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DIRECTLY COMPRESSIBLE COPROCESSED PHARMACEUTICAL EXCIPIENTS

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Abstract

Tablet manufacturing has been easier by the introduction of the direct-compression process and high-speed machines. Thus, increases the demands on the functionality of excipients in terms of flow and compression properties. An efficient way for the manipulation of excipient functionality is provided by co-processing two or more existing excipients. Co-processing is the novel concept in which two or more excipients interacting at the sub particle level, the objective of coproceeing is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients. This review article gives detailed information about the potential advantages of co-processed excipients, various technologies used for co-processing of excipients for direct compression, material characteristics required for co-processing, description of some available co-processed excipients, evaluation parameters for checking the functionality of co-processed excipient and their future prospective.

Keywords: Co-processing, Directly compressible excipients, Direct compression, Ludiflash, Prosolv, Starlac.

Introduction

The International Pharmaceutical Excipient Council (IPEC) defines Pharmaceutical excipients as substances other than the API which have been evaluated for safety and are included in a drug delivery system. For example, excipients can:

- helps in the processing of the drug delivery system,
- protect, enhance stability, patient acceptability or bioavailability,
- assist in product identification, or
- Enhance other attribute of the overall safety, effectiveness or delivery of the drug during storage or use. [(1)]

The most commonly used solid pharmaceutical dosage form, tablet, which was prepared by dry granulation, wet granulation, or direct compression method. Most of the pharmaceutical manufacturing industries use direct

compression method as it requires fewer processing steps. Direct compression is the process in which tablets are prepared directly from the powder blends of active ingredients and excipients. For direct compression it is required that excipient used for formulation should have good flow properties and compression properties. The combinations of existing excipients are another option for improving excipients functionality. [(2)]

Table-1: Comparison of major steps involved in the granulation methods [(3)]

Step	Direct Compression	Dry Granulation	Wet Granulation
1	Mixing/ blending of API and adjuvants	Mixing/ blending of API and adjuvants	Mixing/ blending of API and adjuvants
2	**Compression**	Compression into slugs	Preparation of binder solution
3		Size reduction of slugs and sieving	Mixing of binder solution of step 2 with powder mixture of step 1
4		Mixing of granules with pharmaceutical aids	Wet screening of damp mass
5		**Compression**	Drying of wet granules
6			Resifting of dried granules and blending with pharmaceutical aids
7			**Compression**

Advantages of Direct Compression [(4)]

1. Stability: It is more suitable for hygroscopic and heat sensitive APIs, as it doesn't required wetting and drying steps and hence increases the stability of active ingredients.

2. Less wear & tear of punches: Tablets prepared by slugging or roller compaction involves high compaction pressure. It can be avoided by using direct compression method. Hence the wear and tear of punches and dies are less.

3. Cost Effectiveness: The direct compression method involves fewer steps that are less equipment, lower power consumption, less space, less time and less labour thus reduces production cost of tablets.

3. Faster Dissolution: Disintegration or dissolution is the rate limiting step in absorption of tablets having poorly soluble API prepared by wet granulation. Thus tablets prepared by direct compression disintegrate into API particles rather granules that directly come into contact with dissolution medium and thus comparatively faster dissolution.

5. Other advantages: The chance for contamination is low because the ingredients are processed for a shorter period of time. The validation and documentation requirements are reduced and will become easier due to fewer unit operations. The chance of microbial growth is minimal in case of tablets prepared by direct compression due to the absence of water in granulation.

Limitations of Direct Compression [(3)]

1. Segregation: It is more prone to segregation due to the difference in density of the API and excipients.

2. Variation in functionality: During mixing the dry state of the material may induce static charge and lead to segregation, which may lead to the problems like content uniformity and weight variation.

3. Low dilution potential: Most of the DCE can accommodate only 30-40 % of the poorly compressible active ingredients (e.g acetaminophen) it means the weight of the final tablet which delivers the 500 mg of acetaminophen would be more than 1300 mg. Thus large tablets create difficulty in swallowing.

4. API with low bulk density and/or poor flow properties is difficult to process by direct compression method.

Methods of Preparing Directly Compressible Excipients [(3)]

DCE can be prepared by various methods. The various features of the methods are given in Table 2. Co-processing is the one of the most widely acceptable and commercially applicable method for the preparation of DCE.

Table no. 2: Summary of various methods used to prepare directly compressible excipients[(3)].

