OVERVIEW ON ROLL COMPACTION/DRY GRANULATION PROCESS

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Summary

Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules. Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared by either compression or molding methods. The basic art of tableting by three well known methods includes direct compression, wet granulation and dry granulation. Dry granulation may be used if the materials have sufficient inherent binding or cohesive properties to form granules. Dry granulation refers to the process of granulating without the use of liquids. There are two dry granulation methods used in the pharma industry: slugging and roll compaction. In a roller compactor material particles are consolidated and densified by passing the material between two high pressure rollers. The densified material from a roller compactor is then reduced to a uniform granule size by milling. Roll compaction/dry granulation (RCDG) is a method of choice for processing of physically or chemically moisture sensitive drugs, as no liquid binder is required in the granulation. This literature review illustrates the progress and the use of RCDG in the production of directly compressible excipients, the compaction of drugs and drug formulations.

Key words Tablets, granulation, roll compaction, direct compression, wet granulation

Introduction

Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules. A simplified flow-chart of the relationship of pharmaceutical dosage forms is shown in Figure 1.1. These dosage forms are designed either for improving the physical and mechanical properties of materials during manufacture and/or for providing a desired drug delivery system. The tablets and capsules can be made directly from powders or from

granules and pellets, or from film-coated multiple units. Tablets are now the most popular dosage form, accounting for some 70% of all ethical pharmaceutical preparations produced[1].

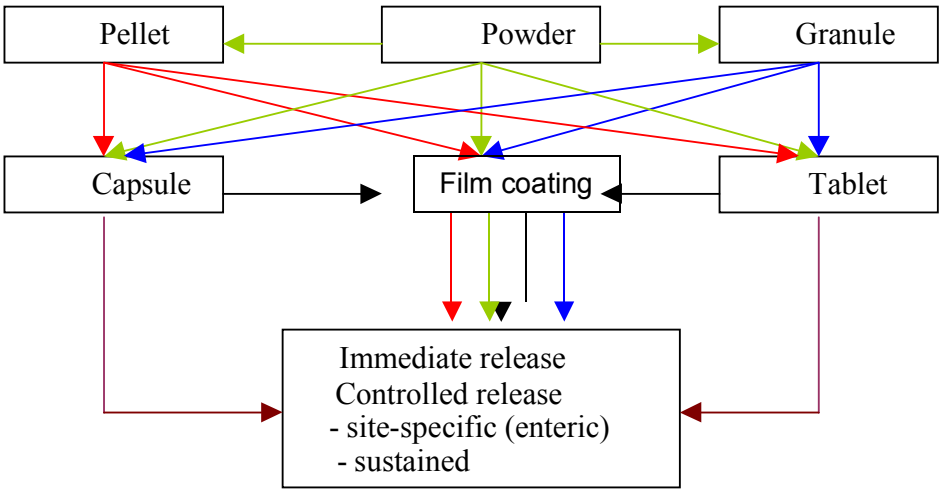

Figure 1 Relationship of pharmaceutical solid dosage forms

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared by either compression or molding methods[2]. Tablets offer advantages over both patients and manufacturers. Tablets are the most popular dosage form due to their simplicity and economy of manufacture, relative stability and convenience in packaging, shipping and storage. For the patient, the ease of manufacturing, convenience in administration, accurate dosing and stability compared to oral liquids, tamper-proofness compared to capsules, safe compared to parenteral dosage forms makes it a popular and versatile dosage form[3].

Manufacturing of tablets requires number of unit operations like product includes weighing, milling, granulation, drying, blending, lubrication, compression and coating.

Granulation

In the pharmaceutical industry, granulation refers to the act or process in which primary powder particles are made to adhere to form larger, multi particle entities called granules. It is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. Granulation is extensively used for the manufacturing of tablets and capsules. The granulation process combines one or more powders and forms a granule that will allow the tableting process to be predictable and will produce quality tablets within the required tablet-press speed range. The chief reasons to granulate powder for the manufacturing of pharmaceutical dosage forms

include prevention of segregation of the constituents of the powder mix, improve the flow properties of the mix and improve the compaction characteristics of the mix. The granulation of toxic materials will reduce the hazard associated with the generation of toxic dust that may arise when handling powders.

