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Co-Processed Excipients: A Review

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Abstract
Co-processing is the way that new excipients coming to the market without undergoing rigorous safety testing of 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 formation of excipients with superior properties compared to simple physical mixtures of their components. The main aim of co processing is to obtain product with an added value related to the ratio of its functionality /price.
Key words: Co- Processed Excipients, Formation, Physical Mixtures, established excipients

Introduction
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 physico-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.

The excipients industry to date has been an extension of the food industry[1]. 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)[2]. IPEC is a tripartite council with representation from the United States, Europe, and Japan and has made efforts to harmonize requirements for purity and functionality testing[3]. The development of new excipients to date has been market driven (i.e., excipients are developed in response to market demand) rather than marketing driven (i.e., excipients are developed first and market demand is created through marketing strategies) and has not seen much activity as shown by the fact that, for the past many years, not a single new chemical excipient has been introduced into the market. The primary reason for this lack of new chemical excipients is the relatively high cost involved in excipients discovery and development. However, with the increasing number of new drug moieties with varying physicochemical and stability properties, there is growing pressure on formulators to search for new excipients to achieve the desired set of functionalities.
Other factors driving the search for new excipients are

- The growing popularity of the direct-compression process and a demand for an ideal filler–binder that can substitute two or more excipients
- Tableting machinery's increasing speed capabilities, which require excipients to maintain good compressibility and low weight variation even at short dwell times.
- Shortcomings of existing excipients such as loss of compaction of microcrystalline cellulose (MCC) upon wet granulation, high moisture sensitivity, and poor die filling as a result of agglomeration[3].
- The lack of excipients that address the needs of a specific patient such as those with diabetes, hypertension, and lactose and sorbitol sensitivity.
- The ability to modulate the solubility, permeability, or stability of drug molecules.

- The growing performance expectations of excipients to address issues such as disintegration, dissolution, and bioavailability.

Sources 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[4]. Any new chemical excipient being developed as an excipient must undergo various stages of regulatory approval aimed at addressing issues of safety and toxicity, which is a lengthy and costly process. In addition, the excipient must undergo a phase of generic development, which shortens the market exclusivity period[5]. The high risk and significant investment involved are not justified in view of the meagre returns from the new excipients. A plausible solution is for excipient and pharmaceutical manufacturers to develop drug products jointly, during which a new excipient becomes part and parcel of the eventual new drug application. This type ofarrangement already has been successfully applied in theintravenous delivery field, in which CyDex and Pfizer workedcollaboratively to obtain the approval of a solubilizer[6-7].

The combined expertise of pharmaceutical and excipient companies can lead to the development of tailor-made innovative excipients. Developing new grades of existing excipients (physicochemical) has been the most successful strategy for the development of new excipients in past three decades[8], a process that has been supported by the introduction of better performance grades of excipients such as pre gelatinized starch, croscarmellose, and crospovidone[9]. However, functionality can be improved only to a certain extent because of the limited range of possible modifications. A new combination of existing excipients is an interesting option for improving excipient functionality because all formulations contain multiple excipients. Many possible combinations of existing excipients can be used to achieve the desired set of performance characteristics. However, the development of such combinations is a complex process because one excipient may interfere with the existing functionality of another excipient. Over the years, the development of single-bodied excipient combinations at a subparticle level, called co processed excipients, has gained importance. New physical grades of existing excipients and co processed excipients are discussed further in the following section of this article that explains particle engineering. Particle engineering is a broad-based concept that involves the manipulation of particle parameters such as shape, size, size distribution, and simultaneous minor changes that occur at the molecular level such as polytypic and polymorphic changes. All these parameters are translated into bulk level changes such as flow properties, compressibility, moisture sensitivity, and machinability.

