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## RECENT ADVANCES IN DIRECT COMPRESSION TECHNIQUE FOR PHARMACEUTICAL TABLET FORMULATION

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### ABSTRACT

*Direct compression technology has been used for the compression of tablets, in which mainly contains hygroscopic and thermolabile active pharmaceutical ingredients (API). It acts as an alternative method to other tablet compression technologies because of its simplicity and economy. During the direct compression of powders of excipient and API is converted into the powder blend by using the different types of mills and sieves which produced identical size of particles, then it is compressed into the tablets. The present review highlights the latest advancements in excipients used in direct compression technologies.*

**Keywords:** *Direct Compression Techniques, Directly Compressed Adjuvant, Naturally Occurring Directly Compressible Excipients, Mouth Dissolving Tablets.*

### INTRODUCTION

The most common method of drug delivery is the oral solid dosage form, of which tablet and capsules are predominate. Tablet are more widely accepted and used compared to capsules for a number of reasons including cost, temper resistance, ease of handling and packaging, ease of identification and manufacturing efficiency.

Since the invention of compressed tablet over 150 years ago by Thomas Brockedon, the tablet has become increasingly popular dosage form. The

pharmaceutical industry has to produce tablets that have consistent quality from batch to batch. Tablets must be strong enough to withstand exertion caused by packing, storage and handling. They must also disintegrate and release drug reproducibly with desired manner in a gastrointestinal tract.<sup>[1]</sup>

### Tablets:

Tablets may be defined as solid unit pharmaceutical dosage forms containing

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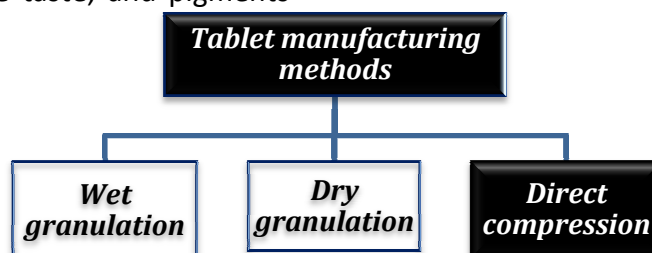
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medicaments with or without suitable excipients & prepared either by compression or molding.<sup>[2]</sup>

It comprises of a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients include diluents, binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tableting; disintegrates to promote tablet break-up in the digestive tract, sweeteners or flavouring agents to enhance taste, and pigments

to make the tablets visually attractive. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance. Tablets are manufactured by wet, dry granulation and by direct compression technique.<sup>[3]</sup>



**Figure 1: Diagrammatic representation of tablet manufacturing methods**

**Direct compression:**

Direct compression is the simplest and most economical method for the manufacturing of tablets because it requires less processing steps than other techniques. Introduction of spray dried lactose (1960) and Avicel (1964) had changed the tablet manufacturing process and opened avenues

of direct compression tableting.<sup>[4]</sup> The term direct compression is used to define the process by which tablets are compressed directly from powder blends of active ingredient and excipients, which flow uniformly in the dies & forms a film compact.<sup>[5]</sup>



**Figure 2: Flow sheet of the direct compression process.**

**Table 1: Different processing steps commonly required in the various tablet preparation techniques.**

Processing steps	Wet granulation	Dry granulation	Direct compression
Raw materials	√	√	√
Weight	√	√	√
Screen	√	√	√
Mix	√	√	-
Compress (slug)	-	√	-
Wet mass	√	-	-
Mill	√	-	-
Dry	√	-	-
Mill	√	√	-
Mix	√	√	-
Compress	√	√	√

**Advantages of direct compression method:**

1. The prime advantage of direct compression over wet granulation is economic due to fewer unit operations.

2. Requirement of minimum number of equipment, power consumption, space, time and labor leading to reduced production cost of tablets.

3. It is more suitable for moisture and heat sensitive APIs because it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental effects.

4. Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations.

5. 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, whereas disintegration or dissolution is the rate-limiting step in absorption in the case of

tablets of poorly soluble API prepared by wet granulation.

6. The high compaction pressure involved in the production of tablets by slugging or roller compaction could be avoided by using direct compression technique.

7. There are minimum chances of wear and tear of punches and dies.

8. Materials are "in process" for a shorter period of time, therefore less chance for contamination or cross contamination, and making it easier to meet the requirement of current good manufacturing practices.