Effect of granule properties on tablet

The granule properties play a pivotal role in the final performance of a tablet; for example, granule size can affect the flow ability and hence, the average tablet weight and weight variation[4]. Having consistent flow of a granulation provides the needed avenues to control tablet weights. Consistent tablet weight will result in repeatable tablet hardness. Improved and homogeneous granulation will improve mixture, its flow ability, compressibility and therefore, improved disintegration with acceptable dissolution rate[5].

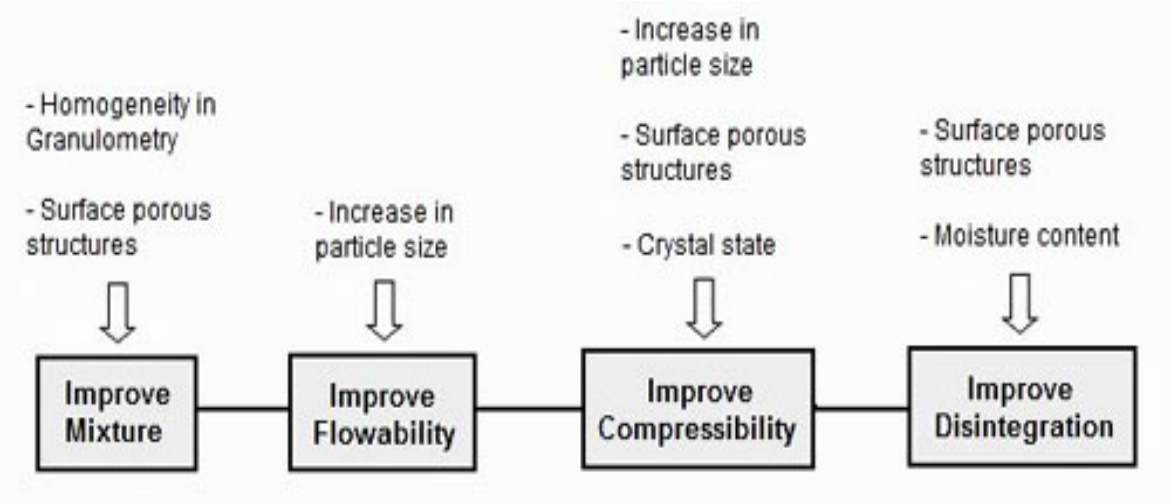

Figure 2 Effect of granules on physico-chemical properties of tablet

Methods of Granulation

The basic art of tableting by three well known methods includes direct compression, wet granulation and dry granulation. The various steps involved in the process of granulation have a significant effect on the particulate characteristics of the resulting granulation[6].

Direct Compression

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pre-treatment of the powder blend by wet or dry granulation procedure is required. Merits over wet granulation process and dry granulation process include more efficient process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients, reduced processing time reduced labour costs fewer manufacturing steps, less number of equipments are required, less process validation, reduced consumption of power, elimination of heat and moisture, thus increasing not only

the stability but also the suitability for thermo labile and moisture sensitive API's particle size uniformity.

Wet Granulation

In wet-granulation, a liquid binder solution is combined with a bed of mixed powders to mass the particles together into granules. The damp mass is then screened, dried and milled to the desired size. The mass may also be dry screened, lubricated and compressed or extruded through a perforated screen and then dried. In drying, it is often desirable to maintain a residual amount of moisture in the granulation in order to maintain a hydrated state and to reduce static electric charges on the particles. Moisture content of the granulation should be uniform.

Wet granulation suffers from a number of disadvantages. A chief disadvantage is the number of separate steps involved as well as the time and labour necessary to carry out the procedure. Further, the use of aqueous solvents is limited by the stability of the product to be granulated. Explosion concerns and environmental regulations may limit the use of certain organic solvents.

Dry Granulation

Dry granulation may be used if the materials have sufficient inherent binding or cohesive properties to form granules. Dry granulation refers to the process of granulating without the use of liquids. There are two dry granulation methods used in the pharma industry: slugging and roll compaction.

