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# NOVEL CO-PROCESS EXCIPIENTS USED TO IMPROVE TABLETTING PERFORMANCE.

**Mayur A. Deore[1]*, Prashant A. Deore[2] and Pratik S. Chaudhari[3]**

[1]Department of Pharmaceutical and Healthcare Management, IES, Management College and Research Centre, Bandra, Mumbai, Maharashtra, India.
[2,3]Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education & Research, Shirpur- 425405, Dhule, Maharashtra, India.

*** Corresponding Author: Mayur A. Deore**
Department of Pharmaceutical and Healthcare Management, IES, Management College and Research Centre, Bandra, Mumbai, Maharashtra,

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**ABSTACT**
Tablets are the most preferred dosage form of pharmaceutical professionals because they can be accurately dosed and provide good patient compliance. The ease of manufacturing, convenience in administration, accurate dosing, and stability compared to oral liquids, tamper proof ness compared to capsules, Safe compared to parental dosage forms makes it a popular and versatile dosage form and can be produced at a relatively low cost. Co-processing is a novel process with the interaction of two or more excipients at the sub particle level which in turn provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients. This main aim of the current review article is to provide a complete overview on recent development in excipient technology and the approaches involved in development of such excipients. The co-processing comprises the most widely explored method for the formulation of directly compressible adjuvants because they are cost effective and can be prepared in-house based on the functionality required. This review highlights the various co processed excipients which will be used to improve the tabletting performance.

**KEYWORD:** Excipient, Co-process excipients, Co-Processing.

## INTRODUCTION

### What Is Co-Processing.[1]

Co-processing is another way that new excipients are coming to market without undergoing the rigorous safety testing of a completely new chemical. It can be defined as combining two or more established excipients by an appropriate process. Co-processing of excipients could lead to the formation of excipients with superior properties compared to the simple physical mixtures of their components.

### Types of Excipients[3]

Generally types of excipients were classified into 4 types which were given below.

1. Single entity excipients.
2. Mixtures or blends of multiple excipients.
3. Novel excipients or new chemical entities.
4. Coprocessed excipients.

### Co-Processed Excipients

Coprocessed excipients are co-processing of two or more than two compendial or non-compendial excipients. They are designed for modification of physical properties which was not achievable by simple physical mixing.[1] Typically they are produced using some form of specialized manufacturing process. The performance benefits relate to the manufacture or performance of the finished pharmaceutical product. This improvement in performance has been a primary drive for the introduction of co-processed excipients into the marketplace. Co-processed excipients are appropriate for consideration as new monographs because one or more of the components may be formed in-situ, or the component may not be isolated prior to coprocessing. That is, the manufacturing process for one component may not have been taken to completion before the addition of the other components and/or the co-processed excipient combination cannot be adequately controlled using the monograph tests for the individual component excipients.[2]

The actual process of developing a co processed excipient involves the following steps:[5]

- Identifying the excipients group to be co processed by carefully studying the material characteristics and functionality requirements
- Electing the proportions of various excipients
- Assessing the particle size required for co processing. This is especially important whenone of

the components is processed in a dispersed phase. Post processing the particle sizeof the latter depends on its initial particle size.

- Selecting a suitable drying process such as spray- or flash drying
- Optimizing the process (because even this can contribute to functionality variations).

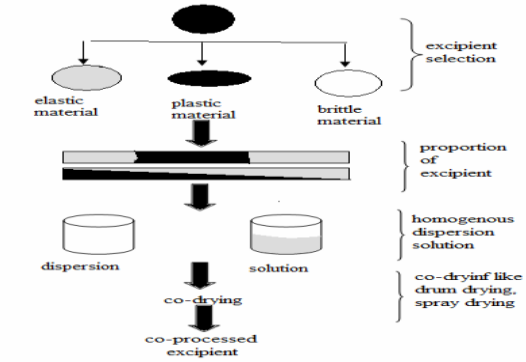


**Fig.No.1: Schematic representation of co processing method.[5]**

**Advantages of Co-Processed Excipients[3]**

The multifold advantages offered by co-processed excipients were given below.

1. Provide a single excipient with multiple functionalities.
2. Removal of undesirable properties.
3. Overcome the limitation of existing excipients.
4. Improvement of organoleptic properties.
5. Production of synergism in functionality of individual components.
6. Reduction of company's regulatory concern because of absence of chemical change during co-processing.
7. Improvement in physico-chemical properties has expanded their use in the pharmaceutical industry.