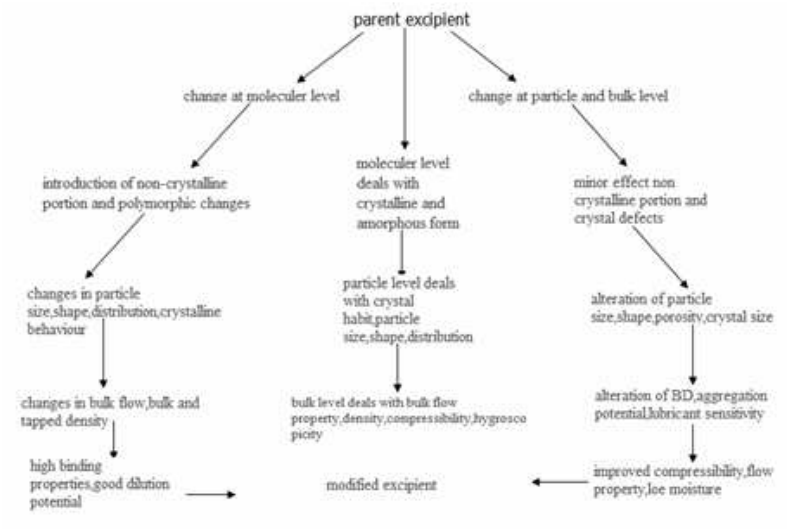

Figure1: The pyramid of solid state

Particle engineering as source of new excipients

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. 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, compactibility, 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[10].Varying the crystal lattice arrangement by playing with parameters such as the conditions of crystallization and drying can create particles with different parameters.

Lactose is examples in which such an approach has been successfully applied. However, particle engineering of a single excipient can provide only a limited quantum of functionality improvement. Co processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients[11] .The availability of a large number of excipients for co processing ensures numerous possibilities to produce tailor-made "designer excipients" to address specific functionality requirements 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.

Table 1: Various particle properties influencing excipient functionality

Particle property	Excipient functionality
Enlargement of particle size	Flowability,compressbility
estricting particle size distribution	Segregation potency
Enlargement of particle porosity	Compressibility, solubility
Surface roughness	Flowability, Segregation potency

Co processing of Excipients

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

1. Identifying the excipients group to be co processed by carefully studying the material characteristics and functionality requirements
2. Electing the proportions of various excipients
3. Assessing the particle size required for co processing. 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.
4. Selecting a suitable drying process such as spray- or flash drying optimizing the process (because even this can contribute to functionality variations).
5. Figure 2 shows a schematic representation of the co processing method.

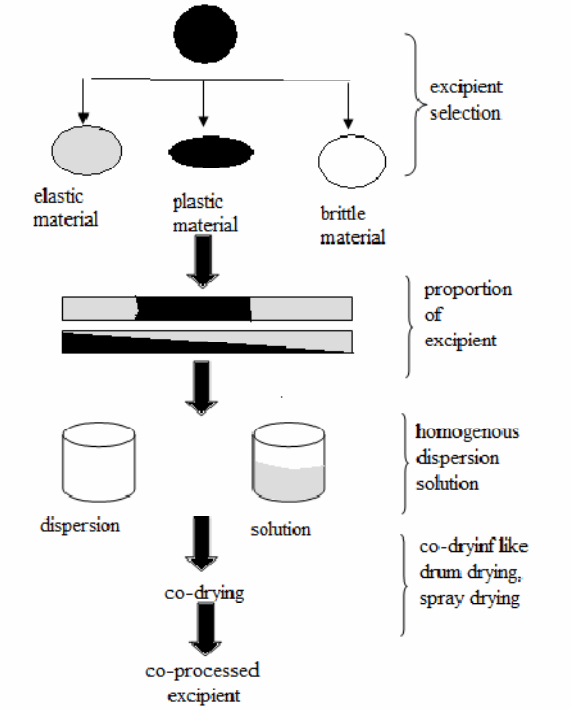

Figure2: Co-processing of excipients

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 theseexcipients 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 C_{13} NMR spectroscopy have detected no chemical changes and indicate a similarity to the physicochemical properties of MCC[12].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 coprocessed 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[13]. The spray-dried product had a spherical shape and even surfaces, which also improved the flow properties.

2. Improved compressibility

Coprocessed 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 coprocessed excipients, when plotted and compared with simple physical mixtures, showed a marked improvement in the compressibility profile. The compressibility performance of excipients such Cellactose[14], SMCC[15-16] and Ludipress[17] 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 quasihornification[18]. 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[19].

