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TO REVIEW ON CO-PROCESSED EXCIPIENTS AND RECENT UPDATE IN THEIR COMMERCIAL PRODUCTION AND APPLICATION IN MANUFACTURE OF TABLETS

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ABSTRACT
The aim of the current review is to provide an in depth, knowledge on recent developments in excipients preparation, technology and approaches involved in their formation and development. Excipients play an important role in dosage form development. In conventional formulation of dosage forms, each excipient is used to provide its required function/performance. Presently, excipient manufacturers have focused their attention on producing multifunctional excipients with improvement in their performance and quality of dosage form. Manipulation in the functionality of excipients is provided by the co-processing of two or more existing excipients. A detailed analysis of co-processed excipients for the manufacture for tablets is provided here.

KEYWORDS: Co-processing, Co-processed excipients, Direct compression, Particle Engineering.

1. INTRODUCTION
Excipients form main bulk of different types of formulations.[1] The International Pharmaceutical Excipients council(IPEC) defines excipients as substances other than the API which are present in the dosage forms or medicines.[2]

In earlier days, excipients were considered inactive ingredients. Over the years pharmaceutical scientists learned that excipients are not inactive and frequently have strong impact on the manufacture/processing, quality, safety, and efficacy of the drug substance in a dosage form.[3]

1.1. Excipients must contain properties as per the following.[4,6] They should be
- Physiologically inert.
- Acceptable to regulatory agencies.
- Physico chemically stable
- Free from microorganisms.
- Should not interfere with the bioavailability of the drug
- Commercially available in the form and purity which commensurate to pharmaceuticalstandards.
- Low cost, inexpensive.
- Meet the standards of regulatory requirements.

1.2. Excipients are used in dosage forms for performing different type of functions, such as
- Binder
- Tablet disintegrant
- For active pharmaceutical ingredients (API) stability
- For API solubility
- To increase API bioavailability
- Drug Release controlling agent

1.3. Classification of excipients[7–9]
Excipients used in the manufacture of tablets are classified into following categories

1. **Diluents**: These are materials which are used to make up required bulk of the tablets when the drug substance is too low not sufficient to produce the bulk.
For Ex. Microcrystalline cellulose, alpha - lactose monohydrate, anhydrous Beta-lactose, spray dried lactose, calcium phosphate dihydrate, sorbitol, dextrose, pregelatinized starch, mannitol, calcium carbonate, calcium lactate, erythritol, magnesium carbonate, magnesium oxide, maltose, xylitol, polydextose
2. **Binders or granulating agents:** Binders are the 'glue' that hold the powder together to form granules.

Binders may be sugars or polymeric materials.
They are the adhesive that are added to tablet formulation to provide Cohesiveness required for bonding together of the granules under compaction to form a tablet.
For Ex. Sugars: liquid glucose, Sucrose syrup
Natural polymers: starch, acacia, tragacanth, gelatin
Synthetic polymers: Polyvinylpyrrolidone (PVP), methyl cellulose.

3. **Disintegrating agents:** A substance added to tablets to facilitate its breaking up into in small particles after administration. A material which has ability to absorb water, increase to promote capillary action or wick up water into tablet core thereby increasing tablet porosity and disintegrate into powder form,
For Ex. starch, alginic acid, sodium cmc, HPMC, agar, guar gum, tragacanth, alginates, magnesium aluminum silicate, ion exchange resin.

4. **Lubricating agents:** These substances reduce friction between surface of tablet and die wall. They are usually hydrophobic in nature,
For Ex. Water soluble: boric acid, sodium acetate, sodium benzoate, SLS
Water insoluble: magnesium stearate, sodium stearate, calcium stearate.
5. **Glidants:** Facilitate flow of granules from hopper to die cavity by reducing inter-particle friction,
For Ex. talc, corn starch.
6. **Antiadherants:** Prevent adhesion of material to the face of punches and die walls, For Ex. talc, aerosol, DL-leucine.

