Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2021, 13(9):01-10

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Co-Processed Excipients: A New Trend of Excipient Technology

Sravya K*, S Venkateswara Rao, K Padmalatha

Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, India

---

ABSTRACT

The single component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately and the cost of new excipient development is very high as it demands toxicity study also. Hence, formulation scientists focused their attention on the production of co-processing of approved excipients with enhanced performance to meet the needs of formulation experts in terms of costs of production, enhanced excipient functionality and quality of tablets. Tablet manufacturing has been changed by the introduction of the direct-compression process and high-speed machines. These two developments have increased the demands on the functionality of excipients in terms of flow and compression properties. Direct compression is the preferred method for the preparation of tablets. The shift in tabletting toward direct-compression and high-speed manufacturing has forced the excipient industry to search for new excipients. The present review focuses on formulation and evaluation techniques of co-processed excipients. The research works done on co-processed materials are enlisted in the review to facilitate further research by research scholars and R & D scientists.

Keywords: Single component excipients; Coprocessed excipients and Direct-compression

---

INTRODUCTION

The oral solid dosage form is the most common method of drug delivery, which tablet and capsules are predominate. Compared to capsules tablet are more widely accepted and used for a number of reasons including cost, temper resistance, ease of handling and packaging, ease of identification and manufacturing efficiency. Over 150 years ago the invention of compressed tablet by William Brockedon, the tablet has become increasingly popular dosage form. The pharmaceutical industry has to produce tablets that have consistent quality from batch to batch. Tablets must be strong enough to withstand exertion caused by packing, storage and handling. They must also disintegrate and release drug reproducible with desired manner in a gastrointestinal tract [1]. Direct compression is the process of a blending of ingredients, the compression mix, without a preliminary granulation or aggregation process of tableting. The compression mix contains the active pharmaceutical ingredient blended with one or more excipients. It has been estimated that less than 20% of pharmaceutical materials can be compressed directly into tablets. The rest of the materials lack flow, cohesion or lubricating properties necessary for the production of tablets by direct compression. The use of directly compressible excipients may yield satisfactory tablets for such materials. The excipients industry has been an extension of the food industry. Moreover, excipients are products of the food industry, which has helped to 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.

Factors Driving the Search for New Excipients

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.

STEPS IN DEVELOPING CO-PROCESSED EXCIPIENTS

In order to design a new co-processed excipient, few steps are important to take into consideration

Identification of the Group of Excipients to Be Co-Processed

A good co-processed excipient should look into the balance between plasticity and brittleness of a material (Marwaha M, Sandhu D, Marwaha RK, 2010). Combination of plastic and brittle material nullifies storage of undesirable elastic energy during the compression. This will produce a product with a small amount of stress relaxation and a reduced tendency of capping and lamination thereby optimum tableting performance (Panda B, *et al*., 2010). The combination of excipient chosen should complement each other and provide synergistic effect to achieve the desirable characteristics.

Assessing the Particle Size

Particle size will affect the compressibility and flowability of the end product. If the participating excipients have variation in initial particle sizes, the focus should be given to produce the final co-processed adjuvant with uniform particle size.

Selecting a Suitable Technique to Co-Process Various Excipient

There are many methods which can be used for co-processing such as wet granulation, melt granulation, freeze drying, spray drying, hot melt extrusion. A comprehensive detail has been provided later in this review.

Optimizing the Process and the Proportion of Each Excipient

Various optimization techniques and experimental designs with sound statistical analysis can be employed to obtain a final product with desired functionalities.

TYPES OF EXCIPIENTS

Single Excipients

Single excipients can be defined as excipients containing one component which is primary component called as excipient.

Mixtures of Multiple Excipients

Simple physical mixture or blends of two excipients by means of low to medium share process where the individual component are mixed together without significant chemical change [2].

New chemical entities

It can be defined as the excipients which are chemically modified to form new excipients. These are generally not listed in FDA inactive ingredient database (IID). These are not fully qualified by existing safety database with respect to currently proposed level of exposure or route of administration.

CO-PROCESSING EXCIPIENTS

Co-Processed Excipients

A co-processed excipients is a combination of two or more compendial or non-compendial excipients designed to physically modify their properties. Many different co-processing methods may be used as spray drying, milling, melt extrusion, granulation [3]. The co-processing excipients leads to formation of excipients granulate with superior of physical mixture of component or with individual components.

