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Review on Co-Processed Excipients

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ABSTRACT: There is need of pharmaceutical industry for excipients with improvised properties to aid fast and cost effective development and processing. This need is due to limitations of existing excipients failing to comply with all the functionalities of an ideal excipient. Co-processed excipient has received much more attention in the formulation development of various dosage forms, specially for tablet preparation by direct compression method. The objective of this review is to discuss the emergence of co-processed excipients as a current and future trend of excipient technology in pharmaceutical manufacturing. Co-processing is a novel concept of combining two or more excipients that possess specific advantages that cannot be achieved using a physical admixture of the same combination of excipients. This review article discusses the advantages of co-processing, the need of co-processed excipient, general steps in developing co-processed excipient, limitation of co-processed excipient, technologies used in developing co-processing excipients, co-processed excipients in the literature, marketed products and future trends.

KEYWORDS: Co-processed excipient, Co-processing,Direct-compression,Partical engineering

I. INTRODUCTION

The International Pharmaceutical Excipients Council (IPEC) defines excipient as substances save for the API that are befittingly evaluated for safety and are by design enclosed in a very drug delivery system (1). Excipient can be classified into four categories generally: Single entity excipient, A physical blend of multiple excipients, New chemical entity excipient and Co-processed excipient. It is generally agreed by the formulation scientist that there is no single-component excipient fulfills all the requisite performance to allow an active pharmaceutical ingredient to be formulated into a specific dosage form (49,50). Excipients are a chemically diverse group of materials, and including all states of matter (solid, liquid, gas and semi-solid). Some may be manufactured using batch processing, but many are manufactured using of the limitations of the active pharmaceutical ingredient(s) (APIs) concerning the manufacture and stability of those products, and to facilitate their use and release and/or delivery of the drug after administration to the patient (2).

TYPE OF EXCIPIENTS:

1. Single entity excipients.
2. Mixtures/blends of multiple excipients.
3. Novel excipients or new chemical organization.
4. Co-process excipients.

1. Single entity excipients: It is defined as excipients containing one component which is the primary component called as single entity excipients (6).

2. Mixture/blends of multiple excipients: Simple physical mixtures of two or compendial /non-compendial excipients by means of low to medium shear process where the individual components are mixed together without significant chemical change for solid mixture/ blends the individual excipient remain physically separate at a particulate level.

3. Novel excipients or new chemical entities: It is defined as excipients which are chemically modified to form new/novel excipients. These are generally not listed in FDA inactive ingredient database. The new excipient means any inactive ingredient that are intentionally added to therapeutic and diagnostic products (7).

4. 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

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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 (2). Co-processing of excipients may lead to formation of new excipients with added value (3).

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 (16), 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 coprocessed (Microcrystalline Cellulose) MCC and glucomannan and galactomanan (17,18).

Aim and Objectives: 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 (4).

NEED: 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. 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. 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.
- Growing performance expectations of excipients to address issues such as disintegration, dissolution, and bioavailability.
- 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.
- Tableting machinery's increasing speed capabilities, which require excipients to maintain good compressibility and low weight variation even at short dwell times (5).

IDEAL PROPERTIES OF CO-PROCESSED EXCIPIENTS:

1. Absence of chemical change:

Many detailed studies of excipient chemical properties after co-processing have proven that these excipients do not show any chemical change. No covalently bonded chemical entity is formed when the individual ingredients are combined to form the co-processed excipients. The absence of the formation of covalent bonds between individual ingredients in the co-processed excipient must be analytically demonstrated over the proposed shelf life or retest period of the co-processed excipient (8). This absence of chemical change helps to reduce a company's regulatory concerns during the development phase.