9. Chance of microbial growth is minimum due to absence of water.<sup>[2]</sup>

**Table 2: Ideal requirements, advantages and limitations of direct compression.**

Ideal requirements	Advantages	Limitations
Flowability	Cost effective production	Segregation
Compressibility	Better stability of API	Variation in functionality
Dilution potential	Faster dissolution	Low dilution potential
Reworkability	Less water and tear of punches	Reworkability
Stability	Simplified validation	Poor compressibility of API
Controlled particle size	Lower microbial contamination	Lubricant sensitivity

#### **Directly compressible adjuvants:**

Simplicity of 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 as shown in table 1. It has been estimated that less than 20% of pharmaceutical materials can be compressed directly into tablets due to lack of flow, cohesion properties and lubrication. Therefore, they must be blended with other directly compressible ingredients to manufacture satisfactory tablets. In development of directly compressible granules by the modification of a single substance, co processing of two or more components was applied to produce composite particles or co-processed excipients. The composite particles or co-processed multi-component-based excipients are introduced to achieve better powder characteristics and tableting properties than a single substance or the physical mixture. The directly compressible adjuvant should be free flowing, in case of Available online on [www.ijprd.com](http://www.ijprd.com)

high-speed rotary tablet machines, so that it ensures 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 die cavities with reproducibility of + 5%. Compressibility is required for satisfactory tableting, i.e., the mass must remain in compact form once compression force is removed. Few excipients can be compressed directly without elastic recovery.<sup>[7]</sup>

#### **FEW EXAMPLES OF DIRECTLY COMPRESSIBLE ADJUVANT:**

##### **Lactose**

Lactose is the most widely used as diluent in tablets. The general properties of lactose that contribute to its popularity as an excipient are cost effectiveness, easy in the availability, bland taste, low hygroscopicity and water solubility. Lactose based tablets exhibit better stability than mannitol and cellulose containing tablets at 40° C and 90% relative humidity (RH) over a 10 week period.

**$\alpha$ -lactose monohydrate**

Coarse sieved fraction of  $\alpha$ -lactose monohydrate (100 mesh) is used in direct compression due to its flowability. It contains about 5% w/w water. Compared to other filler-binders,  $\alpha$ -lactose monohydrate exhibits relatively poor binding properties. It mainly consolidates by fragmentation. It has higher brittleness compared to spray-dried lactose and anhydrous  $\beta$ -lactose.  $\alpha$ -lactose monohydrate (100 mesh) is often combined with microcrystalline cellulose. This combination results in a stronger synergistic effect on disintegration time, whereas the crushing strength increases as the percentage of microcrystalline cellulose in the blend is increased. The strength of tablets compressed from  $\alpha$ -lactose monohydrate increases with a decrease in particle size of the excipient.

**Anhydrous  $\alpha$ -lactose**

Binding capacity of  $\alpha$ -lactose monohydrate increases dramatically by thermal or chemical dehydration. During dehydration,  $\alpha$ -lactose monohydrate changes from single crystals into aggregates of anhydrous  $\alpha$ -lactose particles. The anhydrous crystals are softer, weaker and less elastic. It undergoes brittle fracture much more readily and at lower stress than the lactose monohydrate. The relative slow disintegration of tablets containing anhydrous lactose is the major disadvantage. The anhydrous lactose exhibits lesser tendency for maillard reaction and better reworkability without loss of compressibility than the spray-dried lactose.

**Anhydrous  $\beta$ -lactose**

The commercial product consists of agglomerates of extremely fine crystals. It is produced by roller drying of solution of  $\alpha$ -lactose monohydrate followed by subsequent comminuting and sieving. It has excellent compaction properties and low lubricant sensitivity. It exhibits less brittleness than the  $\alpha$ -lactose monohydrate. Due to low moisture content, anhydrous  $\beta$ -lactose is an ideal excipient for moisture sensitive APIs. The anhydrous  $\beta$ -lactose is produced by crystallization of lactose above 93°C by roller drying. It has relatively better reworkability than other forms of lactose. It has higher dissolution rate than  $\alpha$ -lactose monohydrate. It has solubility up to 10 times higher than the  $\alpha$ -lactose monohydrate. Below 55%

RH, anhydrous lactose with high b-content absorbs very small amount of water and its compression properties were insignificantly affected.

**Spray-dried lactose**

Spray-dried lactose is produced by spray drying the slurry containing lactose crystals. The final product contains mixture of crystals of lactose monohydrate and spherical agglomerates of small crystals held together by glass or amorphous material. The former contributes fluidity and the latter gives the compressibility to the product. It has excellent flow properties and binding properties. It deforms plastically compared to the same sized  $\alpha$ -lactose monohydrate particles. Amorphous portion of the spray-dried lactose is responsible for the better binding and plastic deformation. Compressibility is affected if it is allowed to dry below a level of 3% w/w moisture. Disintegrant is required in the formulations containing spray-dried lactose. The tablets require a lubricant, but the lubricant does not affect binding. It has poor reworkability. Spray-dried lactose discolours with certain API containing an amine group.

