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Roller Compaction Design and Critical Parameters in Drug Formulation and Development: Review

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Abstract: Roller compaction is a dry granulation technology in which powder is densified between two counter rotating rolls by the application of mechanical pressure as powder passes through the rolls. Dry granulation process powders consist of the active pharmaceutical ingredient and excipients, e.g., diluents, disintegrants, and lubricants, are mixed in suitable blender. The powder mixtures are then roller compacted and size reduced to form granules. Roller compaction is usually prefer to overcome unfavorable physical properties of powders and APIs, such as poor flow, low bulk density, blend uniformity, segregation of powder blends by optimizing process parameter and selection of excipients. Roller compaction process has significant effect on particles size distribution, flowability, homogeneity, compressibility, compactability of active pharmaceutical ingredients and excipients and thus can affect consequently dissolution profile, disintegration time, hardness and other post compression parameter of tablet. Roller compaction process offers advantageous as compared with wet granulation process such as simple manufacturing procedure, easier scale up, high volume production output, and relatively low operational costs. Roller compaction process excludes liquid solvent or binder solution. This process is also energy efficient and suitable for processing pharmaceutical agents that are sensitive to moisture and heat. Good quality granules can be obtained by optimizing roller compaction process parameter such as compression force, roller speed, screw feeder speed, roll gap and milling.
Keywords: Roller compaction, Dry Granulation, process parameter, Tablet.

Introduction[1-6]:

Many components of solid dosages form including excipients and drug substances are passed through multiple processes of manufacturing and thus end with final product.The pharmaceutical industry uses granulation methods to enlarge and densify small powder particles into larger ones that improves powder flow without segregation so that the material can be processed effectively and efficiently into solid dosage forms. There are two pharmaceutical methods of granulation, wet Granulation and dry granulation.

Roller compaction is a unit operation in the dry granulation process, a pressure-induced agglomeration technique in which granules are prepared with acceptable flowability, compaction properties, compositional uniformity, and chemical stability especially for moisture and heat sensitive drug formulations. During the dry granulation process the dry powders of the active ingredient and excipients, e.g., dry binders, disintegrants, diluents and lubricants, are mixed in a blender. The powder mixtures are then roller compacted and size reduced to form granules. The resulting granules are blended with lubricant and either encapsulated or compressed into a tablet.During the roller compaction operation, API and all the excipients are uniformly mixed to form powder blends and are passed continuously through the gap between a pair of rotating compression rolls to form solid ribbons or sheets.Such ribbons or sheets arepassed through a mill or granulator equipped with screen of suitable mesh size to form dry granules. Roller compaction is usually composed of feed hopper, screw feeder or gravity feeder,two counter rotating rollers of equal diameter, flake crusher, and screens for milling process.

Dry granulation by roller compaction has various advantages such as simplicity of manufacturing procedure, cost-advantages, easier scale up and large production output. In roller compaction process there is no liquid or drying process involved so this process is more suitable for moisture and heat sensitive drug formulation.As compared to direct compression, roller compaction process can run more efficiently with high drug loading, improve flow, and content uniformity without material segregation.

Formulation design[7-11]:

Formulation and development of product by Roller compaction is initiated with studying physical and chemical properties of drug Substance and excipients.Afterword's challenges involved in the formulation development are identified.Challenges would be high drug loading, poor flow, poor compactibility, high compressibility, low density etc. Proper selection of formulation composition and excipients level can balance the poor physical properties of drug substance, thus greatly improve the processiblity of the powder mixture.Size enlargement of fine particle by binding of particles is the important factor in roller compaction.

For roller compaction process selection of powder material is very critical.Selection of powder material is based on particle size and morphological form. These two attributes of power material affects on flowability of granules and mechanical strength of tablets.Roller compaction may be unsuitable if the material is strongly adhesive to metal surfaces or non-compressible in nature. The robustness of roller compaction is also dependent on the variability of mechanical properties of API. The drug compaction capacity can vary, depending on the dose and API bulk properties.

In the dry granulation process active pharmaceutical ingredient is sifted through sieve and mixed with inert excipient powdersin suitable blender. The powder mixture is then usually blended with a lubricant. The lubricated powder is then transferred to hopper, which then reaches to the screw feeder. The feed material is conveyed to the counter-rotating rolls and thus feed material gets compacted. Afterword the compacted ribbons or flakes are milled to form granules.The powder which receives insufficient pressure to form ribbons is bypassed into separate chute.The milled granules are blended with extra-granular powder and finally lubricated.

