"Slugging to Roller Compaction: Technology Scale Up, Process Optimization and SeDeM Analysis Of granules"

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MASTER OF PHARMACY

IN

PHARMACEUTICAL TECHNOLOGY AND BIOPHARMACEUTICS

BY

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April 2012

CERTIFICATE

This is to certify that the dissertation work entitled "Slugging to Roller Compaction: Technology Scale Up, Process Optimization and SeDeM Analysis Of granules" submitted by Mr. Divij Vinodbhai Shah with Regn. No. (10MPH104) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Technology and Biopharmaceutics" is a bonafide research work carried out by the candidate at the Piramal Pharmaceutical Development Services under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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DECLARATION

I hereby declare that the dissertation entitled "Slugging to Roller Compaction: Technology Scale Up, Process Optimization and SeDeM Analysis Of granules" is based on the original work carried out by me under the guidance of Dr. Vinay Patil, Group Leader, Fromulation Development, Piramal Pharmaceutical Development Services and Dr. Tejal Mehta, Professor and Head, Department of Pharmaceutics and pharmaceutical technology, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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A C K N O W L E D G E M E N T

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INDEX

Slugging to Roller Compaction: Technology Scale Up, Process Optimization and SeDeM Analysis Of granules

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Granulation is the process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. Powders are often granulated to improve their flow behaviour. Roll compaction/Slugging is a widely used process for granulation without water. This method allows the granulation of materials sensitive to moisture and heat. The purpose of the study was to provide platform for technology transfer i.e. slugging to roller compaction. The study was carried out to relate envelope density of the slugs and roller compacted ribbons. Slugging was carried out by Korsch XL 100 by applying 3^2 full factorial designs in order to obtain three different envelop densities. Roller compaction was carried out by Chilsonator IR220 by using Central Composite design to minimize the number of runs. In this part of the work, envelope densities obtained from slugging trials was target. SeDeM analysis, a newer concept was used in the study to check the suitability of granules, obtained after milling of slugs and ribbons, for direct compression. The newer graphical method provided the practical evidence that particles of blend were converted in to granules and hence compressibility became better to that of original powder blend. The properties of granules obtained from two different processes but having same envelope density were very similar which shown the reliability of method as well as the correlation point can be used for technology transfer to get same envelope density of granules by both the method. Hence it can be concluded that technology transfer could be possible by using SeDeM analysis and experimental designs which shown better reliability.

2.1 INTRODUCTION TO GRANULATION:

In the pharmaceutical industry, the preferred tablet production method is direct tableting. Until the late 1950s the vast majority of tablets produced in the world were manufactured by a process requiring granulation of the powdered constituents prior to tableting. However, it is often necessary to improve the material's compaction and flow properties in order to obtain uniform die-filling and to produce tablets of adequate quality. These properties are commonly enhanced by converting fine powders into larger agglomerates by the process of granulation [(1).]

Granulation is the process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. Granulation normally commences after initial dry mixing of the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved. After granulation the granules will either be packed (when used as a dosage form), or they may be mixed with other excipients prior to tablet compaction or capsule filling [(2)].

The granulation process of size enlargement used within the pharmaceutical industry has its roots in ancient times. The practice of delivering medicinal powder by hand rolling into a pill by using honey or sugar has been used for centuries. It is still the practice to deliver the botanical and herbal extract in homeopathic and ayurvedic branches of medicine, which are still practiced in India along with allopathic medicine. The term ‘‘granulated’’ material is derived from the Latin word ‘‘granulatum,’’ meaning grained. The granulated material can be obtained by direct size enlargement of primary particles, or size reduction from dry compacted material. In modern times, granulation technology has been widely used by a wide range of industries, such as coal, mining, and agrochemical. These industries employ agglomeration techniques to reduce dust, provide ease of handling, and enhance the material's ultimate utility [(3)].

The term ‘‘granulated’’ material is derived from the Latin word ‘‘granulatum,’’ meaning grained. The granulated material can be obtained by direct size enlargement of primary particles, or size reduction from dry compacted material. The classical granulation process using either wet or dry methods is employed in the process industries. Pharmaceutical granulation process is used for tablet and sometimes capsule dosage forms; however, in some applications the process is used to produce

spherical granules for the modified release indications or to prepare granules as sprinkles to be used by pediatric patients [3].

Reasons for granulation [2-3]:

(a) To prevent segregation of the constituents of the powder mix:

Segregation (or demixing) is due primarily to differences in the size or density of the components of the mix, the smaller and/or denser particles concentrating at the base of a container with the larger and/or less dense ones above them. An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule, and segregation of the ingredients will not occur (Fig. 1). It is also important to control the particle size distribution of the granules because, although the individual components may not segregate, if there is a wide size distribution the granules themselves may segregate. If this occurs in the hoppers of sachet filling machines, capsule-filling machines or tablet machines, products with large weight variations will result. This is because these machines fill by volume rather than weight, and if different regions in the hopper contain granules of different sizes (and hence bulk density), a given volume in each region will contain a different weight of granules. This will lead to an unacceptable distribution of the drug content within the batch of finished product, even though the drug is evenly distributed, weight per weight, through the granules.

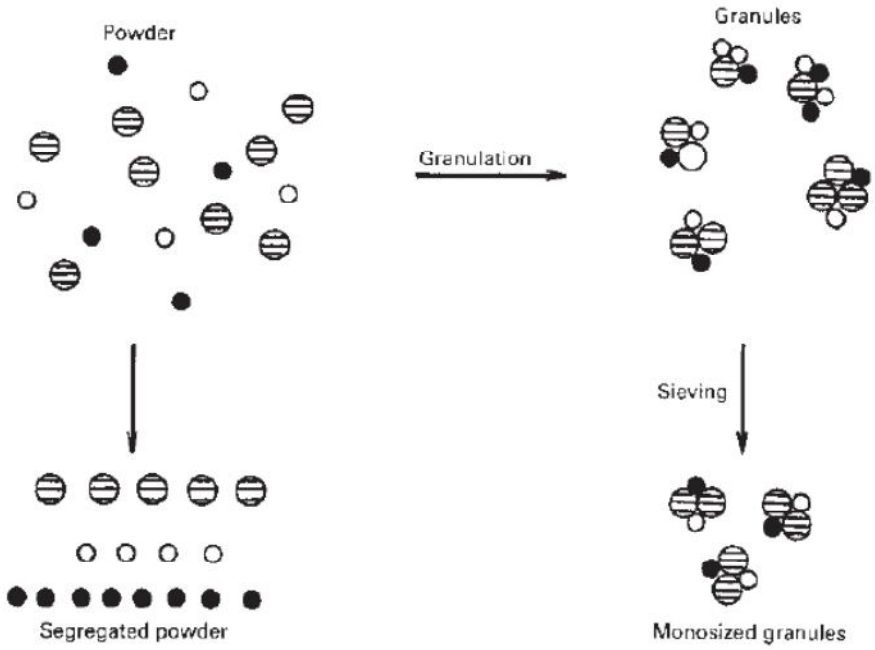


Figure 1 Granulation to Prevent Segregation

(b) To improve the flow properties of the mix:

Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well. Poor flow will often result in a wide weight variation within the final product owing to variable fill of tablet dies etc. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties.

(c) To improve the compaction characteristics of the mix:

Some powders are difficult to compact even if a readily compactable adhesive is included in the mix, but granules of the same formulation are often more easily compacted and produce stronger tablets. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granule. Often solute migration occurring during the post granulation drying stage results in a binder-rich outer layer to the granules. This in turn leads to direct binder–binder bonding, which assists the consolidation of weakly bonding materials.

(d) The granulation of toxic materials will reduce the hazard associated with the generation of toxic dust that may arise when handling powders. Suitable precautions must be taken to ensure that such dust is not a hazard during the granulation process. Thus granules should be non-friable and have a suitable mechanical strength.

(e) Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder.

Granulation may reduce this hazard, as the granules will be able to absorb some moisture and yet retain their flowability because of their size.

(f) Granules, being denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment.

(g) Other reasons:

- To increase the uniformity of drug distribution in the product.
- To densify the material.
- To enhance the flow rates and rate uniformity.
- To facilitate metering or volumetric dispensing.
- To reduce dust.
- To improve the appearance of the product.

Granulation methods can be divided into two types: wet methods, which use a liquid in the process, and *dry* methods in which no liquid is used.

2.1.1. WET GRANULATION (INVOLVING WET MASSING)

Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid. The fluid contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol, either alone or in combination. The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved adhesive (also referred to as a binder or binding agent) which is used to ensure particle adhesion once the granule is dry. Water is commonly used for economical and ecological reasons. Its disadvantages as a solvent are that it may adversely affect drug stability, causing hydrolysis of susceptible products, and it needs a longer drying time than do organic solvents. This increases the length of the process and again may affect stability because of the extended exposure to heat [(2)]. Different operations and processes are involved in wet granulation process. The most important ones, which can affect the tablets of the resulting granulation, are: (see figure 2) [(6)].

- Preparation of the powder mixture with screening and mixing
- Spraying with solution to the appropriate wetness
- Drying the solid - liquid mixture
- Milling the dry granulate to proper particle size

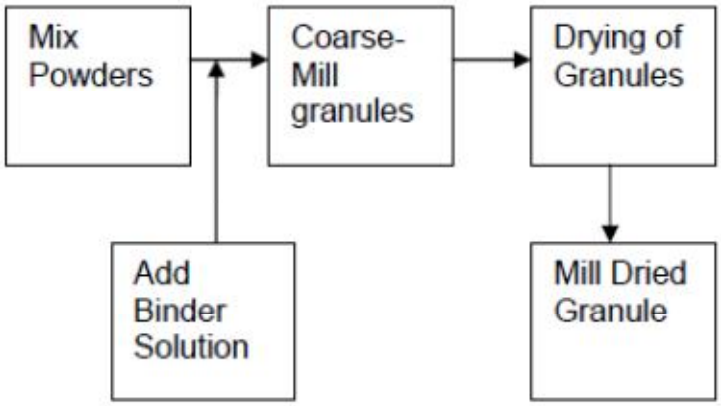


Figure 2 Flow Sheet of Granule production

2.1.2. DRY GRANULATION

In the dry methods of granulation, the primary powder particles are aggregated under high pressure. There are two main processes. Either a large tablet (known as a ‘slug’) is produced in a heavy-duty tabletting press (a process known as ‘slugging’) or the

powder is squeezed between two rollers to produce a sheet of material ('roller compaction'). In both cases these intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction. The unused fine material may be reworked to avoid waste. This dry method may be used for drugs that do not compress well after wet granulation, or those which are sensitive to moisture [(2)]. Slugging is also called as a pre-compression process for the formation of extra large tablets (slugs), usually of variable weight, due to poor flow of the drug powder. The resulting slugs are subsequently broken down into granules, which are recompressed to obtain the final tablets. The procedure is applicable to the dry granulation of hydrolysable drugs, such as aspirin, which are not amenable to wet granulation [(4)].

Amongst the main drawing cards dry granulation is its simplicity and being a continuous process with a considerably larger throughput than wet granulation. However, dry granulation has been associated with technical challenges regarding the flowability of the granulate and its recompactibility, which means that until now wet granulation has been chosen in approximately 70% of cases despite the higher cost and lower efficiency ratios achieved [(7)]. Recent advances in formulation technologies have led to a shift from traditional wet granulation to dry granulation manufacturing processes in the development of solid oral dosage forms. This change has come about largely because of process expedition, easy handling, and time and cost savings; the wet granulation process requires multiple steps that involve agglomeration (granulation), drying, sieving, particle size reduction, and blending [(8)]. Dry granulation is suitable for medium and high-dose drugs and is particularly applicable for active pharmaceutical ingredients (APIs) that are heat and moisture sensitive [(9)].

Mechanisms of granule formation

In the dry methods, particle adhesion takes place because of applied pressure. A compact or sheet is produced which is larger than the granule size required, and therefore the required size can be attained by milling and sieving. In wet granulation methods, liquid added to dry powders has to be distributed through the powder by the mechanical agitation created in the granulator. The particles adhere to each other because of liquid films, and further agitation and/or liquid addition causes more particles to adhere. The precise mechanism by which a dry powder is transformed into a bed of granules varies for each type of granulation equipment, but the mechanism

discussed below serves as a useful broad generalization of the process. The proposed granulation mechanism can be divided into three stages.

Nucleation

Granulation starts with particle–particle contact and adhesion due to liquid bridges. A number of particles will join to form the pendular state illustrated in **Figure 3.** Further agitation densifies the pendular bodies to form the capillary state, and these bodies act as nuclei for further granule growth.

Transition

Nuclei can grow in two possible ways: either single particles can be added to the nuclei by pendular bridges, or two or more nuclei may combine. The combined nuclei will be reshaped by the agitation of the bed. This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. Providing that this distribution is not excessively large, this is a suitable end-point for granules used in capsule and tablet manufacture, as relatively small granules will produce a uniform tablet die or capsule fill. Larger granules may give rise to problems in small-diameter dies owing to bridging across the die and uneven fill.

Ball growth

Further granule growth produces large, spherical granules and the mean particle size of the granulating system will increase with time. If agitation is continued, granule coalescence will continue and produce an unusable, overmassed system, although this is dependent upon the amount of liquid added and the properties of the material being granulated. Although ball growth produces granules that may be too large for pharmaceutical purposes, some degree of ball growth will occur in planetary mixers and it is an essential feature of some spheronizing equipment.

The four possible mechanisms of ball growth are illustrated in Figure **3.**

Coalescence Two or more granules join to form a larger granule.

Breakage Granules break into fragments which adhere to other granules, forming a layer of material over the surviving granule.

Abrasion *transfer* Agitation of the granule bed leads to the attrition of material from granules.This abraded material adheres to other granules, increasing their size.

Layering When a second batch of powder mix is added to a bed of granules the powder will adhere to the granules, forming a layer over the surface and

increasing the granule size. This mechanism is only relevant to the production of layered granules using spheronizing equipment.

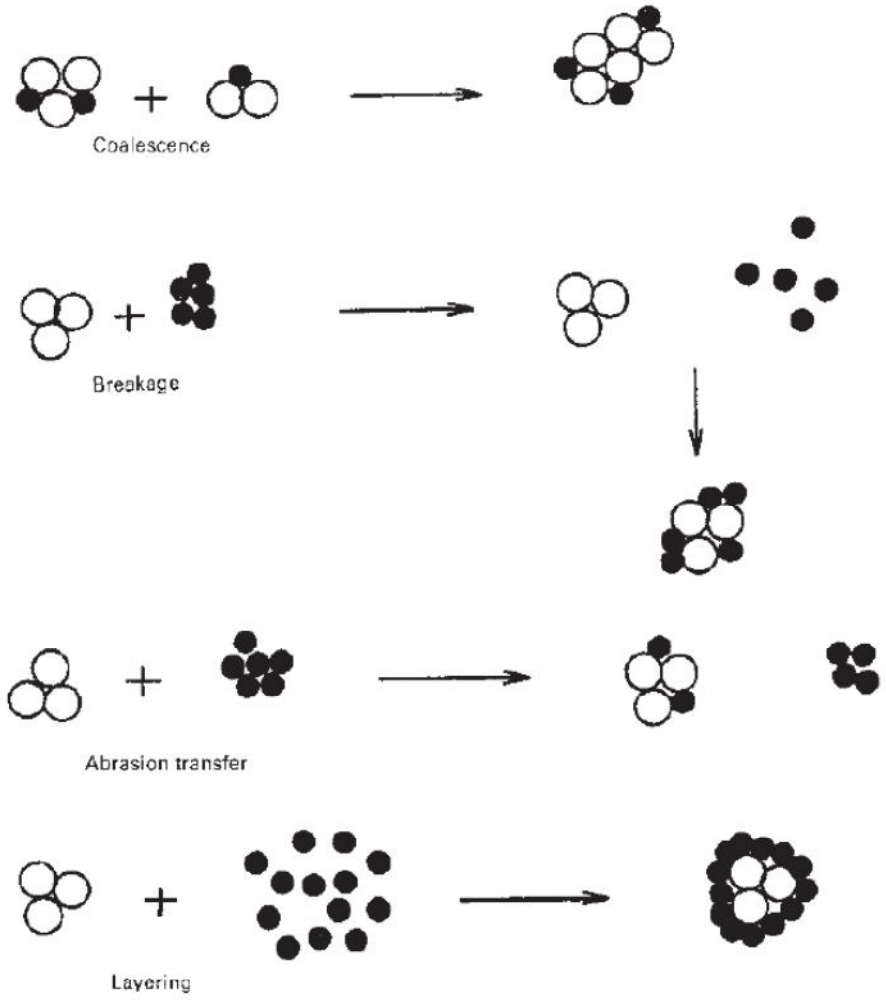


Figure 3 Mechanisms of ball growth during granulation

There will be some degree of overlap between these stages and it will be very difficult to identify a given stage by inspection of the granulating system. For end-product uniformity it is desirable to finish every batch of a formulation at the same stage, and this may be a major problem in pharmaceutical production. Using the slower processes, such as the planetary mixer, there is usually sufficient time to stop the process before overmassing occurs With faster granulation equipment the duration of granulation can only be used as a control parameter when the formulation is such that granule growth is slow and takes place at a fairly uniform rate. In many cases, however, the transition from a non-granulated to an overmassed system is very rapid, and monitoring equipment is necessary to stop the granulation at a predetermined point, known as granulation end-point control.