**Agglomerated lactose**

It is a granulated form of  $\alpha$ -lactose monohydrate with improved binding properties. Tablettose is an example of agglomerated  $\alpha$ -lactose demonstrates good flowability. It has binding property better than the  $\alpha$ -lactose monohydrate but not as good as spray-dried lactose.

**Microcrystalline cellulose**

Microcrystalline cellulose (MCC) is purified partially depolymerized cellulose, prepared by treating  $\alpha$ -cellulose with mineral acids. It is a white, crystalline powder composed of agglomerated porous microfibers. After purification by filtration and spray-drying, porous microcrystal are obtained. It occurs as a white odourless, tasteless crystalline powder composed of porous particles of an agglomerated product. Apart from its use in direct compression, MCC is also used as a diluent in tablets prepared by wet granulation, as filler in capsules and for the production of spheres. In the pharmaceutical market, it is available under the brand names of Avicel, Emcocel, Vivacel etc.

**Ethylcellulose**

Tablets which contain ethylcellulose and it is prepared by direct compression the release rate of

tablets is dependent on the ethyl cellulose particle size, and compaction force.

#### **Sucrose**

Sucrose is widely used as filler in chewable tablets and as a binder in wet granulation. A co-processed sucrose based directly compressible adjuvant containing 95% sucrose and 5% sorbitol. It is found that tablets with higher strength, which disintegrates faster can be produced using this material than tablets made with commercially available directly compressible sugars. Recently, directly compressible sugar is introduced by British sugar. It is a free flowing, directly compressible sugar comprising 95% sugar and 5% maltodextrin. It confirms to British pharmacopoeia monograph for compressible sugar.

#### **Di-Pac**

Di-Pac is a directly compressible, co-crystallized sugar consisting of 97% sucrose and 3% modified dextrin. It is a free flowing, agglomerated product consisting of hundreds of small sucrose crystals glued together by the highly modified dextrin. At high moisture level, Di-pac begins to cake and lose its fluidity. Tablets containing a high proportion of Di-pac tend to harden after compression at higher RH. Its sweet taste makes it suitable for most directly compressible chewable tablets.

#### **Nu-Tab**

Nu-Tab is a roller compacted granulated product consisting of sucrose, invert sugar, and cornstarch and magnesium stearate. It has better flowability due to relatively larger particles but has poor colour stability compared to other directly compressible sucrose and lactose. It is primarily used for preparation of chewable tablets by direct compression.

#### **Emdex and maltrin**

Emdex is produced by hydrolysis of starch and consists of aggregates of dextrose microcrystals intermixed and cohered with a small quantity of higher molecular weight sugars. Emdex occurs as white, free flowing, porous spheres which are water soluble and nonhygroscopic. It is generally used in directly compressible chewable tablets because of its sweet taste. It has good binding properties and slight lubricant sensitivity. It exhibits high moisture sensitivity, at room temperature and at 50% RH, the crushing strength of tablets

decreases dramatically, whereas during storage at 85% RH tablets are liquefy. Tablets containing theophylline prepared using Emdex exhibited higher mechanical strength, faster disintegration and rapid drug release than the tablets prepared from Maltrin M150.

#### **Mannitol**

It is water soluble, non-hygroscopic and produces a semi-sweet, smooth, cool taste. It can be advantageously combined with other direct compression excipients. It is frequently used in chewable tablets.

#### **Starch**

Dextrinized rice, corn, wheat and tapioca starches prepared by dextrinization exhibited very good flow, compression properties and disintegration qualities for direct compression tableting. Dextrinized tapioca starch was found to be the best. Preflo starch exhibited high bulk density and good flowability than starch 1500 and Star Tab as directly compressible excipients. Preflo starch containing tablets exhibited prolonged disintegration time (30 min) than the Starch 1500 (3.5 min). Preflo cornstarch formed harder tablets compared to Preflo potato starch. The directly compressible starch (Starch 1500) is relatively fluid, did not require a lubricating agent when compressed alone, more effective as a dry binder and gives equivalent or faster disintegration and dissolution compared to starch USP. Due to improved flowability and compressibility pregelatinized starch can be used as a binder in direct compression.

