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A REVIEW ON FUNCTIONALITY ASSESSMENT OF MULTIFUNCTIONAL EXCIPIENTS

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ABSTRACT: Multifunctional excipients are class of excipients that includes pre-processed and co-processed excipients that provide added functionalities to the formulation. Functionality is a desirable property of the material that aids manufacturing and improves the quality and performance of the material. This review article reveals with the functionality evaluation of excipients that include surrogate functionality and explicit functionality of excipient. The surrogate functionality gives information that predicts whether or not a particular excipient is likely to have the requisite functionality to produce a product that will meet finished product specifications in all respects. The explicit functionality means the ability of excipient to develop an appropriate formulation of a drug and a useful manufacturing process to create a tablet. Compactibility of excipient is a capability of the material to form coherent agglomerates after compression, has been analyzed by compact density, tensile strength, solid fraction, bonding index, *etc*. The compatibility mainly depends upon the material property like plastic and elastic.

INTRODUCTION: As pharmaceutical dosage form are formulated with active substance and excipients. The active substance has pharmacological action and excipients are additive which added to the formulation by means of a variable function. Accordingly International Pharmaceutical Excipient Council; Excipient is defined as "Any substance other than active drug or pro-drug that is included in the manufacturing process or is contained in finished pharmaceutical dosage form".

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Traditionally or as per above definition it means excipient is an inert and cheap vehicle used in dosage form, however excipient has its own function and improves the property of active pharmaceutical ingredient. Then the definition is modified in the National Formulary Admission Policy is "Excipients are any component other than the active substance(s) intentionally added to the formulation of a dosage form." To interpret the adverb 'intentionally' in this definition, we must consider the main administration routes of a medicinal product and the complexity of the roles the excipient must play in their particular formulations.

Excipients Functions: Excipients are employed to carry out different functions that may be grouped into three categories according to whether they influence stability, release, and absorption of the

active principle or manufacturability during the manufacturing process phase.

TABLE 1: EXCIPIENTS FUNCTION

Stability	Drug absorption
Antioxidants	Disintegrants
Chelating agents	Plasticizers
Preservatives	Drug release modifiers
Stabilizers	Penetration enhancers
Buffers	Wetting agents, solvents
pH modifiers	Film Formers
	Bioadhesives
	Encapsulating agents
	Biodegradable polymers
Manufacturability	
Dosage form necessities	Specific technique Properties
Ointment bases	Emulsifying, suspending ag.
Semisolid excipients	Gelling agents, Lubrication
Diluents.	enhancers, Flow, compaction enhancers, Propellants, bulking agents

Tablet is manufactured by wet granulation, dry granulation and direct compression whereas in wet granulation and dry granulation technique various processing steps and manufacturing challenges are involved leading to high cost & time of tablet production [1]. In contrast, the manufacturing of the tablet by direct compression has potential advantages and economic (low labour cost, reduced processing time & low energy consumption). To make tablet by direct compression that required compressible material. As the active substance are not able to compress into a compact (tablet) without the addition of directly compressible excipients.

These excipients are not only directly compressible themselves, but can also be mixed with a large proportion of drug substance with no significant deterioration in tablet quality. In addition to excipients possessing good flow and compression properties, they must also possess the following attributes: 1) particle size distributions that are similar for most active drug substances, thus avoiding segregation during processing. 2) A high bulk density. 3) Batch-to-batch quality must be reproducible [2].

The directly compressible Excipients show dual role in formulation like diluents, it mainly used in relation bulking function but also promotes the binding of the constituent particle of the formulation, termed as filler-binder.

The development of new excipient is market-driven [3] because now new drug moiety is developed has critical physicochemical property that challenges to developed suitable dosage form. The functionality of excipients was improved by physical and chemical modification but mostly physical modification is preferred because the chemical modification is tedious process, costly and time-consuming method because any new chemical excipient has to undergo various stages of regulatory approval, patenting and copyright issues and limited market exclusivity period. Multifunctional excipients are class of excipients that includes preprocessed and co-processed excipients that provide added functionalities to the formulation. *e.g.* Cellactose [4], Coprocessed MCC-Eudrajit [5], Star Ac [6], Ran-Explo-C, Ran-Explo-S [7], Coprocessed Polyox® WSR 301 & Methocel® K4M [8], LubriTose SD [9], EASY Tab [10].