Slugging method

In "slugging" the material to be granulized is first made into a large compressed mass or "slug" typically by way of a tablet press using large flat-faced tooling. A fairly dense slug may be formed by allowing sufficient time for the air to escape from the material to be compacted. Compressed slugs are then comminuting through a desired mesh screen manually or automatically as for example by way of a comminuting mill. Formation of granules by "slugging" is also known as precompression. When tablets are made from the granulated slugged material, the process is referred to as the double compression method.

Various disadvantages of slugging includes single batch processing, frequent maintenance changeover, poor process control, poor economies of scale, low manufacturing throughput per hour, excessive air, sound pollution, increased use of storage containers, more energy and time required to produce 1 Kg of slugs than 1 Kg of roller compact[7].

Roller compactor method

Dry granulation may also be performed using a "roller compactor". In a roller compactor material particles are consolidated and densified by passing the material

between two high-pressure rollers. The densified material from a roller compactor is then reduced to a uniform granule size by milling.

Roller compaction dry granulation process is capable of handling a large amount of material in a short period of time. As a special subtype briquetting utilizes special designed compaction rolls which divides the compacted powder in pieces (briquettes). For dry granulation the compaction force in extend and uniformity of distribution is essential in regard to uniformity of granules porosity to ensure uniform hardness and disintegration of the final product. Because of its advantages, roll compaction is being increasingly used as a granulation technique, but it is not a simple process and may involve many variables for example roll pressure, roll speed, horizontal/vertical feed screw speed, roller gap, screen size. These parameters need to be optimized depending on the materials and the type of equipment used in order to obtain products of desirable quality.

Another granulation method now a day's coming into importance is melt granulation. Melt granulation is a process by which powders are agglomerated with the aid of a binder, in either a molten state or a solid state that melts during the process. The apparatus of choice is a high-shear mixer, where the temperature of a powder can be raised above the melting point of a meltable binder by either a heating jacket or frictional forces generated by the impeller blades. Determination of the granulation end-point regarding temperature is crucial for the melt granulation. Therefore the process is difficult to control. Furthermore, often the granulation mass adheres to the walls of the granulator bowl generating a not uniform mass regarding distribution of the components, content uniformity of the API and particle size distribution[8].

Advantages of Roll Compaction/Dry Granulation Process (RCDG)

Roll compaction is a method of choice for processing of physically or chemically moisture sensitive drugs, as no liquid binder is required in the granulation. This is suitable for compounds that either have a low melting point or degrade rapidly during heating, as the method does not involve any drying step[9]. RCDG is useful technique for processing of drugs having low and inconsistent bulk and tap densities with very fine and inconsistent particle sizes and/or poor flow properties and poor compatibility[10]. RCDG leads to minimized batch to batch variation with improved product quality due online control and automation of processing settings. The process potentially more easily scalable and may be able to reduce development time due to continuous processing with high productivity and less energy consumption[11,12]. Roll compaction can handle high drug loading improve flow and content uniformity as well as prevent segregations when compared direct compression that can cause problem with high dose drugs, specially for drugs with low bulk density[8,10]. RCDG results in granules that form porous tablets thus allowing water to penetrate more easily into the tablet. This leads to improved disintegration behaviour of tablets[13]. There is reduction in a material loss during processing and capping tendency of tablets[14].

The various steps involved in granulation technology are shown in figure 3.

