IJBPAS, June, 2025, 14(6): 3195-3221

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

A REVIEW ON PHARMACEUTICAL CO- PROCESS EXCIPIENTS

SAHOO S*, BAROT J, PRADHAN PK, PATEL S, PATEL M AND MESHRAM DB

Pioneer Pharmacy College, Vadodara, Gujarat, India - 390019

***Corresponding Author: Dr. Satyajit Sahoo: E Mail: satyajitppdc@gmail.com**

Received 15th Feb. 2024; Revised 19th March 2024; Accepted 3rd Aug. 2024; Available online 1st June 2025

https://doi.org/10.31032/IJBPAS/2025/14.6.9070

ABSTRACT

Now-a-days there is increasing demands of improved excipients functionality due to limitations of existing excipients failing to comply with all the functionalities of an ideal excipient. Co-processing represents a simple, efficient and economical approach for the development of high-functionality excipients. Co-processed excipient has received much more attention in the formulation development of various dosage forms, especially for tablet preparation by direct compression method. 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. 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 companies. 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 recent development in excipient technology and the approaches involved in development of such excipients.

Keywords: Co-processed excipient, Excipient technology, Direct-compression, Tablets

INTRODUCTION

Co-processing is termed as the physical mixing of two or more compendial or non-compendial pharmaceutical substances without significant chemical change to transform their properties which leads to the development of excipients with superior properties over conventionally available excipients **[1]**. In recent years scientists have

found out that single-component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured **[1, 2]**. 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) **[3]**.

Development of co-processed excipients starts with the selection of the excipients to be combined, their targeted proportion, selection of preparation method to get optimized product with desired physio-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. 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 mini granules. Segregation is diminished by adhesion of the actives on the porous particles making process validation and in process control easy and reliable **[1, 3]**.

ADVANTAGES OF CO-PROCESS EXCIPIENTS

- Provide a single excipient with multiple functionalities.
- Overcome the limitation of existing excipients.
- Improvement of organoleptic properties.
- Production of synergism in functionality of individual components.
- Improvement in physico-chemical properties has expanded their use in the pharmaceutical industry.
- Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations.
- The prime advantage of direct compression over wet granulation is economic since the direct compression requires fewer unit operations
- This is extremely important because the official compendium now require dissolution specifications in most solid dosage forms.
- The chances of wear and tear of punches and dies are less.

- Better mouth feel and improved palatability
- Removal of undesirable properties.
- Improvement of organoleptic properties
- Delivery of low doses of very potent compounds that require contaminant.
- Improved Flow properties.
- Improved compressibility.
- Better dilution potential.
- Fill weight variation.
- Reduced lubricant sensitivity.

DISADVANTAGES OF CO-PROCESS EXCIPIENTS

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

NEED OF CO PROCESS EXCIPIENTS

Co process excipients, also known as multifunction or combination excipients, are specialized excipients that combine two or more individual excipients into a single entity. These excipients serve a crucial role in pharmaceutical formulation, providing various advantages over single-component excipients. Here are some of the key needs and benefits of Co-process excipients:

1. Enhanced functionality: Co -process excipients are designed to offer improved functionality compared to individual excipients by combining different excipients. This can include improved flowability, compressibility, disintegration, dissolution and stability.
2. Simplified formulation: Co- process excipients can streamline the formulation process by reducing the number of individual excipients required. This simplification and better batch-to- batch consistency.
3. Cost – effectiveness: while Co- process excipients may appear to be more expensive up front, they Can save costs in the long run due to improved functionality and fewer excipients needed overall. Additionally, the reduction in processing steps can lead to cost savings in manufacturing.

4. Improved drug delivery: Co-process excipients can be tailored to enhance drug release profiles, leadings to better control over drug delivery and absorption rates. This is particularly important for drugs with specific release requirements, such as extended-release formulation.
5. Compatibility and stability: Co- process excipients can improve the compatibility between different active pharmaceutical ingredients (APIs) and excipients. Moreover, they can enhance the stability of the final dosage form, leading to longer shelf life and reduced risk of degradation.
6. Regulatory compliance: Co-process excipients can offer more consistent and well- defined properties compared to mixture of individual excipients. This can simplify the regulatory approval process and lead to more predictable and reproducible formulation.
7. Tailored properties: Depending on the specific needs of a drug product, Co – process excipients can be customized to achieve desired characteristic. This flexibility allows formulator to overcome challenges associated with individual excipients that may not me*et al*l the required properties.

Overall, Co- process excipients play a vital role in Morden pharmaceutical development, allowing formularies to optimize drug formulation, improve manufacturing processes and enhance the performance of various dosage forms, ultimately benefiting both patients and the pharmaceuticals industry. It is important to note that the selections of excipients, whether individual Co – processed, should always based on a thorough understanding of the drug's physicochemical properties and the desired performance of the final dosage form **[4]**.

- **TYPES OF EXCIPIENTS:-**

1. Single entity excipients.
2. Mixture/blend of multiple excipients.
3. Novel excipients or New chemical organisation.
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 **[5].**
2. Mixture /blend of multiple excipients: Simple physical mixture of two or compendial/ nok. Compendial excipients by means of low to medium shear process the individual component are mixes together without significant chemical change for solid mixture/blend the individual excipients remain physically separate at a particular level **[6]**.
3. Novel excipients or New chemical entities: it's defined as excipients which are chemically modified to form

New/novel excipients. These are generally not listed in FDA inactive ingredients database **[7]**.

4. Co – process excipients: co-process excipients are combination of two or more compendia or non- compendia excipients designed to physically modify their properties in a manner not achievable by simple physical mixing and without significant chemical change. Many different co-processing methods includes in pharmaceutical formulation development such as spray drying, solvent evaporation, crystallization, melt extrusion and granulation/ agglomeration **[8]**.

ADVANTAGES OF CO-PROCESSED EXCIPIENTS:

- Improving flow properties by controlled optimal particle size and size distribution.
- Improve compressibility ,dilution potential, fill weight variation, flow property, lubricant sensitivity.
- It can be also improving the tablet hardness and decrease disintegration time **[9]**.

HISTORY OF CO – PROCESS 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, 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 **[10, 11]**.

SOURCE OF NEW EXCIPIENTS:-

Excipients with improved functionality can be obtained by developing new chemical excipients, new grades of existing materials, and new combinations of existing materials. Any new chemical excipients being developed as an excipients must undergo various stages of regulatory approval aimed at addressing issues of safety and toxicity, which is a lengthy and costly process also the undergo a phase of generic development, which shortens the market exclusivity period **[12]**.

