Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/14637
DOI URL: http://dx.doi.org/10.21474/IJAR01/14637

RESEARCH ARTICLE

DIRECT COMPRESSIBLE AND CO-PROCESSED EXCIPIENTS- A REVIEW

Dhaneshwar Kumar Vishwakarma Jai Narayan Mishra, Hema Gupta and Anuradha
Kailash Institute of Pharmacy & Management GIDA Gorakhpur.

Manuscript Info

Manuscript History
Received: 28 February 2022
Final Accepted: 30 March 2022
Published: April 2022

Key words:-
Directly Compressible, Co-Processed, Excipients

Abstract

The demands on the functionality of excipients are increasing day by day because of the emergence of high-speed tableting machines and the use of direct compression methods for tableting. Direct compressible is the preferred method for the preparation of tablet. Excipient play an important role in formulating a dosage form. these are the ingredient which along with active pharmaceutical ingredient make up the dosage forms. Excipient act as protective agent, bulking agent and can also be used sources of excipients along with their uses, and these Can be used for different activities. The current review article highlights the information about Direct compressible and co-processing excipients and their advantages. Also, the recent developments in excipient technology with special emphasis on natural combinations that could be used as co-processed excipients are briefly discussed.

Introduction:-

The post hundred years tablet manufacture have developed materials and processes that can produce compressed tablets containing a precise amount of an active ingredients (API) at high speed and at relatively low cost. The development in the field of (API), excipient and tableting machine during the past decades has made tablet manufacturing a science and the tablet the most commonly used in the dosages form. Prior to the late 1950s, the literature contained few references on the direct compressible of pharmaceuticals. A great deal of attention has been given to both product and process development in the recent years. The availability of materials, new forms of old materials and the invention of new machinery has allowed the production of tablets by simplified and reliable method. In early 1960, the introduction of spray-dried lactose (1960) and Avicel (1964) had changed the tablet manufacture process and opened avenues of direct compression tableting.

Previously, the word "**direct compression**" was used to identify the compression of a single crystalline com- pound (i.e. sodium chloride, potassium chloride, potas- sium 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 ingredient/s and suitable excipients. No pre-treatment of the powder blends by wet or dry granulation is involved. 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 (See Table 1). It has been found that less than 20 % of active pharmaceutical ingredients can be compressed directly into tablets. The rest of the materials have poor flow, cohesion or lubricating properties necessary for the production of tablets by direct compression.

Corresponding Author:- Dhaneshwar Kumar Vishwakarma Jai Narayan Mishra
Address**:-** Kailash Institute of Pharmacy & Management GIDA Gorakhpur.

Table 1:- Major steps involved in the tablet formulation.

Steps	Dry granulation	Wet granulation	Direct compression
1	Milling and mixing of API and Excipients	Milling and mixing of API and Excipients	Milling and mixing of API and Excipients
	⇩	⇩	⇩
2	Slug formation by compression methods	Prepared binder solution	**Compression (tablet)**
	⇩	⇩	
3	Size reduction of slug and sieving(granule)	Prepared moist mass	
	⇩	⇩	
4	Mix granule with other excipients	Moist screening of damp mass	
	⇩	⇩	
5	**Compression (tablet)**	Dry the granules and sieved the dry granules	
		⇩	
6		Mix granule with other excipients	
		⇩	
7		**Compression (tablet)**	

Directly compressible excipients

IPEC(The International Pharmaceutical Excipients Council) 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, bio- availability 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. The desired activity, the excipients equivalent of the active ingredient's efficacy, is called its Functionality. The hidden 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.

To develop and deliver a stable, uniform and effective drug product, it is important to know the properties of the API alone and in combination with all excipients based on the requirements of the dosage form and processes applied.

Ideal requirement of direct compressible adjuvants

1. Flow properties
2. Compression properties
3. Dilution properties
4. Stability
5. Controlled particle size

Advantage of direct compression

1. Cost effective formulation (less equipment, lower power consumption, less space, less time and less labor)
2. Best stability of API (by reducing detrimental effects)
3. More suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps.
4. Faster dissolution
5. Less chance of wear and tear of punches
6. Simple validation process
7. Lower microbial contamination (Due to the absence of water in granulation)

Limitation of direct compression

1. Chance of segregation (due to the difference in density of the API and excipients and dry mixing may develop static charge)

2. Variation in functionality (segregation leads to the problems like weight variation and content uniformity)
3. Poor compressibility of API
4. Lubricant sensitivity
5. Directly compressible excipients are the specialty products produced by patented spray drying, fluid bed drying, roller drying or co-crystallization (products are relatively costly)
6. Low dilution potential (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).