#### **Advantose 100**

It is a spray-dried maltose having spherical particles with an optimal combination of fine and coarse particles that contributes superior flow. Compared to microcrystalline cellulose, spray dried maltose can tolerate significantly greater compression force without capping upon ejection from the tablet die, it has low hygroscopicity and low reactivity than microcrystalline cellulose.

#### **Dicalcium phosphate dihydrate**

Dicalcium phosphate is the most common inorganic salt used in direct compression as a filler-binder. Advantage of using dicalcium phosphate in tablets for vitamin and mineral supplement is the high calcium and phosphorous content. Dicalcium phosphate dehydrate is slightly alkaline with a pH

of 7.0 to 7.4, which precludes its use with active ingredients that are sensitive to even small amount of alkali (i.e. ascorbic acid). It exhibits high fragmentation propensity.

#### Emcompress

Emcompress consists of aggregates of small primary particles of dicalcium phosphate. Unlubricated emcompress tablets are difficult to eject from dies, therefore, it requires high lubrication. Hardness of tablets containing emcompress is insensitive to tablets machine speed and lubricant such as magnesium stearate due to the fragmentation behaviour during compression and consolidation. It can be good

directly compressible adjuvant when used in combination with microcrystalline cellulose or starch.

#### Inulin

Particles of inulin with larger size showed better flowability. A high lubricant sensitivity was found for amorphous inulin with a low amount of entrapped air. The disintegration/ dissolution time increased with decreasing chain length of the inulin. Hollow inulin particles have an increased compactibility as compared with solid inulin particles and a strongly reduced lubricant sensitivity.

**Table 3: Summary of various directly compressible adjuvant and its methods of preparation.**

Directly compressible adjuvants	Methods of preparation	Advantages and limitations
Ethylcellulose, methylcellulose, hydroxypropyl methylcellulose, and sodium carboxymethyl cellulose from cellulose. Cyclodextrin from starch, lactitol.	Chemical modification	Relatively expensive
Dextrates or compressible sugar, Sorbital.	Physical modification	Relatively simple and economical
$\alpha$ -lactose monohydrate (100#), dibasic dicalcium phosphate.	Grinding and/or sieving	Compressibility may also alter because of changes in particle properties such as surface area and surface activation.
$\beta$ -lactose, Dipac.	Crystallization	Impart flowability to excipient but not necessarily self-binding properties. Require stringent control on possible polymorphic conversions and processing conditions.
Spray dried lactose, Emdex, Fast Flo lactose, Avicel, Karion Instant, Advantose 100.	Spray drying	Spherical shape and uniform size gives spray-dried materials good flowability, poor reworkability.
Granulated Lactitol, Tablettose.	Granulation/ Agglomeration	Transformation of small, cohesive, poorly flowable powders into a flowable and directly compressible.
Anhydrous $\alpha$ -lactose.	Dehydration	Increased binding properties by thermal and chemical dehydration.

#### EXAMPLES OF NATURALLY OCCURRING DIRECTLY COMPRESSIBLE EXCIPIENTS:

##### Soy polysaccharide

According to Khalidindi *et al* 1982 Soy polysaccharide is a natural superdisintegrant it does not contain any starch or sugar so can be used

in nutritional products. Soy polysaccharide is a group of high molecular weight polysaccharides obtained from soybean. Recently it is used as a disintegrating agent in tablets made by direct compression using lactose and dicalcium phosphate dihydrate as fillers. Sodium carboxy-

methyl cellulose and corn starch were used as control disintegrants. Soy polysaccharide performs well as a disintegrant in direct compression formulations in comparison to cross-linked CMC.

#### **Chitin and chitosan**

A natural polysaccharide Chitin ( $\beta$ -(1 $\rightarrow$ 4)-N-acetyl-D-glucosamine) is obtained from crab and shrimp shells. Chitin possesses amino group covalently linked to acetyl group as compared to free amino group in chitosan. Chitosan is the popularly known natural polysaccharide used for its versatile applications in pharmaceutical industry. Chitosan is commercially produced by deacetylation of chitin, which is the structural element in the exoskeleton such as crabs, shrimp and cell walls of fungi. When chitin was included in the conventional tablets, the tablets disintegrated within 5 and 10 minutes irrespective of solubility of the drug [Bruscato et al 1978].

#### **Mango peel pectin**

Mango peel is a good source for the extraction of pectin of good quality, suitable for the preparation of acceptable jelly. Mango peel contains 20–25% of the mango processing waste. Pectin is a complex hetero-polysaccharides which is a hydrophilic colloid. In 2011 Malviya *et al* evaluate that mango peel pectin stand as a good candidate as superdisintegrant though, not as good as synthetic superdisintegrant but it may be used in the formulation of fast dispersible tablets, due to its good solubility and higher swelling index.