7. **Organolaptic additives:** those include,
- Colouring agents

For Ex. yellow and red iron oxide, carminic acid,
- Flavouring agents

For Ex. sucrose, sorbitol, aromatic oil (clove, peppermint oil)
- Sweetening agents

For Ex. saccharin sodium, mannitol, sucrose, dextrose
- Adsorbents

For Ex. silica, magnesium oxide, magnesium aluminum silicate, tricalcium phosphate
- Preservatives

For Ex. methyl paraben, propyl paraben, sodium citrate.
- Miscellaneous

For Ex. vitamin A, vitamin E, vitamin c, stearic acid, sodium citrate

2. Production of Tablets

Tablets are the most commonly used solid oral dosage forms which are generally prepared by either wet granulation, dry granulation, or direct compression.[10] (Table 1)

Table 1: Steps involved in different tablet manufacturing processes.

Step	Direct compression	Dry granulation	Wet graduation
1	Blending /mixing of API and excipients	Blending /mixing of API and excipients	Blending /mixing of API and excipients
2	Compression	Compression into slugs	Preparation of binder solution
3		Size reduction ofslugs and sieving	Massing of binder solution of step 2 with powder mixture of step 1
4		Mixing of milled slug with excipients	Wet screening of damp mass
5		Compression	Drying of wet granules
6			Resifting of dried granules and blending with excipients
7			Compression

Presently most of the pharmaceutical manufacturing industries opt for direct compression in tableting because it requires fewer processing steps, simplified validation, elimination of heat and moisture, economy, and improved drug stability as compared to wet granulation technique. The term 'direct compression' (DC) is the process by which tablets are prepared directly from powder blends of active ingredients and suitable excipients. For direct compression excipients used for formulation should have good flow and compressibility.[11,12]

3. Directly Compressible Adjuvants (Excipient)

Functional purpose served by an excipient in its dosage form can be attributed as its characteristic which is essential for the manufacturer to avoid batch to batch variation in order to ensure good manufacturing practice.[13]

It is essential to know the properties of the active ingredient alone and its combination with all other ingredients based on the requirements of the dosage form and processes applied in order to deliver a stable, uniform and effective pharmaceutical product. Excipients are usually produced by batch processes; hence, there is a possibility of batch-to-batch variation from the same manufacturer. Excipients derived from various sources may not have the identical qualities when used in a particular composition. Users may wish to verify equivalency in final performance or evaluate such attributes before usage to ensure interchangeability in such situations. Such tests are thus related to the functionality that the excipients impart to a specific formulation.[14]

Controlling functionality is just as crucial as ensuring identification and purity.[15]

Excipients with most favorable functionality are needed to ensure smooth tablet production on modern machines.[16]

Introduction of special force feeder to improve flow of granules from hopper is considered a significant advancement in direct compression technology.[17]

3.1. Ideal requirements for a directly compressible adjuvant(Excipients)

a) Flowability

The directly compressible excipient should be free flowing in nature. This property is considered to be important in order to provide homogenous and rapid flow of drug-excipient powder mix for uniform die filling in tableting using high speed rotary machines. The dwell time is generally in terms of millisecond for the required amount of powder mix to be transferred into the die cavity with and accuracy and reproducibility of + or – 5%. Problems related to tablet making are due to incorrect powder flow, non-uniformity in blending under or over weight of final product and errors in die filling.[18]

b) Compressibility

Satisfactory tablet making requires proper compressibility of powder mix because it must remain in the compact form after ingestion of the tablet. There are very few excipients which possess this property without causing elastic recovery. Therefore the relation between compaction pressure and the volume of the powder mix has a great impact on compressibility of directly compressible excipient.[19,20]

c) Stability

It is necessary that a directly compressible excipient possess stability both physically and chemically. For example, it should be able to withstand its degradation by atmosphere, moisture, temperature and aging.[21]

d) Control of Particle Size

Both API and a directly compressible excipient should possess equivalent particle size distribution in final mix and the same should be observed in all the batches. Uniform blending of API with excipients ensure reproducibility in batches.[22]

e) Re-workability

Sometimes batches of tablets have to be broken down in order to correct certain parameters while evaluating the final product. Therefore selection of directly compressible excipient should be such that after recompressing either loss in flowability or compressibility is not observed. Final batch of tablets should retain all characteristics.

f) Dilution Potential

Dilution potential is also considered to be effective in satisfactory compression of the powder mix into tablets using a particular directly compressible excipient. If such excipient has high dilution potential it is beneficial to compress the tablets having a minimum possible weight, therefore we can say that dilution potential and compressibility of an API-excipient mixture are interrelated.[23]

3.2. Co-processing

There is hardly any excipient that possess all favorable characteristics for direct compression. Excipients functionality can be improved by any of the following ways, 1. developing new chemical excipient molecule 2. making better grade of currently available excipient 3. combining currently available excipient in an innovative manner.[24] Manipulation of excipient functionality can be done mostly by either co-processing, that is combining multiple excipients and processing them together or using a new technology known as particle engineering of more than two excipients.

