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A REVIEW ONAPPLICATION OF MULTIFUNCTIONAL SPRAY-DRIED EXCIPIENT FOR NEW PRODUCT DEVELOPMENT

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ABSTRACT:

A number of changes have been made to the tablet manufacturing process, including the introduction of direct compression and the use of high-speed machines. Due to advanced technologies, there has been an increased demand for developing unique excipient functionalities. Multifunctional excipients make use of their flow and compression properties. Because of its simplicity and cost effectiveness, the direct compression method is a highly preferred method of tablet production. It encourages researchers to conduct more extensive research and analysis in order to develop newer excipients with improved tableting properties. For the introduction of the new class of excipients known as co processed spray dried excipients, a spray drying technique was used in conjunction with extensive use of particle engineering and material sciences. To improve the compressibility and flow properties of poorly compressible drugs, multifunctional excipients are used.

Keywords: Multifunctional excipients, direct compression, co-processing, spray drying

INTRODUCTION:

HISTORYOF DIRECTLY COMPRESSIBLE EXCIPIENTS:

Previously, co-processing in the pharmaceutical industry had begun in the late 1980s with the introduction of co-processed microcrystalline cellulose and calcium carbonate, which was followed by the 1990 introduction of cellactose.[7] .

ADVANTAGES OF DIRECT COMPRESSION:

In contrast to solvent evaporation, the prime advantage of direct compression is economic, since fewer unit operations are required. Lowering these aspects helps reduce equipment, power consumption, space, and time while also reducing the tablet production cost. In direct compression, the method eliminates wetting and drying steps, making it more suitable for moisture and heat sensitive APIs. Because of this, it increases the stability of active ingredients and reduces detrimental effects. The likelihood of dissolution profile changes occurring on tablet preparation is less in those that are made using direct compression on storage than in those that are made using

granulation. Incorporating dissolution specifications is extremely critical because the compendium now requires them in nearly all solid dosage forms. in the case of poorly soluble API tablets prepared by wet granulation, disintegration or dissolution is the rate-limiting step. Rather than forming a powder or a granule, which are handled directly by the dissolution fluid, tablets containing API are pulverized by a direct compression process, which disintegrates the tablets into APIs instead of powders or granules. Lugging or roller compaction causes higher compaction pressure than direct compression, but by implementing direct compression, this extra compaction pressure can be avoided. Wear and tear is less on punches and dies because of their effectiveness. Therefore, due to the shorter time period in which materials are being processed, the chance of contamination or cross-contamination is reduced, and it becomes easier to meet current GMP requirements. chance of microbial growth is nearly nonexistent when tablets are prepared using direct compression.[4].

TABLE:1 METHODS OF PREPARING DIRECTLY COMPRESSIBLE EXCIPIENTS

Method	Advantages and limitations	Examples
Chemical modification	Relatively expensive , Requires toxicological data, Time consuming	Ethyl cellulose, Methyl cellulose, Hydroxypropylmethylcellulose, carboxy methyl cellulose from cellulose , lacitol cyclodextrin from starch,
Physical modification Grinding /sieving	Relatively simple and economicalcompressibility may alter	Dextrose or Compressible sugar , Sorbitol, α-Lactose monohydrate, Dibasic calcium phosphate
Crystallization	Impart flowability to excipients, Requires stringent control on possible polymorphic conversions and processing conditions.	β-Lactose, Dipac
Spray drying	Spherical shape and uniform size, 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	Anhydrous α- Lactose

CO-PROCESSED EXCIPIENTS:

Co-processing is another method for bringing new excipients to market without having to go through the extensive safety testing required for a completely new compound. It is defined as the use of an appropriate process to combine two or more existing excipients.

When excipients are processed together, they can form excipients with superior properties to normal physical blends of their constituents. The main goal of co-processing is to create a product with additional value based on its functionality/price ratio[6].