2.1.2.1. Slugging:

Dry granulation operations do not use moisture or heat to process powders into densified granules. The pharmaceutical industry employs two methods of dry granulation: slugging and roller compaction. Little has been written about pharmaceutical dry granulation technology. Its contemporary use in the industry is 50–60 years, beginning in the late 1940s. However, its popularity has risen in the last 15 years in parallel with the increased research on new efficacious active pharmaceutical ingredients (API) in the pharmaceutical industry. A number of these new API cannot be processed so easily using wet granulation and drying processing steps, because of their chemical fragility and sensitivity. Therefore, this pushes the need for the use of dry granulation processing techniques to advance new API in the 21st century. Briefly, in dry pharmaceutical granulation processing, the powder particles are aggregated under high pressure, typically a pressure of 30–70 bar. Particulate matter can be aggregated when compressed at high pressure because of bonding forces developed by the direct contact between the solid surfaces. The high pressure serves to improve the contact area between the surfaces and thus the overall bonding strength. Sometimes a binding agent is needed to provide additional bonding strength. In the pharmaceutical industry, dry granulation processing in the 1950s–1970s favored a process called slugging. This process design consisted of feeding powder into a large compression machine, such as a Stokes D3 type compression machine, where the powder was compressed into large tablets or slugs, typically in the order of 1 in. diameter with a tablet gauge of about 0.25 in. The tablet slugs were subsequently milled by a separate sizing machine to an appropriate particle size distribution, and further processed into pharmaceutical capsules, powder for oral suspensions, sachets, or tablet dosage forms. The slugging process is still used today by only a few manufacturing firms that have old pharmaceutical formulation processes. If a tablet press is used for the compaction process, the term slugging is used. But since particles with a small particle size do not flow well into the die of a tablet press, the results are weight differences from one tablet (slug) to another. This in turn causes large fluctuations in the forces applied onto the individual slugs, with translates in variations of the slug's mechanical strength. Therefore, the properties of these granulates obtained by milling the slugs cannot be controlled well either. This is one of the main reasons why slugging is hardly used any more as a dry granulation method. Today, modern pharmaceutical formulation processes introduced into the Americas, Western Europe, Australia, and parts of Asia do not use this kind

of dry granulation equipment in newly developed formulations. The slugging process is a relic of the past in modern pharmaceutical technology; roller compaction is the key technology to future dry granulation processing. The slugging process is externally influenced by raw material feed properties such as powder cohesiveness, density, flow characteristics, and powder particle size distribution. The slugging machine's design characteristics such as machine type, feed hopper, feed frame, die diameter, tooling features, compression speed, and slugging pressure also influence the slugging process and the final product properties. In general, the key processing operational aspect of slugging is to maintain a uniform powder fill weight into the dies during the dynamics of the slugging process. This assures the best chance to manufacture uniform powder slugs and, ultimately, uniform densified granules. The compression– slugging setup is a key essential to maximizing the slugging throughput and minimizing the hopper feed-frame and die powder flow problems associated with the process. Slugging compression is normally performed at 4–6 tons hydraulic pressure, at a rate of 10–30 turret revolutions per minute. The specific machine tonnage, turret speed, and roll dwell time required for the process are dependent on the powder blend's physical properties, the tooling configuration, machine parts, and ultimately the slug specifications. Typical slugging machine output ranges from 30 to 50 kg/hr and the machines are not instrumented with modern devices to control their performance. The disadvantages with the slugging technology in the pharmaceutical industry are:

- Single batch processing
- Excessive air and sound pollution
- Frequent maintenance changeover
- Increased use of storage containers
- Poor process control
- Increased needs of manufacturing space
- Poor economies of scale
- Increase of logistics
- Low manufacturing throughput per hour
- More energy and time required to produce 1 kg of slugs than 1 kg of roller compact

Unlike the slugging process technology, roller compaction technology is well suited for dry granulation agglomeration in the era of modern development of active pharmaceutical ingredients in pharmaceutical plants [10].

INTRODUCTION TO KORSCH XL 100 USED FOR SLUGGING:

The KORSCH XL100 is an innovative tablet press for product development, scale-up, and clinical batch production. The XL100 offers a new standardin GMP, extreme accessibility to the compression zone, an exchangeable turret for maximum flexibility, and a combination of quick-disconnects and smooths surfaces that permit fast cleaning and changeover. The machine is extremely robust and rugged, offering a pre compression capability of 10 kN, and a main compression capability of 60 kN, contained in a unique structural design that eliminates vibration to the head piece and base frame. Every technical detail of the XL 100 has been meticulously developed for operator convenience and operational excellence. From the special steel for the turret and die table, to the precision toothed belt for the main drive, the XL 100 offers production scale performance in a development scale machine.

Features of Korsch XL100:

- Small Scale.
- Exchangeable Turret Capability 12/10/8 EU or TSM Tools.
- 10 kN Precompression Force.
- 60 kN Main Compression Force.
- 120 RPM Press Speed Capability.
- Fully Instrumented.
- Fully Portable.
- Large Touch Screen Flush Mounted for Ergonomic Operation.
- PharmaResearch® and PharmaControl® Upgrade Possible.

The XL 100 Pro permits the execution of full compaction studies with limited material quantities. The XL100 may be fully instrumented for the measurement of precompression force, main compression force, ejection force (segmented cam), and scrape off force, to permit product development parameters to be evaluated and stored. KORSCH offers the PharmaResearch®, a Windows based data acquisition

system that permits storage, analysis, and export of compression and ejection force data. In combination with PharmaControl® 3 press force control or PharmaResearch®, the XL100 Pro offers a fully integrated solution for expedited product development and clinical batch production.

PharmaResearch® Comprehensive Data Acquisition and Analysis

PharmaResearch® is a Windows-based system that offers data acquisition and analysis for press force and punch displacement data. The system displays press force waveforms in real time and permits on-demand data collection. The system can collect data locally or write the data to a networked SQL server for centralized data storage and analysis. The system can work with the following tablet press instrumentation:

✓ Precompression Force

✓ Main Compression Force

✓ Ejection Force

✓ Scrape-Off Force

✓ Die-Wall Force

✓ Punch Displacement

The data analysis is automatic and provides a statistical assessment of:

✓ Peak Force

✓ Area Under The Force-Time Curve

✓ Contact Time

✓ Rate of Force Application

✓ Rate of Force Decay

2.1.2.2 ROLLER COMPACTION:

The increasing scale of manufacturing pharmaceutical products worldwide, the need for high processing rates, together with increased levels of good manufacturing practices, necessitate controlled dry granulation processes with as few processing steps as possible. This has been accomplished by instrumenting roller compactors to automate and control the mechanical process. Roller compaction technology plays a

very important role in providing competitive cost control, safety, and quality products in the pharmaceutical industry [10].

The aims of roll compaction/dry granulation are an improved handling of the powders due to a larger particle size and a better flowability. Dust problems are minimized or avoided and the die filling during tableting is improved. Also, this is achievable by increasing the bulk density because less air will escape during tableting process. Sometimes the capping of tablets might also be reduced. Roll compaction/dry granulation can be used, if the drug or the excipient is poorly flowing or sensitive to heat or moisture. It can also be used for densification of powders prior to encapsulation [11].

Compacton Theory:

The process of dry granulation relies on interparticulate bond formation. Granule bond formation is characterized in different stages, which usually occur in the following order:

1. Particle rearrangement
2. Particle deformation
3. Particle fragmentation
4. Particle bonding.

Particle rearrangement occurs initially as powder particles begin filling void spaces. Air begins to leave the powder blend's interstitial spaces, and particles begin to move closer together. This action increases the powder blend's density. Particle shape and size are key factors in the rearrangement process. Spherical particles will tend to move less than particles of other shapes because of their close initial packing to one another.

Particle deformation occurs as compression forces are increased. This deformation increases the points of contact between particles where bonding occurs and is described as plastic deformation.

Particle fragmentation follows as the next bonding stage. This occurs at increased compression force levels. At this stage, particle fracturing creates multiple new surface sites, additional contact points, and potential bonding sites. Particle bonding occurs when plastic deformation and fragmentation occur. It is generally accepted that bonding takes place at the molecular level, and that this is due to the effect of van der Waals forces.

When powder granules undergo an applied force or stress, a stress force is released from the granules. The granules attempt to return to their original shape or form; this is described as elastic deformation. A deformation that does not totally recover after the stress is released is a plastic deformation. Elastic and plastic deformations can occur simultaneously, but one effect usually predominates.

Parrott identified three theories of compression bonding: mechanical, intermolecular, and liquid-surface film. Mechanical bonding purports that individual particles undergo elastic, plastic, and brittle deformation. Bonding of this nature occurs because particle surfaces intertwine, forming mechanical bonds. Intermolecular theory identifies that there are some unsatisfied surface ions that have a potential need to bond to one another. Under pressure, intermolecular forces become pushed together close enough so that van der Waals forces can act to consolidate particles. The liquid surface film theory identifies that bonding occurs because of the existence of a thin liquid film. The thin liquid film is generated from pressure induced by the energy of compression. This mechanism acts as a bonding agent promoting mechanical strength and an enlarged particle [(12)].

Mechanisms of Roll Compaction

The principle of compaction is based on equipment design and operating parameters that influence the starting material in a manner to produce an optimum compact. The space between two rolls, where different mechanisms occurs, is generally divided in three regions (see figure 4) [(11)]:

1. Slip region (feeding zone) – this zone is characterized with particles slipping at the roll surface and at the same time rearrangement and de-aeration can occur. The effectiveness of the slip region is related to wall friction and interparticle friction of the feed (10). The speed of the material is lower than the peripheral speed of the rolls.

2. Nip region (compaction zone) – in the nip region, the material is trapped between two rolls and is moving at the same speed as the roll surface. This forces the material through the region of the maximum pressure where the particles deform plastically and/or break. The limit between feeding and compaction zones is the nip angle α. This angle is directly affected by the roll diameter and established in a line through the rolls' centers to a point on both roll where the powder starts to move at the same speed as the roll (see figure 4). To achieve acceptable compaction, the nip angle

should be sufficiently large. It is about 12° and material characteristics, as particle size and density, can have influence on this value.

3. Extrusion region (release zone) – when the roll gap starts to increase, the compacted ribbon exhibits relaxation as it is released from the rolls.

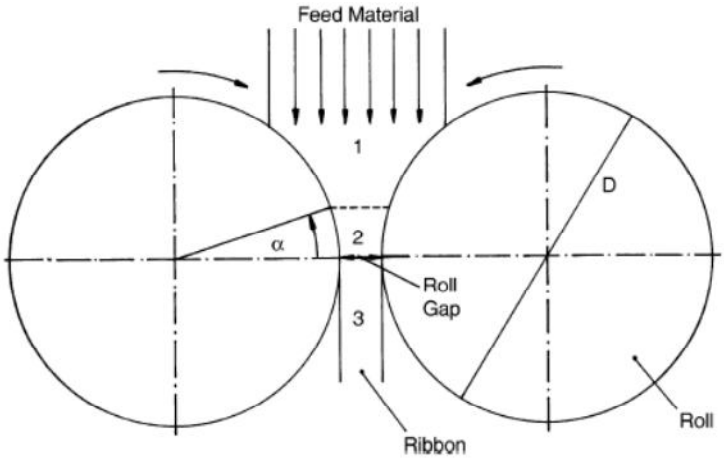


Figure 4 Roll compactor and different zones: 1, feed zone; 2, compaction zone; 3, extrusion zone.

Equation 1 is developed for the linear variation of compact thickness at a specific roll diameter [(14)]

$$e_1 = D\frac{d0}{((d1-d0))(1-\cos[\![\alpha]\!])} \qquad (1)$$

Where e_1 is compact thickness, D is roll diameter, d0 is material density at angle α and d1 is compact density. According to equation 1 it can be concluded that if the same compact thickness is required with different roller diameters, the density of the compacts would be greater with the larger diameter rollers.

Only few suppliers of roll compactors are established in the pharmaceutical field. The machine design differs between suppliers (Fig. 5) [(11)].

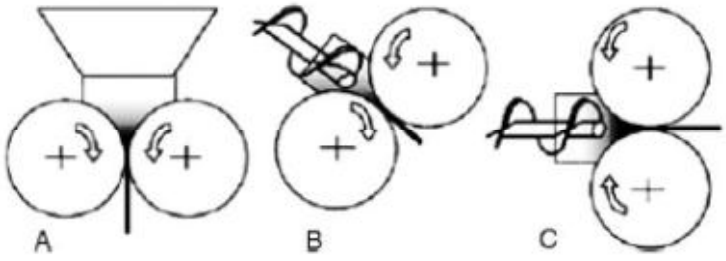


Figure 5 Configuration of roll compactors [(11)]

However, important improvements were implemented by different suppliers during the last decades. The suppliers provide machines in different sizes. Furthermore, the process control depends to a certain extent on the layout of the equipment. For example, if the two rolls are fixed, the compaction force will greatly vary with the fluctuating mass flow. In the case of one movable roll the compaction force can be kept constant by changing the gap width in case of fluctuating mass flow. Another important factor is the roll diameter. Since the nip angle is independent from the roll diameter, a higher roll diameter will result in a higher densification at a constant gap width. Therefore, some machine suppliers only offer machines with the same roll diameter but varying roll width, whereas other suppliers offer machines with different roll diameters.

Model of Roll Compaction Process

Theoretical analysis of the operation of roll-type pressing machines has first been proposed by Johanson in 1965. It was based on understanding the behavior of the material within roll press which involves the interaction between the particles of the material itself as well as the interaction between the material and roll surface. According to Johanson [15] roller compaction involves the continuous shear deformation of the material into a solid mass. The material is assumed to be isotropic, frictional, cohesive and compressible.

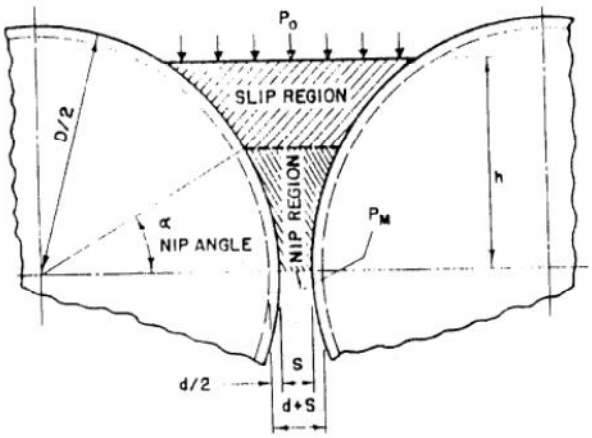


Figure 6 Front view of compactor rolls in horizontal plane.

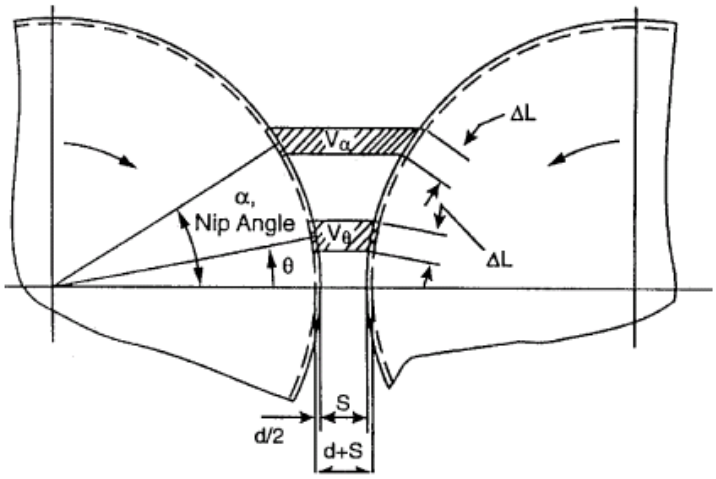


Figure 7 Front view of compactor rolls, depicting nip angle.

In Figure 7, P_0 = horizontal pressure between rolls, θ = angular position of roll bite, α= nip angle, 2d=roll diameter D, h= height above the roll center line at which feed pressure P_0 is applied, Pm= horizontal pressure at θ=0, S=roll gap, ΔL=arc-length segments, V_α =material trapped in volume space described by arc-lengths, V_θ =compressed volume space described by arc-lengths, γ_α and γ_θ respective powder bulk densities in volume spaces V_α and V_θ, and K=a material property constant for a given moisture content, temperature and time of compaction. Johanson stated that the pressure σ_θ at any $\theta < \alpha$ can be determined as a function of the pressure σ_α, at $\theta = \alpha$, by the pressure–density relationship. It was understood that, for increasing pressures, log density was a linear function of log pressure.

Two zones are considered in this approach [16]:

- $\alpha < \theta < \theta h$: slip zones, the rolls moves faster than the powder

- $\theta = \alpha$: the powder sticks to the rolls V powder = V roll

- $0 < \theta < \alpha$: densification takes place

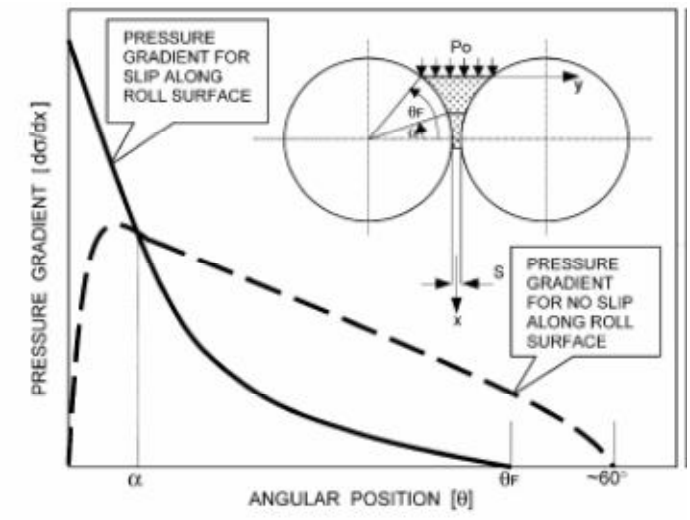


Figure 8 Vertical pressure gradient vs. angular position in roll bite (comparison of different methods)

To determine the nip angle two equations are considered, as it is shown in Figure 8. Determination of the pressure distribution above the nip region was based on the continuous plane-strain deformation and assuming the slip along the roll surface in the slip region, pressure gradient (dσ/dx) is given by the following equation 2.

$$\frac{d\sigma}{dx} = \frac{4\left(\frac{\pi}{2} - \theta - \vartheta\right)\tan\delta}{D/2[1 + \frac{S}{D} - \cos\theta][\cot(A - \mu) - \cot(A + \mu)]} \qquad (2)$$

Where θ is the angular position of the surface of a roll, such that θ = 0 corresponds to the minimum gap, ν acute angle, δ angle of internal friction, μ friction coefficient, and parameter A is given by:

$$A = \frac{\theta + \vartheta + \left(\frac{\pi}{2}\right)}{2} \qquad (3)$$

A typical dσ/dx function is shown by the solid line in Figure 8.

In the nip region no slip occurs along the rolls surface and all material trapped between the rolls at the position of nip angle must be compressed into a compact with a thickness equal to the roll gap. In this case, where slip does not occur, pressure gradient (dσ/dx) is given by equation 4.

$$\frac{d\sigma}{dx} = \frac{K\sigma 0(2\cos\theta - 1 - S/D)\tan\theta}{D/2[\frac{d}{D} + (1 + \frac{S}{D} - \cos\theta)\ \cos\theta]} \quad (4)$$

This function is illustrated by the dashed line in Figure 8. According to Johanson (15) at the nip angle α (equation 5) the pressure gradient in the slip and nip regions are equal

$$\left(\frac{d\sigma}{dx}\right) slip = \left(\frac{d\sigma}{dx}\right) nip \quad (5)$$

The intersection point of two curves (see figure 8.) gives the angles of nip α.

In general, the nip angle strongly depends on the material compressibility factor K, material flow properties, angle of internal friction, angle of wall friction. Dependence on the roll diameter and roll gap is almost negligible, especially when dimensionless roll gap S/D is less than 1 [(13) (15) (16)].

Equipment

The successful roll compaction of a powder depends on the matching powder properties, especially its compressibility and flowability, and to both the design and operating conditions of the compactor [(16)]. In the pharmaceutical field only a few producer of roll compactors are established. Although the general layout of the machines looks alike, there are some features that differ from compactor to compactor. These lead to a type classification:

Roll assembly: rolls can be mounted in a horizontal, inclined and vertical position (see figure 9) [(11)].