**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.[2],[10]

**2. Improved compressibility**

Co-processed excipients have been used mainly in direct compression tabletting because in this process there is a net improved in the flow properties and compressibility profiles and the excipient formed is a filler–binder.[2],[11-13]

**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 excellent compressibility properties to retain good compaction even when diluted with a poorly compressible agent.[2],[19]

**Limitations co-processed excipients.[4]**

**1. 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.

**2. 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.

**3. 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.

**4. 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.

**5. 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.

**Methods of co-processing**

Methods of coprocessing were listed below

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

**1. Spray Drying**

This technique enables the transformation of feed from a fluid state into dried particulate form by spraying the feed into a hot drying medium. It is a continuous particle processing drying operation. The feed can be a solution, suspension, dispersion or emulsion. The dried product can be in the form of powders, granules or agglomerates depending upon the physical and chemical properties of the feed, the dryer design and final powder properties desired.[3]

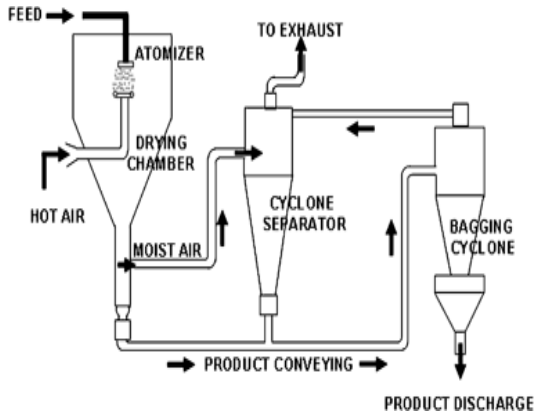


**Fig.No.2: Spray drying process**

**Advantages of spray drying.[4]**

- Possibility to associate non-miscible products in continuous operation.
- It allows blending and drying simultaneously soluble and insoluble compounds.
- Provides opportunity to fix and protect sensitive active compounds on neutral carrier.
- Improves hardness and compressibility.
- Enhances machine tableting speed, decreases disintegration time.
- Ensures a sturdy formulation with less need of maintaining inventory for various excipients.
- It is cost saving due to elimination of wet granulation production steps, which increases productivity and saves reworking expenses.

**Disadvantages[4]**

- Limited versatility in producing particles or structures with the complex morphologies.

**2. Solvent Evaporation**

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.[3]

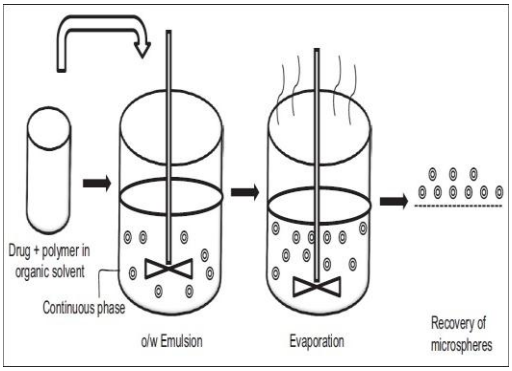


**Fig.No.3: Solvent Evaporation technique**

**3. Crystallization**

Crystallization is the (natural or artificial) `process of formation of solid crystals precipitating from a solution, melt or more rarely deposited directly from a gas. Crystallization is also a chemical solid– liquid separation technique, in which mass transfer of a solute from the liquid solution to a pure solid crystalline phase occurs. Procedure: For crystallization to occur from a solution it must be supersaturated. This means that the solution has to contain more solute entities (molecules or ions) dissolved than it would contain under the equilibrium (saturated solution). This can be achieved by various methods, with (1) solution cooling, (2) addition of a second solvent to reduce the solubility of the solute (technique known as antisolvent or drown-out), (3) chemical reaction and (4) change in pH being the most com mon methods used in industrial practice.[3]