The advancement of co-processed additives starts with the formation of the additives to be coupled, their targeted proportions, the selection of a preparation method to obtain an optimized product with the desired physico-chemical parameters, and it concludes with batch-to-batch variation minimization[2]. In order to obtain the desired product, a low-cost excipient must be combined with the appropriate amount of a functional material, rather than a simple mixture of components. Co-processing is an intriguing method because it only changes the physical structure of the products without changing their chemical structure. By embedding the components within minigranules, a fixed and homogeneous distribution is achieved. The actives' adhesion to the porous particles reduces segregation, making integrated platform and control simple and reliable.[5].

Co-processing is centred on the new idea of two or more excipients interacting at the sub-particle level, with the goal of improving functionality while covering up the undesirable properties of individual excipients. Because there are so many excipients available for co-processing, there are a lot of options for creating custom "designer excipients" to meet specific functionality needs or improve desired excipient properties8. For example, if a filler–binder has a low disintegration property, it can be co-processed with another excipient that has good wetting properties and high porosity because these properties will increase water intake, assisting and increasing tablet disintegration. Spray drying was used to create ‘ready-to-compress' powder blends for direct compression, with no granulation, milling, or mixing stages in between spray drying and compression.[3]

CO PROCESSING OF EXCIPIENTS:

The following are the steps associated with the development of a co-processed excipient:

1. Identification of the excipients group to be co-processed after a thorough examination of the material properties and functionality requirements.
2. Decide on the proportions of different excipients.
3. Identifying the particle size that will be required for co-processing. When one of the components is processed in a dispersed phase, this is especially important. The particle size of the latter after processing is determined by its initial particle size.
4. Choosing a suitable drying method, such as spray drying or flash drying
5. Streamlining the procedure (because even this can contribute to functionality variations).