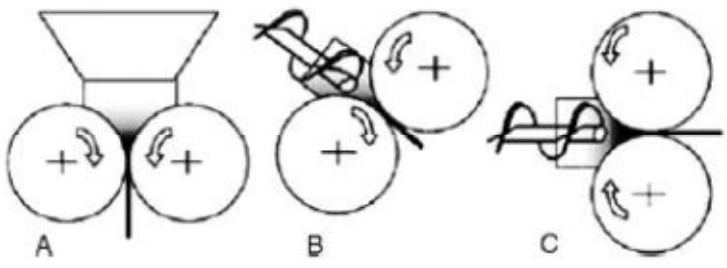


Figure 9 Configuration of roll compactors [(11)]

Horizontal position of rolls is a characteristic for Fitzpatrick Company, Bepex, Komarek (A), inclined for Gerteis (B) and Vertical for Alexanderwerk (C) [11].

The position of the rolls is mainly a manner of design and therefore it only plays minor role. However, the vertical assembly might induce that the nip angles in upper and lower roll differ. This can happen because the direction of force by friction and force of gravity is completely different for the two rolls. If nip angle is quite small the powder might stay in place, showing an increase in temperature, giving reason for concerning a thermal degradation of the material. When vertically assembled rolls are used differences in nip angles should be taken in to account.

- Fixed vs. movable rolls: according to gap system two type of roller compactors exist. One in which the distance between the rolls is constant during the process of powder densification and one in which this distance can be changed. In the first case gap size cannot be varied during the process of compaction. Ribbons which are produced have the same geometrical dimensions, but porosity can be changed with the fluctuating mass flow [11]. Compactors with variable gap system have one fixed and one moveable roll. The consolidating force on the material between two rolls is supplied by hydraulic units (see fig 10). This unit acts upon the floating roll which can move horizontally depending on feeding rate and applied pressure [16].

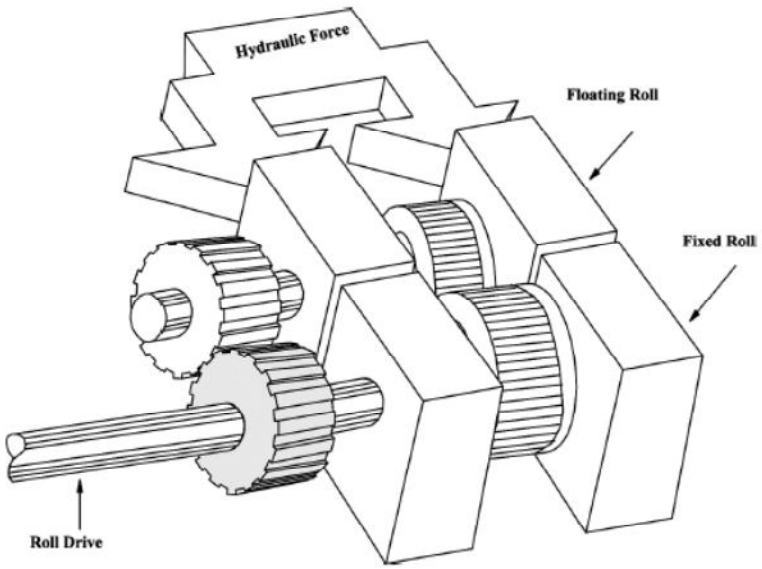


Figure 10 Fixed and floating roll pair.

- Roll surface: Roll surface has an effect on the efficiency and production rate in the powder compaction. According to powder properties different roll surface can be used: smooth, knurled and pocket design (see fig 11)

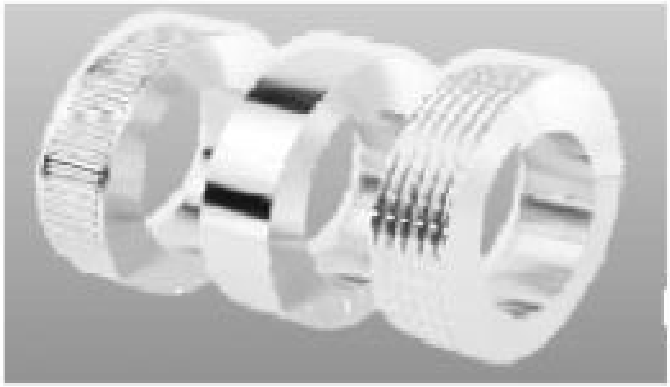


Figure 11 Various roll surfaces for compaction

-Feeding system: three different ways of feeding material into to the compactor exist, gravity transport, single screw feeder and double screw feeder (see figure 12). It must achieve a uniform and continuous flow of material in order to fill the nip between the rolls correctly and sufficiently, so that the formed compacts are not heterogeneous. When powder is dense and free flowing gravity feeder can be used, but for most powders, which are lightweight and do not fly freely single or double screw feeder is required. During feeding, vacuum deaeration can be applied to remove air from a powder with low bulk density.

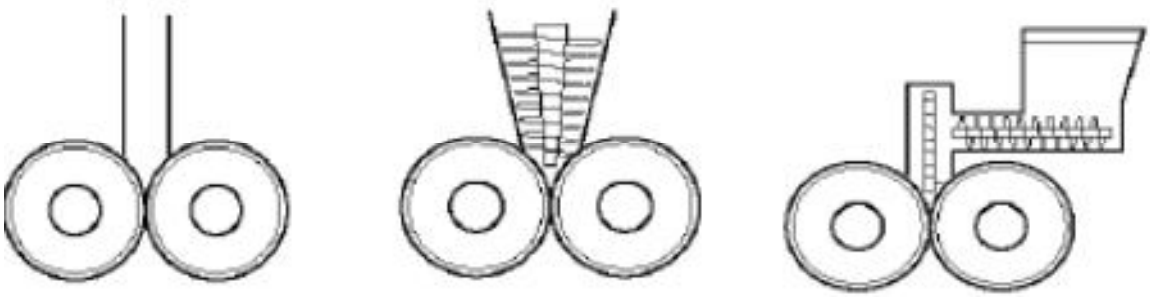


Figure 12 Different feeding system: a) gravity feeder, b) single screw feeder, c) double screw feeder

Process Parameters

Compaction in a roll press is more complicated than it looks at the first sight. Efficiency of roller compaction is based on the equipment design and operating parameters. The main process variables which can affect compaction are:

- Compaction pressure: if pressure is too low there is no compaction, but in the same time if it is too high over compaction will occur.

-Speed of feeding screw (vertical vs. horizontal): speed of vertical and horizontal screw should be optimized otherwise feeding is not continuous and compaction is not homogeneous.

- **Roll speed** affects the compaction by determining the dwell time that material should spend in the nip region which has an impact on the ability of the product to deaereate prior to passing between two rolls.

-Roll gap is the distance between the rolls at their closest 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.

Formulation parameters:

The influence of formulation parameters on the properties of a product cannot be ignored. However, the influence of physical properties of a material, such as particle size and porosity, on its compactibility using roller compaction technique has not been extensively studied. Most of the studies carried out were those to investigate the influence of the physical properties of starting materials employed for manufacturing techniques other than roller compaction. In most cases, roller compaction preceded tabletting. Thus, properties of the resultant tablets were of interest. Only a few studies had been carried out to investigate the properties of flakes produced and their relationship with the resultant granule and tablet properties.

-Effects of size and porosity of particles:

McKenna and McCafferty[(60)] found that smaller particle size of a plastic deforming material, Sta-Rx 1500 and a fragmenting material, lactose, resulted in tablets of higher tensile strength. However, the tensile strength of microcrystalline cellulose (MCC) tablet appeared to be independent of

primary particle size. Binary mixtures of different particle size fractions of α-lactose monohydrate had been investigated [61]. The authors found that tablet crushing strength and tablet specific surface area of various binary mixtures were lower than the values obtained by linear interpolation of tablets compressed from single sieve fractions. The lowest specific surface area and crushing strength were obtained by compacts produced with 40% fine fractions.

-Effect of intrinsic nature of material:

Scientists demonstrated that different roller compaction parameters were required for lactose 200M and maize starch to obtain granules with optimal properties. Lactose, a fragmenting material, required a high roller speed: horizontal screw speed ratio while maize starch, a plastic deforming material, performed better with a low roller speed: horizontal screw speed ratio[43]. Crystalline lactose monohydrate is the most widely used diluent for tablet formulation. It is also referred to as lactose, hydrous lactose or regular lactose. It is usually supplied in powder form (ground) for use as a filler for tablet manufacture, often by the wet granulation technique. For use in direct compression, coarse, regular grade or sieved crystalline fractions of α-lactose monohydrate, particularly the 100-mesh grade, is used because of their better flowability.

Advantages [10]:

- Simplifies processing
- Uses less raw materials
- Facilitates powder flow
- Eliminates water-induced degradants
- Uses minimal energy to operate
- Improves process cycle time
- Requires less man-hours to operate
- Prevents particle segregation
- Improves drug dosage weight control
- Facilitates continuous manufacturing
- Reproduces consistent particle density

- Improves content uniformity
- Produces good tablet and capsule disintegration
- Does not require explosion proof room/ equipment
- Eliminates aqueous and solvent granulating
- Produces a dry product that is process scalable

Disadvantages:

- Weakening or disruption of the crystal lattice
- Production of fines
- Loss of reworkability

Since granulating solvent is not used during dry granulation, solution or solution mediated phase transformations are eliminated, thus the probability of phase transitions with this granulation unit operation is reduced. However, the applied mechanical stresses during processing may lead to phase transformation via the solid-state or melt mechanisms [(18)].

Process Parameters

Besides the type and design of mill, the most important factors which can affect the quality of particles are: feed rate, screen size and rotor speed.

- **Feed rate** controls amount of material that enter to the mill and can control overfeeding or underfeeding. Although, either phenomenon should be avoided, overfeeding is relatively more harmful. When amount of material which is fed is bigger than amount which is discharged it stays in the milling chamber and it leads to greater size reduction, over loads the motor and reduced capacity of the mill [(20)]. In general, the feed rate should be equal to the rate of discharge.

- **Screen**, located directly under the blade, prevents particles to leave the chamber until they are at least the same size as the screen holes. The screen size doesn't necessarily define the particle size of the final product. Depending on rotor speed, particles find various dimension and shape of angle at which they approach the screen. The higher rotor speed will influence the smaller angle under which particles hits the screen. This means that particles will pass through the smaller hole in the screen (see figure 14), leading to smaller particle size of the final product. The

thickness of the screen has influence on the particle size as well. The thicker the screen, the smaller particle can pass the screen (see figure 13)

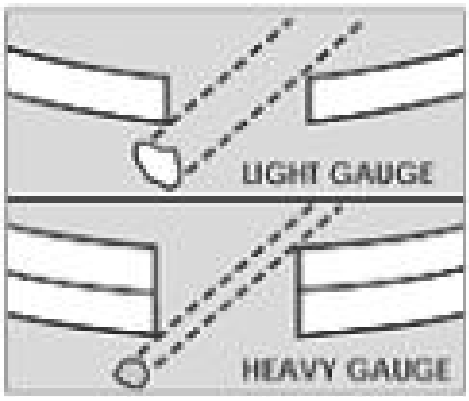


Figure 13 Influence of the screen thickness to particle size

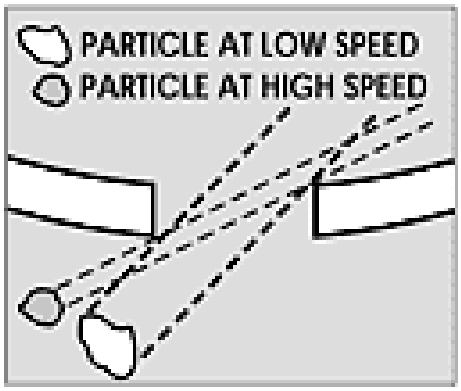


Figure 14 Influence of the rotor speed to particle size

- **Rotor speed** directly affects the particle size range. If all the other variables are the constant, faster rotor speed induces the smaller particle size.

As all processes, milling has some advantages and disadvantages, which should be considered before starting with size reduction of the material.

Milling

The final product of the roller compaction – ribbons, must be subsequently broken to the required particle size. In general, the milling or size reduction is the mechanical process of reducing of the size of particles or aggregates. To initiate reduction of particle size external forces should be applied [(19)].

The milling is affected by a variety of factors and has a direct influence on the quality of the final product. The selection of equipment which should be used for this process is determined by the properties of feed material and specification of the product.

Classification of Mills

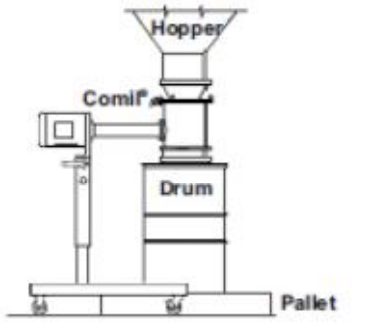
The most convenient classification of size reduction equipment is according to the way in which forces are applied; impact, shear attrition and shear-compression [20].

Table 1 Characteristic of Different Types of Mill

Mechanism of Acting	Example	Particle size
Impact	Hammer mill	Medium to fine
Shear	Extruder and hand screen	Coarse
Attrition	Attrition Oscillating granulator	Coarse to medium
Shear-compression	Comil	Medium to coarse

The type of mill can affect the shape of the granules and throughput, and shape of the granules affect the flow properties.

An impact mill produces sharp and irregular granule where flowability sometimes may be a problem, whereas granules produced by attrition mill are more spherical.



Gravity Feed Self Contained System

Table 2 Advantages and disadvantages of milling

Advantages	**Disadvantages**
-Increase of surface area (increase dissolution and bioavailability) -Enhance content uniformity (increase number of particles per unit weight) -Improve flowability (irregular shape of the material) -Control particle size distribution	-Change in polymorphic form -Possible degradation of the drug

INTRODUCTION TO ROLLER COMPACTOR (FITZ PATTRICK)

MODEL IR220 LAB SCALE CHILSONATOR

The Chilsonator Automated Control System is designed to provide optimum process control with excellent operator interface and data monitoring. The system includes a Programmable Logic Controller which is connected to an Operator Interface Station. The operator is able to view all of the instrument measurements and machine status information in picture form on the control monitor. Features of the Chilsonator Automated Control System include:

• Operator Interface

• On-Line Help and Diagnostic Functions

• Restricted Access of Various Functions

• Maintenance Screen

• Calibration Screen

• Roll Gap Control

• Programmable Recipes

• Historical Trending

• Report Generation

• Alarm Management

• Optional XL Reporter for Data Parameter Logging, Facilitating 21CFR Part II Compliance.

2.1.2.3 TABLETS

As it is explained in the beginning, tablets can be produced from a mixture of a powder, or aggregated particles of a powder (granules). Whatever method is used, the resulting tablets should have certain properties. Tablets have to be enough strong and resistant to abrasion during manufacturing, packaging and use, but in the same time, active material from tablets must be bioavailable. Bioavailability can be monitored by dissolution and disintegration test [22]. In order to achieve these characteristics, active pharmaceutical ingredient is blended with different ingredients having specific functions. The homogeneity of the powder mixture is essential to improve both mechanical and medicinal properties of the tablets.

Although, tablets exist in different forms, the way in which they are produced is in general the same [23].

When a force is applied on a powder bed, a lot of mechanisms become involved in transformation of the powder into a porous, coherent compact called tablet.

According to Nyström [24] five mechanisms are involved in the powder compaction:

1. Particle rearrangement
2. Elastic deformation of particles
3. Plastic deformation of particles
4. Fragmentation of particles
5. Formation of interparticulate bonds

At the beginning of powder compaction, particles are rearranged, and reduction in volume occurs due to closer packing of powder. Depending on the packing characteristics of particles, at certain load no more rearrangement can take place.

As the pressure is increased, the initial particles change shape or deform and further compression leads to some type of deformation (see figure 15). When the load is removed, some particles are able to return to original shape (elastic deformation), whilst other ones are permanently deformed (plastic deformation). The force required to initiate a plastic deformation is noted as yield stress [25]. Brittle particle undergo fragmentation, crashing of the original particles into smaller units. A single particle may pass through several of these stages during compaction [23, 26].

Some materials consolidate by a plastic deformation (microcrystalline cellulose, starch, sodium chloride), some by fragmentation (crystalline lactose, sucrose, Emcompress), but all materials posses both elastic and plastic component [24].

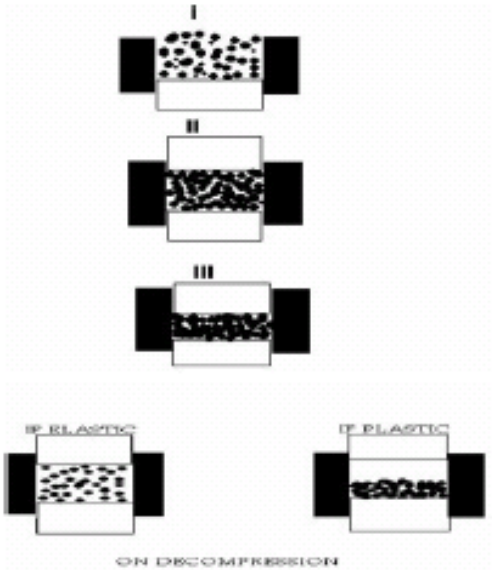


Figure 15 Stages involved in compression (I – III) and decompression

Compression Bonding Mechanisms

When particles get together, adhesive forces are developed, which are responsible for the strength of compacts after compression and compaction [6].

In compression of dry powders, dominating bonds of interparticular adhesion are [6, 24]:

- Solid bridges
- Distance attraction forces (intermolecular forces)
- Mechanical interlocking (between irregular shaped particles)

Solid bridges can be formed at the place where there is a particle-particle contact at an atomic level. Due to their structure, solid bridges seem to be relatively strong bonds and tablets containing this type of bonds can be related with prolonged disintegration time.

Intermolecular forces are all bonding forces which coordinate between surfaces separated with some distance and these forces are relatively weak. In this group are involved: Van der Waals forces, electrostatic forces and hydrogen bonding [24].

Material which is bonded with forces of mechanical interlocking has low strength and accelerated disintegration time, but for producing tablets it requires a high

compression forces. This type of bonds induces the hooking and twisting of the packed material.

Mechanical interlocking and Van der Waals forces are the mechanisms which are included in the process of roller compaction so it could be expected that disintegration time of tablets produced by this method is fast.

Properties of Tableting Materials:

As it is previously explained materials could consolidate by different type of deformation. Materials which are undergoing extensively fragmentation during compaction creates a large number of interparticulate contacts point and relatively weak attraction force, which act over distance. However, even weak attraction force are formed, due to the large number of attractions zones relatively strong compacts could be formed. Less fragmenting materials form a less number of contact points between particles and only if strong attraction forces are created, strong compacts could be formed. Extensively plastic materials could develop a large number of attraction forces and form strong compacts. Due to compression behavior, both fragmenting and plastic behavior materials are considered as bond-forming compression mechanisms. The difference between two mechanisms is that fragmentation affects mainly the number of interparticulate bonding while plastic deformation affects mainly the bonding force of these bonds. This is due to fact that fragmenting material form a large number of bonds, while material with plastic deformation forms a strong attraction force as well.