**4. Melt Extrusion.[3]**

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

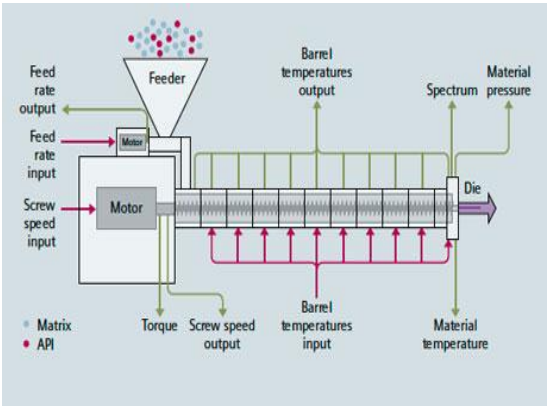


**Fig.No.4: Melt extrusion process**

**Advantages.[4]**

- No use of solvent or water
- Fewer processing steps
- Better alternative for poorly soluble drugs
- Less energy required compared with high shear methods
- More uniform dispersion because of intense mixing and agitation

**Disadvantages.**[4]

- Thermal degradation due to use of high temperature can take place
- Flow properties of the materials are essential for processing

**5. Granulation/Agglomeration**

Granulation is the act or process of forming or crystallizing into grains. Granules typically have a size size enlargement technologies are great tools to modify product properties. Agglomeration of powders is widely used to improve physical properties like: wettability, flowability, bulk density and product appearance. In pharmaceutical industry, two types of granulation technologies are employed, namely, Wet Granulation and Dry Granulation. Wet granulation is the more preferred method for coprocessing.[3]

**Pharmatose DCL 40**

Anhydrous lactose is a free flowing and directly compressible crystalline material with no water of hydration. However, its fluidity is less than optimal as it contains high amount of fines. Furthermore, it picks up moisture to form the hydrated compound at relatively high humidity. This is often accompanied by an increase in the size of the tablets if the excipient makes up a large portion of total tablet weight. Coprocessing of anhydrous lactose (95%) with lactitol (5%) into Pharmatose DCL 40 has helped to overcome these problems. Its flow properties improve because of its spherical form and favorable particle size distribution. The water uptake of Pharmatose DCL 40 at increasing humidity is very low. Moreover, its binding properties and dilution potential are much better than those of all known lactose based products.[8]

**Avicel CE 15**

Avicel CE 15 is a coprocessed excipient of 85% MCC and 15%guar gum, mainly used in chewable tablets. Avicel CE 15 offers improved palatability, creamier mouthfeel with less grittiness and reduced tooth packing.[8]

**Ludiflash**

90% Mannitol, 5% (Crospovidone) 5% (polyvinyl Acetate). It is specially designed for directly compressible, high speed tableting and hard tablet with very low friability. It has good flowability, less water absorption.[8]

***Advantages of Ludiflash.***[4]

- Controlled particle size distribution, particle structure and high bulk density combined to provide good Flowability.
- This combination provides compact, highly porous and fast disintegrating tablets offering exceptional hardness, friability and smooth mouth feel.
- Low hygroscopicity ensures the stability of the active ingredients and of the tablet itself.
- It is cost effective and used for preparation of pellets via wet extrusion. Drug loading was possible up to 30% for Ibuprofen and up to50% for Paracetamol.

**Orocell 200 & Orocell 400**

Composition - Spheronised mannitol with different particle size. Orocell 200 with 90% mannitol (<315µm) Orocell 400 with 90% mannitol (<500µm).

Characteristics - A developed filler-binder with high dilution potential and good disintegrating property useful for orally disintegrating tablets.[8]

**Ludipress®**

It is a combination of three excipients namely lactose monohydrate (93.4%) as a carrier, polyvinyl pyrrolidone (3.2% Kollidon 30) as a binder and crospovidone (3.4% Kollidon CL) as a superdisintegrant.[4]

***Advantages of Ludipress***

- Tablet hardness is not affected by tablet press speed.
- As it is a single integrated product the storage space required is reduced as compared to three different products.
- Similarly the cost for production, analysis and storage are reduced.
- Amount of Ludipress used for active ingredients such as Caffeine (125mg),Hydrochlorothiazide (50mg) and Diazepam (10mg) is 374.5, 279.3 and 487.5 respectively.
- Ludipress exhibits highest flowability and low hygroscopicity followed by Cellactose, Tablettose, Fast Flo lactose and anhydrous lactose as demonstrated by lower static and dynamic angles of repose.