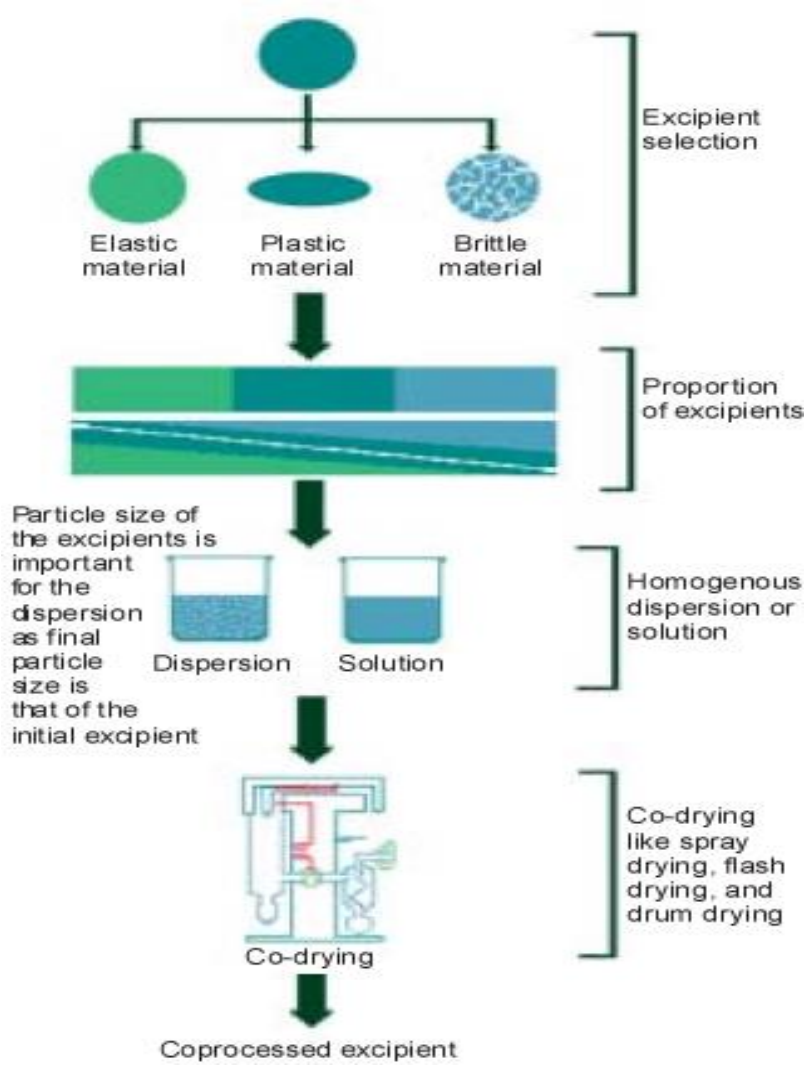

Figure: 1 schematic representation of steps involve in co-processing[6]

PROPERTIES AND ADVANTAGES OF THE CO PROCESSED EXCIPIENTS:

(A) ABSENCE OF CHEMICAL CHANGE:

Excipient chemical composition after co processing have been studied extensively, and it has been assumed that these excipients do not change chemically. Detailed analyses of SMCC using X-ray diffraction, solid-state nuclear magnetic resonance (NMR), IR spectroscopy, Raman spectroscopy, and C13 NMR spectroscopy have revealed no chemical changes, indicating that its physicochemical properties are similar to those of MCC. During the development phase, the lack of chemical change helps to reduce a company's regulatory concerns.[4].

(B) PHYSICOMECHANICAL PROPERTIES:

(I) IMPROVED FLOW PROPERTIES:

Superior flow properties of co-processed excipients are ensured by controlled best possible particle size and particle-size distribution, which eliminates the need for glidants. A comparison of Cellactose flow properties was also carried out. Cellactose had better flow characteristics than lactose or a mixture of cellulose and lactose, according to the angle of repose and the Hausner ratio. The spherical shape and even surfaces of the spray-dried product improved the flow properties as well.

(II) IMPROVED COMPRESSIBILITY:
When plotted and compared to simple physical mixtures, the pressure–hardness relationship of co processed excipients showed a significant improvement in the compressibility profile. Excipients like Cellactose, SMCC, and Ludipress have been shown to have better compressibility than simple physical mixtures of their constituent excipients.[4].

(III) BETTER DILUTION POTENTIAL:
Compressibility even when diluted. Cellactose has greater dilution potential than a physical mixture of its excipient constituents. Potential for dilution is defined as the amount of an active ingredient that can be compressed into tablets with the given directly compressible excipient. Ideally, a directly compressible excipient should have a high dilution potential, thus resulting in the final dosage form having the smallest possible weight. Compressibility of the active pharmaceutical ingredient influences the dilution potential. Compressible excipients should be capable of being reworked and without any loss of flow or compressibility. On recompression, the excipient must demonstrate good tabletability. It must remain chemically and physically unchanged[19].

(IV) FILL WEIGHT VARIATION:
Compared to simple mixtures or parent materials, co-processed excipients show fewer fill weight variation problems. The primary reason this phenomenon occurs is because one particle is "impregnated" into the matrix of another, resulting in reduced rough particle surfaces and better flow properties. Predictable variance is more pronounced with high-speed compression machines.[32].

APPLICATIONS OF CO-PROCESING:
- These multipurpose excipients have drastically reduced the number of incorporating excipients in the tablet, allowing for better compressibility of various poorly compressible drugs.
- Co-processing is intriguing because the products are physically modified in a unique way while the chemical structure remains unchanged.
- Using co-processing, we can achieve functionality synergy.
- Co-processed excipients have the ability to control the drug's solubility and stability.

LIMITATION OF CO-PROCESSED EXCIPIENT:
A major drawback of co-processed excipient blend is that the proportion of the excipients in a blend is fixed, and designing a new formulation may not result in a favorable excipient/dose per tablet ratio. Co-processed adjuvant lacks official recognition in Pharmacopoeia. As a result, the pharmaceutical industry will not accept a combination filler binder until it demonstrates a substantial advantage over inclusion complex of the excipients. though the spray-crystallized dextrose-maltose (Emdex) and compressible sugar are official in USP/NF[4].