Mechanical Properties of Tablets:

The characterization of compressibility and compactibility of the material has very important role in the tablet manufacturing. Compressibility is an ability of a powder to decrease in volume under pressure, and compactibility is the ability of the material to be compressed into a tablet of specified strength [28]. Since the first accurate compaction data were obtained, the use of compaction equations have played an important role to relate the relationship between density or porosity of the compact, and the applied pressure [29,30]. Many compaction techniques are used to characterize the consolidation behavior of pharmaceutical solids.

2.2 INTRODUCTION TO SeDeM ANALYSIS [64-69]:

Thorough preformulation work is the foundation of developing robust formulations. The SeDeM Method is a new graphical method for application in tablet-preformulation studies. This system helps in determining compressibility profile of powdered substances (APIs and excipients) based on their physical characteristics. The expert graphical system provides the magnitude at which powdered substances can be successfully compressed by means of direct compression. This knowledge facilitates required alteration to be done in the powdered substances to be applicable in direct compression technology. By determining whether powders (API or excipients) are suitable for direct compression, the SeDeM profile will inform about the advantages and gaps of those powdered substance to be used in direct compression, so the system informs on whether the direct compression method is appropriate.

PARAMETERS

The system depends upon five factors on the basis of the physical properties of the powdered substances. Five factors comprise of 12 different parameters to characterize galenic properties of powdered substances for determination of appropriateness for direct compression.

Table 3 Factors and parameters used in the system with equation and conversion factor are shown

Incidence factor	Parameters	Equation	Acceptable range	Conversion factor
Dimension	Bulk Density (Da)	Da = P/Va	0–1 g/ml	10v
	Tapped density (Dc)	Dc = P/Vc	0–1 g/ml	10v
Compressibility	Inter particle porosity (Ie)	Ie = Dc −Da/Dc × Da	0–1.2	10v/1.2
	Carr's index (IC)	IC = (Dc − Da/Dc) 100	0–50 (%)	v/5

	Cohesion Index (Icd)	Experimental	0–200 (N)	v/20
Flowability	Hausners ratio (IH)	IH = Dc/Da	3–1	(30-10v)/2
	Angle of repose (α)	tg α = h/r	50–0 (°)	10 − (v/5)
	Powder flow (t”)	Experimental	20–0 (s)	10 − (v/2)
Lubricity/Stability	Loss on drying (%HR)	Experimental	0-10 (%)	10-v
	Hygroscopicity (%H)	Experimental	20–0 (%)	10 − (v/2)
Lubricity/Dosage	Particle size<50μm (%Pf)	Experimental	50–0 (%)	10 − (v/5)
	Homogeneity index (Iθ)	Iθ = Fm / 100 + Δ Fmn	$0–2 \times 10^{-2}$	500v

STEPS TO OBTAIN THE COMPRESSIBILITY PROFILE OF THE POWDERED SUBSTANCES USING SEDEM DIAGRAM:

Step 1: It uses the radar chart (spider chart) for the presentation of data points. The Radar chart is a very effective tool for comparing multiple entities based on different characteristics (i.e. bulk density, carr index etc.). The values obtained from experiments are converted to radius ranging from 0 to 10 with the use of conversion factor. When all values are 10 it will become form of circumscribed regular polygon, drawn by connecting the radius values with linear segments. The figure formed shows the characteristics of the product and each of parameters that determines whether the product is suitable for direct compression.

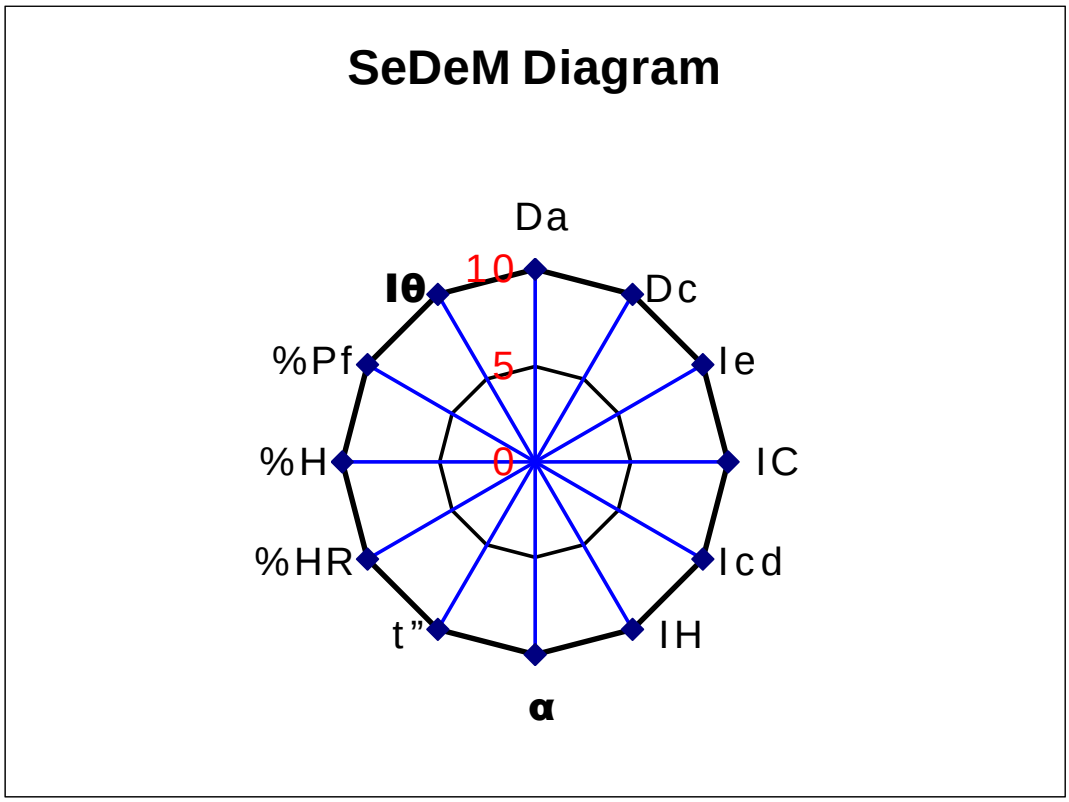


Figure 16 The SeDeM Diagram with 12 parameters.

Step 2: Following indexes are calculated in this step

(1) (Parameter Index)IP= $\frac{n°P\geq 5}{n°Pt}$ (6)

Where:

n°P≥5: Indicates the number of parameters whose value is equal to or higher than 5

n° Pt: Indicates the total number of parameters studied

The acceptability limit would correspond to:

$$IP = \frac{n°P \geq 5}{n°Pt} = 0.5$$

(2)Parameter profile Index (IPP)=Average of (r) all parameters (7)

Average (r) = mean value of the parameters calculated.

The acceptability limit would correspond to: IPP = media (r) = 5

(3) Good Compressibility Index (IGC) =IPP x f

Where

$$f=\text{Reliability factor}=\frac{\text{Polygon area}}{\text{Circle area}}$$

The acceptability limit would correspond to: ICG = IPP x f = 5.

The reliability factor indicates that the inclusion of more parameters increases the reliability of the method. The system depends upon five to six factors on the basis of the physical properties of the powdered substances. For determination of compressibily of the powdered substances five factors comprising of 12 diferent parameters (Table 1) have been used while for the development of platform technology of Oro Dispersible Tablet (ODT) 6 factors comprising of 15 parameters are used to characterize galenic properties of powdered substances. The Number of parameters can be increased or decreased according to the need of research.

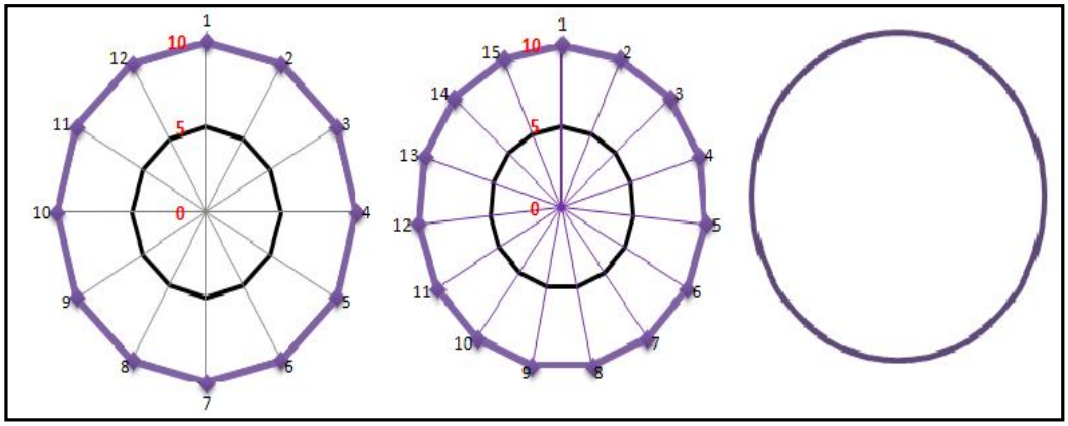


Figure 17 SeDeM diagram (a) 12 parameters (b) 15 parameters (c) infinite parameters

The greater the number of parameters selected, the greater the reliability of the method, in such a way that to obtain a reliability of the 100%, the number of parameters applied would have to be infinite (reliability factor = 1).

Step 3: Interpretation

Table 4 value of IGC with its inference

IGC	INFERENCE
Less than 3	Techniques other than direct compression will be required
Between 3to5	Requires addition of direct compressible excipients
Equal to or More than 5	Suitable for direct compression

The application of the SeDeM Diagram allows the determination of the direct compression behaviour of a powdered substance from the index of parametric profile (IPP) and the index of good compression (IGC), in such a way that an IPP and an IGC equal or over 5 indicates that the powder displays characteristics that make it suitable for direct compression, adding only a small amount of lubricant (3.5% of the magnesium stearate, talc and Aerosil® 200). Also, with IPP and IGC values between 3 and 5, the substance will require a DC diluent excipient suitable for direct compression. In addition, it is deduced that techniques other than direct compression (wet granulation or dry granulation) will be required for APIs with IPP and IGC values below 3.

APPLICATIONS OF SeDeM

(a) Determination of API suitability and calculation of directly compressible Exicipient required for the DC technology:

Inderbir singh et al carried out preformulation study on cefuroxime axetil and paracetamol using SeDeM and proved that both API having Good Compressibility Index (IGC) lower than 3 hence incompatible for direct compression. Another scientist Josep M. Suñé Negre, et al performed the characterization study of API SX-325 using SeDeM Diagram and observed that API is a dusty substance with moderately acceptable compressibility, good fluidity/flowability, lubrication/dosage and poor lubrication /Stability which can be improved by taking measures like drying the material and preparing the tablet in rooms with controlled relative humidity below 25%.Both the research came on a conclusion that SeDeM diagram can be used to characterize the suitability of an API in the formulation for direct compression technology. It is recommended that the selected drugs are required to be blended with suitable excipients so that the radius value of the powder characteristic parameters

will become > 5.0 making IGC acceptable for SeDeM diagram method. In line of these observations SeDeM diagram method could be seen as a useful preformulation tool for galenic characterization of API and excipients with respect to their suitability for direct compression. The proposed equation for the calculation of amount of exciepient required for direct compression on the basis of SeDeM radius is as follows

$$CP=100-\left(\frac{RE-R}{RE-RP}\times 100\right) \quad (8)$$

Where:

CP = % of corrective excipient

RE = mean-incidence radius value (compressibility) of the corrective excipient

R = mean-incidence radius value to be obtained in the blend

RP = mean-incidence radius value (compressibility) of the API to be corrected

The unknown values are replaced by the calculated ones required for each substance in order to obtain R = 5 (5 is the minimum value considered necessary to achieve satisfactory compression)

For example:

Table 5 Example of API with % Corrective excipient

Ingredient	Compressibility radius	Cp
Paracetamol	3.25 (RP)	46.94
Avicel PH101	7.01 (RE)	

(b) Quality control of batches of a single API or excipient used for direct compression:

Through experimental determination of the SeDeM Method parameters, and their subsequent mathematical treatment and graphical expression (SeDeM Diagram), different batches of the same API or excipient can be analysed to determine batch to batch reproducibility. Researcher Pilar Pe´rez et al [(69)] studied the batch to batch variability of glucosamine salt with the use of SeDeM method and found that the manufacturing process of three different batches of API offers good batch to batch

reproducibility and thus batches with the similar pharmaceutical parameters can be generated.

(c) Application of the SeDeM method to differentiate the excipient in the same chemical family:

The SeDeM system is useful in determining the difference in the excipients of the same family with different physical characteristics. For example different grades of lactose belonging to same family but different physical characteristics were evaluated for direct compression in the study done by (Suñé et al, 2008b).

(d) Application of the SeDeM Diagram to differentiate excipients of the same functional type:

Different excipients of the formulation like disintegrants or diluents which have same functionality but belong to different chemical family can be discriminated based on their compressibility with the use of sedem system. This will make easy for the formulator to make a choice between the excipients with the same functionality for the direct compression with the given API. For example different disintegrants were evaluated based on the difference between minor or major compressibility in the study done by Aguilar et al [(67)].

(e) The new model SeDeM-ODT to develop orally disintegrating tablets by direct Compression:

Application of the SeDeM method in evaluating the excipients has been explored in the study done by Josep M. Sun˜e´-Negre et al. They performed the study using 6 different directly compressible diluent used for ODT and established a mathematical equation to determine the best DC diluent based on their compressibility characteristics. Thus from the above study it can be concluded that SeDeM Method is an appropriate system, effective tool for determining a viable formulation for tablets prepared by direct compression, and can thus be used as the basis for the relevant pharmaceutical development.

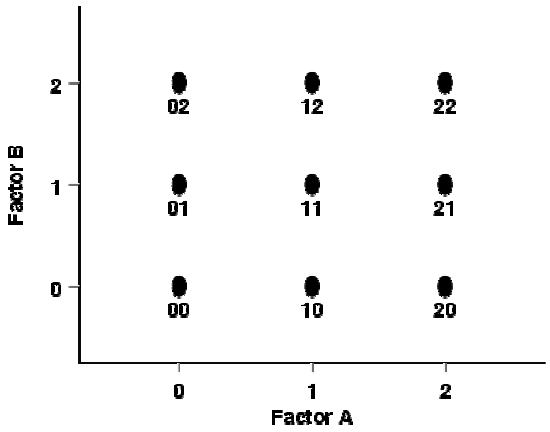
2.3. INTRODUCTION TO 3^2 FULL FACTORIAL DESIGN:

The three-level design is written as a 3k factorial design. It means that k factors are considered, each at 3 levels. These are (usually) referred to as low, intermediate and high levels. These levels are numerically expressed as 0, 1, and 2. One could have considered the digits -1, 0, and +1, but this may be confusing with respect to the 2-level designs since 0 is reserved for center points. The reason that the three-level designs were proposed is to model possible curvature in the response function and to handle the case of nominal factors at 3 levels. A third level for a continuous factor facilitates investigation of a quadratic relationship between the response and each of the factors.

Unfortunately, the three-level design is prohibitive in terms of the number of runs, and thus in terms of cost and effort. For example a two-level design with center points is much less expensive while it still is a very good (and simple) way to establish the presence or absence of curvature. Three-level design may require prohibitive number of runs.

The 3^2 design

This is the simplest three-level design. It has two factors, each at three levels. The 9 treatment combinations for this type of design can be shown pictorially as follows:



A notation such as "20" means that factor A is at its high level (2) and factor B is at its low level (0).

2.4. INTRODUCTION TO OPTIMIZATION DESIGN [70]

Objectives of Response Surface Methodology (RSM)

- Optimizing the process for formulation, i.e. maximizing or minimizing one or more of the responses, keeping the remainder within a satisfactory range.
- Carrying out simulations with the model equation.
- Obtaining a process or product with properties (responses) within a fixed range of values.
- Understanding the process better, thus assisting development, scale-up, and transfer of formulations and processes.
- Being capable of knowing at any time the optimum manufacturing conditions to obtain a product with a particular set of properties.
- Plotting the responses.
- To find the conditions where the result of the process is insensitive to process variation the process being therefore robust.

Central Composite Design

Central composite designs are two level full factorial (2^k) or fractional factorial (2^{k-f}) designs augmented by a number of center points and other chosen runs. These designs are such that they allow the estimation of all the regression parameters required to fit a second order model to a given response.

The simplest of the central composite designs can be used to fit a second order model to a response with two factors. The design consists of a 2^2 full factorial design augmented by a few runs at the center point shown in figure 4 (a). A central composite design is obtained when runs at four other points (-1, 0), (1, 0), (0,-1) and (0, 1) are added to this design. These points are referred to as *axial points* or *star points* and represent runs where all but one of the factors are set at their mid-levels. The number of axial points in central composite design having k factors is 2^k. The distance of the axial points from the center point is denoted by α and is always specified in terms of coded values. For example, the central composite design in Figure 4 (b) has $\alpha = 1$, while for the design of Figure 4 (c) $\alpha = 1.414$. It can be noted that when $\alpha > 1$, each factor is run at five levels ($-\alpha, -1, 0, 1, \alpha$) instead of the three levels of -1,0 and 1.

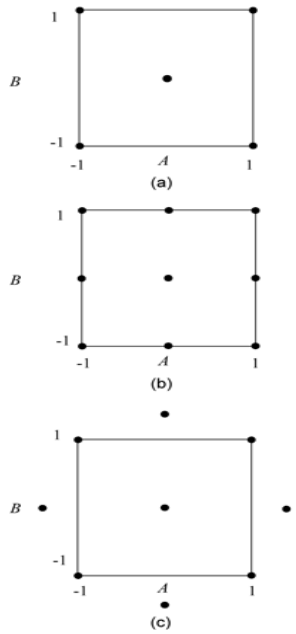


Figure 18 : Central composite designs - (a) shows the 2^2 design with center point runs, (b) shows the two-factor central composite design with $\alpha=1$ and (c) shows the two-factor central composite design with $\alpha=\sqrt{2}$.

Mathematical Model

For analyzing the influence of multiple factors, a mathematical polynomial equation model of design was established. A quadratic model expressed as following equation was used to correlate the theoretical response (Y) to the coded variables (X), where B_0 , Bi , Bii , Bij are the regression coefficients, for intercept, linear, quadratic, and interaction terms respectively.

$$\mathbf{Y= B_0 + B_1X_1 + B_2X_2 + B_{12}X_1X_2.....}$$

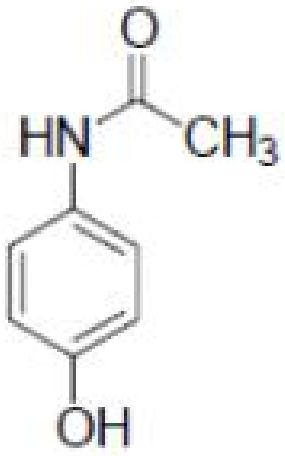
Where X_1 and X_2 are speed and roll pressure respectively. The polynomial equation obtained for each response property was analyzed using RSM. The optimum levels of the selected variables were obtained by solving the regression equation and also by analyzing the response surface contour and surface plots.