Methods	Advantages and Limitations	Examples
Chemical Modification	Relatively expensive, requires toxicological data and time consuming.	Ethyl cellulose, Methyl cellulose, Hydroxypropyl methylcellulose and sodium carboxymethyl cellulose from cellulose. Cyclodextrin from starch, Lactitol.
Physical Modification	Relatively simple and economical	Dextrates or compressible sugar, Sorbitol
Grinding and/or sieving	Compressibility may also alter because of changes in particle properties such as surface area and surface activation.	α-Lactose monohydrate (100 #), Dibasic dicalcium phosphate
Crystallization	Impact flowability to excipient but not necessarily self binding properties. Requires stringent control on possible	β-Lactose, Dipac

	polymorphic conversions and processing conditions	
Spray Drying	Spherical shape and uniform size gives spray dried materials good flowability, poor reworkability.	Spray dried lactose, Emdex, Fast flo lactose, Avicel pH, Karion Instant, TRI-CAFOS S, Advantose 100
Granulation/ Agglomeration	Transformation of small, cohesive, poorly flowable powders into a flowable and directly compressible.	Granulated Lactitol, Tablettose
Dehydration	Increased binding properties by thermal and chemical dehydration.	Anhydrous α lactose

Co-Processing [(5)]

The manipulation of excipient functionality is done by coprocessing or particle engineering of two or more excipients. Co-processed excipients are the result of synergistic properties of existing excipients. Co-processed excipients are a combination of two or more excipients designed to modify their physical properties in a manner not achievable by simple physical mixing and without any chemical change. They have high functionalities as compared to individual excipients like compressibility, better flow property, reduced lubricant sensitivity.

Principle of Co-Processing Based on Particle Engineering [(6)]

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

Material Characteristics in Co-Processing [(5)]

Co-processing is generally conducted with one excipient that is plastic which means that due to applied stress there is a permanent change in shape of material and other one that is brittle which means that on application of stress a rapid propagation of crack throughout the material.

The co-processing performed with a small amount of plastic material and large amount of brittle material, for example Cellactose (Meggle Corp.) in which 75% lactose (brittle material) is co-processed with 25% microcrystalline cellulose (MCC, plastic material), prevents the storage of too much elastic energy during compression, which results in a reduced tendency of capping and lamination and a small amount of stress relaxation.

A combination of brittle and plastic materials is necessary for improving functional properties such as compressibility, strain-rate sensitivity, flow properties, lubricant sensitivity or sensitivity to moisture, or reduced hornification.

The following steps highlights the actual process of developing a coprocessed excipient: [7]

- Identifying the group of excipients to be coprocessed by carefully studying the functionality requirements and material characteristics.
- Selecting the proportions of various Excipients.
- Estimating the particle size required for coprocessing. This is 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 convenient process of drying like spray or flash drying.
- Optimizing the process (because even this can contribute to functionality variations).

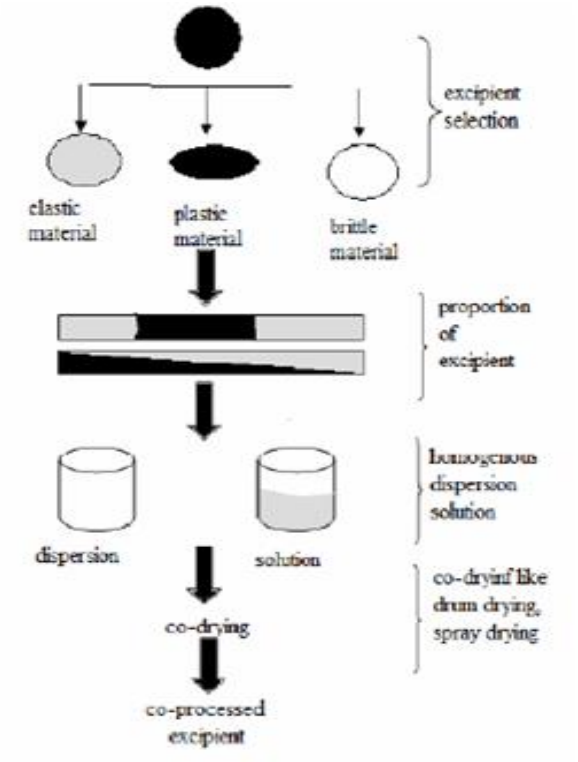

Figure No. 1: Co-processing of excipients.

Table No. 3: Co-processed excipients developed by co-processing brittle and plastic Materials [10].

