"Studies on Optimization of Process Parameters influencing the Content Uniformity of Low dose Active Pharmaceutical Ingredient"

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PHARMACEUTICAL TECHNOLOGY AND BIOPHARMACEUTICS

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CERTIFICATE

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DECLARATION

I hereby declare that the dissertation entitled "Studies on Optimization of Process Parameters influencing the Content Uniformity of Low dose Active Pharmaceutical Ingredient", is based on the original work carried out by me under the guidance of Dr. Vipan Dhall, Vice President, Site Head, Piramal Pharmaceutical Development Services, Prof. Tejal A Mehta (Guide), Professor & Head, Department of Pharmaceutics and Pharmaceutical Technology, Institute of Pharmacy, Nirma University and Mr. Dhaivat Parikh (Co-guide), Assistant professor, 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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SAGAR VIKASCHANDRA PATEL

STUDIES ON OPTIMIZATION OF PROCESS PARAMETERS INFLUENCING THE CONTENT UNIFORMITY OF LOW DOSE ACTIVE PHARMACEUTICAL INGREDIENT

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Mixing of ingredients or dispersion of one phase into another is widely used operation in industry. The aim of these operations is to make homogeneous product using the minimum amount of energy and time. It is a prerequisite for manufacturing of all solid dosage forms which involves powder mixing and it has a critical contribution in achieving the Content Uniformity and Segregation of the blend is the main problem while preparing the tablets using direct compression method. Optimum mixing can be done by using different process parameters like effect of mixing pattern, strength of Active Pharmaceutical Ingredients, shape and size of diluents, and shear force. After studying on the process parameter it can be concluded that mixing pattern has much influence on the Content uniformity and Blend Uniformity. Compared to spherical excipients, fibrous and irregular shape containing excipients increased Content Uniformity, Blend Uniformity and decrease the segregation tendency of the Blend. After applying shear force to the mixture component, Uniformity of blend and Uniformity of dosage form would automatically achieve while segregation potential was decreased. In the present investigation, an attempt has been made to evaluate various process parameters on Content Uniformity of low dose Active Pharmaceutical Ingredients. Metformin Hydrochloride was selected as a model drug. From the preliminary trials and performance qualification of the equipments, 2^3 full factorial design was applied and the effect of Blender Volume, Mixing time and Co-mill mesh size on dependant responses like Uniformity of Content, Uniformity of Blend and Segregation tendency were measured. From the optimization study, it can be concluded that Blender Volume and Blending time were exhibited major effect on Uniformity of dosage form and segregation tendency of blend.

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LIST OF ABBREVIATIONS

ABBREVIATION	FULL FORM
IP	Indian Pharmacopoeia
BP	British Pharmacopoeia
USP	United States Pharmacopoeia
PhEur	European Pharmacopoeia
CU	Content Uniformity
BU	Blend Uniformity
SP	Segregation Potential
Conc.	Concentration
RH	Relative Humidity
USPNF	United States Pharmacopoeia National Formulary
FTIR	Fourier Transfer Infra Red
UV	Ultra Violet
MCC	Micro Crystalline Cellulose
L-HPC	Low substituted Hydroxy-Propyl-Cellulose
IP-QC	In-Process Quality Control
Aerosil	Colloidal Silicon Dioxide
Lactose Monohydrate	Pharmatose DCL11
AV	Acceptance Value
SD	Standard deviation
RSD	Relative Standard Deviation
DT	Disintegration Time
Kp	Kilopond
Sec	Second
T	Target Content
M	Reference Value
°C	Degree centigrade
CPR	Cumulative Percentage Release
µg	Microgram
Avg.	Average
Hr	Hour
min	Minute
nm	Nanometer
Kn	Kilo newton
Atm	Atmospheric pressure
Mg	Milligram
Gm	Gram
Min.	Minimum
Max.	Maximum
PVDF	Polyvinylidene Fluoride
API	Active Pharmaceutical Ingredient
DCP	Dicalcium Phosphate

CHAPTER-1
AIM OF PRESENT INVESTIGATION

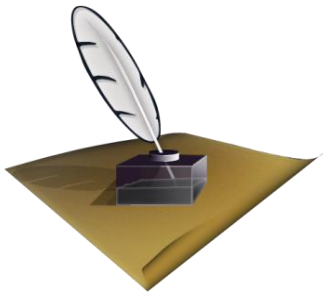
1 AIM OF PRESENT INVESTIGATION

Mixing is most important unit operation in Pharmaceutical manufacturing as it provides homogeneous product using the minimum amount of energy and time. Optimum mixing is a prerequisite for manufacturing of all solid dosage forms which involves powder mixing and it has a critical contribution in achieving uniformity of content. An understanding of powder characteristics and behaviour is essential to control these operations. Difficulties will appear due to the diversity of products in terms of size—particles or granules, shape—irregularly shaped particles, moisture and surface nature—cohesive or non cohesive powders. Poor Content uniformity problems has four main root causes: (i) Weight variability in the finished dose, which is often related to flow properties of the powder stream, (ii) poor equipment design or inadequate operation, (iii) particle segregation (driven by differences in particle properties), and (iv) particle agglomeration, driven by electrostatics, moisture, softening of low melting point components. To overcome this difficulty, same size and density of the excipients, different mixing equipment and different process are used in the industry.

Proportion of excipients mixing with API, strength of API, different shape of the diluents, particle size of API, and shear force were influence on the Uniformity of dosage form, Uniformity of blend and Segregation Potential. Mixing pattern has much influence on the Content uniformity and Blend Uniformity. Low strength of the Active Pharmaceutical Ingredient becomes challenge to achieve better Content uniformity and Blend Uniformity. Compare to spherical excipients, fibrous and irregular shaped excipients increases Content uniformity, Blend uniformity and decrease the segregation tendency of the Blend. It is well known phenomena in pharmaceutical industry that by applying shear force to the mixture component, uniformity of blend and uniformity of dosage form would automatically achieved while segregation potential decreases.

In the present investigation, blending behaviour study was conducted to evaluate effect of Blender volume, Blending time and co-mill mesh size on Uniformity of dosage form, Uniformity of blend and segregation tendency of the blend. Preliminary trials were conducted to evaluate effect of various parameters on Uniformity of dosage form. Concept of Design experiment was utilized to evaluate the effect of Blender Volume, Mixing time and Co-mill mesh size has effect on Uniformity of dosage form and Blend and Segregation Potential. Hence these parameters were considered as Independent factors in optimization design while Relative Standard Deviation of Blend Uniformity, Segregation Potential and Acceptance Value of dosage form were selected as a dependant factors for same. Low blender volume with low mixing time would increase the uniformity while increase in the mixing time would lead to demixing. High blender volume with low mixing time was resulted in improper mixing but at the same time increase in the mixing time will increase the uniformity of the Blend and decrease the segregation potential. Lower mesh size of co-mill increase the uniformity of Blend and tablet and decrease the segregation potential. Metformin was selected as a model drug because of its high cohesivity, poor flow property and high solubility in water. Thus aim of present investigation was to evaluate different process related parameters on Uniformity of the dosage form. Further the design of experiment approach was utilized for optimization of the formulation.

CHAPTER-2
INTRODUCTION



2 INTRODUCTION

2.1 INTRODUCTION TO MIXING PROCESS [1-28]:

Over recent decades the pharmaceutical processing has undergone a rapid transition from being a "processing art" to "processing science". This has been possible due to increasing understanding of processing parameters, better manufacturing equipment and stricter regulatory requirements. Process equipment used in the healthcare industry follow rigid specifications for accuracy, consistency and cleanliness. These regulations ensure that end products are safe, pure, and effective. Optimum mixing is a prerequisite for manufacturing of all solid dosage forms which involves powder mixing and it has a critical contribution in achieving uniformity of content. An understanding of powder characteristics and behavior is essential to control these operations. In particular, mixing equipment employed in the production of pharmaceuticals and medical devices deal with a higher level of complexity because their use is more specialized. Not one design fits all. Mixing is one of the most common pharmaceutical operations. It is difficult to find a pharmaceutical product in which mixing is not done at one stage or the other during its manufacturing. [1]

Mixing may be **defined** as "the process in which two or more than two components in a separate or roughly mixed condition are treated in such a way so that each particle of any one ingredient lies as nearly as possible to the adjacent particles of other ingredients or components". This process may involve the mixing of gases, liquids or solids in any possible combination and in any possible ratio of two or more components. Mixing of a gas with another gas, mixing of miscible low viscosity liquids and mixing of a highly soluble solid with a low viscosity liquid to effect dissolution are relatively simple as compared to the mixing of gases with liquids, mixing of liquids of high viscosity though miscible, mixing of two immiscible liquids such as aqueous and oily solutions to form emulsions, mixing of solids with liquids when the proportion of solids is high and mixing of solids with solids, specialized equipments are required for these operations. Most pharmaceuticals are highly process-dependent. The mixing operation has a decided influence on whether a drug will deliver the accurate dosage, have an acceptable appearance and texture, or be

stable for the appropriate length of time. The importance of proper mixer selection and optimal operation can hardly be over-estimated.

Some of the examples of large scale mixing practiced in pharmacy are:

- Mixing of powders in varying proportions prior to granulation or tabletting
- Dry mixing of the materials for direct compression in tablets
- Dry blending of powders in capsules and compound powders (insufflations).
- Blending of powders in cosmetics in the preparation of face powders, tooth powders
- Dissolution of soluble solids in viscous liquids for dispensing in soft capsules and in the preparation of syrups
- Mixing of two immiscible liquids for preparation of emulsions.

Depending on the flow properties of materials, solids are divided into two types:

1. **Cohesive materials** - These are characterized by their resistance to flow through openings for e.g. wet clay.
2. **Non-cohesive materials** – These materials flow readily such as grain, dry sand, plastic chips etc.

Mixing of cohesive materials is more difficult due to formation of aggregates and lumps. Wet mixing is encountered in pharmacy as an individual operation or as a subsequent step after dry blending. In pharmaceutical practice, solid-solid, solid-liquid and liquid-liquid mixing are generally batch operations where the batch may be as large as one ton.

2.1.1 OBJECTIVES OF MIXING

Mixing can be done for the following reasons:

- To ensure that there is uniformity of composition between the mixed ingredients which may be determined by taking samples from the bulk material and analyzing them, which should represent overall composition of the mixture.

- To initiate or to enhance the physical or chemical reactions e.g. diffusion, dissolution etc.
- Generally mixing is carried out to obtain following type of products:
- When two or more than two miscible liquids are mixed together, this results in to a solution known as true solution.
- When two immiscible liquids are mixed in the presence of an emulsifying agent, an emulsion is produced.
- When a solid is dissolved in a vehicle, a solution is obtained
- When an insoluble solid is mixed with a vehicle, a suspension is obtained.
- When a solid or liquid is mixed with a semisolid base, an ointment or a suppository is produced.
- When two or more than two solid substances are mixed together, a powder is obtained which when filled into capsule shell is known as capsules and when compressed under heavy pressure is called tablet.

2.1.2 TYPES OF MIXTURES [2,8]

Mixtures may be classified as follows:

I. Positive mixtures

II. Negative mixtures

III. Neutral mixtures

I. **Positive Mixtures** – These types of mixtures are formed when two or more than two gases or miscible liquids are mixed together by means of diffusion process. In this case no energy is required provided the time allowed for solution formation is sufficient. These types of materials do not create any problem in mixing.

II. **Negative Mixtures** – These types of mixtures are formed when insoluble solids are mixed with a vehicle to form a suspension or when two immiscible liquids are mixed to form an emulsion. These mixtures are more difficult to prepare and require a higher degree of mixing with external force as there is tendency of the components of these mixtures separate out unless they are continuously stirred.

III. **Neutral Mixtures** – Many pharmaceutical products such as pastes, ointments and mixed powders are the examples of neutral mixtures. They are static in their behavior. The components of such products do not have any tendency to mix spontaneously but once mixed, they do not separate out easily.

Many variations occur within the above explained groups owing to the different physical properties of the components of the mixture like viscosity which might change during mixing, the relative densities of the components, particle size, ease of wetting of solids, surface tension of liquids, while other factors such as the proportions of the components and the required order of mixing may exert an influence.

2.1.3 RATE OF MIXING

Mixing is the process of achieving uniform randomness of the mixed components, which on subdivision to individual doses contains the correct proportions of each component which depends on the amount of mixing done.

In the early stages of mixing, the rate of mixing is very fast because the mixing particles change their path of circulation quickly and find themselves in different environment whereas at the end of the process rate of mixing reaches to almost zero because the particles do not find different environment.

2.1.4 THEORY OF MIXING [9]

A significant aspect in mixing is to define when a particular batch is mixed. This depends on the method used for examining the samples and its accuracy, the number and location of the samples and the desired properties of the mixture. Diverse criteria like electrical conductivity of the samples, specific gravity of the samples, the amount of a key constituent in the samples, the rate of solution of a soluble solid in the samples etc. have been used to determine the uniformity of a mixed batch. Some of the recent methods of analysis include X-ray fluorescence, emission spectroscopy, flame spectrometry, radioactive tracer methods etc. Some other criteria such as the method of sampling, location, size, number of samples, and method of sample analysis and fraction of batch removed for sampling are important. The theory of mixing should also be able to predict the time in which a given batch is adequately

mixed in a given vessel and how much power is used for mixing. Not much is known about the time factor which is largely a function of the characteristics and proportion of the materials being mixed, the size and shape of the container involved, criteria used to determine when mixing is complete and many other factors.

2.1.5 LIQUID MIXING [2,8]

Liquid mixing may be divided into following two subgroups:

1. Mixing of liquids and liquids

a) Mixing of two miscible liquids

b) Mixing of two immiscible liquids

2. Mixing of liquids and solids

a) Mixing of liquids and soluble solids

b) Mixing of liquids and insoluble solids

1. (a) Mixing of two miscible liquids (homogeneous mixtures e.g. solutions) – mixing of two miscible liquids is quite easy and occur by diffusion. Such type of mixing does not create any problem. Simple shaking or stirring is enough but if the liquids are not readily miscible or if they have very different viscosities then electric stirrer may be used.

1. (b) Mixing of two immiscible liquids (heterogeneous mixtures e.g. emulsions) – two immiscible liquids are mixed to effect transfer of a dissolved substance from one liquid to another an eg. of such type of mixing is the extraction of penicillin in the acid form from aqueous solution into the organic solvent amyl acetate, to promote a chemical reaction after transfer of a component, to allow transfer of heat from one liquid to the other or to prepare emulsion. When two immiscible liquids are mixed together in the presence of an emulsifying agent an emulsion is produced. For the production of a stable emulsion, the mixing must be very efficient i.e. continuous without ceasing because the components tend to separate out if continuous work is not applied on them.

2. (a) Mixing of liquids and soluble solids (homogeneous mixtures e.g. solutions)- in this case soluble solids are dissolved in a suitable liquid by means of stirring. It is a physical change i.e. a soluble solid is converted to a solution.

2. (b) Mixing of liquids and insoluble solids (heterogeneous mixtures e.g. suspensions) – when insoluble solids are mixed with a liquid a suspension is produced which is an unstable system. The ingredients of a suspension separate out when allowed to stand for sometime so shear force is essential. The movement of the liquid at any point in the vessel will have three velocity components and the complete flow pattern will depend upon variations in these three components in different parts of the vessel.

The three velocity components are;

• **Radial components**, acting in a direction vertical to the impeller shaft.

• A **longitudinal component**, acting parallel to the impeller shaft.

• A **tangential component**, acting in a direction that is a tangent to the circle of rotation round the impeller shaft. The flow characteristics and mixing behavior of fluids are governed by three primary laws or principles: conservation of mass, conservation of energy, and the classic laws of motion.

2.1.5.1 MIXING MECHANISM [2]

Mixing mechanisms for fluids fall essentially into four categories: bulk transport, turbulent flow, laminar flow, and molecular diffusion. Usually more than one of these processes is operative in practical mixing situations.

1. **Bulk transport** – the movement of a relatively large portion of the material being mixed from one location in the system to another constitutes bulk transport. For bulk transport to be effective it must result in a rearrangement or permutation of the various portions of the material to be mixed. This can be accomplished by means of paddles, revolving blades, or other devices within the mixer arranged so as to move adjacent volumes of the fluid in different directions, thereby shuffling the system in three dimensions.
2. **Turbulent Mixing** – the phenomenon of turbulent mixing is a direct result of turbulent fluid flow, which is characterized by a random fluctuation of the fluid velocity at any given point within the system. Turbulent fluid has different instantaneous velocities at different locations at the same time.

3. **Laminar mixing** – Streamline or laminar flow is frequently encountered when highly viscous liquids are being processed. When two dissimilar liquids are mixed through laminar flow, the shear that is generated stretches the interface between them. If the mixer employed folds the layers back upon themselves, the number of layers, and hence the interfacial area between them, increase exponentially with time.
4. **Molecular diffusion** – The primary mechanism responsible for mixing at the molecular level is diffusion resulting from the thermal motion of the molecules.. The process is described quantitatively in terms of Fick's law of diffusion:

   Dm/dt = -DA dc/dx

   Where, the rate of transport of mass:- dm/dt across an interface of area :- A is proportional to the concentration gradient :- dc/dx, across the interface. The rate of intermingling is governed also by the diffusion coefficient, D,

2.1.6 MIXING SEMI-SOLIDS

Mixing solids with liquids – If the solid is not too coarse, the liquid is not too viscous and the percentage of solids is not too great, solids can be suspended in liquids by the use of a propellers or a flat-bladed turbine in a cylindrical container.

The mechanism involved in mixing semi-solids depends on the character of the material, which may show considerable variation. There is very little difference between liquids at the upper end of the viscosity range and semi-solids capable of flow. Also, when a powder and liquid are mixed, at first they are likely to resemble closely the mixing of powders.

2.1.6.1 THEORY OF MIXING OF SEMI-SOLIDS:

Mixing an insoluble powder with a liquid, a number of stages can be observed as the liquid content is increased. Pellet and Powder state: Addition of a small amount of liquid to a bulk of dry powder causes the solid to ball up and form small pellets. The pellets are embedded in a matrix of dry powder, which has a cushioning effect and makes the pellets difficult to break up. From the overall point of view, the solid is free-flowing and the rate of homogenization is low.

- **Pellet state:** Further addition of liquid results in the conversion of more dry powder to pellets until, eventually, all the material is in the state. The mass has a coarse granular appearance, but the pellets do not cohere and agitation will cause aggregates to break down into smaller granules. The rate of attainment of homogenization is even lower than in the pellet and powder stage and it is the state aimed at in moistening powders for tablet granulation.

- **Plastic state:** As the liquid content is increased further, the character of the mixture changes markedly, aggregates of the material adhere, the granular appearance is lost, the mixture becomes more or less homogeneous and of clay like consistency. Plastic properties are shown, the mixture being difficult to shear, flowing at low stresses but breaking under high stresses. Homogenization can be achieved much more rapidly than in the previous cases. This is the state obtained when making a pill-mass, for example.

- **Sticky state:** Continual incorporation of liquid causes the mixture to attain the sticky state, the appearance becomes paste-like, the surface is shiny, and the mass adheres to solid surfaces. The mass flows easily, even under low stresses, but homogeneity is attained only slowly.

- **Liquid state:** Eventually, the addition of liquid results in a decrease of consistency until a fluid state is reached. In this state, the mixture flows under its own weight and will drain off vertical surfaces.

2.1.7 SOLID-SOLID MIXING (POWDER MIXING) [2,8,10]

In pharmaceutical production when the formulation contains an active ingredient, which is toxic or is present in a concentration of about 0.5% of the total mass then the mixing of solids becomes a critically important operation. Product with too low an active ingredient will be ineffective and a product with too high active ingredient may be lethal. To provide good solid mixing the phenomenon to be avoided or overcome is the tendency of the particles to segregate. Segregation occurs when a system contains particles with different sizes, densities, etc. and motion can cause particles to preferentially accumulate into one area over another.

Powder mixing is a process in which two or more than two solid substances are intermingled in a mixer by continuous movement of the particles. Mainly, the object of mixing operation is to produce a bulk mixture which when divided into different doses, every unit of dose must contain the correct proportion of each ingredient. The degree of mixing will increase with the length of time, for which mixing is done.

Powder mixing is a neutral type of mixing. It is one of the most common operations employed in pharmaceutical industries for the preparation of different types of formulations, e.g. powders, capsules and tablets. When grinding and mixing of different substances is to be done simultaneously then two or more than two substances are fed to the mill one at the same time. To obtain good results of powder mixing the following factors and physical properties of drugs must be taken into consideration before undertaking any kind of powder mixing.

The ease with which different powders blend to a reasonably homogeneous mix varies considerably, being dependent on various physical properties of the individual components and on their relative proportions. It is easier to mix equal weights of two powders of similar fineness and density than to incorporate a small proportion of a fine powder in a large mass of a coarse denser material. Apart from density and particle size, the stickiness of the components to be mixed is also important. Prolonged mixing becomes necessary to effectively distribute materials like lubricants and wetting agents into tablet granules. Also wide differences among properties such as particle size distribution, shape and surface characteristics such as surface area and electrostatic charges may take blending very difficult. Flow characteristics such as angle of repose and ability to flow, abrasiveness of one ingredient upon the other, state of agglomeration of the ingredients, moisture or liquid content of the solids, density, viscosity and surface tension at operating temperature of any liquid added, are some other significant considerations in mixing and selection of mixing equipments. In fact the properties of the blending ingredients dominate the mixing operation.

2.1.7.1 PHYSICAL PROPERTIES AFFECTING MIXING

- **Material density:** If the components are of different density, the denser material will sink through the lighter one, the effect of which will depend on

the relative positions of the material in the mixer. If the denser particles form the lower layer in a mixture at the start of a mixing operation, the degree of mixing will increase gradually until equilibrium is attained, not necessarily complete mixing. If the denser component is above, the degree of mixing increases to a maximum, then dropping to equilibrium as the denser component falls through the lighter one, so that segregation has started. This factor is of practical significance in charging and operating a mixer.

- **Particle size:** Variation in particle size can lead to segregation also since smaller particles can fall through the voids between the larger particles. There will be a critical particle size that can just be retained in the mixed condition, which will depend upon the packing. When the bed of the particles is disturbed, dilation occurs and the greater porosity of open packing allows a large size of particle to slip through the voids, leading to segregation.

- **Particle shape:** The ideal particle is spherical in shape, and further the particles depart from this theoretical form, the greater the difficulty of mixing. If the particles are of irregular shapes, then they can become interlocked leading to a decrease in the risk of segregation once mixing has been achieved.

- **Particle attraction:** Some particles exert attractive forces; this may be due to adsorbed liquid films or electrostatic charges, such particles tending to aggregate. Sine these are surface properties, the effect increases as particle size decreases.

2.1.7.2 PROPORTIONS OF MATERIALS TO BE MIXED

The proportions of materials to be mixed play a very important role in powder mixing. It is easy to mix the powders if they are available in equal quantities but it is difficult to mix small quantities of powders with large quantities of other ingredients or diluents. The practical method for mixing such quantities is that the component present in lesser amount is mixed with an equal amount of the diluent, then a further amount of diluent is incorporated which is almost equal to previous quantities and so on until whole of the diluent has been added. This method is followed for mixing potent substances with diluents. When more than two components are to be mixed,

they should always be mixed in ascending order of their weights so as to ensure uniform mixing of the ingredients.

2.1.7.3 CONDITIONS FOR MIXING

The theory of powder mixing shows four conditions that should be observed in the mixing operation.

- **Mixer volume:** The mixer must allow sufficient space for dilation of the bed. Overfilling reduces the efficiency and may prevent mixing entirely.
- **Mixing mechanism:** The mixer must apply suitable shear forces to bring about local mixing and a convective movement to ensure that the bulk of the material passes through this area.
- **Mixing time:** Mixing must be carried out for an appropriate time, since the degree of mixing will approach its limiting equilibrium value asymptotically. Hence, there is an optimum time for mixing for any particular situation, one should also note that the equilibrium condition may not represent the best mixing if segregation has occurred.

2.1.7.4 MECHANISM OF POWDER MIXING [8]

It has been generally accepted that in all the mixtures, solid mixing is achieved by a combination of one or more of the following mechanisms:

2.1.7.4.1 Diffusive mixing – During this mechanism, mixing occurs by diffusion process by random movement of particles within a powder bed and cause them to change their relative positions.

2.1.7.4.2 Convective mixing – In convective mixing transfer of groups of particles takes place from one location to another by means of blades or paddles of the machine.

2.1.7.4.3 Shear mixing – In shear mixing, slip planes are set up within the mass of material

TABLE 2.1: MIXING MECHANISMS AND EQUIPMENT[2]

Mechanism	Equipment
Diffusion	1)V- Blender 2)Double Cone Blender 3)Bin-Blender 4)Horizontal/Vertical drum 5)Turbula Blender
Convection	1)Ribbon 2)Horizontal High Intensity 3)Verticle High Intensity 4)Diffusion 5)Planetary
Shear (Pneumatic)	1)Fluid Bed 2)Reimelt

Handling the mixed powder

When the mixing operation is completed, the mixer should stop and the powder should be handled in such a way that segregation is minimized. The vibration caused by subsequent manipulation, transport, handling or use is likely to cause segregation. Therefore, a bulk powder_that has been stored or transported should be re-mixed before removing a part of the contents.