2.4. INTRODUCTION TO PARACETAMOL [71, 72]:

Description:

Acetaminophen, also known as Paracetamol, is commonly used for its analgesic and antipyretic effects. Its therapeutic effects are similar to salicylates, but it lacks anti-inflammatory, antiplatelet, and gastric ulcerative effects.

Structure:



Molecular Weight: 151.2 gm/mole

Use:

For temporary relief of fever and minor aches and pains.

Identification

Test A may be omitted if tests B C and D are carried out. Tests B, C and D may be omitted if test A is carried out.

A. Determine by infrared absorption spectrophotometry. Compare the spectrum with that obtained with *paracetamol RS* or with the reference spectrum of paracetamol.

B. Dissolve 50 mg in sufficient *methanol* to produce 100 ml. To 1 ml of this solution add 0.5 ml of *0.1 M hydrochloric acid* and dilute to 100 ml with *methanol*. Protect the resulting solution from bright light and immediately measure the absorbance at the maximum at about 249 nm; absorbance at 249 nm, about 0.44.

C. Boil 0.1 g in 1 ml of *hydrochloric acid* for 3 minutes, add 10 ml of *water* and cool; no precipitate is produced. Add 0.05 ml of *0.0167 M potassium dichromate*; a violet colour develops which does not turn red.

D. Gives the reaction of acetyl groups.

Pharmacodynamics:

Acetaminophen (USAN) or Paracetamol (INN) is a widely used analgesic and antipyretic drug that is used for the relief of fever, headaches, and other minor aches and pains. It is a major ingredient in numerous cold and flu medications and many prescription analgesics. It is extremely safe in standard doses, but because of its wide availability, deliberate or accidental overdoses are not uncommon. Acetaminophen, unlike other common analgesics such as aspirin and ibuprofen, has no anti-inflammatory properties or effects on platelet function, and it is not a member of the class of drugs known as non-steroidal anti-inflammatory drugs or NSAIDs. At therapeutic doses acetaminophen does not irritate the lining of the stomach nor affect blood coagulation, kidney function, or the fetal ductus arteriosus (as NSAIDs can). Like NSAIDs and unlike opioid analgesics, acetaminophen does not cause euphoria or alter mood in any way. Acetaminophen and NSAIDs have the benefit of being completely free of problems with addiction, dependence, tolerance and withdrawal. Acetaminophen is used on its own or in combination with pseudoephedrine, dextromethorphan, chlorpheniramine, diphenhydramine, doxylamine, codeine, hydrocodone, or oxycodone.

Mechanism of action:

Acetaminophen is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin (PG) synthesis. Unlike NSAIDs, acetaminophen does not inhibit cyclooxygenase in peripheral tissues and, thus, has no peripheral anti-inflammatory affects. While aspirin acts as an irreversible inhibitor of COX and directly blocks the enzyme's active site, studies have found that acetaminophen indirectly blocks COX, and that this blockade is ineffective in the presence of peroxides. This might explain why acetaminophen is effective in the central nervous system and in endothelial cells but not in platelets and immune cells which have high levels of peroxides. Studies also report data suggesting that acetaminophen selectively

blocks a variant of the COX enzyme that is different from the known variants COX-1 and COX-2. This enzyme is now referred to as COX-3. Its exact mechanism of action is still poorly understood, but future research may provide further insight into how it works. The antipyretic properties of acetaminophen are likely due to direct effects on the heat-regulating centres of the hypothalamus resulting in peripheral vasodilation, sweating and hence heat dissipation.

Route of elimination:
Approximately 80% of acetaminophen is excreted in the urine after conjugation and about 3% is excreted unchanged.

Half life: 1 to 4 hours

3.1. LITERATURE REVIEW ON GRANULATION:

Malcolm Summers et al [2]: They mentioned that Granulation is the process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on their subsequent use. Granulation normally commences after initial dry mixing of the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved. After granulation the granules will either be packed (when used as a dosage form), or they may be mixed with other excipients prior to tablet compaction or capsule filling. Scientists have described the different types of granulation process as well as mechanism of granulation.

Bryan J. Ennis [31]: He has mentioned that Granulation technology and size-enlargement processes have been used by a wide range of industries, from the pharmaceutical industry to fertilizer or detergent production to the mineral processing industries. Size enlargement generally encompasses a variety of unit operations or processing techniques dedicated to particle agglomeration. He described that an alternative approach to size enlargement is agglomeration by compression, or compaction, where the mixture of particulate matter is fed to a compression device which promotes agglomeration due to pressure. Ether continuous sheets of solid material or solid forms such as briquettes or tablets are produced. Compaction processes range from confined compression devices such as tableting to continuous devices such as roll presses, briqueting machines, and extrusion.

Ennis and Litster [32] have developed the rate processes contribute to granulation. These include wetting and nucleation, coalescence or growth, consolidation, and attrition or breakage. Wetting promotes nucleation of fine powders, or coating in the case of feed particle size in excess of drop size. Often wetting agents such as surfactants are carefully chosen to enhance poorly wetting feeds. In the coalescence or growth stage, partially wetted primary particles and larger nuclei coalesce to form granules composed of several particles. The term nucleation is typically applied to the initial coalescence of primary particles in the immediate vicinity of the larger wetting drop whereas the more general term of coalescence refers to the successful collision of two granules to form a new, larger granule. The nucleation process is strongly linked with the wetting stage. As

granules grow, they are consolidated by compaction forces due to bed agitation. This consolidation stage controls internal granule voidage or granule porosity, and therefore end-use properties such as granule strength, hardness, or dissolution. Formed granules may be particularly susceptible to attrition if they are inherently weak or if flaws develop during drying.

Hans Leuenberger [(33)] described the scale up in the field of granulation and drying. Today the production of pharmaceutical granules is still based on the batch concept. In the early stage of the development of a solid dosage form the batch size is small, e.g., for first clinical trials. In a later stage the size of the batch produced in the pharmaceutical production department may be up to a 100 times larger. Thus the scale-up process is an extremely important one. Unfortunately, in many cases the variety of the equipment involved does not facilitate the task of scale-up. During the scale-up process the quality of the granules may change. A change in granule size distribution, final moisture content, friability, compressibility, and compactibility of the granules may strongly influence the properties of the final tablet, such as tablet hardness, tablet friability, disintegration time, dissolution rate of the active substance, and aging of the tablet. In the following sections, the scale-up process is analyzed, taking into account mathematical considerations of scale-up theory, the search for scale-up invariants, the establishment of in-process control methods , as well as the design of a robust dosage form. In this respect new concepts such as percolation theory play an important role. Finally, a new concept concerning a quasi-continuous production line of granules is presented. This concept permits the production of small-scale batches for clinical trials and of production batches using the same equipment. Thus scale-up problems can be avoided in an elegant and cost-efficient way.

3.2. LITERATURE REVIEW ON SLUGGING:

(1) Sumit Kumar Kochhar et al [34]: investigated Slugging and recompression characterisation of some blends of pharmaceutical excipients in which Slugs of microcrystalline cellulose (MCC), dibasic calcium phosphate (DCP) and spray-dried lactose (SDL) were compressed, either on their own or in various combinations, between 12.7 mm flat faced punches on a single punch tabletting machine at 10 different pressures. 10 tablets of each batch were compressed and the crushing strengths for five were determined. The remaining slugs were screened through an oscillating granulator and recompressed at the same pressure used initially. The crushing strengths of the final tablets were again determined. The mean yield pressures were evaluated for the slugs utilizing Heckel analysis. The results indicated that the hardest tablets were produced using 75% MCC:25% DCP. The mean yield pressure values showed that on addition of a further excipient to MCC there is a move away from predominantly plastic deformation. This was very noticeable with blends of MCC and DCP. The latter excipient has a high mean yield pressure value which implies that it is a brittle material which deforms by fragmentation. It would seem that fragmentation of DCP within the 75% MCC:25% DCP blend enhances bonding on compaction and so leads to increased crushing strength. However, for all slugged tablets there was a reduction in the crushing strength of the tablet after the second, compression for all the materials investigated. This would indicate that the extent of plastic deformation is less when the materials are compressed twice, compared to when the materials are compacted once. It was concluded that the slugging process is therefore independent of an increase in dwell time.

(2) F E Eichie et al has studied Slugging is a pre-compression technique for the dry granulation of hydrolysable drugs (e.g. aspirin). The study was carried out to relate the slugging load to the hardness of the granules and the brittle fracture tendency of the final (recompressed) tablets. Varying compression load were applied to aspirin powder to form slugs, which were subsequently broken down to form granules. These were recompressed to give the final tablets. The hardness of the slugs was determined and taken as measure of the hardness of the resulting granules. The following tableting parameters were measured for the final tablets - tensile strength (T), packing fraction (P_f) and the brittle

fracture index (BFI). A high slugging load was associated with the formation of hard slugs and hence hard granules. Upon recompression the hardest granules formed the hardest tablets (T = 3.29MN m^{-2}) while the softest granules formed the softest tablets (T=1.09MN m^{-2}). In turn, the hardest tablets displayed the highest brittle fracture tendency (BFI = 0.59) compared with the softest tablets (BFI= 0.21). A positive linear correlation existed between tablet hardness (T) and BFI values (r = 0.98). The study showed that excessive slugging load produces hard aspirin granules which in turn yields hard but friable tablets.

(3) J.N. Michaels et al.[55] Theoretical and experimental evidence is given to show that steady states can be reached during agglomerate growth and break-up in high-shear granulation of fine powders. An earlier theoretical model based on simple energy-dissipation considerations hinted at the existence of these states at the point where growth is counterbalanced by breakage. Further theoretical evidence is obtained from molecular dynamic simulations of wet and dry particles situated in a constant shear field where the size distribution of initially identical particles, shifts in time to reach a dynamic steady state. Under the conditions of this steady state, the number of breaking agglomerates approximately equals the number of forming ones to yield a time independent final-size distribution. Experimental evidence to support the theoretical findings is obtained during their research by measuring particle size distributions at line at crucial points during granulation of a typical pharmaceutical powder in a high-shear mixer. In order to reach a steady state, binder addition has to be slow enough and wet massing has to be long enough so that neither has an influence on the final properties of the granules. We show experimentally that if binder is spread properly and homogeneously in the powder and continuous shearing of the wet mass ensures homogeneous, equal growth of the granules, the steady state will only be a function of the total amount of fluid added provided that the shear forces in the machine are maintained constant. These findings are important in that they show that under carefully controlled conditions of binder addition and shear in the mixer; the granulation process is robust and controllable and can, in principle, be scaled up with ease once the powder ingredients and the total amount of binder are fixed.

3.3. LITERATURE REVIEW ON ROLLER COMPACTION:

(1) Parrott E.L. [25]: Parrott identified three theories of compression bonding: mechanical, intermolecular, and liquid-surface film. Mechanical bonding purports that individual particles undergo elastic, plastic, and brittle deformation. Bonding of this nature occurs because particle surfaces intertwine, forming mechanical bonds. Intermolecular theory identifies that there are some unsatisfied surface ions that have a potential need to bond to one another. Under pressure, intermolecular forces become pushed together close enough so that van der Waals forces can act to consolidate particles. The liquid surface film theory identifies that bonding occurs because of the existence of a thin liquid film. The thin liquid film is generated from pressure induced by the energy of compression. This mechanism acts as a bonding agent promoting mechanical strength and an enlarged particle.

(2) Dehont et al. [36]: provided a simplified approach to roller compaction theory (16). They described that powder granules move through stages in the feed area. The material is drawn into the gap by rubbing against the roll surfaces. The densification that occurs in this area is particle rearrangement. Dehont's team noted that nip angle varies according to the material characteristics of particle size and density and the angle is about 12˚. They defined the neutral angle, γ, which corresponds to the point where the pressure applied by the rollers is the greatest on the material. They also defined elastic deformation, δ, and that occurs after the compact begins leaving the compression roll area. They concluded that if the same flake thickness were obtained with different roller diameters, the flake density would be greater with larger-diameter rollers. This is due to the greater nip angle formed with the larger rolls allowing more material to be compacted.

(3) R. W. Heckel [37] considered the compaction of powders analogous to that of a first-order chemical reaction. The pores were the reactant and the densification of the material the product. The proportionality between the change of the density with the pressure and the pore fraction was the process kinetics. Heckel explained mathematical constants that described the compaction behavior of a given powder and developed a mathematical relationship. The expression of density–pressure relationship permitted the determination of density values in the range of the pressures investigated. Heckel described

mathematically that the curved region when plotting ln(1/1-D) vs. P is associated with powder densification. This occurred by a mechanism of individual particle movement in the absence of interparticle bonding. Heckel concluded that the densification represented by the linear region of the plot, ln(1/1-D) vs. P, occurred by plastic deformation of the compact after an appreciable amount of interparticle bonding had taken place. Heckel concluded that density–pressure data indicate that the rate of the change of density with pressure, any pressure, is proportional to the pore fraction in the compact at that pressure.

(4) J. R. Johanson [15] identified, through very comprehensive mathematical models and relationships, material properties, press dimensions, and operating conditions for roll compactors. In part, he explained that roller compaction involves a continuous shear deformation of the granules into a solid mass. To satisfy the theory's assumption, it was postulated that the material be iso-tropic, frictional, cohesive, and compressible. Johanson pointed out that no roller compactor theories at that time determined the angle of the nip and the bulk density at $\theta=\alpha$, except by actually rolling the granular solid in a roll press. He also provided a method to calculate the nip angle and the pressure distribution between the rolls. His calculations determined the pressure distribution above and in the nip area. He provided the technical rationale to calculate the nip pressures in the nip region. Johanson found that the nip angle does not depend on the magnitude of the roll force or the roll diameter. He demonstrated that the nip angle was affected very little by the geometry of the press or the cut grooves on the roll surface. It was mostly influenced by the nature of the materials that were compressed.

(5) Peter Kleinebudde [11] described that Roll compaction/dry granulation (RCDG) is an agglomeration process of growing importance. New machine generations and improvements in instrumentation and process control have resulted in an increasing number of pharmaceutical applications of RCDG. He illustrates the progress and the use of RCDG in the production of directly compressible excipients, the compaction of drugs and drug formulations, and the granulation of inorganic materials, the granulation of dry herbal material and the production of immediate/sustained release formulations. Dry granulation process by roll compaction has product as well as process advantages. In general, a major advantage of dry granulation over wet granulation is the absence of

water or any organic solvents. Therefore, this methodology is especially attractive for drugs, which are moisture or heat sensitive. In addition, this process is environmentally friendly. Also the roll compaction technique provides an efficient and easily automated process. The process is easily scalable, which offers conceptual simplicity and low operational costs. However, compaction in a roll press is still not fully understood.

(6) Leon Farber et al [39] developed model that describes the relationship between roller-compaction conditions and tablet strength is proposed. The model assumes that compaction is cumulative during roller compaction and subsequent granule compaction, and compact strength (ribbon and tablet) is generated irreversibly as if strength is controlled by plastic deformation of primary particles only. Roller-compaction is treated as a compaction step where the macroscopic ribbon strength is subsequently destroyed in milling. This loss in strength is irreversible and tablets compressed from the resulting granulation are weaker than those compressed by direct compression at the same compression force. Roller-compacted ribbons were produced at a range of roll forces for three formulations and subsequently milled and compacted into tablets. Once the total compaction history is taken in account, the compaction behavior of the uncompacted blends and the roller-compacted granules ultimately follow a single master compaction curve—a unified compaction curve (UCC). The model successfully described the compaction behavior of DC grade starch and formulations of lactose monohydrate with 50% or more microcrystalline cellulose, and may be more generally applicable to systems containing significant proportions of any plastically deforming material, including MCC and starch.

(7) Maja ˇSantla et al [40] carried out study to investigate the influence of various powder agglomeration processes on tableting mixture flow and compaction properties. Four different granulation methods of the same model placebo formulation were tested at a semi-industrial scale and their properties were compared to those of the directly compressed mixture. The wet granulated mixtures had superior flow properties compared to other mixtures and showed better compressibility, measured by the Heckel and Walker models. This was attributed to work hardening due to the double particle processing and also to shorter contact times due to higher initial densities of dry granulated mixtures,

allowing a shorter time for deformation. A strong linear correlation was established between the Heckel and Walker coefficients, which were further confirmed by the net energy results of force–displacement measurements. It was shown that the Walker model had slightly better discriminative power to differentiate tableting mixtures according to compressibility. The compactibility was considerably lower for the slugged mixture; however, the roller-compacted mixture produced tablets with unexpectedly high tensile strength. In conclusion, it is important to emphasize those general assumptions like higher porosity provides better compressibility or better compressibility gives better compactibility cannot be established for complex tableting mixtures.

(8) A.V. Zinchuk et al [(41)] developed method for simulation of the roller compaction process using a laboratory scale compaction simulator was developed. The simulation was evaluated using microcrystalline cellulose as model material and ribbon solid fraction and tensile strength as key ribbon properties. When compacted to the same solid fractions, real and simulated ribbons exhibited similar compression behavior and equivalent mechanical properties (tensile strengths). Thus, simulated and real ribbons are expected to result in equivalent granulations. Although the simulation cannot account for some roller compaction aspects (non homogeneous ribbon density and material bypass) it enables prediction of the effects that critical parameters such as roll speed, pressure and radius have on the properties of ribbons using a fraction of material required by conventional roller compaction equipment. Furthermore, constant ribbon solid fraction and/or tensile strength may be utilized as scale up and transfer factors for the roller compaction process. The improved material efficiency and product transfer methods could enable formulation of tablet dosage forms earlier in drug product development.

(9) H. Lim et al [(42)] carried out study with the purpose to assess the porosity variation of roller compacted ribbons made using different process parameters; in addition, the feasibility of using near-infrared chemical imaging (NIR-CI) to evaluate porosity variations was examined. Ribbons of neat microcrystalline cellulose were compacted using a range of roll pressures (RP), roll speeds (RS) and feed screw speeds (FSS). The ribbon porosity decreased as RP increased with the exception of ribbons produced by the combination of high RS and low FSS where increasing RP increases the porosity of the

ribbons. Lower RS was found to produce ribbons with lower porosity and the porosity increases as the RS increased. Increased FSS will decrease ribbon porosity at higher RS while it slightly increase the ribbon porosity at lower RS. A simple linear regression model showed NIR-CI was able to predict the ribbon porosity with a correlation of 0.9258. NIR-CI is able to characterize differences in porosity as a function of position on the ribbon where regions with lower porosity show higher absorbance. Nevertheless, NIR-CI is able to show sinusoidal variation in intensities along the roller compacted ribbon among all settings studied.

(10) Sabine Inghelbrecht et al [43] Different types of microcrystalline cellulose (MCC) and blends of MCC, a mainly plastic deforming material and ibuprofen, used as a mainly fragmenting material were roller compacted. All MCC types, except Avicel® CE-15, produced excellent quality granules but the corresponding tablet mechanical strength was low. Addition of ibuprofen reduced the number of usable roller compactor parameter combinations. The presence of 25% ibuprofen had a negative influence on granule quality while the tablet mechanical strength improved. A further increase of the ibuprofen concentration yielded an acceptable granule quality and a high tablet mechanical strength due to the fragmentation and sintering properties of ibuprofen. It remained difficult to predict the influence of roller compactor pressure on the final tablet mechanical strength. Differences in MCC particle density influenced the dissolution rate more than the particle size. The presence of an additional dry binder did not improve granule strength and decreased the dissolution rate. The *t*90 release values of the 75% ibuprofen tablets were low for hydrophilic gum–MCC associations, Avicel® PH-301 and PH-302.