Excipients co-processed		Improved properties compare to physical blend
Brittle component	**Plastic component**	
Colloidal silicon dioxide	MCC	Novel MCC based excipient is free flowing, posses excellent disintegration properties, has improved compressibility relative to normal commercially available MCC
Dibasic calcium phosphate	HPMC Crosspovidone	Has increased flowability, an increased API loading and blending and higher compactability
Calcium phosphate	MCC	Novel MCC based excipient has improved compactibility and recompactability
B lactose	Sorbitol	Produce tablet with improved recompactibility
Calcium carbonate	MCC	Novel MCC based excipient has improved recompactability
lactose	Polyvinyl pyrrolidine (PVP) Crosspovidone	Novel excipient posses good flowability and good compressibility under low pressure Produce tablets that exhibit excellent disintegration properties coupled with great hardness and low abrasion

Table no. 4: Co-processed excipients developed by co-processing two/three plastic materials[10]

Excipients Co-processed	Improved properties over physical blend
MCC **Guar gum**	Improved smell, text, texture and mouth feel
Mannitol, sorbitol	Good compactibility and less hygroscopicity
MCC **HPMC**	Better flowability and higher compactibility. Retains compressibility on wet granulation
MCC **HPMC** **Crospovidone**	Exhibit enhanced flowability, excellent compactibility, increased API loading and blendability

Advantages of Co-Processing [8]

1) **Enhanced Flow Properties -** Controlled particle size and particle- size distribution improves flow properties without glidants.

2) **Improved compressibility –** Co-processed excipients mainly used in direct compression tablet as it enhances flow properties and compressibility profiles.

3) **Better dilution potential –** Dilution potential is the ability of the excipient to maintain its compressibility even when diluted with another material. Most of APIs are poorly compressible; hence excipients must have better compressibility properties even when diluted with a poorly compressible agent.

4) **Fill weight variation –** Directly Compressible agents show high fill weight variations thus poor flow properties, whereas co processed excipients, have fewer fill weight variation problems, due to impregnation of one particle into the matrix of another, it reduces the rough particle surfaces and creates optimal size distribution, better flow properties.

5) **Reduced lubricant sensitivity –** Many of co processed products consist of a large amount of brittle material such as lactose monohydrate and a lesser amount of plastic material such as cellulose that is fixed between or on the particles of the brittle material. The plastic material gives good bonding properties as it forms a continuous matrix with a large surface for bonding. This large amount of brittle material provides low lubricant sensitivity as it prevents the making of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking the lubricant network.

Coprocessing of Excipients as Source of New Excipients [(9)]

Coprocessing of excipients leads to the formation of excipients with extraordinary properties compared to the simple physical mixtures of their components. The main objective of co-processing is to get a product with additional value related to the ratio of its functionality/price. Development of co-processed directly compressible excipients begins with the selection of the excipients to be combined, their desired proportion, preparation method to get optimized product with required physico-chemical propertiess and it ends with minimizing batch-to batch variations. Co-processing is useful because the products are physically modified without altering the chemical structure.

Major limitation of co-processed excipient mixture is that the ratio of the excipients in a mixture is fixed and for developing a new formulation, a fixed ratio of the excipients may not be a choice for the API and the dose per tablet under development.

Coprocessed excipients lack the official acceptance in pharmacopoeia. Even though the spray-crystallized dextrose-maltose (Emdex) and compressible sugar are co-processed products and are usually considered as single components and are official in USP/NF.

Table no. 5: Coprocessed directly compressible excipients

Co-processed excipients	Trade Name	Manufacturer	Added advantage
Lactose, 3.2% kallidone 30, kallidone cl	Ludipress	Basfag, Ludwigshafen, Germany	Low degree of hygroscopicity, good flowability, tablet hardness independent of machine speed
Lactose, 25% cellulose	Cellactose	Meggle gmbh & co. Kg, Germany	Highly compressible, good mouthfeel, better tabletting at low cost
Sucrose 3% dextrin **Microcrystalline cellulose silicon dioxide**	Dipac Prosolv	Penwest pharmaceuticals company	Directly compressible Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability
Microcrystalline cellulose, guar gum	Avicel ce-15	Fmc corporation	Less grittiness, minimum chalkiness, overall palatability
Calcium carbonate sorbitol **Microcrystalline cellulose, lactose**	Formaxx Microlela	Merck Meggle	Controlled particle size distribution Capable of formulating high dose, small tablets with poorly flowable API
95% β-lactose + 5% lactitol **85% α-lactose mh + 15% native corn starch**	Pharmatose dcl 40 starlac	Dmv veghel Roquette	High compressibility Good flow, low lubricant sensitivity

Technologies Used In Preparation of Co Processed Excipients

1. Roller compaction [(8)]

- The powder blends first pass a powder feeding zone, where most of the rearrangement occurs.
- The dense powders then pass through a compaction zone, where two counter-rotating rolls exert an increasing force for compaction of powder.

