International Journal of Applied Pharmaceutics
Vol 2, Issue 3, 2010

Review Article

COPROCESSING OF EXCIPIENTS: A REVIEW ON EXCIPIENT DEVELOPMENT FOR IMPROVED TABLETTING PERFORMANCE

MINAKSHI MARWAHA*[1], DEEPAK SANDHU[1], RAKESH KUMAR MARWAHA[2]

***[1]SBMNIPS&R, Asthal Bohar, Lecturer, SBMNIPS&R, Asthal Bohar, [2]Maharishi Dayanand University, Rohtak, (Haryana), Pin Code- 124 001,
Email: gndu_research@rediffmail.com, minakshi_rkm@yahoo.co.in**

Received: 25 March 2010, Revised and Accepted: 30 April 2010

ABSTRACT

Tablet manufacturing has been changed by the introduction of the direct-compression process and high-speed machines. These two developments have increased the demands on the functionality of excipients in terms of flow and compression properties. Direct compression is the preferred method for the preparation of tablets. The shift in tabletting toward 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 co-processing is the most widely explored method for the preparation of directly compressible adjuvants because it is cost effective and can be prepared in-house based on the functionality required. This review article is in pursuit of giving detailed information on the sources of new excipients, potential advantages of coprocessed excipients, material characteristics required for coprocessing, methods of preparing directly compressible adjuvants and various coprocessed excipients for direct compression available in the market.

Keywords: Direct compression, co processed excipients, co-processing, directly compressible adjuvants, particle engineering.

INTRODUCTION

Tablets are the most preferred dosage form of pharmaceutical scientists because they can be accurately dosed and provide good patient compliance. They are easy for companies to manufacture and they can be produced at a relatively low cost. The development in the field of APIs, excipients and tabletting machines during the past decades has made tablet manufacturing a science and the tablets the most commonly used dosage form[1-2].This popularity of tablets coupled with an increased understanding of the physics of compression and of manufacturing process variables have matured the manufacture of tablets as a science in its own right[3].

Since the introduction of tabletting process in the early 1840s, numerous changes have taken place, apart from changes in tablet manufacturing, including the establishment of stringent regulatory requirements for the materials that should be used, the establishment of stability requirements, and the development of high-performance tabletting machines that can produce 100,000–200,000 tablets/h[4].Interestingly, such developments have affected the manufacturing process negatively because the number of materials that can fulfil such regulatory and performance requirements has decreased substantially[5].

Shangraw[6] conducted a survey of 58 products in United States of America for the preference for the granulation process. The results were in favour of direct compression. Of the five processes listed in the survey, the average score (1.0 being the perfect score) for direct compression was 1.5 compared to wet massing and fluid bed drying (2.0), wet massing and tray drying (2.5), all-in-one (3.3) and roller compaction (3.6). About 41% of the companies indicated that direct compression was the method of choice, and 41.1% indicated that they used both direct compression and wet granulation. Only 1.7% of the respondents indicated that they never used direct compression and 15.5% indicated that the process was not recommended.

Tablets are manufactured primarily by either granulation compression or direct compression. The latter involves the compression of a dry blend of powders that comprises drugs and various excipients. The simplicity and cost effectiveness of the direct-compression process have positioned direct compression as an attractive alternative to traditional granulation technologies. The demand of excipients with improved functionalities, mainly in terms of flow and compression properties, has increased with the advancement of tablet manufacturing process. Coprocessed excipients are a mixture of two or more existing excipients at subparticle level, offer substantial benefits of the incorporated excipients and minimize their drawbacks. These multipurpose excipients have significantly reduced the number of incorporating excipients in the tablet. The present review discusses the sources of new excipients, potential advantages of coprocessed excipients, material characteristics required for coprocessing, methods of preparing directly compressible adjuvants and various coprocessed excipients for direct compression available in the market.

NEED FOR DEVELOPING NEW EXCIPIENTS

The excipients industry to date has been an extension of the food industry[7]. 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) [8]. 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[9]. 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[10].

- 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[11]. 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[12]. 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 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[13-14]. 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[15], a process that has been supported by the introduction of better performance grades of excipients such as pregelatinized starch, croscarmellose, and crospovidone[16]. 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 sub particle 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.