2. Physico-mechanical properties:

a. Improved flow property: Controlled optimal particle size and particle-size distribution ensures superior flow properties of co-processed excipients without the need to add glidants (9). The volumetric flow properties of SMCC (Silicified Microcrystalline Cellulose) were studied in comparison with MCC. The particle-size range of SMCC was found to be similar to that of the parent excipients (10).

b. Better dilution potential: 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 (11).

c. Fill weight variation: 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 (10). The co-processed excipient made up of calcium phosphate has shown a uniform particle size distribution which leads to lower segregation of particles and hence a lower weight variation as compared to individual excipient (12).

d. Improved compressibility: Co-processed 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 compressibility performance of excipients such Cellactose (19), SMCC and Ludipress have been reported to be superior to the simple physical mixtures of their constituent excipients. Excipients such as MCC lose compressibility upon the addition of water, this phenomenon called as 'quasihornification'. This property is improved, however, when it is co-processed into SMCC.

e. 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. The plastic material provides good bonding (10).

3. Non physico-mechanical proparties:

Pharmaceutical manufacturers have the option of using a single excipient with multiple functional properties, thereby reducing the number of excipients in inventory. Because they can retain functional advantages while selectively reducing disadvantages, co-processed excipients can be used to develop tailor-made designer excipients. This can be helpful in reducing the time required to develop formulations. Improved organoleptic properties such as those in Avicel CE-15, which is a co-processed 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. Although co-processing adds some cost, the overall product cost decreases because of improved functionality and fewer test requirements compared with individual excipients (4).

4. Co-processed excipients and its advantages in Quality by design (QbD):

The advantages of using high performance excipients in QbD include wider design space, lower number of experiments for design of experiment (DOE) studies and flexibility in manufacturability in a wide variety of specifications to meet the design criteria of the formulators. The wider design space means low probability of rejecting raw material batches and low cost, Process analytical tools (PAT) controls in manufacturing and greater flexibility during production phase. Design of space for two critical materials attributes-excipient particle size and excipient loss on drying (LOD) - was evaluated for PanExcea MHC300G excipients with that of MCC. It was found that PanExcea MHC300G excipient, D50 particle size between 105-135 microns and an LOD between 2.8 to 4.4 produced results that satisfied all critical quality attributes (CQA) of the formulation and tablets containing 63.5% Ibuprofen (D50 particle size between 40-70 microns). Formulation of the same active ingredients but with a non-co-processed MCC produced narrower design space specifications compared to a PanExcea MHC300G (12).

ADVANTAGES:

1. Provide a single excipient with multiple functionalities.
2. Overcome the limitation of existing excipients.
3. Improvement of organoleptic properties.
4. Production of synergism in functionality of individual components.
5. Improvement in physico-chemical properties has expanded their use in the pharmaceutical industry.
6. Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations.
7. The prime advantage of direct compression over wet granulation is economic since the direct compression requires fewer unit operations

8. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms.
9. The chances of wear and tear of punches and dies are less.
10. Better mouth feel and improved palatiblity
11. Removal of undesirable properties.
12. Improvement of organoleptic properties.
13. Delivery of low doses of very potent compounds that require contaminent.
14. Improved Flow properties.
15. Improved compressibility.
16. Better dilution potential.
17. Fill weight variation.
18. Reduced lubricant sensitivity

DISADVATAGES:

1. Specialized filling equipment and high temperature enprocessing are required.
2. Some lipidic excipients are not well tolerated by pre-clinical species.
3. The heigh materials losses.
4. Process is expensive because of labour, space, time special equipment and energy requirement.
5. Loss of material during various stages of processing.
6. Moisture sensitive and thermolabile drugs are poor candidates.
7. The frequency of direct interaction of the formulator with the production personal in the manufacturing area will be reduced.
8. Long duration.
9. Large number of equipment are needed.
10. High material loss (13).

SOME LIMITATION OF CO-PROCESSED EXCIPINTS:

Although co-processed excipient shows a list of promising benefits, however, there are few drawbacks in using of co-processed excipient (14).

Moreover, co-processed adjuvant lacks the official acceptance in pharmacopeia (4). For this reason, a co-processed adjuvant is not accepted by the pharmaceutical industry unless it exhibits significant advantages in the tablet compaction when compared to the physical mixtures of the excipients (15).