Different Blenders for Powder Mixing are classified according to the mechanism:-

2.1.7.4.1 DIFFUSION MIXING

1) Turbula Blender [13,14,15]

The TURBULA mixer is used for homogeneous mixing of powdery substances with different specific weights and particle sizes. Producing dry-to wet and wet-to-wet mixtures is also possible. The production process is hygienic and dust-free because the product is mixed in independent containers of variable sizes. The exceptional efficiency of the TURBULA is achieved by the interaction of rotation, translation and inversion as per the geometric theory according to Schatz. The mixing container turns in a three-dimensional motion and the product is subjected to an ever-changing,

rhythmically pulsing motion. The results meet the highest requirements and are achieved in a minimum of time.

2) Conta Blender [15,16]

The Conta Blender is latest addition to the range of blenders which conforms to GMP concepts. Conta Blenders or Container tumblers are used mainly for blending of dry powders for capsule plant, for blending and homogenizing of dried granules for tablet production. It gives uniform mixing / lubrication of powder / granules and better mixing efficiency as compared to conventional Blenders like Double Cone Blender, V Shape Blender, Octagonal Blender, Polygonal Blender, etc. It lays emphasis on dust free transfer of powders / granules at different stages from sizing /dispensing to compression / filling of tablets, capsules or dry powder. In granulation room the dry granules enter to the container for blending through a dust free connection and the same container is loaded over to the blender for blending. This same container after blending raised over the tablet press for unloading in to the tablet press hoppers. The system consists of a mobile bunker, which is clamped to a rotating arm having lifting arrangement. The bunker is loaded with sized granules to be mixed and is clamped to the rotating arm and locked. The material is tumbled in the partial void inside the bin for a predetermined period. The Conta Blender rotates in a diagonal and eccentric plane, shuffling the product intimately and resulting in homogenous blend within 5-20 minutes approx. Conta blender has flexibility of batch volume wherein varying size of containers can be mounted on a drive console, which is equipped with clamping arms. Design of arm is such that the shell is given a tilt of 15^0, thereby giving uniform mixing / lubrication of powder / granules. The Conta Blender is provided with mechanical stopper to the bunker trolley, to ease in locating and unloading the bunker after completion of mixing operation. The drive consists of a brake motor with helical gear box, which is coupled to the rotating arm shaft by gear coupling.

Salient features

- Capacity: 25 Kgs to 500 Kgs.
- Fluid coupling between motors and gear box to take care of initial torque.

- An ideal blender for dry blending of powder and lubrication of granules / powder.
- Tumbling principle of powder in a partial void enables homogenous mixing of active ingredients, additives and raw carrier materials.
- It enables dust free operation in processing area.
- Electric or Manual inching arrangement to bring the arm with bunker back to rest at initial position.
- Control panel is equipped with Programmable Logic Control (PLC) system and MMI for the visual display of the operating parameters.
- Variable frequency drive / AC Inverter for the variable batch speed control

2.1.7.4.2 CONVECTION MIXING [15]

1) Ribbon Mixture :

- Mainly Convective and diffusive in action
- It consists of horizontal cylindrical trough, usually open at top.
- The spiral are rotates and transmit shearing action to the particle. One spiral is right handed and other spiral is left handed, so that material is worked back and forth in the length.
- Shear force are not so high so that aggregates may remain unbroken and movement encourage segregation due to size difference.

Modification:

- To increase the efficiency, use an agitator like plough-shaped shovels which pick up the material and spill it back.
- Shear force are increased by introducing perforated baffles which act as rubbing or gridding element and break down aggregates.
- Intermittent air-blasts also useful.
- Uses: Ribbon blender is used to mix finely divided solid wet solid mass, sticky and plastic solid. Uniform size and density material can easily mix. It is used for liquid-solid and solid-solid mixing.

Disadvantage:

- It is poor mixture because movement of particle is two dimensional.
- Shearing action is less than planetary mixture.
- It is fixed speed drive.

2.1.7.4.3 SHEAR MIXING [21]

1) Fluidize Mixture

The air movement is used for mixing powders. The powders are mixed in stationary cylindrical vessels. Air is admitted at its base at an angle. This gives tumbling action and spiral movement to the powder. Thus mixing is achieved.

Advantage: Air mixture shortens the mixing time.

- It is useful as a through-output.
- Mixing is intimate and efficient.
- It is also used for wet granulation in tablets. With additional attachment this equipment is useful for mixing wet massing and drying in the wet granulation method.

2.1.8 USE OF DIRECT COMPRESSION METHOD[12-23]

Tablets are the unit solid dosage forms meant for oral use and are manufactured by using tablet compression machines. The tabletting mixture that is going to be compressed can be prepared by either of the three techniques- Wet granulation, Dry granulation or Direct-compression. Each of the individual technique mentioned above has their own advantages and disadvantages respectively. But the invention of Direct-compression had increased the production of tablets enormously all over the world due to its advantages over the other two techniques. Direct compression (DC) is a preferred manufacturing process as the continually modernizing pharmaceutical industry strives to improve its manufacturing output while reducing operating costs. The main focus that must be kept in direct compression technique is about the use of direct compression vehicle (DCV). DC technology and the use of modern tableting machines demand that the excipients and API form a compressible mixture with

excellent flowability and a low tendency of particle segregation with good compaction properties. By using DCVs, the flow properties of the drugs with poor flow can be improved and hence can be manufactured by Direct compression technique.

The tabletting blend for a DC process contains the active pharmaceutical ingredient (API), a filler, a binder, a disintegrant, auxiliary excipients (e.g., glidants and solubilizers), and a lubricant.

The choice of tabletting process is highly influenced by the flowability and compressibility of the API-excipients mixture. The particle size/shape, density, moisture content, and composition of the excipients affect flowability and compressibility, which ultimately drives the tabletting process.

TABLE 2.2: COMPARISON OF WET, ROLLER AND DIRECT COMPRESSION [25]

No	WET GRANULATION	No	ROLLER COMPACTION	No	DIRECT COMPRESSION
1	Weighing and dispersing	1	Weighing and dispersing	1	Weighing and dispersing
2	Premixing	2	Premixing/Milling	2	Mixing
3	Preparing granulation solution	3	Roll compaction		
4	Wet massing				
5	Wet screening				
6	Drying				
7	Sizing / Milling	4	Milling		
8	Admixing (disintegrant, glidant, lubricant)	5	Admixing (flow aid, disintegrant, glidant, lubricant)	3	Admixing (disintegrant, glidant, lubricant)
9	Compression	6	Compression	4	Compression

2.1.8.1 ADVANTAGES OF DIRECT COMPRESSION [25]

1. **Cost Effectiveness**: The prime advantage of direct compression over wet granulation is economic since the direct compression requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labor leading to reduced production cost of tablets.

2. **Stability:** Direct compression is more suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps and increases the stability of active ingredients. Changes in Dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations.

3. **Faster Dissolution:** Disintegration or dissolution is the rate limiting step in absorption in case of tablets with poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution.

4. **Less wear & tear of punches:** The high compaction pressure involved in the production of tablets by slugging or roller compaction can be avoided by adopting direct compression. The chances of wear and tear of punches and dies are less.

5. **Other advantages:** As ingredients are processed for a shorter period of time, the chance for contamination is low. Due to fewer unit operations, the validation and documentation requirements are reduced and will become easier. Due to the absence of water in granulation, chance of microbial growth is minimal in case of tablets prepared by direct compression.

2.1.8.2 LIMITATIONS OF DIRECT COMPRESSION: [25]

1. **Segregation:** Direct compression is more prone to segregation due to the difference in density of the API and excipients. The dry state of the materials during mixing may induce static charges and lead to segregation. This may lead to the problems like weight variation and content uniformity.

2. **Cost:** Directly compressible excipients are the speciality products produced by spray drying, fluid bed drying, roller drying or co-crystallization. Hence,the products are relatively costly than the respective raw materials.

3. **Low dilution potential:** Most of the directly compressible materials can accommodate only 30-40 % of the poorly compressible active ingredients like acetaminophen that means the weight of the final tablet to deliver the 500 mg of acetaminophen would be more than 1300 mg. The large tablets may create difficulty in swallowing.

4. **Lubricant sensitivity:** Lubricants have more adverse effect on the filler, which exhibit almost no fracture or shear on compression (e.g. starch 1500).The softening effects as well as the hydrophobic effect of alkaline stearates can be controlled by optimizing the length of blending time to as little as 2-5 min.

5. **Variation in functionality:** There is a lack of awareness in some situations that the excipients behave differently, depending upon the manufacturer so much so that substitution from one source to that of another is not possible. Hence, there is a need for greater quality control in purchasing of raw materials to assure batch uniformity.

2.2 INTRODUCTION TO MEASUREMENT OF HOMOGENEITY OF DOSAGE FORM [29-47]

One of the most common unit operations in preparation of tablets is the physical blending of the active drug substance with one or more excipients. The end point of this process is the material homogeneity as measured by sampling and offline analysis of the powder. Removal of samples is covertly done with a sampling probe called a 'thief 'to withdraw a sample. 'Thief' is a probe designed to extract and collect small volumes of powder from a chosen representative cross section of blender. The resulting samples are then assayed using the same method used to analyze the finished product. 'Content Uniformity' is established if the drug content of the samples conforms to predetermine criteria. This method is influenced by the skill of the operator and often provides false representation of sample due to desegregation and disruption of the powder bed during sampling and transport. Thus, both sampling

and analytical error are likely to incur in these sampling procedure. So validation is mandatory, FDA's 2003 guidance to industry to amend the good manufacturing practice regulation, commercial batch final blend need to be tested routinely for blend homogeneity. Three factors can directly contribute to content uniformity problems i.e.

(i) Non-uniform distribution of drug substance throughout the powder mixture or granulations,

(ii) Segregation of the powder mixture or granulation during various manufacturing process

(iii) Tablet weight variation.

A solid dosage form less than 25 % active or 25 mg active that the USP would require the content uniformity testing on the drug product. Objective of this work is to assess the blend uniformity with three validation batches and establishing the adequacy of mixing for the product. To prove that the data of blending and compression is uniform and the process of blending and compression is within the control from the batches manufactured commercially. [29]

2.2.1 UNIFORMITY OF DOSAGE FORM [30]

Different definition of the Content Uniformity:-

- To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim.
- Dosage units are defined as dosage forms containing a single dose or a part of a dose in each unit.
- The uniformity of dosage units specification is not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for topical administration.
- The term “uniformity of dosage unit” is defined as the degree of uniformity in the amount of the drug substance among dosage units.

The uniformity of dosage units can be demonstrated by either of two methods, Content Uniformity or Weight Variation (see Table No). The test for Content Uniformity is based on the assay of the individual content of drug substance(s) in a

number of individual dosage units to determine whether the individual content is within the limits set. The Content Uniformity method may be applied in all cases. The test for **Content Uniformity** is required for those dosage forms described in (C1)–(C6) below:

(C1) coated tablets, other than film-coated tablets containing 25 mg or more of a drug substance that comprises 25% or more (by weight) of one tablet;

(C2) transdermal systems;

(C3) suspensions or emulsions or gels in single-unit containers or in soft capsules that are intended for systemic administration only (not for those drug products that are intended for topical administration);

(C4) inhalations (other than solutions for inhalation packaged in glass or plastic ampules and intended for use in nebulizers) packaged in premetered dosage units. For inhalers and premetered dosage units labeled for use with a named inhalation device, also see Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers ;

(C5) solids (including sterile solids) that are packaged in single-unit containers and that contain active or inactive added substances, except that the test for Weight Variation may be applied in the special cases stated in (W3) below; and

(C6) suppositories.

The test for **Weight Variation** is applicable for the following dosage forms:

(W1) solutions for inhalation that are packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules;

(W2) solids (including sterile solids) that are packaged in single-unit containers and contain no added substances, whether active or inactive;

(W3) solids (including sterile solids) that are packaged in single-unit containers, with or without added substances, whether active or inactive, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation; and

(W4) hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting Content Uniformity requirements.

The test for Content Uniformity is required for all dosage forms not meeting the above conditions for the Weight Variation test. Where compliance with the Content Uniformity test is required, then, by application of the provision for use of alternative methods provided in the General Notices section of this Pharmacopeia, it is possible for manufacturers to ensure this compliance by application of the Weight Variation test where the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%. This RSD determination may be based on the manufacturer's process validation and product development data. The concentration RSD is the RSD of the concentration per dosage unit (w/w or w/v), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in Table 2. Where the Weight Variation test is used in this way, the product must, if tested, nevertheless comply with the official compendial test for Content Uniformity.

TABLE 2.3: APPLICATION OF CONTENT UNIFORMITY (CU) AND WEIGHT VARIATION (WV) TESTS FOR DOSAGE FORMS[30]

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			25 mg & 25%	<25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			25 mg & 25%	**<25 mg or <25%**
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Suspension, emulsion, or gel for systemic use only, packaged in single-unit containers			CU	CU
Solutions is unit dose container or soft capsules			WV	WV
Inhalations			CU	CU
Transdermal systems			CU	CU
Suppositories			CU	CU
Others			CU	CU

2.2.1.1 CONTENT UNIFORMITY

- Select ≥ 30 dosage units and proceed as follows for the dosage form designated
- Assay 10 unit individually
- Calculate the drug substance (in %) of each unit
- Calculate the acceptance value.
- Where different procedures are used for assay of the preparation and for the content uniformity test, it may be necessary to establish a correction factor to be applied to the results of the latter.

2.2.1.2 REQUIREMENT OF UNIFORMITY OF THE DOSAGE UNITS

- The acceptance value (AV) of the first 10 dosage unit is less than or equal to L1%.
- $AV = |M - X| + ks$……(1)
- If the acceptance value is greater than L1%, test the next 20 units.

- The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to L1% and all individual dosage units fall within the range calculated using L2 factor.

  <[1-(0.01)(L2)]M nor > [1 + (0.01)(L2)]M

  L1 = 15.0, L2 = 25.0

TABLE 2.4: TERMS FOR CALCULATION OF ACCEPTANCE VALUE[30]

Variable	Definition
X	Mean of the individual contents (X_1, X_2…,X_n) expressed as percentage of label claim
X_1, X_2…,X_n	Individual units of the contents tested, expressed as percentage of label claim
n	Sample size (number of units in a sample)
k	Acceptability constant: if n = 10 then k = 2.4 or if n = 30 then k = 2.0
s	Sample standard deviation
RSD	Relative standard deviation (sample standard deviation expressed as percentage of mean)
M	**Reference value**
AV	Acceptance value
L1	Maximum allowed acceptance value, L = 15.0 unless otherwise specified
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M Range: [1 – (0.01)(L2)]M to [1 + (0.01)(L2)]M, L2 = 25.0 unless otherwise specified
T	Target content per unit dosage unit at the time of manufacture expressed as the percentage of label claim, unless otherwise stated T= 100.0% or T is manufacturer's approved dosage content per dosage unit

Calculation of Acceptance Value— Calculate the acceptance value by the formula:

$AV = |M - X| + ks$

if n=10 then k=2.4

if n=30 then k=2.0

M (case 1) when T≤ 101.5

Conditions	**Value**	
If 98.5% ≤ X ≤ 101.5	M = X	AV = ks
If X < 98.5%	M = 98.5%	AV = 98.5 – X + ks
If X > 101.5%	M = 101.5%	AV = X – 101.5 + ks

M (case 2) T > 101.5

Conditions	**Value**	
If 98.5% ≤ X ≤ T%	M = X	AV = ks
If X < 98.5%	M = 98.5%	AV = 98.5 – X + ks
If X > T%	M = T%	AV = X – T + ks

2.2.2 BLEND UNIFORMITY [31,32,33]

Definition: - BUA is an in-process test that is useful for ensuring the adequacy of the mixing of active pharmaceutical ingredients (APIs) with other components of the drug product.

- BUA or homogeneity testing can be applied to all dosage forms, but is recommended for those dosage forms for which the USP requires content uniformity testing (FDA Guidance for Industry, ANDAs: Blend Uniformity Analysis)

- Under current good manufacturing practices (CGMPS), an applicant is required to perform a test or examination on each commercial batch of all products to monitor the output and validate the performance of processes that could be responsible for causing variability, which includes adequacy of mixing to ensure uniformity and homogeneity (21 CFR 211.11 O(a)(3)).

The first step in evaluating the blend uniformity is to obtain the representative sample using good sampling device. A statistically representative sample is random sample, which has the same composition of each component as it is in the blend or any other samples. Unfortunately, it is not technically feasible at this time to consistently obtain the representative blend samples of 1-3 times the unit dosage weight primarily due to

blend sampling errors. Blend sampling errors could come from the design of the sampling thief, the sampling technique, physical/chemical properties of the formulation, material transfer and analytical procedures. A sample removed from the blend may not have exactly the same composition as all other samples taken from the blend because powders usually segregate to some degree due to differences in the flow properties of the individual components in the blend. The design of the sampling thief (shape, length, number of sampling chambers) may affect how the individual components flow into the cavities and the amount of overall blend flow into cavities. The sampling technique is crucial in determining if the samples adequately represent the blend. The insertion orientation, insertion angle, insertion depth and the operator differences, such as force and smoothness of motion, may significantly impact the consistency of sampling. The formulation factors that may contribute to the blend sampling errors include the compressibility, compatibility, flow ability, surface area, inter particle force, lubricity, particle size distribution, density and the drug load in the formulation. Furthermore, the post blending transfer and storage process could have impact on the blends, such as potential segregation. Although blend uniformity may be evaluated by extensive sampling throughout the blender, further sampling from intermediate bulk containers may also be important.

2.2.2.1 Sample Size and Procedures:-

Number of Sample: 6 - 10 points

Potential differences in mixing efficiency associated with specific types of equipment should be considered when determining sampling locations.

Sample Size < 3 x weight individual dose:-

If the firm experiences problems in collecting small samples equivalent to 1 to 3 dosage units and demonstrates that small samples give lower values for BUA due to sampling bias, larger samples (usually no more than 10 dosage units) can be collected. Justification for larger samples should be specific to the application under review. Justification based on literature references is usually not adequate.

Quantity of Sample tested

- The weight of the sample tested should be equivalent to the dosage used

- If a common blend is used for the manufacture of multiple strengths of the drug product, the weight of the sample used should be equivalent to the weight of the lowest strength of the drug product.
- For a drug product where different strengths are not made from the same common blend, BUA for each blend is recommended.

2.2.2.2 Criteria of Blend Uniformity:

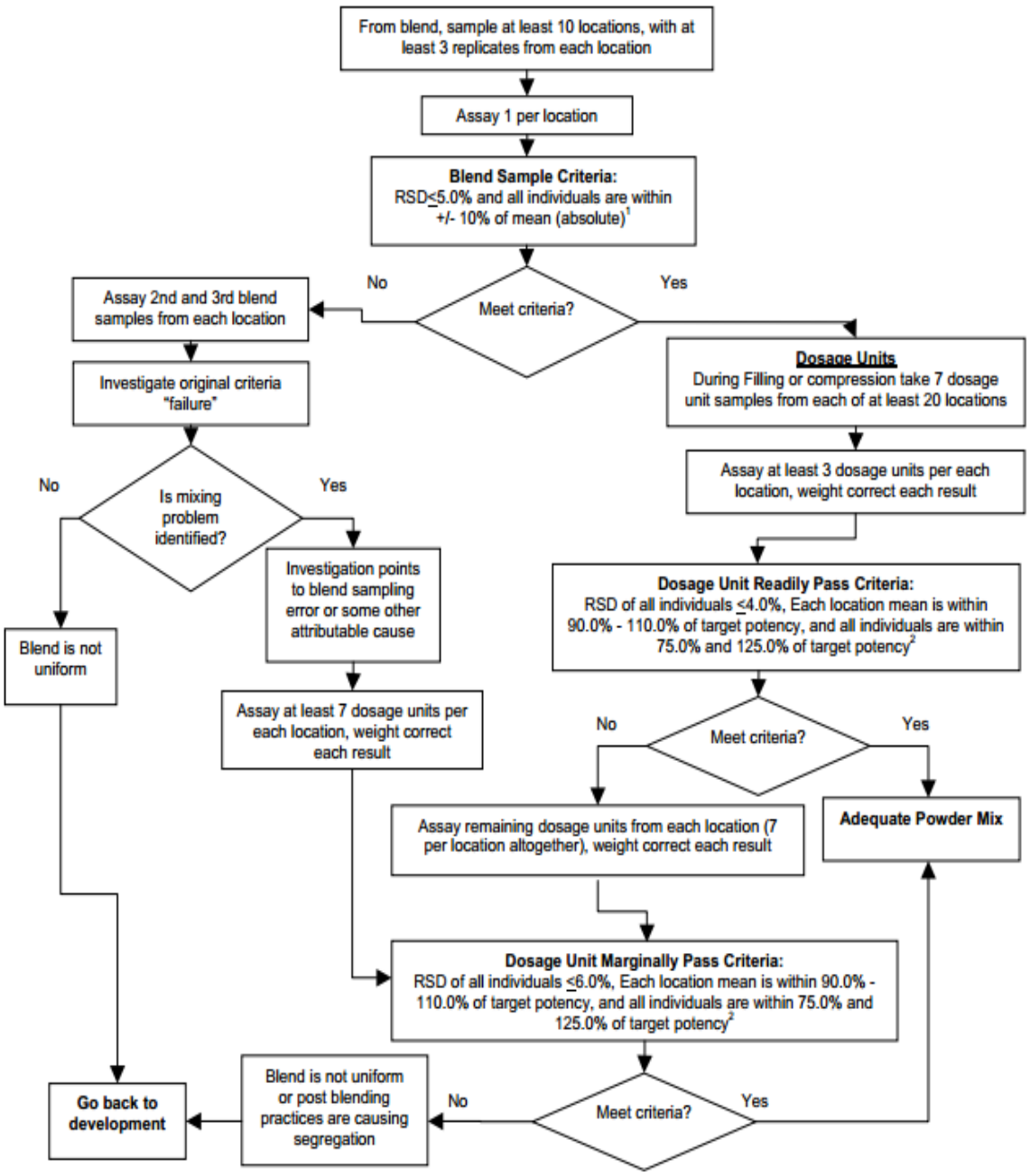


FIGURE 2.1: CRITERIA: UNIFORMITY OF BLEND [31]

2.2.3 SEGREGATION IN DIRECT COMPRESSION:

The handling, storage, flow, and mixing of particulate materials are important processing steps in many industries. During all of these processing steps, product quality may be lowered by a phenomenon known as segregation. Segregation is defined as a demixing process in which components of a mixture separate as long as one component of the mixture is different than another. Size-segregation is the most common in which finer particles gather in the center and larger particles tend towards the walls of storage container. However, other types of segregation caused by density, shape and composition have been observed.

Segregation is a serious problem in the processing and manufacturing of particulate materials. Several studies have investigated segregation for a particular process and reported a segregation coefficient in order to quantify the severity of segregation. Some of the processes that have been studied include discharge from a hopper, vibrated channels, vibrated columns, heap formation, and die filling. Another approach in solving segregation problems was identifying fundamental segregation mechanisms for a given process and determining the dominant mechanism. For example, heap formation is the process in which a stream of powder is deposited onto a flat plate. The powder forms a conical heap as powder is continuously deposited onto itself. It has been shown during this process that fines tend to the center of the conical heap and coarse particles concentrate on the outer boundaries of the cone. The dominant mechanism for this example of size-segregation was identified to be a rolling mechanism. Coarse particles more easily roll down the conical plane formed during deposition. Therefore, fines concentrate at the center due to the inability to roll down the conical plane and coarse particles concentrate at the outer surfaces. A particulate material will flow as long as the process induces enough internal shears to overcome the shear strength of the powder. This is the fundamental approach to hopper design using the Mohr- Coulomb theory and Jenike's Flow/No-Flow hypothesis. It observations have shown that segregation is occurring in a hopper during flow/discharge. Based on these observations, researchers developed a fluidize segregation test apparatus to measure segregation during applying fluidize air. When the shear mechanism was isolated, size-segregation was quantified by measuring the

drainage of fine particles through a bed of coarse particles. This type of segregation is known as percolation.

2.2.3.1 MECHANISM OF SEGREGATION: [1]

Eight unranked main mechanisms of segregation have been identified:

1) **Rolling:** Rolling effects are dominant in heap formation, because segregation in a heap has been described as a surface phenomenon where the heap surface remains constant. Rolling effects are also important, because friction varies as a function of size and stumbling effects, the ability of larger particles to roll over obstacles.

2) **Sieving:** Sieving effects occur in conjunction with rolling effects during heap formation. The larger particles rolling along the surface create a non-blinding screen. This type of segregation continues as long as the large particles are in motion. Sieving effects are also present in die filling.

3) **Push-away and Angle of repose:** Different densities cause push-away effects. A top layer with a higher density will push the bottom layers with lower densities to the side. Therefore, the center core of the powder sample will have a higher density than the wall area of the sample.

4) **Percolation:** Percolation has been studied as a function of vibration and induced by gravity. Vibration can cause a small individual particle to travel downward through the powder mass.

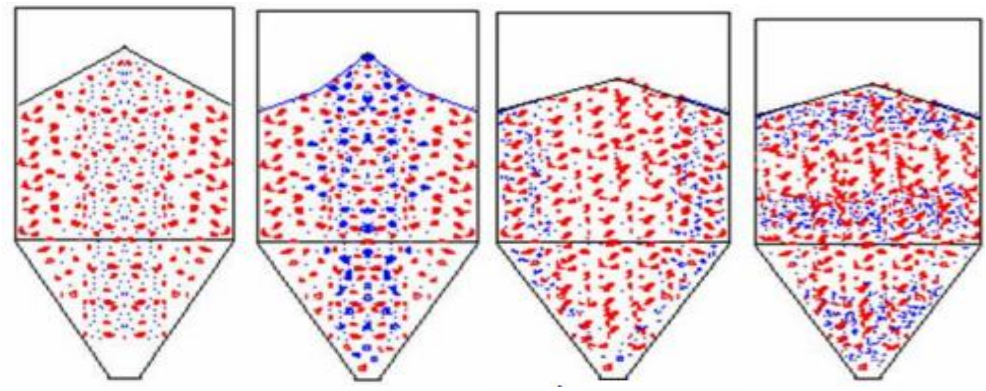
5) **Displacement:** Displacement segregation describes the phenomena in which a single large particle placed at the bottom of a pile of smaller particles travels to the top during vibration. A critical frequency of vibration was found.