High functionality excipients are inactive ingredients that meet four unique criteria. Firstly, they are multifunctional means combine two or more functions through a single ingredient. Secondly, HFE has high inherent functional performance allowing for increased batch sizes and higher drug-loading, even at low usage levels. Thirdly, HFE require no complex processing, making them ideal for direct compression processes. Lastly, HFE imparts their high inherent performance characteristics to the overall formulation. This last criterion is critical and separates HFE from other multi-functional excipients or conventional specialty excipients.

Coprocessing: The growing popularity of the direct compression process and a demand for an ideal filler-binder, the manufacturer can substitute two or more excipient. High-speed tableting machinery requires excipients having good compressibility and low weight variation even at short dwell time.

The lack of excipients, the pharmaceutical industry cannot attend to the need of specific patient (diabetes, hypertension, and lactose & sorbitol sensitivity) and ability to modulate the solubility, permeability or stability of drug moiety. To overcome all above issues & fulfil market demand, the coprocessing of excipient is the ideal way for the development of new excipient.

Coprocessing is combining two or more excipient established excipients by an appropriate process. Coprocessing could lead to the formation of excipients with superior properties compared with a physical mixture of their component. Coprocessed excipients developed by four steps, firstly selection of the group of excipients to combined, second their targeted proportion, third is suitable preparation method to get an optimized product with desired physicochemical parameter and the last one is minimizing avoidance with batch to batch variation.

In co-processed excipient the ratio of excipients mixture is fixed and in case of developing a new formulation, which may not be favourable for the dose and characteristics of the API is a major limitation [11]. A. K. Olowosulu *et al*., had developed directly compressible excipient by coprocessing particles of maize starch and acacia gum. StarAc was developed by co-drying their well-dispersed aqueous mixture and they found that fully pregelatinized form shows superior flowability than partially pregelatinized form. But when Star Ac are compressed into a tablet and evaluated that shows partially pregelatinized form had good crushing strength, friability profile & acceptable tablet disintegration time and fully pregelatinized form did not produce a tablet with acceptable crushing strength & friability profile [6]. Nidhi Garg *et al*., had applied Box-Behnken design to formulate co-processed excipient of dibasic calcium phosphate anhydrous, PEG 4000 & crospovidone by melt granulation method. Coprocessed excipient then compressed into a tablet using aceclofenac as a model drug and that exhibit better hardness, disintegration time & *in-vitro* drug release compared to wet granulation method [12].

Mukesh C. Goel *et al*., developed novel multifunctional co-processed adjuvant consisting of three known diluents that show different consolidation mechanisms. Microcrystalline cellulose, colloidal silicon dioxide, lactose monohydrate & dibasic calcium phosphate dihydrate co-processed by wet granulation method and cross carmellose sodium was used intra-granularly. The desired product characters can be obtained by varying the quantity of MCC (a ductile material that undergoes plastic deformation), lactose (brittle material with low fragmentation propensity) and dibasic calcium phosphate dehydrate (brittle material with high fragmentation propensity) [13]. Alvaro Goyanes *et al*., had investigated extrusion spheronization performance of some mixture of coprocessed MCC & Eudrajit E (as excipient) and sorbitol (as soluble filler-disintegrant) on Hydrochlorothiazide as a model drug. The dissolution rate of a drug from pellet is depending on the content of Eudrajit E and proportion of sorbitol incorporated [5].

The tapioca starch and mannitol were co-processed by co-grinding & co-fusion method. Coprocessed excipients evaluated for precompression and post-compression parameter and it revealed that co-grinding is less effective than the co-fusion method. The novel co-processed tapioca starch and mannitol enhance the flow, packing and compaction properties [14].

Method of Preparation: Melt granulation [10, 12, 15], co-precipitation [16], solvent evaporation method [6, 17, 18], freeze-thaw technique, kneading method [19], melt fusion method [14], Spray-drying [7, 9, 20, 21], wet granulation [22-23], spheronization [5], co-milling [8, 24], and co-crystallization can be used for co-processing. Melt granulation method include first melting of meltable polymer and add blend in it mixed properly followed by sieving of hot mass and then cooling. Co-precipitation Solvent evaporation involves the preparation of solution or dispersion of powder blend in a suitable solvent, evaporate solvent and dry the dispersion and then grinding of dried mass followed by sieving. In Melt fusion method, the blend is melted and cooled then grinding followed by sieving. Spray-drying is a process in which an aqueous or organic dispersion of the materials is sprayed through a nozzle at high pressure, and the droplets formed are rapidly dried and collected as a powder. Wet granulation involves the addition of an aqueous dispersion of a binder to a previously mixed powder blend followed by wet sieving and drying. In the spheronization process, first, the wet mixture of excipient(s) is extruded to produce homogeneous spaghetti-like rods. This extrudate is then converted to beads by using a spheronizer. Co-milling is used to disperse, homogenize and reduce the particle size of excipient mixtures in an aqueous media. In cocrystallization, the two materials are dissolved by heating, followed by cooling at different rates [11].