PRINCIPLE OF CO-PROCESSING (BASED ON PARTICLE ENGINEERING):

Particle engineering is a broad concept that involves the modification of particle parameters like shape, size distribution, and simultaneous minor change (19). Solid substances are characterized by three levels of solid-state. These levels are closely linked to one another, with the changes in one level reflecting in another level. The first level is molecular level which comprises the arrangement of individual molecules in the crystal lattice and includes phenomena such as polymorphism, pseudo-polymorphism, and the amorphous state. The second level is particle level which comprises of individual particle properties such as shape, size, surface area and porosity. The third level is bulk level which comprises of an ensemble of particles and properties such as flowability, compressibility and dilution potential, which are critical factors in the performance of excipients (20).

The co-processed excipient involves actual process the following steps (21,22):

1. Recognition the excipient group to be co-processed by carefully studying. The material characteristics and functionality required.
2. Select the proportions of various excipients.
3. Evaluate the particle size required for co-processing. This is mostly important when one of the components is processed in a dispersed phase post processing, the particle size of the latter depends on its initial article size.
4. Selecting an appropriate drying process such as spray or flash drying optimization. Schematic representation of the co-processing method shown in fig.1

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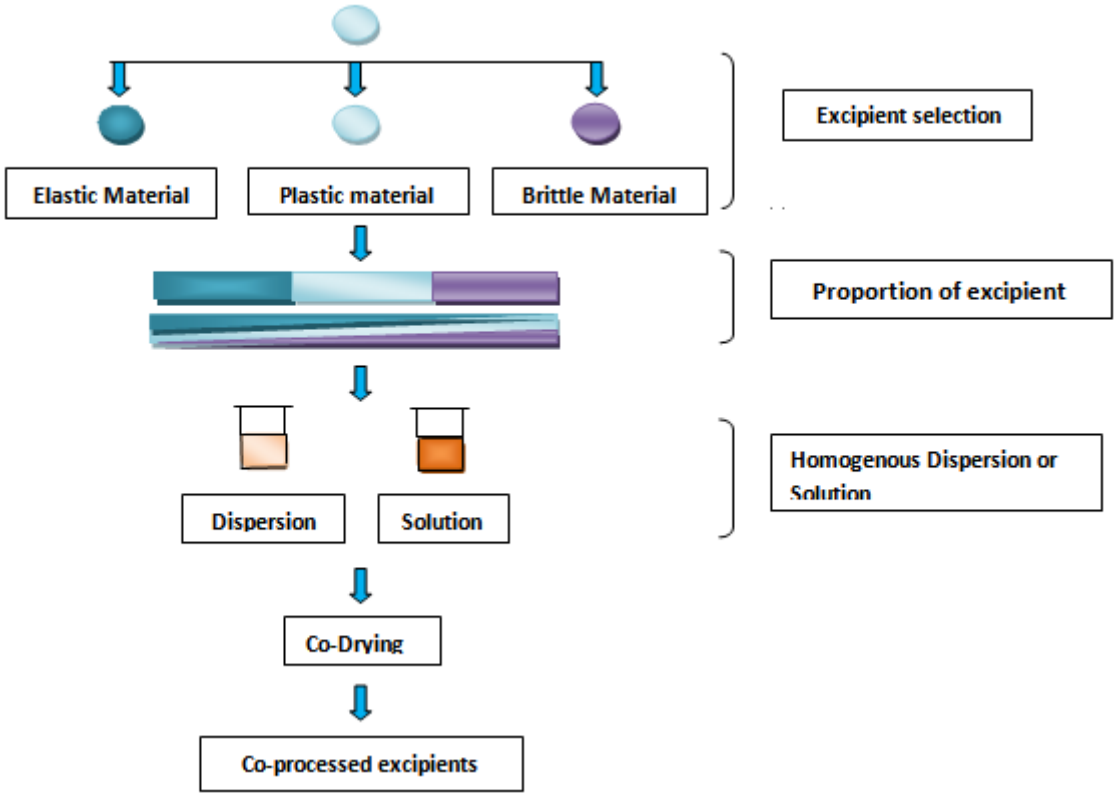

Fig.1: Schematic representation of coprocessing method

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 coprocessing of two or three plastic materials (5).