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 MCC[15].

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[20]. 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.

6. Other properties

Co-processed excipients offer the following additional advantages:

- Pharmaceutical manufacturers have the option of using a single excipient with multiple functional properties, thereby reducing the number of excipients in inventory.
- Improved organoleptic properties such as those in Avicel CE-15 (FMC Corp., Philadelphia, PA), which is a co-processed excipient of MCC, and guar gum were shown to have distinctive advantages in chewable tablets in terms of reduced grittiness, reduced tooth packing, minimal chalkiness, better mouth feel, and improved over all palatability.

Table: 2 Coprocessed directly compressible excipients

Coprocessed excipients	Trade name	Manufacturer	advantage
Lactose,3.2%kallidone kallidone cl	Ludipress	Basfag, ludwigshafen, germany	Low degree of hygroscopicity, good flowability, tablet hardness independent of machine speed
Lactose,25% cellulose	Cellactose	Megglegmbh& co. Kg, 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	Avicel ce-15	Fmc corporation	Less grittiness, minimal chalkiness
Calcium carbonate, sorbitol	Formaxx	Merck	Controlled particle size distribution
Microcrystalline cellulose, lactose	Microlela	Meggle	Capable of formulating high dose, small tablets with poorly flowable active ingredients
95% β- lactose + 5% lactitol	Pharmatose dcl 40	Dmvveghel	High compressibility

Table 3: Summary of various methods used to prepare directly compressible adjuvant

Method	Advantage & limitation	Example
Chemical modification	Expensive, time consuming, require toxicological data	Ethyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, lactitol, cyclodextrin from starch
Physical modification	Simple and economical	Sorbitol, dextrates and compressible sugars
Grinding or sieving	Compressibility may alter because of change in particle properties	Dibasic dicalcium phosphate, α-lactose monohydrate
Crystallization	Impart flow ability to excipient but not self-binding properties, require stringent control on processing	Dipac, β-lactose
Spray drying	Spherical shape and uniform size gives spray dried material good flowability, poor rework ability	Emdex, Avicel PH, advantose100, karion instants
Granulation/agglomeration	Transfer poor flow, cohesive, small particle into flowable and directly compressible	Granulated lactitol, tablettose
Dehydration	Increase binding properties by thermal and chemical modification	Anhydrous α-lactose

Some cost, the overall product cost decreases because of improved functionality and fewer test requirements compared with individual excipients. Because they can retain functional advantages while selectively reducing disadvantages, co-processed excipients can be used to develop tailor-made designer excipients. This can be helpful in reducing the time required to develop formulations.Co-processed excipients can be used as proprietary combinations, and in-house formularies can be maintained by pharmaceutical companies, which could help in developing a formulation that is difficult to reproduce and provides benefits in terms of intellectual property rights.

Direct Compression

Previously, the word ‘direct compression’ was used to identify the compression of a single crystalline compound (i.e. sodium chloride, potassium chloride, potassium bromide, etc.) into a compact form without the addition of other substances. Current usage of the term ‘direct compression’ is used to define the process by which tablets are compressed directly from the powder blends of active ingredients and suitable excipients. No pretreatment of the

powder blends by wet or dry granulation is involved[21]. The simplicity of the direct compression process is apparent from a comparison of the steps involved in the manufacture of tablets by wet granulation, roller compaction and direct compression techniques[22]. It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets. The rest of the materials lack flow, cohesion or lubricating properties necessary for the production of tablets by direct compression. The use of directly compressible adjuvants may yield satisfactory tablets for such materials. Although simple in terms of unit processes involved, the direct compression process is highly influenced by powder characteristics such as flow ability, compressibility, and dilution potential. Tablets consist of active drugs and excipients, and not one drug substance or excipient possesses all the desired physico mechanical properties required for the development of a robust direct-compression manufacturing process, which can be scaled up from laboratory to production scale smoothly. Most formulations (70–80%) contain excipients at a higher concentration than the active drug. Consequently, the excipients contribute significantly to a formulation's functionality and processability.