SPRAY DRYING TECHNOLOGY FOR DEVELOPMENT OF CO-PROCESSED EXCIPENTS:
Continuous spray drying is the continuous transformation of feed from a fluid state into a dried form of powder by spraying the feed into a hot drying medium. If the feed is solution, emulsion, gel, or paste, then it can be pumped and atomized. This process involves generating a concentrated amount of hot air to produce evaporation and drying of liquid droplets. The air carries heat for evaporation and distributes the dried product to

the collector. Air is then exhausted.[10].

This drying method has a wide range of uses in the pharmaceutical industry. Formulation companies are adopting spray drying as the preferred tool for particle engineering, potent drug handling, and continuous production. The review highlights the equipment, advantages, and various applications of spray drying.[10].

Aerosolization of a solution of one or more solids accompanied by evaporation of solvent from the droplets is known as spray drying. This unique unit operation converts liquid to powder in a simple and robust continuous process. There may be solutions, emulsions, pastes, or melts in the liquid. To Spraying the atomized stream with a gas that is hotter than the liquid stream is called spray drying. Higher gas temperature causes evaporation of liquid from droplets, resulting in particles. One of the oldest technologies available for the conversion of a liquid, slurry, or low-viscosity paste to a dry solid in one unit operation is spray drying. Prior to the Second World War, this process had already gained notoriety. Advances in transportation technology allowed more products to be shipped than ever before.

→ Chart 1 gives an outline view of the spray drying process.
→ It show the steps involvs in spray drying process.

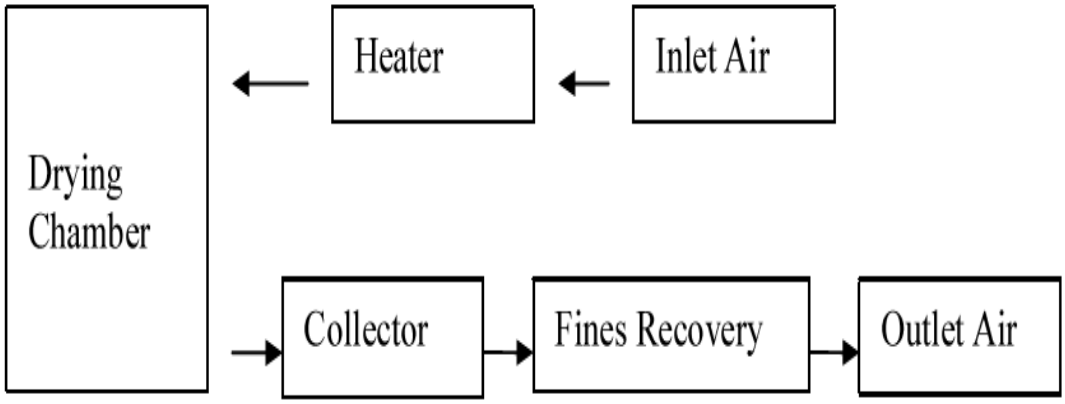

Chart: 1 Outline process steps in spray drying[10]

STAGES OF SPRAY DRYING TECHNOLOGY.

Atomization: Atomization is the process of making fine droplets from a liquid. To obtain the best liquid evaporation conditions, forming a spray with a high surface/mass ratio is critical. In order to atomize a liquid feedstock, a nozzle or rotary atomizer is used. Rotary atomizers use an atomizer wheel that rotates at high speed to atomize the feed.[14].

Three types of atomizers are commercially used namely

1. rotary atomizer,
2. pressure nozzle
3. Two-fluid nozzle.