TABLE 2: EXAMPLE OF COPROCESSING METHODS AND OUTCOME

Method of co-processing	Excipients used	Result
Solvent evaporation	Maize starch and Acacia gum	Better flow property, Improved crushing strength, friability, and disintegration time
Solvent evaporation	Pregelatinized starch, PEG 1500, Aerosil	Directly compressible excipient shows good flow property, tablet strength, friability and disintegration time.
Solvent evaporation	Gelatinised maize starch, Sodium CMC, Microcrystalline cellulose	Excellent flow property with high moisture content and good swelling index, good tablet property except for friability.
Solvent evaporation	1. MCC and Kyron 2. Sucrose and MCC	1. Show immediate release 2. Shows sustained release
Extrusion spheronization	MCC and Eudrajit	High mechanical strength, very good flow property, high dissolution efficiency
Spray drying	1. MCC, Colloidal silicon dioxide and Crospovidone 2. MCC, Colloidal silicon dioxide and SSG	Excellent flow property, high compressibility, low disintegration time and better binding property
Spray drying	Monohydrate lactose and distilled glyceryl monostearate	Directly compressible self-lubricating excipient
Spray drying	Lactose and MCC	Directly compressible excipient for poorly compressible drug
Spray drying	StarCap 1500, Lactose and MCC	Excellent flow character, improve compressibility and good dilution potential (up to 40%)
Roller compaction	Polyethylene oxide and HPMC K4M	Good release retarding property improved flowability and compressibility
Roller compaction/dry granulation	Magnesium carbonate and powdered cellulose	Improved tableting property
Melt granulation	MCC, Crospovidone and PEG 4000	Better flow, satisfactory tableting property, and rapid drug release
Melt granulation	PVP K-30, PEG 4000, Lactose, and MCC	Good flowability, higher disintegration time, exhibited reasonable dilution potential (30% with Acetaminophen & 50% with Metformin HCl)
Melt granulation	Dibasic calcium phosphate, PEG 4000 & Crospovidone	Better hardness, Disintegration Time & in-vitro drug release of Aceclofenac tablet compared to a conventional tablet
Wet granulation	Lactose monohydrate, MCC & Cornstarch	Excellent flow property, directly compressible excipient and enhanced compressibility
Wet granulation	MCC, Colloidal silicon dioxide, lactose monohydrate, dibasic calcium phosphate dihydrate	Blending of MCC and silicon dioxide prior to wet granulation resulted into stronger tablets, co-processed excipient has a low disintegration time
Co-grinding and co-fusion	Tapioca starch & mannitol	Co-grinding was less effective than co-fusion, enhance flow, packing and compaction property
Freeze-thaw	MCC and maize starch composite	Enhance disintegration efficiency and better dilution potential
Freeze-thaw	Mannitol and cellulose	Improved flowability, compactibility and dissolution rate

Functionality Evaluation of Multifunctional Excipient: Excipients are materials which have very distinct properties that impart different types of functionality in various products, depending upon the type of application. Functionality means a desirable property of a material that aids manufacturing and improves the manufacture, quality or performance of the drug product. The physical, chemical and technological properties of excipients affect the functionality of excipients. It can be estimated with the excipients as powders, as a dosage form of the pure excipients and as a formulation of a given drug containing the excipients. In above three levels, first two communicate to a surrogate functionality that belongs to a preformulation and third level communicate to the explicit functionality of the excipient. The surrogate functionality gives information that predicts whether or not a particular excipient is likely to have the requisite functionality to produce a product that will meet finished product specifications in all respects. The explicit functionality means the ability of excipient to develop an appropriate formulation of a drug and a useful manufacturing process to create a tablet.

Many methods of powder characterization have limited value, especially with respect to process

development because they denote only one aspect of powder behaviour. They do not replicate the conditions of powders observe in processing, produce data that does not correlate directly with process performance or because they are poorly defined so results are not repeatable or reproducible. The functionality of tableting excipients evaluated by different testing methods such as bulk density, tapped density, Carr index, particle size distribution, surface morphology and thermal properties that indicate physical property.