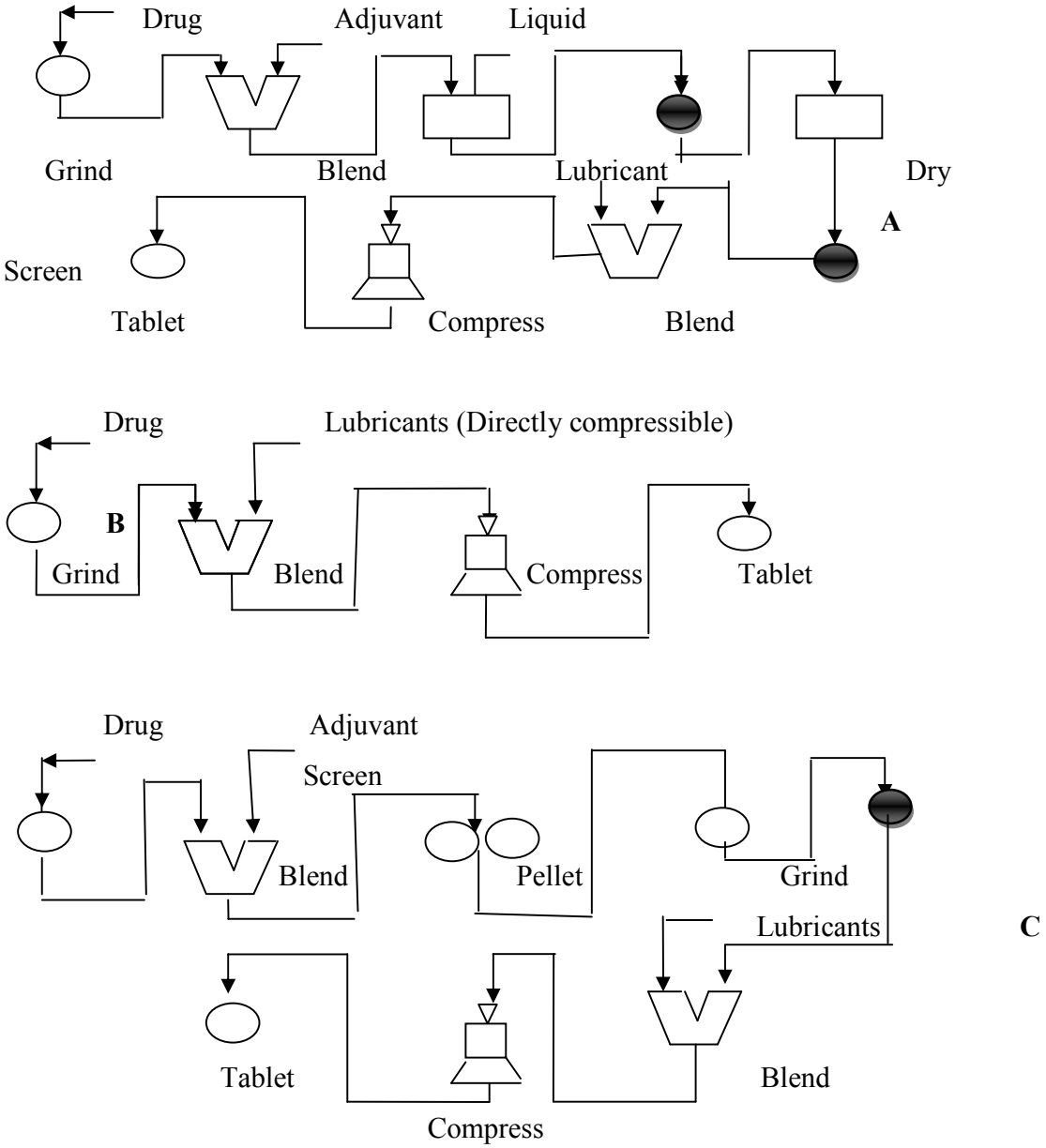

Figure 3 Steps involved in granulation technology, A: Wet granulation, B: Direct compression, C: Dry granulation

The selection of the granulation method should be done on the basis of the physico-chemical properties of the active pharmaceutical ingredient and required excipients used for its formulation.

Basic Process of Roll Compaction/Dry Granulation (RCDG)

Functional principle of roll compaction

Roll compaction is an agglomeration process in which powder is fed by either gravity or by means of a screw feeder through two equal diameter counter-currently rotating rollers. The friction between the material being processed and roller surface brings the powder towards the narrow space between the roll (nip region), where the powder is subjected to high stresses leading to the formation of compact. If the rolls are smooth or fluted or knurled, the material is compacted into dense ribbons (flakes, sheets, strips), whereas pocket rolls will form briquettes. If in-line granulator/mill system is available with the system, it will mill ribbons or briquettes into granules[10,15] otherwise densified sheets (ribbons) can be dry-sized by an oscillating mill, cone mill or impact mill[12,16,17]. The production of either briquets or granules depends on the application. Usually, briquets are produced when large, dense agglomerates are required. Granules are produced when smaller, uniform particles are required for further processing. The produced granules are usually an intermediate product form and subsequently will be fed to a compression machine to ensure more efficient feeding[18] or filled into capsules[19].