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 such as flowability, compressibility, and dilution potential, which are critical factors in the performance of excipients.The fundamental solid-state properties of the particles such as morphology, particle size, shape, surface area, porosity, and density influence excipient functionalities such as flowability, compactability, dilution potential, disintegration potential, and lubricating potential. Hence, the creation of a new excipient must begin with a particle design that is suited to deliver the desired functionalities[17]. Varying the crystal lattice arrangement by playing with parameters such as the conditions of crystallization and drying can create particles with different parameters. It is also possible to engineer particles without affecting the proceeding molecular level. Avicel 101 and 102 (microcrystalline cellulose) and spray dried lactose are 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. A much broader platform for the manipulation of excipient functionality is provided by coprocessing or particle engineering two or more existing excipients. Coprocessing is based on the novel concept of two or more excipients interacting at the subparticle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients[18]. The availability of a large number of excipients for coprocessing ensures numerous possibilities to produce tailor-made "designer excipients" to address specific functionality requirements. Coprocessed excipients are prepared by incorporating one excipient into the particle structure of another excipient using processes such as co-drying. Thus, they are simple physical mixtures of two or more existing excipients mixed at the particle level. Coprocessing was initially used by the food industry to improve stability, wettability, and solubility and to enhance the gelling properties of food ingredients such as co processed glucomannan and galactomanan[19]. Coprocessing of Excipients in the pharmaceutical industry can be dated back to the late 1980s with the introduction of co processed microcrystalline cellulose and calcium carbonate[20], followed by Cellactose (Meggle Corp.,Wasserburg, Germany) in 1990, which is a co processed combination of cellulose and lactose. A similar principle was applied in developing silicified microcrystalline cellulose (SMCC), which is the most widely used co processed excipient[21].

Coprocessing excipients leads to the formation of excipient granulates with superior properties compared with physical mixtures of components or with individual components. They have been developed primarily to address the issues of flowability, compressibility, and disintegration potential, with filler–binder combinations being the most commonly tried. The combination of excipients chosen should complement each other to mask the undesirable properties of individual excipients and, at the same time, retain or improve the desired properties of excipients. For example, if a substance used as a filler–binder has a low disintegration property, it can be coprocessed 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.

COPROCESSING OF EXCIPIENTS AS SOURCE OF NEW EXCIPIENTS

Co-processing is another way that new excipients are coming to market without undergoing the rigorous safety testing of a completely new chemical[22]. It can be defined as combining two or more established excipients by an appropriate process[23]. 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 directly compressible adjuvant 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 randomized embedding of the components in special minigranules minimizes their anisotropic behaviour. So, deformation can occur along any plane and multiple clean surfaces are formed during the compaction process. Thus, the use of the co-processed excipient combines the advantages of wet granulation with direct compression[24]. The use of one-body components is justified if it results in a potentiation of the functionalities over that of the mere dry blend of the components prepared by gravity mixture. This synergistic effect should improve the quality of the tablet equally in all aspects ranging from hardness to dissolution and/or stability. Excipient mixtures in co-processing are produced to make use of the advantages of each component and to overcome specific disadvantages, if any. Most important characteristics are the binding and blending properties of the co-processed excipients, which must be better than those of a physical mixture of the starting materials. Cost is another factor to be considered in the selection of co-processed product.

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[25]. 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, they are commonly considered as single components and are official in USP/NF. Table 1 shows examples of co-processed directly compressible adjuvants.

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

- Identifying the group of excipients to be coprocessed by carefully studying the material characteristics and functionality requirements.
- Selecting the proportions of various Excipients.
- Assessing the particle size required for coprocessing. This is especially important when one of the components is processed in a dispersed phase. Post processing the particle size of the latter depends on its initial particle size.
- Selecting a suitable process of drying such as spray or flash drying.
- Optimizing the process (because even this can contribute to functionality variations).

ROLE OF MATERIAL SCIENCE IN COPROCESSING

Material science plays a significant role in altering the physico-mechanical characteristics of a material, especially with regard to its compression and flow behavior. Coprocessing Excipients offers an interesting tool to alter these physicomechanical properties. Materials, by virtue of their response to applied forces, can be classified as elastic, plastic, or brittle materials. In the truest sense, materials cannot be classified in one category absolutely. Pharmaceutical materials exhibit all three types of behavior, with one type being the predominant response. This makes it difficult to demarcate which property is good for compressibility. Coprocessing is generally conducted with one excipient that is plastic and another that is brittle.

