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Directly Compressible Materials via Co-Processing

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Abstract : Direct compression is the preferred method for the preparation of tablets. The present review outlines the importance of the functionality of the directly compressible adjuvants in the formulation of tablets. Tablet manufacturing has been changed by the direct-compression process and high-speed machines. These two developments have increased the demands on the functionality of excipients in terms of flow and compression properties. Particle engineering of individual excipients and excipients combinations using coprocessing, by sub particle modifications, has provided an attractive tool for developing high functionality excipients that are suited to modern tablet manufacturing processes. The co-processing is the most widely explored method for the preparation of directly compressible excipients because it is cost effective. Hence, the present review focuses on the properties of the co-processed directly compressible adjuvants available in the market.

1. Introduction

Tablets and capsules are the most preferred dosage forms of pharmaceutical scientists and clinicians because they can be accurately dosed and provide good patient compliance, they are ease for companies to manufacture, and they can be produced at a relatively low cost. [1] The development in the field of APIs, excipients and tableting machines during the past decades has made tablet manufacturing a science and the tablets the most commonly used dosage form [2, 3].

The literature contained few references on the direct compression of pharmaceuticals. The simplicity and cost effectiveness of the direct-compression process have positioned direct compression as an attractive alternative to traditional granulation technologies. The availability of new materials, new forms of old materials and the invention of new machinery has allowed the production of tablets by simplified and reliable methods [3].

Table 1: Ideal requirements, advantages and limitations of direct compression [4-6]

Ideal requirement	Advantage	Limitation
Flowability	Cost effective production	Segregation
compressibility	Better stability of API	Variation in functionality
dilution potential	faster dissolution	Low dilution potential
rework ability	Less wear and tear of punches	rework ability
stability	Simplified validation	Poor compressibility of API
Controlled particle size	Lower microbial contamination	Lubricant sensitivity

2. Role of excipients in direct compression [7]

Excipients is a very broad term encompassing dosage makers (filler/binders), disintegrants, drug release modifiers, plasticisers, penetration enhancers, wetting agents, film formers, enteric coating polymers, encapsulating agents etc, which may or may not enhance or modify drug substance absorption. Functions of excipients must perform in direct compression formulations:

- Adequate flow of the tablet mix in the machine hopper to enable uniform fills of the dies. Poor flow properties would result in weight variation outside acceptable limits.
- Sufficient cohesive properties to form a firm, strong tablet under adequate compression force. Poor quality excipients would result in hardness and friability problems.
- Proper lubrication property to prevent binding of the tablets and punches in the dies.
- Result of mixing is uniform to give uniform dosage in each tablet.
- Good disintegration properties to achieve satisfactory release of drug after administration. Excipients must make the tablet mix conducive to usage on high speed tableting machines. The role of excipients thus makes it imperative to study their physical characteristic and not just test them for chemical parameters. The USP-NF-18 mentions loss on drying (LOD), bulk density, degree of polymerisation (DP), particle size distribution, conductivity and assigns only broad outside limits to LOD, DP and conductivity.

3. Advantages of direct compression

- Direct compression is economic compare to wet granulation since it 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.

- 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 [8]. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms [9] .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 contamination or cross contamination, and making it easier to meet the requirement of current good manufacturing practices [10].

- Due to fewer unit operations, the documentation and validation requirements are reduced. Because of the absence of water in granulation, chance of microbial growth is minimal in tablets prepared by direct compression [11].

4. Limitations of direct compression

- Direct compression is more prone to segregation because of the difference in density of the API and excipients [10].

- 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 speciality 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 workability since on preparation of tablets the original spherical nature of the excipient particles is lost.

- API that has poor flow properties and low bulk density is difficult to process by direct compression.

- Lubricants have a more adverse effect on the filler, which show almost no fracture or shear on compression (e.g. starch 1500). The softening effects as well as the hydrophobic effect of alkaline stearates can be controlled by optimising the length of blending time to as little as 2-5 min [8].

- There is a lack of awareness in some condition that the excipient behave differently, depending upon the vendor so much so that substitution from one source to that of another is not possible [9]. Hence, there is a need for greater quality control in purchasing of raw material to assure batch uniformity.

5. Methods of preparing directly compressible excipients

Directly compressible adjuvant can be prepared by various methods. The outline and main features of the methods are depicted in Table 2. Co-processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible adjuvant.

Table 2:Summary of various methods used to prepare directly compressible adjuvant[12]

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	Dibasicdicalcium phosphate, α-lactose monohydrate
Crystallization	Impart flowability 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

6) A need for new excipients

The excipients industry to date has been an extension of the food industry [13]. Moreover the products of the food industry are excipients which 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 primary reason for this lack of new chemical excipients is the relatively high cost involved in discovery and development of excipient. 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.

7) Routes or 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 [14].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 as shown in Figure 1[15]. 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 of arrangement already has been successfully applied in the intravenous delivery field, in which CyDex and Pfizer worked collaboratively to obtain the approval of a solubilizer [16].