The key bonding mechanism involved in compact formation includes strongest solid bridges between particles, weaker attraction intermolecular/long distance forces (van der Waals forces, electrostatic forces, hydrogen bonding) or mechanical interlocking which denotes hooking and twisting of irregularly shaped particles[20]. The most dominant bonding for pharmaceuticals is long distance forces, especially van der Waals forces and hydrogen bonds in some cases whereas; relatively simple molecular structure and plastic deformation e.g. sodium chloride are the prerequisite for solid bridges[14].

During roll compaction, the powder blends are fed into the gap between two rollers (compaction zone) which is divided into three regions namely slip or entry region, nip region and release region. The boundaries between the regions are defined by their angular positions (Figure 2.1). In the slip or entry region powder starts to move but at a speed slower than the roll speed, thus indicating that slips occur therefore termed “slips”. Particle rearrangement and de-aeration may occur, but the pressure exerted on the powder is relatively small. Entry angle, θ_h defines the start of this region and corresponds to the angular position at which there is a finite roll pressure. The nip region starts at a roll angle α, (nip angle), when the wall velocity of the powder becomes equal to that of the rolls. The powder is ‘nipped’ and densification occurs due to the decrease in the gap. This results in a significant increase in the roll pressure. The release region starts when the roll gap starts to increase again and its size depends on the stored elastic strains in the compact, release rate of compact and the roll speed[19,21].

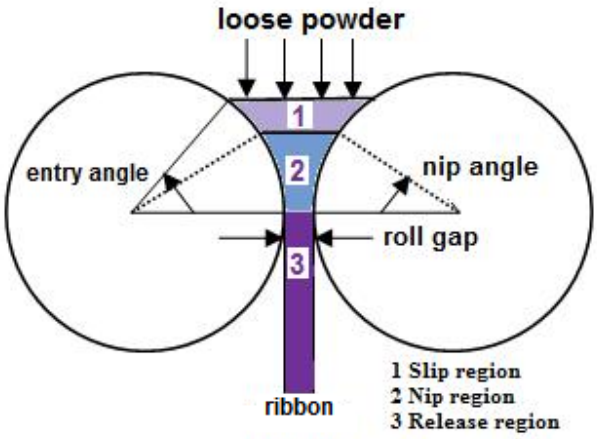

Figure 4 Schematic of the main regions during roll compaction

Requirements for roll compaction

For successful granulation by RCDG technique following conditions should be satisfied : adequate supply of the powder to the nip region and entire conveying of powder entering from nip region into the narrowest part of the roll gap. Uniform distribution of the compaction pressure over the whole roll-gripped mass. Adequate, effective and uniform de-aeration of powder mass via vacuum before it reaches the nip region. Material to be processed should be compressible, should have consistent increase in density with force, suitable for milling operation and recompression, if required[7,13].

Design of Roll Compactors

The roll press/compactor basically consists of a feed system which conveys powder to rolls, a roller compaction system which densifies/compacts loose powder into ribbons or briquettes and/or in-line granulator/mill system which mill ribbons or briquettes into granules and optional accessories to improve process control and automation.

Feed system designs

Feed systems play a vital role in successful formation of compact and control of process parameters. Non-uniform filling/conveying may possibly lead to poor compact quality, generation of excess fines and more un-compacted materials[22]. Two type of feed system are used for powder conveying viz. gravity feeding by use of hopper or force feeding using feed hopper and screw feeder. When the powder is dense and free flowing, gravity feed system can be used[23] reported the use of gravity feeding by a simple hopper, with a simple flap hopper and gravity feeder with flap distribution box. For fine and fluffy powders having poor flow ability and inconsistent bulk density, a feeder is required to provide pre-compression force to the powder as it enters the roller press. This force increases the friction between the powder and the roll surfaces to improve compaction. Two basic types of screw feeders can apply this force: single screw feeder

(Hosokawa Bepex GmbH) and double screw feeder (Gerteis Maschinen + Process engineering AG, the Fitzpatrick Company)[22,23].

