer. The polysaccharide based coprocessed excipient was used as tablet disintegrant and as dispersion or suspension stabilizer in the manufacture of liquid and semi-solid preparation[17].

5) Melt Granulation:

Melt granulation method of co-processing involves mixing, the blend of excipients to be co-processed, with a balance amount of meltable binder (that is binder is in solid state at room temperature but melts in the temperature range of 50-80^{0}C). The mixture is then heated with continuous blending in order to break the mass into agglomerates. The agglomerates are then cooled to room temperature and finally screened to obtain the granules of desired size. Melt granulation technique eliminates the use of water or any other solvent, requires only a short processing time and can be adopted for conventional equipment. Cucula *et al.* described melt granulation technique for coprocessing calcium phosphate with fatty acid wax. The fatty acid wax is preferably glyceryl behenate or glyceryl palmitostearate[18]. Co processing of calcium phosphate with fatty acid wax overcomes the abrasiveness and capping issues normally associated with calcium phosphate. Coprocessed calcium phosphate and fatty acid wax is used in the preparation of venlafaxine HCl modified release tablet and venlafaxine besylate extended release tablet[19].

6) Roller Drying:

Co-processing of excipients *via* roller drying involves preparing a homogenous solution or dispersion of the excipients to be co-processed and then drying of the resultant solution or dispersion on a roller dryer. This technique has been adopted by Meggelaars *et al.* for co-processing lactose with sugar alcohol. The sugar alcohol is preferably sorbitol or lactitol. In this particular case, the rolling temperature should be sufficiently high, so as to obtain a product that consists principally of β-lactose in crystalline form. Novel co-processed β-lactose and sugar alcohol is used as pharmaceutical excipient in the preparation of direct compression tablets with improved hardness.

7) Co-precipitation:

Co-processing of excipients *via* co-precipitation may include any industrial technique known such as wet or dry granulation, pH change co-precipitation, spray drying, freeze drying or simple solution mixing. Co-precipitation by pH change has been adopted by Badwan *et al.* for co-processing starch (corn starch) with silica (colloidal silica). The method involves preparation of an alkaline solution of colloidal silicon dioxide to which corn starch was slowly added with vigorous stirring. The pH of the mixture was adjusted with hydrochloric acid to pH 7.0. The solid particulates of silicate starch were then filtered out and dried up in the oven. The novel silicate starch is used as filler and disintegrant in immediate release solid dosage forms[20].

8) Co-transformation:

Co-processing of excipients *via* co-transformation involves the application of heat or a solvent to temporarily "open-up" the particles of one excipient and then adding another excipient into the "opened-up" particles. This technique has been adopted by Staniforth for coprocessing superdisintegrant with an augmented agent. The superdisintegrant is preferably sodium carboxymethylstarch cross-linked or sodium carboxymethylcellulose cross-linked. The augmenting agent can be a water soluble polymer such as maltodextrin, surfactant such as poloxamer, oil such as stearic acid or a mixture of the above mentioned augmented agent. The co-transformed superdisintegrant has improved compressibility and can, therefore, be used in the formulation of high dose drug[21-23].

9) Milling

Milling or dry grinding for the production of coprocessed excipients may be carried out in a roller mill, a ball mill, a bead mill, a millstone mill, a jet mill, and a hammer mill. Ball milling has been adopted by Rao *et al*. for co-processing cross-linked polyvinylpyrrolidone and calcium silicate. In this particular case, ball mill was operated for hours at a speed of 200 rpm using 25 stainless steel balls. The co-processed binary mixture of cross-linked polyvinylpyrrolidone and calcium silicate enhances the rate and extent of dissolution of a poorly soluble drug[24].

Regulatory Perspective of The Coprocessed Excipient

Combinations of excipients via co-processing do not produce any chemical change in the incorporated excipients and all the reflected changes are at the physical level. Otherwise stated, in case of co-processed excipients, the components, the component combination and the manufacturing process are not novel. The only novel parameters are the physical form and the improved functionality. Hence, the coprocessed excipients do not require any toxicological assessment and can be considered as safe if the parent excipients are generally regarded as safe (GRAS) by the regulatory agencies. A very limited number of co-processed excipients are described in official monograph for example Dispersible Cellulose (British Pharmacopoeia), Compressible Sugar (United States Pharmacopoeia/National Formulary). Their non-official status is the major hindrance to their success in the market place. This obstacle is likely to be overcome in the near future as with IPEC New Excipient Safety Evaluation Procedure (NESEP), excipients now could be reviewed outside the FDA drug approval process (NDA). Positive feedback from IPEC expert committee will limit the risk of FDA rejection of drug based on excipient and could encourage innovation in the excipient industry[36].

Current & Future Developments

The continued popularity of solid dosage forms, introduction of high speed tablet machines, and an

increasing preference for the direct compression process creates a wonderful opportunity for the development of high functionality excipients. A narrow pipeline of new chemical excipients and improved grades of existing excipients has opened the door for the increased use of co-processed excipients. Co-processed excipients offer numerous advantages, especially, simple and cost effective methods of production and reduced data burden. Owing to their non-official status, co-processed excipients are still not widely accepted by the pharmaceutical industry. Considering IPEC initiative in terms of NESEP, the future for co-processed excipients looks very promising. With upcoming newer combination of excipients and newer methods of co-processing, co-processed excipients are for sure going to gain attraction both from academia and pharmaceutical industry.

Conclusion

Co-processed excipient comprises of combining two or more compendial or non-compendial excipients configured to physically alter their attributes in a way not accomplishable by simple physical mixing and without substantial chemical process. Co-processing is undergoing appreciable aid since the individual constituents are added to in a peculiar process without modifying the chemical structure. Co-processing of excipients forced out excipients with superior attributes equated to the simple physical mixtures of their constituents. The primary aspire of co-processing is to find a product with imparted assess accompanying the ratio of its functionality/cost. Almost formulations comprise excipients at a more eminent concentration than the active pharmaceutical ingredient (API) and as a result excipients contribute critically towards processing, stability, safety and functioning of solid dosage forms. The majority of the excipients that are currently obtainable fail to meet the desired set of functionalities in the inventing of different dosage form primarily tablets. Accordingly, create urging for the development of high functionality excipients.

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