The excipients are selected based on following condition

i. Excipients should be chemically compatible with drug substances.
ii. Excipients shouldmeet the compendial or regulatory requirements.
iii. Excipients should help to improve uniformity, flowability, density, compactability, and adhesiveness.

1) Diluents[12-17, 19]:

Diluents mainly facilitate formulation design and API characteristics as well as process development. Commonly Microcrystalline cellulose (MCC), Di-calcium phosphate (DCP), Mannitol, Lactose are used. Diluents play a vital role in modifying the pre-compaction blend properties. Diluent helps to impart uniformity, compactibility, flow, and density to the blends and thus ensuring good ribbons and granule.

a) Di-calcium phosphate (DCP):

Advantage of using di-calcium phosphate in tablets for vitamin and mineral supplement is the high calcium and phosphorous content.It exhibits high fragmentation property. It is an odorless, tasteless, white crystalline powder with shale-like shape and small particle size.DCP (Calipharm D) is brittle in nature and tends to fracture under pressure.

b) Lactose:

Lactoseis directly compressible material to produce dry granules with suitable mechanical properties for tablets. Lactose has been used in pharmaceutical formulation for a long time due to its high stability, low hygroscopicity and relative low cost. As a brittle excipient, lactose is one of the most popular choices to design formulations with desired compressibility and friability.Lactose-basedgranules are finer than the Mannitol-based granules because of the brittleness of lactose.

c) **Mannitol**:

It has high stability to chemical reactions and low hygroscopicity. The substance is soluble in organic solvents, partially insoluble in water, but very slightly soluble in ethanol. It has been adopted for the protection of active ingredients and to enhance dissolution.

d) Microcrystalline cellulose (MCC):

Microcrystalline celluloseis used mostly during drug development. It is widely used in pharmaceutical industry as ideal filler due to its excellent compactibility under a wide range of compaction pressures and its resistance to organic and non-organic contaminants. Different grades of MCC are selected based on requirements on particle size distribution, compressibility, and moisture content.MCC with large particle size can improve powder flowability significantly, and help to achieve excellent content uniformity with minimum weight variation.

2)Binder[15-17]:

Binder plays very important role in densifying powder, particle size distribution, strength of ribbon as well as granules and tablet friability. Low binder concentration reduces the strength of granules and too high binder concentration affects tablet disintegration and dissolution.Commonly used binders are Methylcellulose, Hydroxypropyl methylcellulose, Hydroxypropylcellulose.

3) Disintegrant[14-17]:

A disintegrant is used to break tablets into granules and further into fine particles, and thus helps to achieve satisfactory disintegration time and dissolution rate. Proper control of ribbon and granule porosity can lead to improved disintegration efficiency. Cross Carmellose sodium, Sodium Starch Glycolate, Crosspovidone, starch etc are widely used disintegrant.

4) Lubricant[17-19]:

Lubricant is generally required to improve flowability and to prevent adherence to the tool surfaces for processing the most cohesive feed powders. For roller compaction, lubricants are used in both intragranularly and extragranularly portions. Concentration of lubricant and lubrication mixing time can affect the frictional properties of the final feed material.Magnesium stearate is the most commonly used lubricant. Talc is the second most commonly used lubricant.

5) Glidant[16-20]:

Glidant is added to a great number of roller compaction formulations to improve the flowability of pre-compression powder. They act as ball bearings to reduce the friction among particles. e.g., Silicon dioxide.

Roller compaction theory[20-23]:

Roll compaction is an agglomeration process in which powder is densified by passing through two equal diameter counter rotating rollers. Mixture powder which is to be compacted reaches to roller from screw feeder with different mechanisms.As the powder is compacted, it passes through three different regions. The boundaries between the regions are defined by their angular positions.

