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Scale Up factor determination of V Blender: An overview

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Abstract

Scale-up of mixing operations continues to present a concern to the pharmaceutical development process. 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 This paper discusses the Scale Up factor determination of V Blender and Understanding mixing mechanisms and identifying critical process and material parameters is often a crucial step during process development. 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.

Key Words: Blenders, scale up, mixing operations, V-blenders.

INTRODUCTION

Powder mixing has been the subject of substantial research. This is motivated by applications in a variety of industrial sectors, which include pharmaceuticals, food, ceramics, catalysts, metals,

and polymer manufacturing. In the manufacture of many pharmaceutical products (especially tablets and capsules), dry particle blending is often a critical step that has a direct impact on content uniformity. Tumbling blenders remain the most common means for mixing granular constituents in the pharmaceutical industry. Tumbling blenders are hollow containers attached to a rotating shaft; the vessel is partially loaded with the materials to be mixed and rotated for some number of revolutions. The major advantages of tumbling blenders are large capacities, low shear stresses, and ease of cleaning. These blenders come in a wide variety of geometries and sizes, from laboratory scale (<16 qt) to full-size production models (>500 ft3).A sampling of common tumbling blender geometries include the V-blender (also called the twin shell blender), the double cone, the in-bin blender, and the rotating cylinder.

Understanding mixing mechanisms and identifying critical process and material parameters is often a crucial step during process development. Content uniformity problems have four main root causes: (a) powder stream flow properties [1], (b) poor equipment design or inadequate operation [2], (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 factors. Scale-up of mixing operations continues to present a concern to the pharmaceutical development process. There liable scaling of a process requires an understanding of the effects that processing parameters may illicit on intermediate- and finished-product properties.

Generally, processing conditions are thoroughly examined at small scales during process development of powder formulations .The design and scale-up of blending operations is a multivariate issue; the relative magnitudes of shear, dispersion, and convective forces may be altered as the process is transferred to larger scales [3].A problem with the current scale-up philosophy is a failure in addressing several critical variables. Shear rate and total strain have been shown to affect blend microstructure[4], which may consequently affect the degree of ingredient agglomeration, blend flow properties, tablet hardness and final product dissolution, which may ultimately result in failures during the scale-up process. An example of this includes blend over-lubrication resulting from the increase in shear (per revolution of the blender intensity as a function of increasing scale [5]. In a separate study, blender rotation rates were found to affect the relative standard deviation (RSD) plateau of a given system [6]. Powder cohesion properties also affect the velocity gradient, where inter particulate forces dilate the powder bed density. This may have further implications on downstream processing. Optimization of the blending process requires an understanding of blending mechanisms and critical variables. Although modifications to powder cohesion, blender size, and geometry may not be feasible due to other constraints, operating conditions such as rotation rate and fill level are easier to alter. An understanding of the interactions among these variables is essential .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 [7–9]. Mixing in tumbling blenders is limited in the ability to improve upon component segregation, typically attributable to variations in particle characteristics (e.g., size and shape), once it occurs [10]. Further, initial load configuration (top/bottom and left/right) of the active pharmaceutical ingredient (API) and excipients has been shown to affect the mixing rate [11].

Under the Federal Food, Drug and Cosmetic Act a drug is considered adulterated if it is not produced in conformance to Current Good Manufacturing Practices (CGWs). CGWs are defined in broad terms in 21 Code of Federal Regulations (CFR) Parts 210 and 21 1. The validation of manufacturing processes for pharmaceutical products is one requirement of these regulations. A properly validated process provides a high degree of assurance that the resulting product consistently meets predetermined specifications and quality characteristics. Thus, process validation is not only a legal requirement it is also a good business practice. There is little debate regarding the importance of process validation for pharmaceutical products. Unfortunately, there is less agreement concerning the specific details of the validation process .Common sense dictates that the process validation program for a compressed tablet should include a component that focuses on the final blending step. During this step, various excipients are blended with the granulation in order to facilitate compaction and subsequent dissolution of the tablet. In some products these excipients can represent an appreciable portion of the final dosage form. It is therefore critically important to produce a uniform final blend in order to provide enhanced assurance that the finished product will exhibit acceptable content uniformity. Uniformity of the final blend, however, does not guarantee uniformity of the drug substance in the compressed tablets. Subsequent handling of the blended granulation such as discharge from the blender into drums and tablet press hoppers provide ample opportunity for particle segregation. This can lead to poor drug content uniformity in the finished product.

Thus, a credible process validation program must demonstrate acceptable content uniformity of the final blend and finished product Process validation programs throughout the pharmaceutical industry have been influenced by the opinions recently rendered in United States vs. Barr Laboratories [l2]. In his precedent setting ruling, Judge Alfred Wolin defined some of the CGMP requirements for process validation of oral solid dosage forms in greater detail than is specified in 21 CFR Part 21 1. In particular, Judge Wolin ruled that the appropriate sample size for content uniformity testing of the final blend in validation and ordinary production batches is three times the run weight of the finished product. Based on the testimony of expert witnesses the Court felt that the three times sample size adequately addresses the difficulties associated with sampling small quantities from large volume blends while accommodating the need for testing. The concern is that larger sample sizes could mask in homogeneity of the blend. Furthermore, Judge Wolin ruled that material can be sampled from either a blender or a drum as long as the manufacturer can demonstrate that the samples are representative of all portions and concentrations of the final blend .The Court, in United States vs. Barr Laboratories**,** did not specify the criteria that should be used to evaluate the uniformity of blended granulation .Recent FDA communications [13] suggest, however, that USP Uniformity of Dosage Unit Criteria [85% to 115%] of label claim and relative standard deviations (RSD) that are less than or equal to 6%] are too broad to be applied to blend validation. This is because a freely flowing powder may segregate when discharged from a blender and/or subjected to normal vibration in the hopper of a tablet press. In other words, the uniformity of the final blend should be held to **a** higher standard than that of the tablet in order to provide reasonable assurance that the finished product will exhibit acceptable uniformity. Conceptually, sampling granulation from a blender or container to demonstrate content uniformity is relatively straight forward. In theory, a sample thief designed to extract small volumes of powder can be used to collect samples from **a** blender and/or drum. The sampling locations must be carefully chosen to provide a representative cross-section of the granulation. These locations should include are as that have the greatest potential

to be non-uniform such as near the discharge valve in a ribbon blender or the trunnion region of a V-blender [14]. There samples are then assayed using the same methods used to analyze the finished product. Content uniformity is established if the drug content of the samples conforms pre determined criteria. Although simple in concept, demonstrating content uniformity of unit dose samples of powder blends is complicated by the potential for sampling bias. This bias can occur when small volume samples are extracted with a thief from relatively large volume populations. A sampling thief consists of two concentric tubes. The inner tube is solid except for one or more chambers that allow for sample collection. The outer tube is hollow and contains openings that can align with the chambers on the inner tube; it also has a sharp end to facilitate insertion into the bulk powder. A handle, located at the top of the device, is used to rotate the inner tube within the outer tube in order to open or close the thief. Ideally, during sampling the closed thief is inserted vertically into the desired location within a powder blend. The thief is then opened; this allows the sample to flow into the sampling chamber(s) of the inner tube. The thief is then closed and the sample is withdrawn and collected. A thief is far from an ideal sampling device [15-17]. As it is inserted into a powder blend it can carry material from the upper layers of the mixture downward towards the lower layers.

If the blend has a wide particle size distribution percolation of fines through the coarser material can result in samples that are not representative of the bulk. The forces necessary to insert a long thief through a large volume population can be appreciable; this can lead to compaction and particle attrition. The static pressure of the bulk powder, which forces material into the sample chamber, is significantly greater at the bottom of a large container than in the middle or near the top. If the thief is not used in a perfectly vertical position the angle that it makes with the horizontal can affect the dynamics of the material flowing into the chamber. Special care must be taken to control the orientation of a non-vertical thief since the chamber may be exposed on the top or bottom surface of the device or somewhere in between during sampling. This problem is of particular concern when sampling from different locations within a V-blender where it is difficult to consistently use a thief in a vertical position .Furthermore, since a thief is a static sampling device it violates the two "Golden Rules of Sampling": (i) sample a moving powder and (ii) it is better to sample the entire stream of a flowing powder for short periods of time than a portion of the stream for the whole time [15].All of these factors can result in product adulteration, particle attrition, segregation and overall sampling bias. Sampling bias is of particular concern during validation of pharmaceutical manufacturing processes where minute volumes are sampled from huge populations and then held to very high standards. The problems associated with conducting blend validation with small sample volumes have been discussed in the literature [18]. During process validation it is important to be able to distinguish between a non-uniform blend and biased samples from a homogeneous population. The purpose of this article is to communicate some problems that our firm encountered during validation of the final blending step in a tablet manufacturing process.