PARTICLE ENGINEERING AS SOURCE OF NEW EXCIPIENTS:-

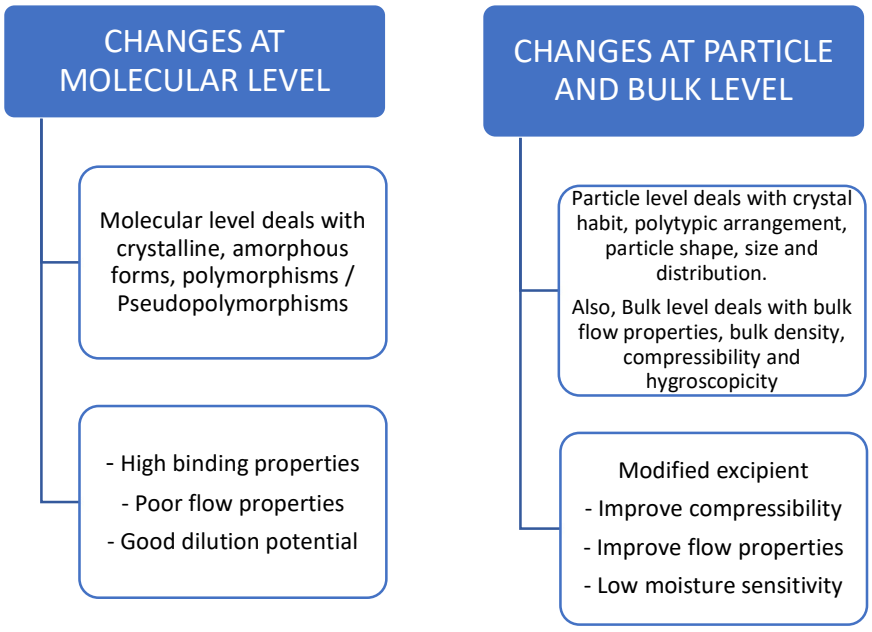


Table 1: Various Particle Properties Influencing Excipients Functionality [13]

Particle property	Excipients functionality
Enlargements of particle size	Flowability, compressibility
Estricting particle size distribution	Segregation potency
Enlargements of particle porosity	Compressibility, solubility
Surface roughness	Flowability, segregation potency

PROPERTIES AND ADVANTAGES OF THE CO PROCESSED EXCIPIENTS:-

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

a) Absence of chemical change

Many detailed studies of excipients chemical properties after co processing have proven that these excipients do not show any chemical change. Detailed studies of SMCC with X-ray diffraction analysis, solidstate nuclear magnetic resonance (NMR), IR spectroscopy, Raman spectroscopy and C13 NMR spectroscopy have detected no chemical changes and indicate a similarity to the physicochemical properties of MCC **[14]**. This absence of chemical change helps reduce a company's regulatory concerns during the development phase.

b) Physico mechanical properties.

1. Improved Flow Properties

Controlled optimal particle size and particle size, distribution ensures superior flow properties of co-processed excipients without the need to add glidants. The volumetric flow properties of SMCC were studied in comparison with MCC. The

particle size range of these excipients was found to be similar to those of the parent excipients, but the flow of co-processed 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 **[15]**. The spray dried product had a spherical shape and even surfaces, which also improved the flow properties.

2. Improved compressibility

Co-processed excipients have been used mainly in direct compression tabletting because in this process there is a net increase in the flow properties and compressibility profiles and the excipient formed is a filler–binder. The pressure– hardness relation of co-processed excipients, when plotted and compared with simple physical mixtures, showed a marked improvement in the compressibility profile. The compressibility performance of excipients such Cellactose **[16]**, SMCC **[17, 18]** and Ludipress **[19]** are superior to the simple physical mixtures of their constituent excipients. Although direct compression seems to be the method of choice for pharmaceutical manufacturing, wet granulation is still preferred because it has the potential advantages of increasing flow properties and compressibility when an extra granular binder introduced, and it achieves a better content uniformity in case of low dose drugs. Excipients such as MCC lose compressibility upon the addition of water, a phenomenon called quasi hornification **[20]**. This property is improved, however, when it is co-processed into SMCC.

3. Better dilution potential

Dilution potential is the ability of the excipient to retain its compressibility even when diluted with another material. Most active drug substances are poorly compressible and as a result, excipients must have better compressibility properties to retain good compaction even when diluted with a poorly compressible agent. Cellactose is shown to have a higher dilution potential than a physical mixture of its constituent excipients **[21]**.

4. Fill weight variation

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

weight variation was studied with various machine speeds for SMCC and MCC and SMCC showed less fill weight variation than MC **[22]**.

5. Reduced lubricant sensitivity

Most co-processed products consist of a relatively large amount of brittle material such as lactose monohydrate and a smaller amount of plastic material such as cellulose that is fixed between or on the particles of the brittle material. 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 **[23]**.

Patent review on co-processed excipients

Patent no.	Co-processed excipient	Process	Advantages
United States patent 4744987	Microcrystalline cellulose-calcium carbonate	• Most preferable ratio of MCC: calcium carbonate is 65:35 to 50:50 • Spray drying of aqueous slurry of excipients	Economical directly compressible excipient blend with good flowability and compressibility, low lubricant sensitivity
United States patent 5686107	Microcrystalline cellulose-galactomannan gum	• The most preferred galactomannan gum is guar gum • High shear stirring of an aqueous slurry of excipients and spray drying.	In chewable tablets: Provide compressibility, improves mouthfeel, eliminate tooth packing and improves patient acceptability
WO 95/17831	Galactomannan-glucomannan	• The most preferred galactomannan is locust bean gum, and glucomannan is konjac • Prepared by co-precipitation technique with IPA	• Dry powder which is soluble in water used as thickeners, viscosifier or gelling agent in food industry
WO 2003/051338	Mannitol-sorbitol	• Spray drying of aqueous slurry of excipients	Rapidly compressible and rapidly dissolved or disintegrated within 60 sec so used for Orally disintegrating tablets.
(WO 2010/132431 A1)	Silicified MCC-a polyol and sugar with or without disintegrant	• Preferable ratio of MCC: Polyol is 1:1	Rapidly disintegration, acceptable mouth feel, low friability, high dilution potential
WO 2014/165246A1	Vinyl lactam derived polymer and deagglomerated co-processing agent	• Vinyl lactam derived polymer is selected from the group consisting of N-Vinyl-2-pyrolidone,poly(vinyl pyrollidone), N-Vinyl-2-caprolactam, etc. • The co-processing agent is silica comprised of fused silica, colloidal silica, silicon dioxide, calcium silicate and/or combinations thereof. • Prepared by passing excipient blend through blender and universal mill	Suitable blend for direct compression, dry granulation or hot melt extrusion processing.