A combination of plastic and brittle materials is necessary for optimum tabletting performance. Hence, coprocessing these two kinds of materials produces a synergistic effect, in terms of compressibility, by selectively overcoming the disadvantages. Such combinations can help improve functionalities such as compaction performance, flow properties, strain-rate sensitivity, lubricant sensitivity or sensitivity to moisture, or reduced hornification.

ADVANTAGES OF COPROCESSING

Improved Flow Properties

Controlled optimal particle size and particle-size distribution ensures superior flow properties of coprocessed 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 Hausher ratio were measured, and Cellactose was found to have better flow characteristics than lactose or a mixture of cellulose and lactose[26]. The spray-dried product had a spherical shape and even surfaces, which also improved the flow properties.

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[27] SMCC[28-29] and Ludipress[30] 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 extragranular 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[31]. This property is improved, however, when it is coprocessed into SMCC.

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[32].

Fill weight variation

In general, materials for direct compression tend to show high fill-weight variations as a result of poor flow properties, but coprocessed 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[28].

Reduced lubricant sensitivity

Most coprocessed 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[33]. 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.

Other properties

Coprocessed 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 coprocessed 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 mouthfeel, and improved overall palatability. Although coprocessing ads

Table 1: Co-processed 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	Dipac		Directly compressible
Microcrystalline cellulose silicon dioxide	Prosolv	Penwest pharmaceuticals company	Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability
Microcrystalline cellulose, guar gum	Avicel ce-15	Fmc corporation	Less grittiness, minimal chalkiness, overall palatability
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	Dmv veghel	High compressibility
85% α- lactose mh + 15% native corn starch	Starlac	Roquette	Good flow, low lubricant sensitivity

Table 2: Comparison of major steps involved in the granulation methods

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 in to slugs	Preparation of binder solution
3		Size reduction of slugs and sieving	Massing of binder solution of step 2 with powder mixture of step
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

Table 3: Ideal requirements, advantages and limitations of direct compression

Ideal Requirement	Advantages	Limitations
Flowability	Cost effective production	Segregation
Compressibility	Better stability of APH	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

- 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, coprocessed excipients can be used to develop tailor-made designer excipients. This can be helpful in reducing the time required to develop formulations.
- Coprocessed 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[34]. 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[35]. Table 2 describes various steps involved in the granulation technology. 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 flowability, compressibility, and dilution potential. Tablets consist of active drugs and excipients, and not one drug substance or excipient possesses all the desired physicomechanical 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 physicomechanical properties of excipients that ensure a robust and successful process are good flowability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity, and good machineability even in high-speed tabletting 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[36]. 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[37].

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-to-batch 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[38].

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[39]. Pharmacopoeial standards do not take into account particle characteristics or powder properties, which determine functionality of excipients[40].

Control of functionality is important as a control of identity and purity. The following reasons can be cited:

- Many excipients have multiple functions (e.g. microcrystalline cellulose, starch).
- There is lack of awareness that the excipients behave differently, depending upon the vendor (i.e. microcrystalline cellulose).
- 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 [40].

IDEAL REQUIREMENTS OF DIRECTLY COMPRESSIBLE ADJUVANTS

The directly compressible adjuvant should be free flowing. Flowability 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 $\pm$ 5%. Many common manufacturing problems are attributed to incorrect powder flow, including non-uniformity in blending, under or over dosage and inaccurate filling[41].

Compressibility is required for satisfactory tabletting, 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 tabletting 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[42].

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[43]. 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 physicomechanical 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. The pros and cons with reference to direct compression are discussed in following section and brief description is given in Table 3.

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 solid dosage 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[43]. 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[44]. 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 reworkability 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 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 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 Table 5. Co-processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible adjuvants[45-46].

Table 4: Examples of some directly compressible adjuvants

Excipient	Brand Name (Manufacturer, Country)
Lactose	Tablettose (Meggle, Germany), Pharmatose(DMV, the Netherland), Fast Flo Lactose (Foremost)
Sucrose	Di-pac(American sugar company, USA), Nutab (Ingredient technology) Inc., USA)
Dextrose	Emdex (Edward mendell, USA), Can Tab (Penwest, USA)
Mannitol	Mannogem 2080 (SPI Polyols, France)
Sorbitol	Neosorb 60 (Roquette, France), Sorbogem (SPI Polyols, France), Sorbidex P (Cerestar, USA)
Lactitol	Finlac DC (Danisco, USA), Lacty-TAB (Purac, USA)
Xylitol	Xylitab (Danisco, USA
Maltodextrin	Maltrin (GPC, USA)
Microcrystalline Cellulose)	Avicel PH (FMC, USA), Emocel(Edward mendell, USA), Vivacel (JRS, USA)