In summary, 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.).Historical practices in pharmaceutical process development have largely involved univariate (OVAT, “one variable at a time”) approaches, where the effects of a single variable are examined for a few conditions

selected based on prior experience from a "safe" subset of the permissible design space. A value of the first variable is then selected and kept constant as a second variable is examined, and so forth. However, as suggested in the Process Analytical Technology (PAT) Guidance [19], the OVAT approach does not effectively address the effect of interactions between multiple process variables. As a result, unless the effects of all variables are nearly independent of one another, the optimal conditions for operating the process will not be determined.

Powder Blend Uniformity - refers to active ingredient (or preservative) distribution or homogeneity in the "final" blend or mix. Powder Blend is encapsulated, tabletted, or filled into single or multiple dosage units.

Adequacy of Mixing - satisfactory blending step to assure uniformity and homogeneity. A term used by the US Food and Drug Administration (FDA).

General mixing guidelines

A. Defining Mixedness

Before specifically addressing scale-up of tumbling blenders, this section discusses some general guidelines that cover the current understanding of the important issues in granular blending. The final objective of any granular mixing process is to produce a homogeneous blend. But even determining mixture composition throughout the blend is a difficulty for granular systems. As yet, no reliable techniques for on-line measuring of composition have been developed; hence, granular mixtures are usually quantified by removing samples from the mixture. To determine blending behavior over time, the blender is stopped at fixed intervals for sampling; the process of interrupting the blend cycle and repeated sampling may change the state of the blend. Once samples have been collected, the mean value and sample variance are determined and then often used in a mixing index. Many mixing indices are available; however, there is no "general mixing index," so the choice of index is left to the individual investigator [20]. Once a measure of mixedness has been defined, it is then tracked over time until suitable homogeneity is achieved. Ideally, this minimum level of variance would stay relatively constant over a sufficiently long time. This procedure is simple in concept, but many problems have been associated with characterization of granular mixtures [21].

B. Mixing Issues in Tumbling Blenders

Mixing in tumbling blenders takes place as the result of particle motions in a thin, cascading layer at the surface of the material, while the remainder of the material below rotates with the vessel as a rigid body. Current thinking describes the blending process as taking place by three essentially independent mechanisms: convection, dispersion, and shear. *Convection* causes large groups of particles to move in the direction of flow (orthogonal to the axis of rotation), the result of vessel rotation. *Dispersion* is the random motion of particles as a result of collisions or interparticle motion, usually orthogonal to the direction of flow (parallel to the axis of rotation). *Shear* separates particles that have joined due to agglomeration or cohesion and requires high forces. While all mechanisms are active to some extent in any blender, tumbling blenders impart very little shear, unless an intensifier bar(I-bar) or chopper blade is used (in some cases, high shear is detrimental to the active ingredient and so is avoided). While these definitions are helpful from a conceptual stand point, blending does not take place as merely three independent, scalable mechanisms. However, attentive planning of the blending operation can emphasize or

de-emphasize specific mechanisms and have significant impact on mixing rate. Most tumbling blenders are symmetrical in design; this symmetry can be the greatest impediment to achieving a homogeneous mixture. The mixing rate often becomes limited by the amount of material that can cross from one side of the symmetry plane to the other [22-28]. Some blender types have been built asymmetrically (e.g., the slant cone, the offset V-blender), and show greater mixing proficiency. Furthermore, by rocking the vessel as it rotates, mixing rate can also be dramatically increased [29]. Asymmetry can be "induced" through intelligent placement of baffles, and this approach has been successfully tested on small scale equipment[,30–32] and used in the design of some commercial equipment .But when equipment is symmetrical and baffles unavailable, careful attention should be paid to the loading procedure, for this can have an enormous impact on mixing rate. Nonsystematic loading of multiple ingredients will have a dramatic effect on mixing rate if dispersion is the critical blending mechanism. For instance, in a V blender, it is preferable to load the vessel either through the exit valve or equally into each shell. This ensures that there are near-equal amounts of all constituents in each shell of the blender. Care must be taken when loading a minor (~1%) component into the blender—adding a small amount early in the loading process could accidentally send most of the material into one shell of the blender and substantially slow the mixing process. Smaller blenders entail shorter dispersal distances necessary for complete homogeneity and thus may not be as affected by highly asymmetrical loading. As a final caution, the order of constituent addition can also have significant effects on the degree of final homogeneity, especially if ordered mixing (bonding of one component to another) can occur within the blend [33]. Inter shell flow is the slowest step in a V-blender, because it is dispersive in nature, while intra shell flow is convective. Both processes can be described by similar mathematics, typically using an equation such as

$$\sigma^2 = Ae^{-kN}$$

where σ is mixture variance, *N* is the number of revolutions, *A* is an unspecified constant, and *k* is the rate constant [34]. The rate constants for convective mixing, however, are orders of magnitude greater than for dispersive mixing. Thus unequal loading across the symmetry plane places emphasis on dispersive mixing and is comparatively slow compared to top-to-bottom loading, which favors convective mixing.

Reasons for Blend Testing

- To optimize the blend time during development phase.
- To demonstrate lack of segregation in bins/drums during material handling.
- To confirm that specified blend conditions produce acceptable uniformity during validation.
- Blend assays can be used to release finished product.

Factors in Blending

- Blender Volume
- Blend times for pharmaceuticals: typically 10-20 minutes.
- Obtain accurate powder density from trials

- Constant batch size
- Visual and calculated observations (before/ after blending)
- Nature of material
- Raw Material physical properties are in control

Weight of Active Pharmaceutical Ingredients(s) per Dosage Form Unit [35-39]

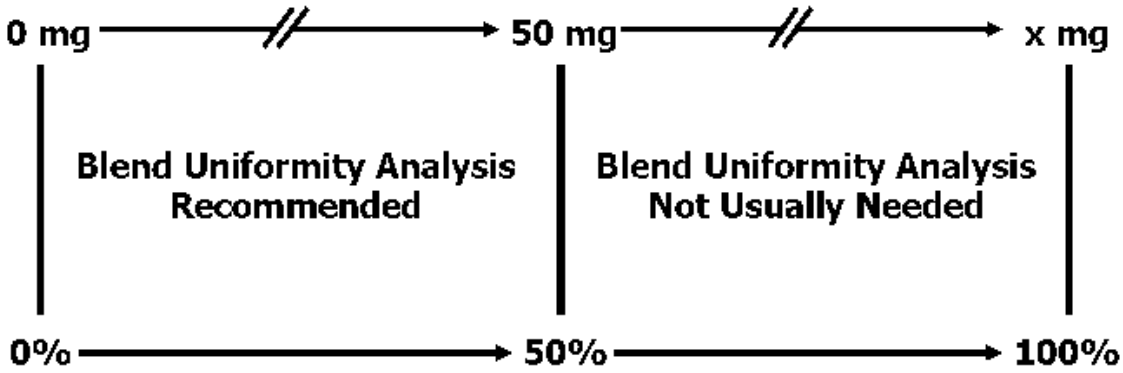


Table 1 : Validation Requirements for Blending Equipment Change[35-39]

Class	Subclass	Example	Recommended Validation Requirements
Same	Same	Same Make/ Model Blender	Ensure sameness*
Same	Same	Tote Bin To Matcon	NONE*
Same	Different**	V-Blender to Bin Blender	Blend Uniformity, Blend Characteristics
Different**	Different	Convection (Planetary) to Diffusion (Bin)	Define Process Parameters Blend Uniformity, Blend Characteristics

Blender [41]

These industrial blenders are sturdily constructed in precise dimension and offer high performance without any hassle. Keeping ourselves abreast of cutting edge technology. They find application for the purpose of mixing and lubricating the granules homogeneously

Type of Blender [41]

Double cone blender

Double cone blender which is an efficient and versatile machine for homogeneously mixing the dry powder and granules. All the contact parts of these blenders are made out of stainless steel of the highest grade. 2/3rd of volume of cone blender is filled to ensure appropriate mixing. These blenders are immensely demanded by pharmaceutical, food, chemical and cosmetic industries.