**MicroceLac® 100**

It is a co-processed product manufactured by spray drying process. It consists ofα-lactose monohydrate (75%) and MCC (25%), also known as Cellactose.[4]

***Advantages of MicroceLac 100***

- It is designed for direct tableting process which combines filling and binding properties of two excipients as they give synergistic effect.
- Used for formulations having high content of active ingredients.
- To provide better tablet performance at lower cost.
- Various studies have revealed that the lactose: MCC ratio of 75:25 and dextrin as a binder are better than the ratio of 85:15 and hydroxypropyl methylcellulose as a binder.

**Dipac**

It is a free flowing agglomerated product consisting of hundreds of small sucrose crystals (97%) glued together by the highly modified dextrin (3%). Its sweet taste makes it suitable for most directly compressible chewable tablets.

**Advantages of Dipac**
High flowability, low hygroscopicity, sweetness, and non-reactivity with other tablet components.

**Prosolv® SMCC**
It is also known as Silicified Microcrystalline cellulose. It consists of microcrystalline cellulose (98%) and fumed colloidal silicon dioxide (2%).[4]

**Advantages of Prosolv**
- It enhances multifunctionality regarding compactibility, flow, blending, lubricant properties and tablet disintegration.
- It is available in three different grades Prosolv SMCC 50, SMCC 90, and SMCC HD 90, which differ in average particle size and bulk density.
- Prosolv is about 20% more compactable than regular cellulose.

**Avicel RC 591 / CL-611**
It is co-processed MCC and sodium carboxymethyl cellulose via co-drying process. Avicel RC (1-2%)/CL (2-3%) dispersible celluloses are used in pharmaceutical suspensions, emulsions, nasal sprays, and creams. Alone MCC and SCMC do not exhibit thixotropy in suspensions. The wide range of thixotropies, viscosities, gel strengths, and dispersion characteristics of Avicel RC/CL provide unparalleled suspension stability and functional versatility.[4]

**Avicel DG**
It consists of MCC 75% (plastic) and dibasic calcium phosphate 25% (brittle) co-spray dried
and is used in dry granulation processes. Intragranular roller compacted MCC losses its capacity to undergo plastic deformation during tablet compression. This leads to wear of machine parts and difficulty in achieving hardness. Extragranular Avicel PH 102 also needs to be added for achieving desired tablet hardness. Due to the presence of DCP, Avicel DG improves roller compaction by enabling continuous processing and eliminating extragranular excipients while maintaining fundamental requirements for disintegration and dissolution.[4]

**F-Melt®**
F-melt contains mannitol, xylitol, MCC, crospovidone as the main ingredients. It is available in two grades; F-Melt® Type C which contains dibasic calcium phosphate anhydrous and FMelt ® Type M contain Magnesium aluminometasilicate, additionally. Type C is for faster disintegration needs, while Type M has better flow properties and improves the overall quality of tablets. Although both types do not differ significantly in their physical properties. F-melt exhibits excellent tableting properties and facilitates rapid water-penetration for a fast disintegration time.[4]

**Pharmaburst™ 500**
Pharmaburst is a co-processed excipient which consists of mannitol, sorbitol, crospovidone and silica; aspartame; and magnesium stearate. Pharmaburst 500 is a ready to use system which has been specifically engineered to manufacture robust, rapidly disintegrating ODTs with superior organoleptic. Pharmaburst can be used on standard tableting equipment to formulate tablets with up to 500mg API. Simple dry blending of API, flavor, color and Pharmaburst 500 is needed. It allows rapid disintegration and low adhesion to punches.

The Loratidine 10mg ODT manufactured with Pharmaburst™ 500 exhibited suitable hardness, low friability and extremely rapid USP/EP disintegration time (4.9 seconds) and extremely rapid oral disintegration time (7 seconds), indicating the utility of Pharmaburst™ 500 in the manufacture of low-dose ODTs.[4]

**PanExcea™MC200G**
It consists of MCC 89% (diluent), hydroxypropylmethyl cellulose2% (binder) and crospovidone 9% (disintegrant) prepared by spray granulation. PanExcea has strong intraparticle bonding bridges between the components which results in a unique structural morphology comprising of open structures or hollow pores. Presence of these pores provides a surface roughness that is the ideal for improved blending with an Active Pharmaceutical Ingredient.[4]

***Advantages of PanExcea™MC200G***
- It increases drug loading capability as a result of the novel particle morphology.
- It optimized powder flow characteristics and compressibility enable direct compression with high speed tableting to enhance productivity.
- It provides desired disintegration times with exceptional tablet hardness.