6) **Trajectory and Air current:** Trajectory effects encompass larger particles traveling further off a chute than do smaller particles. Studies have shown that a large amount of fines were found on the side of a heap closest to the chute. Particulate material filled centrally into a tall bin or hopper that contains a significant amount of fines (defined as 50 μm) creates an air flow channel.

This air flow causes fines to travel to the sides of the silo or hopper and leaves the core filled with coarse particles.

7) **Fluidization:** Fluidization effects are similar to air current effects. During the filling of a hopper, fines become fluidized, or aerated, which enables the coarse particles to fall through the aerated fines.

8) **Impact:** The two mechanisms of impact effects are interparticle collisions and particle boundary collisions. As a small particle collides with a larger particle, the small particle can either stop or increase in velocity. This results in a wider distribution among the fine particles. Impact effects are increased with an increase in flow rate.



(a) (b) (c) (d)

FIGURE 2.2: SEGREGATION PROFILE: - a) Pile b) Angle of repose c) Air entrapment d) Impact of Fluidization[45]

2.2.3.2 DIAGNOSIS SEGREGATION PROBLEM IN EXISTING MIXTURE:

Before design a handling system for a new mixture, It is important to anticipate the mixture's segregation potential so that one can select equipment and configure the system to prevent or minimize segregation problems. While no comprehensive models exist for precisely predicting a mixture's blend composition at all points in a handling system, it's possible to anticipate segregation problems, including segregation type and severity, based on understanding the mixture's physical characteristics. By characterizing the particle size distribution, bulk cohesive strength, and particle densities of each component in the mixture, one can obtain some information about whether the mixture may segregate by sifting, fluidization, or

dusting. Or can obtain much more information about new mixture's segregation potential by conducting segregation tests using "The Jenike Fluidization Segregation Tester". The equipment provide information about whether mixture is likely to segregate by these mechanisms, and the test results also provide a basis for deducing the mixture's dusting segregation potential.

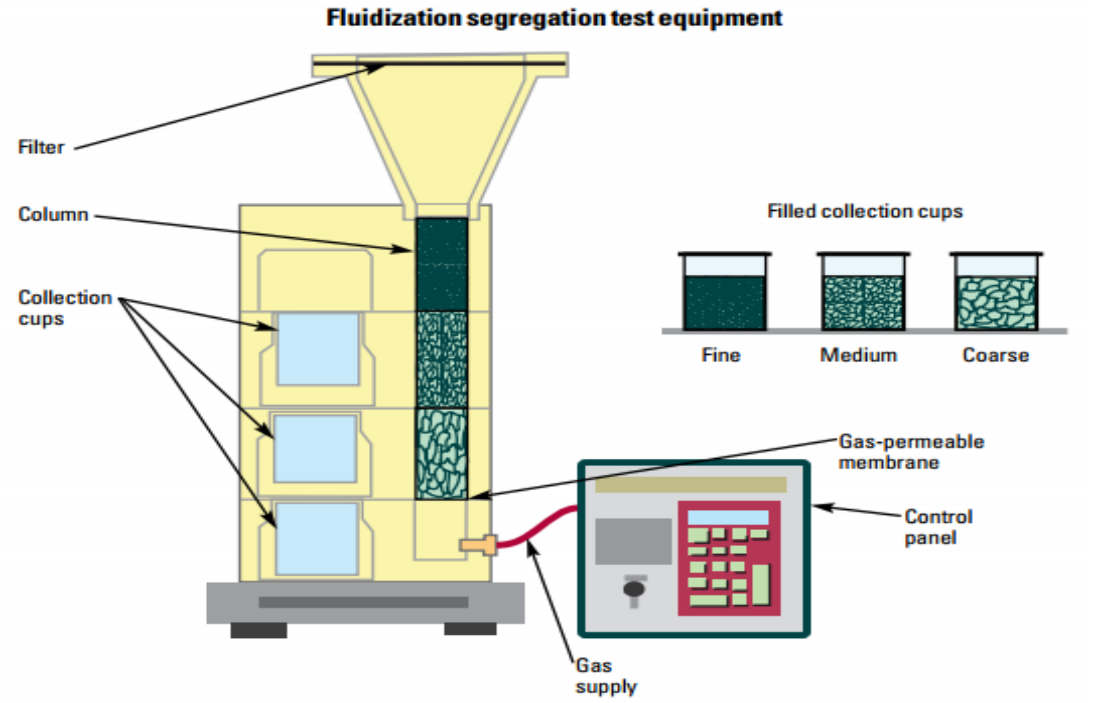


FIGURE 2.3: APPARATUS FOR A FLUIDIZATION SEGREGATION TEST

The apparatus for a fluidization segregation test is shown in Figure 2.3.

The Jenike Fluidization Segregation Tester measures the tendency of powders or other bulk solids to segregate by the fluidization segregation mechanism.

- Simulates the top-to-bottom segregation effects of gas flow through a bulk material, e.g., upon filling a bin, rapid blending, or pneumatic conveying
- Allows comparison of one material to another
- Provides computer controlled gas flow rate for repeatable, operator independent testing.

Fluidization can cause vertical segregation, i.e., horizontal layers of fines and coarse. Fine particles generally have a lower permeability than coarse particles and therefore

tend to retain air longer. Thus on filling a hopper, the coarse particles are driven into the bed while the fine particles remain fluidized near the top surface. This can also occur after tumble blending if the material is fluidized during blending. Air entrainment often develops in materials that contain a significant percentage of particles below 100 microns in size. Fluidization segregation is likely to occur when fine materials are pneumatically conveyed, filled or discharged at high rates, or if gas counter flow is present. General testing procedures pour a measured sample into the assembled tester, using the top of the expansion chamber as a funnel. Place the cap and filter on top of the funnel, and secure. Set the air flow rate and duration on the controller. The fluidization/deaeration cycle proceeds automatically. Once deaeration is complete, rotate the handle to cause the sample contained within each section to drop into its appropriate collection cup. This unique design provides fast, easy sample collection. Split the samples as needed, using proper techniques, to obtain the correct quantity required for analysis.

Primary components:

- Screw-on sealing cap
- Paper filter media (1 pkg. of 100)
- Air/Particle separation chamber / Funnel
- Upper sample chamber section
- Middle sample chamber section
- Lower sample chamber section
- Porous sintered metal air distributor
- Glass sample collection containers
- Air pressure/flow rate and timing controller
- Requires 110v power and regulated air supply.

2.2.3.3 PROPER TECHNIQUE REQUIRED FOR SAMPLE COLLECTION:

It’s not always apparent at what point in a handling system a segregation problem starts, so it’s important to take samples from several system locations and particularly at transfer points to determine where mixture has acceptable composition and the first point at which it begins to segregate. For instance, to find the source of segregation in a bagged product, take a sample inside the bin above the bagging operation and another sample from the bin’s discharge stream. If the bin sample is well-mixed and

the discharge sample is segregated, know that the mixture doesn't start to segregate until it discharges from the bin. When take a mixture sample from a flowing stream, such as from a fill chute, making sure that the sample is representative is especially important. Obtaining a representative sample of a mixture isn't always easy. Analyzing blend quality for instance, for particle size, chemical makeup, or color — often requires relatively small amounts of material. Yet samples collected from a process are almost always larger than such analyses require. As a result, a subsample must be taken from the collected sample for analysis. But taking a random subsample doesn't ensure that the subsample will be representative of the collected sample. For this reason, it's best to use a "**Micro Rotary Riffler**" (also called a Spinning Riffler) or similar device to divide the sample into identical subsamples. A typical rotary riffler, as shown in Figure 2.4, has a hopper that discharges onto a rotating wheel. The wheel is divided into individual sampling cups, and when material is discharged from the hopper, it flows into each sampling cup as each passes in turn under the discharge. In this case sample must capture the stream's entire cross section, because segregation can occur anywhere within the stream. For instance, just inserting a sample cup into the stream will capture only a portion of the stream, and the sample's analysis results can be quite different from those of a sample taken from another portion of the stream. To get an accurate sample from a flowing stream, must collect a cross section of the entire stream, then divide that sample into subsamples for analysis.

FIGURE 2.4: MICRO ROTARY RIFFLER[45]

2.3 INTRODUCTION TO TABLET AND TABLET MANUFACTURING MACHINE (KORSCH XL 100):

2.3.1 TABLETS [46-55]

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 [47]. 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 [48]. 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 [49] 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 No.2.5). 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. [50] Brittle particle undergo fragmentation, crashing of the original particles into smaller units. A single particle may pass through several of these stages during compaction. [48,51]

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. [49]

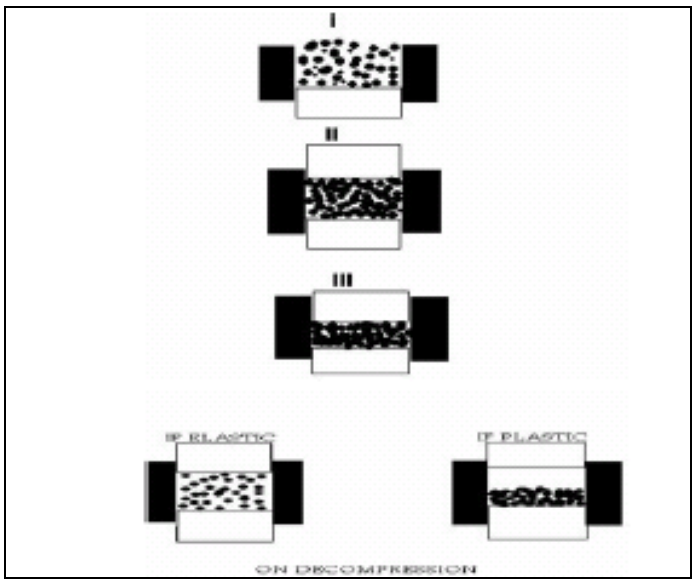


FIGURE 2.5: STAGES INVOLVED IN COMPRESSION (I – III) AND DECOMPRESSION

2.3.1.1 Compression Bonding Mechanisms

When particles get together, adhesive forces are developed, which are responsible for the strength of compacts after compression and compaction. [46]

In compression of dry powders, dominating bonds of interparticular adhesion are: [46]

- 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: Vander Waals forces, electrostatic forces and hydrogen bonding. [49]

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 Vander 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.

2.3.1.2 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.

2.3.1.3 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. [53] 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. [54, 55] Many compaction techniques are used to characterize the consolidation behavior of pharmaceutical solids.

2.3.2 KORSCH XL 100

The KORSCH XL100 is an innovative tablet press for product development, scale-up, and clinical batch production. The XL100 offers a new standard in GMP, extreme accessibility to the compression zone, an exchangeable turret for maximum flexibility, and combinations of quick-disconnects and smooth 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.

2.3.2.1 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

2.4 INTRODUCTION TO 2^3 FULL FACTORIAL DESIGN [56]

The design of an experiment can be simply defined as the plan that governs the plan that governs the performance of an experiment. It is the best interest of pharmaceutical scientist to understand the theoretical formulation and the target processing parameter and the formulation development should be done in the shortest possible time, using minimum number of men's hours and quantity of raw material. The developed formula is then tried at the pilot scale-up therefore, it is very essential to study the formulation from all the perspective at laboratory levels. In addition to the art of the formulations, a statistical technique is available that can aid in the pharmacist's choice of formulation components, which can optimize one or more formulation attributes.

The traditional experiments require greater efforts and time, especially where complex formulations are to be developed. A very efficient way to enhance the value of research and to minimize the process development time is through design experiments. Factorial designs are used in experiments when the effects of different factors or conditions, on experiment results are to be elucidated. Factors may be qualitative or quantitative. The levels of an each factor are the value or designation assigned to combination of all levels of all factor. The effect of a factor is the change in response caused by varying the levels of the factor. The full factorial design is designated by following nomenclature;

$$N=L^K \quad \ldots\ldots (2)$$

Where; K = number of variables, L = number of variables levels, N = number of the experimental trials.

The objective of the factorial design is to characterize the effect of changing the levels of the factor or combination of factors on the response variable. Predictions based on the results of an undesired experiment will be more variable than those, which could be obtained in a designed experiment, in particular factorial design. The optimization procedure is facilitated by construction of an equation that describes the experimental results as a function of the factor levels. A polynomial equation can be constructed, where the coefficients in the equation are related to the effects and

interaction of the factors. The equation constructed form 3n factorial experiment is in the following form.

Y= BO+B1X1+B2X2……BnXn+B12X1X2+B1X12+B22X22 …BmnXn2 …. (3)

Where,

Y= the measured response,

Xi = level of i^{th} factor

Bi,Bj,Bij= the coefficients from the response of the formulation in design,

Bo= Intercept

The magnitudes of the coefficients represent the relative importance of each factor. Once the polynomial equation has been established, an optimum formulation can be found out by grid analysis. With the use of computer a grid method can be used to identify optimum regions, and response surfaces may be depicted. A computer can calculate the response based on equation at many combinations of factor levels. The formulation whose response has optimal characteristics based on the experimenter's specification is then chosen.

2.4.1 2^3 FULL FACTORIAL DESIGNS

The two- level design is written as a 2^3 factorial design. It means that 3 factors are consider, each at 2 levels which are usually referred to as low and high levels. These levels are numerically expressed as -1 and +1. It is a simplest two level design. It has 3 factors each at 2 levels was generated between the factors and responses for determining the levels of factors, which yield optimum responses. A second order polynomial regression equation that fitted to the data is as follows:

Y = b0 + b1X1 + b2X2 + b3X3+ b12 X1X2+ b13X1X3+ b23X2X3…… (4)

Where, b0 is the intercept representing the arithmetic averages of all the quantitative outcomes of eight experimental runs; b1 to b3 are the coefficients computed from the observed experimental values of Y; and X1, X2 and X3 are the coded levels of factors.

The terms XiXj (i and j = 1, 2 and 3) represent the interaction terms. The equation represents the quantitative effect of factors (X1, X2 and X3) upon the each of the responses; Y1 to Y12. Coefficients with one factor represent the effect of that particular factor while the coefficients with more than one factor represent the interaction between those factors. A positive sign in front of the terms indicates synergistic effect while negative sign indicates antagonistic effect of the factors. **ANOVA was applied for estimating the significance of the model, at 5% significance level. A model is considered significant if the p-value is less than 0.05.**

2.4.2 Advantages of factorial design:

1. Minimum number of trials per independent variable is required.
2. Factorial designs have maximum efficiency in estimating main effects.
3. They form the basis for several other designs (like fractional factorial, composite etc.)
4. More information is obtained with less work.
5. They can be used as building block to define a large response surface.
6. The effects are measured with maximum precision.
7. Both quantitative and qualitative variables can be examined and results can be easily interpreted.

2.4.3 Applications:

1. To help and interpret the mechanism of an experimental system.
2. To recommend or implement, a practical procedure or a set of condition, in an industrial manufacturing operation.
3. As a guidance for further experimentations.

2.5 INTRODUCTION TO METFORMIN HYDROCHLORIDE [57-59]

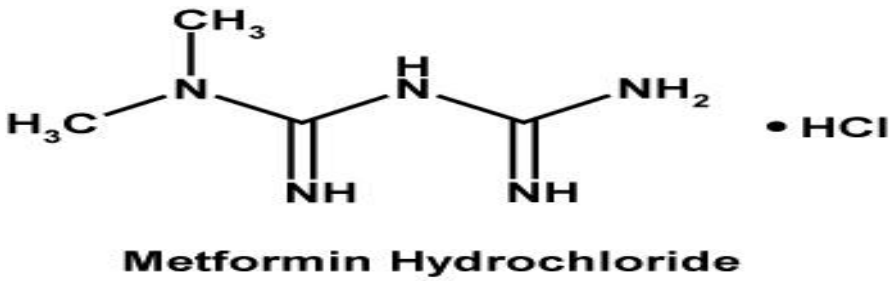


FIGURE 2.6: STRUCTURE OF METFORMIN HYDROCHLORIDE

Metformin Hydrochloride is 1,1-dimethylbiguanide hydrochloride.

MOLECULAR WEIGHT:- 165.6

CATEGORY:- Antidiabetic

OFFICIAL STATUS: - Official in I.P, B.P, USP, J.P

DESCRIPTION:- A white, crystalline powder; hygroscopic

SOLUBILITY:- Freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.

STORAGE: Store protected from light and moisture.

STANDARDS:- Metformin Hydrochloride contains not less than 98.5 per cent and not more than 101.0 per cent of C4H11N5, HCl, calculated on the dried basis.

IDENTIFICATION:-

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

B. Dissolve 25 mg in 5 ml of water, add 1.5 ml of 5 M sodium hydroxide, 1 ml of 1 naphthol solution and, dropwise with shaking, 0.5 ml of dilute sodium hypochlorite solution; an orange-red colour is produced which darkens on keeping.

C. Dissolve 10 mg in 10 ml of water and add 10 ml of a solution prepared by mixing equal volumes of a 10 per cent w/v solution of sodium nitroprusside, a 10 per cent w/v solution of potassium ferricyanide and a 10 per cent w/v solution of sodium hydroxide and allowing to stand for 20 minutes; a wine red colour develops within 3 minutes.

D. Gives reaction A of chlorides

ASSAY

Weigh accurately about 60 mg, dissolve in 4 ml of anhydrous formic acid, add 50 ml of acetic anhydride. Titrate with 0.1 M perchloric acid, determining the end-point potentiometrically. Carry out a blank titration. 1 ml of 0.1 M perchloric acid is equivalent to 0.008281 g of C4H11N5, HCl.

MELTING POINT: 223-226ºC

EXPERIMENTAL WATER SOLUBILITY: Freely soluble as HCl salt

PREDICTED WATER SOLUBILITY: 1.38e+00 g/l

EXPERIMENTAL LOG P/ HYDROPHOBICITY: - 0.5

PREDICTED LOG P: - 1.8

PHARMACOLOGY:

Pharmacodynamics: Metformin is an oral antihyperglycemic agent that improves glucose tolerance in patients with NIDDM, lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with NIDDM or healthy subjects and does not cause hyperinsulinemia. Metformin does not affect insulin secretion. Mechanism of action: Metformin's mechanisms of action differ from other classes of oral antihyperglycemic agents. Metformin decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects are mediated by the initial activation by metformin of

AMPactivated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats. Activation of AMPK is required for metformin's inhibitory effect on the production of glucose by liver cells. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. Metformin administration also increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake. The rare side effect, lactic acidosis, is thought to be caused by decreased liver uptake of serum lactate, one of the substrates of gluconeogenesis. In those with healthy renal function, the slight excess is simply cleared. However, those with severe rena impairment may accumulate clinically significant serum lactic acid levels. Other conditions that may precipitate lactic acidosis include severe hepatic disease and acute/decompensated heart failure.

INDICATIONS AND USAGE FOR METFORMIN

Metformin hydrochloride tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes mellitus.

CONTRAINDICATIONS:-

Metformin hydrochloride tablets are contraindicated in patients with:

- Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascularcollapse (shock), acute myocardial infarction, and septicemia.

- Known hypersensitivity to Metformin hydrochloride.

- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

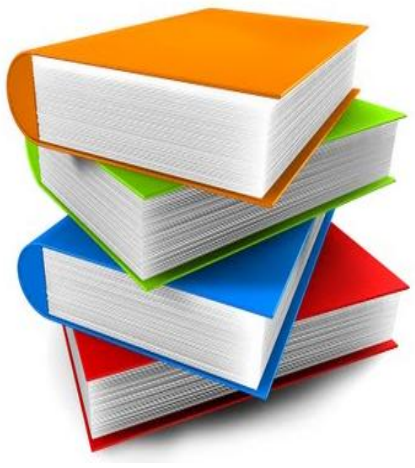
Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

Precautions and Adverse Effects:- Patients with renal impairment should not receive metformin. Other contraindications include hepatic disease, a past history of lactic acidosis (of any cause), cardiac failure requiring pharmacological therapy, or chronic hypoxic lung disease. The drug also should be discontinued temporarily prior to the administration of intravenous contrast media and prior to any surgical procedure. The drug should not be readministered any sooner than 48 hours after such procedures and should be withheld until renal function is determined to be normal. These conditions all predispose to increased lactate production and hence to the potentially fatal complication of lactic acidosis. The reported incidence of lactic acidosis during metformin treatment is less than 0.1 cases per 1000 patient-years, and the mortality risk is even lower. Acute side effects of metformin, which occur in up to 20% of patients, include diarrhea, abdominal discomfort, nausea, metallic taste, and anorexia. These usually can be minimized by increasing the dosage of the drug slowly and taking it with meals. Intestinal absorption of vitamin B12 and folate often is decreased during chronic metformin therapy, and calcium supplements reverse the effect of metformin on vitamin B12 absorption.

Consideration should be given to stopping treatment with metformin if the plasma lactate level exceeds 3 mM or in the setting of decreased renal or hepatic function. It also is prudent to stop metformin if a patient is undergoing a prolonged fast or is treated with a very low calorie diet. Myocardial infarction or septicemia mandates immediate drug discontinuation. Metformin usually is administered in divided doses two or three times daily. The maximum effective dose is 2.5 g/day. Metformin lowers hemoglobin A_{1c} values by about 2%, an effect comparable with that of the sulfonylureas. Metformin does not promote weight gain and can reduce plasma triglycerides by 15% to 20%. There is a strong consensus that reduction in hemoglobin $\mathbf{A_{1c}}$ by any therapy (insulin or oral agents) diminishes microvascular complications. Metformin, however, is the only therapeutic agent that has been demonstrated to reduce macrovascular events in type 2 DM (U.K. Prospective Diabetes Study Group, 1998b). Metformin can be administered in combination with sulfonylureas, thiazolizinediones, and/or insulin. Fixed-dose combinations containing metformin and glyburide (GLUCOVANCE, others), glipizide (METAGLIP), and rosiglitazone (AVANDAMET) are available**.**

CHAPTER-3

LITERATURE REVIEW



3 LITERATURE REVIEW:

3.1 LITERATURE REVIEW ON MIXING STUDIES IN FORMULATION:

- Hongming Li and J. J. McCarthy [41] studied the effects of cohesion on particulate mixing and segregation. They theoretically and experimentally examine the cohesive (here, liquid-bridge induced) mixing and segregation in an annular shear cell. They extend previous theoretical arguments for pseudo-static particle systems to sheared beds and use their theory to develop phase diagrams that correctly predict cohesive particle mixing/segregation. They conclude that the effect of liquid-bridge induced cohesion forces on particle mixing under shear by applying a newly developed heterogeneous characterization tool—Collision Number, Co. They showed that, while the Granular Bond Number, Bog, may be sufficient to determine particle mixing in a system where collision forces are sufficiently small, it is necessary to consider Co in a system where the collision force is comparable to the cohesion force (but larger than the particle weight). This simple characterization measure may serve as a useful tool for controlling particle mixing in a sheared cohesive system.

- S.C. Yang et al [39] investigated the mixing and segregation processes of binary granular mixture with identical sizes but different densities particles subjected to vertical oscillatory excitation. He concluded that the time evolution of pattern formations show that the heavy particles first move toward the center of the bed and then concentrate near the centers of the two convection cells of the vibrated system. The mechanism causing the mixing and segregation is strongly dependent on the momentum exchange of each species which is related to the granular temperature gradients of mixture components. The influences of solid fraction and granular temperature profiles on the mixing of the mixture are examined under different operating conditions. The simulation results show that the granular temperatures of heavy particles are higher than those of light particles, indicating that the granular temperatures do not equilibrate for the mixture system. The convection motion also plays an important role in determining the mixing of the system. For understanding the extent of granular mixing, the segregation intensity was determined to quantify the mixing rate of binary mixtures. The segregation

intensity shows that the mixing rate increases with the vibration strength, but decreases with the initial heights of mixture.

- Edina Vranic and Alija Uzunovic[60] studied influence of tablet splitting on content uniformity of lisinopril/hydrochlorthiazide tablets. As model tablets for this investigation, two batches of lisinopril- hydrochlorothiazide scored tablets labeled to contain 20/12.5 mg were used. Determination of the content uniformity of lisinopril and hydrochlorthiazide was carried out by HPLC method. The results of content uniformity studies for halves of tablets containing combination of lisinopril-hydrochlorthiazide (supposed to contain 50% of stated 20/12.5 mg in the whole tablet) were: 49.60±3.29% and 49.29±0.60% (lisinopril); 50.33±3.50% and 50.69±1.95% (hydrochlorthiazide) for batch I and II, respectively. He concluded that the results obtained in this study support an option of tablet splitting, which is very important for obtaining the required dosage when a dosage form of the required strength is unavailable, and for better individualization of the therapy.

- Ying Zhang and Kevin C. Johnson [61] studied effect of drug particle size on content uniformity of low-dose solid dosage forms. Two low-dose blends were prepared that differed only in the particle size of the drug used to make the blends. The geometric mean particle diameters for the two lots of drug used were 18.5 and 6.1 µm. Samples of the blends approximately equivalent to the unit dose of 10 µg per 99 mg of blend were assayed for potency. For the blend containing the larger particle size drug, the potency range was 88-130% (n = 65) compared to 97-102% (n = 64) for the blend containing the smaller particle size drug. A simple computer method was able to qualitatively simulate the observed potency profiles using only the particle size distribution of the drug and assuming ideal mixing. The method provides guidance in setting particle size specifications to avoid poor content uniformity.