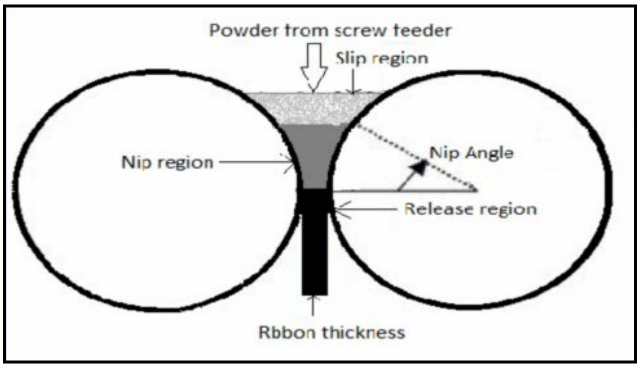

Figure No.1. Roller Compaction Process

1) Slip region (feeding zone):

The slip region is the zone close to the feeding of the powders. The slip region is effectively related to wall friction and interparticle friction of the feed.Material starts to move downward at a rate less than the surface speed causing the formulation “slips”.In this region Particle rearrangement and de-aeration may occur, but the pressure exerted on the powder is relatively small in this region as compared to nip region

2) Nip region (compaction zone):

In the nip region, the material is subjected to maximum stresses between two rolls leading to the formation of solid compact or sheet. In this region powder moves at the same speed as that of roll surface. To achieve acceptable compaction, the nip angle must be sufficiently large.Densification occurs due to the decrease in the gap and results in a significant increase in the roll pressure.

3) Extrusion region(The release region):

In release region there is great decrease in pressure as roll gap starts to increase again as the compact is ejected and can expand due to elasticity.The compacted ribbon exhibits relaxation as pressure is released from the rolls.The beginning of the ejection region is sometimes referred to as a neutral point because it sets the boundary between the region where the material moves at the same speed as wall surface it comes in contact with and the region where the material moves faster than the roll.

Design of RollerCompactor:

Design of roller compaction consists roll design, feeder system design, design of mills and other accessories. Quality of granule depends upon optimization of process parameter.

1. Roller Unit[21-27]:

Roller unit consist of two equal diameter counter rotating roller through which powder is passed and get compacted. Rollers create pressure on powder material and converts into compacted ribbon. Two types of roller compactors are available according the nature of the gap between two rollers, those two types are roller compactor with a fixed gap system and roller compactor with variable gap system. In fixed gap system powder feed is controlled by screw feeder and in variable gap system powder feed is controlled by width between rolls and screw feeder.

Rollers are oriented on the machines in different ways and the design of roller orientation varies from manufacturer to manufacturer.

A) Roller orientation:

Three types of roller orientation are commercially available.

a) Horizontal orientation:

This is most commonly used orientation design.In these design rollers are arranged horizontally. Also it should be noted that the roller orientation defines feeder orientation as well. Usually in Horizontal orientation of rolls material loss is high from bypass. Bypass occurs because material may remain in nip region for certain, uncontrolled time period. This also negatively affects ribbon density as well. Incorporation of side seal in compacter design reduce material bypass. Vertical or inclined feeders are used for horizontally aligned rolls.
E.g. Hosokawa Bepex GmbH, The FitzpatrickCompany, Freund Industrial Co.

b) Vertical orientation:

In vertical orientation direct bypass through rolls is minimised because material movement is not governed by gravity feeding system. Due to the advantage of less bypass of material, this vertical design is preferred for low dose product.

E.g. Alexanderwerk AG.

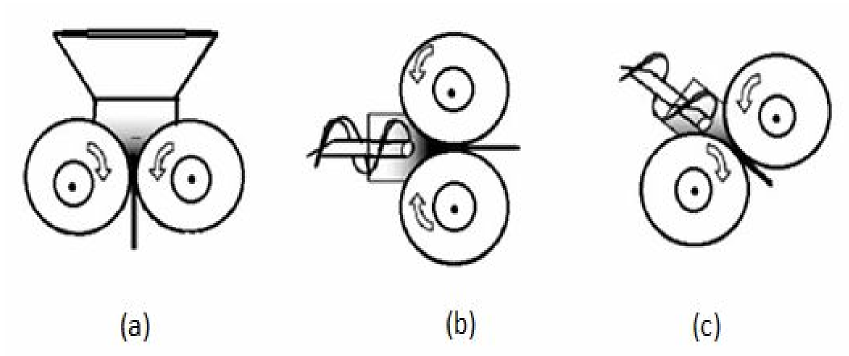

Figure No.2. Roller Orientation.

c) In-cline orientation (position between horizontal and vertical):Such type of design reduces bypass of material up to 10- 15 %.

E.g. Gerteis Maschinen.

B) Roll Surface[28]:

Roll surface is also important in maintaining flow of powder material through nip region. When the roll speed is fast, back pressure is created on the powder leading to the improper flow of material through nip region. Rough roller surface reduce the by-pass material.Types of roll surfaces are smooth, corrugated and fluted rolls.