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 3. Co-processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible adjuvants. Hence, co-processing is discussed in more depth in the present review.

Table 2:- Summary of various methods to prepare direct compressible excipients.

Method	Advantage & limitation	Example
Chemical Modification	Relatively expensive. Time consuming.	Ethyl celluloses, Methylcelluloses
Physical Modification	Relatively simple and economical	compressible sugar, sorbitol
Griding	Compressibility may also alter because of the change in particle properties such as surface aria and surface activation.	Dibasic dicalcium phosphate
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 alpha lactose

Examples of Directly Compressible Adjuvants

1. Lactose -

Lactose is produced from Whey, as a byproduct of cheese and casein production. Lactose may appear in different polymorphs depending on the crystallization conditions. Lactose is the most widely used filler-diluents in tablets. The general properties of lactose that contribute to its popularity as an excipient re cost effectiveness, easy in the availability, bland taste, low hygroscopicity, excellent physical and chemical stability and water solubility.

Lactose Monohydrate-

it very hard crystals and is non-hygroscopic. Alpha- lactose monohydrate (100mesh) is used in direct compressible due to its flowability. It contains about 5% w/w water. Compared to other filler-binders, a-lactose monohydrate exhibits relatively poor binding properties. Alpha lactose monohydrate (100mesh) is often combined with microcrystalline cellulose.

b. Anhydrous a-Lactose-

it is reared by thermal method**.** Binding capacity of a-lactose monohydrate increase dramatically by thermal or chemical dehydration. Lactose monohydrate change from single crystals into aggregates of anhydrous a-lactose particles.Due to low moisture content, anhydrous □- lactose is an ideal excipient for moisture sensitive APIs

c.-Anhydrous b-Lactose-

It is produced by roller drying of solution of a-lactose monohydrate followed by subsequent comminution and sieving. It has excellent compaction properties and low lubricant sensitivity

d.Spray-dried lactose-
it is produced by spray drying the slurry containing lactose crystals. It is crystals of lactose monohydrate and spherical agglomerates of small crystals held together by glass or amorphous material. It has excellent flow properties and binding propertiesGuncel and Lachman were the first to describe the spray-dried lactose. Spray-dried lactose exhibited strong increase in disintegration time with increase in compression force.

Cellulose Derivatives
a. Microcrystalline cellulose (MCC)-
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 sand spray-drying, porous microcrystal is obtained. Microcrystalline cellulose occurs as a white odorless, tasteless crystalline powder composed of porous particles of an agglomerated product.its use in direct compression, microcrystalline cellulose is used as a diluent in tablets prepared by wet granulation, as filler in capsules and for the production of spheres. (Avicel PH 101 & 200). tablets containing Avicel PH102 and PH 200 showed lower crushing strength, shorter disintegration time and small weight variation

b. Hydroxypropyl cellulose –
Alvarez-Lorenzo reported that the difference in flow and compaction properties, the mechanical and microstructural properties of the tablets prepared from various grades of low-substituted hydroxypropyl celluloses is attribute to difference in the specific surface.

c. Ethyl cellulose –
Crowley reported that the release rate of guaifenesin from ethyl cellulose matxic tablets prepared by direct compression was dependent on the ethyl cellulose particle size, and compaction force.

3. SUGARS –
Sucrose is widely used as filler in chewable tablets and as binder in wet granulation**.**

a. 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 loose its fluidity.

b**. Nu-Tab-**
Nu-Tab is a roller compacted granulated product consisting of sucrose, invert sugar, 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.