Table 5: Summary of various methods used to prepare directly compressible adjuvants

Method	Advantages and limitations	Examples
Chemical Modification	Relatively expensive, Requires toxicological data, Time consuming	Ethyl cellulose, Methylcellulose, Hydroxypropyl methylcellulose, and Sodium carboxymethyl cellulose from cellulose, Cyclodextrin from starch, Lactitol
Physical Modification	Relatively simple and economical	Dextrose 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, Dibasic dicalcium phosphate
Crystallization	Impart flowability to excipients but not necessarily self-binding properties. Requires stringent control on possible polymorphic conversions and processing conditions.	β- Lactose, Dipac
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

REFERENCES

1. Sam AP and Fokkens JG. Drug Delivery System: Adding Therapeutic and Economic Value to Pharmacotherapy. Part 2, Pharm. Tech. Eur. 1997; 9:58-66.
2. Rasenack N, Muller BW. Crystal Habit and Tableting Behaviour. Int. J. Pharm. 2002; 244: 45-57.
3. Czelsler JL, Perlman KP. "Diluents," in Encyclopedia of Pharmaceutical Technology, Swarbrick J. and Boylan JC. Eds. (Marcel Dekker, Inc., New York, NY, 1990), pp. 37–83.
4. Hines E. Restocking the Excipient Superstore, www.pharmaquality.com/excipient.html.
5. Shangraw RF. Compressed Tablets by Direct Compression in Pharmaceutical Dosage Forms: Tablets, Leiberman HA, Lachman L, and Schwatz JB. Eds. (Marcel Dekker. Inc. New York, 1990), pp. 195–246.
6. Shangraw RF, Demarest DA. Survey of Current Practices in the Formulation and Manufacture of Tablets and Capsules. Pharm. Technol. 1993; 17: 32- 44.
7. Steinberg M, Blecher L. and Mercill A. From Inactive Ingredients to Pharmaceutical Excipients. Pharm. Technol. 2001; 25 (7): 62–64.
8. IPEC-Americas: Why IPEC-Americas is Needed. http://www.ipecamericas.org.
9. Blecher L. Pharmaceutical Excipients: Producers and Users Strengthen their Voice. Pharm Technol. 1993; 17 (2): 38–39.
10. Tobyn MJ et al. Physicochemical Comparison between Microcrystalline Cellulose and Solidified Microcrystalline Cellulose. Int. J. Pharm. 1998; 169:183–194.
11. Moreton RC. Tablet Excipients to the Year 2001: A Look into the Crystal Ball. Drug Dev. Ind. Pharm. 1996; 22 (1):11–23.
12. Bansal AK. and Nachaegari SK. High Functionality Excipients for Solid Oral Dosage Forms in Business Briefings: Pharmagenerics (World Markets Research Centre, London, UK, 2002), pp. 38–44.
13. CyDex. Innovative Drug Delivery Technologies www.captisol.com .
14. CyDex. Captisol. www.cydexinc.com/CaptisolProductApprovals.pdf.
15. Shangraw RF, Wallace JW. Morphology and Functionality in Tablet Excipients for Direct Compression: Part I. Pharm. Technol. 1981; 5 (9): 69–78.
16. Shangraw RF. Emerging Trends in the Use of Pharmaceutical Excipients. Pharm. Technol. 1997; 21 (6): 36–42.
17. Reimerdes D, Aufmuth KP. Tableting with Coprocessed Lactose–Cellulose Excipient. Manufacturing Chemist, 1992; 63 (12):23–24.
18. Reimerdes D. The Near Future of Tablet Excipients. Manufacturing Chemist. 1993; 64 (7): 14–15.
19. Modliszewski JJ, Ballard DA. Coprocessed Galctomannan–Glucomannan. US Patent No. 5,498,436 to FMC Corporation (Philadelphia, PA) 1996.
20. Dev KM et al. Coprocessed Microcrystalline Cellulose and Calcium Carbonate and Its Preparation. US Patent No. 4,744,987 to FMC Corporation (Philadelphia, PA) 1988.
21. Bolhius GK, Chowhan ZT. Materials for Direct Compaction in Pharmaceutical Powder Compaction Technology. Alderborn G. and Nystrom C., Eds. (Marcel Dekker Inc., New York, NY, 1996): pp. 419–500.