ADVANTAGES

Absence of Chemical Change

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. The detailed studies of SMCC with XRD, NMR, IR spectroscopy and Raman spectroscopy have detected no chemical changes (TobynMJ,et al., 1998).This absence of chemical change helps to reduce a company's regulatory concerns during the development phase.

Physic Mechanical Properties

The volumetric flow properties of SMCC (Silicified Microcrystalline Cellulose) were studied in comparison with MCC (Microcrystalline Cellulose). Calcium phosphate is mostly unsuitable for direct compression processes but when melt granulated with higher fatty acids exhibited excellent flow properties and compressibility as compared to single excipient.

The compressibility performance of excipients such as Cellactose, 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.

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.

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.

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 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 [4].

Non Physico Mechanical Advantages

•Pharmaceutical manufacturers have the option of using a single excipient with multiple functional properties, thereby reducing the number of excipients in inventory.

•Improved organoleptic properties such as those in Avicel CE- 15which 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, better mouth feel, and improved overall palatability.

•Although co-processing ads some cost, the overall product cost decreases because of improved functionality and fewer test requirements compared with individual excipients.

•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.

•Co-processed 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.

Co-Processed Excipients and Its Advantages in Quality by Design

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.

LIMITATIONS

Fixed Ratio

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.

High Cost

Directly compressible co processed excipients are the specialized products which are produced by patented processes like spray drying, fluid bed drying, roller drying etc. Hence, these products are relatively costly than their respective raw materials from which they are made.

Dilution Potential Up To 40%

Most of the directly compressible co-processed excipients have a capacity to accommodate up to 40 % of the poorly compressible active ingredients for example acetaminophen, which would mean that the weight of the final tablet to administer 500 mg of drug would be more than 1.3 grams making the tablet size large and may create difficulty in swallowing.

Lack of Reworkability for Spray Dried Co-Processed Excipients

The original spherical nature of the excipient particles is lost if it is reworked hence loss of its intrinsic property and the increase in disintegration and dissolution profiles.

Lack of Pharmacopoeial Acceptance

Co-processed adjuvant lacks the official acceptance in pharmacopoeia. 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.

Table 1: Ideal requirements, advantages and limitations of direct compression.

Ideal requirements	Advantages	Limitations
Flowability	Cost effective production	Segregation
Compressibility	Better stability of APH	Variation in Functionality
Dilution Potential	Faster Dissolution	Low Dilution Potential
Rework ability	Less Wear and Tear of Punches	Rework ability
Stability	Simplified Validation	Poor Compressibility of API
Controlled Particle Size	Lower microbial contamination	Lubricant Sensitivity

PRINCIPLE INVOLVED IN CO-PROCESSING

The broad concept that involves the modification of particle parameters like shape, size distribution, and simultaneous minor changes is 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. 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 co-processing or particle engineering two or more existing excipients [5].

METHODS OF CO-PROCESSING

Spray Drying process

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.

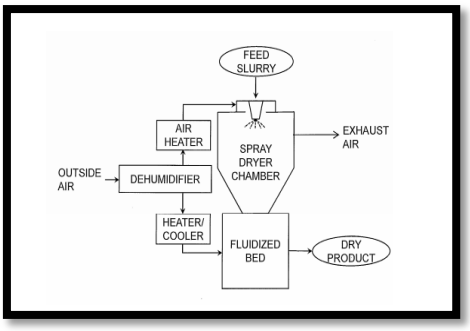

Figure 1: Spray drying process

Solvent Evaporation Process

Solvent evaporation process involves the use of liquid manufacturing vehicle. The coating excipient is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core excipient material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated (if necessary) to evaporate the solvent. Once all the solvent is evaporated, the liquid vehicle temperature is reduced to ambient temperature (if required) with continued agitation. At this stage, the microcapsules can be used in suspension form, coated on to substrates or isolated as powders. The core materials may be either water -soluble or water - insoluble materials.

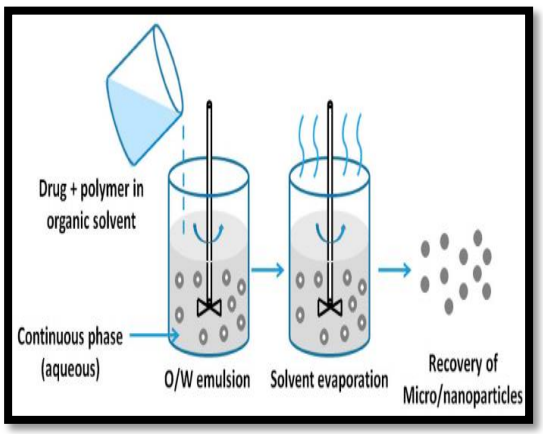

Figure 2: Solvent Evaporation process.