4. Mannitol –
It is water soluble, non- hygroscopic and produces a semi-sweet, smooth, cool taste. It can be advantageously combined with other direct compressible excipients**.**

4. Starch-
1500- It is a directly compressible, free flowing, USP grade of partially hydrolyzed cornstarch. It is prepared by subjecting cornstarch to physical compression or shear stress in high moisture conditions causing an increase in temperature and a partial gelatinization of some of the starch granules. The product is consisting of about 5% free amylose, 15% amylopectin and 80% unmodified starch. It also exhibits self-lubricating property.

5. Dicalcium Phosphate Dihydrate-
Dicalcium phosphate is the most common inorganic salt used in direct compression as a filler-binder. Benefit of using dicalcium phosphate in tablets for vitamin and mineral supplement is the high calcium and phosphorous content. Dicalcium phosphate dihydrate is slightly alkaline with a pH of 7.0 to 7.4, whichprecludes its use with active ingredients that are sensitive to even small amount of alkali (i.e. ascorbic acid).

6. **Fujicalin-**
Fujicalin is a spherically granulated dicalcium phosphate anhydrous prepared by spry-drying. It has lower particle size, high porosity and high specific surface area. Fujicalin gives significantly stronger tablets than Di-Cafos.

Co- processed excipients
It can be defined as combining two or more established excipients by an appropriate process.co-processing of excipients could lead to the formation of excipients with superior properties compare to the simple physical mixture 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.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.Major limitation of co-processed excipients mixture is that the ratio of the excipients in a mixture is fixed and in developing a new formulation, a fixed ratio of the excipients may not be an optimum choice for the (API) and the dose per tablet under development. Co-processed adjuvant lacks the official acceptance in pharmacopoeia. For this reason, a combination filler-binder will not be accepted by the pharmaceutical industry until it exhibits significant advantage in the tablet compaction when compares to the physical mixture 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 UAP/NF.

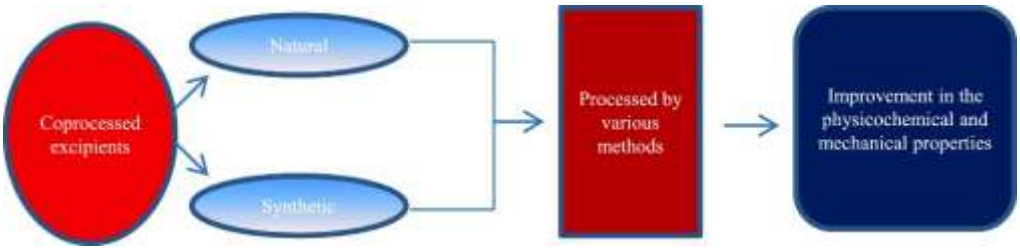

Fig:- Co-processed Directly Compressible excipients.

Example- Co-Processed Directly Compressible excipients
1. Ludipress-
Ludipress, a co-processed product, consists of 93.4% lactose monohydrate, 3.2% polyvinyl pyrrolidone (Kollidon 30) and 3.4% crospovidone (Kollidon CL). It consists of lactose powder coated with polyvinyl pyrrolidone and crospovidone.

2. **Cellactose-**
Cellactose is a co-processed product consistinglactose monohydrate (75%) and cellulose (25%). Apart from good flowability, it has good compactibility. The compactibility is attributed to a synergetic effect of consolidation by fragmentation of lactose and plastic deformation of cellulose .

3. **Pharmatose DCL 40-**
It is a co-processed product consisting of 95% lactose and 5% anhydrous lactitol. Due to spherical shape and favourable particle size, it exhibits good flowability. It has high dilution potential than other lactose based products due to better binding property. It has very low water uptake at high humidity.

4.Prosolv-
It is co-processed silicified microcrystalline cellulose. It consists of 98% microcrystalline cellulose and 2% colloidal silicone dioxide.

5. **StarLac-**
Starlac is a co-processed excipient consists of lactose monohydrate and maize starch produced by spray dry- ing (108) The advantage of Starlac are its good flowabil- ity depending on the spray-drying process, an acceptable crushing force due to its lactose content, its rapid disintegration depending on starch (109). Gohel and Jogani demonstrated use of multiple linear regres- sion in development of co-processed lactose and starch. Authors

concluded that as the lactose/starch ratio increased Carr's index of the adjuvant and crushing strength of the tablets increased while friability decreased. Percentage of starch paste has inverse effect on the friability
As discussed in this review, it is clear that no single excipient fulfils all the optimum requirements. In most instances evaluation of tableting properties of these excipients are required before selecting them as a part of formulation. Each directly compressible adjuvant has merits and demerits hence; there is still need for directly compressible adjuvant, which exhibits a satis- factory performance.