Crushing strength, friability and disintegration time of tablets indicate technological properties such as tableting properties. Also, excipients have been evaluated using also the density, powder flow rate and the tableting and the drug dissolution properties with a model drug. This was made considering that the full characterization of excipients is needed because a different manufacturing process for the same excipients may produce differences in the pharmaceutical products. More recently functionality of celluloses as tablet excipients has been evaluated using technological characteristics or performance tests such as compactibility curves, ejection pressure curves, and the disintegration properties of pure excipients as compressed tablets.

The usefulness of functionality tests include: a) assessment of materials properties with quality control purposes, b) prediction of a material performance in a formulation, from surrogate functionality tests and functionality of materials in other formulations and c) comparison of functionality of excipients from different source and different physical or chemical characteristics [25].

Moisture Sorption Capacity: One gram sample was evenly distributed over the surface of the Petri dish. The sample then exposed to room temperature and 75% relative humidity. The weight gained by the sample over a period of 5 days was recorded and the amount of water absorbed was calculated from the weight difference.

Hydration Capacity: One gram of sample was placed in a test tube and 10 mL of distilled water added and then stoppered. The content was mixed on a vortex mixer for 2 min. The mixture was allowed to stand for 10 min and immediately centrifuged at 1000 rev/min for 10 min. The supernatant was carefully decanted and the sediment was weighed. The hydration capacity was calculated as the ratio of the weight of water uptake to the weight of dry sample [26].

Micromeritics: The term micromeritics was proposed by J. M. Dallavalle to refer to the science of small particle. Dallavalle found that the behaviour and characteristics of small particles brought together broadly scattered information on particle measurements, size distributions, packing arrangements, and the general theory of the physical properties of finely divided substances. In the pharmaceutical industry, micromeritics has a major area of study because it persuades a large number of parameters in research, development, and manufacturing. Micromeritics investigation has involved surface area, particle size and their distribution, the nature of solid surfaces, and particle shapes and it deals specifically with surface area, porosimetry, and density measurements [27]. It has an impact on pharmaceutical processing and performance, hence significance must be given to the impact of these parameters on the robustness of processing. This is valid for API, excipients, and formulations (blends and granulations).

When working with the API, a few large or small particles in a batch can alter the final tablet's content uniformity (potency, segregation), dissolution profile, and/or processing (*e.g.*, flow, compression pressure profile, and granulating properties if it is for dry granulation). API particle size and distribution data information can also help decide whether a direct compression formulation or dry granulation approach is most suitable.

Particle size and size distribution are also important, from a dosage form performance point of view, in that they are critical parameters in assuring that the desired dissolution rate is achieved for oral dosage forms. Several theoretical models for dissolution of powders have been developed. Particle characterization of in-process or final formulation is also critical [28].

Bulk Density: It is the mass of powder divided by bulk volume (without tapping) it is an indicator of powder ability to undergo compression. Low bulk density implies a high tendency of densification.

It is attributable to high particulate irregularities and a highly porous structure. As microcrystalline cellulose has lowest bulk density showing its highest tendency of undergoing compression. Chitosan had the highest true density. The true density of a powder is a property that excludes every void space and it shows the extent to which powder can be compressed.

Therefore, a blend of microcrystalline cellulose and chitosan is superior to the individual constituent in terms of compressibility [26].

Tapped Density: It is mass of powder divided by the volume occupied by the powder after it was tapped for the specific time period. Regularly shaped particle like sphere shows higher tapped density than irregularly shaped particle such as needles. The packing properties of a powder can affect operations critical to solid dosage manufacturing, mainly bulk storage, feeding, and compaction.

True Density: It is an essential parameter for process development and solid dosage manufacturing [28]. The true density is mass of solid divided by solid volume excluding void spaces; they are not a part of molecular packing arrangement. The true density is determined by the following method:

1. Gas Pycnometry or Displacement: It is a non-destructive, reproducible, reliable and easy method for determination of true density. The small amount of sample (1-8 g) is required for a study. True density can be calculated by the weight of the sample divided by powder volume. The volume of the particle is determined by gas adsorption technique like BET technique mainly Helium and Nitrogen gas.

2. Liquid Displacement: The true density (Dt) of a sample was determined using the specific gravity bottle method. A clean, dry 25ml specific gravity bottle was filled with xylene and its weight was determined. Some amount of the xylene was poured out and 1 g sample was placed inside. More xylene was added until the bottle was filled and was wiped dry of excess fluid. Its weight was again determined. The true density (Dt) was calculated using the following equation:

$$D_t = \frac{w}{a + w - b} \times SG \quad \text{.....Eq. 1}$$

Where w is the weight of powder, a is a weight of bottle + xylene; b is a weight of bottle + xylene + powder, and SG is specific gravity of xylene [26].