Excipients Selection Criteria in Co-Processing Crystallization

The combination of excipient selected for co-processing should compatible and non-reactive to each other. For example, two

hexitol group excipient Mannitol: Sorbitol are co-processed to achieve good compressibility as tablet excipient where first is poorly compressible and less hygroscopic and later is good compressible but highly hygroscopic to create balance between plasticity and brittleness. A few other examples of co-processed excipients studied are combination of Lactose: PVP K30: Starch as a ready to use excipient for tablet with diluents, binder and disintegrant property, MCC: Sodium starch glycolate for direct compression immediate release formulations, Dibasic Calcium Phosphate dihydrate co-processed with Pre gelatinise starch for direct compression with binder and diluents property.

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 **[24]**.

Table: 2 Co-processed directly compressible excipients

Co-process excipients	Trade name	Manufacturer	Advantage
Lactose,3.2%kalidonekalidonecl	Ludipress	BASF Pharma, Germany	Low degree of hygroscopicity, good flowability, tablet hardness independent of machine speed
Lactose,25% cellulose	Cellactose	MEGGLE, Germany	Highly compressible, good mouthfeel, better tabletting at low cost
Sucrose 3%, dextrin Microcrystalline cellulose, silicon dioxide	DipacProsolv	Penwest Pharmaceuticals company	Directly compressible, Better flow, reduced sensitivity to wetgranulation, better hardness of tablet, reduced friability
Microcrystalline cellulose, guar gum	AvicelCE 15	IFF corporation	Less grittiness, minimal chalkiness
Calcium carbonate, sorbitol	Formaxx	Merck	Controlled particle size distribution
Microcrystalline cellulose, lactose	Microlela	MEGGLE, Germany	Capable of formulating high dose, small tablets with poorly flowableactive ingredients
95% β lactose + 5% lactitol	LactitolPharmatose DCL 40	DMV Veghel	Good flowability, High compressibility

❖ **PRINCIPLE INVOLVED IN CO-PROCESSING:-**

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 **[25]**.

❖ **COPROCESSING-COMBINATORIAL ENGINEERING:-**

Coprocessing is the novel phenomenon of developing a new single-bodied excipient, interacting two or more excipients at sub-particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual excipients **[26]**. Coprocessing was initially used by the food ingredients such as co-processed glucomannan and galactomannan **[27]**. Co-processed excipients are prepared by incorporating one excipient into the particle structure of another excipient using

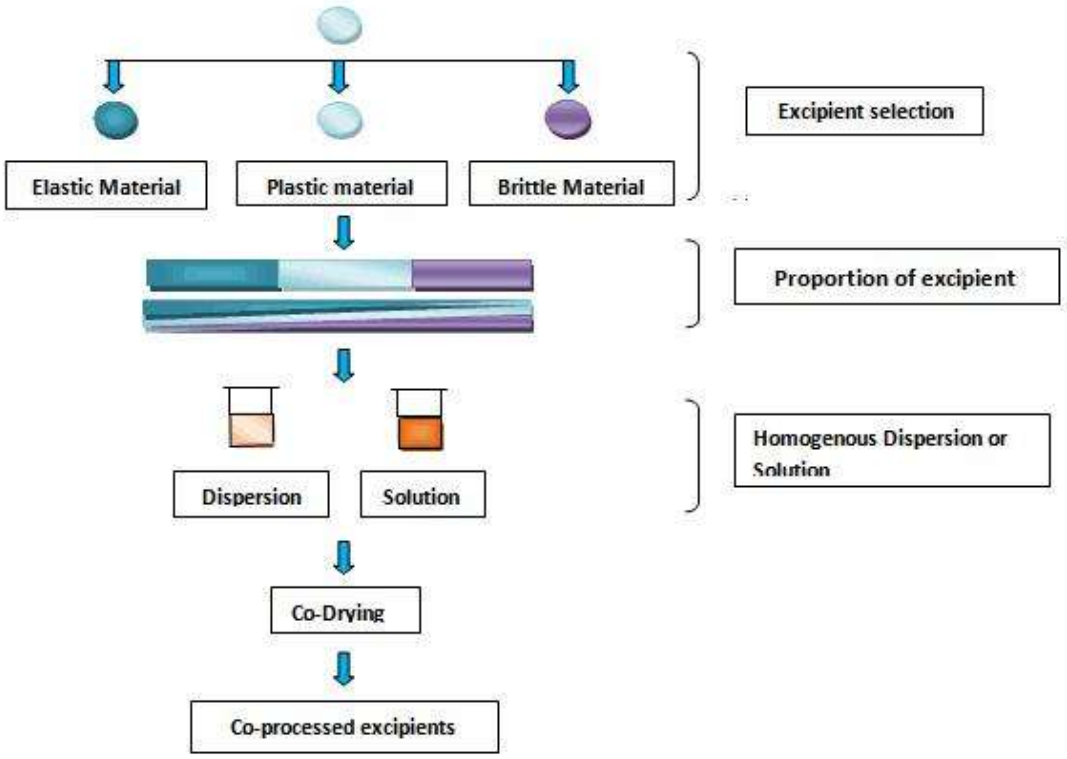
processes such as co-drying or co-precipitation. During this a common dispersion of the under processing excipients is made. Then it is dried and converted into particulate of desirable size range by drying. Thus, they are simple physical mixtures of two or more existing excipients mixed at the particle level to form a single-bodied excipient. The combination of excipients chosen should complement each other to mask the undesirable properties of individual excipients of individual excipients and, at the same time, retain or improve the desired properties of excipients. For example, if a substance used as a filler-binder has a low disintegration property, it can be co-processed with another excipient that has good wetting properties and high porosity because these attributes will increase the water intake, which will aid and increase the disintegration of the tablets.

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

- Identifying the group of excipients to be co-processed 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 flash drying.
- Optimizing the process (because even this can contribute to functionality variations).