**Lubritose™ AN / SD / MCC**
LubriTose™ combines a lubricant with a compression aid, allowing for the blending of the API, followed by tableting, without a final lubricant blend step. It is based on one of the following widely used compression aids, Anhydrous Lactose, Spray Dried Lactose, and MCC, all of which are co-processed with GlycerylMonostearate as the lubricant. The three products are called LubriTose™ AN (Anhydrous Lactose/GlycerylMonostearate), Lubri Tose™ SD (Spray Dried Lactose/GlycerylMonostearate) and LubriTose™ MCC (MCC/GlycerylMonostearate). LubriTose™ SD has the fastest flowability rate of the LubriTose™ systems, creating the capabilities to achieve the highest tablet press speeds. LubriTose™ AN has the fastest dissolution rate and highest degree of moisture stability of the LubriTose™ systems. It is suitable for use in all direct compression applications and in moisture sensitive formulations due to its anhydrous properties and is particularly effective in providing exceptional content uniformity when tableting high bulk density active ingredients. LubriTose™ MCC is specifically designed for use in direct compression, high speed

tableting operations where consistency, production efficiency and cost are essential.[4]

**Cellactose**

Cellactose is a co-processed product consisting a-lactose monohydrate (75%) and cellulose (25%). Coarse and regular grade sieved crystalline fractions of lactose monohydrate have good flow properties but lack compressibility. Co processing of crystalline a –lactose monohydrate with powdered cellulose (Cellactose, Meggle) or MCC (Microcell, Meggle) has resulted in improved bonding ability and excellent flow properties.

Cellactose was designed especially for direct tabletting combined filling and binding properties of the lactose and cellulose provides better tabletting performance at lower cost. It has excellent flowability attributed to its regular particle shape and favorable particle size distribution. Improved compactibility of Cellactose is owing to the principle consolidation mechanism of plastic deformation of cellulose and fragmentation of lactose. Moreover, Cellactose is shown to have a higher dilution potential than a physical mixture of its constituent excipient. The presence of cellulose fibers in the macro porous particles provides good disintegration properties to Cellactose. The moisture sorption of Cellactose is much lower than that of cellulose alone as it is covered with lactose. Belda and Meilck found that Cellactose exhibited improved compactibility but impeded compressibility as compared to powder mixtures, each containing 25% (w/w) of Avicel PH101 or Elcema P100 and 75% Tablettose ® or lactose (100 mesh).[8]

**Starlac**

The latest material on the market is Starlac, a co processed filler-binder consisting of 85% a-lactose monohydrate and 15% native corn starch. Starch is a bi functional excipient, used as binder and disintegrant; however, it exhibits the lowest elastic recovery at high binding capacity. When starch is co processed with a -lactose monohydrate, it resulted in a product with excellent compactibility. Flowability of StarLac is dependent on the spray-drying process. Moreover, starch imparts its rapid disintegration property. Starlac was proven to have improved compactibility and flowability to starch and its physical mixtures. The percentage of starch paste has inverse effect on the friability. It is used in low-dosage and fast dissolving formulations, direct compression, Dry granulation, homeopathic formulation.[8]

**Vitacel®**

Coprocessing of 75% MCC with 25% calcium carbonate was carried out in a weight ratio from about 75:25 to 35:65. The product exhibits low lubricant sensitivity; its compression profile (tablet hardness versus tablet compression force) remains relatively unchanged when various lubricants are employed. This lubricant insensitivity extends both to lubricant level (amount) and lubricant type (magnesium stearate, stearic acid, etc.). Limwong *et al.* fabricated composite particles of rice starch and MCC by spray-drying technique and evaluated its direct compressibility. These composite particles exhibited good compressibility and flowability whereas its tablets show low friability and good self-disintegrating property. Thus, these developed composite particles could be introduced as a new co processed excipient compression excipient.[8]

***Avicel HFE 102***

***Coprocessed*** product of MCC and mannitol has an improved compactibility profile, lubricant sensitivity and ejection profile compared to MCC. Shirwaikar *et al.* used spray drying technique for coprocessing of MCC and mannitol to obtain direct compression excipient. Mannitol and MCC in the ratio 1.25:1 was found to have optimized powder and compressibility characteristics with fast disintegrating property. Evaluatory study on disintegration time and mouthfeel attributes such as grittiness and chalkiness ranked the formulation as the best.[8]