3. Flotation in a liquid

Flow Property: The flowability of powders is intuitively defined as the ease of flow and is related to the change in position of the particles with respect to each other within the assembly forming a powder. The dynamic behaviour of the powder appears to be mainly determined by inter-particle forces and the packing structure. Inter-particle forces and particle packing would be displayed in the compressibility index. Higher compressibility index values are corresponding with higher inter-particle forces and/or denser packing. The compressibility index is inversely proportional to the flowability of powder, so that the inverse of this ratio may be considered as indicative of powders flowability [29]. Carr's compressibility index and Hausner's ratio are used for predicting powder flow characteristics. They are indirect measures of bulk density, size and shape, moisture content, and cohesiveness of materials as all these parameters can influence compressibility [26]. The flow of powder is directly correlated to particle shape and size. Large, spherical particles flow better than smaller, irregularly shaped materials.

Compressibility Index: The compressibility index (CI) is a measure of the tendency of powder to consolidate. It is mainly the inter-particulate interactions. As the free-flowing powder has lower inter-particulate interactions; the bulk and tapped densities will closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions; bridging between particles often results in lower bulk density and a greater difference between the bulk and tapped densities [28]. The compressibility index is calculated by:

$$CI = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \text{.....Eq. 2}$$

Hausner Ratio: Hausner was related to inter-particle friction and as such could be used to predict powder flow properties. The coarse sphere has low inter-particle friction shows approximately 1.2 h, whereas more cohesive, less free-flowing powders such as flakes have Hausner ratios greater than 1.6 [30].

$$HR = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \text{..... Eq.3}$$

TABLE 3: SCALE OF FLOWABILITY FOR COMPRESSIBILITY INDEX AND HAUSNER RATIO

Flow character	Compressibility index	Hausner ratio
Excellent	≤10	1.00 - 1.11
Good	10 - 15	1.12 – 1.18
Fair	16-20	1.19-1.25
Passable	21-25	1.26-1.34
Poor	26-31	1.35-1.45
Very poor	32-37	1.46-1.59
Very, very poor	>38	>1.6

Angle of Repose: Angle of repose is a characteristic related to inter-particulate friction or resistance to movement between particles. According to the USP, it is the constant, three-dimensional angle (relative to the horizontal base) assumed by a cone-like pile of material formed by any of several different methods. Due to the high dependence of the angle of repose measurements on testing conditions, the angle of repose is not a very robust means of quantifying powder flow. The angle of repose and flow-rate through an orifice method require 5-70 grams of material and therefore are not aligned with material-sparing strategies [28].

$$\theta = \tan^{-1} h / r \quad \text{.....Eq. 4}$$

Where θ is the angle of repose, his height of pile, r is the radius of a pile

Powder Flow: The tapped density apparatus used to assess the powder flow. Tapper was adjusted at a rate of 74 taps per minute and to elevate the graduated cylinder up to a height of 15 mm. This device uses a 100-ml graduated cylinder joined to a glass funnel with an orifice of diameter 3, 6, 8, 10, and 14 mm that can be closed. Once the sample is weighed and placed in the closed funnel, the device is started open the orifice of a funnel at the same time. The time required to empty from the funnel 30 g of the powder, through the funnel orifice, is used to calculate the flow rate (gm/sec) of the powder flow. The assay is repeated 5 times for each one of the selected funnel (opening diameter 3, 6, 8, 10, and 14 mm), sieving the powder through a mesh number 20# after each measurement. The average of 5 repetitions is taken as the flow rate [25, 29].

Variation in flow rate may observe on its repeatability, because of the removal of air in the powders and formation of agglomerates. This variation in assessment of flow rate was avoided by shifting powder through a sieve and aerating the powder after each test.

The powders flow rate is linked to the opening size and not only to the properties of the flowing material while the compressibility index and the Hausner ratio are more linked to powder properties. In general, the compressibility index and Hausner ratio are related to powders properties and tell us if the flow properties of powders are better or worse. On the other hand, the flow rate gives results depending not only on the properties of the material but also on the interaction of the powder with the orifice. The flow rate is more useful to predict the performance of materials using processing equipment with orifices or means of access that restrict the powders flow [29].