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

EXCIPIENT CO-PROCESSED		IMPROVED PROPERTIES COMPARE TO PHYSICAL BLEND
BEITTEL 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
Dibasic calcium phosphate	HPMC crospovidone	Has increased flowability, an increased API loading and blendin and higher compactability
Calcium phosphate	MCC	Novel MCC based excipient has improved compactability and recompactability
β lactose	Sorbita	Produce tablet with improved recompactability
Calcium carboante	MCC	Novel MCC based excipients has improved recompactability
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

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

EXCIPIENTS CO-PROCESSED	IMPROVE PROPERTIES OVER PHYSICAL BLEND
MCC Guar gum	Improved smell, taste, texture and mouth feel.
Mannitol,Sorbitol	Good compactability and less hygroscopicity
MCC HPMC	Better flowabilty and higher compactability. Retains compressibility on wet granulation
MCC HPMC Crospovidone	Exhibit enchanced flowability, excellent compactability, increased API loading and blendability

II. METHODS OF CO-PROCESSED EXCIPENTS

1. Spry drying
2. Wet granulation
3. Melt extrusion
4. Granulation
5. Hot melt extrusion
6. Roller drying
7. Co-transformation
8. Milling
9. Solvent evaporation

1. Spray drying: (23)

This spray drying technique allow the conversion of feed from a fluid state into dried particle. The feed can be a solution ,suspension, dispersion or emulsion .the dried product can be form in the powders, granules or agglomerates and these are depending upon the physical and chemical properties of feed and the dryer design final powder properties required. it is a continuous particle processing drying operation. the spray drying process parameter like inlet air temperature ,atomization air pressure, feed rate, liquid viscosity, solid content in feed, disc speed can be help in design particle with desire characteristics. hence spray drying process can be desire as consisting of four steps:

- Atomization of the liquid into droplets.
- Contact of the droplet with the warm drying gas.

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- Fast evaporation of the droplets to form dry particles.
- Recovery of the dry particles from the drying gas, using a cyclone.

Advantages of spray drying :

- Possibility to associated non-missible products in continuous operation.
- It allows blending and drying simultaneously soluble and insoluble compound.
- Provides opportunity to fix and protect sensitive active compound on natural carrier.
- Improves hardness and compressibility.
- Enhances machine tableting speed, decreases disintegration time.

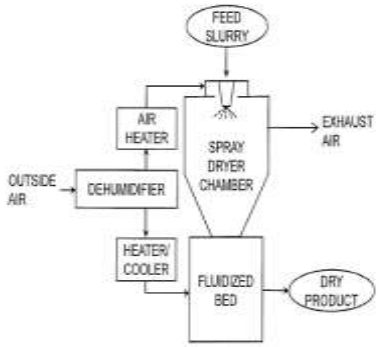

Fig:2 Sprey drying method

2. Wet granulation:

Wet granulation is a conventional and simple method for coprocessed adjuvant production. Fluid bed granulators and highshear mixers are two commonly used equipment used for the same. In fluid bed granulation, the powder mix is subjected to fluidization by a flow of air injected upwards through the bottom screen of the granulator. The binding solution is sprayed in the opposite direction to the air flow on the powder bed. The solid particles are mixed with the liquid droplets and hit the bed which results in adhesion and eventually the formation of granules. Partial drying by the fluidizing air occurs continuously during granulation (24-26). In high-shear granulation, an impeller maintains the powder in agitation in a closed vessel. The binder solution is sprayed from the top. Development of large agglomerates is prevented by high shear force. With the new single-pot technology, drying occurs in the same system. The granules formed are understandably denser than those obtained in fluid bed granulation (26).

3. Melt extrusion:

Melt extrusion is a process of formation of small beads, pellets from the molten mass which is extruded through extruder. Extruders consist of four distinct parts (31):

1. An opening though which material enters the barrel that may have a hopper that is filled with the materials to be extruded.
2. A conveying section (process section), which comprises the barrel and the screws that transport, and where applicable, mix the material.
3. An orifice (die) for shaping the material as it leaves the extruder.
4. Downstream auxiliary equipment for cooling, cutting and/or collecting the finished product. Example: Compressol S [Mannitol, Sorbitol] (23,32).