- The particles deform, fragment, and bond to form ribbons, as the pressure goes up further into the compaction zone.

Advantages

- It is widely applied to dry granulation.
- It has good control of process and cost-advantages compared to wet granulation.
- This process is more suitable for water or heat sensitive drugs, as no liquid or drying is involved.
- Roller compaction can handle high drug loading as compared to direct compression and also improves flow and content uniformity, and prevent segregation.

Disadvantages

- Loss of compactibility or dissolution problem.

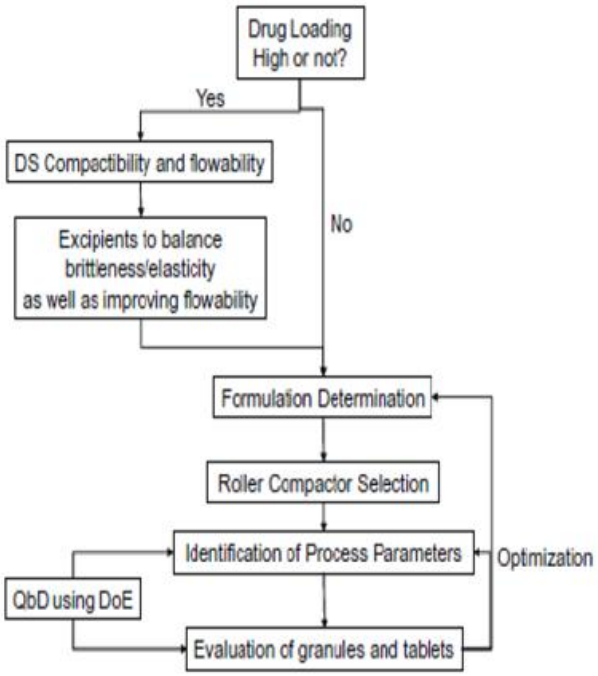

Figure No. 2: A brief flow chart for formulation and process development using roller compaction.

2. Wet granulation [8]

- Co-processing of excipients using wet granulation technique simply involves wet massing of the blend of the excipients to be co-processed with a granulating liquid, wet sizing, drying and finally screening of dry granules.
- Processing takes place in two types of closed granulating systems: one is fluid bed granulators and another is high-shear mixers. The two techniques differ fundamentally on the mode of granule growth and technically on the mode of solid agitation.

Fluid bed granulation

- The excipient mixture is maintained as a fluidized bed by a flow of air injected upwards from the bottom screen of the granulator.
- The other excipient solution is sprayed above the excipient bed, in a direction opposite to the air flow.
- During granulation partial drying by the fluidizing air occurs continuously.
- The process continues till all the powder has been agglomerated, and it needs to be stabilized as far as moisture balance is concerned.

High-shear granulation

- An impeller keeps the powder in agitation in a closed vessel, and here also a binder solution is sprayed from the top.
- The first nuclei of future granules will form as the liquid droplets disperse in the powder.
- The agitation forces stops the formation of large agglomerates, because they would be too fragile to sustain the shear.
- The existing agglomerates undergo densification as mixing and spraying proceeds, whereby the internalized binder is squeeze out to the surface of the wet agglomerates. It makes the agglomerates harder, and their surface more adhesive.

Advantages

- Provides better control of drug content uniformity at low drug concentrations
- Control of compactibility (brittle fracture) and product bulk density, even for high drug contents.
- Cost-effective