Drying and particle formation: Process gas (air or nitrogen) is brought into contact with the atomized feed, and evaporation begins. Temperature, flow rate, and droplet size determine drying processes. A particle forms and begins to fall as the liquid rapidly evaporates from the droplet.[11].

Recovery: The exhaust gases powder is recovered using a cyclone or a bag filter. The entire process takes a few seconds at most. Also, the liquid is dried, collected, and delivered for further treatment without any intermediate manual handling. Using spray

drying for multiple products and industry capacities ranging from a few g/h to 80 tons/h is possible.[14].

PRINCIPLE:

There are three fundamental steps involved in spray drying.

1) Atomization of a liquid feed into fine droplets.
2) Mixing of these spray droplets with a heated gas stream, allowing the liquid to evaporate and leave dried solids.
3) Dried powder is separated from the gas stream and collected.

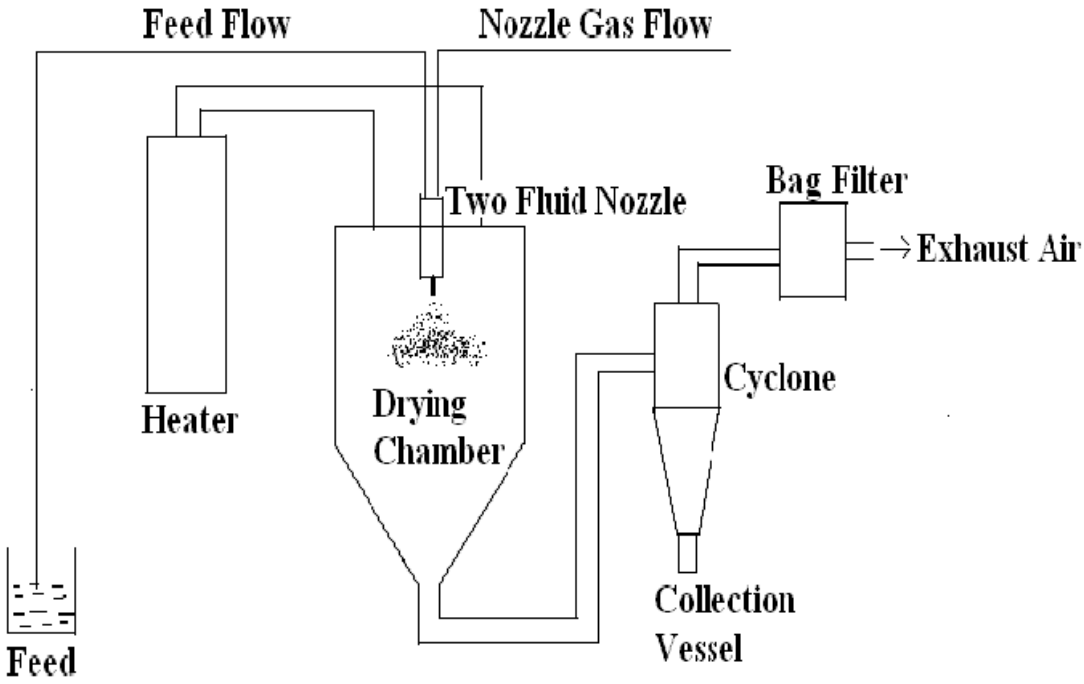

Figure: 2 the Spray Dryer [11]

Figure: 2 the Spray Dryer Lab spray dryer (EU 222 advanced) ElectrolabultimaCONCEPT OF SPRAY DRYING TECHNIQUE

There has been a lot of interest in particle production as of late. Spray technology has been applied to the manufacture of particle-based products ranging from pharmaceutical direct compression excipients and/or granulations to microencapsulated flavors.[2]

The two-primary spray-drying and spray-congealing techniques are being used. It is mainly about evaporation in spray drying, whereas in spray congealing, the change is from a liquid to a solid. However, energy flow is different. To spray dry, energy is applied to the droplet, forcing evaporation of the medium, resulting in both energy and mass transfer. Spray congealing melts the melted, forcing the solidified to form. For small-scale production, the most widely used process is spray drying. This product is uniquely suited for the continuous production of dry solids in powder, granulate, or agglomerate form from liquid feedstocks. As a result, spray drying is an ideal process where the final product must comply with precise quality standards for particle size distribution, residual moisture content, bulk density, and particle shape. [26]

Rotary (wheel) or nozzle atomizers produce the sprays. When moisture is lost from the droplets, the particles dry out. The drying chamber releases powder continuously. Settings are chosen based on the drying characteristics of the product and powder specification.