Octagonal blender

The Octagonal Blender is an efficient and versatile blending machine for mixing and lubrication process of dry granules homogeneously. Two third of the volume of the Cone Blender is filled to ensure proper mixing .The Octagonal Blender gives best result for granules due to very slow speed and octagon shape of container. It can be used for Pharmaceutical, Food, Chemical and Cosmetic products etc. In Octagonal Blender the granules comes from all sides due to the octagonal shape of the product container, hence requirement of RPM is less. Suitable mainly for Crystalline & Granular type material. This type of material gets sufficient continuous movement due to their shape if container has only slow movement and will results in good quality.

Ribbon blender

The Ribbon Blender is an efficient and versatile blending machine for mixing of dry granules & powders homogeneously. Approximate two third of the volume of the container of ribbon blender is filled to ensure proper mixing. The ribbon blender gives best result for mixing of dry powder & granules due to the design and shape of the mixing ribbon and product container. It can be used for Pharmaceutical, Food, Chemical and Cosmetic products etc. Material should be charge from the top side. There are port/ports should be provided on the top cover to charge the material as well as for air vent. One discharge valve provided at the bottom side at center of the container. The discharge height could be adjust as per the requirement, so that material gets discharge in the other container directly, so that material handling time for discharge is nil and the operation is dust free. In Ribbon Blender the powder moves from center to the end of container and end of container to the center of container. Hence requirement of total mixing time is very less and the RPM required are also very less. The dry material gets sufficient continuous movement due to the shape & movement of ribbon & shape of the container., which moves material for good quality of blending. The unit is consist of one electrical motor, one worm reduction gear, belt drive between motor and gear, couple drive between gear to (ribbon) mixing stirrer. Container having four nos. of legs with discharge valve & top cover. Both end of mixing shaft is sealed with bush & PTFE gland housing & safety guards are provided on all moving parts.

Conta blender

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. This is a closed and contained system where by a single step transfer material from container of the Conta blender is transferred to the tablet press hopper .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 .These granules can be mixed and lubricated in this blender, Main advantage of this system is that it is totally dust free. Also another advantage is adaptability of this system to handle more than one sizes of bunkers or containers. This adaptability makes it a very useful machine for any tablet or capsule plant

V-Blender [40]

There are three popular shapes of tumble blenders: the V-Blender, the double cone, and the slant cone. The "V" Blender is an efficient and versatile blending machine for mixing and lubrication process of dry powders homogeneously. Approximate two third of the volume of the Blender is

filled to ensure proper mixing. The "V" Blender gives best result for powders due to suitable medium speed and "V" shape of container. Tumble blenders rely upon the action of gravity to cause the powder to cascade within a rotating vessel. The V-Blender (also known as a twin shell blender) is one of the most commonly used tumbling blenders. The blending performance of this type of blender has shadowed many of the members in the blender family. They offer both short blending times and efficient blending.

The primary mechanism of blending in a V-Blender is diffusion. Diffusion blending is characterized by small scale random motion of solid particles. Blender movements increase the mobility of the individual particles and thus promote diffusive blending. Diffusion blending occurs where the particles are distributed over a freshly developed interface. In the absence of segregating effects, the diffusive blending will in time lead to a high degree of homogeneity.

V-Blenders are therefore preferred when precise blend formulations are required. They are also well suited for applications where some ingredients may be as low as five percent of the total blend size. Normal blend times are typically in the range of 5 to 15 minutes depending on the properties of material to be blended.

Advantages of V-Blender

- Particle size reduction and attrition are minimized due to the absence of any moving blades. Hence it can be used for fragile materials
- Charging and discharging of material is easy.
- The V-blender is good for blending dry powders and granulated products
- The shape of blender body results in a near complete discharge of product material, clearly an added advantage over horizontal blenders.
- The absence of shaft projection eliminates product contamination.
- V-blenders are easy to clean. Internal attachments like lump breakers and liquid dispensers widen the applications of this blender.

Disadvantages of V-Blender

- They require high headroom for installation and operation.
- They are not suited for blending particles of different sizes and densities which may segregate at the time of discharge.

V-Blender with Intensifier Bar

A V-Blender can be provided with high-speed intensifier bars (or lump breakers) running through trunnions into the vessel, along with spray pipes for liquid addition. The intensifiers may be provided for disintegration of agglomerates in the charge material or those formed during wet mixing.

Applications

- Ability to accomplish dry as well as wet mixing.
- Suitability for mixing of fine as well as course particle compositions.
- Suitability for mixing of cohesive powders.
- Provision of intensifier bars may have the following disadvantages:
- Undesired particle attrition.

- Intensifier bar shaft sealing problems.
- Cleaning problems.

Table 2 : Selection of blender[35-39]

Blend material	Type	Blender
Non-cohesive blend	flows & mixes easily	i. Bin Blender ii. Twin Shell iii. Other precision, rotational blender
Cohesive blend	lumpy, not free-flowing	i. Twin Shell w/ I-Bar ii. Colette iii. Lodige
Ordered Mix	drug << excipient	i. Tumbling mixers, ii. cone mixer

Table 3 : Classification of blender on the basis of Mechanism [35-39]

Mechanism	**Equipment**
Diffusion (Tumble)	i. V-Blender (Twin Shell) ii. Double Cone Blender iii. Bin Blender iv. Horizontal/Vertical Drum
Convection (Paddle or Plow)	i. Ribbon ii. Horizontal High Intensity iii. Vertical High Intensity iv. Diffusion (with I-Bar) v. Planetary
Pneumatic (Expansion with Gas)	i. Fluid Bed ii. Reimelt

Table 4: Quality attributes of Mixing

Unit operation	**Process parameter**	**Quality attributes**
Mixing	Type and geometry of mixer Order of addition Mixer load level Number of rotations (time and speed) Agitating bar (on/off pattern)	Blend uniformity Particle size distribution Bulk/tapped density Moisture content Flow properties

Blender Rotation

The V-Blender is made of two hollow cylindrical shells joined at an angle of 75° to 90°. The blender container is mounted on trunnions to allow it to tumble. As the V-blender tumbles, the material continuously splits and recombines, with the mixing occurring as the material free-falls randomly inside the vessel. The repetitive converging and diverging motion of material

combined with increased frictional contact between the material and the vessel's long, straight sides result in gentle yet homogenous blending. **[35-39]**