- Chen Mao et al. [40]studied harnessing ordered mixing to enable direct-compression process for low-dose tablet manufacturing at production scale. They showed that excellent content uniformity of a drug product can be accomplished through direct

compression, when ordered mixing was introduced as part of the manufacturing process. They discovered that excipients with round morphology and rugged surface, which enabled "depth-filling" pattern and multi-layer coverage of API on carrier particles, can give rise to ordered mixtures with greater carrier capacity, stronger adhesive forces, and reduced ordered unit segregation tendency. They developed a sample-saving, bench-scale diagnostic tool which can successfully evaluate the sifting-driven segregation tendency of powder blends. They further identified the conical screen milling process as a robust approach to produce stable ordered mixtures, due to the physical impact and mixing behavior involved in the milling process. This systematic approach, developed on the basis of mechanistic understanding of the critical material and process attributes forordered mixing and segregation, allowed them to consistently manufacture tablets with high content uniformity both at 1-kg scale and 40-kg scale. Through this study, they demonstrated that common risks associated with the direct-compression process at production scale, such as content uniformity, can be mitigated by understanding and manipulating the particle–particle structures and interactions of the formulation components.

- Joseph Kushner IV [13]Incorporated Turbula mixers into a blending scale-up model for evaluating the effect of magnesium stearate on tablet tensile strength and bulk specific volume. To address need for lubrication blending scale-up, 2:1 blends of microcrystalline cellulose and spray-dried lactose or dibasic calcium phosphate were mixed with 1% magnesium stearate using Turbula bottle blenders, varying bottle volume, V (30–1250 mL); bottle headspace fraction, Headspace (30–70%); and the number of blending cycles, r (24 to ~190,000 cycles). The impact of lubrication blending on tensile strength and bulk specific volume quality attributes, QA, was modeled by mathematical equation. The factor of 1.5 captures the bottle dimensions and the more complex mixing dynamics of the Turbula blender. Their lubrication blending process model is valid for scale-up from 30-mL to 200-L blenders. Assessing bulk specific volume may provide a simpler, more material-sparing means for determining γ than tensile strength, since these QAs exhibited similar γ values.

- R. Hogg [62] studied mixing and segregation in powders and their evaluation, mechanisms and processes. Mixing in powders generally results from relative motion of groups of particles −convective mixing −or of individuals −diffusive mixing. Segregation or demixing occurs when the motion of individual particles is biased according to their particular characteristics −size, shape, composition etc. In the absence of such bias, individual motion invariably leads to homogenization of the mixture.

- Fernando J. Muzzio et al. [63] studied effects of rotation rate, mixing angle, and cohesion in two continuous powder mixers by using a statistical approach. They examine the effect of rotation rate, mixing angle, and cohesion on the powder residence time and the content uniformity of the blend exiting from two continuous powder mixers. In addition, differences in mixing performance between the two blenders are examined. Analysis of variance is used to determine significance of main effects and their interactions. The results show that the effect of powder cohesion is scale-dependent, having a significant effect in the larger mixer. The overall rotation rate was the least influential parameter in terms of content uniformity. The residence time is significantly affected by both rotation rate and mixing angle.

- Alena Kukukova et al. [64] define mixing and segregation in three dimensions of a key process variable. The first dimension is the intensity of segregation quantified by the normalized concentration variance (*CoV*); the second dimension is the scale of segregation or clustering; and the last dimension is the exposure or the potential to reduce segregation. The first dimension focuses on the instantaneous concentration variance; the second on the instantaneous length scales in the mixing field; and the third on the driving force for change, i.e. the mixing time scale, or the instantaneous rate of reduction in segregation. With these three dimensions in hand, it is possible to speak more clearly about what is meant by the control of segregation in industrial mixing processes. In this paper, the three dimensions of segregation are presented and defined in the context of previous definitions of mixing, and then applied to a range of industrial mixing problems to test their accuracy and robustness.

- William R. Ketterhagen et al. [65] investigates the causes and extent of segregation of granular materials during discharge from a hopper using the discrete element method. Aquasi-three-dimensional, wedge-shaped hopper is modeled using two parallel periodic boundary conditions. The effects of various particle properties, such as diameter ratio, mean size, and mass fraction of each species, as well as hopper geometries, such as the height, width, outlet width, and wall angle, on the segregation results are examined. Additionally, the effects of friction coefficient and hopper fill methods are investigated. Results show that many factors affect the extent of segregation during hopper discharge, but some of the key factors include the particle diameter ratio, mass fraction, and ratio of hopper outlet to mean particle diameter as well as the hopper wall angle and wall roughness. Additionally, the method used to fill the hopper is shown to play a significant role in determining the segregation upon discharge. Visualization of the internal hopper flow patterns gives insight into the causes of segregation, which then aids in the proposal of various recommendations for reducing the extent of segregation during hopper discharge.

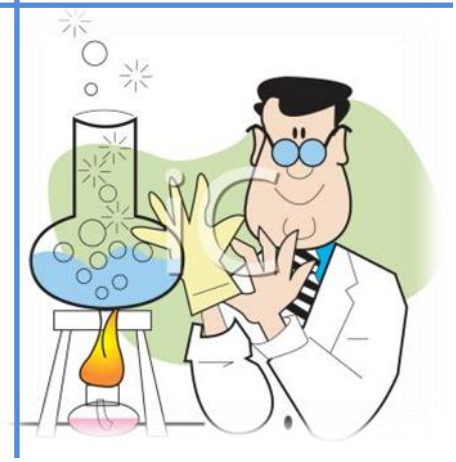
- Sanjay K. Singhai et al. [19] overviewed Scale Up factor determination of V Blender. There liable scaling of a process requires an understanding of the effects that processing parameters may illicit on intermediate- and finished-product properties. V-blenders, tote blenders, and double-cone blenders are examples of batch blenders that vary in geometric design. For these systems, variables such as blender size and fill level may affect mixing behavior The main variables known to affect mixing performance are: (1) the design of the mixing system (e.g., geometry and blend mechanism), (2)blender size, (3) the fill level, (4) the blender loading mode, (5) the speed of rotation of the blender, and (6)the material properties of the ingredients being mixed(particle size, shape, and density, etc Content uniformity problems have four main root causes: (a) powder stream flow properties, (b) poor equipment design or inadequate operation, (c) particle segregation due to differences in particle properties, and (d) particle agglomeration, driven by electrostatics, moisture, softening of low melting point components, as well as other factor As a result, unless the effects of all variables are nearly independent of one another.

- G. Léonard et al. [66] studied an experimental investigation of effusivity as an indicator of powder blend uniformity. The objective of their work was to gain insight into the accuracy, sensitivity and limitations of effusivity as an indicator of blend uniformity. Two series of experiments were carried out. First, monitoring experiments were used to determine and compare the optimal blending times of a pharmaceutical mixture obtained by three different methods: effusivity, density and UV spectroscopy. A second series of experiments was conducted to quantify the influence of density on effusivity measurements. The potential of effusivity to be used as a tool for assessing blend uniformity is discussed. In particular, the results from these experiments reveal that the accuracy of effusivity in determining optimum blending times depends on the blend physical characteristics and is significantly influenced by density.

- S. Lakio et al. [67] evaluated how different granule size distributions affect the tablet compression process. The emphasis was on developing new analytic methods for compression data for entire batch. In all, 18 batches of granules containing theophylline and lactose were tabletted, using an instrumented eccentric tabletting machine. During tablet compression, upper and lower punch forces were recorded. Mathematical methods were developed for analyzing the compression data during tabletting. The results suggested two types of undulation in the tabletting data: (1) short-time scale variation or tablet-to-tablet changes in force data and (2) long-time scale undulation describing the changes occurring throughout the tabletting process, such as segregation. These undulation phenomena were analyzed, using various mathematical methods. In addition the results suggest that smaller particles have better tabletting properties, to a certain limit. However particle size alone cannot explain the tabletability of granules.

CHAPTER-4

EXPERIMENTAL WORK



4 EXPERIMENTAL WORK:

4.1 MATERIALS AND EQUIPMENTS:

TABLE 4.1: LIST OF MATERIALS USED

Materials	Name of Company
Metformin Hydrochloride	Auro Laboratories Limited, Thane, India
Lactose Monohydrate (Pharmatose DCL 11)	DMV-Fonterra Excipients, Germany
Starch 1500	Colorcon, Indianapolis, USA
Microcystalline Cellulose PH-102	FMC Biopolymers, Wallingstown
L-HPC LH11	Shin-Etsu Chemicals Co.Ltd, Japan
Dicalcium Phosphate	Innophos, Chicago
Magnesium stearate	Ferro Corporation, Cleveland
Aerosil-200	Evonik Industries, Germany

TABLE 4.2: LIST OF EQUIPMENTS USED

Equipments	Company Name
Electronic Weighing Balance	Mettler Toledo, Mumbai, India
Sieve Shaker	Retsch GmbH, Germany
Roche Friabilator	Labindia FT020,Thane, India
Tap density tester	Labindia TD1025, Thane, India
Tablet Compression machine	Korsch, Silverwater, Australia
UV Spectrophotometer	Shimadzu 1800, Shanghai, China
Disintegration apparatus USP	Labindia DT1000, Thane, India
Hardness Tester	Dr. Schleuniger Pharmatron 8M, Switzerland
Turbula Blender	WAB (Willy A.Bachofen AG Maschinenfabrik), Mahopac, New York
Tray Drier	Precikot Pharma Pvt Ltd, Thane, India
16 station punching machine	Cadmach CMD4 (D tooling), Ahmedabad, India
Segregation tester	Jenike&Johanson INC, USA
Ring Shear Tester	Dr. Dietmar Schulze Wolfenbuttel, Germany
Conta Blender	STM, SamsTechnaMech, Thane, India
Quadro Co-mill	Quadro Engineering, Waterloo, Canada
Rotary Micro Riffler	Quantachrome Instruments, Florida, USA

4.2 DRUG PROFILE CHARACTERISATION

TABLE 4.3: DRUG IDENTIFICATION (METFORMIN HCl AS PER IP):

No	Test	Specification	Result
1	Description	White crystalline powder	Complies
2	Solubility	Freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.	Complies
3	Identification		
	(a)By IR spectra	IR Spectra of sample is concordance with working std	Complies
	(b)By chemical test	An orange red colour is produce	Complies
	(c)By chemical test	A wine red colour develops within 3 min	Complies
	(d)Reduction of chloride	Gives positive reaction of chlorides	Complies
	(e)Melting point	Between 222^0 C to 226^0 C	225^0 C
4	Related Substance		
	(a)Cyanoguanidine	Not more than 0.020 %	0.009%
	(b)Any other impurity	Not more than 0.100 %	0.064 %
5	Heavy metals	Not more than 20 ppm	Less than 20 ppm
6	Sulphated ash	Not more than 0.10%	0.04%
7	Loss on drying (100-105^0C for 5 hrs)	Not more than 0.50%	0.19 %
8	Assay on dried basis(By potentiometer)	Not less than 98.50 % and not more than 101.00 % on dried basis	99.80 %
9	Additional test: Particle size	100 % particle should be pass through 100 mesh	Complies

4.2.1 ESTIMATION OF METFORMIN HYDROCHLORIDE:

PREPARATION OF STANDARD CALIBRATION CURVE OF METFORMIN HCl IN DISTILLED WATER

- **Preparation of standard stock solution**

10mg of drug was weighed accurately and transferred to the 100ml volumetric flask. Then distilled water was added to dissolve it and sonicated for 15 mins and then volume was made up to the mark with distilled water to obtain 100 µg/ml solutions as stock solution.

- **Preparation of standard calibration curve**

From the stock solution 0.1, 0.2, 0.6, 0.8, 1.0, 1.2, 1.6 and 2.0 ml was pipetted out and transferred to 10ml volumetric flask. Volume was made up to the mark with the distilled water to obtain the metformin concentration of 1, 2, 6, 8, 10, 12, 16 and 20 ppm respectively. The wavelength of maxima of metformin in the solution was found to be at **232 nm**. Absorbance of each solution was measured at ƛmax 232 nm. The assay was performed in triplicate and average absorbance was mentioned below:

TABLE 4.4: ABSORBANCE OF METFORMIN HCl IN DISTILLED WATER

Linearity of Metformin HCl		
Conc.(µg/ml)	**Average Absorbance**	**Relative Standard Deviation**
1.00	0.080	0.002
2.00	0.157	0.001
6.00	0.484	0.001
8.00	0.638	0.001
10.0	0.797	0.001
12.0	0.953	0.001
16.0	1.267	0.002
20.0	1.583	0.001
Correlation Coefficient (r)	0.9999	
Y-intercept	0.002	
Slope of regression line	0.079	

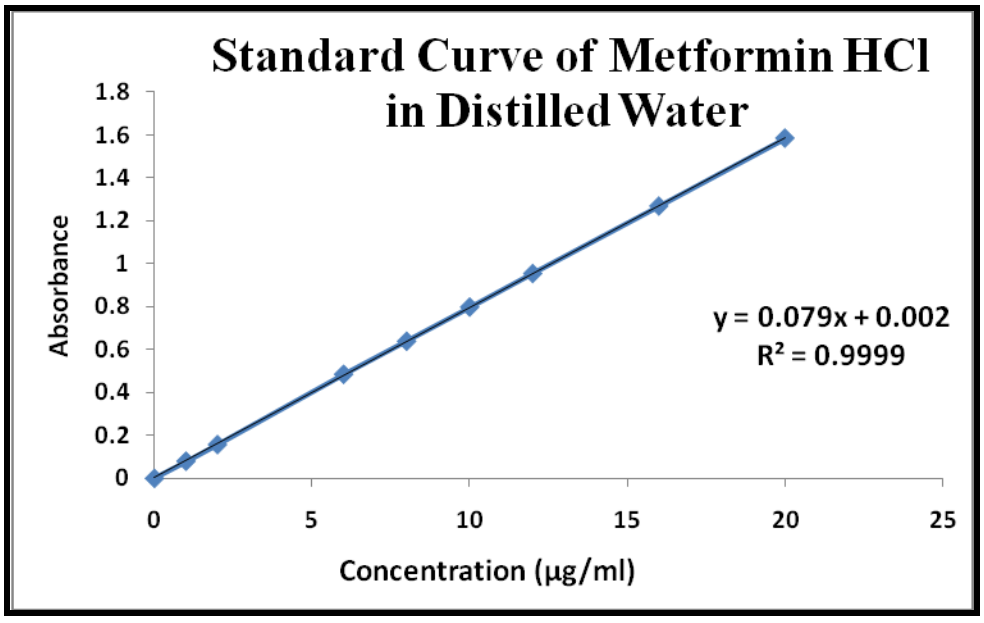


FIGURE 4.1: STANDARD CURVE OF METFORMIN HCl IN DISTILLED WATER

4.3 METHODOLOGY:

4.3.1 General method for preparation of the tablet was given below:

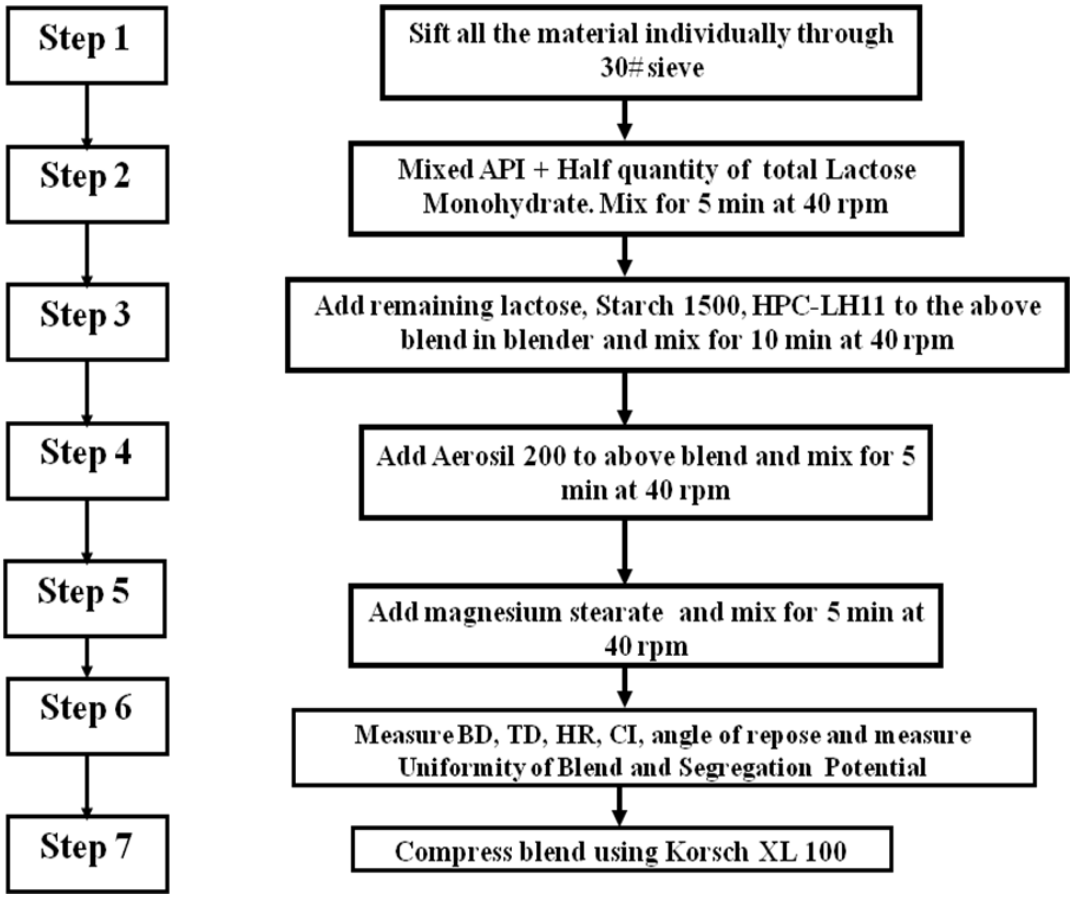


FIGURE 4.2: GENERAL METHOD FOR PREPARATION OF THE TABLET

Batch 1 was prepared by using single step mixing. General method for preparation of the tables was followed in Batch 2, Batch 3, Batch 4, Batch 5 and Batch 6. Shear force was applied through Co-mill between step 2 and step 3 in Batch 7, Batch 8, Batch 9, Batch 10 and Batch 11. Shear force was applied after mixing API with half quantity of the lactose. After that remaining excipients with aerosil were passed through Co-mill. This procedure was done similarly as in Batch 9, Batch 10 and Batch 11 where 2 times, 3 times and 6 times co-mill were applied. The blend was mixed in turbula blender for 20 min at 40 rpm. Remaining steps were followed same as given in general method for preparation of blend.

4.3.2 EVALUATION PARAMETERS OF TABLETS: [68-70]

4.3.2.1 Bulk Density (D_b):

Bulk density, tap density, Hausner ratio and Carr's index were measured by Labindia TD1025. It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$\mathbf{D_b} = \frac{\mathbf{M}}{V_0} \quad \text{..... (5)}$$

Where, M is the mass of powder, V_0 is the Bulk volume of the powder.

4.3.2.2 Tapped Density (D_t):

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

$$\mathbf{D_t} = \frac{\mathbf{M}}{V_t} \quad \text{..... (6)}$$

Where, M is the mass of powder, V_t is the tapped volume of the powder.

4.3.2.3 Angle of Repose:

The frictional forces in a loose powder can be measured by the angle of repose, θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

$$\theta = \tan^{-1}\frac{h}{r} \quad \text{..... (7)}$$

Where, θ is the angle of repose, h is the height in cms, r is the radius.

TABLE 4.5: ANGLE OF REPOSE

Sr. No.	Angle of Repose (θ)	Type of Flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very Poor

4.3.2.4 Carr's Index (I):

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$I = \frac{D_t - D_b}{D_t} \quad \text{..... (8)}$$

Where, Dt is the tapped density of the powder. Db is the bulk density of the powder.

TABLE 4.6: CARR'S INDEX

Sr. No.	Carr's Index (I)	Type of Flow
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair to Passable
4	23-35	Poor
5	33-38	Very Poor
6	>40	Very Very Poor

4.3.2.5 Hausner ratio (H):

Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula.

$$H = \frac{D_t}{D_b} \quad \text{..... (9)}$$

Where, Dt and Db are tapped density and bulk density respectively.

TABLE 4.7: HAUSHNER RATIO

Haushner ratio	Type of flow
<1.25	Good Flow
>1.25	Poor Flow

4.3.2.6 Hardness:

Hardness of the tablets were measured using Dr. Schleuniger Pharmatron apparatus. It is expressed in Kp.

4.3.2.7 Friability (F):

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). Average 6.6 gm of tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for four mins. The tablets were weighed again (W_{final}). The percentage friability was then calculated by:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} X100 \quad \text{..... (10)}$$

4.3.2.8 Weight Variation:

Ten tablets were selected randomly from the lot and weighed individually to check for weight variation. USP and BP limit for weight variation in case of tablets weighing upto 80 mg is ± 10%.

4.3.2.9 Thickness:

The thickness of the tablets were measured by Thermonik Tablet Taster, DTH – 250. It is expressed in mm.

4.3.2.10 *In Vitro* Disintegration Time:

The *In vitro* disintegration time was determined using Labindia DT1000 disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

4.3.2.11 Uniformity of dosage form:

Stratified sampling is necessary to check the Content Uniformity in Low dose API
Stratified sampling can be done by 2 ways:-

1) Samples were collected from the different places within the container

2) Samples were collected during the Compression at different time intervals

Blend in each batch was 400 gm which gave approximate 5333 tablets. During the compression 10 tablets containing sample were taken from every 300 tablets. 10 samples were collected and each of the samples, 1 tablet was taken and Content Uniformity was measured.

Calculation of Uniformity of dosage form

- If strength of API is <25 mg or <25 % of dose and ratio of drug then Content Uniformity is necessary
- Select ≥ 30 dosage units and proceed as follows for the dosage form designated
- Assay 10 unit individually
- Calculate the drug substance (in %) of each unit
- Calculate the acceptance value.

  $AV = |M - X| + ks$

  If n=10 then k=2.4

  If n=30 then k=2.0

TABLE 4.8 CALCULATION OF AV VALUE

Conditions	Value	
If 98.5% ≤ X ≤ 101.5	M = X	AV = ks
If X < 98.5%	M = 98.5%	AV = 98.5 – X + ks
If X > 101.5%	M = 101.5%	AV = X – 101.5 + ks

4.3.2.12 Blend Uniformity:

After the completion of the lubrication step, samples were collected from the blender with the help of the Sampling rod immediately. Samples were placed at different position and that also from different side, samples were collected (Table no: 4.9) in 2X quantity. (2X: Double the quantity than dosage form)

TABLE 4.9: SAMPLE POSITION FOR COLLECTION

Place	Sample Collected		
Top	Left	Centre	Right
Bottom	Left	Centre	Right

Criteria for the measure the Blend Uniformity:-

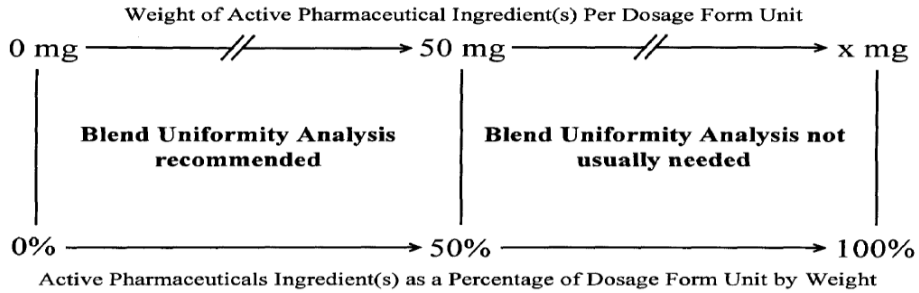


FIGURE 4.3: CRITERIA OF BLEND UNIFORMITY

- Number of Sample : 6 - 10 points

- Potential differences in mixing efficiency associated with specific types of equipment should be considered when determining sampling locations.
- Sample Size ≤ 3 x weight individual dose
- If the firm experiences problems in collecting small samples equivalent to 1 to 3 dosage units and demonstrates that small samples give lower values for BUA due to sampling bias, larger samples (usually no more than 10 dosage units) can be collected. Justification for larger samples should be specific to the application under review. Justification based on literature references is usually not adequate.
- Assay (mean or individual results) : 90.0 – 110.0 %
- RSD NMT 5%

4.3.2.13 Segregation Potential:-

- There are no defined criteria available for measuring the segregation tendency in the blend.
- **Jenike Fluidization Segregation Tester** was used to measure the segregation tendency in the blend. Force data applied for the Segregation test are as below :-

TABLE 4.10: FORCE DATA FOR SEGREGATION TEST:-

Ramp to High	**Ramp to Low**	**Ramp to 0**
30 (sec)	30 (sec)	30 (sec)
Hold High	**Hold High**	**Total**
30 (sec)	120 (sec)	240 (sec)
High Flow	**Low Flow**	**Actual Flow**
14 (atm)	4 (atm)	1 to 14 (atm)

Approximate 75 gm of the blend was taken and transferred to the equipment. The air flow is adjusted and test was started. After completion of the test, samples were collected from three different locations Top, Middle and Bottom.