Effect of Lubricant on the Flowability: Pharmaceutical powders are composed of various particle sizes. In a mixture of these particles, the fine tends to occupy the empty spaces left by the large ones, increasing their packing and obstructing their flowability. In spite of this, when the amount of these fine particles is small, they might function as rolling bearings for the large particles, facilitating its slipping and flowability. This factor would also contribute to the mechanism of action of magnesium stearate, to increase the flowability of powders. Some of the excipients like lactose and spray dried granules, Di-Pac, Lactose-316 Fast Flo and binary mixtures of Avicel PH102 and lactose 316 (1:1) shows above effect.

The addition of 1% of magnesium stearate improved the flow properties of these materials. However, larger amounts of lubricant do not always increase the improvement of flowability of powders. Lubricant proportions between 2 and 5% may decrease the flowability of the powder. There appears to be an optimum of the lubricant

proportion to improve the flowability of each powder. The addition of higher amounts of lubricant may produce no further effect or deteriorate the optimal flow properties of powders [29].

Porosity: Porosity is a function of the voids in a powder column and in general all pore space is considered, including both inter & intra-particulate voids.

$$\text{Porosity} = 1 - \rho_{A} / \rho_{T} \quad \text{.....Eq. 5}$$

Where ρ_A is the apparent density, ρ_T is the true density

The volume of powder column and its corresponding porosity can be measured either during compression or after ejection of the compact from the die. Instrumentation of a tablet press enables continuous monitoring of the powder column height during the volume reduction process. This method is referred to as "in die" or "at pressure". In the "ejected tablet" or "at zero pressure" method the dimensions of a compact are measured [31].

Compactibility: A pharmaceutical tablet has been described in physical terms as a large cluster of particles, held together by bonds active in interparticle surfaces. The compactibility, defined as the capability of a material to form coherent agglomerates after compression, has been analyzed by studying the evolution of tablet tensile strength with increasing compaction pressure. The mechanical strength of a tablet provides a measure of the bonding potential of the material concerned and this information can be used as a functionality parameter in the selection of excipients. Tablets must have sufficient mechanical strength to resist crumbling or breaking when being handled or processed, especially during packaging and transporting.

In the case of lactose compatibility, the tensile strength has been observed to increase with an increasing compaction pressure up to a pressure of about 400 MPa. Thereafter, with increasing compaction pressure, the tablet tensile strength leveled out. The overall compatibility profile tended to be sigmoidal in shape. Compactibility profiles with sigmoidal shape have been described with an equation based on the Weibull distribution. As per Diaz and Villafuerte, this model has been used to describe the compatibility of celluloses as indicative of their functionality as tablet excipients.

$$\ln(-\ln(1-D/dmax)) = n * \ln Pc + I \quad \text{.....Eq. 6}$$

Where: *D* denotes the tablet's hardness or crushing strength, *Dmax* the maximal tablet hardness obtained, *Pc* the compaction pressure, *n* the slope of the curve, and *I* the intercept of the curve [25].

Compact Characterization: The importance and impact of physical & chemical properties of materials on the processing of powder were proved by various investigations, for example, the flow property mainly depends on the particle size and shape. The compact mechanical properties have great importance for dosage form development & manufacturing particularly for tablet formulation. Mechanical properties are the material properties under an applied load like elasticity, plasticity, viscoelasticity, bonding, and brittleness.

The surface energy and elastic deformation properties influence individual particle true areas of contact. Plastic deformation likely occurs to some extent in powder beds depending on the applied load, and almost certainly it occurs during the compaction of powders into tablets. Certainly, at asperities, local regions of high pressure can lead to localized plastic yielding.

Electrostatic forces can also play a role in powder flow, depending on the insulating characteristics of the material and environmental conditions. Particle size, shape, and size distribution have also been shown to influence flow and compaction. A number of environmental factors such as humidity, adsorbed impurities (air, water, *etc*.), consolidation load and time, direction and rate of shear and storage container properties are also important.

The mechanical properties of material play an important role in powder flow and compaction. These properties are critical properties that influence the true areas of contact between particles. Therefore, it is essential to characterize the properties. Reliable mechanical property information can be useful in helping to choose a processing method such as granulation or direct compression, selecting excipients with properties

that will mask the poor properties of the drug or helping to document what went wrong, for example, when a tableting process is being scaled up or when a new bulk drug process is being tested. Since all of these can influence the quality of the final product, it is to the formulator's advantage to understand the importance of the mechanical properties of the active and inactive ingredients and to be able to quantify the properties.