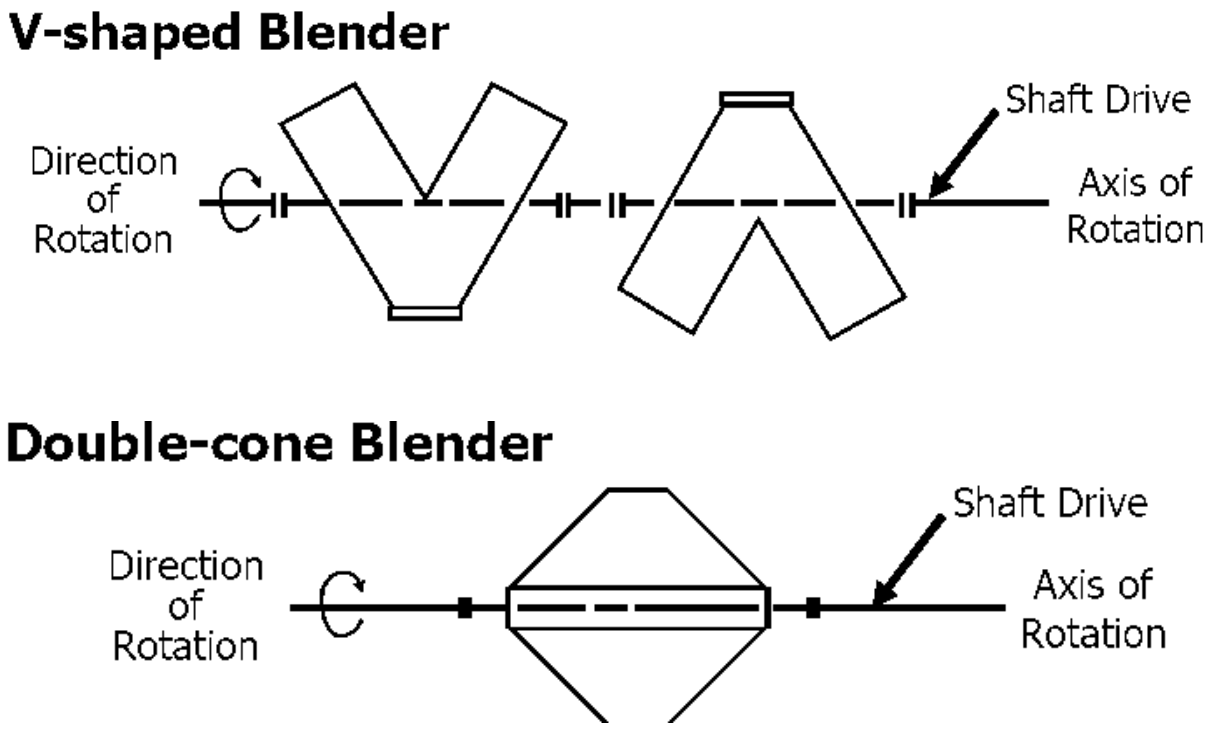
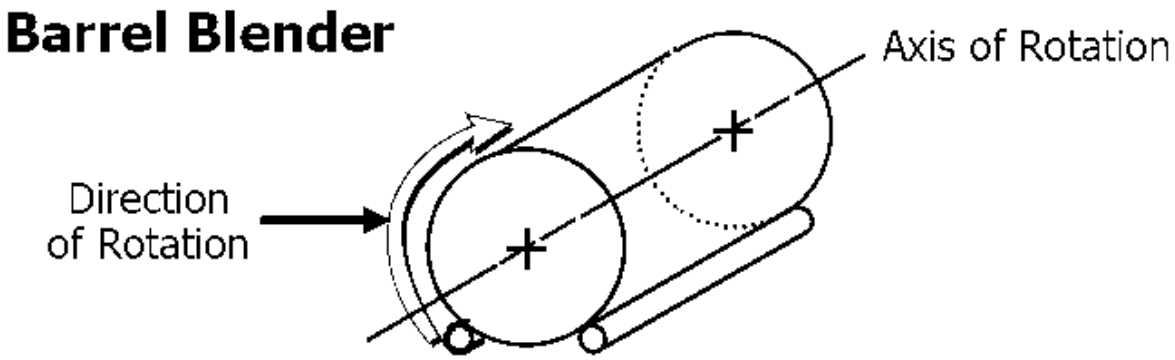


Fig A1 -Direction Of Rotation



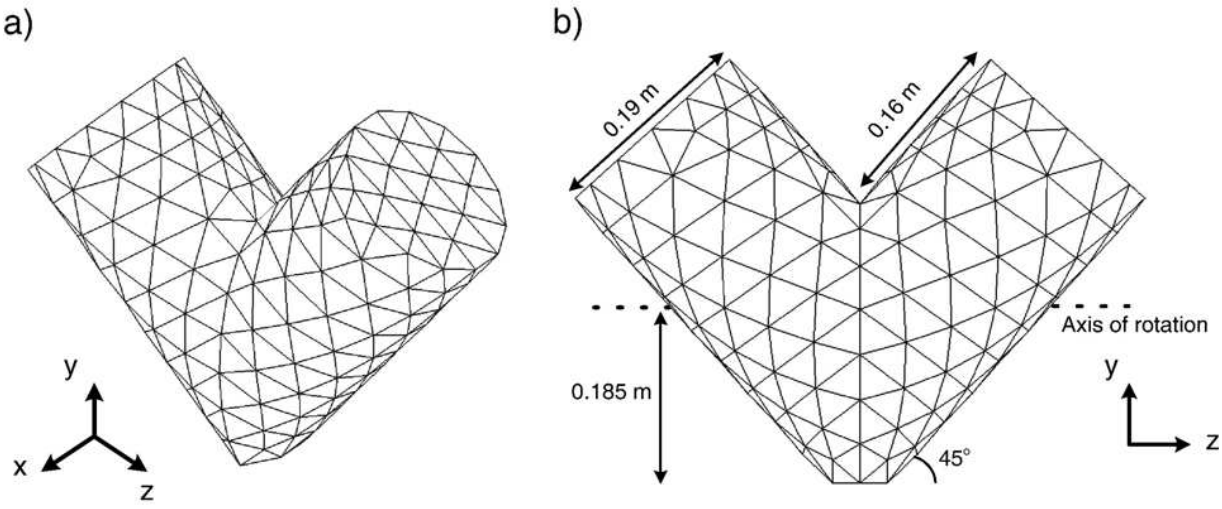
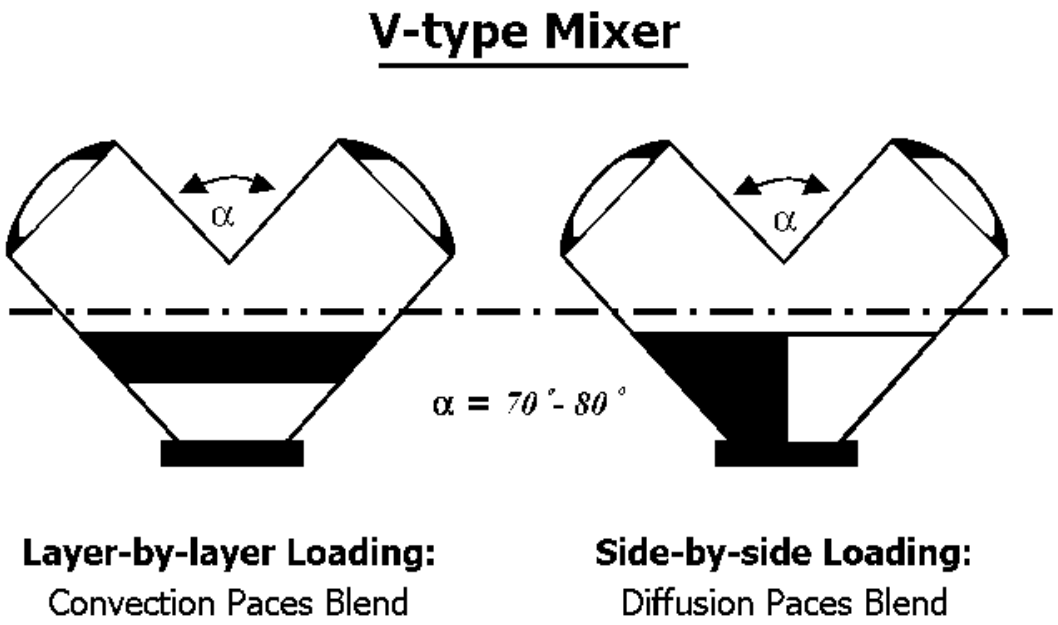


Fig A2 -Direction Of Rotation

Powder loading [42]

The method by which materials are initially loaded into the blender vessel is a parameter that has been shown to affect the mixing performance of tumbling blenders .The method by which material are initially loaded in to the blender vessel Top to Bottom and Left to Right. In the top-to-bottom configuration, one powder is initially loaded into the vessel. Above this powder bed another powder is layered. In the left to right configuration, a separator is initially inserted into the vessel where one side of the mixer is loaded with one powder and the other side with another. The top-to-bottom loading resulted in significantly faster mixing rates than left-to-right loading.



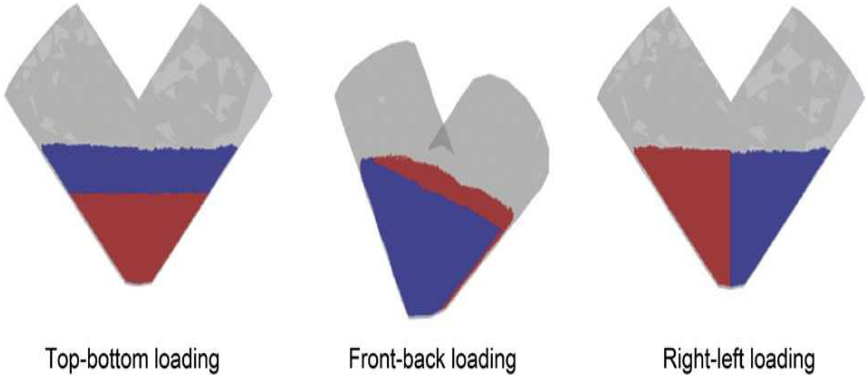


Fig B- Powder Loading

The charging of material into the V-Blender is through either of the two ends or through the apex port. Studies on V-blenders have demonstrated that for solid powders which have similar size and shape, there is no mechanism to move the powders across the line of symmetry of the blender. For such materials, care must then be taken to load each side of the blender equally to ensure the desired homogeneity of blends.