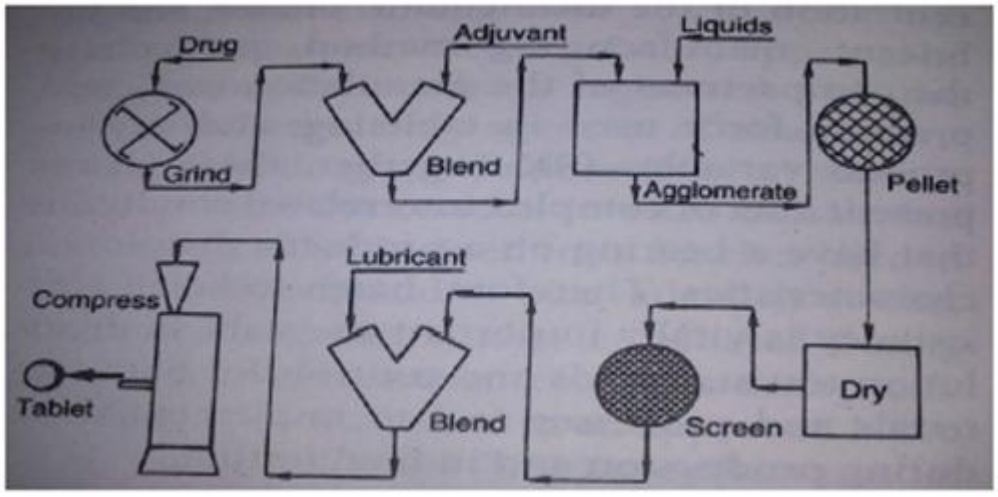

Figure No. 3: Flow chart of wet granulation.

3. Melt extrusion [5]

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

Advantages

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

Disadvantages

- Due to use of high temperature thermal degradation can occur.
- Flow properties of the materials are important.

Pharmaburst is manufactured by this process.

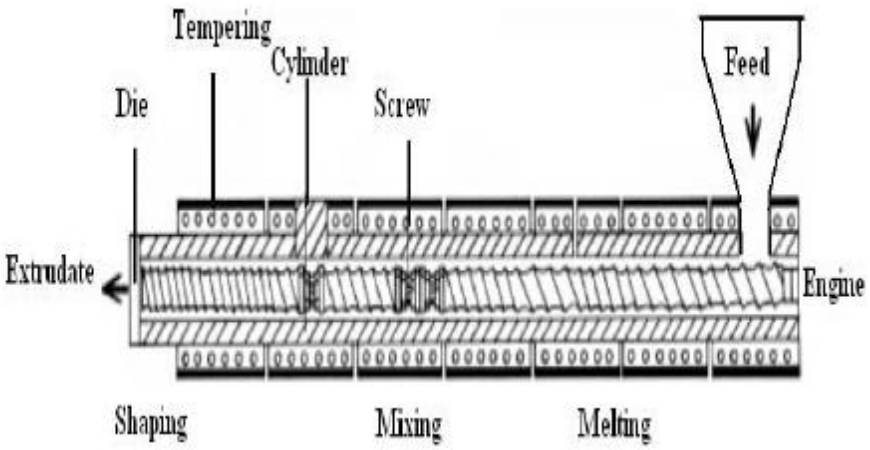

Figure No. 4: Melt extrusion process.

4. Melt Granulation [10]

- Melt granulation method of co-processing involves mixing, the blend of excipients to be co-processed, with a balance amount of meltable binder (that is binder melts in the temperature range of 50-800C and is in solid state at room temperature).
- In order to break the mass into agglomerates, the mixture is heated with continuous blending.
- The agglomerates are then cooled to room temperature and finally screened to obtain the granules of desired size.

Advantages

- It eliminates the use of water or any other solvent

- Short processing time
- It can be adopted for conventional equipment.

5. Spray drying [5, 10]

- Spray drying is a process of inculcating of solid or dry ingredients during drying, by atomizing active compounds in the form of suspension or in solution form.
- Co-processing of excipients using spray drying technique involves atomizing the solution or homogenous dispersion of the excipients to be co-processed into fine droplets.
- Fine droplets are then thrown radially into moving stream of hot gas. The increased droplet surface area and high temperature causes the formation of spherical particles, which makes them suited for the direct compression process.
- Precise control of various spray drying process parameters like atomization air pressure, inlet air temperature, feed rate, liquid viscosity, solid content in the feed, disc speed can help in designing particles with desired characteristics.

Advantages

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

Disadvantages

- It has limited versatility in producing particles or structures with the complex morphologies
- It has rapid drug release rates often exhibiting a burst effect

Co-processed excipients such as Dipac, Pharmatose DCL40, Fast Flo Lactose, Avicel PH, Microcelac 100 and Ludipress are manufactured by this process.

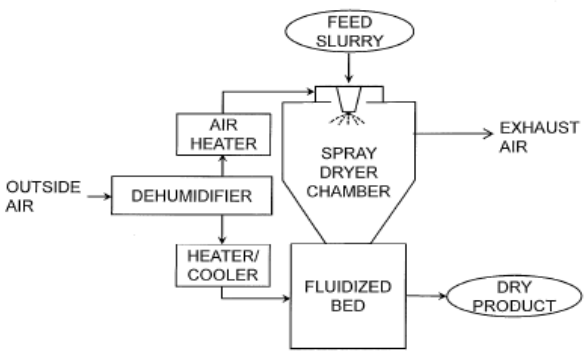

Figure No. 5: Spray drying process.