For larger roll widths double screw feeder system is convenient to feed powder uniformly across the entire roll**.** The horizontal screw fixed in the powder reservoir[24] conveys powder from the feed hopper to the vertical screw (temping screw) and each vertical screw partially de-aerates, pre-compresses and force-feeds the powder down into the nip region[18,22,24].

Technological advances in feed system have led to the introduction of patented combi vent feeder which consist integrated whole unit having the feed hopper with a stirrer inside, the screw feeder and the vacuum system. The stirrer inside the hopper ensures even powder flow towards screw feeder. The vacuum system assists transport of difficult transportable, high voluminous and fluidizing materials. Further, fines/over sizes or additional additives can be uniformly re circulated into the process due to the availability of additional feed hopper chamber[25].

Roller unit

The roller unit includes two equal diameter counter rotating rollers. Two different types of roll compactors are commercially available: fixed gap systems[26] and those which allow variable gap size due to moveable rolls (Gerteis Maschinen Process engineering)[27]. The gap width between rollers is pre-defined and fixed when roll compactor with fixed rollers is used. In these systems material flow is controlled by screw feeder speed only to get a constant densification of the material between two rollers. In latter system even compaction force is achieved by control of both the gap width and the screw feeder speed[22]. Additionally, movable gap systems have less bypass propensity[27]. By changing roll gap, density profile of the compacts can also be changed with changed robustness of the granules which subsequently effect mechanical properties of the tablets[28].

In fixed gap systems ribbons of same geometrical dimensions are produced but non-homogenous powder feed between the rollers is observed which leads to a change in porosity of the produced ribbons and variation in compaction pressure is also observed. This may lead to non desirable changes in product quality. In variable gap systems, at a given compaction pressure, actual gap size mainly results from screw feeder speed, roll speed and density of the fed powder. Thus, transportation of non-free-flowing powder and resulting changes in powder density may only lead to gap size variations which causes non-uniform ribbon thickness, with negligible effects on porosity due to maintenance of constant compaction pressure[27].

Bypass is un-granulated material that circumvents the rolls completely, or passes between the rolls without being adequately compacted and is major cause of segregation of blend and consequently content uniformity. Three major factors which influence bypass includes roller surface roughness/design, roll orientation and vacuum de-aeration.

Roll surface roughness/design

The roll surface is important in maintaining a back pressure on the powder flow so that the powder does not pass through the nip region faster than the rolls are turning. Bypass can be minimized by use of rolls having greater roll roughness or use of textured surface (knurled). Three different types of continuous ribbon rolls are available with different surface designs intended to maintain this back pressure. These include knurled roll, serrated roll and smooth roll[29].

Roller orientation

Three types of roll orientation are commercially available as shown in figure 5

- *Horizontal orientation:* available from Hosokawa Bepex GmbH, The Fitzpatrick company, Freund Industrial Co.
- *Vertical orientation:* available from Alexanderwerk AG
- *In-cline orientation (position between horizontal and vertical):* available from Gerteis Maschinen + Processengineering AG