In simple terms, the direct-compression process is directly influenced by the properties of the excipients. The physic mechanical properties of excipients that ensure a robust and successful process are good flow ability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity, and good machinability even in high-speed tableting machinery with reduced dwell times. The majority of the excipients that are currently available fail to live up to these functionality requirements, thus creating the opportunity for the development of new high functionality excipients.

Directly Compressible Adjuvants

The International Pharmaceutical Excipients Council (IPEC) defines excipient as Substances, other than the API in finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing or to aid manufacture, protect, support, enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use[23]. Solvents used for the production of a dosage form but not contained in the final product are considered to be excipients, i.e. the granulation fluids, which might be dried off later, should comply with relevant requirements of pharmacopoeia unless adequately justified. Excipients no longer maintain the initial concept of "inactive support" because of the influence they have both over biopharmaceutical aspects and technological factors. The desired activity, the excipients equivalent of the active ingredient's efficacy, is called its Functionality. The inherent property of an excipient is its functionality in the dosage form. Determination of an excipient's functionality is important to the excipient manufacturer in its assessment of the proper level of GMP, and yet the drug manufacturer may withhold this information until well into the development process[24].

In order to deliver a stable, uniform and effective drug product, it is essential to know the properties of the active ingredient alone and in combination with all other ingredients based on the requirements of the dosage form and processes applied. Excipients are usually produced by batch process; hence, there is a possibility of batch-tobatch variation from the same manufacturer. Excipients obtained from the different sources may not have identical properties with respect to use in a specific formulation. To assure interchangeability in such circumstances, users may wish to ascertain equivalency in final performance or determine such characteristics before use. Such tests are thus related to the functionality, that the excipient impart to a specific formulation[25].

In order to manufacture any finished product with consistent quality, standardization of raw materials in the drug formulation is necessary for its acceptance by regulatory authorities and pharmaceutical formulators. Unfortunately, such performance standards have not been included in pharmacopoeia primarily because their specifications have always been based on chemical purity and because it is not possible to standardize performance criteria[26]. Pharmacopoeial standards do not take into account particle characteristics or powder properties, which determine functionality of excipients. Control of functionality is important as a control of identity and purity[27].

The following reasons can be cited:

1. Many excipients have multiple functions (e.g. microcrystalline cellulose, starch).
2. There is lack of awareness that the excipients behave differently, depending upon the vendor (i.e. microcrystalline cellulose).
3. As a consequence, excipients with optimal functionality are needed to ensure smooth tablet production on modern machines. The introduction of special force feeder to improve flow of granules from hopper marked a significant advancement in direct compression technology[27].

Ideal Requirements of Directly Compressible Adjuvants

The directly compressible adjuvant should be free flowing. Flow ability is required in case of high-speed rotary tablet machines, in order to ensure homogenous and rapid flow of powder for uniform die filling. During the short dwell-time (milliseconds), the required amount of powder blend should be transferred into the die cavities with

reproducibility of ± 5%. Many common manufacturing problems are attributed to incorrect powder flow, including non-uniformity in blending, under or over dosage and inaccurate filling[28]. Compressibility is required for satisfactory tableting, i.e., the mass must remain in the compact form once the compression force is removed. Few excipients can be compressed directly without elastic recovery. Hence, the directly compressible diluents should have good compressibility, i.e. relation between compaction pressure and volume.

Dilution potential can be defined as the amount of an active ingredient that can be satisfactorily compressed in to tablets with the given directly compressible excipient. A directly compressible adjuvant should have high dilution potential so that the final dosage form has a minimum possible weight. The dilution potential is influenced by the compressibility of the active pharmaceutical ingredient. A directly compressible adjuvant should be capable of being reworked without loss of flow or compressibility. On recompression, the adjuvant should exhibit satisfactory tableting characteristics. The adjuvant should remain unchanged chemically and physically. The directly compressible adjuvant should not exhibit any physical or chemical change on ageing and should be stable to air, moisture and heat.