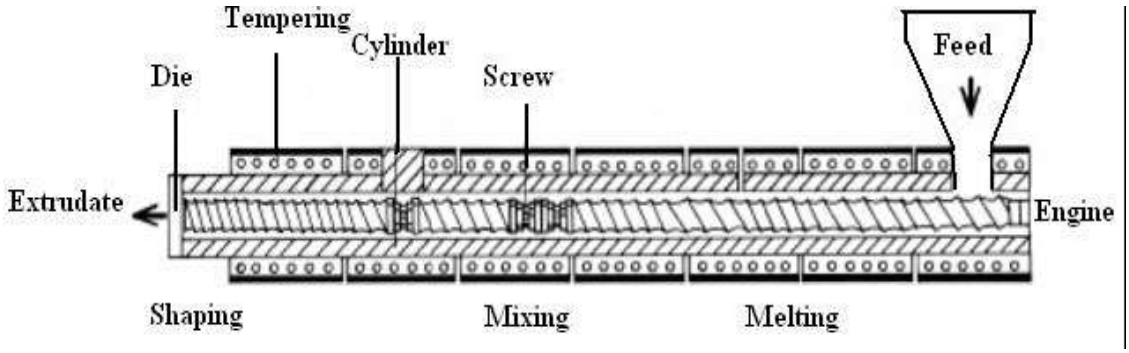

Fig.3: Melt Extrusion process

Advantages:

- Excellent repeatability
- Complicate and intricate shapes are possible.
- Time required is less

Disadvantages:

- Equipment and die cost high.
- Minimum economic length high

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4. Granulation/agglomeration:

Granulation is the process of forming or crystallizing into grains. granules have a size range between 0.2 to 4.0 mm depending on their use. synonym of granulation is "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 (6).

Advantages:

- It eliminates the use of water or any other solvent.
- Short processing time.
- It can be suitable for conventional equipment.

5. Hot melt extrusion:

Hot melt extrusion uses heat with a temperature greater than 80°C. This method is not suitable for thermo labile materials. The excipients are melted and then pressurized through the die and solidify into a variety of shapes. The solvent is not required in the process as the molten polymer can function as a thermal binder.

6. Roller drying:

A roller dryer is used to dry the homogeneous solution or dispersion containing the pre-blended excipients. Meggelaars et al. (1996) applied this technique to co-process lactose with sorbitol and lactitol. The temperature used was sufficiently high to obtain an end product that consists principally of β-lactose in crystalline form. The temperature used was sufficiently high to obtain an end product that consists principally of β-lactose in crystalline form.

7. Co-transformation:

Co-transformation technique involves the application of heat or solvent effect to "open-up" (swelling) the particle of one excipient. The other excipients are incorporated into the "opened-up" structure of the aforementioned excipient. The augmented excipient strengthens the functionality of the end product.

8. Milling:

A roller mill, ball bill, bead mill, millstone mill, jet mill or a hammer mill can be used to perform milling or dry grinding. The excipients are premixed and passed through a high-speed milling machine. During the process of milling, the particles come in contact with each other and form bonds when they are subjected to force to mill or pass through the screen. Rao et al. (2012) applied this technique to coprocess cross-linked polyvinylpyrrolidone and calcium silicate.

9. Solvent evaporation:

Solvent evaporation takes place in a liquid manufacturing vehicle. The coating excipient is dissolved in a volatile solvent which is immiscible with the liquid manufacturing vehicle, followed by dissolving or dispersing the core excipient in the coating solution. Agitation force is applied to achieve the desired encapsulation size. Heat is used to evaporate the solvent (26).

III. CHARACTERIZATION OF NEW CO-PROCESSED EXCIPIENT PREPARED (36-40)

The new co-processed excipient prepared was evaluated for the following:

- **Solubility:** Solubility of PGS-PEG-Aerosilcoprocessed excipient was tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents such as alcohol, dichloromethane, chloroform, acetone and petroleum ether. pH: The pH of 1% w/v slurry was measured. Melting Point: Melting point was determined by using melting point apparatus (Digimelt).
- **Swelling Index:** The new excipient prepared(200 mg) was added to 10 ml of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersions in the tubes were allowed to stand for 12 h. The volume of the sediment in the tubes was recorded. The swelling index of the material was calculated as follows.