Filling [43]

Blending efficiency is affected by the volume of the material loaded into the blender. The recommended fill-up volume for the V-Blender is 50 to 60% of the total blender volume. For example, if the fill of material in the blender is increased from 50% of the total volume to 70% of the total volume, the time taken for homogenous blending may be doubled.

Speed [43]

Blender speed may also be a key to mixing efficiency. At lower blender speeds, the shear forces are low. Though higher blending speeds provide more shear, it can lead to greater dusting resulting in segregation of fines. This means that the fines become air-borne and settle on top of the powder bed once the blender has been stopped. There is also a critical speed which, if approached will diminish blending efficiency considerably. As the revolutions per minute increase, the centrifugal forces at the extreme points of the blender will exceed the gravitation forces required for blending. Consequently the powder shall tend to gravitate to the outer walls of the blender shell. As the size of the blender increases, the rotational speed decreases usually in proportion to the peripheral speed of the blender extreme. V-Blenders are designed to operate at 50% to 80% of the critical speed. Discharge from the V-blender is normally through the apex port which is fitted with a discharge valve.

Scale-up approaches [44-47]

- **Froude number**

The Froude number Fr.no=Ω²×R/g, where (is the rotation rate, *R* is the vessel radius, and *g* is the acceleration from gravity) is often suggested for tumbling blender scale-up .This relationship balances gravitational and inertial forces and can be derived from the general equations of motion for a general fluid. Unfortunately, no experimental data have been offered to support the validity of this approach. Continuum mechanics may offer other dimensionless groups, if a relationship between powder flow and powder stress can be determined .However, Fr is derived from equations based on continuum mechanics, whereas the scale of the physical system for

blending of granular materials is on the order of the mean free path of individual particles, which may invalidate the continuum hypothesis. A less commonly recommended scaling strategy is to match the tangential speed (wall speed) of the blender; however, this hypothesis also remains untested (Patterson-Kelly, personal communication, 2000).

- **.Rayleigh's Method**

Our hypothesized set of variables that is believed to govern particle dynamics in tumbling blenders is shown in Table. Using these variables and the Rayleigh method,
we derive the following equation:

$$V = k\Omega^a R^b d^c g^e$$

Table 5: Variables Important to Scaling Particle Velocities

Variable	Symbol	Dimensions
Particle velocity	V	*L*/*T*
Vessel rotation rate	Ώ	1/T
Vessel radius	R	L
Acceleration from gravity	g	L/T^2
Particle diameter	d	L

L - length; T- time.

Applying the rule of dimensional homogeneity and making *c* and *e* the unrestricted constants leads to

$$V = k\Omega^{1-2e} R^{1-c-e} d^c g^e$$

To solve Eq. a correlation relating particle velocities to vessel radius and rotation rate is discussed in the forthcoming sections.

Table 6 : Scale-Up of Blending [35-39]

Working Capacity (L)	Typical RPM	Typical Amount (Kg)
20-50	25-30	8-30
250	23-28	80-150
500	12-18	200-300
2000	8-12	800-1200

Sampling method and location [48]

For each treatment condition powder sample were taken after 2-2 min time interval using a groove sampler .The groove sampler consist of a hollow sleeve surrounding a solid inner steel rod possessing a groove along most of the length of rod . Rotating the inner pipe relative to the outer pipe open and closed the groove sampler. The sampler was inserted in to powder bed and rotated to trap material within sampling cavity .After removed from powder bin the sampler was then placed horizontally on a stand while open and the entire device was rotated to discharge the collected material in a series of a small tray and sampling location was constant for each experiment .

Sampling Thief

A schematic diagram of the sampling thief, which was constructed in our machine shop, is presented in Figure-C It is made of 316 stainless steel except for the handle, outer sleeve and sampling chamber inserts which are constructed of TEFLONTM to minimize binding. This thief was designed to remove three separate unit dose samples that contain X mg of DS and three separate samples that contain 2X mg of DS per stab. The six sampling ports are aligned vertically near the bottom of the thief; the three smaller ports are situated below the three larger ports. A sliding outer sleeve is used to cover the ports after the thief is removed from the bulk blend and is raised to reveal one port at a time as the samples are discharged into separate collection vials. The thieves used to sample the validation batches at the two manufacturing sites were different but identical lint design. One unit dose sample from each set at each location within the V-blender (a total of 30 samples) and one unit dose sample from each location within each hopper (15 samples per hopper) were submitted to our QC Laboratories for analysis. The entire sample was assayed for DS using an HPLC method, the same method used to analyze the final tablets. The remaining samples were saved as retains for further analysis as necessary.

Thief sampling probe

A sample thief comprising: an outer hollow rod with an open end; a piston with a plunger end inserted within the outer hollow rod; and the outer hollow rod having an adjustable means. The thief operates by inserting the thief into a blend to be sampled just above the area of the blend to be sampled; adjusting the plunger so that a cavity greater than the desired sample size is created; compacting the sample into the thief; removing the thief from the blend; ejecting the excess sample to a predetermined point; and collecting the sample.

i. A sample thief for sampling a pharmaceutical blend comprising: (a) an outer hollow rod having a top open end and a bottom open end, wherein the bottom open end is beveled; (b) a piston having a plunger at the bottom open end; wherein said plunge has a lower surface, and wherein the position of said piston within the outer hollow rod is adjustably fixable by an adjustable means such that a cavity of predetermined size is created, and wherein said cavity is defined by the space between said bottom open end of the outer hollow rod and the lower surface of said plunger
ii. A sample thief according to claim 1 wherein said outer hollow rod has an inner surface and an outer surface, wherein said plunger forms a seal with the inner surface of the outer hollow rod.
iii. A sample thief according to claim 1 wherein the adjustable means comprises threads.

iv. A sample thief according to claim 1 wherein the adjustable means is a series of teeth on the outer hollow rod and a protrusion or rod on the piston which can be locked with the teeth of the outer hollow rod.

v. A process to sample a pharmaceutical blend comprising:

- Inserting a sample thief according to claim 1 into a pharmaceutical blend such that the bottom open end of the thief is located just above the area of the pharmaceutical blend to be sampled;
- Adjusting the adjustable means so that a cavity greater than the size of the desired volume of sample is created;
- Lowering the thief further into the pharmaceutical blend;
- Removing the thief from the pharmaceutical blend;
- Ejecting the excess sample to a predetermined point;
- Collecting the sample.

Sampling Technique for the Plug Thief

Figure 1 contains a diagram of the plug thief, which was constructed of stainless steel. Blend samples were taken in triplicate by inserting the thief into the powder mixture to the desired location with the rod pushed through the tube such that its tip extended approximately3/8 inch beyond the end of the tube. (Note that the tip of the plunger is round rather than flat to minimize the plugging action of the thief as it penetrated the powder bed.) The plunger was withdrawn to the desired distance to obtain the proper weight of sample (target was 200 mg or 2_ tablet weight), and the entire thief was pushed down to force a plug of powder into the vacated cavity. Caution was exercised to ensure that the rod did not move while the sample was being pulled to avoid excess weight variation or premature discharge of the sample. Once the thief was withdrawn from the blend, the powder plug was discharged directly into a suitable container, and the entire sample was analyzed for drug content. Prior to taking the next sample, the thief was wiped with either a low lint cloth (pilot-scale batches) or antistatic cloth (commercial-scale batches) to remove any residual powder, except in instances otherwise noted. When sampling the commercial-scale batches, both the blending container and the thief were grounded.