❖ **CO PROCESSING OF EXCIPIENTS:-**

They are following steps:



1. Identifying the excipients groups to be Co process by carefully studying the material characteristics and functionality requirements.
2. Electing the proportion of various excipients.
3. Assessing the particle size required for Coprocessing. This is especially important when one of the components is processed in a disperse phase. Post processing the practical size of the latter depends on its initial practical size.
4. Selecting a suitable drying process such as spray-or flash drying optimising the process.
5. Figureshow a schematic chart of the Coprocessing method.

Table 3: Co-Processed Excipients Developed By Co-Processing Brittle And Plastic Materials

EXCIPIENT CO-PROCESSED		IMPROVED PROPERTIES COMPARE TO PHYSICAL BLEND
VITAL COMPONENT	PLASTIC COMPONENT	
Colloidal silicon dioxide	MCC	Novel MCC based excipient is free flowing ,posses excellent disintegration properties has improved compressibility relative to normal off the shelf commercially available MCC
Dibasic calcium phosphate	HPMC cross povidone	Has increased flowability, an increased API loading and blending and higher compact ability
Calcium phosphate	MCC	Novel MCC based excipient has improved compact ability and recompact ability
β lactose	Sorbitol	Produce tablet with improved recompact ability
Calcium carboante	MCC	Novel MCC based excipients has improved recompact ability

Table 4: 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	Better flowabilty and higher compactability. Retains compressibility on wet granulation Exhibit enchanced flowability, exce
HPMC Crospovidone	Exhibit enchanced flowability, excellent compactability, increased API loading and blendability

METHODS OF CO-PROCESSED EXCIPIENTS:-

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

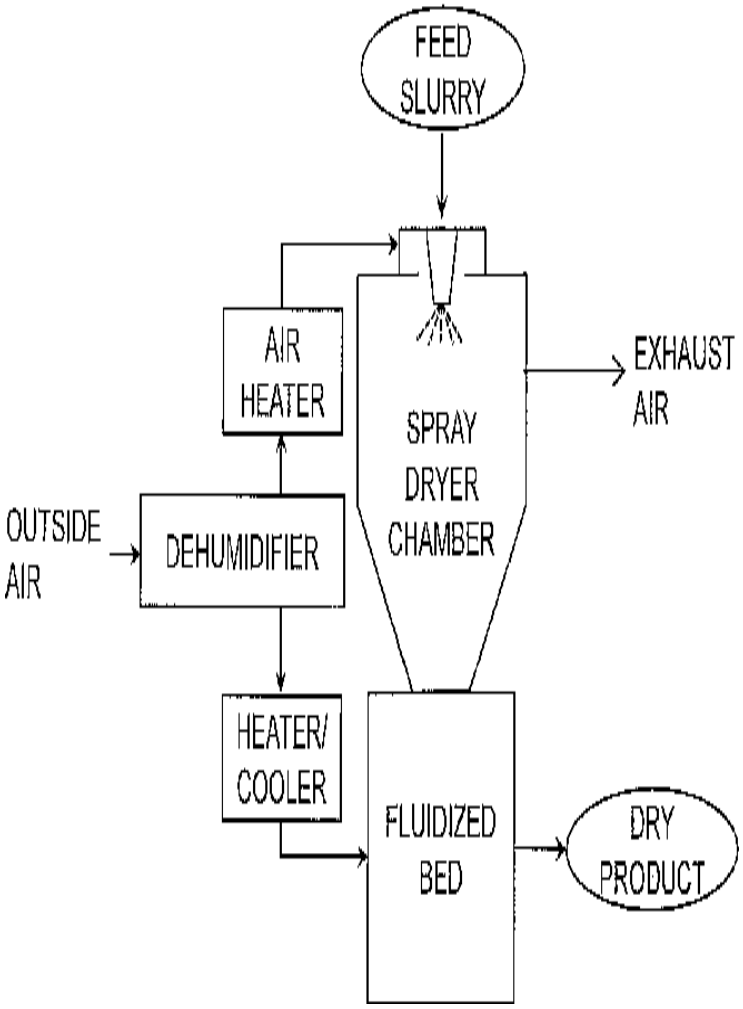
1. Spray drying

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 **[28]**:

- Atomization of the liquid into droplets.
- Contact of the droplet with the warm drying gas.
- Fast evaporation of the droplets to form dry particles.
- Recovery of the dry particles from the drying gas, using a cyclone.

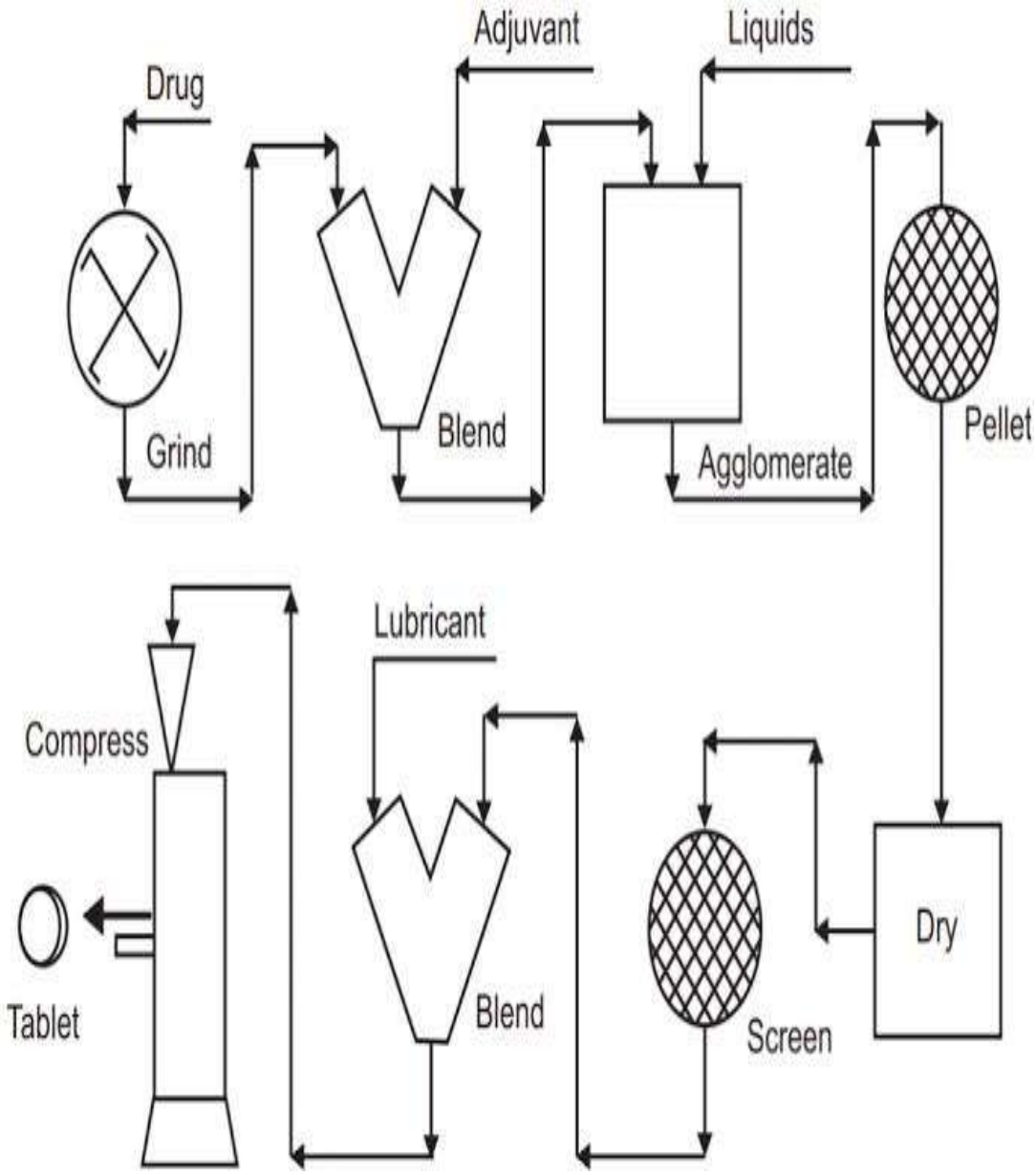
Advantages of spray drying:

- Possibility to associated non-miscible 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.



2. Wet granulation:

Wet granulation is a conventional and simple method for co-processed adjuvant production. Fluid bed granulators and high shear 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 **[29,30]**. 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 **[31]**.


Adjuvant
Liquids
Drug
Grind
Blend
Agglomerate
Pellet
Lubricant
Compress
Tablet
Blend
Screen
Dry

3. Melt extrusion

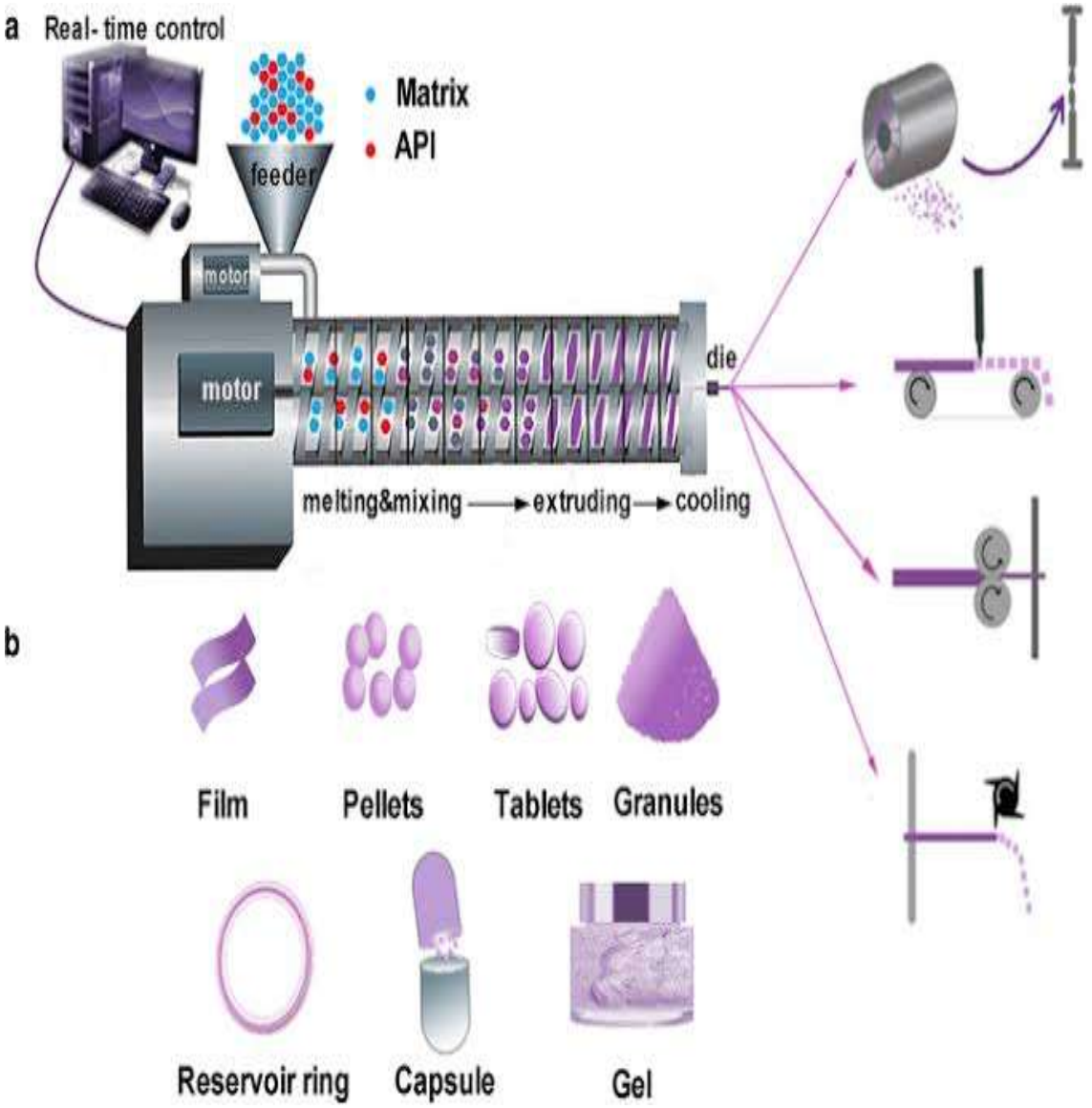
Melt extrusion is a process of formation of small beads, pellets from the molten mass which is extruded through extruder **[32,33]**. Extruders consist of four distinct parts **[34]**

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



- Advantages:-

1. Excellent repeatability
2. Complicate and intricate shapes are possible.
3. Time required is less

- Disadvantages:-

1. Equipment and die cost high
2. Minimum economic length high

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"".