**Advantose FS 95**

Fructose is a monosaccharide widely available from nature having very desirable sweetness and a natural food orientation that makes it suitable to use in pharmaceutical formulations. Fructose is, however, not directly compressible. Fructose granules agglomerated from a water solution are hard and the compressibility is unsatisfactory. Advantose FS 95 direct compression fructose is a co-dried system of fructose and a small amount of starch, which turns fructose into an excellent excipient for pharmaceutical, nutraceuticals and chewable vitamin applications. The particle size distribution of Advantose FS 95 fructose significantly improves the flow properties. The Advantose FS 95 product has lower hygroscopicity than standard fructose, making it easier to handle with improved compressibility.[8]

**Xylitab ®**

coprocessed directly compressible excipient of xylitol and sodium caboxymethyl cellulose is marketed as Xylitab ® (Danisco A/S, Copenhagen, Denmark). Xylitab has a cool taste, great stability and is ideal for all tablet forms. Morris et *al.* Evaluated Xylitab 100 and Xylitab 200 for compaction, flow, lubrication requirements and dilution potential. Compaction profiles, flow behavior, and dilution potential of xylitab was found to be acceptable and the authors concluded that xylitab can be successfully utilized as direct compression chewable tablet.[8]

***Nu-Tab***

Nu-Tab is a roller compacted granulated product consisting of sucrose, invert sugar, cornstarch and magnesium stearate. It has better flowability due to relatively larger particles but has poor colour stability compared to other directly compressible sucrose and

lactose. It is primarily used for preparation of chewable tablets by direct compression excipient.[9]

**Table No.1: Lists some of the marketed co processed excipients along with their manufacturers and benefit.[6],[7]**

| Brand name | Adjuvant | Application | Advantages | Company, country |
|---|---|---|---|---|
| Cellactose | MCC, lactose | High-dosage tablet, herbal formulations | Highly compressible, good mouth feel, low cost | Meggle, Germany |
| Pearlitol SD | Granulated Mannitol | for chewable and effervescent tablet, Diluents for capsules andsachets may require higher level of lubricant (magnesium stearates) | - | Roquette, France |
| Ludipress | Lactose, PVP, Crosspovidone | For use in chewable tablets andlozenges, foreffervescent tablets and as bulking agent for modified Release formulations. | good flowability, low hygroscopicity, hardness independent of machine speed | BASF, Germany |
| Starlac | Lactose , maize Starch | – | Good flow | Roquette, France |
| Pharmatose DCL 40 | Anhydrous lactose, lactitol | – | High compressibility, low lubricant sensitivity | DMV Netherland |
| Avicel CE-15 | MCC, Guar gum | – | Improved palatability, less grittiness, reduced tooth packing, | FMC USA |
| Prosolv | MCC, colloidal Silica | – | better flow , hardness, reduced friability | Pen west USA |
| PanExcea MC200G | Mannitol (75%), calcium silicate (25%). Particle size: 50% (103 µm) | -- | High performance, rapid disintegration, direct compression excipient for oro-dissolving tablets formulation | Avantor Performance Materials, Inc./Center Valley, PA, USA |
| Mannogem™ EZ | Spray dried direct compression mannitol Particle size: 60% (75–150 µm) | -- | Assist in formulating difficult to use non-hygroscopic ODT containing fine drugs | SPI Pharma™, Inc., New Castel, DE, USA |
| Pharmaburst ™ C1 | Mannitol 84%, crospovidone 16%, silicon dioxide <1% | -- | High compactibility, high loading in small diameter tablets, smooth mouth feel, rapid disintegration | SPI Pharma™, Inc., New Castel, DE, USA |
| Isomalt galenIQ–721 | 1-*O*-D-glucopyranosyl-D-mannitol dehydrate and 6-*O*-D-glucopyranosyl-D-sorbitol (1:3) Particle size: 90% (360 µm), 50% (220 µm) | -- | Highly soluble agglomerated spherical isomalt for fast dissolving and very fast disintegrating direct compression tablet preparations | BENEO–Palatinit GmbH (Mannheim, Germany) |

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