Co-processing is defined as interaction of more than two excipients at sub-particle level in order to improve their functionality synergistically. This process may eliminate undesirable characteristics of individual excipient. One can also form a new granular excipient by way of co-processing which leads to better granuation and faster tableting in comparison with the tablet opting from just physical mixture of individual excipient.[25,26]

Co-processing is also defined as 'combination of two or more compendial or non compendial excipients by modifying their physical properties in a manner that can not be achievable by simple physical mixing and without significant chemical changes.[27]

4. Co-Processed Excipients

Co-processing was originally adopted by food industry for improvement in stability, wettability, solubility and to strengthen gelling of food substances, for example co-processed glucomannan and galactomannan.[28] This concept was introduced in pharmaceutical industry in late 1980s with a co-processed combination of MCC (micro crystalline cellulose) with calcium carbonate.[29]

Cellactose (Meggle company, Wasserburg, Germany) was manufactured in 1990 which is a co-processed form of 75% cellulose with 25% lactose. Then silicified microcrystalline cellulose (SMCC), a popular co-processed excipient was also developed.[30]

4.1. Advantages of co-processed excipients.[20,31]

a. Single excipient provides multiple function
b. Improve flow properties: no need to add glidants. For example, improved flow property of co-processed excipients is achieved in case of spray drying because of their spherical shape.
c. Overcome the limitation of existing excipients

d. Improvement of organoleptic properties
e. By using these excipients, tablets are manufactured by direct compression method
f. Removal of undesirable properties
g. Better mouth feels and improved palatability
h. Improved Compressibility
i. It can also improve the tablet hardness
j. Decrease disintegration time
k. Decrease weight variations during tablet manufacturing
l. Reduce lubricant sensitivity
m. Better dilution potential: Most active drug moieties are poorly compressible and as a result, excipients must possess better compressibility to retain good compaction even when added with poorly compressible agent. Cellactose shows higher dilution potential than just making a physical mixture of its constituent excipients, namely cellulose and lactose in a suitable proportion.

4.2. Disadvantages
- Material loss at different phases of processing
- Expensive due to factors such as, labour, space, time, special equipment and energyrequirement.
- Time consuming.

5. Important Considerations In Co-Processing
1. Preliminary study should be carried out on excipients to be selected for co-processing in order to study their characteristics and functionalities.
2. Determine their ratio to be used for co-processing.
3. Study particle size distribution of each excipient to be co-processed.
4. Out of an available technique, select the most suitable one for co-processing.

5.1. Excipients Selection Criteria in Co-Processing
Selected excipient must be compatible and inert with each other. Co- processing is generally done by one excipient which is plastic in nature and another one is brittle in nature. For optimum tableting performance combination of both excipients are mandatory. Maarschalk report that the co-processing done with a large amount of brittle excipient and a small amount of plastic excipient, in case of Cellactose 75% lactose(brittle) is co – processed with 25% cellulose which is plastic in nature. This particular combination of excipients prevent storage of large amount of elastic energy during compression, which results in a limited amount of stress relaxation and reduced tendency of capping and lamination. This type of combination in co-processing can help in improvement of compaction performance, lubricant sensitivity or sensitivity to moisture.[20]

5.2. Methods involved in co-processing
a. Spray drying
b. Roller compaction
c. Solvent evaporation
d. Crystallization
e. Milling
f. Granulation/agglomeration
g. Melt extrusion

a. Spray drying
This technique involves conversion of either a solution or a suspension or a dispersion or an emulsion into a dried powder, agglomerates or granular form. Factors to be considered are physical and chemical characteristics of individual excipient, design of the equipment used and required final product properties. In case of spray drying inlet air temperature, atomization air pressure, rate of initial inlet, viscosity of the fluid, percent of solid present in the feed, rpm of disc are important factors to be considered. The procedure involves following steps (a) dispersed fluid to be sprayed in the form of droplets with introduction of warm drying gas simultaneously (b) rapid evaporation of droplets in the form of dry particles. (c) recovery of dry particles. This is a continuous operation. Rapid drying of solid particles takes place. This can be employed in drying and co-processing heat- resistant materials. It may result in improvement in hardness and compressibility.[33]

For Ex. - spray-dried co-processed excipient.