Segregation Potential was measured in the blend by 2 different ways.

1) Assay procedure

2) Particle Size Distribution

After the segregation test samples were transferred into the Micro Rotary Riffler for equally distribution. Example: Micro Rotary Riffler has divided the sample into 8 equal parts. So for collecting 2X sample (2X*8) blend were transferred into the Micro Rotary Riffler. So each portion has 150 mg blend. From this 3 samples are collected and Segregation Potential through Assay procedure was measured.

4.3.3 PRELIMINARY TRIALS:

Preliminary trial was done to measure the flow property of the blend and different evaluation parameters for tablets like, disintegration time, hardness, thickness and friability and weight variation.

TABLE 4.11: COMPOSITION FOR PRELIMINARY TRIAL WITHOUT API

Sr. No	Ingredients	Qty. per Tablet(mg)	Quantity (%)	Qty per Batch(gm)
1	Lactose Monohydrate	64.50	86.00	334.04
2	Starch 1500	4.95	6.60	26.40
3	L-HPC LH 11	4.875	6.50	26.0
4	Aerosil 200	0.375	0.50	2.0
5	Magnesium Stearate	0.300	0.40	1.60
Total		**75.00**	**100.0**	**400.1**

4.3.3.1 Preparation of blend for preliminary Batch:

- All the excipients were weighed accurately as shown in table no 4.11. Except lubricant, all the excipients were mixed manually for 10 min.
- Lubricant was added and mixed again manually for 5 min.

- Blend was compressed using Korsch XL100 tablet punching machine and evaluated.

TABLE 4.12: FORCE DATA OF COMPRESSION MACHINE OF KORSCH XL 100 DURING TABLETTING:

NA	Main compression (kN)		Pre-compression(kN)		Ejection (N)	Scrap-off (N)
	Upper	Lower	Upper	Lower		
Force	1.7	1.8	0.2	1.2	2.9	0.8
Turret RPM : 20			**Tool used:** 7 X 4.6 mm oval shape, with break line			
Weight knob : 4.8			**Thickness knob :** 1.5			
OBSERVATION : Breaking of edges of the tablet, some time chipping was also observed						

4.3.3.2 EVALUATION OF BLEND AND TABLET:

4.3.3.2.1 IPQC of Blend:-

TABLE 4.13: IPQC OF THE BLEND

IPQC OF BLEND	
Bulk Density (g/ml)	0.5860
Tapped Density (g/ml)	0.6418
Compressibility Index (CI)	8.69
Hausner's Ratio	1.09
Flow Property	Excellent

4.3.3.2.2 IPQC of Tablets:-

TABLE 4.14: IPQC OF THE TABLETS

IPQC OF TABLETS						
No.	**DT (sec)**	**Thickness (mm)**	**Hardness (kp)**	**weight (mg)**	**Friability (%)**	
1	17	3.05	2.5	77.2	No. of tablets	88
2	15	3.07	2.4	73.4		
3	20	3.08	3.5	72.9	Initial weight	6.623
4	14	3.04	2.9	74.1		
5	18	3.08	2.8	73.6	Final weight	6.599
6	16	3.09	3.0	73.2		
7	NA	3.04	3.2	73.2	Diff. in weight	0.024
8		3.03	2.9	75.8		
9		3.09	2.8	73.3	% Friability	0.36
10		3.07	2.7	73.7		
Avg.	16.6	3.06	2.8	74.0	Observation	Pass
Min.	14	3.03	3.5	72.9		
Max.	20	3.09	2.4	77.2		

4.3.3.3 Observations:

- IPQC of the blend and tablets were found within the limits.
- During compression, breaking of the tablets edges and chipping were observed.

  Possible solution:
- Increasing the concentration of the Magnesium Stearate up to 1%.

4.3.3.4 RESULT AND DISCUSSION:

Results from the preliminary trial indicated that flow property of the blend was excellent. All the parameters like Hardness, thickness, friability and disintegration

time were found within limit. But during Compression (instrument KORSCH XL 100) edges of tablet were broken and sometimes chipping was also observed. Breaking of edges and chipping in the tablet was reduced by increasing concentration of Magnesium stearate in further batches.

4.3.4 PREPARATION OF SAMPLE SOLUTION:

4.3.4.1 UNIFORMITY OF DOSAGE FORM:

10 stratified sample of tablet was taken and dissolved into 10 different 200ml volumetric flask. Then 100ml distilled water was added to dissolve the tablet and sonicated for 5 min. Then volume was made up to the mark with the distilled water and filtered with 0.45µm PVDF filter and absorbance was measured at 232nm.

4.3.4.2 SEGREGATION POTENTIAL AND BLEND UNIFORMITY:

Samples were taken according to the sampling procedure as mentioned above. Samples were transferred into 200ml volumetric flask and 100 ml distilled water was added and sonicated for 5 min. Then volume was marked up to 200 ml. 10ml solution was pipetted out and transferred into 20ml volumetric flask and made up to the mark with distilled water. It was than filtered with 0.45µm PVDF filter and absorbance was measured at 232nm.

Equation for measurement of % Assay:

$$\%\ \text{Assay of BU} = \frac{Au * \text{Preparation of STD} * \text{Avg Wg} * 100}{As * \text{Preparation of Sample} * \text{taken Wg} * \text{Label Claim}} \quad \text{..... (11)}$$

4.4 EFFECT OF PROPORTION OF EXCIPIENTS MIXING WITH API:-

Two different processes were taken for preparation of blend and its effect on Uniformity of dosage form and Uniformity blend was observed. The composition of ingredients is given in Table 4.15.

TABLE 4.15: COMPOSITION OF INGREDIENTS FOR BATCH 1 AND BATCH 2

Sr. No	Ingredients	Batch 1(mg)	Batch 2(mg)
1	Metformin HCl	**1.880**	**1.880**
2	Lactose Monohydrate	62.16	62.16
3	STARCH 1500	4.95	4.95
4	L-HPC LH 11	4.875	4.875
5	Aerosil 200	0.375	0.375
6	Magnesium Stearate	0.750	0.750
Total (mg)		75.0	75.0

4.4.1 PROCEDURE FOR PREPARATION OF BLEND AND SAMPLE SOLUTION

4.4.1.1 PREPARATION OF BLEND FOR BATCH 1:-

- Single step mixing was done in Batch 1.
- All the excipients as given in table 4.15 were weighed accurately except lubricant mixed manually for 10 min. Lubricant was added and mixed again manually for 5 min. Blend was compressed using Korsch XL100 tablet punching machine.

4.4.1.2 PREPARATION OF BLEND FOR BATCH 2:

- Steps for preparation of blend of batch 2 were prepared in similar ways as given in section no. 4.3.1.

4.4.1.3 PREPARATION OF SAMPLE SOLUTION OF BATCH 1 & BATCH 2:

- For measurement of Uniformity of dosage form, Uniformity of blend and Segregation tendency of blend samples, solutions were prepared as given in section no 4.3.4

4.4.2 EVALUATION

- Evaluation parameters of the blends and tablets have been mentioned in section no 4.3.2.

4.4.3 RESULT

4.4.3.1 IPQC of Blend and Tablets:-

TABLE 4.16: IPQC OF BLEND OF BATCH 1 & 2

IPQC of Blend		
	Batch 1	**Batch 2**
Bulk Density (g/ml)	0.5855	0.5860
Tapped Density (g/ml)	0.6418	0.6418
Compressibility Index (CI)	8.77	8.69
Hausner's Ratio	1.09	1.09
Flow Property	Excellent	Excellent

TABLE 4.17: IPQC OF TABLETS OF BATCH 1 & 2

		Batch 1	**Batch 2**
DT (sec)	**Average**	16.6	15
	Minimum	14	14
	Maximum	20	19
Hardness (kp)	**Average**	2.8	2.71
	Minimum	2.5	2.4
	Maximum	3.5	3.1
Thickness (mm)	**Average**	3.06	3.055
	Minimum	3.03	3.01
	Maximum	3.09	3.09
Weight (mg)	**Average**	74.0	74.927
	Minimum	72.9	73.05
	Maximum	77.2	75.64
% Friability		0.36	0.34

From the above observation it can be concluded that flow property of blend was excellent and IPQC of the tablets were within USP limit.

4.4.3.2 Content Uniformity:-

TABLE 4.18: EFFECT OF PROPORTION OF DILUENTS MIXING WITH API ON % ASSAY OF UNIFORMITY OF DOSAGE FORM

Sample	Batch 1	Batch 2
1	115.0	102.7
2	103.2	101.6
3	106.8	100.7
4	90.5	104.3
5	98.8	103.5
6	80.1	99.2
7	102.4	103.2
8	101.7	102.9
9	94.2	99.2
10	91.9	99.1
SD	11.7	2.0
RSD	12.1	1.9
AV (n=10)	**29.3**	**4.8**

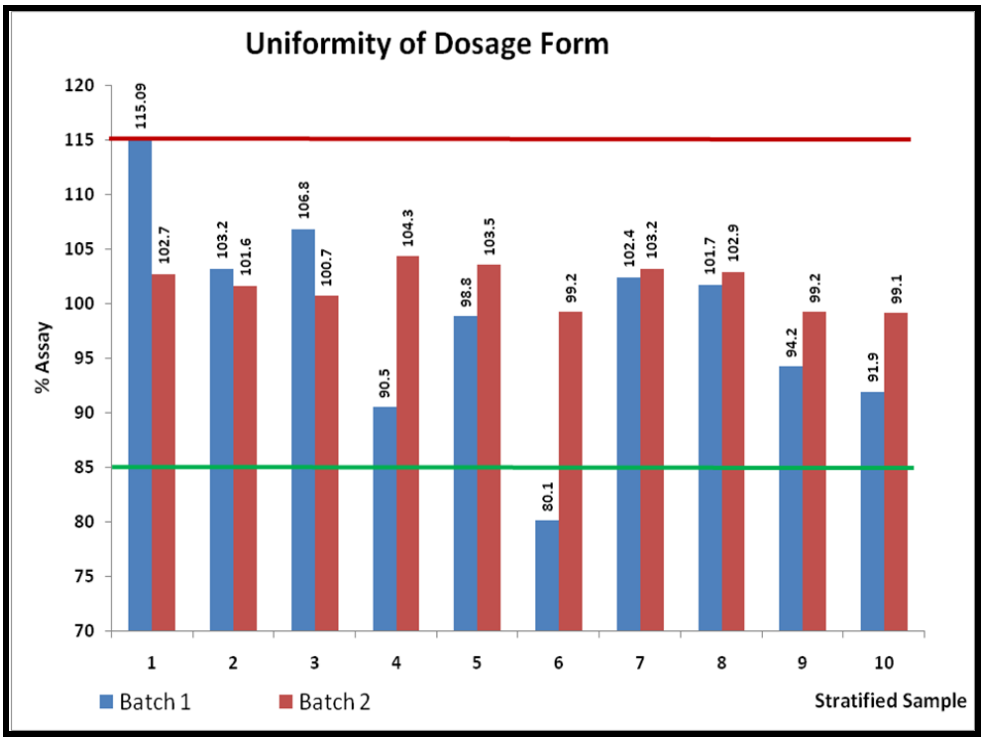


FIGURE 4.4: COMPARATIVE EFFECT OF MIXING PATTERN OF DILUENTS ON UNIFORMITY OF DOSAGE FORM

4.4.3.3 Segregation Potential:-

TABLE 4.19: EFFECT OF PROPORTION OF DILUENTS MIXING WITH API ON % ASSAY OF SEGREGATED BLEND

Sample	Batch 2
Top 1	121.8
Top 2	119.5
Top 3	96.2
Middle 1	113.6
Middle 2	89.8
Middle 3	70.9
Bottom 1	121.6
Bottom 2	88.2
Bottom 3	88.3
Average	**101.1**
SD	18.49845
RSD	18.29718

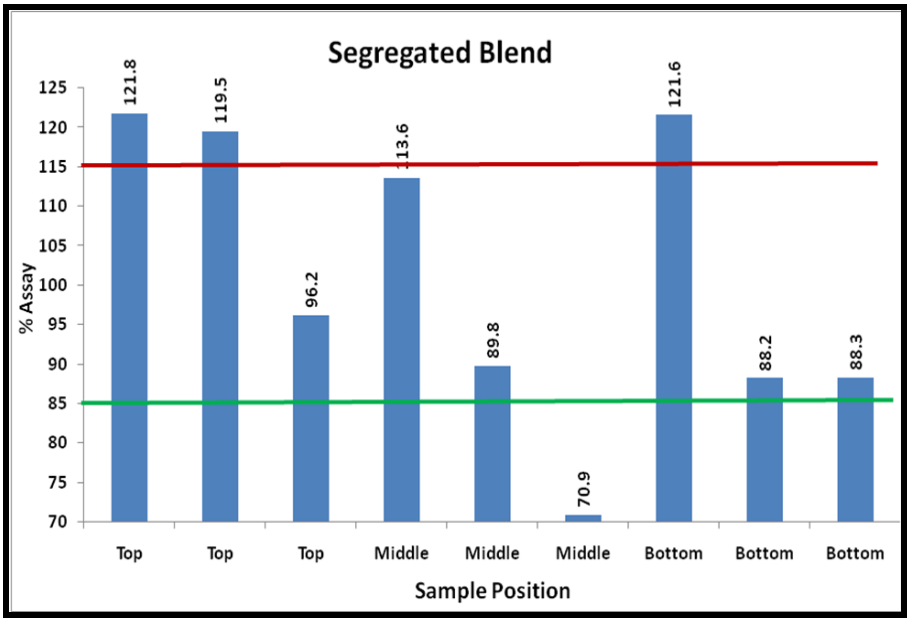


FIGURE 4.5: COMPARATIVE EFFECT OF MIXING PATTERN OF DILUENTS ON SEGREGATED BLEND

4.4.4 DISCUSSION

Two different procedures for preparation of blends were used and effect of proportion of excipients mixing with API in Batch 1 and Batch 2 was measured. The blend was characterized for flow and compression behavior. The result (Table 4.16) shown indicates excellent flow property. The results of disintegration time, hardness, thickness, friability and weight variation were shown in Table 4.17. All these parameters were found within limits. A result of Content Uniformity is shown in Table 4.18 and Figure 4.4 and result of segregation potential is shown in Table 4.19 and Figure 4.5. Batch 2 was shown high Content Uniformity compared to the Batch 1. The AV value of Batch 1 was 29 which were outside the USP criteria. Whereas the AV value of the Batch 2 was within limit, but Segregation Potential of Batch 2 shown higher segregation tendency. From the above result, it can be concluded that segregation occurred in the blend. In further experiment, method for preparation of blend of Batch 2 was used for the further Batches and the effect of strength of API on CU, BU and segregation potential were measured.

4.5 EFFECT OF STRENGTH OF API

To measure the effect of strength of API on Uniformity of dosage form, Uniformity of blend and Segregation potential, 2.50% API of dosage form was taken in Batch 2 and 0.66% API was taken in Batch 3**.** The composition for Batch 2 and Batch 3 is given in Table 4.20.

TABLE 4.20: COMPOSITION OF INGREDIENTS FOR BATCH 2 AND BATCH 3

Sr No	Ingredients	Batch 2 (mg)	Batch 3(mg)
1	Metformin HCl	**1.880**	**0.50**
2	Lactose Monohydrate	**62.16**	**63.55**
3	STARCH 1500	4.95	4.95
4	L-HPC LH 11	4.875	4.875
5	Aerosil 200	0.375	0.375
6	Magnesium Stearate	0.750	0.750
	Total	75	75

4.5.1 PROCEDURE FOR PREPARATION OF BLEND AND SAMPLE SOLUTION

4.5.1.1 Preparation of blend for Batch 2 and Batch 3:-

- Procedure for preparation of blend for Batch 2 and Batch 3 were same as given in section no 4.3.1.
- The concentration of API was different in Batch 2 and Batch 3.

4.5.1.2 Preparation of sample solution of Batch 2 and Batch 3:

- For measurement of Uniformity of dosage form, Uniformity of blend and Segregation tendency of blend samples solutions were prepared as given in section no 4.3.4

4.5.2 EVALUATION

Evaluation parameters of the blends and tablets have been mentioned in section no 4.3.2.

4.5.3 RESULTS

4.5.3.1 IPQC of Tablets:-

TABLE 4.21: IPQC OF TABLET OF BATCH 2 & 3

		BATCH 2	BATCH 3
DT (sec)	Average	15	16.5
	Minimum	14	13
	Maximum	19	20
Hardness (kp)	Average	2.7	2.8
	Minimum	2.4	2.2
	Maximum	3.1	3.5
Thickness (mm)	Average	3.05	3.05
	Minimum	3.01	3.02
	Maximum	3.09	3.10
Weight (mg)	Average	74.92	73.8
	Minimum	73.05	72.9
	Maximum	75.64	77.2
% Friability		0.34	0.26

From the results shown in Table 4.21, it can be concluded that disintegration time, hardness, thickness and friability were found within the limit.

4.5.3.2 Content Uniformity:-

TABLE 4.22: EFFECT OF API STRENGTH ON % ASSAY UNIFORMITY OF DOSAGE FORM

Sample	Batch 2	Batch 3
1	102.7	92.1
2	101.6	96.7
3	100.7	76.4
4	104.3	99.9
5	103.5	76.4
6	99.2	93.4
7	103.2	105.5
8	102.9	83.7
9	99.2	87.8
10	99.1	91.2
SD	2.0	9.4
RSD	1.9	10.5
AV (n=10)	4.8	30.8

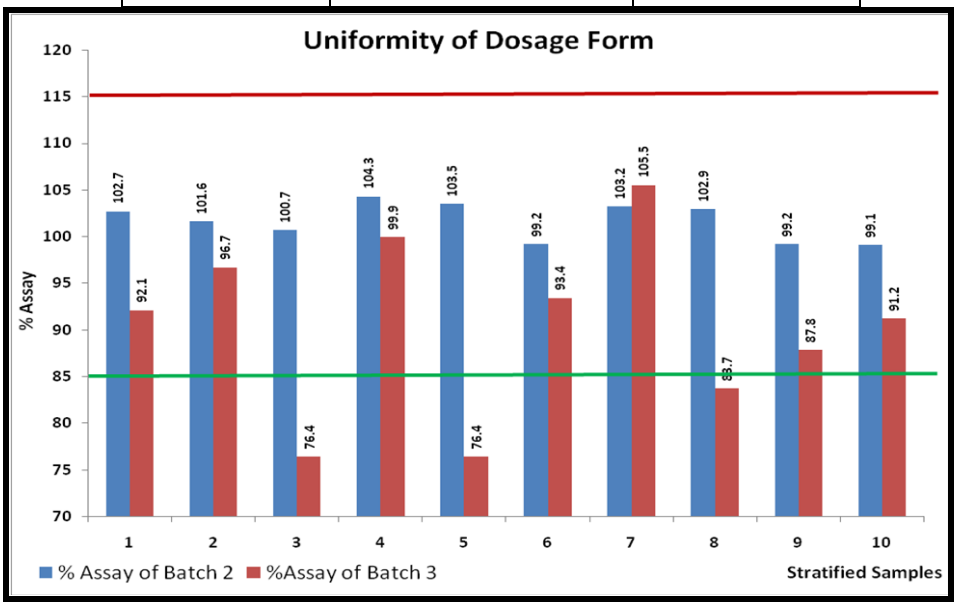


FIGURE 4.6: COMPARATIVE EFFECT OF API STRENGTH ON % ASSAY OF UNIFORMITY OF DOSAGE FORM

4.5.3.3 Segregation Potential:-

TABLE 4.23: EFFECT OF API STRENGTH ON % ASSAY OF SEGREGATED BLEND

Sample	Batch 2	Batch 3
Top 1	121.8	98.2
Top 2	119.5	125.5
Top 3	96.2	120.7
Middle 1	113.6	103.7
Middle 2	89.8	109.4
Middle 3	70.9	121.4
Bottom 1	121.6	109.9
Bottom 2	88.2	105.3
Bottom 3	88.3	144.9
Average	101.1	115.44
SD	18.49845	14.30613
RSD	18.29718	12.39222

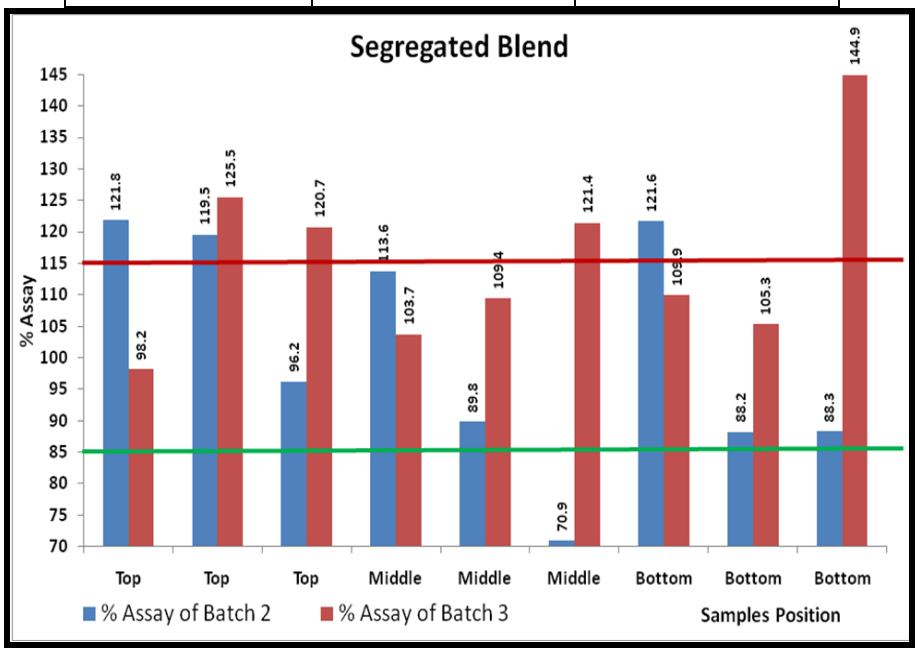


FIGURE 4.7: COMPARATIVE EFFECT OF API STRENGTH ON % ASSAY OF SEGREGATED BLEND

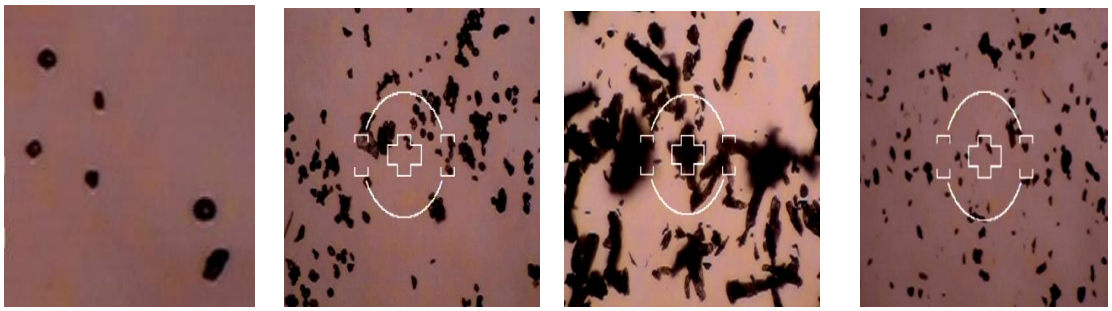
4.5.4 DISCUSSION

Two different strength of API was taken and effect on Content Uniformity and Blend Uniformity were measured. The results of IPQC were found within limits. From the experiment, it was observed that strength of the API influences the Content Uniformity (Table 4.22 and Figure 4.6) as well as Segregation Potential (Table 4.23 and Figure 4.7). It was observed that in Batch 3 which contained 0.66 % API shows improper distribution of drug content in the blend. AV value of Batch 3 was found outside the accepted limit of USP, whereas the AV value of Batch 2 is within limit. Batch 2 with higher strength API shows more uniformly distribution of API into the Blend compared to Batch 3. Batch 2 and Batch 3 both showed high segregation tendency. When comparing the strength of the API, Batch 3 had much lower amount of API comparing to the Batch 2, so procedure for preparation of blend or excipients shown no significant effect on distribution of drug in the blend. So in further trials preparation of the blend was kept same and 0.66% API strength was used and the effect of different shape and size containing excipients on Content Uniformity, Blend Uniformity and Segregation Potential were done.

4.6 EFFECT OF SHAPE/ TYPE OF DILUENTS

In this experiment effect of different shape of the diluents on Uniformity of dosage form, Uniformity of Blend and Segregation tendency were measured. In Batch 3, Batch 4, Batch 5 and Batch 6 respectively lactose monohydrate, starch 1500, microcrystalline cellulose and dicalcium phosphate (di-tab) were taken as major diluents. The composition for different Batches is given in Table 4.24.

4.6.1 Microscopy of the Different Diluents:



a) Lactose **b) Starch** **c) MCC** **d) Di tab**

FIGURE 4.8: SHAPE OF THE DIFFERENT DILUENTS

TABLE 4.24: COMPOSITION OF BATCH 3, BATCH 4, BATCH 5 AND BATCH 6

No	Ingredients	Batch 3(mg)	Batch 4 (mg)	Batch 5(mg)	Batch 6(mg)
1	Metformin HCl	**0.50**	**0.50**	**0.50**	**0.50**
2	Lactose Monohydrate	**63.55**	**4.95**	**4.95**	**4.95**
3	STARCH 1500	4.95	63.55	-	-
4	MCC	-	-	**63.55**	-
5	Dicalcium phosphate	-	-	-	**63.55**
4	L-HPC LH 11	4.875	4.875	4.875	4.875
5	Aerosil 200	0.375	0.375	0.375	0.375
6	Magnesium Stearate	0.750	0.750	0.750	0.750
Total (mg)		75	75	75	75

4.6.2 PROCEDURE FOR PREPARATION OF BLEND AND SAMPLE SOLUTION

4.6.2.1 Preparation of Blend for Batch 3, Batch 4, Batch 5 and Batch 6:-

- There was only change in the different type of diluents otherwise all the procedure were same as given in section no 4.3.1

4.6.2.2 Preparation of sample solution of Batch 3, Batch 4, Batch 5 and Batch 6:

- For measurement of Uniformity of dosage form, Uniformity of blend and Segregation tendency of blend samples solutions were prepared as given in section no 4.3.4

4.6.3 EVALUATION

- Evaluation parameters of the blends and tablets have been mentioned in section no 4.3.2.