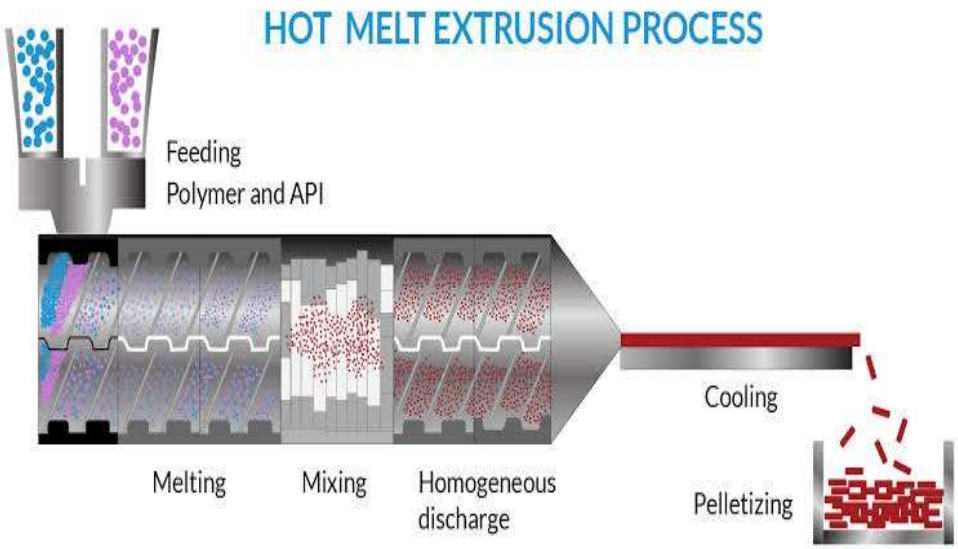
Agglomeration processes or in a more general term particle size enlargement technologies are great tools to modify product properties. Agglomeration of powders is widely used to improve physical properties like wettability, flowability, bulk density and product appearance **[35]**.

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 **[36, 37]** 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 **[38, 40]** 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 **[39]**.

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 **[40]**.

The new co-processed excipient prepared was evaluated **[41, 42]** for the following:

- **Solubility: Solubility of PGS-PEG-**

  Aerosil coprocessed 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 **[42]** 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) X 100
(Volume of sediment in light liquid paraffin)

- 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.
- 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:

$$CI = V_0 - V \times 100$$

EVALUATION PARAMETERS OF CO-PROCESSED EXCIPIENT

- **Solubility**

Solubility **[43]** 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.

- **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 **[44,45]** using benzene as liquid. 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 **[45]**.

- **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 **[46,47]**.

- **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.

- **Percentage fines**

The percentage fine is defined as the percentage of the sample passed through a 200 mesh (74 mm) sieve. The sample is agitated on a sieve shaker on a 200 mesh for 5 min for finding percentage fines.

- **Equilibrium moisture sorption (EMS)**

The moisture sorption isotherm is determined by the gravimetric method.

- **Heckel's plot**

The directly compressible adjuvant should exhibit good pressure- volume profile. The sample is compressed in a hydraulic press using and matching die at pressures of 1, 2, 3, 4, 5 and 6 tons for 1 min. The compacts are stored over silica gel for 24 hr to allow elastic recovery, hardening and prevent falsely yield low values before evaluations. Weight, diameter, and thickness of the compacts are determined, and data are processed using Heckel equation **[47,48]**.

$$\ln [1/(1-D)] = kP+A$$

where k and A are constant, D and P are the packing fraction and pressure respectively.

- **Compact elastic relaxation**

The sample is compressed in a hydraulic press using and matching die at pressures of 1, 2, 3, 4, 5 and 6 tons for 1 min. Compact height is measured with an electronic digital caliper after immediate ejection of compact from the die and stored in a desiccator **[49]**. After five days, compact height is measured again, and elastic relaxation (ER) is expressed in percentage as per equation

$$\% ER = 100* (Hb-Ha)/Ha$$

where, ER is elastic recovery, Hb and Ha are the compact height after five days of storage and immediately after ejection, respectively.

Evaluation parameters of tablets which depends on nature of co-processed excipients

- **Composite index**

  On completion of the individual experiment, a weighted composite index is used to designate a single score utilizing two responses, For example, Carr's index (%), and crushing strength

[50]. As the relative contribution of each individual constraint to the "true" composite score is unknown, a decision was made to assign an arbitrary value of one-half to each of the two response variables. In one variable (For example, Carr's index) lowest value is assigned as a score equal to 50, and the highest value is assigned zero scores in all batches as lower Carr's index is required for better flow. Second variable (For example, crushing strength) highest value is assigned a score equal to 50 and the lowest value is assigned zero scores.

Composite Index = (Transformed value of Carr's Index+Transformed value of crushing strength)

- **Lubricant sensitivity ratio**

Co-processed excipient and magnesium stearate are mixed and compressed into tablets. The lubricant sensitivity ratio (LSR) is calculated as per equation.

$$LSR = H_0 - H_{lub} / H_0$$

Where, H_0 and H_{lub} are the crushing strengths of tablets prepared without and with lubricant, respectively.

- **Dilution potential study**

Dilution potential is the amount of poorly compressible drug that can be satisfactorily compressed into a tablet with a directly compressible excipient. The drug is added in increasing order (10%, 20%, etc) into tablets with a co-processed excipient and maximum concentration at which satisfactory tablets are produced can be concluded. High dilution potential helps to produce tablets with less weight **[51]**.

- **Adhesion tendency**

The co-processed excipient is mixed with drug and sieved for 10 min. To promote the separation of drug particles from carrier excipient particles, different negative pressures were used during sieving. The oversize fraction is analyzed, and the amount of drug adhering to this oversize fraction is calculated as a percent of the initial concentration and expressed as % adhesion **[52]**.

- **Stability study as per ICH guideline**

Optimized co-processed excipients and final dosage forms like tablets, pellets, etc. are stored at room temperature as well as accelerated conditions (40 °C/75%RH) and observed for changes.

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

co processed 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 **[53]**.