22. Russell R. Synthetic Excipients Challenge All-Natural Organics —Offer advantages/ Challenges to Developers and Formulators. Pharm. Technol. 2004; 27: 38-50.
23. Reimerdes D. The Near Future of Tablet Excipients. Manuf. Chem. 1993; 64:14-15.
24. Reimerdes D, and Aufmuth, KP. Tabletting with Co-processed Lactose-Cellulose Excipients. Manuf. Chem. 1992; 63: 21-24.
25. Bolhuis GK and Chowhan ZT. Materials for Direct Compression. Pharmaceutical Powder Compaction Technology, Vol-7, Marcel Dekker, USA: 1996: 419-499.
26. York P. Crystal Engineering and Particle Design for the Powder Compaction Process. Drug Dev. Ind. Pharm. 1992; 18 (6, 7): 677–721.
27. Belda PM, Mielck JB. The Tableting Behavior of Cellactose Compared with Mixtures of Celluloses with Lactoses. Eur. J. Pharm.Biopharm. 1996; 42 (5): 325–330.
28. Sherwood BE, Becker JW. A New Class of High Functionality Excipients: Solidified Microcrystalline Cellulose. Pharm. Technol. 1988; 22(10): 78–88.
29. Allen JD. Improving DC with SMCC. Manufacturing Chemist. 1996; 67 (12): 19–20, 23.
30. Schmidt PC and Rubensdorfer CJW. Evaluation of Ludipress as a Multipurpose Excipient for Direct Compression Part I: Powder Characteristics and Tableting Properties. Drug Dev. Ind. Pharm. 1994; 20 (18): 2899–2925.
31. Staniforth JN and Chatrath M. Towards a New Class of High Functionality Tablet Binders: Quasi-Hornification of Microcrystalline Cellulose and Loss of Functionality. Pharm. Res. 1996; 13 (9): 208.
32. Flores LE, Arellano RL, and Esquivel JJD. Study of Load Capacity of Avicel PH-200 and Cellactose, Two Direct-Compression Excipients, Using Experimental Design. Drug Dev. Ind. Pharm. 2000; 26 (4): 465–469.
33. Maarschalk KVDV and Bolhius GK. Improving Properties of Material for Direct Compaction. Pharm. Technol. 1999; 23 (5): 34–46.
34. Shangraw RF. Direct Compression Tableting, Encyclopedia of Pharmaceutical Technology, Vol-4, Marcel Dekker, USA, 2nd ed., 1988: 85-160.
35. Shangraw RF. Compressed Tablets by Direct Compression Granulation Pharmaceutical Dosage Forms: Tablets, Vol-1, Marcel Dekker, USA, 2nd Ed, 1989: 195-246.
36. Robertson MI. Regulatory Issues with Excipients. Int. J. Pharm. 1999; 187: 273-276.
37. Silverstein I. Excipient GMP Quality Standards. Pharm. Technol. 2002; 25: 46-52.
38. Armstrong NA. Functionality Related Tests for Excipients. Int. J. Pharm. 1997; 155: 1-5.
39. Banker UV. Role of Ingredients and Excipients in Developing Pharmaceuticals. Manuf. Chem. 1994; 65: 32-34.
40. Reimerdes D. The Near Future of Tablet Excipients. Manuf. Chem. 1994; 64:14-15.
41. Smewing J. Powder flow analysis- the solution, Manuf. Chem. 2002; 32-33.
42. Jivraj M, Martini LG, and Thomson CM. An Overview of the Different Excipients useful for the Direct Compression of Tablets. *PSTT*. 2000; 3: 58-63.
43. Rubinstein MH. Tablets Pharmaceutics: The Science of Dosage of Form, Churchill, UK, 1st ed., 1998: 304- 321.
44. Ibrahim YK and Olurinola PF. Comparative Microbial Contamination Levels in Wet Granulation and Direct Compression Methods of Tablet Production. Pharm. Acta. Helv. 1991; 66: 298-301.
45. Shangraw RF, Wallace JW and Bowers FM. Morphology and Functionality in Tablet Excipients for Direct Compression. Pharm. Technol. 1987; 11: 136-143.
46. Bolhuis GK, and Chowhan ZT. Materials for Direct Compression. Pharmaceutical Powder Compaction Technology, Vol-7, Marcel Dekker, USA, 1996: 419-499.