Elastic Deformation: Generally, during the initial stages of deformation, a material is deformed elastically. A change in shape caused by the applied stress is completely reversible, and the specimen will return to its original shape on the release of the applied stress. During elastic deformation, the stress-strain relationship for a specimen is described by Hooke's law:

$$\sigma = E \times \epsilon \qquad \text{.....Eq. 7}$$

Where: E is referred to as Young's modulus of elasticity, σ is the applied stress, ϵ is the strain.

The region of elastic deformation of a specimen is shown graphically in **Fig. 1**. As long as the elastic limit is not exceeded only elastic deformation occurs. Elastic strain results from a change in the intermolecular spacing and at least for small deformations is reversible.

Plastic Deformation: Plastic deformation is the permanent change in the shape of a specimen due to applied stress. Plastic materials deform by plastic deformation. The onset of plastic deformation is seen as curvature in the stress-strain curve shown in **Fig. 1**. Plastic deformation is important because it "allows" pharmaceutical excipients and drugs to establish large true areas of contact during compaction that can remain on decompression and strong tablets can be prepared.

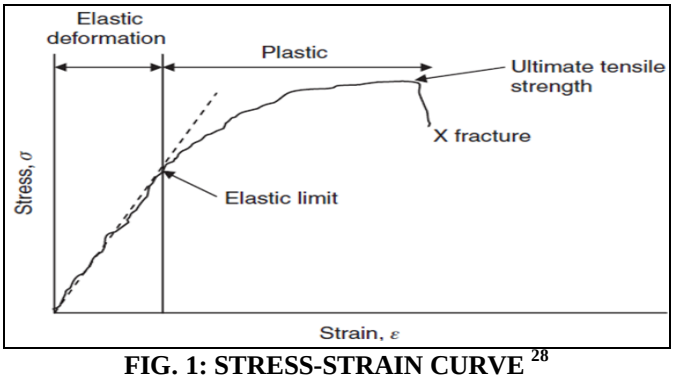

FIG. 1: STRESS-STRAIN CURVE [28]

Plastic deformation, unlike elastic deformation, is generally not accurately predicted from atomic or molecular properties. Rather, plastic deformation is often determined by the presence of crystal defects such as dislocations, grain boundaries, and slip planes within crystals. Slip planes may exist within crystals due to molecular packing arrangements that result in weak interplanar forces. Processes that influence these (*e.g.*, crystallization rate, solvent, temperature) can be expected to influence the plastic deformation properties of materials, and hence the processing properties. The plastic properties of a material are often determined by an indentation test. Both static and dynamic test methods are available, but all generally determine the pressure necessary to cause permanent and non-recoverable deformation.

Brittle and Ductile Fracture: Under compression brittle materials are consolidated predominantly by fragmentation and compaction is often less influenced by speed due to rapid fragmentation and prolonged exposure to the force has a limited effect on tablet properties. Fracture is the separation of a body into two or more parts. A brittle fracture occurs by the rapid propagation of a crack throughout the specimen. Conversely, a ductile fracture is characterized by extensive plastic deformation followed by fracture. Ductile failure is not typically seen with compacts of pharmaceutical materials. The characteristic snap of a tablet during hardness testing is indicative of a brittle fracture.

Viscoelastic Properties: Viscoelastic properties can be important; viscoelasticity reflects the time-dependent nature of stress-strain. A basic understanding of viscoelasticity can be gained by considering processes that occur at a molecular level when a material is under stress. Applied stress, even when in the elastic region, effectively moves atoms or molecules from their equilibrium energy state. With time, the rearrangement of atoms or molecules can occur.

The stress-strain relationship can, therefore, depend on the time frame over which the test is conducted. In compacting tablets, for example, it is frequently noted that higher compaction forces are required to make a tablet with a given strength when the compaction speed is rapid. All pharmaceutical materials are viscoelastic; the degree to which their

mechanical properties are influenced by rate depends on the material [28].

Compact Density: Select five tablets randomly from each batch and weighed individually. The diameter and thickness of the tablets were also determined using a micrometer screw gauge (Vernier calliper). The compact density (CD) was determined using the following equation:

$$CD = m / \pi r^2 h \quad \text{..... Eq. 8}$$

Where m is the mass of tablet, r is the radius, and h is the thickness.

Tensile Strength: The crushing strength (F) of the five selected tablets per batch was determined using Monsanto hardness tester. The tensile strength (TS) was determined using the value of crushing strength and the corresponding values of diameter and thickness.

$$TS = 2F / \pi dt \quad \text{.....Eq. 9}$$

Where F is the crushing strength, d is the diameter, and t is the thickness of tablets [26].