Table 5: Some Examples Of Marketed Co-Processed Excipients [54-55]

Co process excipients	Manufacturer	Components %	Benefits
Ludipress R	BASF	Lactose monohydrate93.4 Kollidon30- 3.2 Kollidon CL-3.4	Lowhygroscopicity, good flowability, constant tablet weigh
Ludiflash	BASF	Mannitol-90 Kollidon CL_SF-5 Kollidon SR30D	Rapidly disintegration, mechanically stable tablet
Avicel CE15	FMC	MCC_85 Guar-15	Less grittiness, improve tablet Palatability
ProSolv R	JRS	MCC-98 silicon Dioxide-2	Better flow, less sensitive to wet granulation, better tablet hardness
Pharmaburst TM 500	SPI pharma	Mannitol, sorbitol,crospovidoneand silica;aspartame;andmangnesium stearate	Rapidly disintegrating With superior organoleptic properties
PanExceaTM MC200G	J.T.Baker	MCC-89 hydroxypropylmethayl Cellulose-2 Crospovidon-9	Enable direct compromise with high speed tableting
LubriTose AN	Kerry bio function ingredients	Anhydrous Lactose, GlyceryMonostearate	Eliminate the need for adding a separate lubricant

❖ CONCLUSION :-

Co-processed excipient comprises of combining two or more compendial or non-compendial excipients. They are configured for physically alteration of their attributes which are not accomplished by simple physical mixing and chemical process. Co-processing is done by adding the individual constituents in a particular process without modifying the chemical structure. Co-processed excipients can be used to reduce drug dosages, minimize side effects. So, medicines prepared by using co-processed excipients provides better and safe medicines. Co-processed excipients solve the issues of precompression parameters, compressibility, palatability, disintegration, dissolution and sticking which conventional individual excipients might have. Thus, there is vast scope and demand of co-processed excipients for pharmaceutical industries. Moreover, IPEC is drafting a guideline to facilitate development and adoption of co-processed excipients.

ACKNOWLEDGEMENTS

I would like to thank all co-authors.

REFERENCES

[1] Patil Atul, Kundu Subrata, Srinivasan Ganga. A Review on co - process excipients: A Novel approach in formulation development International Journal of Pharmaceutical Innovation. 2013; 3(5): 25-41.

[2] Steinberg M, Blecher L, Mercil A. Form Inactive Ingredients to Pharmaceutical Excipients. Pharma.Technol.2001;25(7)62-64.2.

[3] Ashok Thulluru, C. Madhavi, K. Nandini, S. Sirisha, D. Spandana. Co-Processed Excipients: New Era in Pharmaceuticals. Asian J. Res. Pharm. Sci. 2019; 9(1):01-05.

[4] B. Soujanya, G. Pavani Priya, T.E.G.K. Murthy. Co-Processing of Excipients: A Review on Excipient Development for Improved tabletting Performance. Res. J. Pharm. Dosage Form. & Tech. 2015;7(2):149-155.

[5] Chaudhari, P.D., Phatak, A.A., Desai U. A review: Co-processed excipients–An alternative to novel chemical entities. International Journal of Pharmaceutical and chemical sciences.2012;1(4):1480-1498.

[6] Desai U., Chavan R., Mhatre P., Chinchole R. A Review: Co-processed Excipients. International Journal of Pharmaceutical Sciences Review and Research. 2012;12(2):93-105.

[7] Uma R.G. Overview of Co-processed excipient use to improve tableting performance, Journal of Advanced Drug Delivery.2014:1(4).

[8] Patil A, Kundu S, Shrinivasan G, Review on co-process excipients: A Novel Approach in formulation Development. International Journal of Pharmaceutical Innovations. 2013;3(5):25-4.

[9] Siraj S.N., Kausar S.H., Khan G.J. and Khan T. Formulation and Evaluation of Oral Fast Dissolving Tablet of Ondansetron Hydrochloride by Co-Process Excipients. Journal of Drug Delivery and Therapeutics.2017;7(5):102-108.

[10] Bolhius GK. and Chowhan ZT. Materials for Direct Compaction in Pharmaceutical Powder Compaction Technology, Alder born G and Nystrom C, Eds. Marcel Dekker Inc., New York, NY;1996:419– 450.

[11] Satkar Namrata, Shinde Samrudh, Madane Poonam, Chaugule Pranjal, Chaugule N.B. A Brief

Review on Co-Processed Excipients, 2023, IJIRT, 10(7):266-272.

[12] Ayyapan J, Umapathi P, Darlin Quine. Development and evaluation of a directly compressible Co-processed sustained release agent for tablets. Int J Pharmacy PharmSci.2010; 2: 201-205.

[13] Gupta Piyush, Nachaegari Satish K, Bansal Arvind K. Improved Excipient Functionality by Co-processing. 2006;109-112.

[14] York P. Crystal Engineering and Particle Design for the Powder Compaction Process. Drug Dev. Ind. Pharm. 1992; 18(6, 7): 677–721.

[15] Belda PM, Mielck JB. The Tableting Behavior of Cellactose Compared with Mixtures of Celluloses with Lactoses. Eur. J. Pharm. Biopharm. 1996; 42(5): 325–330.

[16] Sherwood BE, Becker JW. A New Class of High Functionality Excipients: Solidified Microcrystalline Cellulose. Pharm. Technol. 1988; 22(10): 78–88.

[17] Allen JD. Improving DC with SMCC. Manufacturing Chemist. 1996; 67(12): 19–23.

[18] Schmidt P C and Rubensdorfer C J W; Evaluation of Ludipress as a Multipurpose Excipient for Direct Compression Part I: Powder Characteristics and Tableting Properties. Drug Dev Ind Pharm. 1994; 20 (18):2899-2925.

[19] Compression Part I: Powder Characteristics and Tableting Properties. Drug Dev. Ind. Pharm. 1994; 20(18): 2899–2925.

[20] Staniforth JN and Chatrath M. towards a New Class of High Functionality TabletBinders: Quasi-Hornification of Micro-crystalline Cellulose and Loss of Functionality. Pharm. Res. 1996; 13(9): 208.

[21] Flores LE, Arellano RL, and Esquivel JJD. Study of Load Capacity of Avicel PH-200 and Cellactose, Two Direct-Compression Excipients, Using Experimental Design. Drug Dev. Ind. Pharm. 2000; 26(4): 465–469.