Sampling Technique for the Pocket Thief

Figure E is a diagram of the pocket thief, which was constructed of stainless steel. Blend samples were taken in triplicate by inserting the thief in the closed position into the mixture to the desired location. The inner rod was rotated to align the sampling chamber with the opening in the outer sheath (open position), allowing powder (target weight 200 mg or 2_ tablet weight) to flow into the thief. The thief was returned to the closed position and removed From the blending container. The powder sample was discharged directly into a suitable container, and the entire sample was analyzed for drug content. Prior to taking the next sample, the thief was wiped with either a low-lint cloth (pilot-scale batches) or antistatic cloth (commercial-scale batches) to remove any residual powder. When sampling the commercial-scale batches, both the blending container and the thief were grounded.

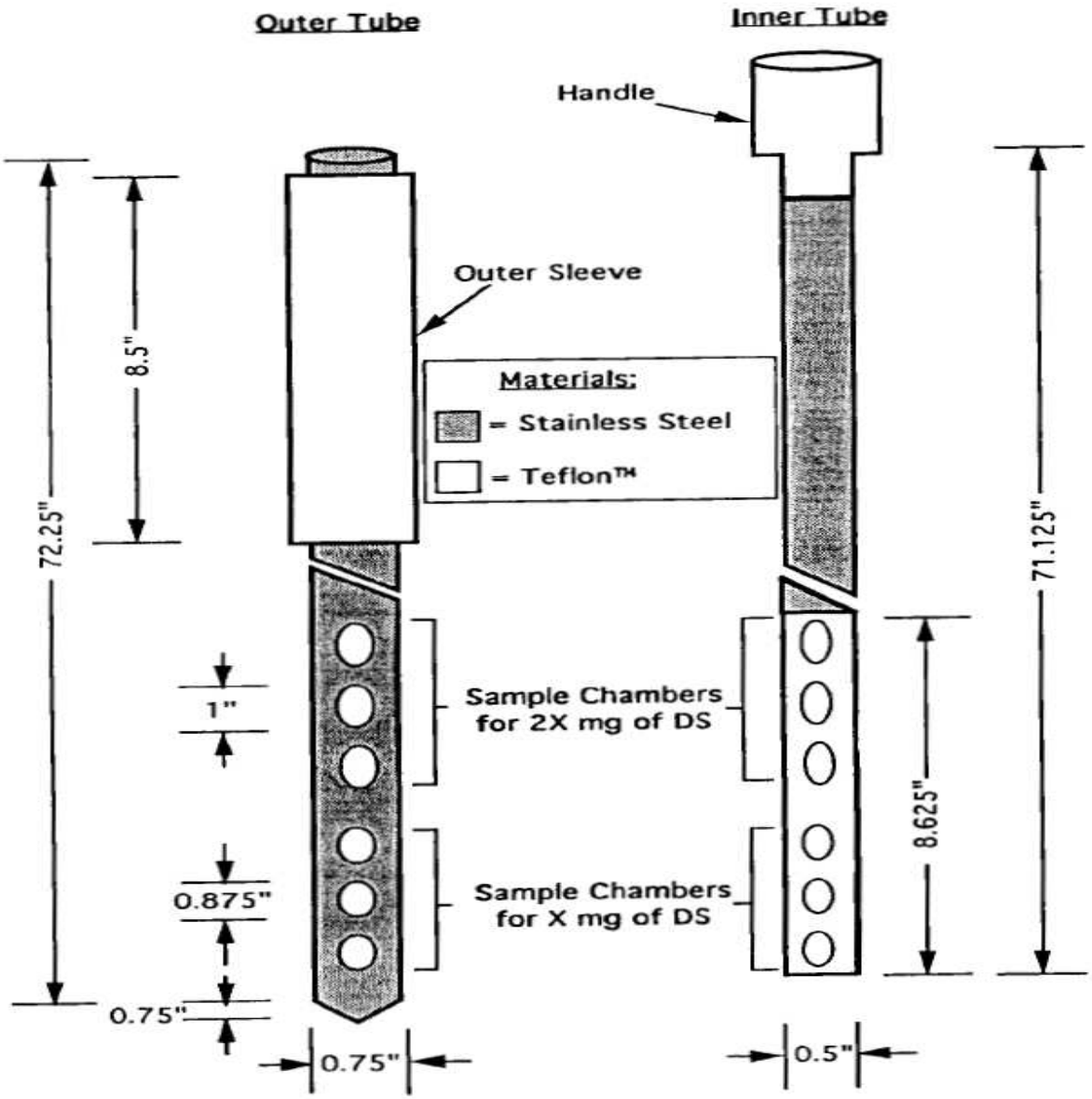


Fig C -Sampling Thief

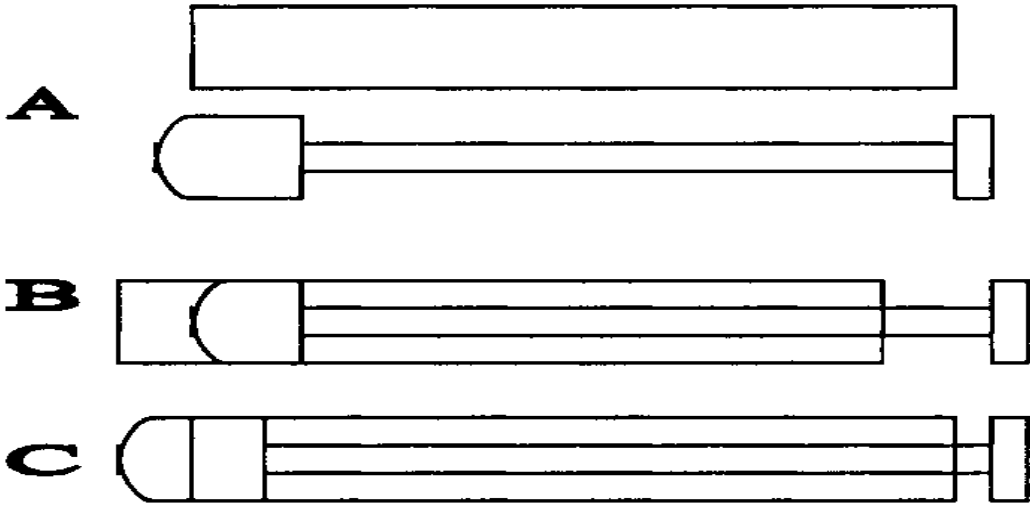


Figure D. Diagram of plug thief: (A) disassembled; (B) open (sampling) position; (C) closed (insertion or sample discharge) position.

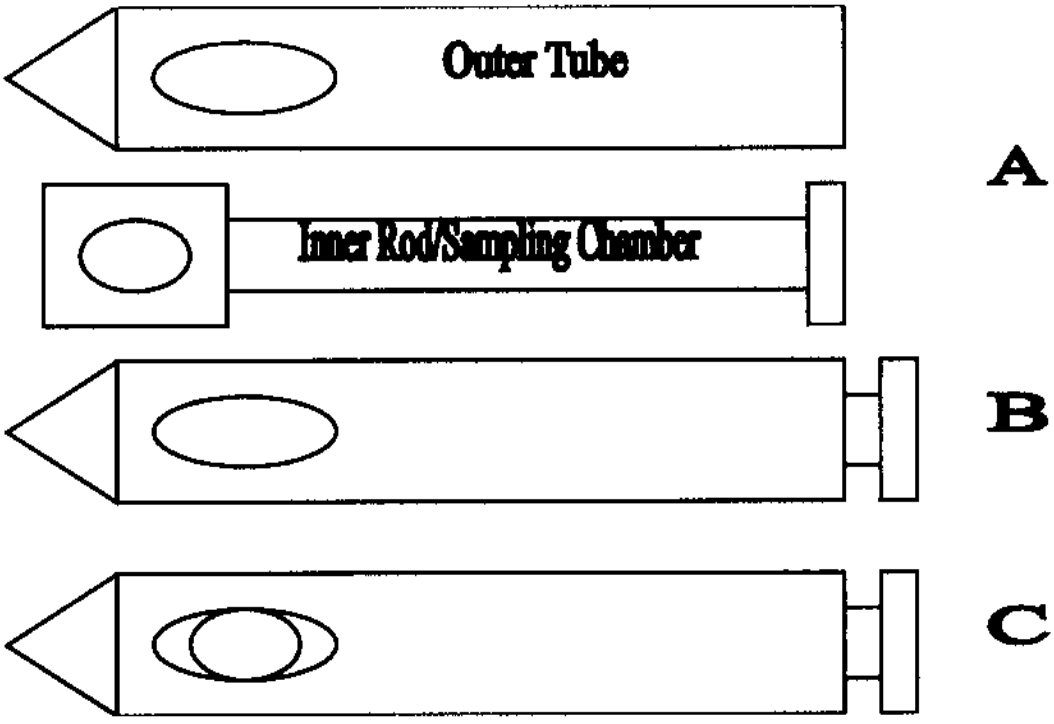


Figure E. Diagram of pocket thief: (A) unassembled; (B) closed position; (C) open position.