(11) S. Patel et al. [44] investigated the effect of roller compaction pressure on the bulk compaction of roller compacted ibuprofen using instrumented rotary tablet press. Three different roller pressures were utilized to prepare granules and Heckel analysis, Walker analysis, compressibility, and tabletability were performed to derive densification, deformation, course of volume reduction and bonding phenomenon of different pressure roller compacted granules. Nominal single granule fracture strength was obtained by micro tensile testing. Heckel analysis indicated that granules prepared using lower

pressure during roller compaction showed lower yield strength. The reduction in tabletability was observed for higher pressure roller compacted granules. The reduction in tabletability supports the results of granule size enlargement theory. Apart from the granule size enlargement theory, the available fines and relative fragmentation during compaction is responsible for higher bonding strength and provide larger areas for true particle contact at constant porosity for lower pressure roller compacted granules. Overall bulk compaction parameters indicated that granules prepared by lower roller compaction pressure were advantageous in terms of tabletability and densification. Overall results suggested that densification during roller compaction affects the particle level properties of specific surface area, nominal fracture strength, and compaction behavior.

(12) Paul J. Sheshkey et al. [45] studied the Effects of roller compaction variables like roll and feed screw speeds and applied roll pressure; roll design, granulation technologies and concentration of HPMC polymer on the physical properties of and subsequent drug release from, a model controlled release drug formulation. The result showed that differences in roller compaction equipment variables and roll surface design had a relatively small effect on these properties; granulation methods had the greatest effect on crushing strength; and high levels of HPMC increased bulk and tap densities, decreased tablet crushing strength and increased time to release. None of the variables affected tablet friability. Roller compaction variables such as feed screw speed and roll speed have little effect on the physical properties of the tablets or their drug release profiles. Roll surface design had no measurable effect on particle size distribution, tablet friability, crushing strength or drug release. The granulation methods had varying effects on tablet properties and drug release. They mentioned that high HPMC level resulted in increased bulk and tap densities, decreased tablet crushing strength. Polymer level did not affect tablet friability.

(13) Franziska Freitag et al [46] studied the effect of roll compaction/dry granulation on the particle and bulk material characteristics of different magnesium carbonates were evaluated. The flowability of all materials could be improved, even by the application of low specific compaction forces. The tablet properties made of powder and dry granulated magnesium carbonate were compared. Roll compaction/dry granulation resulted in a

modified compactibility of the material and, consequently, tablets with reduced tensile strength. The higher relative tap density of the compacted material does not allow a densification to the same extent as the uncompacted powder. The degree of densification during tableting can be expressed as the ratio of the relative tablet density to the relative tap density of the feed material. Increasing the specific compaction forces resulted in higher apparent mean yield pressure, gained from Heckel plots, of all materials analysed. The partial loss of compactibility leads to the demand of low loads during roll compaction. Comparing the tablet properties of different magnesium carbonates reveals an obvious capping disposition. However, it depends on the type of magnesium carbonate, the specific compaction force and also on the tableting force applied.

(14) Ervina Hadˇzovi´ et al [47] investigated that Roller compaction is a dry granulation method which results in tablets with inferior tensile strength comparing to direct compaction. The effect of roller compaction on compressibility and compactibility of tablets prepared from Theophylline anhydrate powder, Theophylline anhydrate fine powder and Theophylline monohydrate was investigated by measuring tensile strength of tablets as well as calculating compressibility and compactibility parameters by Leuenberger equation. The tablets under the same conditions were prepared by direct compaction and roller compaction. The binary mixtures of Theophylline anhydrate powder, Theophylline anhydrate fine powder, Theophylline monohydrate and microcrystalline cellulose were prepared in order to determine the optimal ratio of active material and excipients which delivers a sufficient mechanical strength of tablets. Tensile strength of MCC tablets and compactibility parameters calculated by Leuenberger equation after roller compaction was significantly decreased, while THAP, THAFP and THMO tablets showed only a minor reduction in compactibility and compressibility. Adding MCC to a mixture with Theophylline showed that the right choice and ratio of excipients can enable a sufficient mechanical strength of the tablets after roller compaction.

(15) Shawn A. Mitchell et al [48] enhanced the dissolution rate of poorly water-soluble drugs with hypromellose using a compaction process without the use of solvent or heat addition. Low viscosity hypromellose or low viscosity MC can be used to enhance

dissolution of poorly water-soluble drugs through a compaction process. Compacted then milled dry mixtures of drug and hypromellose maintained intimate contact between hypromellose and drug particles during dissolution, enhancing drug dissolution relative to drug alone and also relative to loosely-mixed drug and hypromellose powders. Roller compaction and slugging were each successful in combining drug and polymer to improve drug dissolution rates. These compaction procedures produced drug: hypromellose agglomerates with dissolution rates approximately 9 times faster than drug alone for nifedipine and naproxen, and at least 5 times faster than drug alone for CBZ. Drug distribution *vs.* particle size in compacted agglomerates was remarkably similar for the three drugs tested. Thus, compacting hypromellose and drug appears to have potential in normalizing drug dissolution regardless of the particle size distribution of drug itself. This study demonstrated that by keeping poorly water-soluble drugs and hypromellose particles in close proximity, drug dissolution rates were enhanced. The compaction methods in this study may provide a lower cost, quicker, readily scalable alternative for poorly water-soluble drugs.

(16) B. Rambali et al [49] prepared Miconazole buccal tablets via a dry granulation process. By applying a factorial design (2^4), the roll compactor parameters (compaction force, gap between the rolls, type of the rolls (smooth, ribbed) and the sieve aperture) were optimised for the tablet strength. The compaction force and the roll type significantly affected the tablet strength. Afterwards, a quarter fractional factorial design (2^{5-2}) was applied, consisting of the four compactor parameters and additionally the compression pressure, in order to optimize these parameters for the dissolution profile and the buccal bio-adhesion characteristics (bio adhesive force and energy). In order to evaluate the dissolution profiles properly, the similarity factor between sample and a zero-order release reference profile was used. The compression pressure and the roll type significantly affected the dissolution profile. The sieve aperture had a significant effect on the buccal adhesion properties and the compaction force had a significant effect on the dissolution profile and the bio-adhesive energy. The gap between the rolls affected the bio-adhesive force significantly.

(17) M.G. Herting et al. [50] studied the influence of particle size of MCC, as a binder, and theophylline, as an active pharmaceutical ingredient on the process of roll compaction/dry granulation a D-optimal design of experiments. Examined parameters were particle size of both starting materials, fraction of theophylline and ribbon porosity. Therefore, different binary mixtures were roll compacted, dry granulated and compressed into tablets. Flowability of powders and granules and tensile strength of tablets made from powders or granules were the focus of this study. This study showed that a decrease in particle size of MCC or theophylline resulted in an increase of tensile strength even after roll compaction/dry granulation. Comparing tensile strength of tablets made from powder using large size MCC with ones made from granules with small sized MCC revealed that the tensile strength of tablets produced from granules was equal or even higher than tensile strength from direct compressed tablets. Furthermore, using small sized MCC instead of large sized MCC led to larger granules with better flowability. It is shown that the fraction of binder can be reduced without a loss of tensile strength of the final tablets by size reduction of MCC.

(18) A.M. Miguélez-Morán et al [51] described that Roller compaction is a continuous dry granulation process for producing free flowing granules in order to increase the bulk density and uniformity of pharmaceutical formulations. It is a complicated process due to the diversity of powder blends and processing parameters involved. The properties of the produced ribbon are dominated by a number of factors, such as the powder properties, friction, roll speed, roll gap, feeding mechanisms and feeding speed, which consequently determine the properties of the granules (size distribution, density and flow behaviour). It is hence important to understand the influence of these factors on the ribbon properties. In this study, an instrumented roller press developed at the University of Birmingham is used to investigate the effect of lubrication on the density distribution of the ribbons. Three different cases are considered: (1) no lubrication, (2) lubricated press, in which the side cheek plates of the roller press are lubricated, and (3) lubricated powder, for which a lubricant is mixed into the powder. In addition, how the powders are fed into the entry region of the roller press and its influence on ribbon properties are also investigated. It is found that the method of feeding the powder into the roller press plays a crucial role in determining the homogeneity of the ribbon density. For the roller press used in this study,

a drag angle (i.e., the angle formed when the powder is dragged into the roller press) is introduced to characterise the powder flowpattern in the feeding hopper. It is shown that a sharper drag angle results in a more heterogeneous ribbon. In addition, the average ribbon density depends upon the peak pressure and nip angle. The higher the peak pressure and nip angle are, the higher the average ribbon density is. Furthermore, the densification behaviour of the powder during roller compaction is compared to that during die compaction. It has been shown that the densification behaviour during these two processes is similar if the ribbons and the tablets have the same thickness.

(19) N. Mueller, F. Ecker [(52)] carried out study with the purpose to investigate the correlation between granule strength and granule friability of dry granulated materials and their influence on tablet tensile strength. Granules need a certain mechanical resistance to tolerate the stress during subsequent processes like tableting, capsule filling, transportation and packaging. Attrition behaviour and granule strength are properties that describe the granule resistance. Granule strength measurement by compressing of individual granules is a laborious procedure, because of the required high number of single measurements. In comparison, attrition measurements are quicker test methods and therefore better suited for routine quality control. Results provided the information that Higher compactability implies higher values of granule strength and lower values of granule attrition. With increasing granule strength the obtained tablet tensile strength of the Vivapur tablets decreases. Granulac granules show no differences. The friability as well as the strength of granules are appropriate parameters to describe robustness. In our experiments these two properties correlate (for every single excipient), so that one can decide which one should be used for quality tests. The use of granule strength to predict the properties of recompacted tablets is questionable.

(20) D.Z. Bozic et al. [(53)] The effect of dry granulation (roller compaction and slugging) on compactibility and tablet capping tendency in a formulation with macrolide antibiotic and microcrystalline cellulose (MCC) was investigated. Direct tableting of this formulation revealed a pronounced capping tendency. Both dry granulated systems exhibit better compactibility and significant reductions in capping tendency compared to direct tableting. The capping tendency was also reduced through the use of

precompression during direct tableting. The main volume reduction mechanism for macrolide antibiotic is fragmentation; this was confirmed by Heckel analysis, the lubricant sensitivity test, and SEM images. The yield pressure (*P*y) of the direct tableting system is lower than the *P*y of dry granulated systems, which indicates the lower plasticity of dry granulated systems. These findings do not explain the lower capping tendency of dry granulated systems compared to direct tableting. The main differentiating bonding mechanism is attributed to long distance intermolecular bonds due to the intense amorphization of macrolide antibiotic that occurs during dry granulation. Amorphization leads to a significant increase in surface free energy and consequently stronger long distance bonding between particles, which can withstand elastic relaxation and therefore reduce the capping problem. Solid bridges probably do not make a notable contribution to the mechanical strength of tablets, due to the brittle nature of the particles and the complex molecular structure of macrolide antibiotic.

(21) George W. Gereg et al [(54)] developed a method to determine whether a drug candidate, excipient, or formula mix is suitable for dry granulation by roller compaction. Process parameters were determined with this model at laboratory-bench scale, and these parameters were translated directly to large-scale process equipment, thus saving time and materials during early product development. Various lactose materials, available as lactose monohydrate or spray-dried lactose monohydrate, were used as the model compounds. Results indicated that a parametric correlation can be made between laboratory bench and production scale and many process parameters can be transferred directly. The objectives were to characterize properties of the material, to identify process parameters suitable to achieve the necessary particle size and density using the dry granulation process, and then to translate laboratory information to a production-scale roller compactor. They concluded that This study provides a method to predict whether a material is suitable for dry granulation. For a material to be dry granulated, it must be compressible, have a consistent increase in density with force, and be suitable for milling and possible recompression. Information generated in the laboratory on a hydraulic press can be correlated and scaled up to a production-scale roller compactor to produce dry-granulated material that has very similar powder–granule characteristics.

(22) Niklas Sandler et al Solid dosage form manufacture still remains the most common in the production of pharmaceutical products. Established granulation processes can benefit from novel technical improvements, which can in turn enhance the behavior and properties of the process intermediates, that is, granules. These improvements in the manufacturing process can ultimately shorten development times, provide processing solutions for challenging materials and improve quality of drug delivery systems. They have given the overview of the latest trends in research with regard to roller compaction technology. Pneumatic dry granulation is also discussed as a new development with the potential to improve and extend the use of dry granulation processes, which can result in a substantial contribution to drug delivery system development and drug product manufacture. Dry granulation techniques, and more specifically roller compaction, can provide many advantages over the more established wet granulation techniques. There is still problemswith roller compaction such as high amounts of fines and poor flow of granulate. Technical innovations that improve existing processes will have a considerable impact on development times and contribute to improved material processability and behavior of the end product. Pneumatic dry granulation has the potential to provide such alternatives.

(23) Steve Boswell, Geoff Smith described that although tablet manufacture is traditionally a batch based wet granulation process, there are many advantages to be gained by adopting dry granulation, including lower costs and increased yields. The simplicity of dry granulation could also enable it to become one of the main technologies for continuous processing. After several years of establishing new ways of analysing drug variability and quality in various manufacturing process stages, the industry is moving away from conventional batch sampling and analysis to embrace more advanced techniques that analyse consistency in real time. The challenge now is for the industry to take this QbD concept and look at its manufacturing processes in lean terms to adapt for a more efficient future. Tablet manufacture is traditionally a batch-based wet granulation process. Dry granulation, on the other hand, can be used as a semibatch process but could also emerge as one of the main continuous processing solutions due to its simplicity. There are other forms of dry granulation, but the most commonly used is roller compaction, which is a continuous technology by design that has been significantly

further developed in recent years. In particular, a number of important changes have been made that differentiate novel technologies from conventional roller compactors. Combined with PAT techniques, roller compaction can help achieve a continuous granulation process. Depending on the objectives and site PAT strategy, measurements prior to the process can be taken to establish raw material consistency and blend uniformity. Essentially, this will enable a consistent processing window with established boundary limits to be achieved.

(24) Scientists from atacama lab described most of the oral solid dosage form products are wet granulated due to the limitations of dry granulation. They showed how to extent the use of dry granulation method with the novel Pneumatic Dry Granulation (PDG) process in order to avoid the problems and to archive a high-quality product with a cost-efficient formulation. A rapidly disintegrating Paracetamol tablet is used as a sample product and it is compared with the product having the fastest dissolution profile in the market. First, they explain the principles of the method and show the structural difference between materials compacted with various compaction forces, and then they described the results of the comparison between a dry granulated Paracetamol tablet and the reference tablet. They show that the structure and surface of the granules is different between the traditional and the pneumatic dry granulation methods, and then they showed that the disintegration profiles of the tablets are comparable. The compaction force has direct implication to the quality of the granules. High compaction force is evidently disadvantageous whereas the granules compacted with low compaction force have numerous advantageous properties. Most importantly, there are practically no deformations and the individual particles have the same properties as the raw powder. From the manufacturing and development point of view, the advantages are undeniable. The formulation is very straightforward and the process for manufacturing the tablets is highly cost-efficient. Atacama Labs developed the formulation in fraction of time compared to a typical solid dosage form development effort. The advent of continuous processing will increase the importance of dry granulation method. The ability to broaden the set of applicable materials makes the Pneumatic Dry Granulation optimal platform for the development of continuous processes.

(25) Gupta, Morris, and Peck [59] from Purdue University Industrial Physical Pharmacy School began a series of noninvasive real-time investigations. Evaluating roller compaction by NIR in the dynamic mode, the team monitored the variation of compacted ribbon strength that could adversely affect particle size and distribution of granules obtained after milling a compact. Their thinking was that both the ribbon strength and the particle-size distribution can be determined off-line but it is time consuming. The ability to use NIR spectra to quantify the compact strength, the particle size, and to estimate post milling particle-size distribution could be done in real time. The most obvious NIR spectral change that occurs in compacts or tablets prepared under increasing pressure is an upward shift in the NIR spectral baseline. Scientists used the slope of the best-fit line through spectra to quantify this upward shift and found a linear correlation between this slope and the tablet hardness determined by the diametral compression test. Gupta et al. applied this treatment to correlate the slope of the best-fit line through the NIR spectra with the strength of compacts was determined using the three-point beam bending technique. Additionally, slope values were correlated to the particle-size distribution of granules produced from milled compacts. Realtime on-line techniques were used to monitor the roller compaction unit operation for microcrystalline cellulose and 10% active blend. The spectra collected on the different compact segments prepared from the same material under the same roller compactor settings showed little variation, suggesting good reproducibility in the data collection by the NIR sensor. A significant shift in the NIR spectra was observed for compacts prepared at different roll speeds.

3.4. LITERARURE REVIEW ON PARACETAMOL:

Falzone *et al.* [62] used acetominophen as the model drug to investigate the influence of roller compaction parameters on particle size distribution and recompression of materials. The effect of the roller compaction parameters depended considerably on the raw material used. Only the compressibility index of acetaminophen blend could be modelled by a quadratic regression model. All of the three roller compaction parameters, roller, horizontal feed and vertical feed speeds as well as some other interactions had significant effects on the compressibility index. The mean particle size of the granules was less than or equal to the size of the starting material. SEM studies confirmed that fragmentation of acetaminophen crystals during roller compaction led to this observation. A general model for the materials could not be determined because the actual effects of compaction parameters also depended on the bonding and deformation characteristics of the material for compaction.

Turkoglu *et al.* [63] investigated the effect of binder type (HPMC, PEG, carbopol) and concentration (5, 10, 20%), number of roller compaction passes (one or two) and addition of extragranular MCC on the properties of resultant tablets. Acetaminophen exhibits a high elastic deformation and produces weak compacts. It is difficult to produce tablets without a prior granulation process. The results (ejection force, crushing strength, friability and disintegration time) were modelled using artificial neural networks and genetic algorithms. Out of 42 experiments, 30 were used to train the network and 12 were used to test the prediction capacity of neural network and genetic algorithm. Genetic algorithm predictions of tablet characteristics were much better than the artificial neural networks. Optimisation based on genetic algorithm was performed and showed that HPMC at 20% and two roller compaction passes produced mechanically acceptable tablets. PEG and carbopol also produced acceptable tablets with potential sustained release capabilities. In addition, using PEG as a binder had the extra advantage of not requiring an external lubricant during tabletting.