➢ **Material and method[34]**

The co-processed excipient formed by the spray drying method using microcrystalline cellulose (MCC), lactose monohydrate (Lactose) and starcap 1500 (comprised of corn starch and pregelatinized (starch). Optimization of the components of excipients is done by D-optimal mixture design. From the desirability function of co-processed excipient the optimized composition was found. The optimized composition of the co-processed excipients were measured to be 30% MCC, 25% lactose, and 45% starcap. Now accurately measured and weighed proportions of component excipients are added to distilled water and are mixed using a magnetic stirrer until homogeneous suspension is formed. Based on the results obtained from preliminary studies it was decided to prepare a total of 10% w/v suspension of component excipients. Spray drying of this suspension was performed using a laboratory scale spray dryer based on the preliminary studies, process parameters were set as follows:
- Inlet air temperature- 190°C.
- Outlet air temperature- 95°C.
- Feed rate- 4ml/min.
- Aspiration rate- 48 N/m3/h.
- Atomization pressure-2 bar

➢ **Observation[34]**

The observation related to effect of concentration concludes that there is decrease in value of angle of repose, Carr’s index and Hausner’s ratio with increase in concentration of starcap 1500. It can also be concluded that as the concentration of lactose increase, there is an increases in the values of angle of repose, Carr’s index and Hausner’s ratio.

➢ **Result[34]**

Etodolac, a drug with poor compressible model demonstrated improvements in the compressibility on formulation with this co-processed excipient. On using MCC, lactose and starcap a high co-processed excipient with high functionality can be formed which can replace these individual excipients. Etodolac tablets manufacturing by using this co- processed excipient are evaluated for different tablet parameters and they give the results are shown as per the following: such as,

- Hardness – 4.6kg/cm²
- Friability- 0.48%
- Disintegration time – 477s

b. Roller compaction

In this system uniform powder of the excipients to be co-processed is compacted between counter rotating rollers to form ribbon of compacted material that is then processed into granules. Roller compaction is suitable for co-processing of moisture or high temperature sensitive excipients on the grounds that there is no drying.[3]

For Ex. – compaction of two excipients

➢ **Materials and method**:

Polyethylene oxide and hydroxyl propyl methyl cellulose are components of a co-processed excipient and was prepared using roller compaction technique. These polymers were precisely weighed according to the desired ratio (1:9 to 9:1) and mixed for 10 minutes to get a homogenous mixture. The roller compactor was employed to compact these mixes (Clit roller compactor, India). The ribbons were screened using sieves of 40# and 60#. The fine powder was then recycled to produce uniform-sized granules. Approximately 9 cycles of roller compaction were completed to get the appropriate particle size. These granules are used in tablet formation by direct compression.[35]

➢ **RESULT**

Assessment of polyethylene oxide and hydroxy propyl methyl cellulose and their co- processed excipients was done by angle of repose, Carr's compressibility etc. and the observation made showed substantial improvement its characteristics such as, flowability and compressibility than the mixture of their individual excipients counterparts. The optimum tablet making ratio was found to be 7:3 & 8:2 (polyethylene oxide: hydroxyl propyl methyl cellulose) with moisture content <1% and appropriate swelling property to be (40-50 %).[35]

c. Solvent evaporation

This method is carried out in the liquid vehicle. The coating excipients are dissolved in the volatile solvent which are immiscible with liquid vehicle. With the use of agitation, a core excipient substance to be microencapsulated is dissolved or disseminated in a coated polymer solution. To obtain the proper size microcapsule, the core coating material combination is disseminated in the liquid production vehicle phase. Then mixture is heated to evaporate the liquid vehicle and then decrease the temperature with agitation to form microcapsule.[2]

Example of co-processed excipient formulated by solvent evaporation method.

➢ **Materials and method[36]**

Co-processing of lactose, pvp with crosspovidone is done by rotary evaporation method. Processing of lactose with water as a solvent by using rotary evaporator. Weigh accurately 5 g of lactose was added into sufficient quantity of water. Water was evaporated at 800°C using rotary evaporator at 150 rpm under vacuum. The dry powder was removed and sieve no.16 was used. Co-processing of lactose-pvp-crospovidone (87:10:3) was done by rotary evaporator at 800°C and at 150 rpm under vacuum.