Sampling Schemes for Blends and Tablet Cores

Figure 3 contains the sampling scheme used for pilot scale batches 1–3. Figure F contains the sampling scheme used for commercial-scale batches 4–10. Tablets were sampled from the press at defined intervals throughout the entire course of the compression process, including beginning and end-of-run samples.

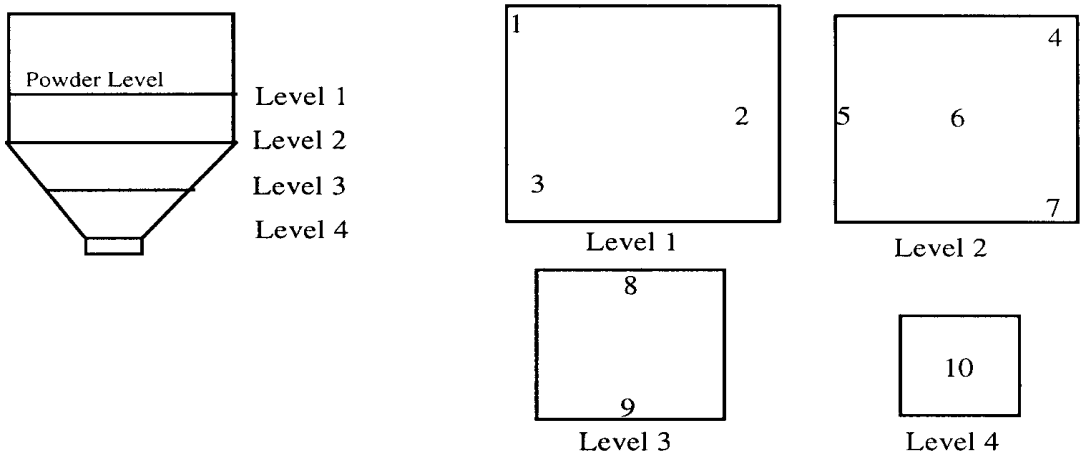


FIG F - Sampling schemes for blends and tablet cores

Sampling Location [35-39]

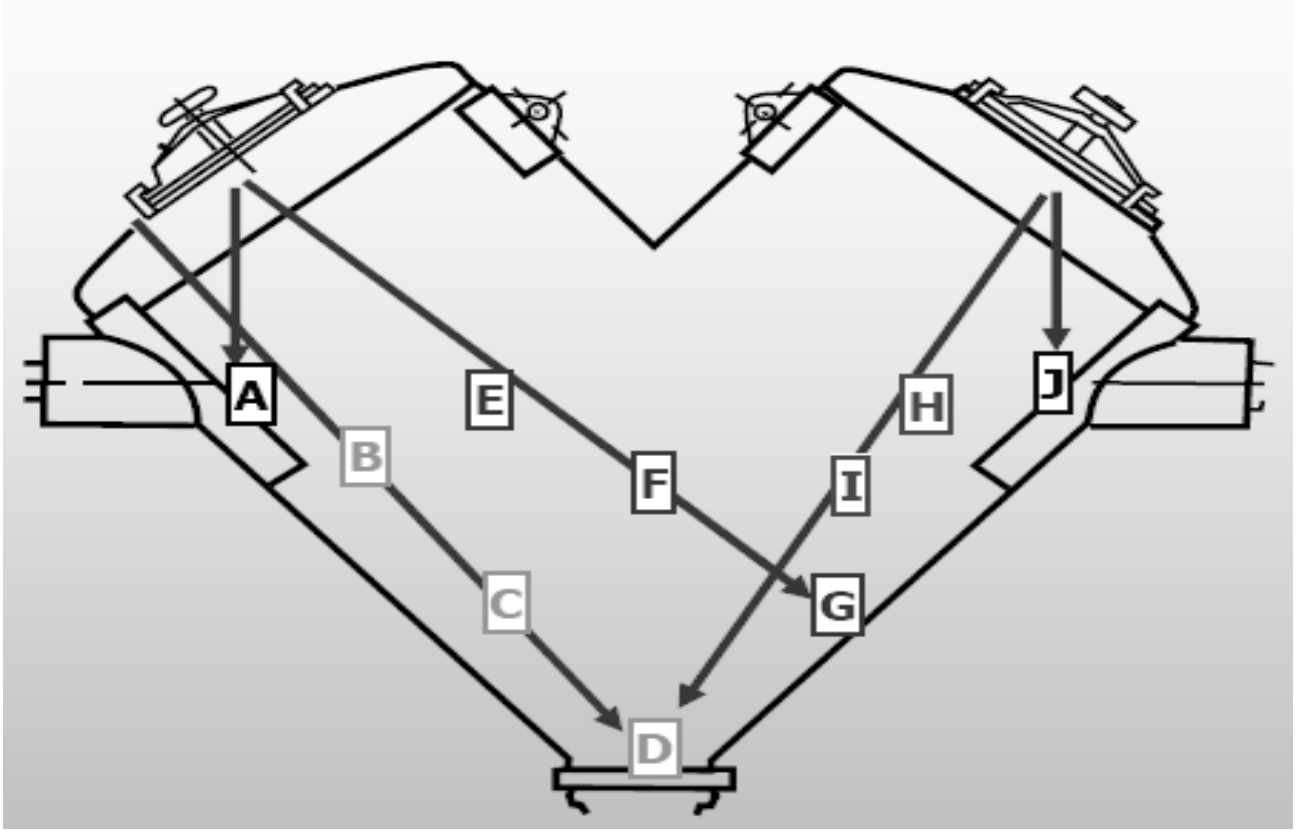


Fig G- V Blender

Table 7 : Sampling Location

Sample set	Symbol	Location
1	A	Left-left-top
2	B C D	Left-left-middle Left-left-bottom Discharge port
3	E F G	Left-center-middle Center-center-center Right-right-bottom
4	H I	Right-right- top Right-right-middle
5	J	Right-Right-Top

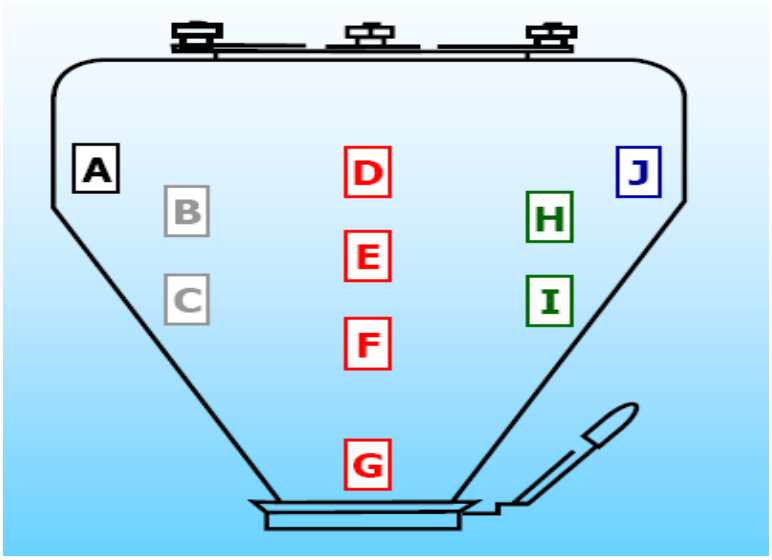


Fig H- Bin Blender

Table 8: Sampling Location

Sample set	Symbol	Location
1	A	Left- top
2	B C	Back -top Back -middle
3	D E F G	Center –top Center –middle-top Center –bottom Discharge port
4	H I	Front - top Front -bottom
5	J	Right-Top