1.2.5 APPLICATIONS OF SPRAY DRYING TECHNOLOGY:

1. Particle size and distribution have improved, as well as appearance and texture.
2. Additionally, spray drying can improve flow property, compressibility, bulk density, dispersibility, and solubility of various drug and pharmaceutical excipients.
3. It has many non-pharmaceutical and pharmaceutical applications.
4. It is used for tableting constituents, vaccines, vitamins, blood products, enzymes, hormones, algae, yeast extracts.
5. When drying specific products, spray drying plants are exactly what is needed.

APPLICATION IN PRIMARY PHARMACEUTICALS &EXCIPIENTS:

Most active pharmaceutical ingredients are produced by extraction or chemical synthesis. Most of the time, the material is crystallized mechanically. The procedure typically substitutes spray drying. which controls the residual moisture content of the powder and creates materials with a tailored particle size distribution, morphology, and nature with unique properties.

Some excipients, such as lactose, can also be dried using a spray drying process. It also has better flowability.[3]

IMPROVE BIOAVAILABILITY:

Crystalline forms of modern therapeutic compounds often have low aqueous solubility and low dissolution rates. It reduces the bioavailability of the API, sometimes causing it to fail to have a therapeutic effect. With spray drying, you can mix APIs with polymers in amorphous, stable solid dispersions, increasing dissolution rates.[21] This API can only be crystallized when its drying rate is unbeatable. This way of enhancing the dissolution rate can open the door for new treatments that currently sit on the shelf due to low bioavailability.

ENCAPSULATION OF DRUG IN VARIOUS DOSAGE FORMS:

For efficient encapsulation, the drug is dissolved or suspended in a suitable (either aqueous or non-aqueous) solvent containing polymer materials. After drying, the solution or suspension is atomized and microparticles are formed. Encapsulation has many commercial and medical advantages for drug developers. It can be used to provide prolonged antibiotic dosing. Encapsulation is also an effective way to treat chronic illnesses, e.g., cancer or AIDS, and reduces side effects. This practice is applied to mask the taste and the protection of the API. Using spray drying and spray congealing, you can create particles that create controlled release patterns and other properties.[10].

ADVANTAGES OF SPRAY DRYING:

- → Able to operate in applications that range from aseptic pharmaceutical processing to ceramic powder production.
- → Can be designed to virtually any capacity required. Feed rates range from a few pounds per hour to over 100 tons per hour.
- → Can be designed to virtually any capacity required. Feed rates range from a few pounds per hour to over 100 tons per hour.
- → Operation is continuous and adaptable to full automatic control.
- → A great variety of spray dryer designs are available to meet various product specifications.
- → As long as they are can be pumped, the feedstock can be abrasive, corrosive, flammable, explosive or toxic.

DISADVANTAGES OF SPRAY DRYING:

- → It is not typically well suited for producing granules with mean particle size >200 mm.
- → It also has poor thermal efficiency at lower inlet temperatures and the exhaust air stream contains heat, which often requires sophisticated heat exchange equipment for removal.
- → Skill is require to operate the spray dryer
- → Proper care must be taken during the handling of spray drying.
- → Proper selection of solvent is require during the spray drying.