➢ **Result[36]**

Processed lactose had a significantly different Carr's index and Hausner's ratio than unprocessed lactose, which revealed an increase in compressibility. It was also compressed at a lower pressure. Co-processed excipients' Carr's index and Hausner's ratio were lower, demonstrating their directly compressible nature. Compressed tablets had a good hardness, were less friable, and disintegration time was within acceptable limits.

Evaluation of simple excipient and co-processed excipient

Simple lactose excipient:	**Co-processed excipient**
Pre compression parameters:	pre compression parameters:
• Carr's index- 31.03	Carr's index – 18.23
• Hausner's ratio - 1.45	Hausner's ratio – 1.203
Post compression parameters:	Post compression parameter:
• Tablets are not formed	Hardness: 3.7 kg
	Friability: 0.51%
	Disintegration time:38 sec

d. Crystallization

This method is very commonly used for co-processing. In this method prepareed the solution of excipients at the supersaturated conditions. After sometimes crystals are obtained using different methods such as (1) solution cooling, (2) addition of a second solvent to reduce the solubility of the solute (3) Chemical reaction and (4) change in pH. Then crystals are separated from the solvent by filtration. [37]

Example of co-processed excipient manufacturing by crystallization method.

➢ **Materials and method[38]**

Di-pac is a mixture of 97 % sucrose and 3 % maltose dextrin which was manufactured by the company using crystallization and it was directly compacted and tableted.

➢ **Result[38]**

Resulting co-processed material Di-Pac It has a direct compacting property, better flow property, low hygroscopicity and low moisture content (LOD <1%), it prevents degradation of API. Di-Pac is a readily soluble, it effects on the Solubility of the ingredients and reduces the need for disintegrants.

e. Granulation/agglomeration

Granulation is the act or process of forming or crystallizing into grains, granules typically have a size range between 0.2 to 4.0 mm depending on subsequent use. Agglomeration process also known as size enlargement technologies are great tools to enhance properties of product.

Agglomeration of powders is widely used to enhance physical properties like wettability, flowability, bulk density, and product appearance. In pharmaceutical industry, two types of granulation are widely known, they are wet granulation and dry granulation. Wet granulation is generally more accurate and preferred method used for co-processing.[39]

Example of co-processed excipient manufacturing by granulation technique.

➢ **Material and method[40]**

Co-processing of crospovidone (5-10%w/w), polyethylene glycol 4000 (5-15% w/w) with dibasic calcium phosphate is done by granulation technique. Weigh accurately and mix all the three excipients and transfer on a heated porcelain dish at a maintained temperature 60°C.This powder blend was heated for a specified time period (4-12 min) at 60°C in order to break the mass into granules. The porcelain dish was removed after the stipulated period of heating, and the granules were cooled to room temperature with constant stirring. The granules were passed through #30.

➢ **Result[40]**

These co-processed excipients served two purposes. Firstly, it ensured multi functionality in the manufacturing of tablets thereby, reducing the number of excipients in the inventory. Secondly, this being a combination of brittle (dibasic Calcium phosphate) and plastic material (crospovidone) ensured better compressibility for manufacturing of tablets by direct compression.

f. Melt extrusion

Flowability, bulk density, wettability and product appearance can be improved or enhanced using this technique. One of the widely used technique in pharma industry, a solvent free technique utilizes the solidified agglomerate of co-processed excipients with metal - binder that are passed through a sieve forming beads or small pellets which are than extracted.[11]

➢ **Material and method[41]**

Co-processing of mannitol and sorbitol is done by the melt extrusion method by the SPI pharma as a trade name 'compressol'.

➢ **Result[41]**

Compressol has a better flow property, lower hygroscopicity, improve compressibility than mixture obtained by simple mixing of both components.