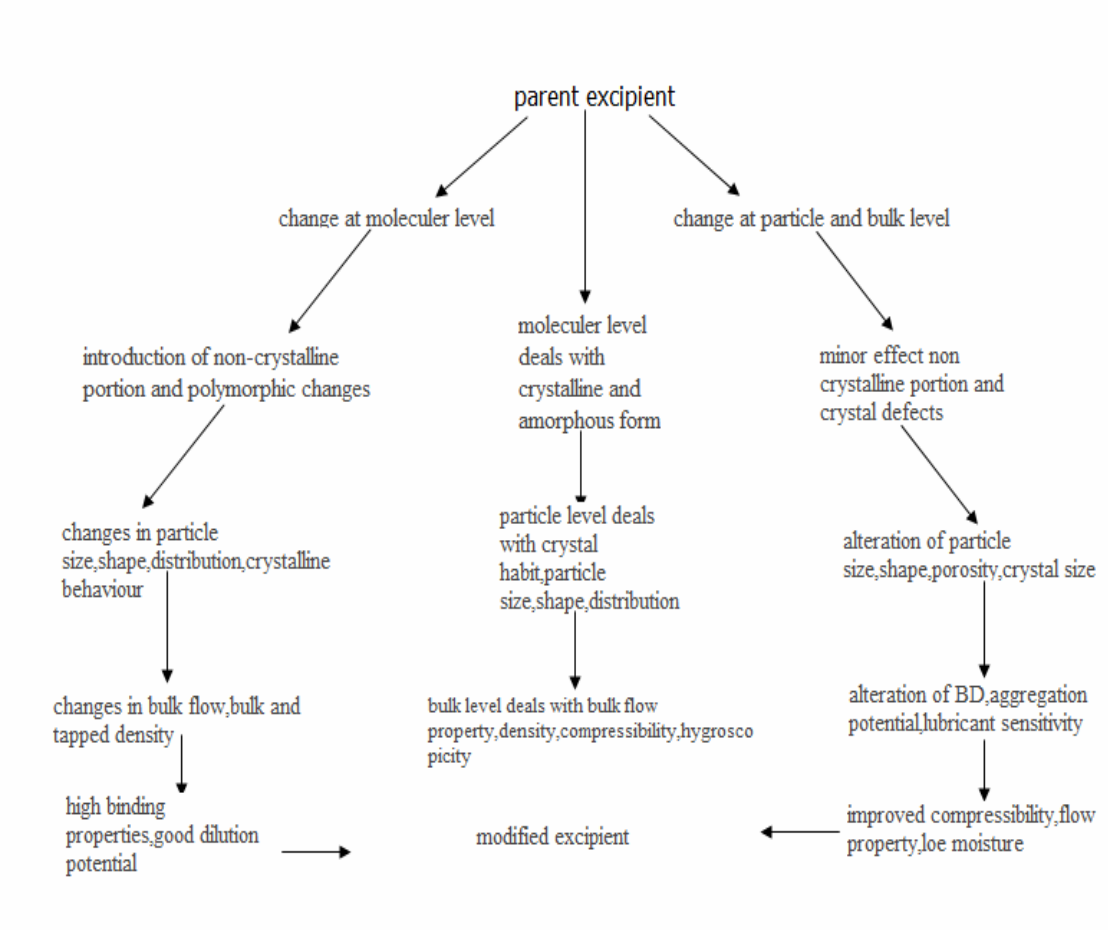

Figure 1: The pyramid of solid state

Developing new grades of existing excipients (physicochemical) has been the most successful strategy for the development of new excipients in past three decades [17] a process that has been supported by the introduction of better performance grades of excipients such as pregelatinized starch, croscarmellose, and crospovidone[18]. However, functionality can be improved only to a certain extent because of the limited range of possible modifications. 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 excipients combinations at a sub particle level, called co processed excipients, has gained importance [14]. 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 that changes such as flow properties, compressibility, moisture sensitivity, and machineability.

8) Co-processing

Co-processing is another way that new excipients are coming to market without undergoing the rigorous safety testing of a completely new chemical [19]. It can be defined as combining two or more established excipients by an appropriate process [20] .Co processing of excipients could lead to the formation of excipients with superior properties compared to the simple physical mixtures of their components. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price.

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 minigranules. Segregation is diminished by adhesion of the actives on the porous particles making process validation and in process control easy and reliable. [21]

9) 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 [21] .Varying the crystal lattice arrangement by playing with parameters such as the conditions of crystallization and drying can create particles with different parameters.

Table 3: Various particle properties influencing excipient functionality

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

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 [20] 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.

10) Co processing of excipients

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

- 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 when one of the components is processed in a dispersed phase. Post processing the particle size of the latter depends on its initial particle size.
- Selecting a suitable drying process such as spray- or flash drying
- Optimizing the process (because even this can contribute to functionality variations). Figure 2 shows a schematic representation of the co processing method.