6. Co-Precipitation[(10)]

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

7. Co-Transformation [(10)]

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

8. Milling[10]

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

Examples of Co-Processed Excipients

1. Co processing of lactose:[11,12]

- Processing of lactose into small α-lactose monohydrate agglomerates (e.g., Pharmatose DCL 15, Tablettose) or spray-dried lactose was performed to enhance its direct compression characteristics.
- This processed lactose has better fluidity and compactibility than normal lactose. Thus, the compressibility of spray-dried lactose is borderline, and furthermore, it has relatively poor dilution potential.
- On initial compaction the spray-dried lactose loses its compressibility and it does not lend itself to rework.
- The binary mixtures of crystalline α-lactose monohydrate with MCC, povidone or starch have been tried but it only increases the compressibility of the mixtures but no improvement in flow ability as compared with pure α-lactose monohydrate. Thus, efforts were made towards the development of co processed lactose.

Ludipress: [8, 13]

- Co processing of 93.4% α-lactose monohydrate with 3.4% crospovidone and 3.2% povidone resulted in Ludipress (BASF AG, Ludwigshafen, Germany), that is a suitable filler for direct compression on high speed presses.
- It is tasteless, odorless, white free-flowing granules specially developed for direct compression process, but is also suitable as filler for hard gelatin capsules.
- The binding properties of Ludipress, both lubricated and unlubricated with 1% magnesium stearate, are good and much better than those of the physical mixture.
- Ludipress exhibited better flow rate compared to Avicel PH 101 and has the highest flow property among various lactose based directly compressible excipients (Cellactose, Tablettose, Fla flo lactose) as inferred from its lower dynamic and static angle of repose than other excipients.

- Ludipress, when used in high amount, can extend the sustaining effect of the formulation to some extent.
- At low compression force Ludipress gives harder tablets but the addition of disintegrant and glidant is needed.
- The binding capacity of Ludipress was superior than that of microcrystalline cellulose.

Cellactose: [14,15]

- Cellactose is a co-processed product consisting α-lactose monohydrate (75%) and cellulose (25%).
- Co processing of crystalline α–lactose monohydrate with MCC (Microcell, Meggle) or powdered cellulose (Cellactose, Meggle) has resulted in improved bonding ability and excellent flow properties.
- It has excellent flow property attributed to its regular particle shape and favorable particle size distribution.
- Cellactose have a higher dilution potential than a physical mixture of its constituent excipient.
- The moisture sorption of Cellactose is much lower than that of cellulose as it is covered with lactose.
- Cellactose exhibit the dual consolidation behaviour as it contains a fragmenting component (lactose) and a substance that consolidates primarily by plastic deformation (Cellulose).

Microcelac 100: [16,17]

- Microcelac 100 is another marketed spray-dried product, containing a MCC (25%) and lactose monohydrate (75%).
- Microcelac with both filling properties of lactose and binding capacity of MCC provides better tabletting performance at low cost.
- Zvolánková and Muzíková found that the tablet strength from pure Cellactose 80 was lower than that of those from MicroceLac 100 both with and without the lubricant in the compression forces of 6 and 8 kN.
- The Disintegration time of the tablets from Cellactose 80 was longer than those from MicroceLac 100, except the tablet materials having 0.4% sodium stearylfumarate (Pruv) with a compression force of 6 kN.

Starlac: [16]

- It is a coprocessed filler-binder contains 85% α-lactose monohydrate and 15% native corn starch.
- Starch is a bifunctional excipient, used as disintegrant and binder; however, it exhibits the lowest elastic recovery at high binding capacity.
- When starch is co processed with α-lactose monohydrate, it resulted in a product with excellent compactibility.
- The Volume–pressure deformation properties of StarLac are dependent on the lactose properties.

- Flow property of StarLac is dependent on the spray-drying process. Starch imparts its rapid disintegration property.

Pharmatose DCL 40: [16]

- Anhydrous lactose is a directly compressible and free flowing crystalline material with no water of hydration.
- It has less fluidity than optimal as it contains high amount of fines.
- Coprocessing of anhydrous lactose (95%) with lactitol (5%) into Pharmatose DCL 40 has help to overcome these problems.
- Pharmatose DCL 40 has improved flow properties because of its spherical shape and favorable particle size distribution.
- At increasing humidity the water uptake of Pharmatose DCL 40 is very low.
- Its dilution potential and binding properties are better than those of all known lactose based products.