Table 8: List of web sites of directly compressible adjuvant manufacturers.

Table 3:- Co-processed direct compressible excipients.

S. No.	Brand Name	Excipients	Manufacturer, country
1.	Starlac	Lactose, maize starch	Roquette, France
2.	Di -pac (5)	Sucrose, dextrin	American sugar, USA
3.	Cellactose	MCC, Lactose	Meggle, Germany
4.	Avicel CE 15	MCC, guar gum	FMC, USA
5.	Plasdone S-630	Vinyl acetate and vinyl pyrrolidone	ISP, USA

Conclusion:-

Tablet manufacture has taken a new dimension since the advents of direct compression technology. Although a vast majority of drug substance are not in themselves suitable for direct compression, the technique has recently grown in importance due to the commercial availability of suitable machinery and direct compressible excipients which possess good flow and compressibility properties. these excipients play a pivotal role in formulating stable, result oriented drug delivery system with an improved physical, chemical and mechanical properties. Co-processed excipient is a promising tool in pharmaceutical excipient development

References:-

1. Banker, U. V; role of ingredients and excipients in Developing Pharmaceutical, Manuf. Chem, 65:32-34, 1994.
2. Gohel, M.C, Patel, L.D, Amin, A.F, Jogani, P.D, Bajaj, S.B, and Patel, G.J, Studies in improvements of flow and Compressional characteristics of Lactose, int. J. pharm. Excip, 1:86-92, 1999.
3. Gohel, M.C, and Jogani, P.D, Functionality Testing of a Multifunctional Directly compressible Adjuvant Containing Lactose, Polyvinylpyrrolidone and Croscarmellose Sodium, Pharm. Technol, 25, 64-82, 2002.
4. Gohel, M.C, and Jogani, P.D, An Investigation of the direct compression characteristics of Co-processed Lactose Microcrystalline Cellulose, Using Statistical Design, Pharm. Technol, 22:54-62, 1999.
5. Sam, A. P., and Fokkens, J. G., Drug Delivery Sys- tem: Adding Therapeutic and Economic Value to Pharmacotherapy. Part 2, Pharm. Tech. Eur., 9: 58-66, 1997.
6. Rasenack, N., and Muller, B. W., Crystal Habit and Tableting Behaviour, Int. J. Pharm., 244: 45-57, 2002.
7. Khan, K. A. and Rhodes, C. T., The Production of Tablets by Direct Compression, Can. J. Pharm. Sci., 8:1-5, 1973.
8. Shangraw, R. F., Compressed Tablets by Direct Com- pression Granulation Pharmaceutical Dosage Forms: Tablets, Vol-1, Marcel Dekker, USA, 2nd ed, 195-246,1989.
9. Shangraw, R. F., Direct Compression Tableting, Encyclopedia of Pharmaceutical Technology, Vol-4, Marcel Dekker, USA, 2nd ed., 85-160, 1988.
10. Shangraw, R. F., and Demarest, D. A., Survey of Current Practices in the Formulation and Manufac- ture of Tablets and Capsules, Pharm. Technol., 17: 32- 44, 1993.
11. Reimerdes, D., The Near Future of Tablet Excipi- ents, Manuf. Chem., 64:14-15, 1993.
12. Jivraj, M., Martini, L. G., and Thomson, C. M., An Overview of the Different Excipients Useful for the Direct Compression of Tablets, PSTT, 3: 58-63, 2000.
13. Puri, V., and Bansal, A., Pharmaceutical Technology: Challenges and Opportunities, Crips, 2: 2-11, 2001.
14. Joshi, V., Excipient choice in solid dosage forms, Drug. Del. Technol., 2 : http://www.drugdelivery-tech.com/cgi-bin/articles.cgi?idArticle=69, 2002,
15. Guo, J., Lactose in Pharmaceutical Applications, Drug. Del. Technol., 4: http://www.drugdelivery-tech.com/cgi-bin/issues.cgi?idIssue=26, 2004.