S.I (%) = (Volume of sediment in water -Volume of sediment in light liquid paraffin)/(Volume of sediment in light liquid paraffin)×100

- **Moisture Absorption:** The hygroscopic nature of the new excipient prepared was evaluated by moisture absorption studies in a closed desiccator at 84% relative humidity and room temperature.
- **Particle Size:** Particle size analysis was done by sieving using standard sieves. Density: Density (g/cc) was determined by liquid displacement method using benzene as liquid.

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- **Bulk Density:** Bulk density (g/cc) was determined by three tap method in a graduated cylinder.
- **Angle of Repose:** Angle of repose was measured by fixed funnel method.
- **Compressibility Index:** Compressibility index (CI) was determined by measuring the initial volume (Vo) and final volume (V) after hundred tapings of a sample of modified starches in a measuring cylinder. CI was calculated using the equation Compressibility index:

$$\mathbf{CI} = \left(\frac{(V_0 - V)}{V_0}\right) \times 100$$

IV. 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 Pharma copoeia/ 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 industry36 (41).

V. LITERATURES

MCC and mannitol

Slurry of MCC and mannitol were sprayed dried to spherical particulate. The composition had an improved compatibility profile, lubricant sensitivity, and ejection profile compared to the physical mixture and individual component (27).

Calcium phosphate and MCC

Thoorens et al. (2011) invented a calcium phosphate and MCC coprocessed excipient by mixing the aqueous slurries of microcrystalline cellulose and calcium phosphate, followed by drying such slurries to produce particulate products. The end product exhibited improved compatibility, as compared to dry physical blends of the same components (28).

Dicalcium phosphate and carboxy methyl cellulose sodium

The invention was developed by Ambore et al. (2014) using coprecipitation technique. Carboxymethylcellulose was dispersed in water to allow it to swell. Dicalcium phosphate was dispersed in another portion of water. The two portions of dispersion were mixed and dried in tray dried. The invention was reported to have better flowability and dilution potential (29).

Dibasic calcium phosphate, HPMC and crospovidone

Deorkar et al. (2011) formulated an invention by co-processing dibasic calcium phosphate as a brittle material component, HPMC as binder and crospovidone as a disintegrant. The invention showed an increased flowability, API loading, and blendability and higher compatibility.

Sodium carbonate and polyethylene glycol

The invention is a pH modifier developed by Davar et al. (2010) using a fluid bed spray granulation method. Polyethylene glycol protects sodium carbonate from moisture which results in caking. The said invention was applied in the non-effervescent pharmaceutical composition of zolpidem and scopolamine.

Starch and magnesium silicate

Adnan et al. (2011) co-processed starch with magnesium silicate. Starch was suspended in a suspension first followed by addition of magnesium silicate. The suspension was then filtered, washed and dried. The dried product was used to prepare tablets with high mechanical strength, short disintegration time and low lubricant sensitivity (26).

Lactose, MCC and cornstarch

Akram et al. (2011) developed co-processed micro-granules of lactose monohydrate, MCC and cornstarch by wet granulation. The finished product was claimed to have the strong

binding ability, fast disintegration time and improved flow property (26).

MCC and methylcellulose

Augello and Vladyka (1999) invented a co-processed excipient by wet granulating MCC and methylcellulose. The compositions were then subjected to spheronizing into spheres having a smooth uniform surface. The end product serves as a coating polymer which provides complete taste masking of a bitter drug such as ibuprofen while having no adverse impact on the bioavailability of the drug (30).

β-lactose and sorbitol

Meggelaars et al. (1996) prepared a homogeneous mass consisting of a dried solution of high β-lactose content with sorbitol ranges from 1-15% % w/w. Roller drying technique was used in the drying process. The excipient can be used to prepare tablet with exclusive hardness (26).

Dicalcium phosphate and carboxy methyl cellulose sodium

The invention was developed by Ambore et al. (2014) using coprecipitation technique. Carboxy methyl cellulose was dispersed in water to allow it to swell. Dicalcium phosphate was dispersed in another portion of water. The two portions of dispersion were mixed and dried in tray dried. The invention was reported to have better flowability and dilution potential (29).