5.3. Evaluation parameters of co-processed excipient

5.3.1. Pre compression parameters[42,43]

a. Solubility: Solubility of co-processed excipient was tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents such as alcohol, dichloromethane, chloroform, etheretc.

b. Bulk density: This can be measured by pouring the excitement in cylinder without tapping.This can give idea about porosity of material.

c. Tapped density: Density will be measured after tapping the material in the cylinder. Tape density is always higher than the bulk density because, volume of material will be decreaseafter taping.

d. Hausner's ratio: The ratio of tapped density to bulk density is known as Hausner's ratio. The flow property is calculated using the equation shown below, and the lower the value of Hausner's ratio, the better.

e. Hausner's ratio = Tapped Density/ Bulk Density

f. Compressibility Index: Compressibility index (CI) was determined by measuring initial volume (Vo) and final volume (V) after hundred tapings of a sample in the measuring cylinder. CI was calculated by using this formula,

g. CI= Vo-V/Vo ×10

h. Angle of repose: Angle of repose was determined by the fixed funnel Method. It is definedas the greatest feasible angle between the surface of the powder pile and the horizontal plane. Lower the angle of repose indicates good flow property. This can be

Calculated using this formula

Tan Θ=h/r

i. No chemical changes: Various study of the chemical properties of co-processed excipientproved that these excipients do not show any chemical changes. Detailed study of co- processed excipient with X-ray diffraction analysis, solid state nuclear magnetic resonance (NMR), IR spectroscopy detected no chemical changes and indicate a similarity to the physicochemical properties with physical mixture of the excipients. The absence of the chemical changes helps in reducing company's regulatory concerns during the development phase.

j. **Heckel equation**: The Heckel equation is used for the study of the compressibility behaviour of the co-processed excipient and physical mixture having the same composition. Co-processed was compressed in hydraulic press and matching die at pressure of 1, 2, 3, 4, 5 and 6 t for 1 min. Before evaluation, the compacts were placed on silica gel for 24 hours to allow for elastic recovery and hardening, as well as to avoid falsely low yield values.Determination of thickness, weight, diameter of the compacts is done. After that the data was processed using Heckel equation and the mean yield pressure (Py) from the reciprocal of K was obtained by regression analysis of the liner portion of the plot. Ln (1/1-D) =Pk+A. D is the packing fraction, and P is the pressure, where A and k are constants.

Table 2: Flow characteristics.

Flow characteristics	Angle of repose (Flow)	Carr's index	Hausner's ratio
Excellent	25-30	≤10	1-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.60

5.3.2. Post compression parameters[17,44]

(a) Weight variation test: Uniformity in the weight of tablet can be checked by weight variation test. In this test, twenty tablet are weighed individually and the average weight iscalculated. The individual tablet weight are then compared to the average weight. Not more than two of the tablets must differ from the average weight by not more than the percentagedisplay in table-3.

Table 3: Official standards as per I. P.

Sr. no.	Average weight of tablet	% weight variation acceptance (+or-)
1	84 or less mg	10%
2	84-250 mg	7.5%
3	>250 mg	5%

(b) Test of Hardness: Hardness is also known as 'crushing strength test 'Tablets must have aspecific level of strength or hardness to survive mechanical shocks during production, packaging, and transportation. 'The force necessary to break a tablet' is defined as tablet hardness. It is expressed in the kg/cm².

Factor affecting to hardness

- Force provide for the compression
- Moisture content
- Binder concentration

Equipment used for the hardness measurement.

- Monsanto hardness tester
- Pfizer hardness tester
- Strong cobb hardness tester
- Erweka hardness testerOfficial standard for hardness:
- Standard limit for the hardness of uncoated tablets as per IP – 4-10 kg/cm².

(c) Friability test: Physical strength of uncoated tablet upon exposure to mechanical shock and attrition can be determined by the friability test. The Roche friabilator is commonly used to measure it.

Procedure

- Take 20 tablets, weigh them, and place them into friabilator.
- Now, rotate the drum at 25 rpm for 4 minute.
- After that, measure the final weight of tablets and calculate the friability by using this formula, % friability=Wi – Wf/Wi x 100 Wi= initial weight Wf=final weightStandard for friability.
- % friability should be up to 0.5 to 1 % for compressed tablets.

(d) Time for disintegration is a process in which tablets are break up into granulesor smaller particles once the tablet is exposed to the gastric fluid. Disintegration apparatusis generally used for this evaluation.

According to I. P., there is an official standard for disintegration time,

- Uncoated compressed tablets-15 min
- Sugar coated tablet-60 min
- Film coated tables -30min
- Enteric coated tablet-60 min

(e) Time for dissolution -When a dosage form is swallowed in the gastric fluid, the rate at which itreleases the active ingredient is critical to ensure that the drug is

delivered properly. The dissolution rate refers to the rate at which a medication is released.
Name of dissolution apparatus as per U. S. P.