3.5. LITERATURE REVIEW ON SeDeM ANALYSIS:

(1) Josep M. Suñé Negre, et al [64] has found that thorough preformulation work is the foundation of developing robust formulations. The SeDeM Method is a new graphical method for application in tablet-preformulation studies. This system helps in determining compressibility profile of powdered substances (APIs and excipients) based on their physical characteristics. The expert graphical system provides the magnitude at which powdered substances can be successfully compressed by means of direct compression. This knowledge facilitates required alteration to be done in the powdered substances to be applicable in direct compression technology. The system depends upon five factors on the basis of the physical properties of the powdered substances. Five factors comprise of 12 diferent parameters to characterize galenic properties of powdered substances for determination of appropriateness for direct compression.

(2) Inderbir singh, Pradeep Kumar [65] studied the direct compression suitability of active pharmaceutical ingredients by SeDeM diagram method. Cefuroxime axetil (CfA) and paracetamol (PCM) were employed for SeDeM studies as these powders are well-characterized and known to be particularly difficult with respect to flowability and compactibility. Twelve different selected pharmacotechnical parameters were determined experimentally and were treated mathematically for being expressed in graphic representation as SeDeM diagram. Parameter index, parameter profile index and good compression index were calculated for both the selected drugs. Good compression index was found to be 2.19 and 1.36 for CfA and PCM, respectively, indicating poor direct compression characteristics of the selected drugs. The results from this SeDeM diagram method are in line with the previously reported studies where it was established as a reliable method for preformulation studies and as a quality control tool for studying batch-to-batch reproducibility of APIis. Furthermore, it once again established the notion that blending poorly compressible drugs with suitable ingredients followed by SeDeM studies could be used as method for identifying best excipient and calculating maximum amount of excipient required for direct compression of API.

(3) J.M. Suñé-Negre et al.[66] As a methodology for characterizing substances in relation to their viability in direct compression, the SeDeM Diagram Expert System may be

considered an open system in terms of the number of parameters applied and the optimization of these parameters. With the experience acquired from applying the SeDeM Diagram, in this study, they proposed optimizing the parameters corresponding to the Hausner index (IH) and relative humidity (%HR) in order to simplify the mathematical calculation, so that it provides reliable data that can be extrapolated. The proposed optimization does not involve a conceptual change in the parameters considered nor did a significant change in the results obtained compare with the previous calculation methodology initially established for the SeDeM Diagram Expert System, which means that the conclusions obtained by applying this method are equivalent. They proposed adopting the linear method for calculating the radius of %HR, as it does not affect the decision regarding the choice of the appropriate excipient to correct the profile for direct compression of an API or regarding the proportion of the API in comparison with the ranges method. The stability (L/S) function, which is the mean of the parameters % relative humidity (%HR) and hygroscopicity (%H), presents statistically equivalent results regardless of whether the calculation is carried out using the ranges method or the linear method, as there are no statistically significant differences.

(4) Johnny Edward Aguilar-Díaz et al [(67)] used the new SeDeM Diagram expert system to analyze the suitability of 43 excipients for direct compression with disintegrant properties from eight chemical families. The SeDeM Diagram expert system is a new method for use in tablet preformulation and formulation studies. It provides the profile of a substance in powder form in terms of its suitability for direct compression. This study, which was based on the current concept of “Quality by Design ICH Q8”, evaluated the pharmacotechnical properties of disintegrants in powder form and selected the candidates that were most suitable for direct compression and their use in formulation of orally disintegrating tablets (ODT). To achieve this, each disintegrant and its chemical families were individually analyzed. It was concluded that nine disintegrants had an SeDeM value with the index of good compression (IGC) over 5. Most of these disintegrants were from the microcellulose family. Other disintegrants had indexes that were close to 5. It is assumed that these excipients can be used in direct compression, when they are added to other excipients.

(5) Josep M. Suñé Negre, et al [68] has applied the new SeDeM Method for the study of the galenic properties of excipients in terms of the applicability of direct-compression technology. Through experimental studies of the parameters of the SeDeM Method and their subsequent mathematical treatment and graphical expression (SeDeM Diagram), six different DC diluents were analysed to determine whether they were suitable for direct compression (DC). Based on the properties of these diluents, a mathematical equation was established to identify the best DC diluent and the optimum amount to be used when defining a suitable formula for direct compression, depending on the SeDeM properties of the active pharmaceutical ingredient (API) to be used. The results obtained confirm that the SeDeM Method is an appropriate system; effective tool for determining a viable formulation for tablets prepared by direct compression, and can thus be used as the basis for the relevant pharmaceutical development.

(6) Pilar Pe´rez et al [69] proposed new SeDeM Method for testing the batch-to-batch reproducibility of the same active pharmaceutical ingredient (API) in powder form. The procedure describes the study of the galenic properties of substances in powder form in terms of the applicability of direct compression technology. Through experimental determination of the SeDeM Method parameters, and their subsequent mathematical treatment and graphical expression (SeDeM Diagram), three batches of the same API were analysed to determine whether it was suitable for direct compression. Batch-to-batch reproducibility of the results was verified. It was concluded that the SeDeM Method is suitable for testing batch-to-batch reproducibility of characteristics in powdered APIs substances. The results obtained confirm that the SeDeM Method is a useful, effective tool for drug-preformulation studies providing the pharmacotechnical data required when formulating a drug in tablet form. In addition, the results were effective for defining the most appropriate manufacturing technology.

4.4.5 Results and Discussions for Factorial Design:

(1) Envelope Density:

The envelope density of various formulations is shown in the table. It was found that the envelope density ranged between 1.07 to 1.43 gm/cm^3, which indicates the sensitivity towards the critical factors studied.

The obtained data were fitted in two factor interaction model in Design Expert Software Version 8.0 to describe the relationship between critical factors and response. The results are shown in the equation

It can be observed from the plots that the envelope density remained constant with the increase in turret speed and increased with increase with the weight of slugs. From the ANOVA analysis it was found that target weight was the significant factor which affects the envelope density of the slugs.

The bulk compaction parameters exhibit different trend in densification and volume reduction depending on the pressure utilized during the compaction. As the amount of material incresed, pressure required for densification process incresed. Thus, increase in amount of material directly increase densification process due to higher volume reduction process. Turret speed would affect the dwell time which was not significantly give its effect on densification process.

(2) Compression Force:

The compression force of various formulations is shown in the table. It was found that the compression force ranged between 8.39 to 39.35 kN, which indicates the sensitivity towards the critical factors studied. The compression force had a range of more than four fold suggesting the fine control of the selected factors to get the compression force.

The obtained data were fitted in two factor interaction model in Design Expert Software to describe the relationship between critical factors and response. The results are shown in the equation

It can be observed from the plots that the compression force remained constant with the increase in the turret speed and increased with the increase in the target weight. From the ANOVA analysis it was found that target weight was the significant factor which affects the compression force of slugs. Compression force was not affected by turret speed while weight of slugs increased pressure required for compaction and thus force required compaction was increased as the force is directly propotional to pressure. This is as a result of increased bonding strength with increased compaction load .

(3) Carr's index:

The carr's index of various formulations is shown in the table. It was found that the compression force ranged from 20 to 33.33, which indicate the sensitivity towards the critical factors studied. The obtained data were fitted in two factor interaction model in Design Expert Software to describe the relationship between critical factors and response. The results are shown in the equation

It can be observed from the plots that carr's index remained constant with the increase in the target weight and maxima value was seen on middle value of turret speed. From the ANOVA analysis it was found that no significant factors which affect the carr's index of granules after milling of slugs. Carr's index was affected by change in bulk densities and tapped densities. Here, bulk and tapped densities were varied with turret speed as well weightof slugs and hence both factors were not significant for carr's index.

(3) Good Compressibility Index (IGC):

The Good Compressibility Index of various formulations is shown in the table. It was found that the compression force ranged from 4.78 to 5.83, which indicate the sensitivity towards the critical factors studied. The obtained data were fitted in two factor interaction model in Design Expert Software to describe the relationship between critical factors and response. The results are shown in the equation

It can be observed from the plots that IGC remained constant with the increase in the target weight and increased with increase in turret speed. From the ANOVA analysis it was found that both the factors were significant factors which affect the good compressibility index of granules prepared after milling of slugs.

IGC mainly varied with change in radius of different parameters (i.e. Bulk and tapped density, carr's index etc). Sheskey et al. (1994, 1995) compacted powder blends of HPMC at various roller pressure levels and found that larger granules were produced with higher compaction pressure. Based on this fact granules obtainrd higher compaction force having larger size henge it would be having higher density values, higher homogenity index,higher compressibility and thus value of IGC increasaed with incraesed value of weight.

4.4.6 SeDeM ANALYSIS OF GRANULES PREPARED FROM SLUGS

PREPARATION GRANULES:

- Slugs were transferred to Co-Mill and milling was done at 1200rpm. Granules were collected from the bottom of the mill.
- Granules were subjected for different tests to perform SeDeM analysis in order to evaluate suitability of the compression of the blend.

4.4.6.1 Introduction of SeDeM Analysis:

The SeDeM Method is a new galenic method for application in tablet-preformulation studies. It provides information about the suitability of active ingredients or excipients in powder form for direct compression. This information indicates the degree to which substances can be successfully compressed by means of direct compression technology. The SeDeM Method makes it possible to detect the properties of the powder that need to be adjusted to facilitate formulation of the end product for direct compression. The SeDeM Method is therefore also a useful tool for studying the reproducibility of the process used for preparing a powder substance and, consequently, for validating the preparation system.

Factors and parameters used in the system with equation and conversion factor are shown:

Table 4.9 SeDeM Analysis Factors

Incidence factor	Parameters	Equation	Acceptable range	Conversion factor
Dimension	Bulk Density (Da)	Da = P/Va	0–1 g/ml	10v
	Tapped density (Dc)	Dc = P/Vc	0–1 g/ml	10v
Compressibility	Inter particle porosity (Ie)	Ie = Dc −Da/Dc × Da	0–1.2	10v/1.2
	Carr's index (IC)	IC = (Dc − Da/Dc) 100	0–50 (%)	v/5
Flowability	Hausners ratio (IH)	IH = Dc/Da	3–1	(30-10v)/2
	Angle of repose (α)	tg α = h/r	50–0 (°)	10 − (v/5)

Lubricity/Stability	Loss on drying (%HR)	Experimental	0-10 (%)	10-v
Lubricity/Dosage form	Particle size<50µm (%Pf)	Experimental	50–0 (%)	10 − (v/5)
	Homogeneity index (Iθ)	Iθ = Fm / 100 + Δ Fmn	$0–2 \times 10^{-2}$	500v

Parameters:

(1) Bulk Density, Tap Density and Carr's Index:

The bulk and tapped densities were measured in a 100 ml graduated measuring cylinder in Tap density tester. The tapped volume was noted after 500 tapping followed by 750 taps if difference in volume is less than 3%. If difference is more than 3% then granules were subjected for 1250 taps to bring the difference in volume less than 3% .Carr's Index was determined by the following formula:

$$\text{Carr's Index} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \times 100 \quad (12)$$

(2) Inter Particle Porosity:

Inter particle porosity can be calculated by following equation:

$$Ie = \frac{Dc - Da}{Dc \times Da} \quad (13)$$

Where;

Dc= Tapped Density

Da= Bulk Density

(3) Hausner's Ratio:

It is a ratio of Tapped density and bulk density.

$$IH = \frac{Dc}{Da} \quad (14)$$

Where;

Dc= Tapped Density

Da= Bulk Density

(4) Angle of Repose:

It can be calculated by keeping funnel at 2cm above the flat surface and allowed the powder to pass through funnel. Radius of circle was measured which was created by powder.

$$\tan\theta = \frac{h}{r} \quad (15)$$

Where;

h= height of hip (2cm)

r= radius of circle created by hip.

(5) Loss on drying:

It can be measured at 105˚C for 5 min. by using Moisture Analyser (Metller Toledo). %Weight loss would give the value of loss on drying.

$$\text{Loss on drying} = \frac{\text{Initial weight-final weight}}{\text{Initial Weight}} \times 100 \quad (16)$$

(6) Fraction of the particle having size <50µm (%Pf) and Homogenity Index (Iθ):

Sieve analysis was carried out to calculate %Pf and Iθ.

Homogenity index was calculated by following equation:

$$\mathbf{I\theta} = \frac{\mathbf{Fm}}{\mathbf{100 + (dm - dm - 1)Fm - 1 + (dm + 1 - dm)Fm + 1 + (dm - dm - 2)Fm - 2 + (dm + 2 - dm)Fm + 2 + (dm - dm - n)Fm - n + (dm + n - dm)Fm + n}}$$

Where;

- Iθ=Relative homogeneity index. Particle-size homogeneity in the range of the fractions studied;
- Fm=percentage of particles in the majority range;
- Fm−1=percentage of particles in the range immediately below the majority range;
- Fm+1=percentage of particles in the range immediately above the majority range;
- n=order number of the fraction studied under a series, with respect to the major fraction;
- dm=mean diameter of the particles in the major fraction;
- dm−1=mean diameter of the particles in the fraction of the range immediately below the
  majority range;
- dm+1=mean diameter of the particles in the fraction of the range immediately above the majority range.

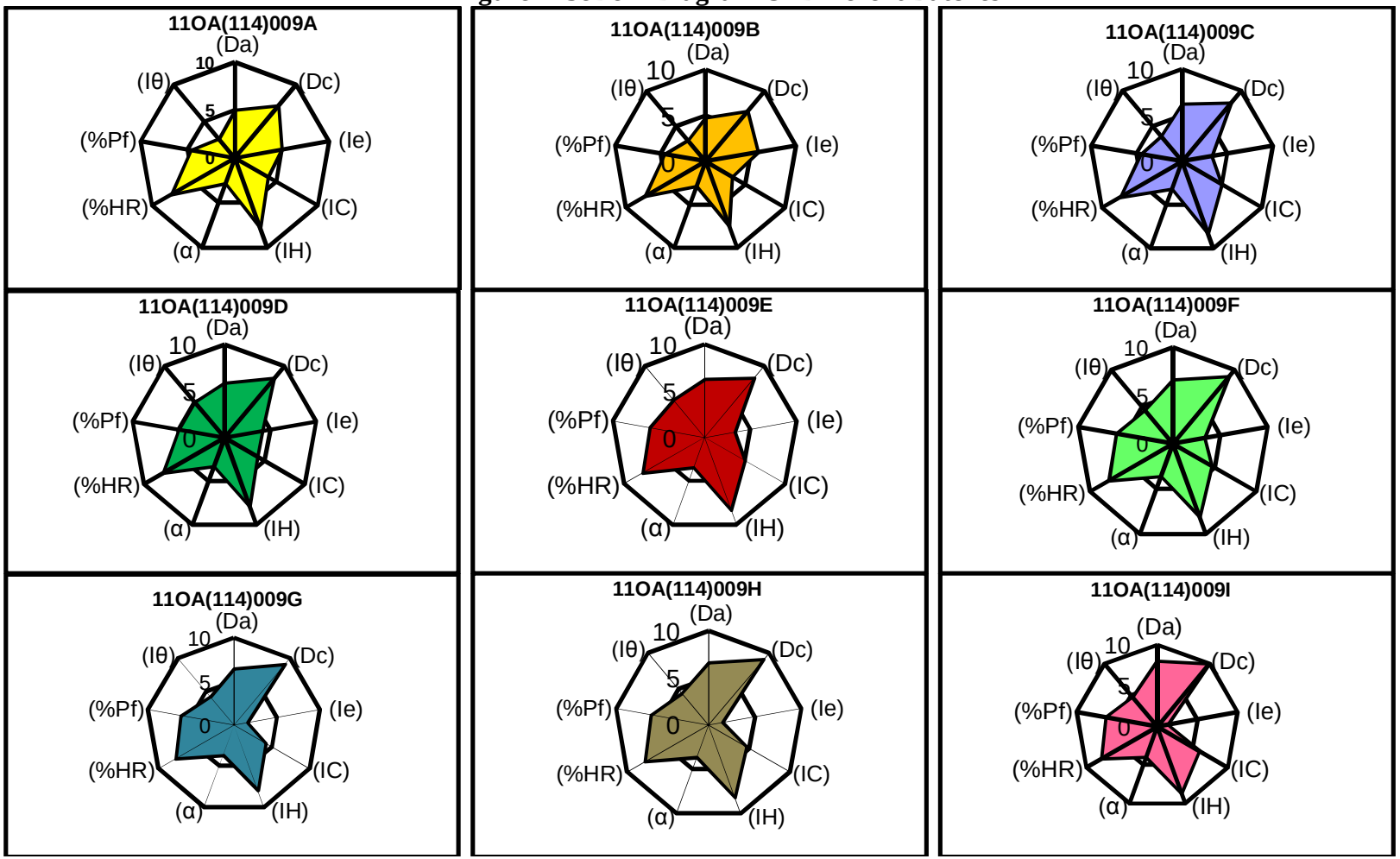
Table 4.10 Sieve Analysis Table for Homogenity Index

Sieve	Average of diameter (µm)	corresponding diameter	Dif of dm with major component	Corresponding fraction
30-40	507.5	dm+4	428.5	fm+4
40-80	298.5	dm+3	219.5	fm+3
80-100	163	dm+2	84	fm+2
100-140	127	dm+1	48	fm+1
140-270	79	Dm	0	fm
270-325	48	dm-1	31	fm-1
325-plate	44	dm-2	35	fm-2

Table 4.12 Indexes for different batches for various parameters

Batch No	Indexes			Inference
	Parameter Index(IP)	Parameter Profile Index (IPP)	Good Compressibility Index (IGC)	
11OA(114)009A	0.55	5.19	4.78	Not directly compressible
11OA(114)009B	0.55	5.17	4.76	Not directly compressible
11OA(114)009C	0.55	5.57	5.12	Directly compressible
11OA(114)009D	0.55	5.70	5.24	Directly compressible
11OA(114)009E	0.66	5.95	5.48	Directly compressible
11OA(114)009F	0.55	5.98	5.5	Directly compressible
11OA(114)009G	0.55	5.67	5.22	Directly compressible
11OA(114)009H	0.55	5.79	5.33	Directly compressible
11OA(114)009I	0.66	6.34	5.83	Directly compressible

Figure 1 SeDeM Diagram Of Different Batches



Result and Discussion of SeDeM analysis:

All the batches having passable value of parameter index as all the values of parameter index were more than 0.5 as per requirement. Flow property and homogeneity index of granules were very poor which lead to value of radius less than 5 for the both the parameters. The granules prepared by high compression force resulted in higher compressibility index (IGC) and thus become suitable for direct compression while some were not because of less compressibility index (IGC). These deficiencies were reflected graphically in the SeDeM Diagram, which showed that a large shaded area (activity area) (the greater the shaded area, the more suitable the characteristics for direct compression) was present for most of the parameters. However, some parameters showed a small shaded area, thus indicating that the powder was not suitable for direct compression. Study showed that at some forces gave negative impact on powdered material which finally leads to decrease in compressibility and thus higher force was required for compaction.