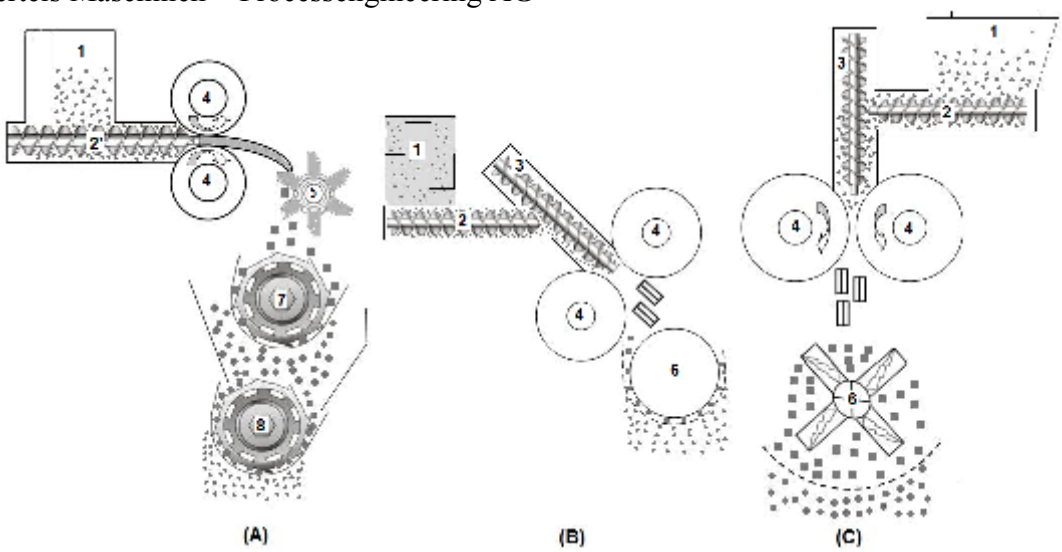

Figure 5 Sketch of a roll compaction process using three different roll orientations (A) Vertical, (B) Inclined, (C) Horizontal
1: Filling hopper, 2: Feeding auger/screw feeder, 2': Screw feeder, 3: Tamping auger, 4: Rolls, 5: Flake crusher, 6: Granulator, 7 and 8: Two stage diagonal granulation system using coarse and fine granulator, respectively.

The roll orientation plays significant role in generation and minimization of bypass. In horizontal roll orientation the loss of material due to bypass is high as compared to other designs. Loss of un-compacted material is minimal in vertical orientation due to independence of feed to gravitational forces. The use of inclined roll orientation decreases bypass from 15-20% to 7%[27]. In horizontal orientation material may remain in nip region for certain, uncontrolled time period which may negatively affect ribbon uniformity[30]. Incorporation of side seals (sealing strips) in compactor design reduces

material bypass but this does not have significant effect to reduce material passing through the rolls without being sufficiently compacted.

Vacuum de-aeration

This is an optional feature and usually applied during feeding to remove excess air from a fine powder with low bulk density. The application of vacuum eliminates entrained air that can cause the powder to resist the pre-compression force applied by the screw feeder. This technique is particularly useful for process with no screening or recycling steps or for greatly increasing the compaction efficiency of roll compactor. Vacuum de-aeration requires a vacuum pump system which is linked to the feeder and removes the powder's entrained air through a filter before the powder enters the roller press[18].

Granulator/mill system

Granulation/milling of ribbons or biquerette obtained from compaction can be done using an in-line oscillating rotor-granulator or separate granulation in an oscillating mill, a cone mill or impact mill. In most of the equipments in-line granulator can be used in two ways viz. use of coarse and fine (two stage) granulator (WP120 Pharma, Alexanderwerk AG, Germany) to get desired sized granules or use of fine (single stage) granulator (WP150 Pharma, Alexanderwerk AG, Germany) in which fines and oversize are separated using sifter and recycled via vacuum conveying system. An in-line rotor granulator system consists of a rotor that runs in a conventional U-shaped or diagonal positioned screen. The rotor pulls the material into the working gap and crushes it allowing the material to pass through the desired mesh size. By the use of diagonal oriented screen output is increased due to more mass holding of the material against the screen as compared to conventional U-shaped screen.

Accessories

In some roll compactor systems a pre-breaker/flake crusher is located between rolls and granulator for coarse crushing of compacted ribbons/flakes. While in others gravity feeder or screw feeder does not provide enough flow of the powder material therefore use of feeder vibrator can be worthy. Feeder vibrator breaks stagnant powder bed and assists their flow toward rollers and help in densification and de-aeration of the powder[8]. Increase in temperature during compaction may harm product quality especially in case of temperature sensitive drugs. Roll cooling system can be used to cool the system.

Conclusion

This review indicates the effect of multiple variables of roll compactor e.g. hydraulic pressure, roller speed, roller gap, roll surface, granulator speed and screw feeder speed on the granule deliverable properties of product. The granule deliverable properties studied are flowability, bulk and tapped densities, particle size distribution. Roll compaction is a method of choice for processing of physically or chemically moisture sensitive drugs, as no liquid binder is required in the granulation.

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