- Type 1-Basket type apparatus
- Type 2-Paddle apparatus
- Type 3-Reciprocating cylinder
- Type 4-Flow through cell
- Type 5-Paddle over disk
- Type 6- Rotating cylinder
- Type 7- Reciprocating holderAccording to I. P.
- Type 1-Paddle apparatus
- Type 2-Basket apparatusStandard as per U. S. P.
- 75% of drug should be dissolved within 45 min

5.4. A regulatory perspective of the co-processed Excipients
Combination of excipients by co-processing does not have any chemical modification in the incorporated excipients. If the parental excipient is likewise GRAS-certified by the regulatory industry, co-processed excipients can be considered generally regarded as safe (GRAS) due to the absence of chemical changes during processing. When compared to physical agencies, these show substantial advantages in tablet compaction. As a result, no additional toxicity studies are required for these excipients. Only a few co excipients, such as dispersible cellulose in B.P. and compressible sugar in U.S.P., are listed in official monographs. Their non- compendial character is the most significant impediment to co-processed excipients' market success. This barrier will be overcome in the coming future by the new excipient safety evaluation procedure (NESEP) and now, excipients could be reviewed outside the FDA drug approval process. Supportive opinion from experts of IPEC team will reduce the risk of FDA dismissal of drug based on excipient and could stimulate innovation in the pharmaceutical Industry.[45]

5.5. Example of marketed co- processed excipient.[2,46] Example of some of the marketed coprocessed excipients are as per the following (table 4)

Table 4: Example of marketed co- processed excipients.

Co-process excipient	Trade name	Advantages	Company name
Lactose, 25% cellulose	Cellactose	High compressibility, good mouthfeel	Meggle pharma
Lactose, 3.2% Kollidon 30	Ludipress	Good flowability, tablethardness	BASF pharma
95% β lactose, 5% lactitol	Pharmatosedcl 40	High compresiibility	DFE pharma
Starch 15 %, lactose 85%	Starlac	Good flow property, high Compressibility	Meggle pharma
Microcrytalline cellulose,lactose	Microcelac	Capable of formulatinghigh dose, good flowability	Meggle pharma
Microcrystalline cellulose85%, guar gum 15%	Avicel CE 15	Less gritiness, reducedtooth packing, minimal chalkiness, improved Palatability	Dupont pharma
Mannitol 84%,crosspovidone 16% , silicon dioxide <1%	Pharmaburst	High compactibility, highloading in small diametertablet, rapid disintegration	S. P. I. Pharma
95% B-lactose, 5% lactitol	Pharmatosedcl 40	High compressibility	D. M. V
Orocell 200 with 90% mannitol, Orocell 400 with90% mannitol	Orocell 200& Orocell 400	A development filler binder with high dilutionpotential and good disintegrating propertyuseful for oral disintigrating tablet	J. R. S.

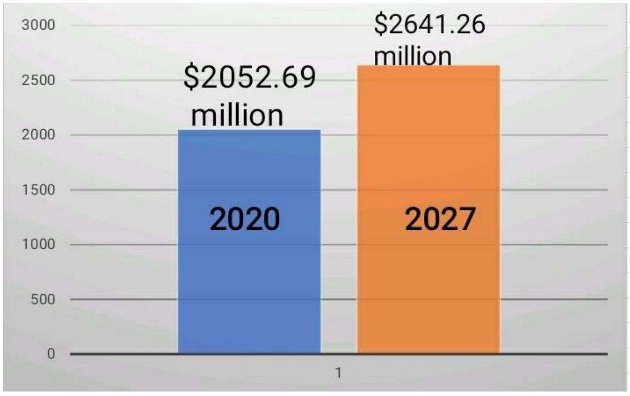

Fig. 1: Global co-processed excipients market 2020-2027.

5.6. Global market of co-processed Excipient[47]

As per verified market research, the global co-processed excipients market was valued at USD2,052.69 Million in 2019 and is projected to reach USD 2,641.26 Million by 2027, at a CAGR (compound annual growth rate) of 3.48% from 2020 to 2027.(Fig. 1)

Key company profile: The major players in the market are: BASF SE, Meggle, SPI pharma, Avantor, Colorcon, Lubrizol Corporation, DFE Pharma, Seppic, Merck, Dupont, DMV, JRS etc.

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