Crystallization Process

Crystallization is the (natural or artificial) process of formation of solid crystals precipitating from a solution, melt or more rarely deposited directly from a gas. Crystallization is also a chemical solid– liquid separation technique, in which mass transfer of a solute from the liquid solution to a pure solid crystalline phase occurs.

Procedure

Crystallization occur from a solution and 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.

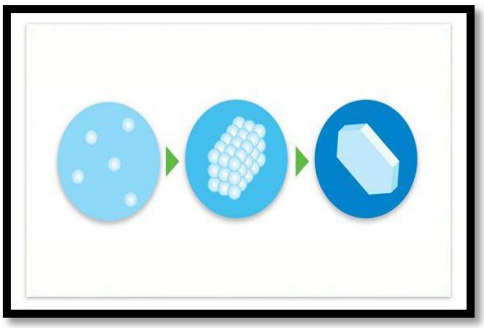

Figure 3: Crystallization Process

Melt Extrusion Process

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

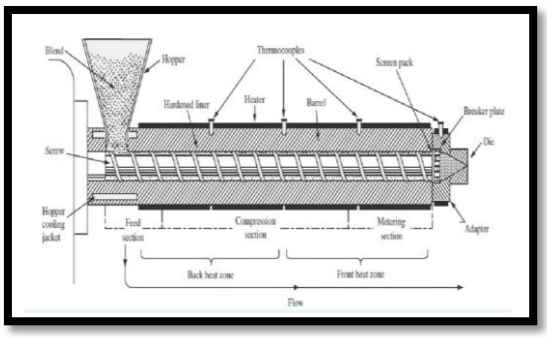

Figure 4: Melt Extrusion Process

Granulation/agglomeration Process

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 co-processing.

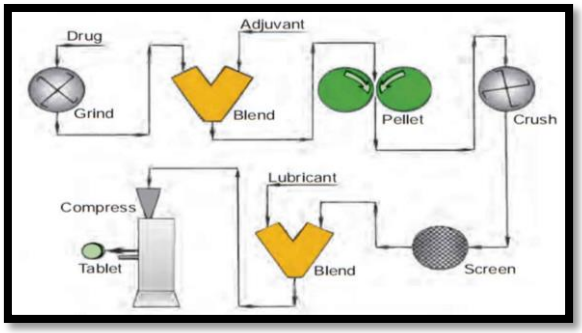

Figure 5: Dry granulation process

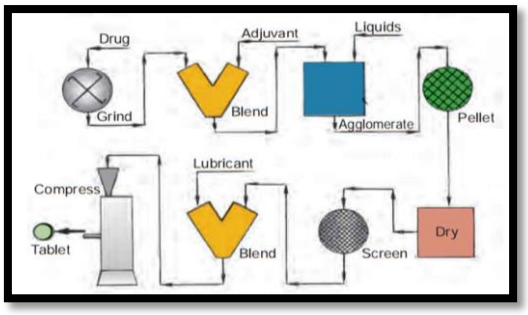

Figure 6: Wet granulation Process

Table 2: Some examples of commercially available co-processed excipients

Trade name	Manufacturer	Components	Claimed benefits
Pharmatose® DCL40	DMV	ß-lactose, Lactitol	High Compressibility Low lubricant sensitivity
Ludipress®	BASF	Lactose ,PVP	Low hydroscopicity Good flow ability Constant tablet weight
ProSolv®	JRS	MCC Silicon Dioxide	Better flow, less sensitivity to wet granulation, better tablet hardness
Xylitab® 200	Danisco	Xylitol Na CMC	Directly compressible
Avicel ® CE-15	FMC	MCC Guar	Less grittiness, improved tablet palatability
Di-Pac®	Domino	Sucrose Maltodextrin	For direct compression

EVALUATION PARAMETERS OF CO-PROCESSED EXCIPIENT

Solubility

Solubility of co-processed 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**.**

Porosity:

Total intra-particle porosity, pore area, and pore size distribution are determined using a mercury porosimeter.