4.5 FORMUALTION OF RIBBONS

4.5.1 PRELIMINARY TRIALS

Table 4.13 Preliminary trials for roller compaction

Trial no	Roller Compacter Parameters				Observation
	Horizontal Feed Screw Speed (Rpm)	Roll Speed (rpm)	Roll Pressure (bar)	Roll gap (mm)	
1	12	3	15	1.7	No ribbons obtained
2	15	4	20	2.0	Ribbons obtianed
3	15	5	25	2.0	Ribbons obtained
4	15	6	30	2.0	Ribbons obtained
5	20	5	25	2.5	Ribbons splitteed from sides
6	25	6	30	2.9	No ribbons obtained
7	15	7	35	-	Materials slipped from the rolls

Results and Discussions:

At lower roller speed material could not be compacted and hence ribbons could not be obtained. At higher roll speed as well as at high feed screw speed materials slipped from rolls because more amount of materials reached to nip region and hence could not be compacted. Roll gap changed with variation in feed screw speed. So it was mandatory to keep roll speed at15 rpm to maintain roll gap 2mm. Thickness of ribbons need to be kept 2mm to mimic the thickness of slugs and thus, feed screw speed kept at 15 rpm. From the above results we can conclude that roll speed and roll pressure could be taken as two parameters for central composite design.

From preliminary trials of the batches prepared, different envelope density of ribbons were yet to be achieved. Hence, **Central Composite Design** was adopted in order to

obtain the three envelope density with minimum possible trials. Here, **Central Composite Design** was adopted in order to systematically evaluate the effect of independent process variables (i.e. roll speed of and roll pressure of chilsonator) on different responses.

4.5.2 FORMULATION OF RIBBONS BY APPLYNIG CENTRAL COMPOSITE DESIGN FOLLOWED BY MILLING

Ribbons of the blend are prepared using chilsonator-IR 220 at different Roll Pressure and Roll speed. Serrated rolls are use which is having 25 mm thickness. Combination of roll pressure and roll speed are obtained by applying central composite design. Ribbons are collected and subjected to milling in Co-Mill at 1200 rpm through 1mm sieve.

4.5.2.1 INTRODUCTION AND APPLICATION OF CENTRAL COMPOSITE DESIGN IN EXPERIMENTAL WORK

The simplest of the central composite designs can be used to fit a second order model to a response with two factors. The design consists of a 2^2 full factorial design augmented by a few runs at the center point shown in figure 4 (a). A central composite design is obtained when runs at four other points (-1, 0), (1, 0), (0,-1) and (0, 1) are added to this design. These points are referred to as *axial points* or *star points* and represent runs where all but one of the factors are set at their mid-levels. The number of axial points in central composite design having k factors is 2^k. The distance of the axial points from the center point is denoted by α and is always specified in terms of coded values. For example, the central composite design in Figure 4 (b) has α = 1, while for the design of Figure 4 (c) α = 1.414. It can be noted that when α > 1, each factor is run at five levels (- α, - 1, 0 , 1 , α) instead of the three levels of 1,0 and 1.

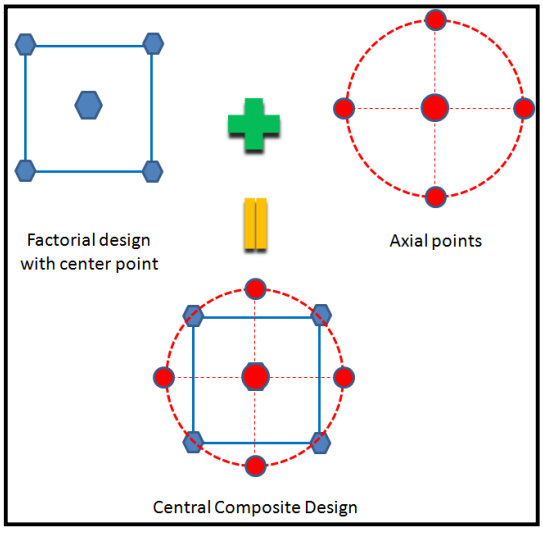


Figure 2 Central Composite Design

Table 4.14 Independent Variables and Their Coded Levels Investigated In Central Composite Design

FACTORS	LIMIT				
	-1.41	**-1**	**0**	**+1**	**+1.41**
ROLL SPEED (rpm)	3.6	4	5	6	6.4
ROLL PRESSURE (bar)	18	20	25	30	32

Table 4.15 Formulation of Ribbons Using Central Composite Design

RUN	CODED VALUE		ACTUAL VALUE	
	A	**B**	**A**	**B**
	SPEED (rpm)	**PRESSURE (bar)**	**SPEED (rpm)**	**PRESSURE (bar)**
1	-1	-1	4	20
2	1	-1	6	20
3	0	-1.41	5	18
4	0	0	5	25
5	1	1	6	30
6	-1	1	4	30
7	0	1.41	5	32
8	-1.41	0	3.6	25
9	1.41	0	6.4	25
10	0	0	5	25
11	0	0	5	25
12	0	0	5	25
13	0	0	5	25

4.5.3 EVALUATION OF RIBBONS PREPARED BY CHILSONATOR IR 220

(1) Envelope Density:
Envelope density can be measured by Geopyc 1360 Density tester. In Geopyc density tester dryflow was used which tend to fill the void spaces present between the particles of the material and thus gave volume difference obtained from the blank run. Instrument displayed displaced volume as well as envelope density of previously weighed ribbons.

(2) Roll Force:
Chilsonator IR 220 displayed the value of force applied by rolls to obtain ribbons.

(3) Carr's index:
Carr's index can be measured by same method used for granules prepared by slugging.

(4) Good Compressibility Index (IGC):
IGC can be measured by SeDeM analysis.

IGC	**INFERENCE**
Less than 3	Techniques other than direct compression will be required
Between 3to5	Requires addition of direct compressible excipient
Equal to or More than 5	Suitable for direct compression

.5.4 RESULTS AND DISCUSSIONS FROM CENTRAL COMPOSITE DESIGN:
(1) Envelope Density:

The envelope density of various formulations is shown in the table. It was found that the envelope density ranged between 1.08 to 1.58 gm/cm^3, which indicates the sensitivity towards the critical factors studied.

The obtained data were fitted in two quadratic model in Design Expert Software to describe the relationship between critical factors and response. The results are shown in the equation

It can be observed from the plots that the envelope density may increase with the increase in the speed and increased with the increase in roll pressure. Interaction of the two factors resulted in increase in envelope density which can be seen in the equation. From the ANOVA analysis it was found that p value of roll speed, roll pressure and interaction term B^2 were less than 0.05 and hence they were significant factors which affect the envelope density of the ribbons.

The nip angle defines the size of the nip region and the compression duration, while the maximum pressure (*P*max) at the neutral angle indicates the maximum degree of densification. These two parameters are determined by both the inherent powder properties (internal friction, cohesion and the friction between the powder and the tooling) and processing conditions, such as roll speed and roll gap. Here, pressure produced higher densification and thus envelope denstiy increased with increase in roll pressure. At higher Roll Speed, the entrapped air had amore difficulty leaving the powder mass as the dwell time was reduced; hence, the faster Roll Speed with shorter compaction dwell time and constant Feed Screw Speed with a constant powder delivery rate yields ribbons with the highest porosity among all settings studied.

(2) Roll Force:

The roll force of various formulations is shown in the table. It was found that the roll force ranged between 4 to 6.2 kN, which indicates the sensitivity towards the critical factors studied.

The obtained data were fitted in two quadratic model in Design Expert Software version 8.0 to describe the relationship between critical factors and response. The results are shown in the equation

It can be observed from the plots that the roll force did not vary with change in roll speed if roll pressure kept constant while it increased with the increase in roll pressure. Interaction of the two factors resulted in decrease in roll force which can be seen in the equation. From the ANOVA analysis it was found that roll pressure having p value less than 0.05 and it was the significant factor which affects the roll force of the ribbons. Roll force was not affected by roll speed while roll pressure increased force required for compaction and thus roll force required for compaction was increased as the force is directly propotional to pressure. This is as a result of increased bonding strength with increased compaction load . At higher Roll Speed of, the rollers rotate faster, reducing compaction dwell time for material under pressure which in turn, reduces time for particle rearrangement and bonding. Thus, roll speed shown very less effect on roll force.

(3) Carr's index:

The Carr's index of various formulations is shown in the table. It was found that the Carr's index ranged from 18.91 to 28.60, which indicates the sensitivity towards the critical factors studied.

The obtained data were fitted in two quadratic model in Design Expert Software to describe the relationship between critical factors and response. The results are shown in the equation

It can be observed from the plots that the carr's index varied with change in roll speed and pressure. Interaction of the two factors resulted in the increase in carr's index which can be seen in the equation. From the ANOVA analysis it was found that interaction A^2 having significant effect on the carr's index of the granules obtained after milling of ribbons. Here, powder entered in compaction zone at the same rate as feed screw kept constant on 15 rpm but dwell time required for compaction was varied with roll speed and hence bulk and tapped densities changed with roll speed which finallly gave its effect on carr's index. The effect of roll pressure was not significant because pressure removed entrapped air from bulk with same rate if roll speed kept constant but due to variation in roll speed, dwell time would be varied and hence roll pressure did not affect carr's index. Roller speed had a greater influence than screw speed on roller compaction of the materials studied. The negative influences of poor powder flowability could be overcome by the use of a low roller speed. Certain combinations of screw and roller speeds were unsuitable for production of flakes, indicating that downward force exerted by the feeder had to be in equilibrium with the inward directing force exerted by the rollers. Excessive downward force adversely affected the roller compaction process, resulting in low product yield and/or flakes of less desirable quality.

(4) Good Compressibility Index:

The Good Compressibility index of various formulations is shown in the table. It was found that the IGC ranged from 4.82 to 6, which indicates the sensitivity towards the critical factors studied.

The obtained data were fitted in two quadratic model in Design Expert Software to describe the relationship between critical factors and response. The results are shown in the equation

It can be observed from the plots that the IGC increase with increase in roll speed as well as roll pressure. Interaction of the two factors gives the negative result IGC which can be seen in the equation. From the ANOVA analysis it was found that A,B,B^2 were the significant factors which affects the good compressibility index of the granules obtained after milling of ribbons. Good compressibility index was a fianl output of SeDeM analysis which comprised of 9 different parameters. Here, compressibility increased with increase in roll pressure because high roll pressure removed entrapped air in large amount. Simillarly flow property also became good as the particles converted in to large granules. In addition, radius of homogenity index having higher value to that of original blend due to dry granulation process which lead change in size of particles. Thus, good compressibility index having higher values when both parameters gave their effect combindly which can be shown from response surface plots.

4.4.5 SeDeM ANALYSIS OF GRANULES PREPARED FROM RIBBONS

PREPARATION OF GRANULES:

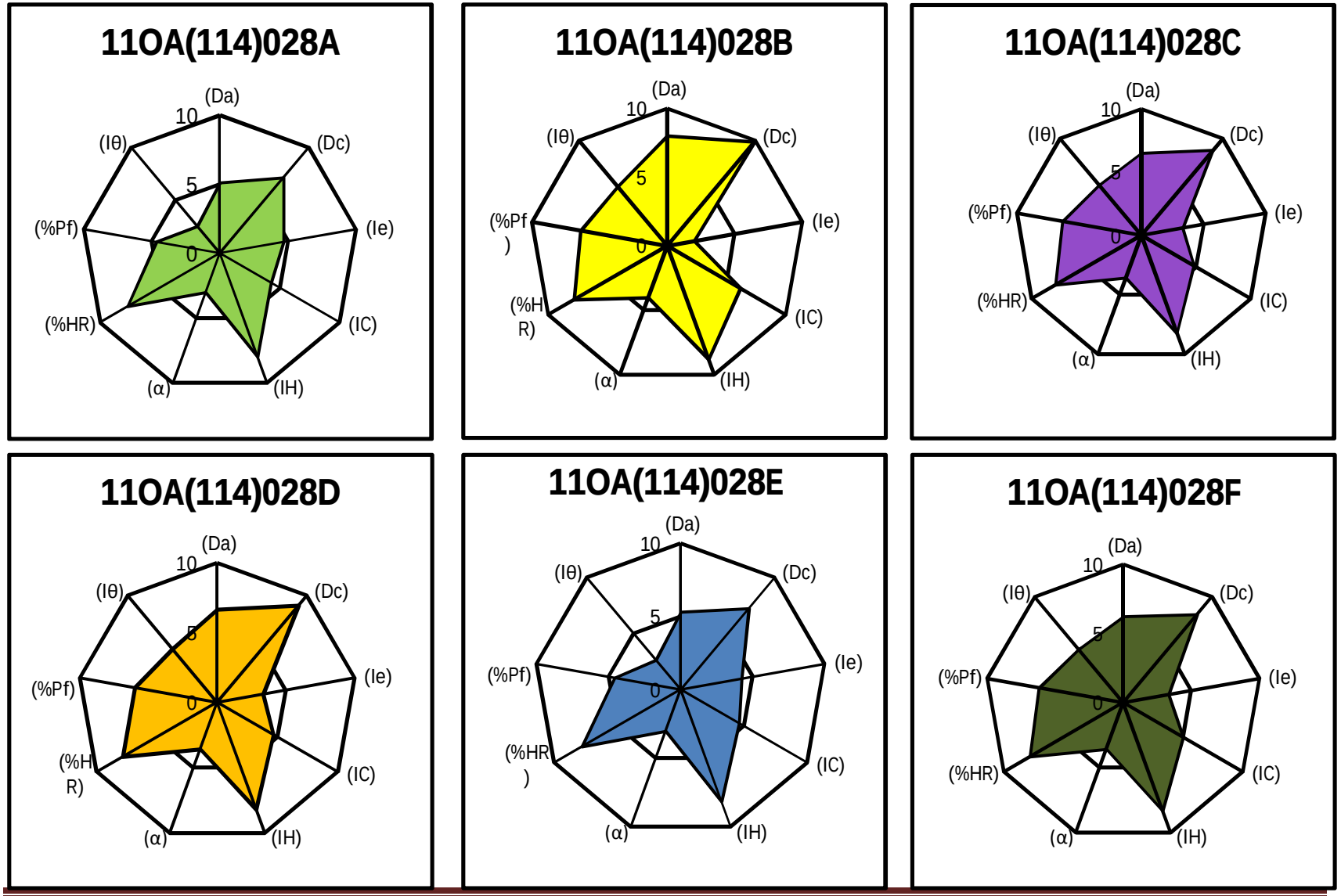
- Ribbons were transferred to Co-Mill and milling was done at 1200rpm. Granules were collected from the bottom of the mill.
- Granules were subjected for different tests to perform SeDeM analysis in order to evaluate suitability of the compression of the blend.

Table 4.17 Parameters of SeDeM Analysis

Incidence factor	Parameters	Equation	Acceptable range	Conversion factor
Dimension	Bulk Density (Da)	Da = P/Va	0–1 g/ml	10v
	Tapped density	Dc = P/Vc	0–1 g/ml	10v

	(Dc)			
Compressibility	Inter particle porosity (Ie)	Ie = Dc −Da/Dc × Da	0–1.2	10v/1.2
	Carr's index (IC)	IC = (Dc − Da/Dc) 100	0–50 (%)	v/5
Flowability	Hausners ratio (IH)	IH = Dc/Da	3–1	(30-10v)/2
	Angle of repose (α)	tg α = h/r	50–0 (°)	10 − (v/5)
Lubricity/Stability	Loss on drying (%HR)	Experimental	0-10 (%)	10-v
Lubricity/Dosage	Particle size<50µm (%Pf)	Experimental	50–0 (%)	10 − (v/5)
	Homogeneity index (Iθ)	Iθ = Fm / 100 + Δ Fmn	$0–2 \times 10^{-2}$	500v

Figure 3 SeDeM Diagram of Different batches



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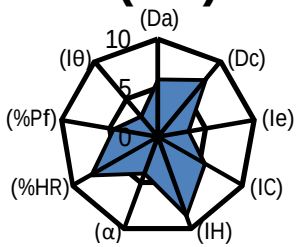

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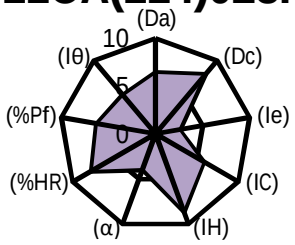

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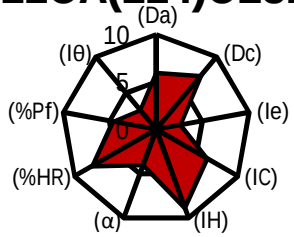

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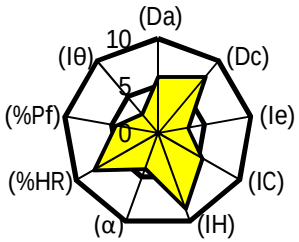

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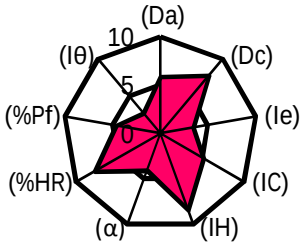

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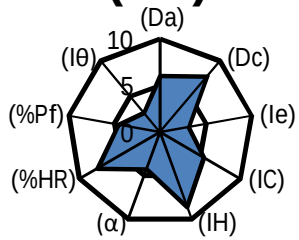

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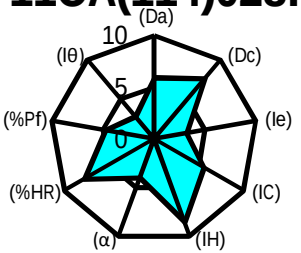

Result and Discussion of SeDeM analysis:

All the batches having passable value of parameter index as all the values of parameter index were more than 0.5 as per requirement. Flow property and homogeneity index of granules were very poor which lead to value of radius less than 5 for the both the parameters. The granules prepared by high roll force resulted in higher compressibility index (IGC) and thus became suitable for direct compression while some were not because of less compressibility index (IGC). These deficiencies were reflected graphically in the SeDeM Diagram, which showed that a large shaded area (activity area) (the greater the shaded area, the more suitable the characteristics for direct compression) was present for most of the parameters. However, some parameters shown a small shaded area, thus indicating that the powder was not suitable for direct compression.

Table 4.20 Parameters of Slugging and Roller Compaction to get Same Envelope Density

Envelope density	Parameters

(gm/cm^3)	Slugging		Roller Compaction	
	Turret speed (rpm)	Weight of Slugs (mg)	Roll speed (rpm)	Roll pressure (bar)
1.08	20	500	4	20
1.26	20	580	6	20
	30			
	40			
1.43	20	660	5	32
	30			
	40			

CONCLUSION:

The granule properties prepared from slugs as well as ribbons can be correlated successfully with the help of SeDeM analysis as well as with the help of experimental designs. Study showed that envelope density highly affected by roll pressure or compression force in case of roller compaction and slugging respectively. SeDeM analysis was the reliable method for evaluation of powdered materials (API or blend) and to get suitability for direct compression of the same. The properties of granules obtained from two different processes but having same envelope density were very similar which shown the reliability of method as well as the correlation point can be used for technology transfer to get same envelope density of granules obtained by both the method. Polynomial equation obtained from experimental designs from both the studies can be used in future to get value of process parameters. This platform technology can be used for process scale up as well as for technology transfer. Hence it can be concluded that technology transfer could be possible by using SeDeM analysis and experimental designs which shown better reliability.

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