[22] Bolhuis GK, Chowhan ZT. Materials for Direct Compression, Pharmaceutical Powder Compaction Technology, Vol-7, Marcel Dekker, USA, 419-499, 199

[23] Gohel MC, Jogani PD. Exploration of melt granulation technique for the development of co-processed directly compressible adjuvant

containing lactose and microcrystalline cellulose. Pharm Dev Technol.2003; 8: 175–185.

[24] Dr. Chris Moreton., "Functionality and Performance of Excipients in Quality by Design", world, PartIX: New excipients. American Pharmaceutical Review,April 2010.

[25] Bansal AK and Nachaegari SK. "Co processed excipient for solid dosage form." PharmTechnol, 2004; 52-64.

[26] Bolhius GK and Chowhan ZT. Materials for direct compaction in pharmaceutical powder compaction technology, G. Alderborn and C. Nystrom, Eds. Marcel Dekker Inc. New York, NY. 1996; 419-500.

[27] Modliszewski JJ and Ballard DA. Co-processed Galctomannan lucomannan, US patent No.5, 498, 436 to FMC Corporation (Philadelphia, PA) 1996.

[28] Nadavadekar, P. and Koliyote. S, Co-processed excipients for orally disintegrating dosage form, International Journal of Pharma Research and Review. 2014; 3(4): 95-100.

[29] Morin G, Briens L. A comparison of granules produced by high-shear and fluidized-bed granulation methods. AAPS PharmSciTech. 2014;15(4):1039-48.

[30] Bauer K, Streb M. Co-processed granules of disintegrating agents. EP1201709, 2002.

[31] Liew Kai Bin, Anand Gaurav, Uttam Kumar Mandal, A Review on Co-processed excipients: Current and Future trend of Excipient Technology", International Journal of Pharmacy & Pharmaceutical Sciences. 2019; 11(1): 1-9.

[32] Uma R.G., Overview of Co-processed excipient use to improve tableting performance, Journal of advanced drug delivery. 2014; 1(4).

[33] Nadavadekar, P. and Koliyote. S, Co-processed excipients for orally disintegrating dosage form, International Journal of Pharma Research and Review,2014;3(4):95-100.

[34] Rao *et al*. Preparation and characterization of a novel co-processed excipient of chitin and crystalline mannitol. AAPS PharmSciTech. 2012; 11(4): 1558-71.

[35] Daraghmeh N, Rashid I, Al Omari MM, Leharne SA, Chowdhry BZ, Badwan A. Preparation and characterization of a novel co-processed excipient of chitin and

crystalline mannitol. AAPS PharmSciTech. 2010;11(4):1558-71.

[36] Bauer KH. Co-processed polysaccharide. product with in soluble carboxymethylcellulose. EP1070740, 2001.

[37] Pawar S. B., Ahirrao S. P., Kshirsagar S. J. Review on novel pharmaceutical co-processed excipients. Pharmaceutical resonance. 2009; 2(1): 14-20.

[38] Liew Kai Bin, Anand Gaurav, Uttam Kumar Mandal, "A Review on Co-processed excipients: Current and Future trend of Excipient Technology, International Journal of Pharmacy and Pharmaceutical Sciences.2019;11(1):1-9.

[39] K.P.R. Chowdary and Sunil Kumar, Formulation development of selected drugs by direct compression method. IJPRD.2011;3(6):273-279.

[40] Martin A. Micromeritics. In: Martin A, 8th ed. Physical Pharmacy. Baltimore, MD: Lippincott. Williams & Wilkins. 2023: 423- 454.

[41] Cooper J, Gunn C, "Tutorial Pharmacy: Powder flow and compaction"; In: Carter SJ. 12th Eds., CBS Publications. 2008: 211-233.

[42] Aulton ME, Wells TI. Pharmaceutics; The Science of dosage form design.6th ed. London, England: Churchill Livingstone.2021:89-90.

[43] K.Ramya, K. P. R. Chowdary Vikas, Preparation, Charact-erization and Evaluation of A New Co-processed Excipients As Directly Compressible Vehicle In Tablet Formulation, Journal of Global Trends in Pharmaceutical Sciences. 2013;4(4):1322-1328.

[44] Daraghmeh N, Rashid I, Al Omari MM, Leharne SA, Chowdhry BZ, Badwan A. Preparation and characterization of a novel co-processed excipient of chitin and crystalline mannitol. AAPS Pharm SciTech. 2010;11(4):1558-71.

[45] Biwajit P, Abhinav R, Vaishali K., Co- processed pharmaceutical excipients formulation aspects, Physical Characteristics and Role as a Pharmaceutical-Aid. Pharma Tutor Pharmacy Infopedia, 2013.

[46] Bob ES, Amenia, Edward AH, John HS. Pharmaceutical excipient having improved compressibility. US Patent 5585115,1996.

[47] John K. Tillotson, Pharmaburst TM500: Optimized, Evolutionary

ODT Performance, SPI Pharma, 2013.

[48] Patil Vishal Satish, Bhujbal Nikhil S. and Oswal Rajesh J. A Review on Pharmaceutical Co-Excipients International Journal of Modern Pharmaceutical Research.2022, 6(2), 40-43.

[49] S. B. Pawar, S. P. Ahir Rao, S. J. Kshirsagar. Review on Novel Pharmaceutical Co-processed Excipients Pharmaceutical Resonance.2019; 2(1):14-20.

[50] Adi IA, Moawia MA. Compaction Mechanism and Tablet Strength of Cellactose R. Jordan Journal of Pharmaceutical Sciences.2008;1(1):71-82.

[51] Sharma S.K., Alam, M.N. Jaimini, M., Chatterjee A. and Mohan S., Co-processed excipients: A Review, International Journal of Current Trends in Pharmaceutical Research.2013;1(3):205-214.

[52] Nadavadekar, P. and Koliyote, S., Coprocessed excipients for orally disintegrating dosage form. International Journal of Pharma Research & Review.2014;3(4): 95-100.

[53] Kumari M.S., Prasanth C.H., Bhargavi C.S., Kumari M.P. and Ushasri S. Reassessment of novel co-processed multifunctional excipients. Int Res J Pharm App Sci.2013; 3(4):122-8.

[54] Gangurde. A., Patole. R.K., Sav. AK. and Amin. P.D., A novel directly compressible Co-processed excipient for sustained release formulation. Journal of Applied Pharmaceutical Science. 2013; 3(9), pp. 89-97

[55] Gohel MC. A review of directly compressible Excipients. Journal of Pharmaceutical Sciences.2005; 8: 76-93.