4.6.4 RESULTS

4.6.4.1 IPQC of Blend and Tablets:-

TABLE 4.25: IPQC OF BLEND OF BATCH 3,4,5 & 6

		Batch 3	Batch 4	Batch 5	Batch 6
IPQC OF BLEND	Bulk Density (g/ml)	0.5860	0.5978	0.3733	0.6579
	Tapped Density (g/ml)	0.6418	0.7489	0.4740	0.8333
	Compressibility Index (CI)	8.69	20.17	21.24	21.04
	Hausner's Ratio	1.09	1.25	1.27	1.20
	Flow Property	Excellent	Fair	Passable	Fair
FORCE DATA	Weight Knob	4.8	5.0	8.0	4.8
	Thickness Knob	1.5	0.7	1.8	0.7

TABLE 4.26: IPQC OF TABLETS OF BATCH 3, 4, 5 & 6:-

IPQC OF TABLETS					
		Batch 3	**Batch 4**	**Batch 5**	**Batch 6**
DT (sec)	**Average**	16.5	50.16	2.66	2.3
	Minimum	13	40	2	1
	Maximum	20	62	4	4
Hardness (kp)	**Average**	2.82	2.21	3.4	2.98
	Minimum	2.2	2.0	3.0	2.7
	Maximum	3.5	2.3	3.8	3.2
Thickness (mm)	**Average**	3.05	3.153	3.03	2.47
	Minimum	3.02	3.12	3.00	2.45
	Maximum	3.10	3.18	3.11	2.50
Weight (mg)	**Average**	73.8	73.9	75.96	76.44
	Minimum	72.9	71.9	75.0	75.1
	Maximum	77.2	77.0	76.3	78.9
% Friability		0.26	0.5888	0.34	0.04

Results of IPQC of Blend are given in Table 4.25. From the result it can be observed that lactose shown excellent flow property compare to starch, MCC and Dicalcium phosphate. Starch 1500 and DCP show fair flow property. MCC shows passable flow property. Results of IPQC of tablets are shown in Table 4.26. From the results it can be concluded that all the parameters were found within the limit.

4.6.4.2 Content Uniformity:-

TABLE 4.27: EFFECT OF DIFFERENT DILUENTS ON % ASSAY OF UNIFORMITY OF DOSAGE FORM

Sample	Batch 3	BATCH 4	BATCH 5	BATCH 6
1	92.1	96.5	95.9	103.4
2	96.7	92	100.2	96
3	76.4	92.4	97.5	97.4
4	99.9	91.5	98	99.6
5	76.4	99.8	93.4	97.8
6	93.4	84	93.6	97.6
7	105.5	90.6	96.1	90.9
8	83.7	102.4	104.8	100.7
9	87.8	93.4	101	99.6
10	91.2	104.3	92.5	102.3
SD	9.4	6.1	3.9	3.5
RSD	10.5	6.5	4.0	3.8
AV (n=10)	30.8	18.5	10.4	8.5

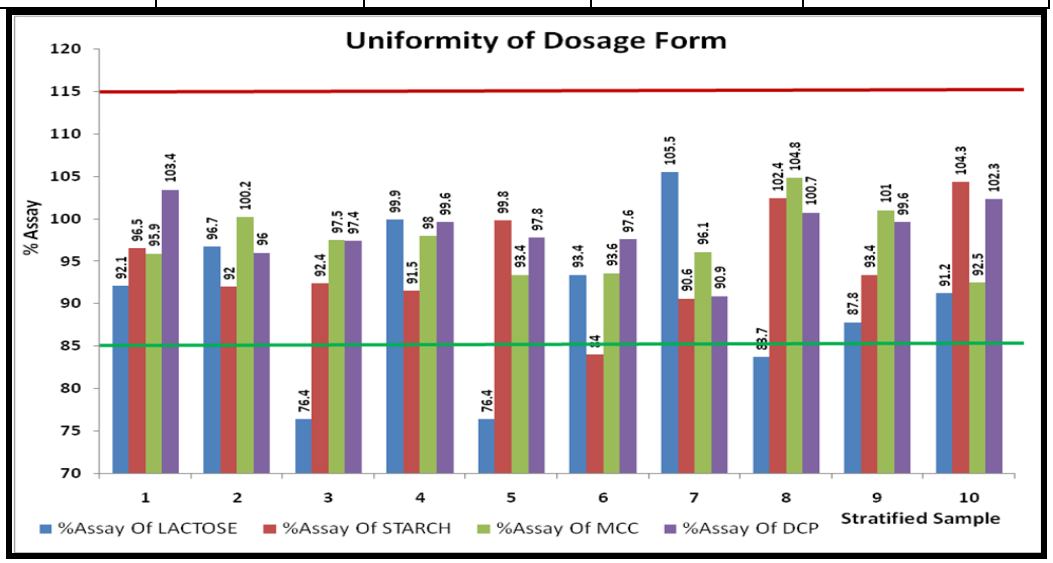


FIGURE 4.9: COMPARATIVE EFFECT OF DIFFERENT DILUENTS ON UNIFORMITY OF DOSAGE FORM

4.6.4.3 Segregation Potential:-

TABLE 4.28: EFFECT OF DIFFERENT DILUENTS ON % ASSAY OF SEGREGATED BLEND

Sample	Batch 3	BATCH 4	BATCH 5	BATCH 6
Top 1	98.2	101.2	93.5	96.3
Top 2	125.5	97.6	92.8	97.1
Top 3	120.7	74.8	97.6	102.9
Middle 1	103.7	108.1	92	102.7
Middle 2	109.4	106.2	89.4	100.1
Middle 3	121.4	105.5	92.3	92.9
Bottom 1	109.9	105.7	95.8	99
Bottom 2	105.3	101.1	95.1	98.3
Bottom 3	144.9	106.6	94.7	101.3
Average	115.44	100.8	93.68	98.95
SD	14.30613	10.302	2.417	3.29
RSD	12.39222	10.220	2.580	3.27

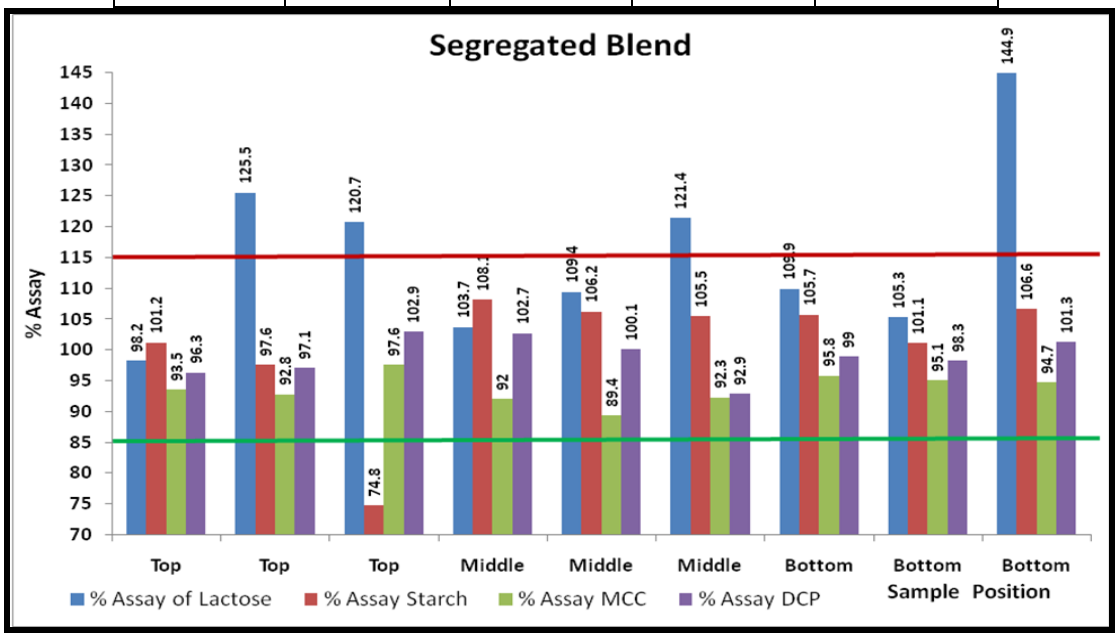


FIGURE 4.10: COMPARATIVE EFFECT OF DIFFERENT DILUENTS ON SEGREGATED BLEND

4.6.4.4 Blend Uniformity:-

TABLE 4.29: EFFECT OF DIFFERENT DILUENTS ON % ASSAY OF UNIFORMITY OF BLEND

Sample	Batch 3	Batch 4	Batch 5	Batch 6
Top L	89.8	98.7	93.6	89.2
Top C	90.3	101.2	93.3	95.6
Top R	96.1	88	93.3	104.7
Bottom L	92.8	100	94.4	90.7
Bottom C	107.4	96.5	94.4	97.5
Bottom R	105.8	107.4	96.7	93.2
Average	97.03	98.63	94.28	95.15
SD	7.75	6.37	1.28	5.58
RSD	7.94	6.45	1.30	5.86

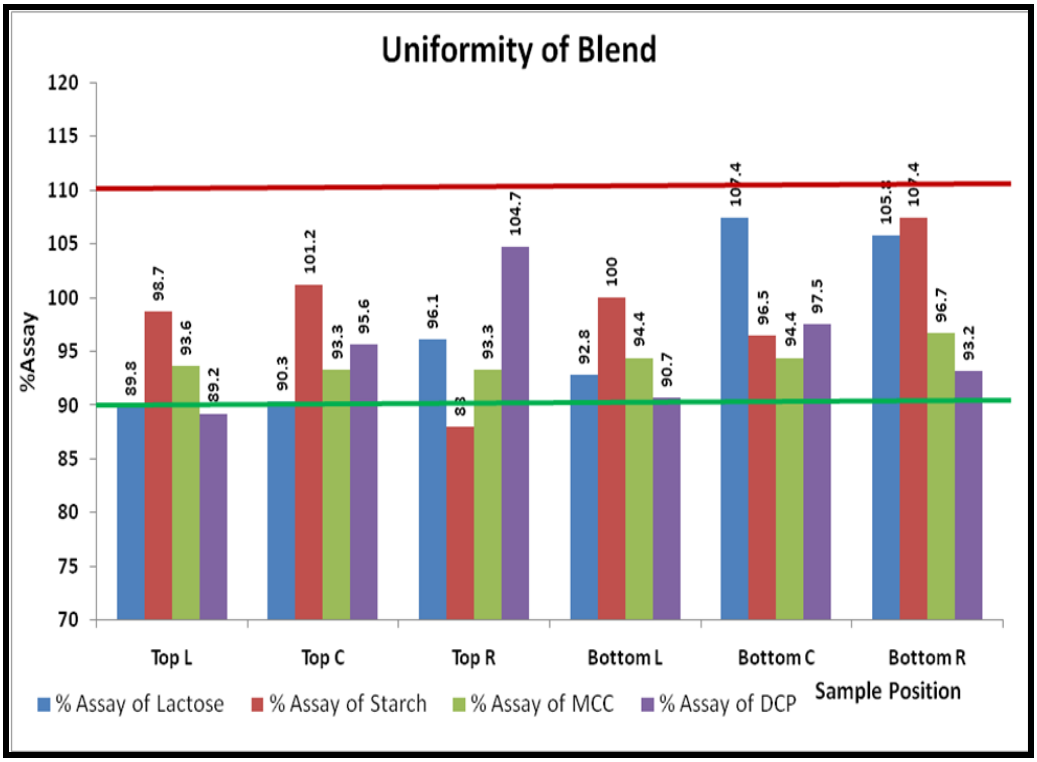


FIGURE 4.11: COMPARATIVE EFFECT OF DIFFERENT DILUENTS ON UNIFORMITY OF BLEND

4.6.5 DISCUSSION

It was observed that size and shape of different diluents influence the Content Uniformity, Blend Uniformity and Segregation Potential. Results for Content Uniformity is given in Table 4.27 and Figure 4.9, results for segregation potential is given in Table 4.28 and Figure 4.10 and results for Blend Uniformity is given in table 4.29 and Figure 4.10. From the result it can be concluded that diluents shape and size can significantly affect Content Uniformity, Segregation Potential and Blend Uniformity. Microscopy (Figure 4.8) of different diluents showed that**,** lactose monohydrate had spherical shape. Starch 1500 had irregular but somehow fibrous shape. Micro-crystalline cellulose had fibrous shape and Dicalcium phosphate had irregular shape with rough surface. MCC PH 102 is fibrous material if compared with lactose and starch. Fibrous materials increase the Content Uniformity and Blend Uniformity by adhering drug particle on its surface. Starch surface is irregular and somewhat fibrous which helped to increase the uniformity of API in blend. The rough surface of Dicalcium Phosphate carries the drug particle on its surface and increases CU and BU. Lactose particles are completely spherical with smooth surface compared to DCP so it shown lack of uniformity of API in the Blend. This could be the possible reason for Lactose Monohydrate showing lower Content uniformity and Blend Uniformity and higher Segregation Potential. In further experiments, Lactose Monohydrate was used as diluent and shear force was applied to increase the Content Uniformity and Blend Uniformity.

4.7 EFFECT OF SHEAR FORCE (CO-MILL) AND EFFECT OF PARTICLES SIZE OF API

In this experiment combine effect of shear force and particle size of the API on the Content Uniformity, Blend Uniformity and Segregation Potential were measured. Batch 3 was taken in which shear force was not applied and particle size of API greater than 200µm. In batch 7 shear forces was applied on same particle size, but in Batch 8 shear force was applied on particle size of API containing less than 75 µm**.**

TABLE 4.30: COMPOSITION OF BATCH 3, BATCH 7 AND BATCH 8

Sr. No	Ingredients	Qty. per Tablet(mg)	Quantity (%)	Qty per batch (g)
1	Metformin HCl(model drug)	**0.5**	**0.666**	**2.6675**
2	Lactose Monohydrate	**63.55**	**84.73**	**339.049**
3	Starch 1500	4.95	6.60	26.40
4	L-HPC LH 11	4.875	6.50	26.0
5	Aerosil 200	0.375	0.50	2.0
6	Magnesium Stearate	0.750	1%	4.000
Total		**75.00**	**100.0**	**400.1**

4.7.1 PROCEDURE FOR PREPARATION OF BLEND AND SAMPLE SOLUTION

4.7.1.1 Preparation of Blend for Batch 3, Batch 7 and Batch 8:-

- Preparation of blend of Batch 3 was same as shown in the 4.3.1
- Shear force was applied between step 2 and step 3 in the general preparation of blend in Batch 7 and Batch 8.
- Other steps were same as shown in the general preparation of blend given in section no 4.3.1.

4.7.1.2 Preparation of sample solution of Batch 3, Batch 7 and Batch 8:

- For measurement of Uniformity of dosage form, Uniformity of blend and Segregation tendency of blend samples solutions were prepared as given in section no 4.3.4.

4.7.2 EVALUATION

- Evaluation parameters of the blends and tablets have been mentioned in section no 4.3.2.

4.7.3 RESULTS

4.7.3.1 IPQC of Tablets:-

TABLE 4.31: IPQC of TABLETS OF BATCH 3, 7 & 8

		Batch 3	Batch 7	Batch 8
DT (sec)	**Average**	16.5	17.3	14.5
	Minimum	13	13	12
	Maximum	20	22	18
Hardness (kp)	**Average**	2.82	2.51	2.66
	Minimum	2.2	2.2	2.4
	Maximum	3.5	3.0	3.1
Thickness (mm)	**Average**	3.05	3.03	3.065
	Minimum	3.02	3.01	3.03
	Maximum	3.10	3.09	3.10
Weight (mg)	**Average**	73.8	74.21	75.51
	Minimum	72.9	72.5	75.0
	Maximum	77.2	76.5	76.2
% Friability		0.26	0.15	0.023

From the result shown in Table 4.31, it can be concluded that all parameter were found within the limit.

4.7.3.2 Content Uniformity:-

TABLE 4.32: EFFECT OF SHEAR FORCE AND SIZE OF API ON % ASSAY OF UNIFORMITY OF DOSAGE FORM

Sample	Batch 3	BATCH 7	BATCH 8
1	92.1	96.8	90.7
2	96.7	96.6	95
3	76.4	102.3	93.3
4	99.9	99.6	93
5	76.4	95.8	98.5
6	93.4	104.2	96.3
7	105.5	98.8	93.3
8	83.7	94	98.4
9	87.8	96.4	103.4
10	91.2	97.6	104
SD	9.4	3.1	4.5
RSD	10.5	3.2	4.6
AV (n=10)	30.8	7.7	12.7

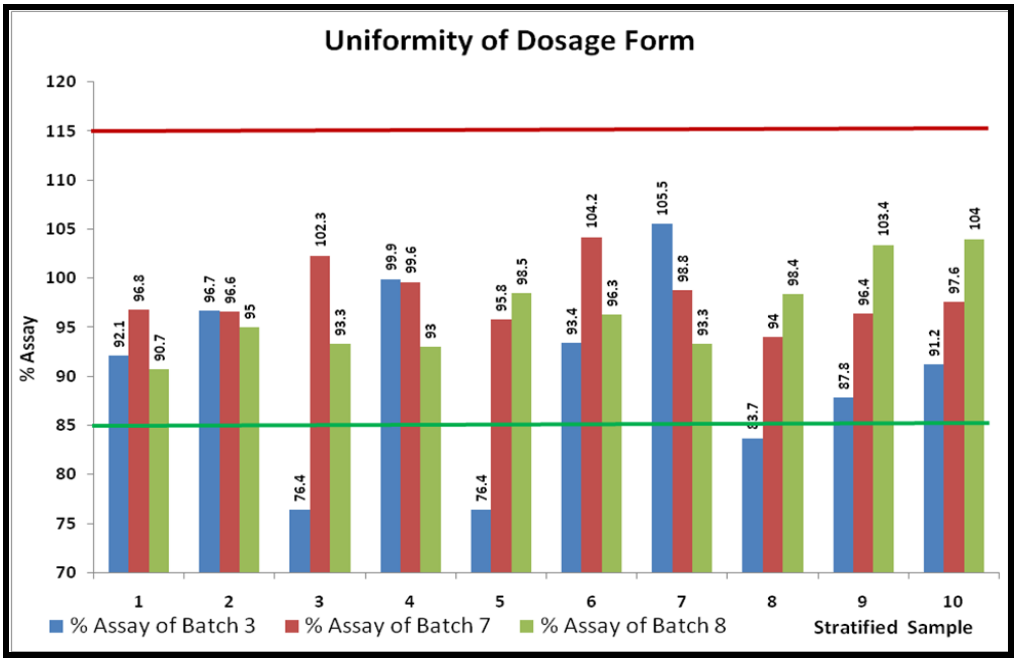


FIGURE 4.12: COMPARATIVE EFFECT OF SHEAR FORCE AND SIZE OF API ON UNIFORMITY OF DOSAGE FORM

4.7.3.3 Segregation Potential:-

TABLE 4.33: EFFECT OF SHEAR FORCE AND SIZE OF API ON %ASSAY OF SEGREGATED BLEND

Sample	Batch 3	BATCH 7	BATCH 8
Top 1	98.2	92.7	102.3
Top 2	125.5	97.5	99.2
Top 3	120.7	91.4	95.7
Middle 1	103.7	107.3	101.7
Middle 2	109.4	99.7	101.9
Middle 3	121.4	90.3	100.9
Bottom 1	109.9	95.1	93.3
Bottom 2	105.3	98	94.2
Bottom 3	144.9	96.8	93.2
Average	115.44	96.53	98.04
SD	14.30613	5.13	3.90
RSD	12.39222	5.32	3.98

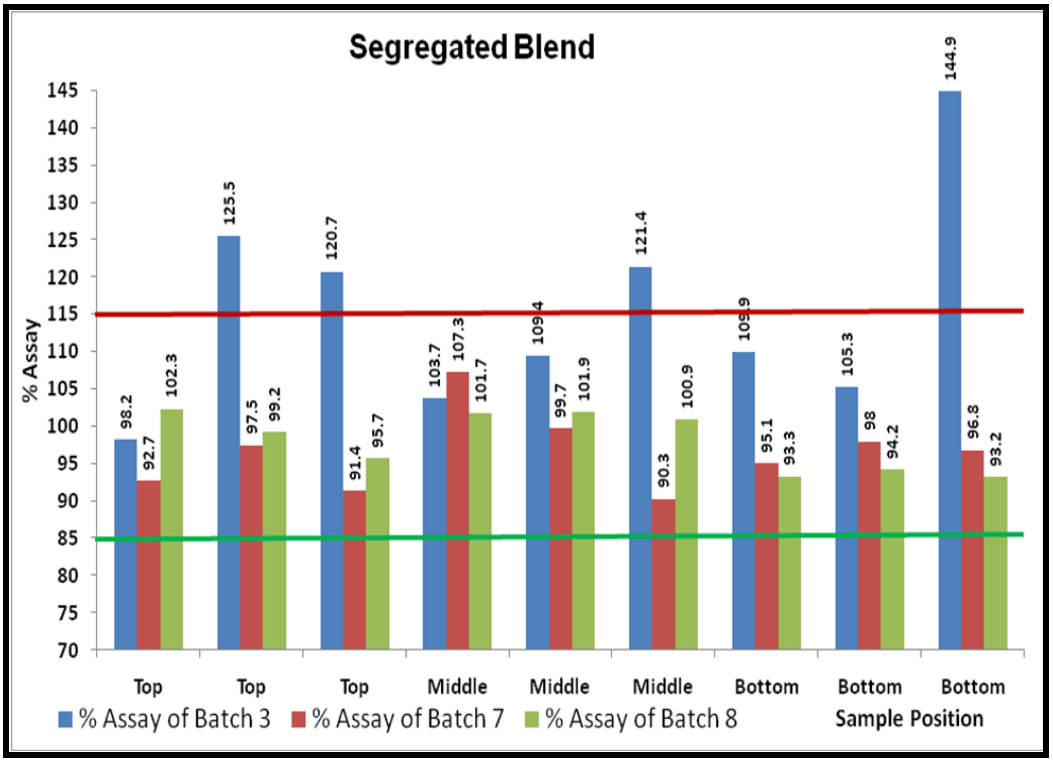


FIGURE 4.13: COMPARATIVE EFFECT OF SHEAR FORCE AND SIZE OF API ON SEGREGATED BLEND

4.7.3.4 Blend Uniformity:-

TABLE 4.34: EFFECT OF SHEAR FORCE AND SIZE OF API ON %ASSAY OF UNIFORMITY OF BLEND

Sample	Batch 3	Batch 7	Batch 8
Top L	89.8	88.8	94.6
Top C	90.3	96.4	95
Top R	96.1	99.3	99.1
Bottom L	92.8	95.2	95.7
Bottom C	107.4	100.7	99.7
Bottom R	105.8	99.9	99.9
Average	97.03	96.71	97.33
SD	7.75	4.42	2.48
RSD	7.94	4.57	2.55

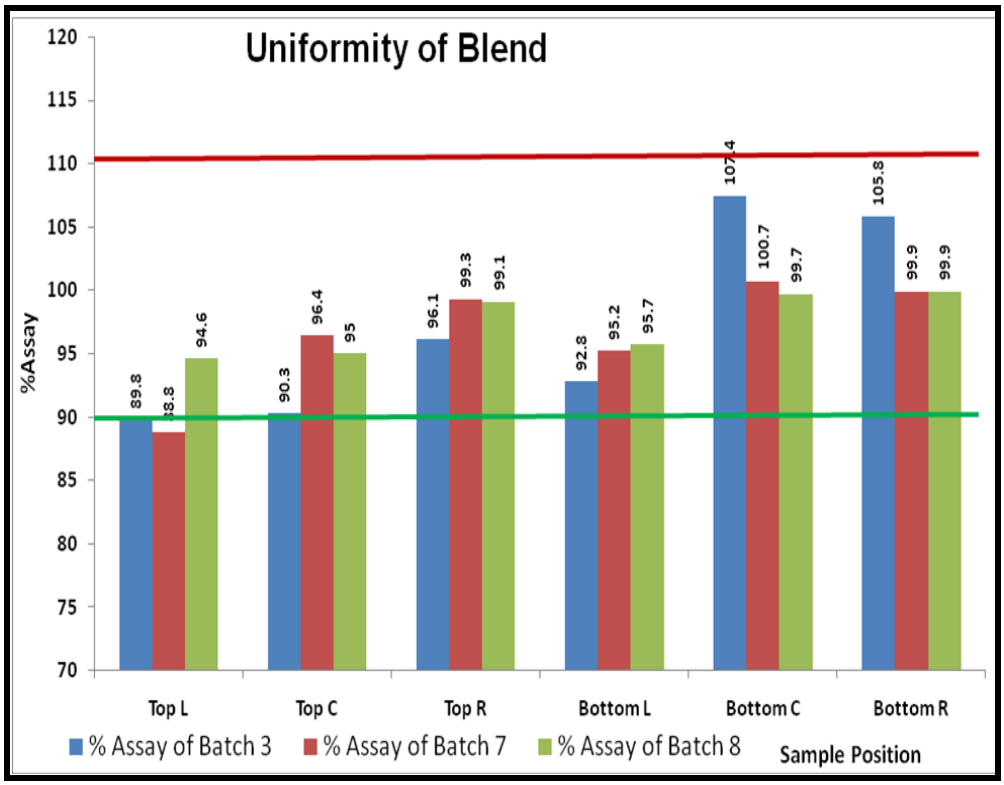


FIGURE 4.14: COMPARATIVE EFFECT OF SHEAR FORCE AND SIZE OF API ON UNIFORMITY OF BLEND

4.7.4 DISCUSSION

Particle size of the API can influence the Content Unifority and Segregation Potential (Table 4.33 and Figure 4.13). By decresing the particle size, it increases the Content Uniformity to some extent in case of comparing higher particle size of API. It should be noted that reducing particle size was an attempt to improve Content Uniformity, it can even increase the segregation tendency of the drug particles to aggregate due to incresing surface area of API. However it did not show promising result. By comparing the result of Batch 3 and Batch 7, it was observed that by increasing in the shear force, Uniformity of dosage form (Table 4.32 Figure 4.12) and Uniformity of Blend (Table 4.34 and Figure 4.14) was increased. After applying shear force to the blend, it increases the Content Unniormity and Blend Uniformty and decreases Segregation Potential. When applying shear force to the blend two processes occured in the blend.