2. Co processing of cellulose:

- MCC is a commonly employed direct compression excipients with good lubricity, low hygroscopicity and highest dilution potential.
- During wet granulation MCC loses its compressibility on addition of water. This phenomenon is known as quasihornification.
- The fluidity of MCC is poor compared to that of most of other direct-compression fillers as it has relatively small particle size.

Prosolv: [8]

- It is co-processed silicified MCC. It consists of 98% MCC and 2% colloidal silicone dioxide results in improved strength of tablet compacts, reduced sensitivity to wet granulation and better flowability than MCC.
- In the presence of magnesium stearate (0.5 %), tablets prepared with Prosolv have maintained tensile strength profiles, whereas the tensile strength of regular cellulose was considerably affected.
- Prosolv is 20% more compactable than regular cellulose.

Avicel CE 15: [17]

- 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 mouth feel with less grittiness and reduced tooth packing.

Vitacel®: [17, 18]

- Coprocessing of 75% MCC with 25% calcium carbonate was done in a weight ratio from about 75:25 to 35:65.
- It exhibits low lubricant sensitivity; its compression profile (tablet hardness versus tablet compression force) remains comparatively unchanged when various lubricants are employed.

Avicel HFE 102: [17]

- Coprocessed product of MCC and mannitol has an improved compactibility profile, lubricant sensitivity and ejection profile compared to MCC.
- Mannitol and MCC in the ratio 1.25:1 was found to have optimized powder with improved compressibility characteristics and fast disintegrating property.

Avicel CL-611: [19]

- Co processed MCC and sodium carboxymethyl cellulose via co-drying process.
- Impart a thixotrophic viscosity profile, and increase formulation stability over a wide range of pH.
- It is used as a stabilizer.

3. Coprocessing of sugars and polyols: [20]

- Sorbitol is widely used as the only ingredient in sugar-free mints and as a vehicle in chewable tablets.
- It has a cool taste and good mouth feel and gives relatively good compacts. But its highly hygroscopic nature leads to its poor powder flowabiltiy and sticking, caking during tabletting.
- Its hygroscopicity has its impact on the physical characteristics of tablets such as hardness, bioavailability and dissolution.
- On the other hand, mannitol does not make as hard a tablet as sorbitol but is less sensitive to humidity.

Compressol S: [20]

- It is directly compressible excipient of mannitol and sorbitol which retains the compaction ability of sorbitol and characteristic mannitol texture with lower hygroscopicity than sorbitol.
- It is 300 times less hygroscopic than sorbitol, which makes it more suitable to use with moisture-sensitive drugs.
- Good compactibility and low hygroscopicity combined with pleasant taste and favorable mouthfeel of Compressol S makes it perfect for use in high dose active nutraceutical and chewable tablet formulations.
- The coprocessed excipient of mannitol and sorbitol can also effectively be included in quick dissolving tablet formulations.

Advantose FS 95: [19,20]

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

Dipac: [20]

- Di-Pac is a directly compressible, co-crystallized sugar consisting of 97% sucrose and 3% modified dextrin.
- It is a free flowing and agglomerated product consisting of hundreds of small sucrose crystals glued together by the highly modified dextrin.
- Di-pac begins to cake and loose its fluidity at high moisture level.
- Tablets containing a high proportion of Di-pac are likely to harden after compression at higher relative humidity.
- Its sweet taste makes it appropriate for most directly compressible chewable tablets.
- Used as sweetener (10-50%), dry binder (5-20%), filler (20-60%) etc.

4. Coprocessing of inorganic fillers: [20,21]

Formaxx:

- Coprocessing of calcium carbonate (70%) with sorbitol (30%) offers a distinct advantage of producing directly compressible calcium carbonate.
- It offers improved flowability, higher compaction properties at low compression forces and has low friability compared to calcium carbonate.
- This distinctive processing of calcium carbonate with sorbitol masks the chalky and gritty taste of calcium carbonate.

Ludiflash:

- It contains 90% Mannitol, 5% polyvinyl Acetate, 5% Crospovidone.

- It is specially designed for directly compressible, high speed of tableting and hard tablet with very low friability.
- It has good flowability, less water absorption.

Orocell 200 & Orocell 400:

- Spheronised mannitol with different particle size.
- Orocell 200 with 90% mannitol (<315µm) Orocell 400 with 90% mannitol (<500µm).
- High dilution potential and good disintegrating property useful for orally disintegrating tablets.

Table no. 6: Flow properties of various co processed excipients.