#### **Agar and treated agar**

It is a dried gelatinous substance obtained from *Gelidium amansii* belonging to family Gelidaceae and also from several other species of red algae like *Gracilaria* (Gracilariaceae) and *Pterocadia* (Gelidaceae). It is yellowish gray or white to nearly colorless, odorless with mucilaginous taste and is occurs as strips, sheet flakes or coarse powder. It consists of two polysaccharides i.e., agarose and agaropectin. Agarose is responsible for gel strength and agaropectin is responsible for the viscosity of its solutions. Due to its high gel strength it is a potential candidate as a disintegrant.

#### **Guar gum**

It is obtained from the endosperm of the seed of the guar plant, *Cyamopsis tetragonoloba* (L) Taub. (syn. *Cyamopsis psoraloides*), it consists of the high molecular weight (approximately 50,000–8,000,000) polysaccharides composed of galactomannans and used as thickener, stabilizer and emulsifier, and approved in most areas of the world (e.g. EU, USA, Japan, and Australia). It is naturally occurring gum (marketed under the trade name jaguar). Physically it is free flowing, completely soluble, neutral polymer composed of sugar units and is approved for use in food. Chemically it is not sensitive to pH, moisture contents or solubility of the tablet matrix. It is not always pure white and sometimes varies in color from off-white to tan tends to discolor with time in alkaline tablets.

#### **Gellan gum**

Gellan gum is a water-soluble polysaccharide obtained from a bacterium i.e., *Pseudomonas elodea*. It is a deacetylated exocellular polysaccharide gum, anionic, high molecular weight produced by the fermentation of pure culture of *Pseudomonas elodea*. In 1997 Antony *et al* said that gellan gum used as disintegrant and its efficiency is better than the other conventional disintegrants such as dried corn starch, explotab, avicel (pH 10.2), Ac-di-sol. and Kollidon CL. Tablet which contain gellan gum as disintegrant, might be disintegrate by the instantaneous swelling when it comes into contact with water and owing to its high hydrophilic nature. The complete disintegration of tablet has proved itself as superior disintegrant.

#### **Plantago ovata seed mucilage**

Several researches shown that the mucilage of *Plantago ovata* seed is used as the natural superdisintegrant and binding agent in tablets which are prepared by direct compression technique. Some time it showed the sustaining properties.

#### **Lepidium sativum mucilage**

It is used as natural excipients due to following various characteristic like disintegrating, binding and gelling etc.

### Gum Karaya

Gum karaya is a vegetable gum produced as exudates of the genus *Sterculia*. Due to its high viscosity nature of gum it is used as binder and disintegrant in tablet formulation. Various researches showed that modified gum act as superdisintegrant in tablet. Gum karaya have good biocompatibility, easy availability and low cost, therefore, it is used as an alternative of synthetic and semi-synthetic superdisintegrant.

### APPLICATION OF DIRECT COMPRESSION TECHNIQUES:

1. **In the manufacturing of orodispersible/ mouth dissolving tablets:** This technique can now be applied to mouth dissolving tablets because of the availability of improved tablet excipients, especially tablet disintegrates and sugar-based excipients.
2. **For the hygroscopic API:** Tablets of hygroscopic API are cannot be manufactured by wet granulation or dry granulation technique due to involvement of water and heat respectively. Therefore it is suitable technique for this type of API.
3. Tablets of low dose API are also manufactured by direct compression method by using direct compression-filler which maintain its compactibility.
4. Tablets containing high loading API with poor compactibility also manufactured by direct compression method. Strong compactibility can achieve by using direct compression-binder. For example MCC or Lactose with superdisintegrant.

### SUMMARY:

This review article provides new advances in excipients used in direct compression technology of manufacturing of tablets, which is exist in pharmaceutical industry. Direct compression technique can be used as alternative for wet granulation and dry granulation, due to its simplified, easier and economical method of pharmaceutical tablet manufacturing. There are various research articles which show the evidence Available online on [www.ijprd.com](http://www.ijprd.com)

of preferred method of tableting i.e., direct compression.

In this article we discussed the naturally occurring excipients for pharmaceutical tablet manufacturing which comes to from the compressible characteristics and flow properties of the material. Few of naturally occurring excipients act as the superdisintegrant. Due to better compatibility, easy availability and low cost of naturally occurring excipients are frequently used in the pharmaceutical industries.

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