EVALUATION PARAMETERS:

EVALUATION OF CO-PROCESSED EXCIPIENTS:

LOOSEBULKDENSITY:

Weigh accurately 5 gm of powder blend, and transferred in 100 ml graduated cylinder.Carefully levelthepowderblendwithoutcompacting,andreadtheunsettled apparentvolume(V_0).Calculatetheapparentbulkdensity ingm/mlbythefollowing formula[9]

Bulk Density = Mass / apparentvolume

TAPPEDBULKDENSITY:

5 gm powder blend, accurately weighed and transferred into a 100 ml graduated cylinder Then, using a mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute, mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight. Initially, tap the cylinder 500 times and measure the tapped volume (V1) to the nearest graduated units; then, tap the cylinder another 750 times and measure the tapped volume (V2) to the nearest graduated units. If the difference between the two volumes is less than 2%, the volume is considered final (V2). Using the formula below, calculate the tapped bulk density in gm/ml.[9]

Tapped Density = Mass / tapped volume

CARR'S INDEX:

The bulk density was calculated by dividing the sample's weight by its volume. After tapping a measuring cylinder 500 times from a height of 2 inch, the quotient of the sample's weight to the volume was calculated. The Carr's index (percentage compressibility) was calculated by multiplying the difference between tapped and bulk density by the tapped density.[21]

$$\text{Carr}\,(\%) = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

PARTICLE SIZE DISTRIBUTION:

A statistical method, such as the frequency curve method, can be used to calculate the particle size distribution. [22] A frequency curve is obtained when the number, or weight, of particles falling within a certain size range is plotted against the size range or mean particle size.[25]

HAUSNER RATIO:

Hausner ratio is the ratio of bulk density to the tapped density.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

ANGLE OF REPOSE:

The angle of repose is a straightforward method for estimating a powder's flow properties.[4] Allowing a powder to flow through a funnel and fall freely onto a surface is a simple way to determine it. The resulting cone's height and diameter are measured, and the angle of repose is calculated using this equation.[28]

$$\tan\theta = \frac{h}{r}$$

Where,
'h' is the height of the powder cone
'r' is the radius of the powder cone.

Table : 3 Standard limit for Angle of Repose

Angle of Repose	Type of Flow
<20	Excellent
20-30	Good
30-34	Passable
>35	Very poor

Table: 4 Effect ofCarr's index andhausner'sratioon flowproperty

Carr's Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

PACKABILITY BY THE KAWAKITA EQUATION:

Packability was evaluated by tapping the spray-dried powder of the optimized batch in a measuring cylinder. The data was analyzed using the Kawakita equation[9]

$$\frac{n}{c} = \frac{1}{ab} + \frac{n}{a}$$

Where,

$$\mathbf{a} = \frac{V0 - Vinf}{V0} \qquad \mathbf{b} = \frac{V0 - Vn}{V0}$$

- → In which**a** and **b** are constants.
- → **" n "** is the tap number.
- → **V0, Vn**, and Vinfare thepowder bed volumes at initial, after n^{th} tapping (5, 10, 15, 20, 25, 50, 75, 100, 200, 300 & 400) and at equilibrium state (500 Th tap), respectively[21].

The SEM, DSC study is also carried out on the spray dried powders[23].

Compatibility study:
The FTIR Spectra or DSC thermogram of pure drug and the FTIR Spectra or DSC thermogram of the Physical Mixture of drug and excipients will be compared to determine drug-excipient compatibility. [27]

CONCLUSION:

It is possible to improve the compressibility and flowability of poor compressible drugs by using multifunctional co-processed spray dried excipients. Co-processed excipients are widely accepted in the Pharma industry due to the number of benefits they offer. Prepared to compact multiple functions of multifunctional excipients to save time and money for all pharmaceutical industries. This spray drying technology is one of the most exciting pharmaceutical development technologies currently. The product goes through an ideal manufacturing process where the end result matches defined quality standards in terms of particle size distribution, residual moisture content, solvent content, density, and morphology. Spray drying has one major advantage that it makes the technology extremely versatile.

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