Trade name	Particle size distribution	Hausner ratio	Bulk Density (g/cm ^{3})	Tapped density (g/cm^3)	Angle of repose	Compressibility index
Ludipress	< 63 µm max. 20% < 20 µm 40 – 65% 400 µm max. 20%	1.20	0.517	0.618	29.5°	16.14
Cellactose	<32 µm <=20% <160 µm 35-65% <200 µm >=80%	1.24	0.38	0.5	32-35°	17.75
MicroceLac100	<32 µm <=15% <160 µm 70% <250 µm >=90%	1.16	0.5	0.6	34°	
Starlac	< 32 µm NMT 15% < 160 µm 35 – 65% < 250 µm NLT 80%	1.19	0.57	0.68	<=29°	16.18
Pharmatose DCL 40	< 45 µm max. 20%< 150 µm 40 – 65%	1.27	0.67	0.85	<=39°	21.18

Evaluation Parameters for Co Processed Excipients

1. Particle size distribution

The particle size distribution can be calculated by statistical method such as frequency curve method. When the number, or weight, of particles lying within a assured size range is plotted against the mean particle size or size range, a so called frequency curve is obtained. [(22)]

2. Carr's index

The bulk density is the quotient of the mass to the volume of sample. The tapped density is the quotient of the mass of the sample to the volume after tapping a measuring cylinder 500 times from a height of 2 inches. Carr's index (percentage compressibility) was calculated as one hundred times the ratio of the difference between the tapped density and bulk density to the tapped density. [(23)]

3. Hausner Ratio

Hausner ratio is the ratio of bulk density to the tapped density. [23]

$$\text{Carr (\%)} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

$$\text{Hausners's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

4. Angle of repose

The angle of repose is a relatively simple technique for evaluating the flow properties of a powder. It can easily be determined by allowing a powder to flow through a funnel and fall freely onto a surface. The height and radius of the resulting cone are measured and the angle of repose calculated from this equation: [24]

$$\text{Tangent (angle of repose)} = \frac{\text{height of funnel orifice}}{\text{average radius of pile}}$$

Current Status of Co-Processed Excipient Monographs in NF [19]

Co-processed excipients are appropriate for consideration as new monographs since one or more of the components may be formed in situ, or the component may not be isolated prior to co processing. Which means that, 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 single component excipients. The co-processed excipient monographs meet current NF submission requirements as defined by the following: Each of them is either included in an approved drug application (in the FDA inactive ingredient database) or has a Generally Recognized as Safe (GRAS) designation. The excipients typically are manufactured using some type of specialized manufacturing process such as high-shear dispersion, granulation, spray drying, or melt extrusion. Such combination excipients produced using these specialized manufacturing processes is commonly called co-processed excipients.

A Regulatory Perspective of the Excipient Mixtures [25]

With the absence of a chemical change during processing, if the parent excipients are GRAS-certified by the regulatory agencies then the co processed excipients can also be considered as safe (GRAS). Hence, these excipients do not require additional toxicological studies.

Future Prospective [21]

The obvious advantages of solid dosage forms and changing technological requirements will keep alive the search for newer excipients. They are playing a vital role in the development of easy dosage forms which are resistant to

atmosphere. The newer excipients are required to be compatible not only with the latest technologies and production machineries, but also with the innovative active principles such as those originating from biotechnology. The enhanced chemical, physical and mechanical properties of such excipients as compared to existing excipients, have helped to solve formulation problems such as flowability, compressibility, hygroscopicity, palatability, dissolution, disintegration, sticking, and dust generation. The advantages of these excipients are numerous, but further scientific investigation is required to estimate the mechanisms underlying their performance. With development a number of new chemical entities rising day by day, there is a huge scope for further development of and use of these excipients in future.

Conclusion

To achieve greater productivity and good quality product in tablet manufacturing specially on the new generation High-speed machines the main challenges are the powder flow properties and compressible characteristics of the materials to be compressed. The conventional method of wet granulation has drawbacks in terms of achieving batch-to-batch reproducibility and superior productivity, particularly in low particle size range. So comparing to wet granulation, direct compression method has fewer steps and batch to batch reproducibility.

Therefore, directly compressible co-processed excipients with superior functional property could be the alternating way to overcome the problems associated with single polymer alone.

The main obstacle in the success of co-processed excipients is the noninclusion of their monographs in official pharmacopeias, which discourages their use by pharmaceutical manufacturers. With recommendations from IPEC and the continual efforts of excipient manufacturers, these products could find their way into official monographs, either as mixtures or as single-bodied excipients.

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