Smooth and corrugated rolls are the most commonly used in pharmaceutical industry. Smooth rolls can minimize sticking problems.Corrugated rolls are therefore particularly suitable for increasing bulk density of light, fluffy, aerated materials.

2) Feeder design[15, 27- 29]:

The feeder is classified in to gravity feeder and force feeder. In a gravity feeder, the feed flow control is by use of hopper without an external driving force to compaction zone. When the powder is dense and free flowing gravity feed system can be used. In a force feeder, a rotating screw is installed in the center of the hopper. There are two types of feeders, single screw feeder and double screw feeder. Screw feeding continuously densifies and deaerates the blend. Feeding system is critical for achieving a good compacted product. It is very important to maintain uniform and continuous flow of material in order to fill the nip between the rolls correctly and sufficiently, so that the compacts are formed homogenously.

Feeder orientation depends upon the selection of equipment design considered and character of the blend which is used for compaction.Feeder orientation could be vertical, horizontal, or inclined. Feeder designs play vital role in creating positive pressure that regulates powder flow towards roller.Vertical feeders take advantage of the head pressure in the hopper above the horizontally aligned rolls. The feed screw could be either straight or slightly tapered. In case of light, fluffy and aerated powder tapered screws are better. Such design of powder reduces volume of powder, enhances the deaeration and also gives pre-densification effect. Compared to vertical screw feeders, horizontal screw feeders are advantageous in minimizing leakage and improving press capacity. For some equipment, inclined screw feeders are used as they utilize gravity to feed powder but have less powder leakage.

3) Flake crusher[31]:

Flake crusher is located between roll and granulator. Compacted Ribbon or flake which comes out from roller is crushed by flake crusher and converts in to smaller size pieces. Flake crusher improves material flow by crushing of compacted ribbon. The Flake Crusher is designed for dust free processing.

4) Milling or size reduction[30-35]:

Milling is process in which the ribbons formed during compaction which is crushed by flake crusher to form different size compacted pieces. These different size pieces is required make uniform particle size by using appropriate size screen. Different mill screen orifice size used may be varying with blend to blend for size reduction. Milling improves flowability, particle size distribution, content uniformity and reduce segregation. Screen located directly under the blade or scraper, prevents particles to leave the chamber which are larger than screen orifice size.Size reduction equipment is classify based on according to the way in which forces are applied, impact, shear, attrition and compression.

Table No.1. Type of mills.

Force	Type of mills
Shear	Cut mill
Impact	Cut mill, Hammer mill, and Screen Mill.
Attrition	Ball mill
Compression	Jaw crusher and conical screen mill

5) Deaeration[36]:

Air entrapped during feeding of blend to the rollers can make the ribbon weaker or brittle. Selection of proper feeder screw helps to eliminate air entrapment issue to certain extent. To remove entrapped air deaeration system is sometimes used in the machines. The section consists of a sintered metal or screen that permits air to be removed via a vacuum device

6) **Feeder vibrator[11]:**

To maintain proper uniform continuous flow of feed material powder especially in case of a poor flow powder, a simple gravity feeder and force feeder may not work to be good enough. Installation of a feeder vibrator can be an easy and effective way to improve the flow. By providing a constant driving force, feeder vibrators can break the stagnant powder bed, drive the powder toward the rolls, and help densification and deaeration.

7) Temperature control[11]:

The screw flight can generate a lot of heat when rotating in the powder bed. In a highly packed powder bed, excessive heat may elevate the local temperature, and cause the powder to be partially melted and stuck to the flight. This may even cause batch failure. Inthis case, special flight with a cooling jacket can be used to improve processibility.

Impact of process parameters[1, 19-21, 36-38]:

Roller compaction process parameters have very significant effects on the process feasibility, ribbon quality, granule flowability and blend uniformity. Compaction force, roll speed, screen size, feeder screw speed, and roll gap are the critical parameters needed to be optimized to improve product quality.Efficiency of roller compaction is based on the equipment design and operating parameters.

1) Compaction force:

Sufficient Compaction force is required to compact the loose powder.Under pressure the powder gets densified and bonded to form Ribbon.Increasing roller pressure at certain limit increases ribbon density, granules mean particle size, granule flowability. Optimum compaction force which gives good quality granule may vary with mixture of material. Over compaction force may break the ribbon which results in poor quality granule that may create tablet compression problem such as low hardness, capping, and high friability. For most pharmaceutical formulations, the powder mixtures usually contain both plastic and brittle materials. Also During over compaction force there may be chance of rise in temperature.