Lentinus tuber regium base co-processed excipient

Ugoeze and Nkoro (2015) developed a co-processed excipient by mixing Lentinus tuber regium, sodium bicarbonate, tartaric acid and citric acid using solvent evaporation method. The end product appears as a compactable, tasteless, off-white powder without distinct odor. The flow property, compressibility, and dilution potential were improved (34).

Rice starch and MCC

Limwong et al. (2004) invented a co-processed excipient comprising of rice starch and MCC. Composite particles of rice starch and MCC were fabricated by spray-drying technique to be used as a directly compressible excipient. The compressibility was greater than commercial spray-dried rice starch (Eratab), coprocessed lactose and microcrystalline cellulose (Cellactose), and agglomerated lactose (Tablettose), but, lower than microcrystalline cellulose (Vivapur 101) (35).

Guar gum and MCC

Ratnaraj and Reilly (1997) produced a co-processed excipient for the chewable tablet by thoroughly mixing an aqueous dispersion of MCC and guar gum under high shear conditions at room temperature. The homogenous dispersion was then spray dried to an aggregate powder having substantially spheroidal-shaped particles. The excipient has improved compressibility and mouth feel. It reduces tooth packing (26).

β-lactose and sorbitol

Meggelaars et al. (1996) prepared a homogeneous mass consisting of a dried solution of high β-lactose content with sorbitol ranges from 1-15% % w/w. Roller drying technique was used in the drying process. The excipient can be used to prepare tablet with exclusive hardness (33).

Povidone and glyceryl behenate

Ayyappan et al. (2010) developed a co-processed adjuvant comprising povidone and glyceryl behenate which was claimed to function as binder and lubricant with good flow and compressibility. The co-processed excipient was applied to manufacture tramadol HCl control release tablet and it provided a drug release profile comparable with Zydol SR (26).

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Table 3: Some examples of marketed co-processed excipients(42-48)

CO-PROCESSED EXCIPIENTS	MANUFACTERER	COMPONENTS%	CLAIMED BENEFITS
Ludipress®	BASF	Lactose monohydrate93.4 Kollidon30- 3.2 Kollidon CL-3.4	Low hygroscopicity, good flowability, constant tablet weigh
Ludipress®	BASF	Mannitol-90 Kollidon® CL-SF-5 Kollicoat® SR30D- 5	Rapidly disintegrating, mechanically stable tablets
Avicel ® CE15	FMC	MCC- 85 Guar- 15	Less grittiness, improved tablet palatability
ProSolv®	JRS	MCC- 98 Silicon Dioxide- 2	Better flow, less sensitivity to wet granulation, better tablet hardness
Pharmaburst ™ 500	SPI Pharma	Mannitol, Sorbitol, crospovidone and silica; aspartame; and magnesium stearate	Rapidly disintegrating with superior organoleptic properties
PanExcea™ MC200G	J.T. Baker	MCC-89 Hydroxypropylmethyl cellulose-2 Crospovidone- 9	Enable direct compression with high speed tableting
LubriTose AN	Kerry biofunctional ingredients	Anhydrous Lactose, GlycerylMonostearate	Eliminate the need for adding a separate lubricant

VI. 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 particular process without modifying the chemical structure. Highly functional co-processed excipients can help to reduce drug dosages, minimize side effects and therefore make medicines better and safer.co-processed excipients solve the issues of precompression parameters, compressibility, palatability, disintegration, dissolution, and sticking which conventional individual excipients might have. There is enough scope of development of new co-processed excipients for the demand of pharmaceutical industries. IPEC is drafting a guideline to facilitate development and adoption of co-processed excipients.

RESENT & FUTURE DEVELOPMENT

Co-processed excipients opens the opportunity for development and use of single multifunctional excipients rather than multiple excipients in formulation. 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. To their nonofficial status, co-processed excipients are still not widely accepted by the pharmaceutical industry. Accordig to IPES the future for co-processed excipients looks very promising. With upcoming newer combination of excipients and newer methods of coprocessing, co-processed excipients are for sure going to gain attraction both from academia and pharmaceutical industry.

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