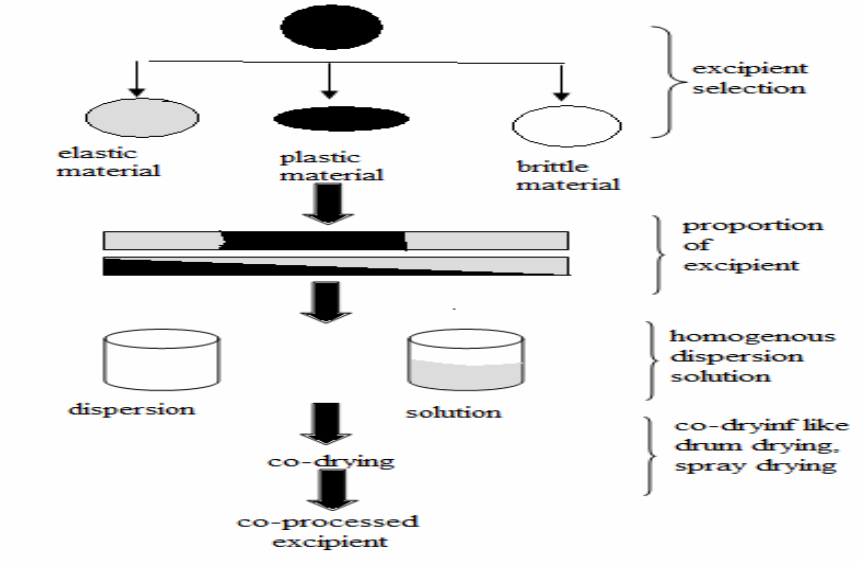

Figure 2: Schematic representation of co processing method.

11) 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 (BASF, Ludwigshafen, Germany);

a) Absence of chemical change

Many detailed studies of excipients chemical properties after co processing have proven that these excipients do not show any chemical change. Detailed studies of SMCC with X-ray diffraction analysis, solid-state nuclear magnetic resonance (NMR), IR spectroscopy, Raman spectroscopy, and C13 NMR spectroscopy have detected no chemical changes and indicate a similarity to the physicochemical properties of MCC[22].This absence of chemical change helps reduce a company's regulatory concerns during the development phase.

b) Physicomechanical properties.

i) 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. 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 [23].The spray-dried product had a spherical shape and even surfaces, which also improved the flow properties.

ii) Improved compressibility

The pressure–hardness relation of co processed excipients, when plotted and compared with simple physical mixtures, showed a marked improvement in the compressibility profile. The compressibility performance of excipients such Cellactose [24], SMCC [25, 26] and Ludipress [27] have been reported to be superior to the simple physical mixtures of their constituent excipients.

iii) Better dilution potential

Dilution potential is the ability of the excipient to retain its compressibility even when diluted with another material. Cellactose is shown to have a higher dilution potential than a physical mixture of its constituent excipients [28].

iv) 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 overall palatability. Although co processing adds some cost, the overall product cost decreases because of improved functionality [29]. And fewer test requirements compared with individual excipients [30]
- 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.
- Coproceseed 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.

12) 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 benefits.

Table 4: Co-processed directly compressible excipients [11, 19-21, 31-38]

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 and sachets may require higher level of lubricant (magnesium stearates)	-	Roquette ,France
Ludipress	Lactose, PVP, Crosspovidone	For use in chew able tab lets and lozenges, for effervescent tablets and as bulking agent for modified release formulations.	good flowability, low hygroscopicity, hardness independent of machine speed	BASF, Germany
Starlac	Lactose , maize starch	In Low-dosage and Fast dissolving formulations,Cores for coating,Homeopathic formulation	Good flow	Roquette, France
Pharmatose DCL 40	Anhydrous lactose, lactitol	-	High compressibility, low lubricant sensitivity	DMV Netherlands
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
DI-PAC	Sucrose, dextrin	-	Directly compressible	American sugar, USA
Advantose FS-95	Fructose, starch	Nutraceuticals and chewable vitamin applications	-	SPI polyols, France
Finlac™ DC	Directly compressible lactitol	Chewable tablets and hard tablets that may be useful in suck able and swallow able applications.	-	-
Plasdone S-630	Vinyl acetate, Venyl pyroliidone	-	-	ISP, USA
Lycatab C	Pregelatinized starch	Filler disintegrate for hard gelatin capsules ,Binder disintegrate for direct compression, Flow aid in powder blends	-	Roquette, France

13) 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 [32] .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. Although the spray-crystallized dextrose-maltose (Emdex) and compressible sugar are co-processed products as single components and are official in USP/NF.

14) 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

agencies [14].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 [32]

15) Conclusion

The tablets prepared by direct-compression and high-speed manufacturing has forced the excipient industry to search for new excipients. The excipient industry, which has largely been an extension of the food industry, has taken up the novel use of particle engineering and material sciences to pave the way for a new category of functional excipients called co processed excipients. The success of any pharmaceutical excipient depends on quality, safety, and functionality. Although the first two parameters have remained constant, significant improvements in functionality open the door for the increased use of co-processed excipients. The co-processed excipients proved to be superior to the physical blend in terms of flow due to size enlargement. The advantages of the proposed method are easy adaptability in industry and the possibility of bypassing the existing patents in the areas of quick disintegration and dissolution.

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