A directly compressible adjuvant should have a particle size equivalent to the active ingredients present in the formulation. The particle size distribution should be consistent from batch to batch. Reproducible particle size distribution is necessary to achieve uniform blending with the active ingredient(s) in order to avoid segregation[29]. Filler-binders should not accelerate the chemical and/or physical degradation of the API(s) or excipients. It should not interfere with the biological availability of active ingredient/s. It should be compatible with all the adjuvants present in the formulation[30]. It should be physiologically inert. It should not interfere with the disintegration or dissolution of the active ingredient. It should be colourless and tasteless. It should be relatively cost effective and available in desired time. It should accept colorants uniformly. It should show low lubricant sensitivity. It should show batch-to-batch reproducibility of physical and physic-mechanical properties. It should possess proper mouth fill, which is defined as the feel or the sensation in the mouth, produced when the excipient is used in chewable tablets.

Advantages of Direct Compression

The prime advantage of direct compression over wet granulation is economic since the direct compression requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost of tablets. Direct compression is more suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental effects. Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations. This is extremely important because the official compendium now requires dissolution specifications in most soliddosage forms. Disintegration or dissolution is the rate-limiting step in absorption in the case of tablets of poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution. The high compaction pressure involved in the production of tablets by slugging or roller compaction can be avoided by adopting direct compression. The chances of wear and tear of punches and dies are less. Materials are ‘in process’ for a shorter period of time, resulting in less chance for contamination or cross contamination, and making it easier to meet the requirement of current good manufacturing practices[30]. Due to fewer unit operations, the validation and documentation requirements are reduced. Due to the absence of water in granulation, chance of microbial growth is minimal in tablets prepared by direct compression[31]. Table 4 describes the examples of some directly compressible adjuvants.

Limitations of Direct Compression

Direct compression is more prone to segregation due to the difference in density of the API and excipients. The dry state of the material during mixing may induce static charge and lead to segregation. This may lead to the problems like weight variation and content uniformity. Directly compressible excipients are the special products produced by patented spray drying, fluid bed drying, roller drying or co-crystallization. Hence, the products are relatively costly than the respective raw materials. Most of the directly compressible materials can accommodate only 30-40 % of the poorly compressible active ingredients like acetaminophen that means the weight of the final tablet to deliver the 500 mg of acetaminophen would be more than 1300 mg. The large tablets may create difficulty in swallowing. All the spray-dried directly compressible adjuvants show poor rework ability since on preparation of tablets the original spherical nature of the excipient particles is lost. API that has poor flow properties and/or low bulk density is difficult to process by direct compression. Lubricants have a more adverse effect on the filler, which exhibit almost nofracture or shear on compression (e.g. starch 1500). The softening effects as well as the hydrophobic effect of alkaline sterates can be controlled by optimizing the length of blending time to as little as 2-5 min. There is a lack of

awareness in some situations that the excipient behave differently, depending upon the vendor so much so that substitution from one source to that of another is not possible. Hence, there is a need for greater quality control in purchasing of raw material to assure batch uniformity.

Methods Of Preparing Directly Compressible Excipients

Directly compressible adjuvants can be prepared by various methods. The outline and main features of the methods are depicted in Table4. Co-processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible adjuvants.

Commercial status of co-processed excipients

Many co processed excipients have been launched in the market in the past few years, and a few formulations are commercially available. Table: 4 lists some of the marketed co processed excipients along with their manufacturers and benefit.

Table4: Co-processed directly compressible excipients

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 tablets ,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

Limitation of co-processed Excipient

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. Co processed adjuvant lacks the official acceptance in pharmacopoeia. For this reason, a combination filler binder will not be accepted by the pharmaceutical mixtures of the excipients. Although the spray crystallized dextrose-maltose (Emdex) and compressible sugar are co-processed products as single components and are official in USP/NF.

A regulatory perspective of the excipient mixtures

With the absence of a chemical change during processing, co processed excipients can be considered generally regarded as safe (GRAS) if the parent excipients are also GRAS-certified by the regulatory industry until it exhibits significant advantages in the tablet compaction when compared to the physical agencies.Hence, these excipients do not require additional toxicological studies. Excipient mixtures or co processed excipients have yet to find their way into official monographs, which is one of the major obstacles to their success in the market place. The mixture of

excipients was presented as a topic to the National Formulary and was assigned a priority on the basis of the use of the mixture in marketed dosage forms in which processing has provided added functional value to the excipient mixture.

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