Quantification of Mixing Performance [42]
Sample was collected and assay (content uniformity) with help of UV, HPLC, Near infrared spectroscopy and variance was determine with help of ANOVA software

Homogeneity –
In order to determine powder homogeneity, the sample-to sample variability was quantified in terms of the RSD. The standard definition of RSD (also known as coefficient of variance (CoV)) is given by:

$$\mathrm{RSD} = \mathrm{CoV} = \frac{s}{\bar{x}}$$

Where's represents the sampling estimate of the standard deviation and x the average of all the samples. As mentioned, samples were retrieved from the vessel using a sampler and subsequently measured via UV. For each radial core position (denoted as j), xi j is a sample concentration, xj is the mean concentration, and Nj is the number of samples in that core. The standard definition of variance (s2) is given by Eq.

$$s^2 = \sum_j \sum_i \frac{(x_{ij} - \bar{x})^2}{N_i}$$

$$\bar{x}_j = \frac{\sum_i x_{ij}}{N_i}$$

Where N is the number of samples and x is the mean composition found using Eq. The total variance is decomposed into two components for axial and radial variability (Eq.

$$s^2 = \frac{1}{N}\sum_j N_j(\bar{x}_j - \bar{x})^2 + \frac{1}{N}\sum_j \sum_i (x_{ij} - \bar{x}_j)^2 \qquad (\text{illegible})$$

Statistically, if random samples are taken from a mixture of average composition q, given the fraction of the first component is P and second component is (1−P),and the mixture has a random structure, the composition of the samples will be normally distributed. The theoretical variance can be calculated for completely random mixtures using Eq. and for nonrandom mixtures using Eq.:

$$\sigma^2 = P\left(1 - \frac{P}{N}\right)$$

$$\sigma^2 = \left[L + \frac{(P(1-P) - L)}{N}\right]^2 L$$

Where L represents a constant for a given mixture or state of mixedness and may be determined experimentally when the value of σ is known for a given value of N. For a system where the two components are completely unmixed, the initial variance $(\sigma_0)^2$ of the sample composition may be calculated using Eq. [21, 25]:

$$\sigma_0^2 = P(1-P)$$

The first term is an estimate of axial variance And the second term, radial variance .Axial variance measures the differences in concentrations between the top and bottom of the powder bed. The ratio of API and excipient the initial RSD would be 5%. This value should represent the largest obtainable variance for this system. The discrepancies in RSD values may be due to the differences in the number of samples retrieved relative to the total powder mass in each vessel.

Mixing rate

Process performance monitoring for each parameter combination was evaluated by mixing rate of API and excipient The mixing rate was computed by Retrieving powder samples from the blender as a function of revolutions. Sample variance and relative standard deviation as a function of vessel revolutions were determined from predicted concentrations. In the absence of segregation, the variance in a blender typically decays to its asymptotic value as an exponential of time. There fore, mixing rate is measured as the slope of the logarithm of the variance. The slope, m, is determined from Eq

$$m = \frac{\sum \left(\text{revolutions}_i - \overline{\text{revolutions}}\right)\left(\log\left(s_i^2\right) - \overline{\log\left(s^2\right)}\right)}{\sum \left(\text{revolutions}_i - \overline{\text{revolutions}}\right)^2}$$

Hausner ratio

Interparticle surface forces such as friction and cohesion are dependent on the total surface area. Since mass is proportional to the volume, the surface area to volume ratio is a good general indication of the “flowability” of a powder system The Hall flow meter and Hausner ratio are two common techniques for analyzing the effect of inter particle forces on the flow behavior of powder systems under the influence of gravity. The Hausner ratio is the ratio of the tapped density to the apparent (poured) density of the powder. The apparent density tends to decrease as the inter particle friction in a powder system increases. The tapped density tends to decrease as well, albeit a lesser extent due to the additional energy imparted from tapping. The cohesive behavior of a powder is a qualitative description of how powder moves .Yield strength increases with powder cohesion because a larger stress is required to deform the powder. A cohesive powder will have a higher Hausner ratio relative to one that is free flowing.

The US Pharmacopoeia defines ranges of the Hausner ratio which describe powder flowability. Hausner ratio values between 1 and 1.11are considered to reflect excellent flow properties. Values greater than 1.6 typically suggest very poor flow, a characteristic of cohesive powders. The larger the surface area to volume ratio, the greater the probability a particle will cling to another

Hausner ratio= Tapped density / Bulk density

Statistical analysis methodology [47]

ANOVA: ANOVA can do any number of analyses with one command. One table is produced for each possible combination of the independent and dependent variables. ANOVA repeats all analyses for each subset of the data defined by the given variable. Each time the value of variable

changes, ANOVA assumes a new subset begins; so the dataset must be in sort order according to variable, or at least grouped by its code values. Additional control is provided by the REPETITION option, used to define multiple analyses for up to 25 categories, which does not require the data to be sorted. Use RECODE and SORTDATA to create appropriate repetition variables and code categories for the desired result.

Missing Data: For each analysis, cases with missing data on the dependent variable are excluded; cases with missing data on the independent variable are optionally excluded.

Analysis of variance **(**ANOVA**)** is a mathematically procedure for partitioning the variability of a data set in to components with different main and interaction effect .the information provide by ANOVA is used to construct statistical test to determine the statistical significance of main effect and interaction .an F statistic is computed for each effect which is used to test hypotheses about the existence of effect of variables .

Degree Of Freedom – to estimate an error term
Df = n-1
Sum Of Square - using SAS version 9.1
P value - using Microsoft excel *pdist* function

CONCLUSION

A systematic, generalized approach for the scale-up of granular mixing devices is still far from attainable. Clearly, more research is required both to test current hypotheses and to generate new approaches to the problem. Still, we can offer some simple guidelines that can help the practitioner through the scale-up process.

1. Make sure that changes in scale have not changed the dominant mixing mechanism in the blender (i.e., convective to dispersive). This can often happen by introducing asymmetry in the loading conditions.
2. Number of revolutions is a key parameter, but rotation rates are largely unimportant.
3. When performing scale-up tests, be sure to take enough samples to give an “accurate” description of the mixture state in the vessel. Further more, be wary of how you interpret your samples; know what the mixing index means and what your confidence levels are.
4. One simple way to increase mixing rate is to decrease the fill level—while this may be undesirable from a throughput point of view, decreased fill level also reduces that probability that dead zones will form.
5. Addition of asymmetry into the vessel, either by design or the addition of baffles, can have a tremendous impact on mixing rate.

Until rigorous scale-up rules are determined, these cautionary rules are the state of the art for now. Scaling rules by scaling particle surface velocities but caution that this work is only preliminary in nature. The best advice is to be cautious—understand the physics behind the problem and the statistics of the data collected. Remember that a fundamental understanding of

the issues is still limited and luck is unlikely to be on your side ;hence, frustrating trial and error is still likely (unfortunately) to be employed.

This paper presented an example of the application of statistical methods to examine the effects of multiple variables on mixing performance. Further, this study enabled the prioritization of the impact of variables using the following order of significance: tote size, cohesion , rotation rate and fill level. Additionally, the results indicated main variables. such as tote size, inherently interact. While this may explain the obscure nature of blending process scale-up, it also suggests that ANOVA methods may be used to unravel some of its complexities. Unfortunately, some of the interactions are difficult to examine in practice. Given the typical small number of experiments that can be conducted in a blending study, the risk of making erroneous assumptions concerning large-scale batch behavior based on small-scale observations is high.

Several additional comments deserve attention:

– Given that blender size likely interacts with other variables, the results obtained at smaller scales (a common practice in many industries) should be evaluated very carefully. Scale-up studies going beyond mere “performance equivalence” and aimed at development of effective scale-up correlations are critical .Material properties of powders clearly play an important, scale-dependent role in blending performance .This study merely touched the surface of assessing these phenomena. Going forward, the pharmaceutical industry should continue to enhance characterization of relevant material properties.
– As previously addressed, materials and processes both exhibit constant variability, making the optimum process a moving target. Additionally, the amount of work needed to identify, characterize, and control all variables affecting product performance is significant. With this in mind, only a first-pass design may be achieved within the short time frames associated with current pharmaceutical product development cycles. However, valuable information is generated by the manufacturing operation, for further refinement of models for the improvement of product performance.

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