1) Breaking and dispersing of API agglomerate**.**

2) Provide intimate contact between the API and carrier particles.

But Segregation Potential was higher than the limit after applying shear force. In further Batches the number of Co-mill cycle were increased and shear force was applied for 2, 3 and 6 times and the Content Uniformity, Blend Uniformity and Segregation Potential were measured.

4.8 EFFECT OF NUMBER OF CO-MILL CYCLE

From the above result it was concluded that shear force can influence the Uniformity dosage form and Uniformity of Blend. In the Batch 9, Batch 10 and Batch 11 respectively increased co-mill cycle up to 2, 3 and 6 times and compared with the Unifomity of dosage form with 1 time co-mill cycle.

4.8.1 COMPOSITION OF BATCH 7, BATCH 9, BATCH 10 AND Batch 11:

- Composition of batch 7, batch 9, batch 10 and batch 11 were found same as mention in the table no 4.30.

4.8.2 PROCEDURE FOR PREPARATION OF BLEND AND SAMPLE SOLUTION

4.8.2.1 Preparation of Blend for Batch 9, Batch 10 and Batch 11:-

- Shear force was applied 2 times, 3 times and 6 times respectively in Batch 9, Batch 10 and Batch 11 between step 2 and step 3 in the general preparation of blend as given in section no 4.3.1.
- Other steps were found same as shown in the general preparation of blend.

4.8.2.2 Preparation of sample solution of Batch 9, Batch 10 and Batch 11:

- For measurement of Uniformity of dosage form, Uniformity of blend and Segregation tendency of blend samples solutions were prepared as given in section no 4.3.4

4.8.3 EVALUATION

Evaluation parameters of the blends and tablets have been mentioned in section no 4.3.2.

4.8.4 RESULT

4.8.4.1 IPQC of Tablets:-

TABLE 4.35: IPQC OF TABLETS OF BATCH 7, 9 & 10

		Batch 7	Batch 9	Batch 10
DT (sec)	**Average**	17.3	15.3	16.16
	Minimum	13	12	11
	Maximum	22	20	25
Hardness (kp)	**Average**	2.51	2.44	2.59
	Minimum	2.2	2.1	2.3
	Maximum	3.0	2.7	2.8
Thickness (mm)	**Average**	3.03	3.03	3.05
	Minimum	3.01	3.01	3.01
	Maximum	3.09	3.08	3.09
Weight (mg)	**Average**	74.21	75.0	74.54
	Minimum	72.5	73.0	71.9
	Maximum	76.5	76.6	78.6
% Friability		0.15	0.39	0.42

From the result shown in Table 4.35, it can be concluded that all parameter were found within the limit.

4.8.4.2 Content Uniformity:-

TABLE 4.36: EFFECT OF SHEAR FORCE ON %ASSAY OF UNIFORMITY OF DOSAGE FORM

Sample	BATCH 7	BATCH 9	BATCH 10
1	96.8	99.4	102.8
2	96.6	97.3	99.6
3	102.3	97.6	101.5
4	99.6	98.1	102
5	95.8	101.2	100.9
6	104.2	97.9	101
7	98.8	102.4	100.9
8	94	97	102.4
9	96.4	97.4	98.5
10	97.6	98.8	98.3
SD	3.1	1.8	1.5
RSD	3.2	1.8	1.5
AV (n=10)	7.7	4.3	3.7

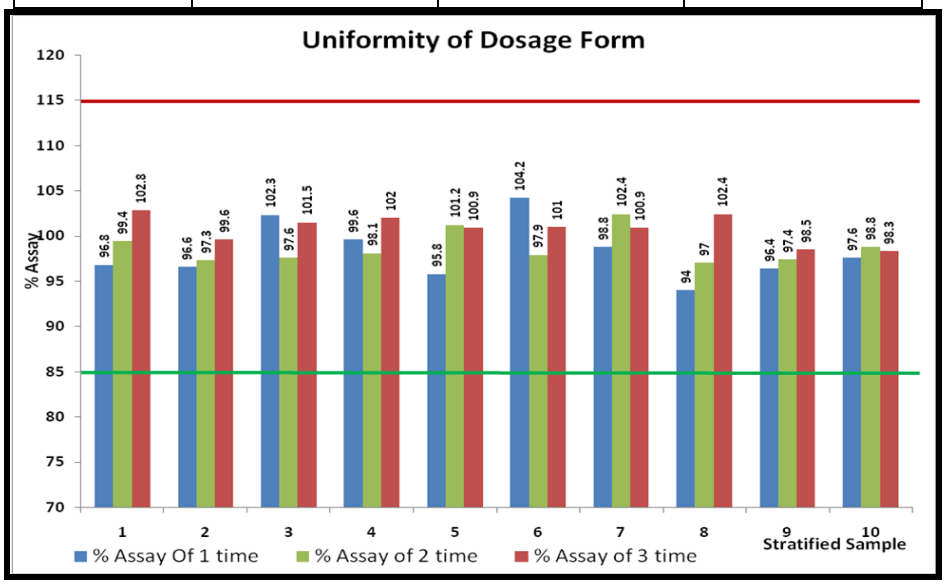


FIGURE 4.15: COMPARATIVE EFFECT OF SHEAR FORCE ON UNIFORMITY OF DOSAGE FORM

4.8.4.3 Segregation Potential:-

TABLE 4.37: EFFECT OF SHEAR FORCE ON %ASSAY OF SEGREGATED BLEND

Sample	BATCH 7	BATCH 9	BATCH 10	BATCH 11
Top 1	92.7	102.6	103.6	102.6
Top 2	97.5	101.4	101.4	103.2
Top 3	91.4	102.2	103.1	104
Middle 1	107.3	90.9	102.6	100.7
Middle 2	99.7	98.3	104.4	100.7
Middle 3	90.3	95.9	92.6	100.4
Bottom 1	95.1	102.5	98.1	99.1
Bottom 2	98	107.6	97.6	100.5
Bottom 3	96.8	99.1	97.5	102.8
Average	96.53	100.01	100.1	101.55
SD	5.13	4.88	3.88	1.63
RSD	5.32	4.87	3.88	1.60

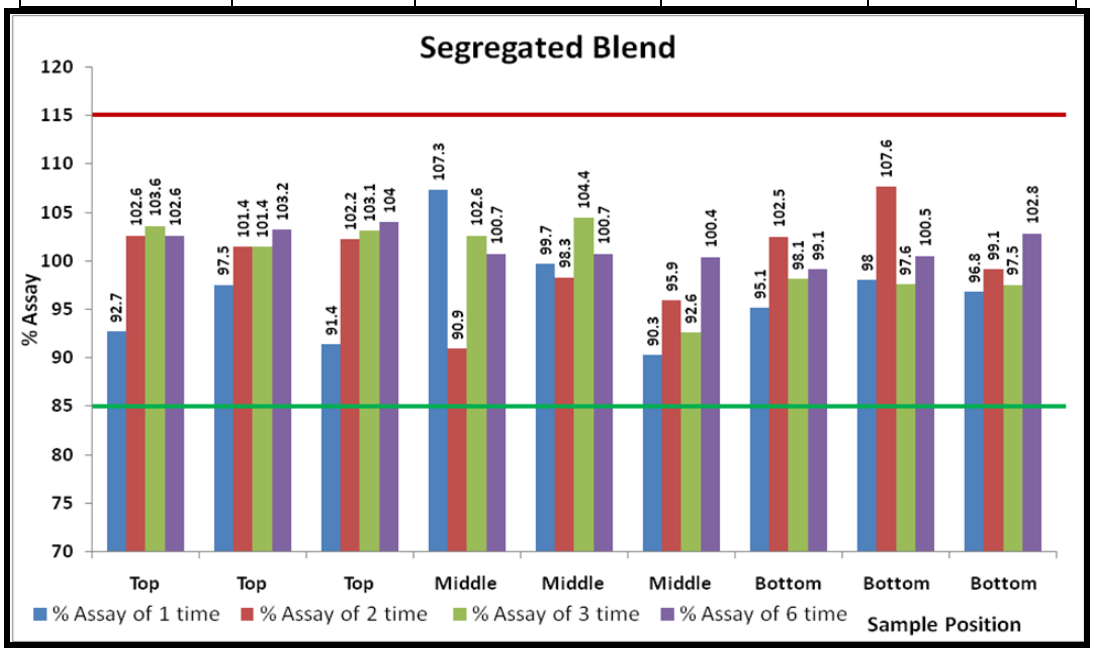


FIGURE 4.16: COMPARATIVE EFFECT OF SHEAR FORCE ON SEGREGATED BLEND

4.8.4.4 Uniformity of Blend:-

TABLE 4.38: EFFECT OF SHEAR FORCE ON %ASSAY OF UNIFORMITY OF BLEND

Sample	Batch 7	Batch 9	BATCH 10
Top L	88.8	97.3	100
Top C	96.4	99.6	97.7
Top R	99.3	96	101.6
Bottom L	95.2	98.3	104.7
Bottom C	100.7	99.1	99.9
Bottom R	99.9	103.7	100.4
Average	96.71	99	100.7167
SD	4.42	2.639	2.325
RSD	4.57	2.666	2.300

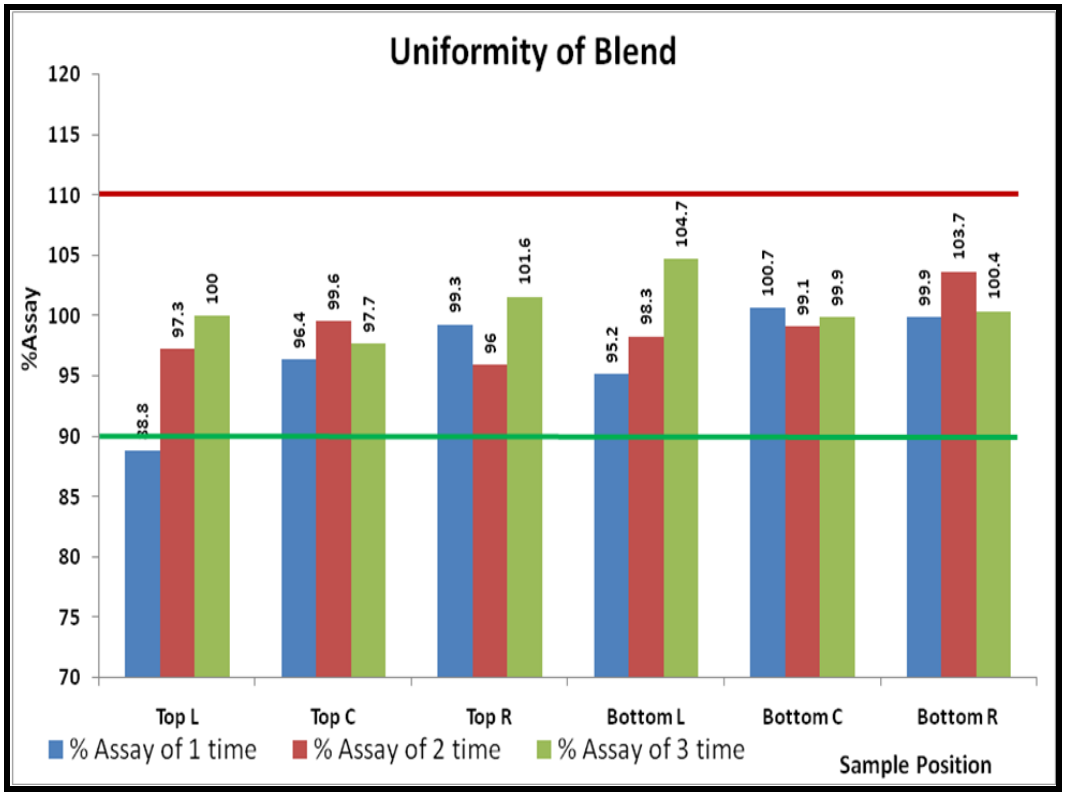


FIGURE 4.17: COMPARATIVE EFFECT OF SHEAR FORCE ON UNIFORMITY OF DOSAGE BLEND

4.8.5 DISCUSSION

From the result, effect of Co-mill cycle on CU, BU and Segregation Potential has been observed. When Co-mill cycle was increased up to 2, 3 and 6 times, there were tremendous increase in Content Uniformity (Table 4.36 and Figure 4.15) and Blend Uniformity (Table 4.38 and Figure 4.17) and decreases in the Segregation Potential (Table 4.37 and Figure 4.16). There might be chances of dusting during Co-mill. When 6 times Co-mill cycles was applied, there might be chances of loss of blend which may occur due to dusting. But there was no effect on Segregation Potential due to dusting. It was observed that there were chances of loss of collective blend. Measuring the Particle Size Distribution of the Batch 7 and Batch 10 did not show much difference on the particle size. It is observed that increase in the milling cycle did not decrease the particle size of the blend.

4.9 MEASUREMENT OF THE CONTENT UNIFORMITY IN HALF OF THE TABLET [60]

After increasing milling cycle, it was observed that Uniformity of Dosage form and Uniformity of Blend were increased, but it was also necessary to achieve the Content Uniformity in half of the tablets. So samples were taken from Batch 4 (1 time co-mill) and Batch 6 (3 times co-mill) and compared the Uniformity of the dosage form with whole tablets.

Dose-related adverse effects of medications are a major problem in modern medical practice. The "correct" dose, based on drug guidelines in package inserts, may not be correct for many patients. Broad variation in drug response among patients is a common phenomenon in clinical practice. The ability to match doses to patients depends on the availability of multiple dose sizes and adequate dose-response information. These are not always provided, so splitting of the tablets is sometimes necessary. Tablet splitting or dividing has been an accepted practice for many years as a means of obtaining the prescribed dose for medication. Patients may be required to split tablets to;

1) Obtain the required dosage when a dosage form of the required strength is unavailable

2) Provide appropriate fractional doses in a flexible dosing regimen or in a gradually increasing or decreasing dosage regimen

3) Begin therapy with the lowest possible dose to decrease the incidence of adverse effects or to gauge an individual patient's response

Uneven splitting of a tablet may result in significant fluctuations in the administered dose. This may be clinically significant for drugs with a narrow therapeutic range. For many drugs, especially those with long half-lives and/or a wide therapeutic range, dose fluctuations are unlikely to be clinically significant.

.Tablets can be split manually into two portions by breaking with the fingers along a scored line, cutting with a knife or using a specially designed tablet splitter. Uneven division of the tablet or a degree of wasting may occur as some tablets crumble or

break into more than two parts. Irregularly shaped tablets may be difficult to load and may not easily be split into equal halves.

The aim of this study was to: **Determine Content Uniformity of the whole as well as half tablet as per dosage requirement of patients.**

4.9.1 PREPARATION OF SAMPLE SOLUTION OF BATCH 4 & BATCH 6:

4.9.1.1 CONTENT UNIFORMITY:

Taken 10 stratified samples of tablets was taken manually cut in to two part from the break line and dissolved half part of the tablet into 10 different 25ml volumetric flask. Then 15ml distilled water was added to dissolve the tablet and was sonicated for 5 min. Then volume was made up to the mark with the distilled water and was filtered with 0.45µm PVDF filter and absorbance was taken at 232nm.

4.9.2 RESULT

4.9.2.1 Content Uniformity:-

TABLE 4.39: % ASSAY OF UNIFORMITY OF DOSAGE FORM OF HALF TABLET OF BATCH 4 AND BATCH 6

Sample	Batch 4	BATCH 6
1	98.6	101.4
2	89.9	102.3
3	104.5	101.2
4	96.6	99.9
5	93.1	99.4
6	94.9	101.4
7	99.1	101.2
8	103.4	93.1
9	96.6	96.4
10	98.3	96.8
SD	4.4	2.9
RSD	4.5	3.0
AV (n=10)	11.6	7.1

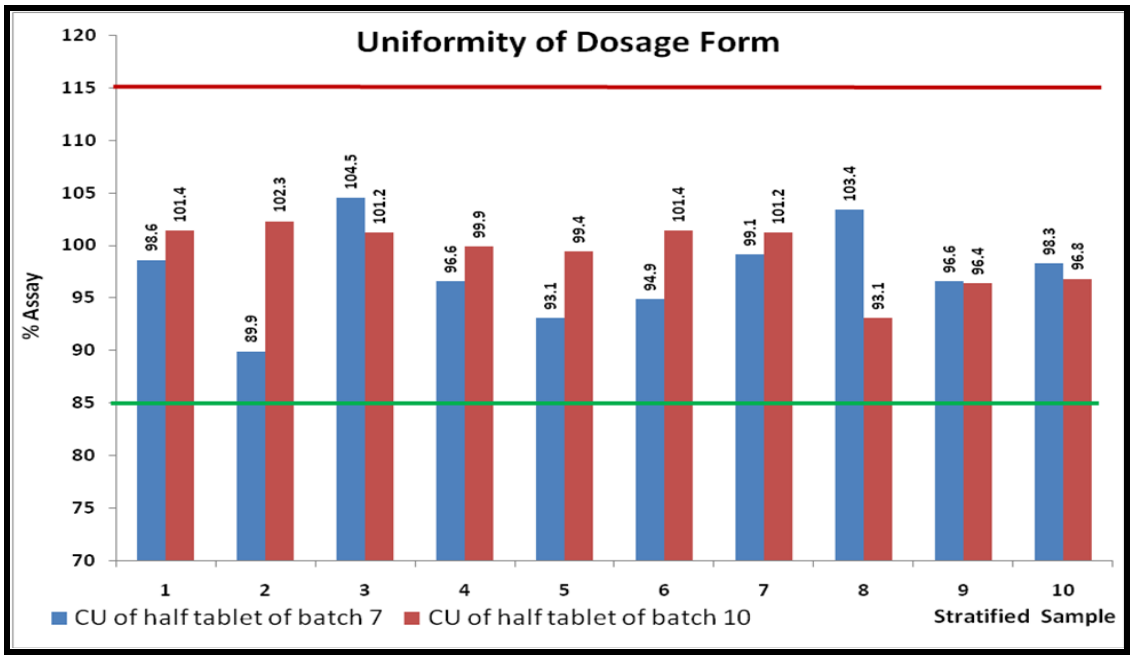


FIGURE 4.18: COMPARISON OF UNIFORMITY OF DOSAGE FORM OF HALF TABLET OF BATCH 4 AND BATCH 6

4.9.3 DISCUSSION

Results of the Uniformity of dosage form are given in Table 4.39 and Figure 4.18. From the result, Content Uniformity of whole tablet of Batch 4 and Batch 6 found similar to the half of the tablet of Batch 4 and Batch 6. Breaking of the tablet just by little pressure is the worst case in which the tablet can be divided into unequal portion. Although breaking the tablets using manual method, the Content Uniformity was achieved within the limit. This indicated that Content Uniformity was achieved in the dosage form. Thus, studies indicated that mixing pattern different shape of the diluents and shear force has major effect on Content Uniformity, Blend Uniformity and Segregation Potential. Thus, it was further optimized by Concept of design of experiments on the basis of performance qualification of the equipment and the results of preliminary trails.

4.10 INTRODUCTION TO 2^3 FULL FACTORIAL DESIGNS:

The two- level design is written as a 2^3 factorial design. It means that 3 factors are consider, each at 2 levels which are usually referred to as low and high levels. These levels are numerically expressed as -1 and +1. It is a simplest two level design. It has 3 factors each at 2 levels was generated between the factors and responses for determining the levels of factors, which yield optimum responses. In this 4 centre points are taken. A second order polynomial regression equation that fitted to the data is as follows:

$$Y = B_0 + B1X1 + B2X2 + B3X3 + B12\ X1X2 + B13X1X3 + B23X2X3$$

Where, B_0 is the intercept representing the arithmetic averages of all the quantitative outcomes of twelve experimental runs; B1 to B3 are the coefficients computed from the observed experimental values of Y; and X1, X2 and X3 are the coded levels of factors. The terms XiXj (i and j = 1, 2 and 3) represent the interaction terms. The equation represents the quantitative effect of factors (X1, X2 and X3) upon the each of the responses with 4 centre point; Y1 to Y12. Coefficients with one factor represent the effect of that particular factor while the coefficients with more than one factor represent the interaction between those factors. A positive sign in front of the terms indicates synergistic effect while negative sign indicates antagonistic effect of the factors. ANOVA was applied for estimating the significance of the model, at 5% significance level. A model is considered significant if the p-value is less than 0.05.

4.10.1 OPTIMIZATION OF UNIFORMITY OF DOSAGE FORM USING RESPONSE SURFACE METHODOLOGY

From the above trials and performance qualification of the instrument found that Blender Volume, Blending time and Co-mill mesh size influence the Content Uniformity, Blend Uniformity and Segregation Potential. Hence these factors were further optimized with the use of experimental design and evaluated with use of design expert software version 8.0.7.1 while statistical analysis was done using statistical software.

A 2^3 FFD was used for optimizing the formulation. The studied factors were:-

- Blender Volume (X1)
- Co-mill mesh size(X2)
- Blending Time (X3)

The responses studied were as follows:-

- Uniformity of Blend RSD (Y1)
- Segregation Potential RSD (Y2)
- AV value (Y3)

These studied factors along with their levels and experimental formulations are summarized in the below Table

TABLE 4.40: FULL FACTORIAL EXPERIMENTAL DESIGN: FACTORS

FACTORS	LEVELS		
	-1	**Center Point**	**+1**
A = Blender Volume(ml)	30%	50%	70%
B = Co-mill mesh size (µm)	457	610	813
C= Blending time (min)	20	30	40

TABLE 4.41: FORMULATION DESIGN AS PER THE 2^3 FULL FACTORIAL EXPERIMENTAL DESIGNS

BATCH NO.	RUN	FACTORS			RESPONSES		
		A	B	C	RSD of BU	RDS of Segregated Blend	AV value
B1	1	-1	-1	-1	2.47	2.8	7.1
B2	2	1	-1	-1	3.57	4.2	7.7
B3	3	-1	1	-1	3.31	3.96	12
B4	4	1	1	-1	5	5.41	11.5
B5	5	-1	-1	1	4.3	4.75	13.7
B6	6	1	-1	1	2.2	2.52	6.1
B7	7	-1	1	1	5.54	5.9	14.2
B8	8	1	1	1	2.59	2.88	7.1
B9	9	0	0	0	3.19	3.35	8
B10	10	0	0	0	3.27	3.78	7.7
B11	11	0	0	0	3.33	3.57	8.4
B12	12	0	0	0	3.53	3.8	9.4

4.10.2 EVALUATION PARAMETERS:

4.10.2.1 Blend Uniformity:-

- After completion of lubrication step 6 Samples were collected from different location through sampling Rod. .

  Top: - Left, Center, Right

  Bottom: - Left, Center, Right

Criteria for the measurement of the Blend Uniformity:-

- Number of Samples : 6 - 10 points
- Potential differences in mixing efficiency associated with specific types of equipment should be considered when determining sampling locations.
- Sample Size $\leq$ 3 x weight individual dose

- If the firm experiences problems in collecting small samples equivalent to 1 to 3 dosage units and demonstrates that small samples give lower values for BUA due to sampling bias, larger samples (usually no more than 10 dosage units) can be collected. Justification for larger samples should be specific to the application under review. Justification based on literature references is usually not adequate.

- Assay (mean or individual results) : 90.0 – 110.0 %

- RSD NMT 5%

- Equation for measurement of % Assay of Blend Uniformity :-

$$\%\ \text{Assay of BU} = \frac{Au * \text{Preparation of STD} * \text{Avg Wg} * 100}{As * \text{Preparation of Sample} * \text{taken Wg} * \text{Label Claim}} \quad \text{..... (12)}$$

4.10.2.2 Segregation Potential:-

- There are no defined criteria available for measurement of the segregation tendency in the blend.