Particle sizes analysis

Mean particle size of co-processed excipient is analyzed by sieve analysis method.

Loss on Drying (LOD)

A sample of co-processed excipient is spread in a Petri dish, and the dish is placed in hot air oven at 100 °C for 3 hr. The percentage decrease in weight is noted to calculate loss on drying as per equation.

Compatibility of Co-Processed Excipient

The sample is compressed in a hydraulic press at compression forces of 0.5, 1.0, 1.5, 2.0 and 3.0 tons, using flat face punches. The hardness of each compact is measured using a hardness tester.

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.

Density

Density (g/cc) was determined by liquid displacement method using benzene as liquid.

Table 3: Recent Research on Co-processed Excipients for Direct Compression

Co-processed excipients	Technology	Drugs studied (category)
Crospovidone-Croscamellose sodium	Solvent evaporation	Metoclopramide (antiemetic)
Crospovidone-Sodium starch glycolate	Solvent evaporation	Metoclopramide (antiemetic)
Mannitol Microcrystalline Cellulose pH 101	Spray drying	Glipizide (Anti diabetic
Lactose and Mannitol	Melt granulation	Acetaminophen (NSAID) Paracetamol (antipyretic)
Pre gelatinized starch Microcrystalline Cellulose	Gelatinizing potato starch in presence of MCC	Sulphamethoxazole (Anti bacterial) Paracetamol (Antipyretic) Aceclofenac (NSAID)
Mannitol: Cellulose	Freeze thawing technique	Aceclofenac (NSAID) Nimesulide (NSAID) Metformin (antidiabetic)
Cellulose- Ethyl cellulose	Kneading method	Pioglitazone (antidiabetic) Gliclazide (antidiabetic)
Starch –PEG 1500	Gelatinizing potato starch in the presence of PEG 1500	Pioglitazone (antidiabetic) Gliclazide (antidiabetic)
Microcrystalline cellulose with SSL Hydroxypropyl cellulose	Spray drying	Tizanidine Hydrochloride(Centrally acting muscle relaxant)
Pregelatinized starch Polyvinylpyrrolidone	Gelatinizing potato starch in the presence of PVP	Ritonavir, Efavirenz, Stavudine (anti reteroviral)
Directly compressible co-processed sustained release multifunction agent (DCCSRA) comprising Povidone K 25 : Glyceryl behenate	Hot melting	Tramadol Hcl (analgesic)
Chitosan and Aerosil	Co-precipitation method	Metoclopramide (antiemetic)
Crospovidone: Sodium starch glycolate	Solvent evaporation	Cefeximetrihydrate (oral cephalosporin) Ibuprofen (NSAID)
Microcrystalline cellulose, Colloidal silicon dioxide and Sodium starch glycollate	Spray drying	Diclofenac sodium (NSAID) Iron polymaltose (Treatment of iron deficiency anaemia) Amoxicillin trihydrate (antibiotic)
Crospovidone: Croscarmellose	Solvent evaporant	Chlorthalidone (Antihypertensive and antidiuretic)

CONCLUSION

The co-processed excipients play a pivotal role in formulating stable, result oriented drug delivery system with an improved physical, chemical and mechanical properties. Furthermore, co-processed excipients solve the issues of precompression parameters, compressibility, palatability, disintegration, dissolution, and sticking which conventional individual excipients might have. Co-processed excipient is a promising tool in pharmaceutical excipient development. The existing co-processed adjuvants cannot fulfill all the functionalities required for preparation of various novel formulations. Cost is another factor that incurs increased the price of the final product. So, there is enough scope of development of new co-processed excipients to meet the demand of pharmaceutical industries. It is expected that advanced research in academia and pharmaceutical industry will surely bridge this gap in the near future.

REFERENCES

[1] Gohel MC, Parikh RK, Brahmbhatt BK, et al. *AAPS Pharm Sci Tech*. **2007**; 8(1), 63-69.

[2] Barakat NS, Elbagory IM, Almurshedi AS, et al. *Drug Deliv*. **2009**; 16(1), 57-65.

[3] Kanojia N, Kaur L, Nagpal M, et al. *IJTRM*. **2013**;1(1), 81-107

[4] York P. *Drug deliv Indian pharm*. **1992**; 18(7), 677-721.

[5] Tobyn MJ, McCarthy GP, Staniforth JN, et al. *Int J Pharma*. **1998**; 169(2): 183-194.