2) Roll gap:

Roll gap is the distance between the rolls at their nearest point. This is the critical parameter of compaction and one that needs to be stabilized by the process parameters mentioned above. It is in a function of pressure applied to the rolls and the amount of material that is passed between them. Roller gap exhibited a significant impact on ribbon density, granule flowability, ribbon hardness and granules content uniformity. Roller compaction force increases with decrease of roller gap.

3) Screw speed:

Screw speed is a critical process parameter in the roller compaction.Optimum range of screw speed depends upon powder material flow, roller speed and roller gap. When screw speed is low, material reaches in nip region in insufficient quantity resulting in to formation of ribbons with low strength. High screw speed may cause a highly densified zone in the nip area, and cause melting or caking of particles on the flight. High screw speed is not solution for poor flow materials.In case of vertical and horizontal screw needs to maintain optimum screw speed for homogeneous compaction. Generally the feed rate should be equal to the rate of discharge.

4) **Roll speed:**

Roll speed is inversely related to dwell time for particle compaction which affect ribbon density. Roller speed needs to be adjusted in accordance to feeder screw speed and flow of powder.When roller speed is high material passing through rollers is being inadequately compacted ultimately result blend segregation and consequently loss of content uniformity.

5) **Milling:**

Ribbons size reduction can be done by applying force which result desired size granules.Desired granule size required for uniform particle size distribution, good flowability, compressibility. The mill screen orifice size directly impacts particle size distribution which can potentially impact granule uniformity and flowability.If excessive fines are generated in the milling process, it densifies the blend and thus affects flowability. Excessive quantity of fine subsequently affect on content uniformity, tablet hardness in tablet compression. Milling screen orifice size and milling speed which shows significant impact on granules flowability,granules uniformity, and particle size distribution.

Physical Property Measurements[14, 39]:

A) Relative density or Ribbon Solid Fraction:

RD= ED /TD= 100 – n/100

Where RD is relative density of ribbons; ED is the envelope density of ribbons; TD is the true density of the granules milled from ribbons; n is the sample porosity.

The true density of granulated materials was determined using a helium pycnometer. The envelope density of each ribbon sample was measured by a GeoPyc® 1360 envelope density.

B) Ribbon Tensile Strength:

Characterize the mechanical strength of ribbons by using Texture Analyzer can be a powerful tool.The tensile strength of the ribbons was quantified by a three-point beam bending test using a texture analyzer via the following equation.

$TS = 3 F L / 2 W T^2$

where TD is the tensile strength at fracture; F is the force applied at fracture; W and T are the width and thickness of flat-faced rectangular compacts fabricated from ribbons, respectively; L is the gap distance between two supporting beams underneath the compact. A Texture Analyzer (TA) consists of a mechanically stable framework, where a vertically movable arm, equipped with a load cell, applies defined force to the material under investigation via variable tools.

Tensile strength is defined as the minimum tensile stress required for fracture initiation within a compact.

C) Granule Particle Size Distribution:

The particle size distribution of powder mixture is measured by using a particle size analyser (Sympatec, Helos model). The analyser is based on the laser diffraction principle and it is a dry measurement technique.Each sample was measured in triplicate and the average particle size distribution was calculated.

D) Granule Bulk and Tapped Density:

The bulk density, D_B of granules was determined by the weight of granules filled into a 25 mL graduated cylinder. The tapped density, D_T of granules was determined by tapping the filled graduated cylinder for 1250 taps using a tap density tester and Carr's compressibility index (CI) of ribbons was then calculated.

E) Granule Flow Evaluation:

Flow properties of granules are assessed using an avalanche tester, angle of repose, shear cell testing that measured the avalanche time distribution of tested powders tumbling inside a slowly rotating drum over a time period.

Conclusion:

With technological advances in drug development, dry granulation by roller compaction is more advantageous than wet granulation process with simple manufacturing process, low operational cost, no use of liquid solvent, large scale production and suitability for heat and moisture sensitive drug. Selection of drug and excipient for roller compaction is based on their physical and chemical attributes.Selection of formulation design and process parameter play vital role in roller compaction.Optimization of process parameters such as compression force, roll speed, roll gap, screw speed, milling speed, and milling screen orifice size is essential and critical in roller compaction. Roller compression affects particles size distribution, flowability, homogeneity, compressibility, compactability of active pharmaceutical ingredients, and such parameters can inturn affect dissolution profile, disintegration time, hardness and other post compression parameter of tablets.

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