Solid Fraction (SF): Tye and co-workers showed that tablet solid fraction (SF) was the primary factor determining tablet strength for several pharmaceutical excipients (both brittle and ductile) over an extremely wide range of compaction speeds (dwell times from 10 m sec to 90 sec). The solid fraction (SF) of a compact can be calculated based on the true density (D_t) of the material, the tablet volume (V), and the tablet weight (Wt).

$$SF = Wt / Dt \times V \quad \text{.....Eq. 10}$$

The relationship between the solid fraction, also referred to as relative density, and porosity (ϵ) is:

$$\epsilon = 1 - SF \quad \text{.....Eq. 11}$$

Bonding index: The objective of bonding index is to assess the survival of strength during decompression. It is calculated by:

$$BI = TS / F \quad \text{.....Eq. 12}$$

Where, TS is the tensile strength of the compact at a given solid fraction (typically 0.85 or 0.9 as defined by the user) F is the permanent deformation pressure (*i.e.*, hardness) of a compact at the same solid fraction.

The bonding index (BI) is the ability of a material is to maintain a high fraction of the bond that was created during compression. A high bonding index indicates a larger portion of the strength remained intact after decompression, and low bonding index indicates that less of the strength remains. The bonding index reflects the tendency of material remains intact after compression. The material has good bonding indices make a strong tablet. A bonding index in excess of 0.01 (range 0.001 to 0.06) is typically desired.

Ejection Pressure: Apart from the compatibility properties of powders to be compacted as tablets, there are some other powders properties that are involved in the tablet manufacturing process. The friction between tablet and die wall are unimportant if they are a low but tableting problem like lamination, the abrasion on the tablet surfaces or the impossibility to eject the tablets occur when powder friction is high. In this way, the functionality of the excipients is related to a possible reduction of ejection pressure of tablets made of mixtures with a given drug or formula.

Pharmaceutical excipients that decrease friction at the interface between a tablet surface and the die wall during ejection that reduces wear on punches and dies prevent sticking to punch faces and improve the manufacturing efficiency of solid preparations. The force or pressure necessary to eject a tablet involves the distinctive peak force required to initiate ejection by breaking the die-wall tablet adhesion. The second stage involves the force required to push the tablet up the die wall, and the last force is required for the ejection of a tablet from the die.

Microcrystalline cellulose tablets exhibit such a low coefficient of friction that they may need no lubricant. Moisture can significantly reduce the force required to initiate ejection by the breaking of tablet/die-wall adhesions. The lubricity of a material can be defined as freedom from friction or the property which diminishes friction. In this sense, lubricity is the measure of the reduction in friction. The lack of lubricity observed by amoxicillin can only be overcome with elevated Alfacel proportions. The greater the ejection pressures of the tablets the worse the lubricity [25].

Friability: Friability test was used to determine tablet strength. Roche friability tester was used for testing friability. The present test subjected a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed 6 tablets was placed in Roche friability tester which was then operated for 100 revolutions *i.e.* 4 min. The tablets were then dusted and reweighed. Tablets lose less than 1.0% of their weight is generally considered acceptable. Percent friability (% F) was calculated as follows [32]:

% F = Initial weight – Final weight × 100 / Initial weight ..... Eq. 13

Disintegration Time: Disintegration time was performed by using USP tablet disintegration testing apparatus at 37 ± 2 °C as per USP guidelines [32].

***In-vitro* Dissolution Studies:** The *in-vitro* release rate of the drug from the tablets was determined using the USP type apparatus. The rotation speed and temperature were kept at 100 rpm & 37 ± 0.5 °C. The 900 mL 0.1N HCl (pH 1.2) was selected as dissolution media and sink condition maintained by 10 mL dissolution medium at a periodic time interval of 1 h. The samples were filtered through a Whatman filter paper and assayed by the suitable analytical test as per standard. Six tablets of each formulation were used in the dissolution test. The dissolution apparatus and dissolution medium are selected depending upon the type of dosage form. Variation in dissolution condition mainly varied according to an oral drug delivery system.

CONCLUSION: Traditionally, the excipient defined inert and cheap vehicle used in dosage form but excipient has its own function in the pharmaceutical dosage form and improved the property of active pharmaceutical ingredient. The functionality of excipient is improved in various ways; the coprocessing is an economical, simple and efficient approach to improve particle engineering of two or more excipients. The functionality of excipient is analyzed by a different method that determines the physical-chemical and technological properties of excipients, which deals with the surrogate and explicit functionality.

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