- **The Jenike Fluidization Segregation Tester** was used to measure the segregation tendency of the blend. Approximately 75 gm of the blend was taken and transfer to the equipment and samples were collected from three different location Top, Middle and Bottom. These samples were individually transfered to the Micro Rotary Riffler and from this blend. It was equally divided into 8 samples and from this 3 samples were taken and segregation potential was measured.

$$\%\ \text{Assay of SP} = \frac{Au * \text{Preparation of STD} * \text{Avg Wg} * 100}{As * \text{Preparation of Sample} * \text{taken Wg} * \text{Label Claim}} \quad \text{..... (13)}$$

4.10.2.3 Uniformity of Dosage:-

- If strength of API is <25 mg or <25 % of dose and ratio of drug then Content Uniformity is necessary
- Select ≥ 30 dosage units and proceed as follows for the dosage form designated
- 10 units were assayed individually.
- The drug substance (in %) of each unit was calculated.
- The acceptance value was calculated using formula.

Calculate the acceptance value by the formula:

- AV = |M - X| + ks
- if n=10 then k=2.4
- if n=30 then k=2.0

TABLE 4.42: CALCULATION OF AV VALUE

Conditions	Value	
If 98.5% ≤ X ≤ 101.5	M = X	AV = ks
If X < 98.5%	M = 98.5%	AV = 98.5 – X + ks
If X > 101.5%	M = 101.5%	AV = X – 101.5 + ks

4.10.3 RESULTS AND DISCUSSION

8 Batches were prepared as given in 4.41 and 4 check point batches were prepared to evaluate effect of independent factor like Blender Volume, Blending time and Co-mill mesh size on dependant factor like Content Uniformity, Blend Uniformity and segregation potential. Multiple regression analysis was performed using Design expert software version 8.0.7.1 and polynomial equation was generated for each response.

4.10.3.1 Uniformity of Blend:-

Polynomial equation for Response Surface graph of Uniformity of Blend:-

BU (Y1) = 3.525 – 0.2875 A + 0.4875B + 0.035 C - 0.0325AB – 0. 98 AC - 0.08 BC

..... (14)

TABLE 4.43: RESULTS OF ANOVA FOR SELECTED MODEL FOR BLEND UNIFORMITY

ANOVA for selected factorial model					
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob > F**
Model	10.29235	6	1.715391	21.2827	0.0053
A-Blender Volume %	0.63845	1	0.63845	7.92121	0.0481
B-Co-mill mesh size	1.90125	1	1.90125	23.58870	0.0083
C-Blending Time	0.0098	1	0.0098	0.12158	0.7449
AB	0.00845	1	0.00845	0.10483	0.7623
AC	7.6832	1	7.6832	95.32506	0.0006
BC	0.0512	1	0.0512	0.635235	0.4701
Curvature	0.22815	1	0.22815	2.830645	0.1678
Residual	0.3224	4	0.0806		
Lack of Fit	0.2592	1	0.2592	12.30379	0.0393
Pure Error	0.0632	3	0.02106		

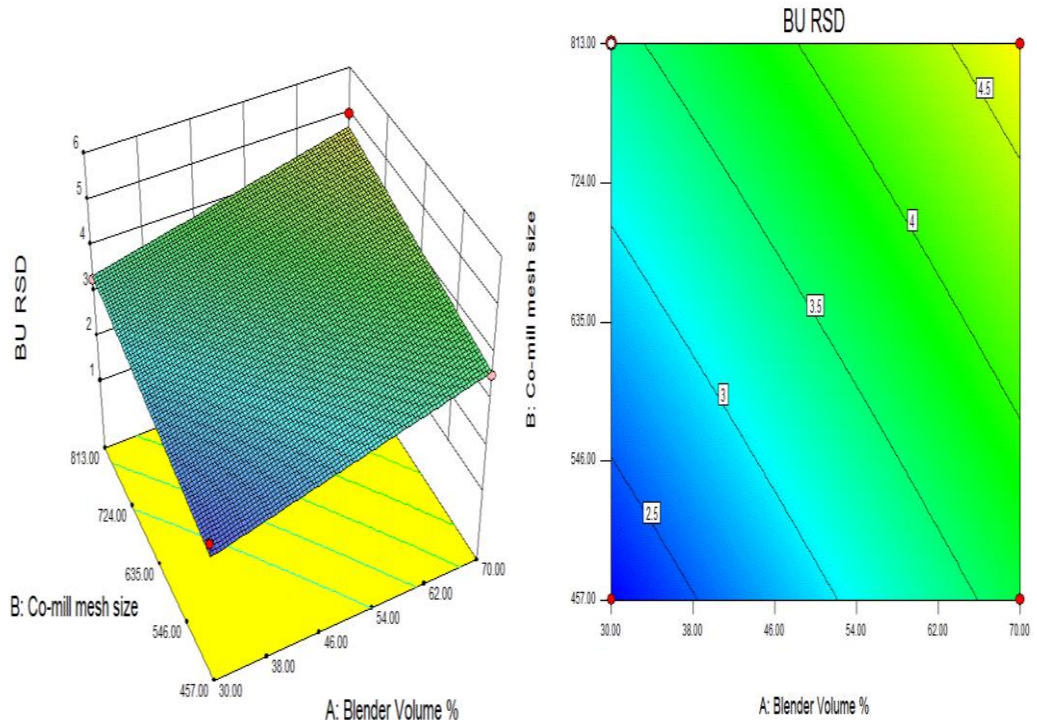


FIGURE 4.19: RESPONSE SURFACE PLOT AND CONTOUR PLOT OF BLEND UNIFORMITY AT 20 MIN BLENDING TIME

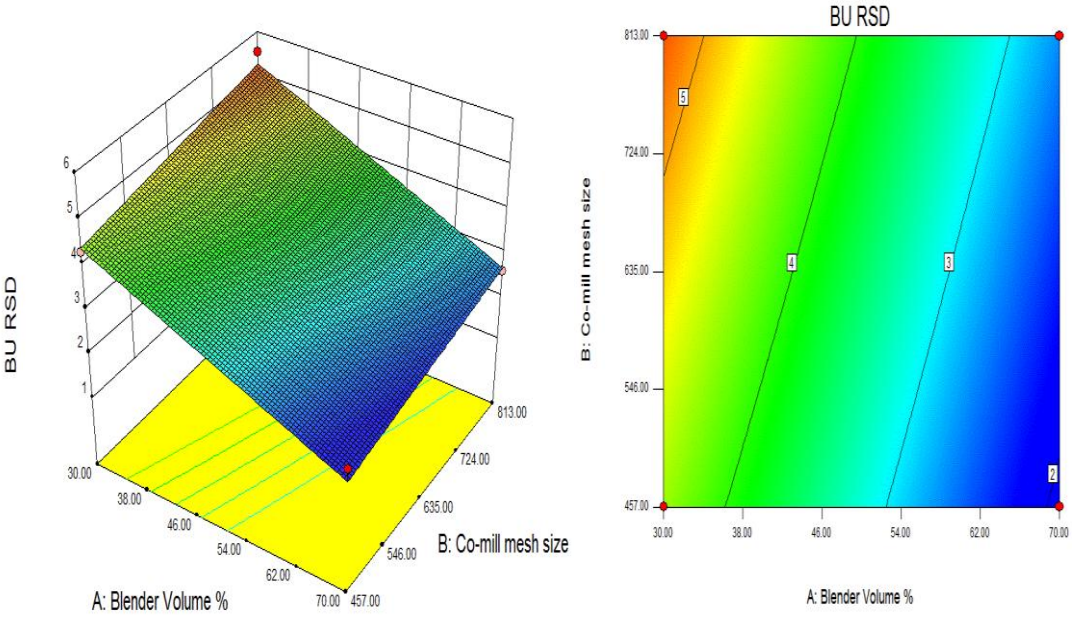


FIGURE 4.20: RESPONSE SURFACE PLOT AND CONTOUR PLOT OF BLEND UNIFORMITY AT 40 MIN BLENDING TIME

From the above polynomial equation (Eq. 14) it was concluded that factor A (blender volume) decreased, there was decrease in RSD value which shows Uniformity in blend. When Factor B (Co-mill mesh size) increased, RSD value was also increased and Uniformity of blend was decreased. From the response surface plot (Figure 4.19 and 4.20), it was concluded that Blending time and Blender volume influence the Uniformity of Blend. Low Blending time with respect to low Blender volume indicated higher Uniformity, but when increasing the blending time it decreased the Uniformity of the Blend. Higher Blender volume with respect to lower blending time resulted in improper mixing while increasing in Blending time Uniformity of Blend was increased. Decreasing the Co-mill mesh size, the Uniformity of blend was little increased.

4.10.3.2 Segregation Potential:-

Polynomial equation for Response Surface graph of Segregation Potential:-

SP (Y2) = 3.91 – 0.3 A + 0.485 B – 0.04 C – 0.0925 AB – 1.0125 AC – 0.1075 BC

..... (15)

TABLE 4.44: RESULT OF ANOVA FOR SELECTED MODEL FOR SEGREGATED BLEND

ANOVA for selected factorial model					
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob > F**
Model	10.97675	6	1.829	33.0376	0.0023
A-Blender Volume %	0.72	1	0.72	13.0022	0.0226
B-Co-mill mesh size	1.8818	1	1.881	33.9828	0.0043
C-Blending Time	0.0128	1	0.012	0.2311	0.6558
AB	0.06845	1	0.068	1.2361	0.3285
AC	8.20125	1	8.201	148.103	0.0003
BC	0.09245	1	0.092	1.66952	0.2659
Curvature	0.48735	1	0.487	8.80090	0.0413
Residual	0.2215	4	0.055		
Lack of Fit	0.0882	1	0.0882	1.9849	0.2536
Pure Error	0.1333	3	0.0444		

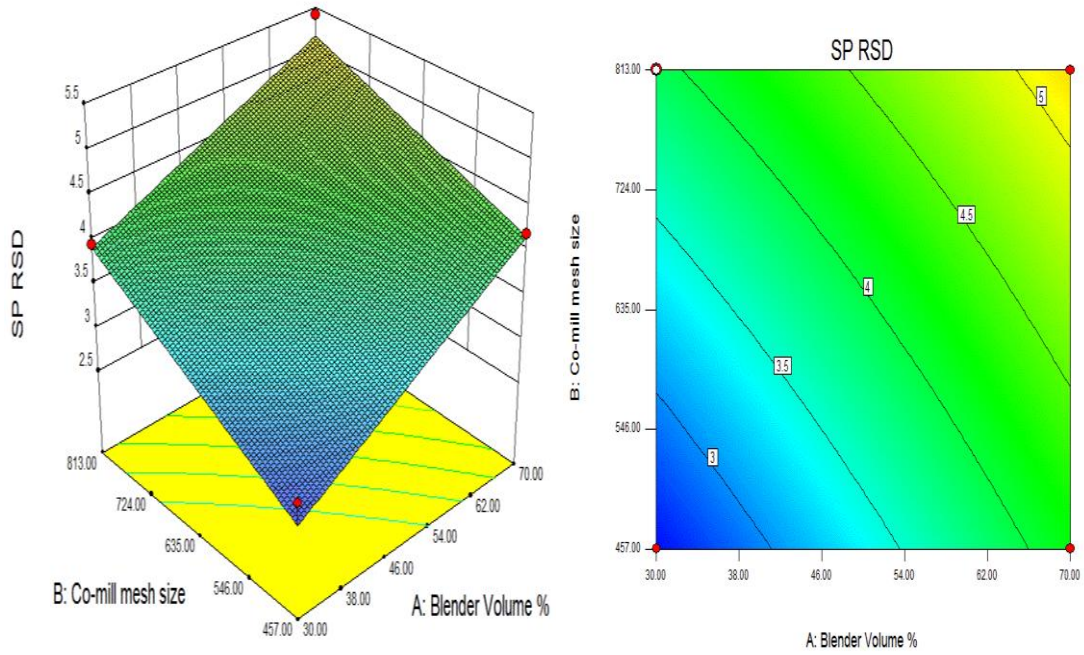


FIGURE 4.21: RESPONSE SURFACE PLOT AND CONTOUR PLOT OF SEGREGATED BLEND AT 20 MIN BLENDING TIME

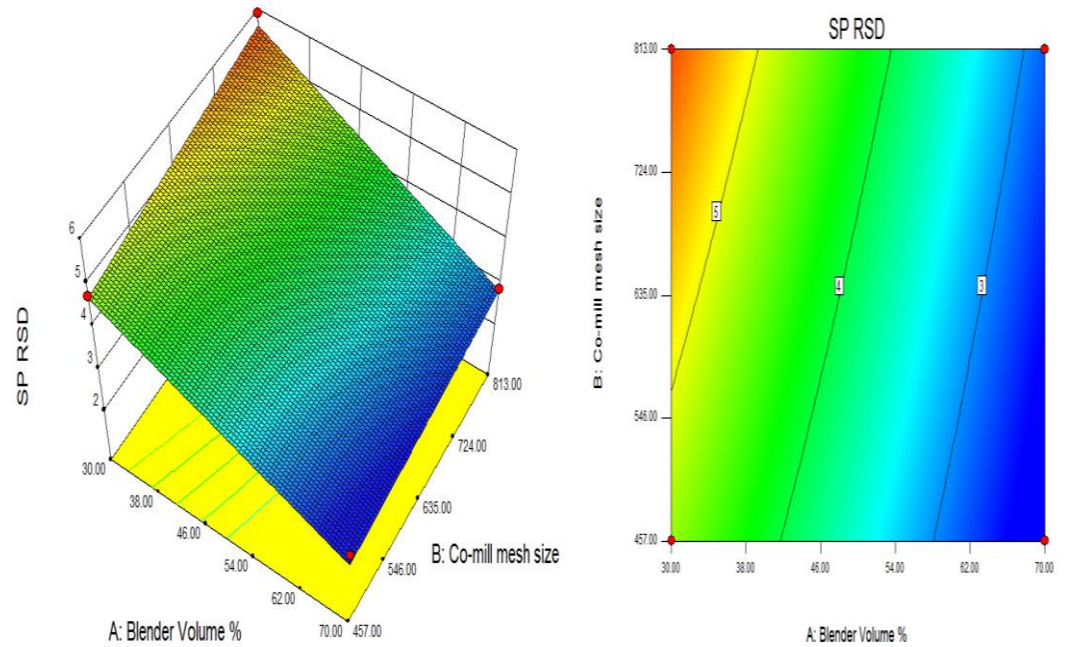


FIGURE 4.22: RESPONSE SURFACE PLOT AND CONTOUR PLOT OF SEGREGATED BLEND AT 40 MIN BLENDING TIME

From the polynomial equation (Eq. 15) it was concluded that factor A (blender volume) and factor C (blending time) decreased, there was decrease in RSD value which shows decreased segregation potential in the blend. When Factor B (Co-mill mesh size) increased, RSD value was also increase and segregation tendency of the blend was increased. From the response surface plot (Figure 4.21 and 4.22) it was concluded that blending time and Blender volume influences the Segregation potential. Low Blending time with respect to low Blender volume shows lower segregation potential and mixing was proper, but when increasing the time it leads to demixing. Higher Blender volume with respect to lower blending time resulted in improper mixing while increasing the Blending time decreases the segregation tendency of the Blend. Decreasing the size of Co-mill mesh there was slight decreased in the Segregation potential.

4.10.3.3 Uniformity of Dosage Form:-

Polynomial equation for Response Surface graph of Uniformity of Dosage form:-

CU (Y3) = 9.40 – 1.825 A + 1.275 B + 0.35 C – 0.075 AB - 1.85 AC – 0.9 BC... (16)

TABLE 4.45: RESULTS OF ANOVA FOR SELECTED MODEL FOR CONTENT UNIFORMITY

ANOVA for selected factorial model					
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-value Prob > F**
Model	74.535	6	12.422	25.255	0.0038
A-Blender Volume %	26.645	1	26.64	54.170	0.0018
B-Co-mill mesh size	13.005	1	13.0	26.439	0.0068
C-Blending Time	0.98	1	0.98	1.9923	0.2309
AB	0.045	1	0.045	0.0914	0.7774
AC	27.38	1	27.38	55.664	0.0017
BC	6.48	1	6.48	13.174	0.0222
Curvature	6.4066	1	6.406	13.024	0.0226
Residual	1.9675	4	0.491		
Lack of Fit	0.32	1	0.32	0.5827	0.5008
Pure Error	1.6475	3	0.549		

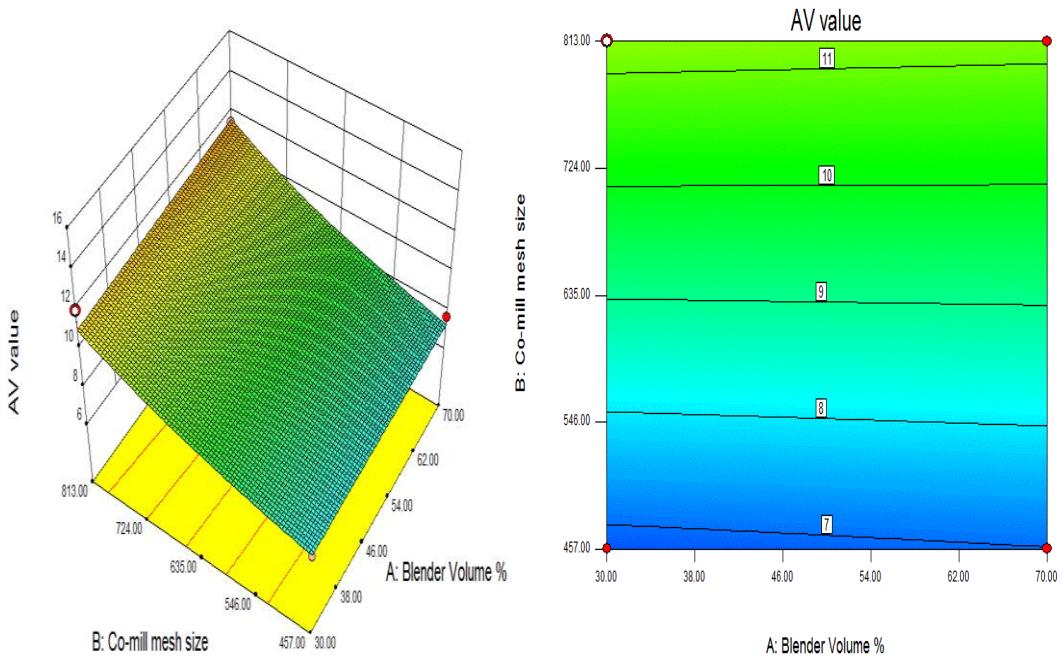


FIGURE 4.23: RESPONSE SURFACE PLOT AND CONTOUR PLOT OF CONTENT UNIFORMITY AT 20 MIN BLENDING TIME

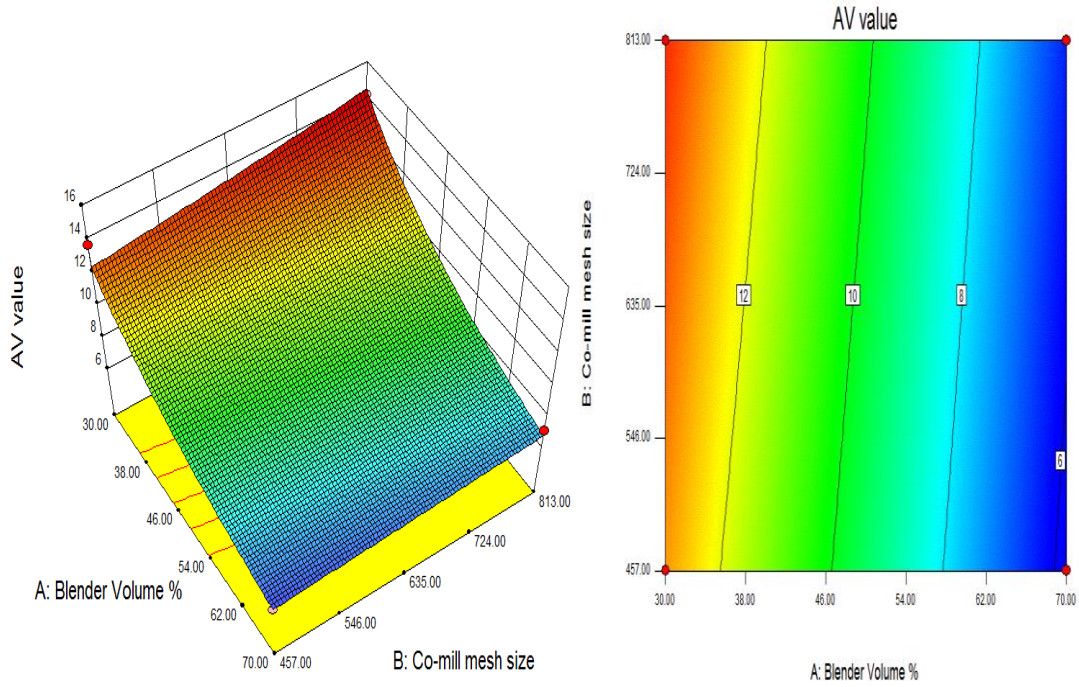


FIGURE 4.24: RESPONSE SURFACE PLOT AND CONTOUR PLOT OF CONTENT UNIFORMITY AT 40 MIN BLENDING TIME

From the polynomial equation (Eq. 16) and response surface plot (Figure 4.23 and 4.24), it shows that combine effect of Blender volume on Blending time and Co-mill mesh size influence the Uniformity of dosage form. Low Blending time with respect to low Blender volume shows higher Uniformity in dosage form and AV value within limit, but when increasing the time it led to segregation and hence increasing in AV value. When low Blending time was applied to higher Blender volume, it resulted in improper mixing while increasing in the Blending time Uniformity of dosage form was achieved. Decreasing the size of Co-mill mesh there was increase in the Uniformity of dosage form.

4.10.3.4 EFFECT OF BLENDER VOLUME, CO-MILL MESH SIZE AND BLENDING TIME:-

From the optimization study, it can be concluded that low blender volume with low mixing time would increase the Uniformity while increasing the mixing time would lead to demixing. High blender volume with low mixing time was resulted in improper mixing but at the same time increasing the mixing time will increase the uniformity of the Blend and decrease the segregation potential. Lower mesh size of Co-mill increases the uniformity of Blend and tablet and decreases the segregation potential

CHAPTER-5

SUMMARY

5 SUMMARY

Over recent decades the pharmaceutical processing has undergone a rapid transition from being a "processing art" to "processing science". This has been possible due to increasing understanding of processing parameters, better manufacturing equipment and stricter regulatory requirements. Optimum mixing is a prerequisite for manufacturing of all solid dosage forms which involves powder mixing and it has a critical contribution in achieving Uniformity of Content. An understanding of powder characteristics and behaviour is essential to control these operations.

Mixing is defined as the process in which two or more than two components in a separate or roughly mixed condition are treated in such a way so that each particle of any one ingredient lies as nearly as possible to the adjacent particle of other ingredient or component. Mixing is energy consuming process which produces a random distribution of particles. It is dependent on the probability that an event happens in a given time and once the desired mixing has been attained, it is essential that the particles in the mix cease movement so that the system may exist in a state of static equilibrium without segregation. Some of the parameters affecting efficient mixing are: a) Particle parameters like particle size, particle shape, size distribution, particle density, cohesivity, hygroscopicity and hardness. Advancement in processing parameters by optimization (various processes related parameters) has put a stringent control on factor leading to segregation in powder mixing.

Present study was done to increase the Uniformity of Blend as well as dosage form by decreasing the Segregation Potential in directly compressible method using metformin as a model drug. To achieve the same, different approaches were implemented like effect of different proportion of excipients interaction with API, effect of strength of API, effect of different shape and size of excipients and effect of shear force to the blend.

Mixing pattern has much influence on the Content Uniformity and Blend Uniformity. Low strength of the API becomes challenge to achieve better Content Uniformity and Blend Uniformity. After comparing with spherical excipients, fibrous and irregular shape containing excipients had more ability to distribute the drug in all over blend. That's the reason to increase Content Uniformity, Blend Uniformity and decrease the segregation tendency of the blend in the fibrous material. It was well known phenomena in pharmaceutical industry that by applying shear force to the mixture component, Uniformity of Blend and Uniformity of dosage form would automatically achieved while segregation potential decrease. After applying shear force to the blend achieved the Uniformity of the dosage even in half tablet.

From the preliminary trials effect of different factors on the Uniformity of dosage form was evaluated and from that Blender Volume, Blending time and Co-mill mesh size were selected for further optimization using 2^3 Full factorial design with 4 centre point to check

the reproducibility of the results. Results were evaluated based on three responses such as Uniformity of Blend, Segregation Potential and Uniformity of Dosage form.

From the optimization study, it was concluded that Blender volume and Blending time have major effect on Uniformity of Blend and Uniformity of the Dosage form. Low Blender volume with low mixing time would increase the Uniformity in Blend due to more head space available for the Blend in the Blender, so less time required for the uniform mixing of the blend and decrease the segregation potential while increase in the mixing time would lead to demixing and increase the segregation tendency of the Blend. High blender volume with low mixing time was resulted in improper mixing due to less head space available for the blend in the Blender. But at the same, increase in the mixing time would increase the Uniformity of the Blend and decrease the segregation potential. Increasing the mixing time with respect to high Blend volume there were increased the Content Uniformity, Blend Uniformity and decreased the segregation tendency. Co-mill mesh size had little influence on the Uniformity of Blend and Segregation potential. Lower mesh size increased the time for the blend to remain in Co-mill, so higher shear force were applied to the blend and increase the Uniformity of Blend, Uniformity of dosage form and decrease the segregation potential.

Thus, the present study concluded that Uniformity of dosage form is an important aspect for any formulation to become effective therapeutic action and thereby to provide effective in therapeutic action to obtain accurate Content Uniformity. However optimization of important process parameter is very essential to develop robust formulation in short time with minimum efforts.

CHAPTER-6

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6 REFERENCES

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